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# Interventions for fatigue in people with kidney failure requiring dialysis (Review)

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# TABLE OF CONTENTS

[Intervention Review]

# Interventions for fatigue in people with kidney failure requiring dialysis

Patrizia Natale[1,2,3], Angela Ju[2], Giovanni FM Strippoli[1,2,4], Jonathan C Craig[4,5], Valeria M Saglimbene[2,6], Mark L Unruh[7], Giovanni Stallone[3], Allison Jaure[2,8]

[1]Department of Precision and Regenerative Medicine and Ionian Area (DiMePre-J) Nephrology, Dialysis and Transplantation Unit, University of Bari Aldo Moro, Bari, Italy. [2]Sydney School of Public Health, The University of Sydney, Sydney, Australia. [3]Nephrology, Dialysis and Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy. [4]Cochrane Kidney and Transplant, Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia. [5]College of Medicine and Public Health, Flinders University, Adelaide, Australia. [6]Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy. [7]University of New Mexico, Department of Internal Medicine, Albuquerque, New Mexico, USA. [8]Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia

**Contact:** Patrizia Natale, natale.patrizia@gmail.com.

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## ABSTRACT

### Background

Fatigue is a common and debilitating symptom in people receiving dialysis that is associated with an increased risk of death, cardiovascular disease and depression. Fatigue can also impair quality of life (QoL) and the ability to participate in daily activities. Fatigue has been established by patients, caregivers and health professionals as a core outcome for haemodialysis (HD).

### Objectives

We aimed to evaluate the effects of pharmacological and non-pharmacological interventions on fatigue in people with kidney failure receiving dialysis, including HD and peritoneal dialysis (PD), including any setting and frequency of the dialysis treatment.

### Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 18 October 2022 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Registry Platform (ICTRP) Search Portal and ClinicalTrials.gov.

### Selection criteria

Studies evaluating pharmacological and non-pharmacological interventions affecting levels of fatigue or fatigue-related outcomes in people receiving dialysis were included. Studies were eligible if fatigue or fatigue-related outcomes were reported as a primary or secondary outcome. Any mode, frequency, prescription, and duration of therapy were considered.

### Data collection and analysis

Three authors independently extracted data and assessed the risk of bias. Treatment estimates were summarised using random effects meta-analysis and expressed as a risk ratio (RR) or mean difference (MD), with a corresponding 95% confidence interval (CI) or standardised MD (SMD) if different scales were used. Confidence in the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

**Main results**

Ninety-four studies involving 8191 randomised participants were eligible. Pharmacological and non-pharmacological interventions were compared either to placebo or control, or to another pharmacological or non-pharmacological intervention. In the majority of domains, risks of bias in the included studies were unclear or high.

In low certainty evidence, when compared to control, exercise may improve fatigue (4 studies, 217 participants (Iowa Fatigue Scale, Modified Fatigue Impact Scale, Piper Fatigue Scale (PFS), or Haemodialysis-Related Fatigue scale score): SMD -1.18, 95% CI -2.04 to -0.31; $I^2$ = 87%) in HD.

In low certainty evidence, when compared to placebo or standard care, aromatherapy may improve fatigue (7 studies, 542 participants (Fatigue Severity Scale (FSS), Rhoten Fatigue Scale (RFS), PFS or Brief Fatigue Inventory score): SMD -1.23, 95% CI -1.96 to -0.50; $I^2$ = 93%) in HD.

In low certainty evidence, when compared to no intervention, massage may improve fatigue (7 studies, 657 participants (FSS, RFS, PFS or Visual Analogue Scale (VAS) score): SMD -1.06, 95% CI -1.47, -0.65; $I^2$ = 81%) and increase energy (2 studies, 152 participants (VAS score): MD 4.87, 95% CI 1.69 to 8.06, $I^2$ = 59%) in HD.

In low certainty evidence, when compared to placebo or control, acupressure may reduce fatigue (6 studies, 459 participants (PFS score, revised PFS, or Fatigue Index): SMD -0.64, 95% CI -1.03 to -0.25; $I^2$ = 75%) in HD.

A wide range of heterogenous interventions and fatigue-related outcomes were reported for exercise, aromatherapy, massage and acupressure, preventing our capability to pool and analyse the data.

Due to the paucity of studies, the effects of pharmacological and other non-pharmacological interventions on fatigue or fatigue-related outcomes, including non-physiological neutral amino acid, relaxation with or without music therapy, meditation, exercise with nandrolone, nutritional supplementation, cognitive-behavioural therapy, ESAs, frequent HD sections, home blood pressure monitoring, blood flow rate reduction, serotonin reuptake inhibitor, beta-blockers, anabolic steroids, glucose-enriched dialysate, or light therapy, were very uncertain.

The effects of pharmacological and non-pharmacological treatments on death, cardiovascular diseases, vascular access, QoL, depression, anxiety, hypertension or diabetes were sparse. No studies assessed tiredness, exhaustion or asthenia. Adverse events were rarely and inconsistently reported.

**Authors' conclusions**

Exercise, aromatherapy, massage and acupressure may improve fatigue compared to placebo, standard care or no intervention. Pharmacological and other non-pharmacological interventions had uncertain effects on fatigue or fatigue-related outcomes in people receiving dialysis. Future adequately powered, high-quality studies are likely to change the estimated effects of interventions for fatigue and fatigue-related outcomes in people receiving dialysis.

## PLAIN LANGUAGE SUMMARY

**Are interventions for fatigue effective among people with kidney failure requiring dialysis?**

**What is the issue?**

Fatigue is a frequent and debilitating symptom that can limit life participation in people receiving dialysis. Fatigue is linked to impaired quality of life, cardiovascular disease, death and depression in people on dialysis. Several potential interventions, including drugs or other non-pharmacological treatments (e.g. exercise, diet, massage, aromatherapy, acupressure), have been evaluated for their effect on fatigue in people on dialysis.

**What did we do?**

We evaluated whether drugs or other non-pharmacological interventions are beneficial for adults and children receiving haemodialysis or peritoneal dialysis to manage fatigue. We evaluated all clinical studies available and summarised the results. We evaluated how certain we could be about the evidence related to interventions for fatigue using a system called "GRADE".

**What did we find?**

Ninety-four studies involving 8191 randomised participants were available. Patients in the studies were given a drug, non-pharmacological intervention, standard care or a sugar pill (placebo). The treatment they received was decided by random chance. The studies were generally short-term (over a few months). There were no studies in children. Exercise, aromatherapy, massage and acupressure improve fatigue compared to placebo or standard care. Drugs or other non-pharmacological interventions have uncertain effects on fatigue in people on dialysis.

**Conclusions**

Exercise, aromatherapy, massage and acupressure improve fatigue compared to placebo or standard care. It remains uncertain whether drugs or other non-pharmacological interventions have any impact on fatigue in people on dialysis when compared to a sugar pill, standard care or other treatments for fatigue.

## SUMMARY OF FINDINGS

### Summary of findings 1. Exercise versus control for people receiving dialysis

**Exercise versus control for people receiving dialysis**

**Patient or population:** people receiving dialysis

**Settings:** multinational

**Intervention:** exercise

**Comparison:** control

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (RCTs) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Control | Exercise | | | | |
| **Fatigue**<br>**(IFS, MFI, PIPER, or HD-related fatigue scale)**<br>median follow-up: 2.7 months | The mean score for fatigue ranged across control groups from 29.75 to 81.17 (IFS, MFI, PFS, or HD related fatigue scale) | The standardised mean of fatigue in the intervention group was 1.18 lower than the control group (95% CI 2.04 lower to 0.31lower) | -- | 217 (4) | ⊕⊕⊖⊖<br>**low** [1,2,3] | Exercise may improve fatigue compared to control in people undergoing HD |
| **Weakness** | Not reported | Not reported | -- | -- | -- | No studies reported this outcome |
| **Energy** | Not reported | Not reported | -- | -- | -- | No studies reported this outcome |
| **Tiredness** | Not reported | Not reported | -- | -- | -- | No studies reported this outcome |
| **Exhaustion** | Not reported | Not reported | -- | -- | -- | No studies reported this outcome |
| **Asthenia** | Not reported | Not reported | -- | -- | -- | No studies reported this outcome |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk Ratio; **IFS:** Iowa Fatigue Scale; **MFI:** Multidimensional Fatigue Inventory; **PFS:** Piper Fatigue Scale; **HD:** haemodialysis.

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Evidence certainty was downgraded by one level due to study limitations
[2] Evidence certainty was downgraded by one level due to imprecision (Optimal Information Size (OIS)) not met and indirectness in outcome measure
[3] Evidence certainty was downgraded by one level due to inconsistency

## Summary of findings 2. Aromatherapy versus placebo or standard care for people receiving dialysis

**Aromatherapy versus placebo or standard care for people receiving dialysis**

**Patient or population:** people receiving dialysis

**Settings:** multinational

**Intervention:** aromatherapy

**Comparison:** placebo or standard care

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (RCTs) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo or standard care | Aromatherapy | | | | |
| **Fatigue**<br>**(PIPER, BFI, FSS, RFS)**<br>median follow-up: 0.9 months | The mean score for fatigue ranged across control groups from 6.21 to 45.1 (PFS, BFI, FSS, RFS) | The mean fatigue in the intervention group was 1.23 lower than the control group (95% CI 1.96 lower to 0.50 lower) | -- | 542 (7) | ⊕⊕⊖⊖ **low** [1,2,3] | Aromatherapy may improve fatigue compared to placebo or standard care in people undergoing HD |
| **Weakness** | Not reported | Not reported | -- | -- | -- | No studies reported this outcome |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Energy** | Not reported | Not reported | -- | -- | -- | No studies reported this outcome |
| **Tiredness** | Not reported | Not reported | -- | -- | -- | No studies reported this outcome |
| **Exhaustion** | Not reported | Not reported | -- | -- | -- | No studies reported this outcome |
| **Asthenia** | Not reported | Not reported | -- | -- | -- | No studies reported this outcome |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk Ratio; **PFS:** Piper Fatigue Scale; **BFI:** Brief Fatigue Inventory; **FSS:** Fatigue Severity Scale; **RFS:** Rhoten fatigue scale; **HD:** haemodialysis.

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Evidence certainty was downgraded by one level due to study limitations
[2] Evidence certainty was downgraded by one level due to imprecision (Optimal Information Size (OIS) not met and indirectness in outcome measure
[3] Evidence certainty was downgraded by one level due to inconsistency

## Summary of findings 3. Massage versus no intervention for people receiving dialysis

**Massage versus no intervention for people receiving dialysis**

**Patient or population:** people receiving dialysis

**Settings:** multinational

**Intervention:** massage

**Comparison:** no intervention

| **Outcomes** | **Illustrative comparative risks* (95% CI)** | | **Relative effect (95% CI)** | **No. of participants (RCTs)** | **Quality of the evidence (GRADE)** | **Comments** |
|---|---|---|---|---|---|---|
| | **Assumed risk** | **Corresponding risk** | | | | |
| | **No intervention** | **Massage** | | | | |
| **Fatigue (PFS, FSS, VAS)** | The mean score for fatigue ranged across control | The mean fatigue in the intervention group was 1.06 lower | -- | 657 (7) | ⊕⊕⊖⊖ **low** [1,2,3] | Massage may improve fatigue compared to not inter- |

| | | | | | | |
|---|---|---|---|---|---|---|
| median follow-up: 0.9 months | groups from 5.17 to 80.74 (PFS, FSS, or VAS scores) | than the control group (95% CI 1.47 lower to 0.65 lower) | | | | vention in people undergoing HD |
| **Weakness** | Not reported | Not reported | -- | -- | -- | No studies reported this outcome |
| **Energy (VAS)** median follow-up: 0.9 months | The mean score for energy ranged across control groups from 18.93 to 21.97 (VAS) | The mean energy in the intervention group was 4.87 more than the control group (95% CI 1.69 more to 8.06more) | -- | 152 (2) | ⨁⨁◯◯ **low** [1,3] | Massage may increase energy compared to not intervention in people undergoing HD |
| **Tiredness** | Not reported | Not reported | -- | -- | -- | No studies reported this outcome |
| **Exhaustion** | Not reported | Not reported | -- | -- | -- | No studies reported this outcome |
| **Asthenia** | Not reported | Not reported | -- | -- | -- | No studies reported this outcome |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk Ratio; **PFS:** Piper Fatigue Scale; **FSS:** Fatigue Severity Scale; **VAS:** Visual Analogue Scale; **HD:** haemodialysis.

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Evidence certainty was downgraded by one level due to study limitations
[2] Evidence certainty was downgraded by one level due to imprecision (Optimal Information Size (OIS)) not met and indirectness in outcome measure
[3] Evidence certainty was downgraded by one level due to inconsistency

### Summary of findings 4. Acupressure versus placebo or control for people receiving dialysis

| **Acupressure versus placebo or control for people receiving dialysis** |
|---|
| **Patient or population:** people receiving dialysis |

**Settings:** multinational

**Intervention:** acupressure

**Comparison:** placebo or control

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (RCTs) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo or control | Acupressure | | | | |
| **Fatigue**<br>**[PFS, revised PFS, FI]**<br>median follow-up: 1 month | The mean score for fatigue ranged across control groups from 4.7 to 125.1 (PFS, revised PFS, FI) | The standardised mean of fatigue in the intervention group was 0.64 lower than the control group (95% CI 1.03 lower to 0.25 lower) | -- | 459 (6) | ⊕⊕⊖⊖<br>**low** [1,2,3] | Acupressure may reduce fatigue compared to placebo or control in people undergoing HD |
| **Weakness** | Not reported | Not reported | -- | -- | -- | No studies reported this outcome |
| **Energy** | Not reported | Not reported | -- | -- | -- | No studies reported this outcome |
| **Tiredness** | Not reported | Not reported | -- | -- | -- | No studies reported this outcome |
| **Exhaustion** | Not reported | Not reported | -- | -- | -- | No studies reported this outcome |
| **Asthenia** | Not reported | Not reported | -- | -- | -- | No studies reported this outcome |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk Ratio; **PFS:** Piper Fatigue Scale; revised **PFS:** revised Piper Fatigue Scale; **FI:** Fatigue Index; **HD:** haemodialysis.

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

1 Evidence certainty was downgraded by one level due to study limitations
2 Evidence certainty was downgraded by one level due to imprecision (Optimal Information Size (OIS)) not met and indirectness in outcome measure
3 Evidence certainty was downgraded by one level due to inconsistency

# BACKGROUND

## Description of the condition

Fatigue is common in people on dialysis, and it is associated with an increased risk of death, cardiovascular disease (CVD), depression and impaired quality of life (QoL) (Chiaranai 2016; Evangelidis 2017; Jhamb 2008; Ju 2021; Manera 2019). The prevalence of fatigue is estimated to range from 42% to 89% in adult patients on haemodialysis (HD) and peritoneal dialysis (PD) (Chang 2001; Jhamb 2008; Maruyama 2021; Picariello 2017a; Yngman-Uhlin 2010).

Fatigue is defined as a continuum sense of tiredness or exhaustion that can prevent patients from being able to do their usual activities (Jhamb 2008; Ju 2018b; Lee 1991).

The causes of fatigue are complex and multifactorial and may be related to uremia, anaemia, inflammation, fluid shifts and metabolic processes (Ju 2018a). For patients receiving HD, physiological factors, such as anaemia, have been shown to be associated with fatigue, and studies suggest that the use of erythropoietin stimulating agents (ESAs) to treat anaemia improves QoL, fatigue and energy levels in patients on HD (Johansen 2012; Ross 2003). Cytokines may contribute to fatigue in people on HD as elevated levels of pro-inflammatory cytokines are seen in kidney failure requiring kidney replacement therapy (KRT) (Artom 2014; Bergstrom 2000; Rao 2007; van Sandwijk 2019). Treatment-related factors such as dialysis frequency or modality have also been shown to affect fatigue (Jhamb 2008; Picariello 2017a). Post-dialysis fatigue is an intense fatigue experienced by patients after an HD session (Bossola 2020). Patients who received daily HD have reported less post-dialysis fatigue than those who had more days off between dialysis sessions, suggesting that this symptom may be related to treatment frequency. Modalities, such as nocturnal dialysis, may help patients recover from post-dialysis fatigue faster (Liangos 2010). Psychosocial and lifestyle factors correlated with fatigue in HD include depression, physical inactivity, and poor sleep quality (Jhamb 2008; Maruyama 2021).

In the PD population, clinical factors associated with fatigue scores include cholesterol, weekly creatinine clearance, transferrin, alkaline phosphatase, and serum intact parathyroid hormone (Chang 2001; Tian 2020).

Fatigue can be extremely debilitating (Chiaranai 2016; Debnath 2021; Horigan 2013; Yngman-Uhlin 2010), and patients experience a limitation in freedom, a loss of sense of self and social connectedness (Davey 2019; Monaro 2014). Fatigue has recently been established by patients and health professionals as a core outcome to be reported in all trials in people receiving HD (Evangelidis 2017; Tong 2017).

## Description of the intervention

As the causes of fatigue are uncertain and likely to be multifactorial, a range of pharmacological (including ESAs), novel anaemia therapies or levocarnitine) and non-pharmacological interventions (such as diet, massage, aromatherapy, meditation, cognitive behavioural therapy (CBT) or frequency of dialysis treatments) were considered.

## How the intervention might work

Both pharmacological and non-pharmacological interventions may improve fatigue. For example, ESAs or other interventions to achieve higher haemoglobin (Hb) targets and levocarnitine to modify the effects of defective fatty-acid metabolism have been shown to improve symptoms of fatigue (Foley 2009; Johansen 2012; Ossareh 2003; Schreiber 2005). Recently, hypoxia-inducible factors (HIF), a new class of drugs to treat anaemia, might be effective in the treatment of fatigue, but data are still sparse (Chertow 2021). Non-pharmacological interventions that focus on psychosocial and lifestyle aspects, including diet, exercise, sleep, foot reflexology, aromatherapy and yoga, may also help to improve fatigue (Eglence 2013; Habibzadeh 2020; Karadag 2019; Salehi 2020; Yurtkuran 2007). Physical activity may improve fatigue through indirect effects on cytokine levels or by increasing muscle strength (Jhamb 2008). CBT has also demonstrated improvement in sleep and fatigue in this population (Chen 2008; Chen 2011a; Unruh 2020). Frequent and longer dialysis treatment may reduce post-dialysis fatigue and improve general well-being (Bossola 2020). However, the exact causal mechanism of improvements seen in these studies remains unknown.

## Why it is important to do this review

It is widely known that fatigue is one of the most common and debilitating symptoms experienced by people on dialysis. In the HD population, fatigue has been consistently identified as the most critically important outcome and a high research priority in people on HD (Evangelidis 2017; Ju 2018a; Urquhart-Secord 2016). The last decade has seen a growing number of studies on pharmacological and lifestyle interventions to improve fatigue. There have been systematic reviews focusing on one particular type of pharmacological intervention, such as levocarnitine (Schreiber 2005) or ESAs (Johansen 2012). Few systematic reviews have been published on non-pharmacological interventions for fatigue (Astroth 2013; Bouya 2018; Melo 2020; Song 2018). Furthermore, it is unclear how the efficacy of these interventions compares to pharmacological interventions.

In this review, we summarised and synthesised all current evidence of the benefits and harms of interventions that have been evaluated for their impact on fatigue in people on dialysis. The definition of fatigue and fatigue-related outcomes were reported according to the definition provided by the authors. We considered all pharmacological and non-pharmacological interventions as the potential causes of fatigue are diverse and likely to be multifactorial. In doing so, this review may shed light on any existing evidence for an intervention that effectively reduces or manages fatigue. Information on the efficacy of different interventions and other factors that facilitate or challenge the improvement of fatigue will allow clinicians to provide effective care for their patients' experience of this debilitating symptom. Furthermore, as fatigue is associated with other outcomes such as death, cardiovascular diseases and broader QoL, improvement in this symptom may translate into better patient outcomes overall.

# OBJECTIVES

We aimed to evaluate the effects of any pharmacological and non-pharmacological interventions on fatigue in people with kidney failure requiring dialysis, such as HD and PD, including any setting (e.g. dialysis performed in the clinic or at home) and frequency.

# METHODS

## Criteria for considering studies for this review

### Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth, or other predictable methods) of interventions whereby fatigue or fatigue-related outcomes were reported as either primary or secondary outcome.

### Types of participants

#### *Inclusion criteria*

Patients of any age with kidney failure on any form of dialysis. The dialysis treatment could be performed both in the clinic and at home. Any frequency of the dialysis treatment was included.

#### *Exclusion criteria*

None.

### Types of interventions

We considered any intervention affecting levels of self-reported fatigue in patients on dialysis. Studies were included if fatigue was reported as an outcome.

- Pharmacological treatment (including but not limited to): psychostimulants (amphetamines, modafinil, armodafinil, methylphenidate, pemoline), amantadine, corticosteroids (dexamethasone, prednisone, methylprednisolone), donepezil, antidepressants (selective serotonin reuptake inhibitors, paroxetine), anxiolytics, ESAs, HIF, human growth hormone, tumour necrosis factor (TNF) inhibitor, acetylsalicylic acid, megestrol acetate, alfacalcidol and intravenous (IV) levocarnitine
- Non-pharmacological treatment (including but not limited to): nutrition (albumin, diet), therapeutic exercise (e.g. inspiratory muscle training exercise, aerobic exercise), alternative and complementary medicine (acupressure, Chinese herbal medicine and acupuncture), psychosocial (psychotherapy, psycho-education such as cognitive restructuring, coping strategies, stress management), educational (goal-setting, providing information/advice on symptom management/ nutrition).

Any mode, frequency, prescription, and duration of therapy were considered. The intervention may be administered at any time or day (i.e. dialysis or non-dialysis days) and in clinical or non-clinical settings.

### Types of outcome measures

We used time points of measurements as reported by investigators, as well as assessing the outcome measures at the end of the treatment.

#### *Primary outcomes*

Fatigue and fatigue-related outcomes such as tiredness, exhaustion, weakness, energy/vitality and asthenia that have been assessed through any self-report measure (open-ended questionnaires such as fatigue diary, fatigue-specific scales (e.g. Functional Assessment of Chronic Illness Therapy Fatigue subscale (FACIT-F), Chalder Fatigue Scale (CFS)), or fatigue sub-scale as part of a measure assessing a broader construct (e.g. Short Form-36 (SF-36), or visual analogue scale (VAS)). We considered all patient-reported outcome measures for fatigue, given the lack of validation work conducted in the dialysis population. To avoid misinterpretation of the data, definitions of fatigue and fatigue-related outcomes were reported according to the definitions provided by the authors. Fatigue and fatigue-related outcomes (including tiredness, exhaustion, weakness, energy/vitality and asthenia) were assessed separately.

#### *Secondary outcomes*

QoL, depression, anxiety, death (any cause and cardiovascular), vascular access, CVD, hypertension, diabetes, sleep and mood.

## Search methods for identification of studies

No restrictions based on the date of the study publications, language, or publication were applied when searching and selecting studies for inclusion. The search was conducted with the Cochrane Kidney and Transplant Information Specialist using search terms relevant to this review.

### Electronic searches

We searched the Cochrane Kidney and Transplant Register of Studies up to 18 October 2022 through contact with the Information Specialist using search terms relevant to this review. The Register contains studies identified from the following sources:

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these searches, as well as a list of hand-searched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about Cochrane Kidney and Transplant.

See Appendix 1 for search terms used in strategies for this review.

### Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.
3. Grey literature sources (e.g. abstracts, dissertations, and theses), in addition to those already included in the Cochrane Kidney and Transplant Register of Studies, were also searched.

## Data collection and analysis

### Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts were screened independently by three authors (PN, AJ, VS). Three authors (PN, AJ, VS) independently assessed retrieved abstracts and, if necessary, the full text of these studies to determine which studies satisfy the inclusion criteria.

### Data extraction and management

Data relating to study design (RCT, quasi-RCT), participant characteristics (e.g. age, gender, dialysis vintage, comorbidity), interventions (pharmacological, non-pharmacological) and outcomes (as described above) were extracted. Three authors (PN, AJ, VS) independently carried out data extraction using a standard data extraction form. Studies reported in non-English languages were translated before assessment. Where more than one publication of a study exists, the publications were grouped together, and the report with the most complete data was included in the meta-analyses. Where relevant outcomes are only published in earlier versions, these data were used. Any discrepancies between published versions were highlighted. Any further information required from the original author was requested by written correspondence, and any relevant information obtained in this manner was included in the review. Disagreements were resolved by consensus in consultation with another author (AJ).

### Assessment of risk of bias in included studies

The following items were independently assessed by two authors (PN, VS) using the risk of bias assessment tool (Higgins 2022) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at risk of bias?

### Measures of treatment effect

For dichotomous outcomes (e.g. adverse events, cardiovascular events, death), results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used to assess the effects of treatment (e.g. depression, fatigue), the mean difference (MD) was used, or the standardised mean difference (SMD) if different scales were used.

### Unit of analysis issues

#### *Cluster-randomised studies*

We anticipated that studies using clustered randomisation had controlled for clustering effects. In case of doubt, we contacted the first authors to ask for individual participant data to calculate an estimate of the intracluster correlation coefficient (ICC). If this was not possible, we obtained external estimates of the ICC from a similar study or from a study of a similar population as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2022). When the ICC was established, we used it to re-analyse the study data. If ICCs from other sources were used, we reported this and conducted sensitivity analyses to investigate the effect of variations in the ICC.

#### *Cross-over studies*

We included all randomised cross-over studies in the systematic review if they report a paired (comparison within the patient) analysis using all periods. If not, we only used the data from the first period.

#### *Studies with more than two treatment arms*

If more than one of the interventions is a fatigue intervention, and there is sufficient information in the study to assess the similarity of the interventions, we combined similar interventions to allow for a single pair-wise comparison.

### Dealing with missing data

Any further information required from the original author was requested by written correspondence (e.g. emailing the corresponding author), and any relevant information obtained in this manner was included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population were carefully performed. Attrition rates, for example, drop-outs, losses to follow-up and withdrawals, were investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) were critically appraised (Higgins 2022).

### Assessment of heterogeneity

We first assessed the heterogeneity by visual inspection of the forest plot. We quantified statistical heterogeneity using the $I^2$ statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). A guide to the interpretation of $I^2$ values was as follows:

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of $I^2$ depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P value from the $Chi^2$ test or a CI for $I^2$) (Higgins 2022).

### Assessment of reporting biases

If possible, funnel plots were used to assess for the potential existence of small study bias (Higgins 2022). There were insufficient studies per comparision to do this.

### Data synthesis

Data were pooled using the random-effects model but the fixed-effect model was also used to ensure robustness of the model chosen and susceptibility to outliers.

### Subgroup analysis and investigation of heterogeneity

We reported the results of our findings separately, focusing on fatigue, as reported by the authors. Adverse effects were tabulated and assessed with descriptive techniques, as they were likely to be different for the various interventions used. Where possible, the risk differences with 95% CI were calculated for each adverse effect, either compared to no treatment or to another agent.

Based on available data, we planned to perform the following subgroup analyses.

- Age: < 18 years versus ≥ 18 years; and < 64 years versus ≥ 64 years
- Gender: female versus male
- Risk of bias: high versus low (versus unclear) (allocation concealment, blinding of outcome assessors, incomplete outcome data)
- Indication: studies targeting fatigue versus reporting fatigue
- Intervention type: pharmacological versus non-pharmacological
- Presence of comorbidities: CVD (yes versus no), diabetes (yes versus no), hypertension (yes versus no), depression (clinical diagnosis versus none)
- Fatigue outcome measures used: validation data available versus de novo
- Dialysis type: PD versus HD
- Dialysis vintage: < 5 years versus ≥ 5 years

### Sensitivity analysis

We planned to perform sensitivity analyses in order to explore the influence of the following factors on effect size:

- Repeating the analysis excluding abstract-only publication
- Repeating the analysis excluding industry-funded studies
- Repeating the analysis, taking account of the risk of bias (allocation concealment)
- Repeating the analysis, excluding any very long or large studies, to establish how much they dominate the results.

### Summary of findings and assessment of the certainty of the evidence

We presented the main results of the review in 'Summary of findings' tables. These tables presented key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2022a). The 'Summary of findings' tables also included an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008; GRADE 2011). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2022b). We presented the following outcomes in the 'Summary of findings' tables:

- Fatigue
- Weakness
- Energy
- Tiredness
- Exhaustion
- Asthenia

## RESULTS

### Description of studies

The following section contains broad descriptions of the studies considered in this review. For further details on each individual study, please see Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

### Results of the search

After searching the Specialised Register, a total of 311 records were identified. After screening titles, abstracts, and full-text review, 94 studies (249 reports) were included, and 16 studies (43 reports) were excluded. Sixteen ongoing studies were identified. One study states recruitment was completed in 2010 (NCT00440869); however, no results have been identified. These 17 studies will be assessed in a future update of this review (Figure 1).

**Figure 1. Flow diagram of study selection**

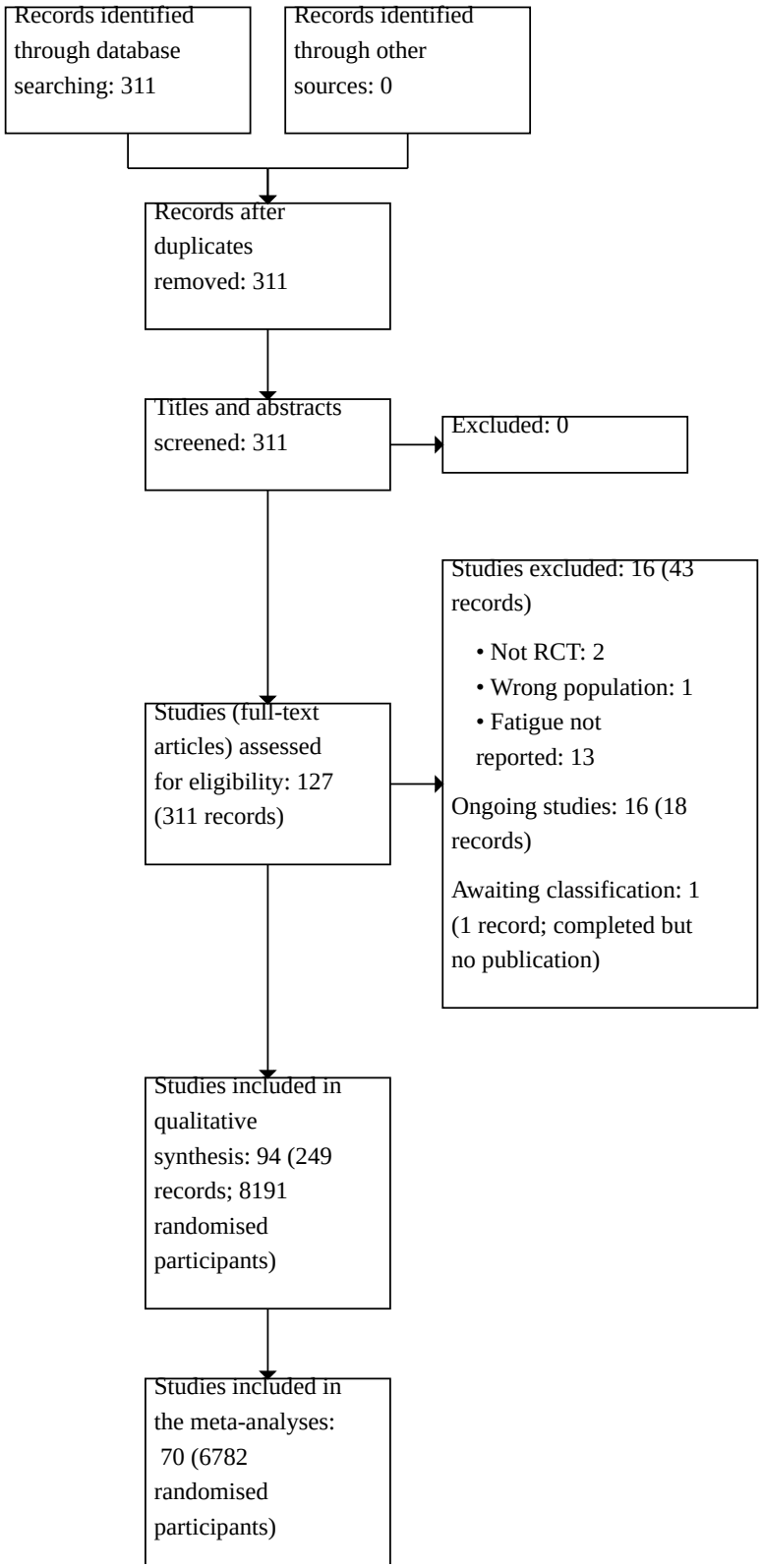


**Figure 1. (Continued)**

participants)

### Included studies

The Characteristics of included studies tables reported the characteristics of the participants and the interventions in the included studies. A total of 94 studies (8191 randomised participants) were included in this review.

#### *Study design, setting and characteristics*

Four studies had a quasi-randomised design, two studies had a cluster-randomisation design, 13 studies had a cross-over design, and the remaining studies were RCTs. Studies were conducted from 1979 to 2022 in Australia (two studies), Brazil (three studies), Canada (seven studies), China (one study), Denmark (one study), Egypt (two studies), Germany (one study), Greece (four studies), Hong Kong (one study), India (two studies), Iran (22 studies), Italy (one study), Japan (four studies), Switzerland (one study), Taiwan (11 studies), Turkey (nine studies), the UK (three studies), the USA (15 studies), were performed in multinational setting (two studies) or did not report information about the country (two studies). Study follow-up ranged from one week (four studies) to 21.8 months (one study), with a median of 1.8 months. Fourteen studies received funding from pharmaceutical companies. Six studies were available only as conference abstracts.

#### *Study participants*

Three studies were conducted in people with PD, five studies in people with both HD and PD, one study was performed in people with either HD or haemodiafiltration (HDF), one study did not specify the type of dialysis, whilst all other studies were performed in people receiving HD. The mean dialysis vintage ranged from 0.3 to 12.7 years, with a median of 4.1 years. The sample size varied from five to 596 participants, with a median of 61 participants. The mean study age ranged from 38 years to 69 years, with a median of 56 years. No studies evaluated treatment in children.

Thirteen studies included people with and without cardiovascular comorbidities at baseline; one study excluded people with CVD, while one study included only patients with previous CVD. Forty-seven studies included people with and without diabetes. Of these studies, only one study reported subgroup analyses for people with and without diabetes. Two studies did not include people with diabetes, while one study was performed in people with diabetes. Thirty-three studies were performed in people with and without hypertension; one study did not include people with hypertension, while one study was focused only on people with hypertension. Clinical diagnosis of depression was rarely reported: two studies excluded people with depression, two studies included only people with depression at baseline, and one study included people with and without depression.

The definition of fatigue and fatigue-related outcomes were reported according to the definition provided by the authors. Fatigue was assessed using different tools (see Appendix 3).

- Kidney Disease Questionnaire (KDQ) (Brass 2001; Canadian EPO 1990)
- Piper Fatigue Scale (PFS) (Amini 2016; Bicer 2022; Eroglu 2022; Kaplin Serin 2020; Mohamed 2014; Muz 2017; Roshanravan 2016; Ozdemir 2013; Sabouhi 2013; Tsay 2004a; Tsay 2004b)
- Revised PFS (Cho 2004)
- 36-item Short-Form Health Survey (SF-36) (ASCEND 2016; Fatigue-HD 2019; Johansen 2006)
- Kidney Disease Quality of Life-Short Form (KDQOL-SF) (Fukuda 2015; PEDAL 2020)
- Fatigue Severity Scale (FSS) (Ahmady 2019; Bagheri-Nesami 2016; Chen 2008a; Chen 2011a; Fatigue-HD 2019; Habibzadeh 2020; Karadag 2019; Lazarus 2020; Mohajeranirad 2021; Mohammadpourhodki 2021; Shahdadi 2016)
- Multidimensional Fatigue Inventory (MFI-20) (Balouchi 2016; Biniaz 2015; Salehi 2020)
- VAS for Fatigue (VAS-F) (Bicer 2022; Cecen 2021; Schardong 2021; Unal 2016; Yurtkuran 2007)
- FACIT-F (Parfrey 2005)
- Profile of Mood States Fatigue subscale (POMS-F) (Johansen 1999; Johansen 2006)
- Fatigue Index (FI) (Su 2009)
- Rhoten fatigue scale (RFS) (Varaei 2020)
- Brief Fatigue Inventory (BFI) (Hadadian 2018; Hassanzadeh 2018; Lin 2011)
- CFS (fatigue severity) and Work and Social Adjustment Scale (fatigue-related functional impairment) (Picariello 2018)
- Standardized Outcomes in Nephrology - Haemodialysis (SONG-HD) Fatigue score (SWIFT 2020)
- Modified Fatigue Impact Scale (MFIS) (Fatigue-HD 2019)
- Hemodialysis-Related Fatigue Scale (HFS) (Huang 2021)
- KDQ (Semeniuk 2000)
- Iowa Fatigue Scale (IFS) (Soliman 2015)
- The name of the tool used for assessing fatigue was not clearly stated (Babamohammadi 2006; Grigoriou 2021; Krase 2022)

Seven studies reported fatigue only as an adverse event.

#### *Interventions*

A broad range of interventions have been reported in the included studies.

##### Non-physiological neutral amino acids versus placebo

- L-threo-3,4-dihydroxyphenilserine (L-DOPS) (Akizawa 2002)
- L-carnitine (Bellinghieri 1983; Brass 2001; Fatouros 2010; Semeniuk 2000)

##### Serotonin reuptake inhibitor versus placebo

- Sertraline (ASSertID 2015)

**Beta-blockers versus angiotensin-converting enzyme inhibitors**

- Atenolol versus lisinopril (HDPAL 2014)

**Anabolic steroids versus placebo**

- Nandolone decanoate (Johansen 1999; Johansen 2006)

**Anabolic steroids versus exercise**

- Nandrolone decanoate (Johansen 2006)

**Anabolic steroids alone versus anabolic steroids plus exercise**

- Nandrolone decanoate (Johansen 2006)

**Anabolic steroids plus exercise versus exercise alone**

- Nandrolone decanoate (Johansen 2006)

**Anabolic steroids plus exercise versus placebo**

- Nandrolone decanoate (Johansen 2006)

**Iron replacement product versus placebo**

- Ferumoxytol versus saline sterile injection (Singh 2008a)

**Continuous erythropoietin receptor activation (C.E.R.A)**

- C.E.R.A once/week versus C.E.R.A once every two weeks, both groups using EPO alpha (BA16285 2007)

**Erythropoietin stimulating agents versus placebo**

- Erythropoietin (EPO) alpha to achieve a Hb target of 9.5 to 11.0 g/dL (low-target group) or 11.5 to 13.0 g/dL or 13.5 to 16 g/dL (high-target group) (Canadian EPO 1990; Lillevang 1990)

**Haemoglobin targets**

- EPO alpha to achieve a Hb target of 9.5 to 10.5 g/dL (normal-target group) or 13.0 to 14.0 g/dL (high-target group) (Foley 2000; Parfrey 2005)
- EPO alpha to achieve normal HB target group to subnormal HB target group with or without ESA (Linde 2001)

**Nutritional supplementation versus placebo**

- Nutritional drink supplementation (containing vitamin B1, vitamin B2, niacin, vitamin B6, vitamin B12, folic acid, vitamin C, carnitine, coenzyme Q10, naive galacto-oligosaccharide, and zinc) (Fukuda 2015)
- Ascorbic acid (vitamin C) (Biniaz 2015; Singer 2010)
- Helichrysum Psudoplicatum supplementation (Mohajeranirad 2021)

**Dialysate sodium concentration**

- Dialysate sodium versus another concentration of dialysate sodium in general (Barre 1988; Mohamed 2013)
- Steady dialysate sodium versus linear sodium ramping (Sang 1997)
- Steady dialysate sodium versus stepwise sodium ramping (Sang 1997)
- Linear sodium ramping versus stepwise sodium ramping (Sang 1997)

**Glucose-enriched dialysate**

- Dialysis sessions with dialysate containing glucose 400 mg/100 mL to dialysis sessions with dialysate of the same composition but without glucose (Leski 1979)
- Glucose-enriched dialysate (200 mg/100 mL) to dialysate without glucose (Raimann 2010)

**Cold versus warm dialysis**

- Cold temperature dialysis (35.5°C) to warm temperature dialysis (37°C) (Sajadi 2016)

**Citrate versus standard care**

- Citrate dialysate to standard dialysate (Schmitz 2016)

**Cuprophan versus polysulfone**

- Cuprophan low flux dialyser membranes to polysulfone low flux dialyser membranes (Singh 2003)

**Cuprophane versus polymethyl-methacrylate**

- Cuprophan low flux dialyser membranes to polymethyl-methacrylate (PMMA) low flux dialyser membranes (Sklar 1998)

**Frequent versus conventional haemodialysis**

- Frequent HD (six times/week) to conventional HD (three times/week) (FHN DAILY 2007; FHN NOCTURNAL 2007)

**Haemodialysis with sodium bath versus isolated ultrafiltration**

- Hypernatric HD with 150 to 155 mEq/L sodium bath (two cycles) to isolated ultrafiltration (two cycles) (Sklar 1999)

**Haemodialysis with sodium bath versus isolated diffusion**

- Hypernatric HD with 150 to 155 mEq/L sodium bath (two cycles) to isolated diffusion (two cycles) (Sklar 1999)

**Haemodialysis with sodium bath versus sham procedures with or without recirculation**

- Hypernatric HD with 150 to 155 mEq/L sodium bath (two cycles) to sham procedures with isolated membrane (two cycles) or sham procedures without recirculation exposure to a dialysis membrane (two cycles) (Sklar 1999)

**Isolated ultrafiltration versus isolated diffusion**

- Isolated ultrafiltration (two cycles) to isolated diffusion (two cycles) (Sklar 1999)

**Isolated ultrafiltration versus sham procedures with or without recirculation**

- Isolated ultrafiltration (two cycles) to sham procedures with isolated membrane (two cycles) or sham procedures without recirculation exposure to a dialysis membrane (two cycles) (Sklar 1999)

**Isolated diffusion versus sham procedures with or without recirculation**

- Isolated diffusion (two cycles) to sham procedures with isolated membrane (two cycles) or sham procedures without recirculation exposure to a dialysis membrane (two cycles) (Sklar 1999)

**Blood flow rate reduction versus standard care**

- Blood flow rate reduction of 100 mL/min to a minimum of 300 mL/min (Duggal 2019)

**Self-blood pressure monitoring versus ambulatory blood pressure monitoring**

- Home blood pressure (BP) monitoring to predialysis BP monitoring (BOLD 2020)

**Relaxation versus no intervention**

- Progressive muscle relaxation or relaxation exercise (Amini 2016; Hadadian 2018; Kaplin Serin 2020)
- No specified relaxation technique (Hassanzadeh 2018)

**Relaxation versus aromatherapy**

- Benson relaxation technique to inhalation of lavender essential oil (Hassanzadeh 2018)

**Relaxation versus exercise**

- Progressive muscle relaxation to aerobic exercise (Amini 2016)

**Relaxation plus music therapy versus no intervention**

- Benson technique plus music therapy (Eroglu 2022)

**Meditation versus no intervention**

- Brief mindfulness meditation (Thomas 2017)
- Yoga (Reilly-Spong 2015; Yurtkuran 2007)

**Exercise versus placebo or control**

- Aerobic exercise (Amini 2016; Figueiredo 2018; Krase 2022; PEDAL 2020)
- Leg ergometry exercise (Chang 2010; Konstadinidou-ND 2002; Salehi 2020)
- Muscle function (Johansen 2006)
- Personal Energy Planning (PEP) programme (Fatigue-HD 2019)
- Hybrid exercise (Grigoriou 2021)
- Breathing-based leg exercises (Huang 2021)
- Range of motion (ROM) exercise (Soliman 2015)
- Inspiratory muscle training (Figueiredo 2018; Pellizzaro 2013)
- Electrical muscle stimulation (Suzuki 2018)
- Peripheral muscle training (Pellizzaro 2013)

**Exercise versus another exercise**

- Inspiratory muscle training versus aerobic exercise (Figueiredo 2018)
- Respiratory muscle training versus peripheral muscle training (Pellizzaro 2013)

**Aromatherapy versus standard care**

- Lavender essence (Ahmady 2019; Bagheri-Nesami 2016; Karadag 2019; Mohammadpourhodki 2021; Varaei 2020)
- Sweet orange oil and lavender oil (Muz 2017)
- Orange essence (Ahmady 2019; Mohammadpourhodki 2021; Varaei 2020)
- Not specified aromatherapy (Hassanzadeh 2018)

**Aromatherapy versus another type of aromatherapy**

- Lavander extract versus orange extract (Ahmady 2019; Balouchi 2016; Jalalian 2015; Mohammadpourhodki 2021; Varaei 2020)

**Massage versus no intervention**

- Slow-stroke back massage (Hasankhani 2013; Shahdadi 2016)
- Foot reflexology (Cecen 2021; Ozdemir 2013; Roshanravan 2016)
- Slow-stroke back massage or foot reflexology (Unal 2016)
  - NOTE: outcome data provided were not extracted for slow-stroke back massage since two different massages were compared with the control
- Hand massage (Cecen 2021)
- Olive oil massage (Lazarus 2020)
- Chamomile, almond or no oils (Habibzadeh 2020)

**Massage versus another type of massage**

- Foot reflexology versus back massage (Unal 2016)
- Hand massage versus foot massage (Cecen 2021)
- Chamomile or almond versus no oils (Habibzadeh 2020)

**Massage versus sham massage**

- Foot reflexology (Roshanravan 2016)

**Sham massage versus no intervention**

- Foot reflexology without pressing certain parts of the foot (Roshanravan 2016)

**Acupressure versus placebo or control**

- Transcutaneous electrical acupoint stimulation (TEAS) versus no intervention (Vishnevskii 2014)
- Far-infrared (FIR) rays on each acupoint versus no intervention (Lin 2011)
- FIR rays versus heath pad therapy (Su 2009)
- Acupressure versus routine unit care or no intervention (Cho 2004; Sabouhi 2013; Tsay 2004a)
- Acupressure or TEAS versus control (Tsay 2004b)
  - NOTE: outcome data were not extracted for TEAS since two different acupressure techniques were compared to the control
- Acupressure versus placebo (Bicer 2022)

**Acupressure versus another type of acupressure**

- Acupressure versus TEAS (Tsay 2004b)

**Acupressure versus sham acupressure**

- Acupressure (Sabouhi 2013; Tsay 2004a)
- Herbal acupoint therapy (Tsai 2016)
- TEAS versus TEAS-sham group (Hadadian 2016)

**Sham acupressure versus standard care**

- Sham acupressure performed away from the actual intervention site with or without usual care (Sabouhi 2013; Tsay 2004a)

**Cognitive-behavioural therapy versus no intervention**

- CBT for fatigue (BReF intervention) versus waiting-list control (Picariello 2018)

#### Cognitive-behavioural therapy versus education

- CBT versus sleep hygiene education (Chen 2008a; Chen 2011a)

#### Cognitive-behavioural therapy versus serotonin reuptake inhibitor

- CBT versus sertraline (ASCEND 2016)

#### Education versus control

- Nurse-led case management programme (Chow 2010; Li 2014b; Mohamed 2014)
- Pharmacist-led pharmaceutical care plus routine care (Dashti-Khavidaki 2013)
- Physical education program (Motedayen 2014)
- Home-care educational program (Babamohammadi 2006)
- Usual care (SOCIABLE 2017; SWIFT 2020)

#### Anti-thrombotic polymethyl-methacrylate versus placebo

- Anti-thrombotic polymethyl-methacrylate membrane (VENOUS 2020)

#### Light versus no intervention

- Photobiomodulation therapy (Schardong 2021)

### Excluded studies

Thirty-three studies were excluded. The reasons for exclusion were:

- Not randomised (Eglence 2013; Laupacis 1992)
- Wrong population (TREAT 2005)
- Fatigue was not reported as either a primary or secondary outcome (13 studies: CHAIR 2015; Churchill 1987; Dashti-Khavidaki 2011; Gram 1998; Heshmatifar 2015; Heshmati Far 2015; Macagnan 2019; Nakamoto 2008; Sharp 2005; Shimizu 1983; Siami 1991; Tawney 2000; Tsai 2015).

### Studies awaiting classification

One study stated recruitment was completed in 2010; however, no published results have been identified (NCT00440869).

### Ongoing studies

We identified 16 ongoing studies.

- Intradialytic yoga versus usual care (ACTRN12617000420347)
- Intradialytic yoga versus educational program (NCT02361268)
- Home-based physical training versus non-training group (ACTRN12618000724279)
- Intradialytic exercise versus not intervention (Cardoso 2019; CTRI/2018/02/012021)
- Walking, resistance training or combination training (ACTRN12620000408987)
- Virtual reality versus standard care (Burrai 2019a)
- High-dose HDF continuation versus conventional high-flux HD (CONVINCE 2020)
- Self-management strategies versus dietary information (NCT01620580)
- Individual face-to-face educational intervention session versus usual care (Sharma 2022)
- Motor cortex, dorsolateral prefrontal cortex or sham treatments (Quintiliano 2019)
- Psychosocial counselling sessions led by a social worker versus usual care (van der Borg 2016)
- CBT (TĀCcare or technology-delivered health education) versus no treatment (TACcare 2018)
- Plantar electrical nerve stimulation versus non-functional device (Hamad 2021)
- CBT versus trazodone versus placebo (SLEEP-HD 2021)
- Intradialytic creatine supplementation creatine supplementation (0.5, 1.0, 1.5 or 2.0 mM) versus placebo (van der Veen 2021)

## Risk of bias in included studies

The risk of bias for studies overall are summarised in Figure 2 and the risk of bias in each study is described in Figure 3.

**Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**

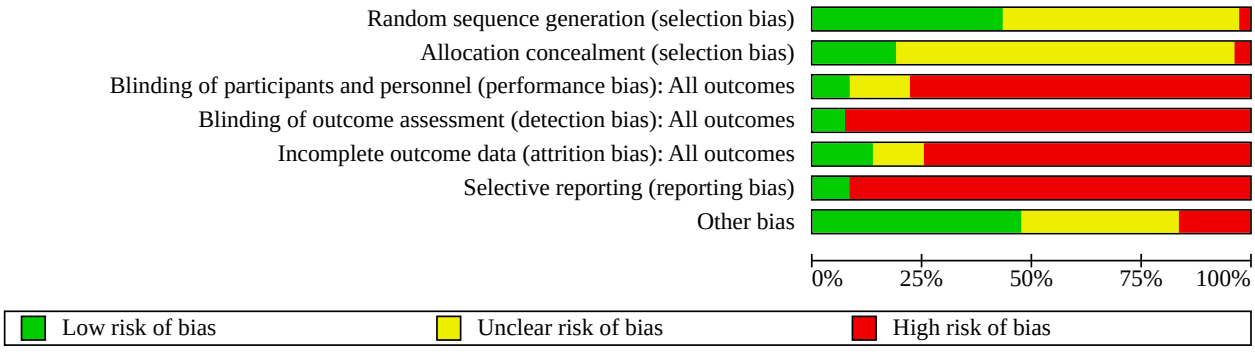


**Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**

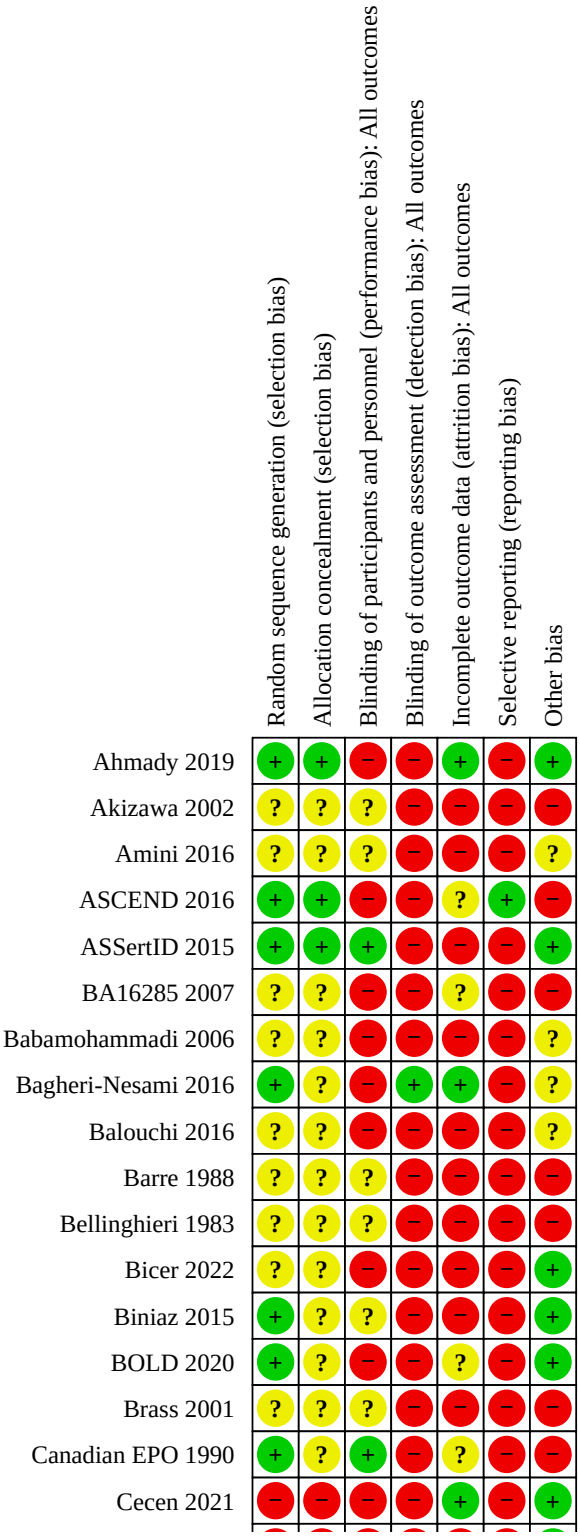


**Figure 3. (Continued)**

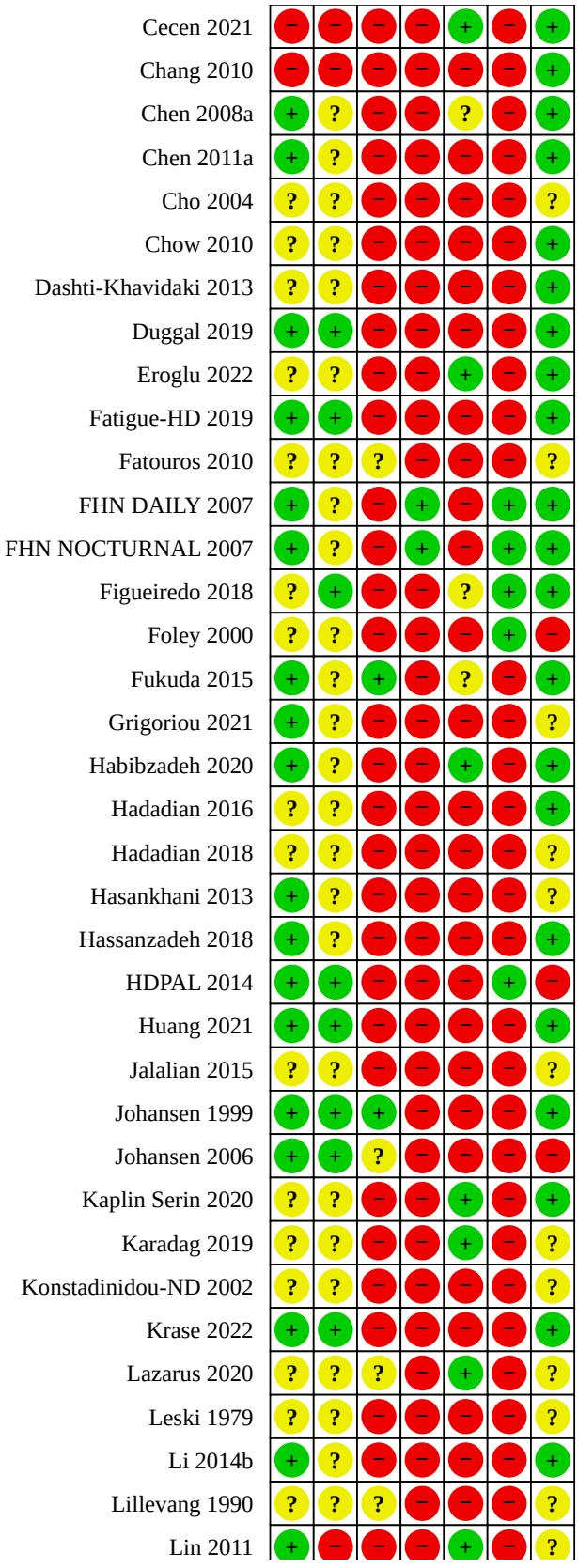


**Figure 3. (Continued)**

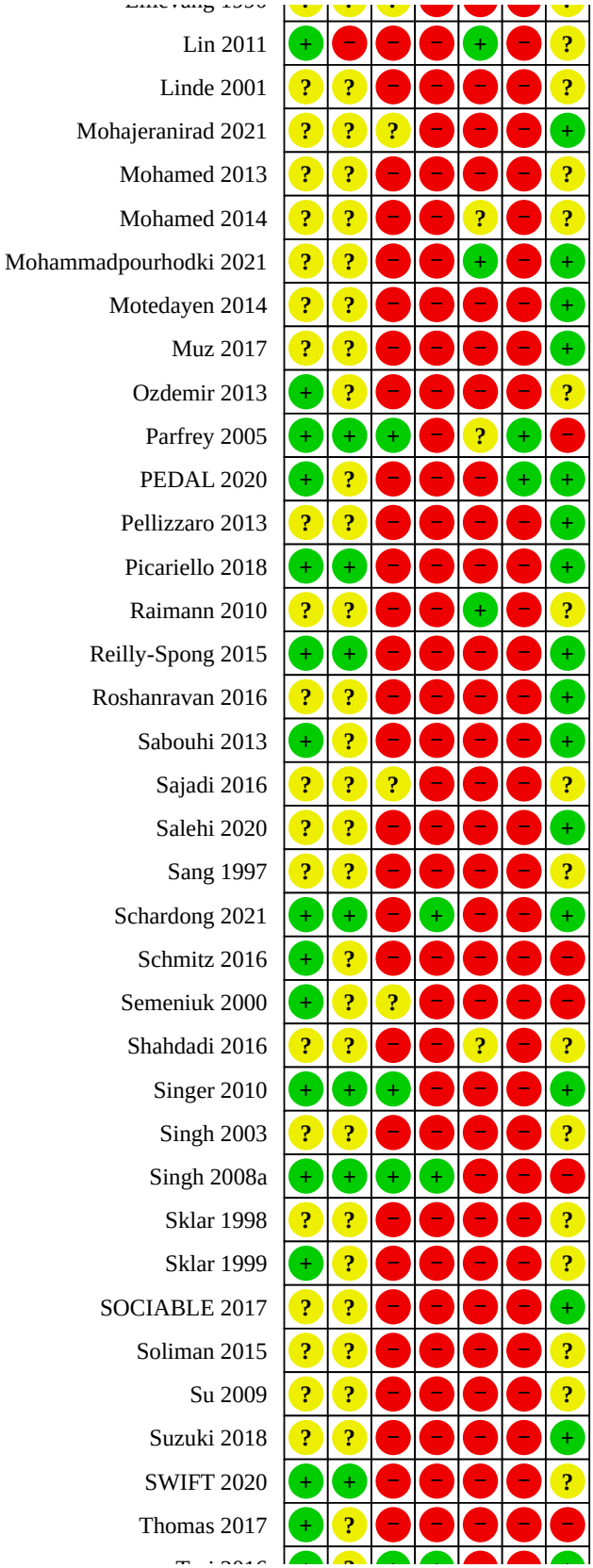
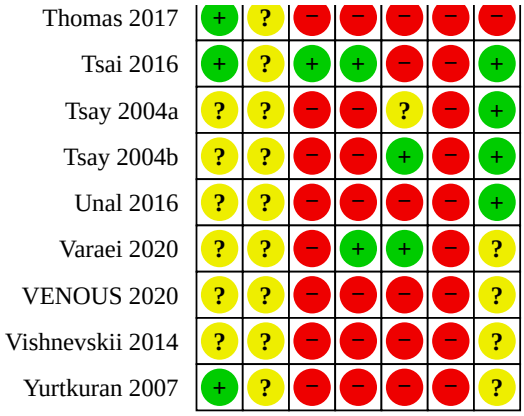


**Figure 3. (Continued)**




### Allocation

#### *Random sequence generation*

Forty-one studies were judged to be low risk for adequately providing methods used for random sequence generation. Fifty-one studies were judged to be unclear risk as they stated to be randomised but provided no further details on how this was undertaken. Two studies were judged to be high risk.

#### *Allocation concealment*

Allocation concealment was assessed as adequate in 18 studies, high risk in three studies, and unclear risk in 73 studies.

### Blinding

#### *Performance bias*

Eight studies were blinded and considered to be at low risk of bias for performance bias, and 73 studies were not blinded and were considered at high risk of performance bias. Thirteen studies were assessed as unclear risk of bias.

#### *Detection bias*

Blinding of outcome assessment was judged to be at low risk in seven studies, and 87 studies were considered at high risk of detection bias.

### Incomplete outcome data

Data follow-up was complete in 13 studies, incomplete in 63 studies, whilst 18 studies were assessed as unclear risk of bias.

### Selective reporting

Eight studies reported expected and clinically-relevant outcomes and were deemed to be at low risk of bias, and 86 studies did not report key patient-centred outcomes, including fatigue, cardiovascular disease, death and vascular access.

### Other potential sources of bias

Forty-five studies appeared to be free from other sources of bias, 15 studies reported other sources of bias (including the role of funding source and/or imbalance in baseline treatment groups). It was unclear risk whether 34 studies had other sources of bias.

## Effects of interventions

See: **Summary of findings 1** Exercise versus control for people receiving dialysis; **Summary of findings 2** Aromatherapy versus placebo or standard care for people receiving dialysis; **Summary of findings 3** Massage versus no intervention for people receiving dialysis; **Summary of findings 4** Acupressure versus placebo or control for people receiving dialysis

### Non-physiological neutral amino acids versus placebo

Three studies (Akizawa 2002; Bellinghieri 1983; Brass 2001) compared non-physiological neutral amino acids, including L-DOPS (Akizawa 2002) and L-carnitine (Bellinghieri 1983; Brass 2001) to placebo in people receiving HD, during a median follow-up of 1.8 months. The certainty of the evidence was very low.

#### *Fatigue*

Compared to placebo, non-physiological neutral amino acids had uncertain effects on fatigue (Analysis 1.1 (1 study, 180 participants): KDQ score; MD -0.05, 95% CI -0.44 to 0.34; very low certainty evidence).

### Change in fatigue

Compared to placebo, non-physiological neutral amino acids had uncertain effects on the change in fatigue (Analysis 1.2 (1 study, 180 participants): KDQ score; MD 0.20, 95% CI -0.08 to 0.48; very low certainty evidence).

### Number of participants with improvement in fatigue

Compared to placebo, non-physiological neutral amino acids had uncertain effects on the improvement in fatigue (Analysis 1.3 (1 study, 121 participants): RR 1.25, 95% CI 0.80 to 1.95; very low certainty evidence).

### Number of participants with aggravation of fatigue

Compared to placebo, non-physiological neutral amino acids may reduce the number of participants with aggravation of fatigue, but the evidence is very uncertain (Analysis 1.4 (1 study, 121 participants): RR 0.18, 95% CI 0.06 to 0.52; very low certainty evidence).

**Death (any cause)**

Compared to placebo, non-physiological neutral amino acids had uncertain effects on death (any cause) (Analysis 1.5: 3 studies, 356 participants), as no events were reported in the eligible studies.

**Cardiovascular death**

Compared to placebo, non-physiological neutral amino acids had uncertain effects on cardiovascular death (Analysis 1.6: 2 studies, 163 participants), as no events were reported in the eligible studies.

**Quality of life (overall)**

Compared to placebo, non-physiological neutral amino acids had uncertain effects on the overall QoL (Analysis 1.7 (1 study, 180 participants): KDQ score; MD -0.02, 95% CI -0.35 to 0.31; very low certainty evidence).

**Change in quality of life (overall)**

Compared to placebo, non-physiological neutral amino acids had uncertain effects on the change in overall QoL (Analysis 1.8 (1 study, 180 participants): KDQ score; MD 0.15, 95% CI -0.08 to 0.38; very low certainty evidence).

**Depression**

Compared to placebo, non-physiological neutral amino acids had uncertain effects on depression (Analysis 1.9 (1 study, 180 participants): KDQ score; MD -0.17, 95% CI -0.59 to 0.25; very low certainty evidence).

**Change in depression**

Compared to placebo, non-physiological neutral amino acids had uncertain effects on change in depression (Analysis 1.10 (1 study, 180 participants): KDQ score; MD 0.13, 95% CI -0.21 to 0.47; very low certainty evidence).

**Hypertension**

Compared to placebo, non-physiological neutral amino acids had uncertain effects on hypertension (Analysis 1.11 (1 study, 193 participants): RR 1.47, 95% CI 0.06 to 35.48; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Relaxation versus no intervention**

Three studies (Amini 2016; Hassanzadeh 2018; Kaplin Serin 2020) compared progressive muscle relaxation (Amini 2016; Kaplin Serin 2020) or Benson muscle relaxation techniques (Hassanzadeh 2018) to no intervention in people receiving HD during a median follow-up of 1.4 months. The certainty of the evidence was very low.

***Fatigue***

Compared to no intervention, relaxation may improve fatigue, but the evidence is very uncertain (Analysis 2.1 (3 studies, 234 participants): PFS or BFI score; SMD -1.51, 95% CI -2.28 to -0.73; $I^2$ = 85%; very low certainty evidence). Substantial heterogeneity was observed between the studies.

***Death (any cause)***

Compared to no intervention, relaxation had uncertain effects on death (any cause) (Analysis 2.2: 1 study, 96 participants), as no events were reported.

***Cardiovascular death***

Compared to no intervention, relaxation had uncertain effects on cardiovascular death (Analysis 2.3: 1 study, 96 participants), as no events were reported.

***Anxiety***

Compared to no intervention, relaxation had uncertain effects on anxiety (Analysis 2.4 (1 study, 68 participants): Beck Anxiety Index (BAI) score; MD -1.40, 95% CI -4.55 to 1.75; very low certainty evidence).

***Sleep quality***

Compared to no intervention, relaxation may improve sleep quality, but the evidence is very uncertain (Analysis 2.5 (1 study, 68 participants): Pittsburgh Sleep Quality Index (PSQI) score; MD -6.52, 95% CI -7.60 to -5.44; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Relaxation versus exercise**

Amini 2016 compared progressive muscle relaxation versus aerobic exercise in people receiving HD, during a follow-up of 1.8 months. The certainty of the evidence was very low.

***Fatigue***

Compared to exercise, relaxation may reduce fatigue, but the evidence is very uncertain (Analysis 3.1 (1 study, 65 participants): PFS score; MD -17.66, 95% CI -30.32 to -5.00; very low certainty evidence).

***Anxiety***

Compared to exercise, relaxation had uncertain effects on anxiety (Analysis 3.2 (1 study, 65 participants): BAI score; MD -1.52, 95% CI -6.46 to 3.42; very low certainty evidence).

***Sleep quality***

Compared to exercise, relaxation had uncertain effects on sleep quality (Analysis 3.3 (1 study, 65 participants): PSQI score; MD 0.31, 95% CI -0.51 to 1.13; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Relaxation plus music therapy versus no intervention**

Eroglu 2022 compared relaxation plus music therapy to no intervention in people receiving HD during a follow-up of 2.3 months. The certainty of the evidence was very low.

***Death (any cause)***

Compared to no intervention, relaxation plus music therapy had uncertain effects on death (any cause) (Analysis 4.1: 1 study, 62 participants), as no events were reported.

***Cardiovascular death***

Compared to exercise, relaxation plus music therapy had uncertain effects on cardiovascular death (Analysis 4.2: 1 study, 62 participants), as no events were reported.

No other primary or secondary outcomes were reported.

**Meditation versus no intervention**

Two studies (Thomas 2017; Yurtkuran 2007) compared meditation, including brief mindfulness meditation (Thomas 2017) or yoga (Yurtkuran 2007), to no intervention in people receiving HD during a median follow-up of 2.4 months. The certainty of the evidence was very low.

***Fatigue***

Compared to no intervention, meditation may reduce fatigue, but the evidence is very uncertain (Analysis 5.1 (1 study, 37 participants): VAS score; MD -3.60, 95% CI -6.99 to -0.21; very low certainty evidence).

***Death (any cause)***

Compared to no intervention, meditation had uncertain effects on death (any cause) (Analysis 5.2: 2 studies, 81 participants), as no events were reported in the eligible studies.

***Cardiovascular death***

Compared to no intervention, meditation had uncertain effects on cardiovascular death (Analysis 5.3: 2 studies, 81 participants), as no events were reported in the eligible studies.

***Depression***

Compared to no intervention, meditation had uncertain effects on depression (Analysis 5.4 (1 study, 32 participants): Patient Health Questionnaire (PHQ score); MD 2.00, 95% CI -1.90 to 5.90; very low certainty evidence).

***Change in depression***

Compared to no intervention, meditation had uncertain effects on change in depression (Analysis 5.5 (1 study, 32 participants): PHQ score; MD -1.00, 95% CI -4.02 to 2.02; very low certainty evidence).

***Anxiety***

Compared to no intervention, meditation had uncertain effects on anxiety (Analysis 5.6 (1 study, 32 participants): Generalized Anxiety Disorder (GAD) score; MD 1.90, 95% CI -1.31 to 5.11; very low certainty evidence).

***Change in anxiety***

Compared to no intervention, meditation had uncertain effects on change in anxiety (Analysis 5.7 (1 study, 32 participants): GAD score; MD -0.10, 95% CI -3.37 to 3.17; very low certainty evidence).

***Sleep disturbance***

Compared to no intervention, meditation had uncertain effects on sleep disturbance (Analysis 5.8 (1 study, 37 participants): VAS score; MD -0.90, 95% CI -5.35 to 3.55; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Exercise versus control**

Nine studies (Amini 2016; Chang 2010; Huang 2021; Krase 2022; Konstadinidou-ND 2002; PEDAL 2020; Salehi 2020; Soliman 2015; Suzuki 2018) compared to exercise, including aerobic exercise (Amini 2016; Krase 2022; PEDAL 2020), leg ergometry exercise (Chang 2010; Konstadinidou-ND 2002; Salehi 2020), breathing exercise (Huang 2021), range of motion exercise (Soliman 2015), and electrical muscle stimulation (Suzuki 2018), to control in people receiving HD, during a median follow-up of 2.7 months. Control included different types of intervention, according to the authors' definition (e.g. no intervention, standard care, education, a combination of two different types of exercise programmes). The certainty of the evidence was low to very low (Summary of findings 1).

***Fatigue***

Compared to control, exercise may improve fatigue (Analysis 6.1 (4 studies, 217 participants): IFS, MFIS, PFS, or HFS score; SMD -1.18, 95% CI -2.04 to -0.31; $I^2$ = 87%, low certainty evidence). Substantial heterogeneity was observed between the studies.

***Number of participants reporting fatigue***

Compared to control, exercise had uncertain effects on the number of participants reporting fatigue (Analysis 6.2 (1 study, 58 participants): RR 5.17, 95% CI 0.32 to 84.13; very low certainty evidence).

***Change in fatigue***

Compared to control, exercise may improve change in fatigue, but the evidence is very uncertain (Analysis 6.3 (1 study, 67 participants): SF-36 score; MD -21.25, 95% CI -35.96 to -6.54; very low certainty evidence).

***General fatigue***

Compared to control, exercise may improve general fatigue, but the evidence is very uncertain (Analysis 6.4 (1 study, 37 participants): MFIS score; MD -3.36, 95% CI -5.68 to -1.04; very low certainty evidence).

***Physical fatigue***

Compared to control, exercise may reduce physical fatigue, but the evidence is very uncertain (Analysis 6.5 (1 study, 37 participants): MFIS score; MD -2.97, 95% CI -5.04 to -0.90; very low certainty evidence).

***Mental fatigue***

Compared to control, exercise may reduce mental fatigue, but the evidence is very uncertain (Analysis 6.6 (1 study, 37 participants): MFIS score; MD -3.62, 95% CI -5.65 to -1.59; very low certainty evidence), compared to control.

***Number of participants with moderate fatigue***

Compared to control, exercise had uncertain effects on the number of participants with moderate fatigue (Analysis 6.7 (1 study, 30 participants): RR 0.05, 95% CI 0.00 to 0.86; very low certainty evidence).

***Number of participants with severe fatigue***

Compared to control, exercise had uncertain effects on the number of participants with severe fatigue (Analysis 6.8: 1 study, 30 participants), as no events were reported in the eligible study.

***Vitality***

Compared to control, exercise had uncertain effects on vitality (Analysis 6.9 (1 study, 26 participants): SF-8 score; MD 1.70, 95% CI -2.89 to 6.29; very low certainty evidence).

***Energy/fatigue***

Compared to control, exercise had uncertain effects on energy/fatigue (Analysis 6.10 (1 study, 236 participants): KDQOL-SF score; MD 0.00, 95% CI -6.56 to 6.56; very low certainty evidence).

***Death (any cause)***

Compared to control, exercise may result in little to no difference in death (any cause) (Analysis 6.11 (8 studies, 739 participants): RR 0.87, 95% CI 0.43 to 1.76; $I^2$ = 0%, low certainty evidence).

***Cardiovascular death***

Compared to control, exercise had uncertain effects on cardiovascular death (Analysis 6.12 (5 studies, 587 participants): RR 0.61, 95% CI 0.10 to 3.62; very low certainty evidence).

***Quality of life (overall)***

Compared to control, exercise had uncertain effects on the overall QoL (Analysis 6.13 (1 study, 232 participants): KDQOL score; MD 4.40, 95% CI -0.77 to 9.57; very low certainty evidence).

***General health***

Compared to control, exercise may improve general health, but the evidence is very uncertain (Analysis 6.14 (1 study, 26 participants): SF-8 score; MD 5.30, 95% CI 1.09 to 9.51; very low certainty evidence).

***Anxiety***

Compared to control, exercise had uncertain effects on anxiety (Analysis 6.15 (1 study, 67 participants): KDQ score; MD 0.12, 95% CI -5.09 to 5.33; very low certainty evidence).

***Cardiovascular events***

Compared to control, exercise had uncertain effects on cardiovascular events (Analysis 6.16: 1 study, 58 participants), as no events were reported.

No other primary or secondary outcomes were reported.

**Exercise plus nandrolone versus no intervention plus nandrolone placebo**

Johansen 2006 compared exercise plus nandrolone to the group that did not perform exercise plus nandrolone placebo in people receiving HD during a follow-up of 2.7 months. The certainty of the evidence was very low.

***Fatigue***

Compared to no exercise and nandrolone placebo, exercise plus nandrolone had uncertain effects on fatigue (Analysis 7.1 (1 study, 36 participants): SF-36 score; MD 0.60, 95% CI -2.08 to 3.28; very low certainty evidence).

***Change in fatigue***

Compared to no exercise and nandrolone placebo, exercise plus nandrolone had uncertain effects on change in fatigue (Analysis 7.2 (1 study, 36 participants): SF-36 score; MD -2.30, 95% CI -6.46 to 1.86; very low certainty evidence).

***Death (any cause)***

Compared to no exercise and nandrolone placebo, exercise plus nandrolone had uncertain effects on death (any cause) (Analysis 7.3 (1 study, 40 participants): RR 0.33, 95% CI 0.01 to 7.72; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Exercise versus exercise**

Figueiredo 2018 compared inspiratory muscle training to aerobic training in people receiving HD during a follow-up of 3.7 months. The certainty of the evidence was very low.

***Death (any cause)***

Compared to aerobic training, inspiratory muscle training had uncertain effects on death (any cause) (Analysis 8.1 (1 study, 24 participants): RR 0.39, 95% CI 0.02 to 8.69; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Single exercise versus combined exercises**

Figueiredo 2018 compared a single exercise (inspiratory muscle training or aerobic training) to combined exercises in people undergoing HD during a follow-up of 3.7 months. The certainty of the evidence was very low.

***Death (any cause)***

Compared to combined exercises, inspiratory muscle training or aerobic training had uncertain effects on death (any cause) (Analysis 9.1 (1 study, 37 participants): RR 0.54, 95% CI 0.04 to 7.97; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Education versus control**

Eight studies (Babamohammadi 2006; Chow 2010; Dashti-Khavidaki 2013; Fatigue-HD 2019; Li 2014b; Mohamed 2014; Motedayen 2014; SOCIABLE 2017) compared education, including nurse-led case management programmes (Chow 2010; Li 2014b; Mohamed 2014), pharmacist-led pharmaceutical care plus routine care (Dashti-Khavidaki 2013), physical education programme (Motedayen 2014), personal energy planning programme (Fatigue-HD 2019), home-care educational programme (Babamohammadi 2006), and SOCIABLE (Seniors Optimizing Community Integration to Advance Better Living with End-stage kidney disease) services (SOCIABLE 2017) to control in people receiving HD or PD, during a median follow-up of 2.7 months. Control included different types of intervention, according to the authors' definition (e.g. not intervention, standard care, routine hospital discharge service,

standard nursing instruction and routine hospital care). The certainty of the evidence was low or very low.

***Fatigue***

Compared to control, education had uncertain effects on fatigue (Analysis 10.1 (2 studies, 177 participants): PFS score; SMD -0.23, 95% CI -0.97 to 0.52; $I^2$ = 72%; very low certainty evidence). Moderate heterogeneity was observed between the studies. Note: the name of the questionnaire for fatigue was not clearly stated in Babamohammadi 2006.

***Remission to fatigue***

Compared to control, education had uncertain effects on remission to fatigue (Analysis 10.2 (1 study, 66 participants): RR 9.00, 95% CI 0.50 to 160.78; very low certainty evidence) in people receiving HD.

***Medium fatigue symptoms***

Compared to control, education had uncertain effects on medium fatigue symptoms (Analysis 10.3 (1 study, 66 participants): RR 1.50, 95% CI 1.00 to 2.26; very low certainty evidence) in people receiving HD.

***Severe fatigue symptoms***

Compared to control, education may decrease severe fatigue symptoms, but the evidence is very uncertain (Analysis 10.4 (1 study, 66 participants): RR 0.29, 95% CI 0.12 to 0.70; very low certainty evidence) in people receiving HD.

***Weakness***

Compared to control, education may slightly decrease weakness, but the evidence is very uncertain (Analysis 10.5 (1 study, 37 participants): fatigue questionnaire score; MD 0.91, 95% CI 0.07 to 1.75; very low certainty evidence) in people receiving HD. Note: the name of the questionnaire for fatigue was not clearly stated in Babamohammadi 2006.

***Energy/fatigue***

Compared to control, education had uncertain effects on energy/fatigue (Analysis 10.6 (2 studies, 220 participants): KDQOL score; MD 4.50, 95% CI -0.55 to 9.54; $I^2$ = 0%, low certainty evidence) in people receiving PD.

***Death (any cause)***

Compared to control, education had uncertain effects on death (any cause) (Analysis 10.7 (5 studies, 314 participants): RR 0.94, 95% CI 0.25 to 3.57; $I^2$ = 22%, low certainty evidence) in people receiving HD or PD.

***Cardiovascular death***

Compared to control, education had uncertain effects on cardiovascular death (Analysis 10.8: 2 studies, 110 participants), as no events were reported in the eligible studies in people receiving HD.

***Quality of life (overall)***

Compared to control, education had uncertain effects on the overall QoL (Analysis 10.9 (2 studies, 220 participants): KDQOL score; MD 1.86, 95% CI -2.96 to 6.69; $I^2$ = 0%, low certainty evidence) in people receiving PD. Data for QoL were assessed as QoL and overall health.

***Sleep (overall)***

Compared to control, education may improve sleep (overall) (Analysis 10.10 (2 studies, 220 participants): KDQOL score; MD 7.46, 95% CI 2.04, 12.87; $I^2$ = 0%, low certainty evidence) in people receiving PD.

No other primary or secondary outcomes were reported.

**Nutritional supplementation versus placebo**

Three studies (Biniaz 2015; Fukuda 2015; Singer 2010) compared nutritional supplementation, including nutritional drink supplementation (Fukuda 2015) or vitamin C supplementation (Biniaz 2015; Singer 2010), to placebo in people receiving HD or PD during a median follow-up of 2.7 months. The certainty of the evidence was very low.

***Fatigue***

Compared to placebo, nutritional supplementation had uncertain effects on fatigue (Analysis 11.1 (2 studies, 230 participants): VAS or MFIS score; SMD -0.33, 95% CI -1.16 to 0.50; $I^2$ = 86%; very low certainty evidence) in people receiving HD. Substantial heterogeneity was observed between the studies.

***Vitality***

Compared to placebo, nutritional supplementation had uncertain effects on vitality (Analysis 11.2 (1 study, 173 participants): KDQOL-SF score; MD 3.70, 95% CI -2.70 to 10.10; very low certainty evidence) in people receiving HD.

***General health***

Compared to placebo, nutritional supplementation had uncertain effects on general health (Analysis 11.3 (1 study, 173 participants): KDQOL-SF score; MD 4.70, 95% CI -0.94 to 10.34; very low certainty evidence) in people receiving HD.

***Death (any cause)***

Compared to placebo, nutritional supplementation had uncertain effects on death (any cause) (Analysis 11.4: 1 study, 75 participants), as no events were reported in people receiving HD or PD.

***Cardiovascular death***

Compared to placebo, nutritional supplementation had uncertain effects on cardiovascular death (Analysis 11.5: 1 study, 75 participants), as no events were reported in people receiving HD or PD.

***Sleep problems***

Compared to placebo, nutritional supplementation had uncertain effects on sleep problems (Analysis 11.6 (1 study, 173 participants): KDQOL-SF score; MD -0.24, 95% CI -1.41 to 0.93; very low certainty evidence) in people receiving HD.

No other primary or secondary outcomes were reported.

**Cognitive-behavioural therapy versus no intervention**

Picariello 2018 compared CBT to no intervention (waiting-list control) in people receiving HD during a follow-up of three months. The certainty of the evidence was very low.

***Fatigue***

Compared to no intervention, CBT had uncertain effects on fatigue (Analysis 12.1 (1 study, 18 participants): CFS score; MD -3.67, 95% CI -9.55 to 2.21; very low certainty evidence).

***Death (any cause)***

Compared to no intervention, CBT had uncertain effects on death (any cause) (Analysis 12.2: 1 study, 24 participants), as no events were reported.

***Cardiovascular death***

Compared to no intervention, CBT had uncertain effects on cardiovascular death (Analysis 12.3: 1 study, 24 participants), as no events were reported.

***Depression***

Compared to no intervention, CBT had uncertain effects on depression (Analysis 12.4 (1 study, 18 participants): PHQ score; MD -1.86, 95% CI -8.29 to 4.57; very low certainty evidence).

***Anxiety***

Compared to no intervention, CBT had uncertain effects on anxiety (Analysis 12.5 (1 study, 16 participants): GAD score; MD -0.01, 95% CI -4.83 to 4.81; very low certainty evidence).

***Sleep quality***

Compared to no intervention, CBT had uncertain effects on sleep quality (Analysis 12.6 (1 study, 16 participants): PSQI score; MD 1.39, 95% CI -1.54 to 4.32; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Cognitive-behavioural therapy versus education**

Two studies (Chen 2008a; Chen 2011a) compared CBT to education in people receiving HD during a median follow-up of 1.2 months. The certainty of the evidence was very low.

***Fatigue***

Compared to education, CBT had uncertain effects on fatigue (Analysis 13.1 (1 study, 72 participants): FSS score; MD -0.30, 95% CI -1.07 to 0.47; very low certainty evidence).

***Number of participants with a decline in fatigue***

Compared to education, CBT had uncertain effects on the number of participants with a decline in fatigue (Analysis 13.2 (1 study, 72 participants): RR 1.61, 95% CI 1.10 to 2.36; very low certainty evidence).

***Death (any cause)***

Compared to education, CBT had uncertain effects on death (any cause) (Analysis 13.3: 2 studies, 106 participants), as no events were reported in the eligible studies.

***Cardiovascular death***

Compared to education, CBT had uncertain effects on cardiovascular death (Analysis 13.4: 2 studies, 106 participants), as no events were reported in the eligible studies.

***Depression***

Compared to education, CBT had uncertain effects on depression (Analysis 13.5 (1 study, 72 participants): Beck Depression Inventory (BDI) score; MD -2.30, 95% CI -8.29 to 3.69; very low certainty evidence).

***Number of participants with a decline in depression***

Compared to education, CBT had uncertain effects on the number of participants with a decline in depression (Analysis 13.6 (1 study, 72 participants): RR 1.64, 95% CI 1.06 to 2.54; very low certainty evidence).

***Anxiety***

Compared to education, CBT had uncertain effects on anxiety (Analysis 13.7 (1 study, 72 participants): BAI score; MD -3.10, 95% CI -8.81 to 2.61; very low certainty evidence).

***Number of participants with a decline in anxiety***

Compared to education, CBT had uncertain effects on the number of participants with a decline in anxiety (Analysis 13.8 (1 study, 72 participants): RR 1.45, 95% CI 0.92 to 2.29; very low certainty evidence).

***Sleep (overall)***

Compared to education, CBT may improve sleep (overall), but the evidence is very uncertain (Analysis 13.9 (1 study, 72 participants): PSQI score; MD -1.70, 95% CI -3.39 to -0.01; very low certainty evidence), compared to education.

No other primary or secondary outcomes were reported.

**Cognitive-behavioural therapy versus serotonin reuptake inhibitor**

ASCEND 2016 compared CBT to serotonin reuptake inhibitor (sertraline) in people receiving HD during a follow-up of 2.7 months. The certainty of the evidence was very low.

***Death (any cause)***

Compared to serotonin reuptake inhibitor, CBT had uncertain effects on death (any cause) (Analysis 14.1 (1 study, 120 participants): RR 5.00, 95% CI 0.25 to 102.00; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Aromatherapy versus placebo or standard care**

Seven studies (Ahmady 2019; Bagheri-Nesami 2016; Hassanzadeh 2018; Karadag 2019; Mohammadpourhodki 2021; Muz 2017; Varaei 2020) compared aromatherapy, including lavender essence (Ahmady 2019; Bagheri-Nesami 2016; Karadag 2019; Hassanzadeh 2018; Mohammadpourhodki 2021; Varaei 2020) or sweet orange and lavender oil (Muz 2017) to placebo or standard care in people receiving HD, during a median follow-up of 0.9 months. Aromatherapy was delivered as massage aromatherapy (Mohammadpourhodki 2021; Varaei 2020), while all other studies delivered aromatherapy as inhalation. The certainty of the evidence was low to very low (Summary of findings 2).

***Fatigue***

Compared to placebo or standard care, aromatherapy may improve fatigue (Analysis 15.1 (7 studies, 542 participants): FSS, RFS, PFS or BFI score; SMD -1.23, 95% CI -1.96 to -0.50; $I^2$ = 93%, low certainty evidence). Substantial heterogeneity was observed between the studies.

***Change in fatigue***

Compared to placebo or standard care, aromatherapy may improve change in fatigue, but the evidence is very uncertain (Analysis 15.2 (1 study, 60 participants): FSS score; MD 6.86, 95% CI 4.76 to 8.96; very low certainty evidence).

***Vitality***

Compared to placebo or standard care, aromatherapy had uncertain effects on vitality (Analysis 15.3 (1 study, 105 participants): FSS score; MD 0.07, 95% CI -6.89 to 7.03; very low certainty evidence).

***Death (any cause)***

Compared to placebo or standard care, aromatherapy had uncertain effects on death (any cause) (Analysis 15.4: 6 studies 473 participants), as no events were reported in the eligible studies.

***Cardiovascular death***

Compared to placebo or standard care, aromatherapy had uncertain effects on cardiovascular death (Analysis 15.5: 6 studies, 473 participants), as no events were reported in the eligible studies.

***Quality of life (overall)***

Compared to placebo or standard care, aromatherapy may improve the overall QoL, but the evidence is very uncertain (Analysis 15.6 (1 study, 105 participants): SF-36 score; MD 16.20, 95% CI 9.16 to 23.24; very low certainty evidence).

***Global sleep quality***

Compared to placebo or standard care, aromatherapy may improve global sleep quality, but the evidence is very uncertain (Analysis 15.7 (1 study, 62 participants): PSQI score; MD -10.96, 95% CI -12.47 to -9.45; very low certainty evidence).

***Change in global sleep quality***

Compared to placebo or standard care, aromatherapy may increase change in global sleep quality, but the evidence is very uncertain (Analysis 15.8 (1 study, 62 participants): PSQI score; MD 11.59, 95% CI 10.21 to 12.97; very low certainty evidence).

***Sleep disturbance***

Compared to placebo or standard care, aromatherapy may reduce sleep disturbance, but the evidence is very uncertain (Analysis 15.9 (1 study, 62 participants): PSQI score; MD -0.91, 95% CI -1.14 to -0.68; very low certainty evidence).

***Change in sleep disturbance***

Compared to placebo or standard care, aromatherapy may improve change in sleep disturbance, but the evidence is very uncertain (Analysis 15.10 (1 study, 62 participants): PSQI score; MD 0.90, 95% CI 0.75 to 1.05; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Aromatherapy versus another type of aromatherapy**

Balouchi 2016 compared two different aromatherapy techniques (lavender versus orange extract) in people undergoing HD during a follow-up of 0.5 months. The certainty of the evidence was very low.

***Fatigue***

Compared to orange extract, lavender extract had uncertain effects on fatigue (Analysis 16.1 (1 study, 30 participants): MFIS score; MD -2.00, 95% CI -6.92 to 2.92; very low certainty evidence)

No other primary or secondary outcomes were reported.

**Aromatherapy versus relaxation**

Hassanzadeh 2018 compared aromatherapy (lavender essence) to relaxation techniques in people undergoing HD during a follow-up of 0.9 months. The certainty of the evidence was very low.

***Fatigue***

Compared to relaxation, aromatherapy may reduce fatigue, but the evidence is very uncertain (Analysis 17.1 (1 study, 70 participants): BFI score; MD -1.48, 95% CI -1.92 to -1.04; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Massage versus no intervention**

Seven studies (Cecen 2021; Habibzadeh 2020: Lazarus 2020; Ozdemir 2013; Roshanravan 2016; Shahdadi 2016; Unal 2016) compared massage, including slow-stroke back massage (Shahdadi 2016), slow-stroke back massage or foot reflexology (Unal 2016), foot reflexology (Ozdemir 2013; Roshanravan 2016; Unal 2016), foot massage with chamomile oil, almond oil or no oils (Habibzadeh 2020), and olive oil massage (Lazarus 2020), to no intervention in people receiving HD, during a median follow-up of 0.9 months. The certainty of the evidence was low or very low (Summary of findings 3).

***Fatigue***

Compared to no intervention, massage may improve fatigue (Analysis 18.1 (7 studies, 657 participants): FSS, RFS, PFS or VAS score; SMD -1.06, 95% CI -1.47, -0.65; $I^2$ = 81%, low certainty evidence). Substantial heterogeneity was observed between the studies.

***Change in fatigue***

Compared to no intervention, massage may reduce the change in fatigue, but the evidence is very uncertain (Analysis 18.2 (1 study, 120 participants): FSS score; MD -0.91, 95% CI -1.40 to -0.42; very low certainty evidence).

***Number of participants with severe fatigue***

Compared to no intervention, massage may reduce the number of participants with severe fatigue (Analysis 18.3 (1 study, 200 participants): RR 0.15, 95% CI 0.09 to 0.27, low certainty evidence).

***Energy***

Compared to no intervention, massage may increase energy (Analysis 18.4 (2 studies, 152 participants): VAS score; MD 4.87, 95% CI 1.69 to 8.06, $I^2$ = 59%; low certainty evidence). Moderate heterogeneity was reported between studies.

***Death (any cause)***

Compared to no intervention, massage had uncertain effects on death (any cause) (Analysis 18.5 (3 studies, 404 participants): RR 1.53, 95% CI 0.06 to 36.31; very low certainty evidence).

***Cardiovascular death***

Compared to no intervention, massage had uncertain effects on cardiovascular death (Analysis 18.6: 2 studies, 320 participants), as no events were reported in the eligible studies.

***Quality of life (overall)***

Compared to no intervention, massage had uncertain effects on the overall QoL (Analysis 18.7 (1 study, 120 participants): KDQOL-SF score; MD 3.27, 95% CI -1.82 to 8.36; very low certainty evidence).

***Change in quality of life (overall)***

Compared to no intervention, massage may increase change in the overall QoL, but the evidence is very uncertain (Analysis 18.8 (1 study, 120 participants): KDQOL-SF score; MD 2.54, 95% CI 2.06 to 3.02; very low certainty evidence).

***Sleep (overall)***

Compared to no intervention, massage may improve sleep (overall), but the evidence is very uncertain (Analysis 18.9 (1 study, 70 participants): PSQI score; MD -6.34, 95% CI -7.42 to -5.26; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Massage versus sham massage**

Roshanravan 2016 compared massage to sham massage in people receiving HD during a follow-up of 0.9 months. The certainty of the evidence was very low.

***Fatigue***

Compared to sham massage, massage may slightly reduce fatigue, but the evidence is very uncertain (Analysis 19.1 (1 study, 51 participants): PFS score; MD -0.63, 95% CI -1.22 to -0.04; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Sham massage versus no intervention**

Roshanravan 2016 compared sham massage to no intervention in people receiving HD during a follow-up of 0.9 months. The certainty of the evidence was very low.

***Fatigue***

Compared to no intervention, sham massage may slightly reduce fatigue, but the evidence is very uncertain (Analysis 20.1 (1 study, 52 participants): PFS score; MD -0.76, 95% CI -1.23 to -0.29; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Massage versus another type of massage**

Two studies (Habibzadeh 2020; Unal 2016) compared massage to another type of massage in people receiving HD during a median follow-up of 1.5 months. Unal 2016 compared foot reflexology to back massage, while Habibzadeh 2020 compared foot massage with chamomile oil or almond oil to massage without oil. The certainty of the evidence was low or very low.

***Fatigue***

Compared to back massage or massage without oil, foot reflexology, chamomile, or almond oil may slightly reduce fatigue (Analysis 21.1 (2 studies, 160 participants): VAS or FSS score; MD -0.77, 95% CI -1.10 to -0.43; low certainty evidence).

***Change in fatigue***

Compared to back massage, foot reflexology may slightly reduce the change in fatigue, but the evidence is very uncertain (Analysis 21.2 (1 study, 90 participants): FSS score; MD -0.50, 95% CI -0.95 to -0.05; very low certainty evidence).

***Energy***

Compared to back massage, foot reflexology may increase energy, but the evidence is very uncertain (Analysis 21.3 (1 study, 70 participants): VAS score; MD 4.54, 95% CI 1.28 to 7.80; very low certainty evidence).

***Death (any cause)***

Compared to massage without oil, foot massage with chamomile or almond oil had uncertain effects on death (any cause) (Analysis 21.4: 1 study, 90 participants), as no events were reported.

***Cardiovascular death***

Compared to massage without oil, foot massage with chamomile or almond oil had uncertain effects on cardiovascular death (Analysis 21.5: 1 study, 90 participants), as no events were reported.

***Quality of life (overall)***

Compared to massage without oil, foot massage with chamomile or almond oil may increase the overall QoL, but the evidence is very uncertain (Analysis 21.6 (1 study, 90 participants): KDQOL-SF score; MD 4.60, 95% CI 0.74 to 8.46; very low certainty evidence).

***Change in quality of life (overall)***

Compared to massage without oil, foot massage with chamomile or almond oil may increase change in the overall QoL, but the evidence is very uncertain (Analysis 21.7 (1 study, 90 participants): KDQOL-SF score; MD 1.87, 95% CI 1.30 to 2.44; very low certainty evidence).

***Sleep (overall)***

Compared to back massage, foot reflexology may improve sleep (overall), but the evidence is very uncertain (Analysis 21.8 (1 study, 70 participants): PSQI score; MD -2.80, 95% CI -3.87 to -1.73; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Erythropoietin stimulating agents versus placebo**

Two studies (Canadian EPO 1990; Lillevang 1990) compared ESA to placebo in people receiving HD during a median follow-up of 3.9 months. The certainty of the evidence was very low.

***Fatigue***

Compared to placebo, ESA had uncertain effects on fatigue (Analysis 22.1 (1 study, 99 participants): KDQ score; MD 0.70, 95% CI 0.26 to 1.14; very low certainty evidence).

***Weakness***

Compared to placebo, ESA had uncertain effects on weakness (Analysis 22.2 (1 study, 99 participants): KDQ score; MD 1.00, 95% CI 0.29 to 1.71; very low certainty evidence).

***Energy***

Compared to placebo, ESA had uncertain effects on energy (Analysis 22.3 (1 study, 99 participants): KDQ score; MD 0.40, 95% CI -0.43 to 1.23; very low certainty evidence).

***Death (any cause)***

Compared to placebo, ESA had uncertain effects on death (any cause) (Analysis 22.4 (2 studies, 137 participants); RR 0.17, 95% CI 0.01 to 4.15; very low certainty evidence).

***Cardiovascular death***

Compared to placebo, ESA had uncertain effects on cardiovascular death (Analysis 22.5: 1 study, 19 participants), as no events were reported.

***Depression***

Compared to placebo, ESA had uncertain effects on depression (Analysis 22.6 (1 study, 99 participants): KDQ score; MD 0.20, 95% CI -0.35 to 0.75; very low certainty evidence).

***Clotting of vascular access***

Compared to placebo, ESA had uncertain effects on clotting of vascular access (Analysis 22.7 (1 study, 118 participants): RR 5.64, 95% CI 0.75 to 42.16; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Normal haemoglobin target with erythropoietin stimulating agents (ESA) versus subnormal or high haemoglobin target with or without ESA**

Three studies (Foley 2000; Linde 2001; Parfrey 2005) compared ESA (normal Hb target) versus subnormal or high Hb target with or without ESA. Two studies (Foley 2000; Parfrey 2005) compared EPO alpha to achieve a target Hb of 9.5 to 10.5 g/dL (normal Hb target group) or 13.0 to 14.0 g/dL (high Hb target group) in people receiving HD. Linde 2001 compared EPO alpha to achieve a normal Hb target with a subnormal Hb target with or without ESA in people receiving HD and PD during a median follow-up of 14.3 months. The certainty of the evidence was low or very low.

***Fatigue***

Compared to a high Hb target with ESA, a normal Hb target had uncertain effects on fatigue (Analysis 23.1 (1 study, 582 participants): FACIT-F score; MD -3.30, 95% CI -7.32 to 0.72; very low certainty evidence).

***Change in fatigue***

Compared to a high Hb target with ESA, a normal Hb target had uncertain effects on change in fatigue (Analysis 23.2 (1 study, 582 participants): FACIT-F score; MD -2.21, 95% CI -4.98 to 0.56; very low certainty evidence).

***Vitality***

Compared to a high Hb target with ESA, a normal Hb target had uncertain effects on vitality (Analysis 23.3 (1 study, 564 participants): FACIT-F score; MD -2.90, 95% CI -7.06 to 1.26; very low certainty evidence).

***Change in vitality***

Compared to a high Hb target with ESA, a normal Hb target may reduce change in vitality, but the evidence is very uncertain (Analysis 23.4 (1 study, 564 participants): FACIT-F score; MD -3.52, 95% CI -6.51 to -0.53; very low certainty evidence).

***Death (any cause)***

Compared to a high Hb target with ESA or a sub-optimal Hb target with or without ESA, a normal Hb target had uncertain effects on death (any cause) (Analysis 23.5 (3 studies, 1085 participants): RR 1.05, 95% CI 0.71 to 1.56; $I^2$ = 0%; very low certainty evidence) in people receiving HD and PD.

***Cardiovascular events***

Compared to sub-optimal Hb target with or without ESA, a normal HB target had uncertain effects on cardiovascular events (Analysis 23.6 (1 study, 344 participants): RR 1.30, 95% CI 0.68 to 2.48; very low certainty evidence) in people receiving HD and PD.

***Cardiovascular events***

Compared to a high Hb target with ESA, a normal Hb target had uncertain effects on cardiovascular events (Analysis 23.7 (1 study, 146 participants): RR 1.00, 95% CI 0.44 to 2.26; very low certainty evidence).

***Arteriovenous access thrombosis***

Compared to a high Hb target with ESA, a normal Hb target had uncertain effects on arteriovenous access thrombosis membrane (Analysis 23.8 (1 study, 146 participants): RR 1.67, 95% CI 0.64 to 4.35; very low certainty evidence).

***Hypertension***

Compared to a high Hb target with ESA, a normal Hb target may have little or no effect on hypertension (Analysis 23.9 (1 study, 596 participants): RR 0.90, 95% CI 0.74 to 1.11, low certainty evidence).

***Myocardial infarction***

Compared to a high Hb target with ESA, a normal Hb target had uncertain effects on myocardial infarction (Analysis 23.10 (1 study, 596 participants): RR 0.56, 95% CI 0.17 to 1.91; very low certainty evidence).

***Congestive heart failure***

Compared to a high Hb target with ESA, a normal Hb target had uncertain effects on congestive heart failure (Analysis 23.11 (1 study, 596 participants): RR 1.08, 95% CI 0.48 to 2.40; very low certainty evidence).

***Permanent catheter thrombosis***

Compared to a high Hb target with ESA, a normal Hb target had uncertain effects on permanent catheter thrombosis (Analysis 23.12 (1 study, 596 participants): RR 1.11, 95% CI 0.43 to 2.84; very low certainty evidence).

***Arteriovenous graft loss***

Compared to a high Hb target with ESA, a normal Hb target had uncertain effects on arteriovenous graft loss (Analysis 23.13 (1 study, 596 participants): RR 0.99, 95% CI 0.40 to 2.45; very low certainty evidence).

***Arteriovenous fistula thrombosis***

Compared to a high Hb target with ESA, a normal Hb target had uncertain effects on arteriovenous fistula thrombosis (Analysis 23.14 (1 study, 596 participants): RR 0.79, 95% CI 0.53 to 1.19; very low certainty evidence).

***Arteriovenous fistula loss***

Compared to a high Hb target with ESA, a normal Hb target had uncertain effects on arteriovenous fistula loss (Analysis 23.15 (1 study, 596 participants): RR 0.89, 95% CI 0.54 to 1.46; very low certainty evidence).

***Permanent catheter loss***

Compared to a high Hb target with ESA, a normal Hb target had uncertain effects on permanent catheter loss (Analysis 23.16 (1 study, 596 participants): RR 0.85, 95% CI 0.29 to 2.49; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Frequent versus conventional haemodialysis**

Two studies (FHN DAILY 2007; FHN NOCTURNAL 2007) compared frequent HD (six times/week) with conventional HD (three times/week) in people receiving HD during a median follow-up of 12 months. The certainty of the evidence was very low.

***Death (any cause)***

Compared to conventional HD, frequent HD had uncertain effects on death (any cause) (Analysis 24.1 (2 studies, 332 participants): RR 0.66, 95% CI 0.25 to 1.74; $I^2$ = 0%; very low certainty evidence).

***Cardiovascular events***

Compared to conventional HD, frequent HD had uncertain effects on cardiovascular events (Analysis 24.2 (1 study, 245 participants): RR 0.19, 95% CI 0.01 to 3.96; very low certainty evidence).

***Depression***

Compared to conventional HD, frequent HD had uncertain effects on depression (Analysis 24.3 (1 study, 189 participants): BDI score; MD -1.80, 95% CI -4.45 to 0.85; very low certainty evidence).

***Vascular access outcomes***

Compared to conventional HD, frequent HD may increase the number of vascular access outcomes, but the evidence is very uncertain (Analysis 24.4 (2 studies, 332 participants): RR 1.53, 95% CI 1.13 to 2.07; $I^2$ = 0%; very low certainty evidence).

***Access loss***

Compared to conventional HD, frequent HD had uncertain effects on access loss (Analysis 24.5 (2 studies, 332 participants): RR 1.21, 95% CI 0.72 to 2.03; $I^2$ = 0%; very low certainty evidence).

***Access stenosis***

Compared to conventional HD, frequent HD had uncertain effects on access stenosis (Analysis 24.6 (2 studies, 332 participants): RR 1.10, 95% CI 0.37 to 3.25; $I^2$ = 0%; very low certainty evidence).

***Access thrombosis***

Compared to conventional HD, frequent HD had uncertain effects on access thrombosis (Analysis 24.7 (2 studies, 332 participants): RR 1.53, 95% CI 0.28 to 8.51; $I^2$ = 28%; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Home versus pre-dialysis blood pressure monitoring**

BOLD 2020 compared home BP monitoring to pre-dialysis BP monitoring in people receiving HD during a follow-up of 4 months. The certainty of the evidence was very low.

***Number of participants reporting fatigue***

Compared to pre-dialysis BP monitoring, home BP monitoring had uncertain effects on the number of participants reporting fatigue (Analysis 25.1 (1 study, 50 participants): RR 0.94, 95% CI 0.61 to 1.45; very low certainty evidence).

***Death (any cause)***

Compared to pre-dialysis BP monitoring, home BP monitoring had uncertain effects on death (any cause) (Analysis 25.2: 1 study, 50 participants), as no events were reported.

***Cardiovascular death***

Compared to pre-dialysis BP monitoring, home BP monitoring had uncertain effects on cardiovascular death (Analysis 25.3: 1 study, 50 participants), as no events were reported.

No other primary or secondary outcomes were reported.

**Blood flow rate reduction versus standard care**

Duggal 2019 compared blood flow rate reduction to standard care in people undergoing HD during a follow-up of 0.9 months. The certainty of the evidence was very low.

***Death (any cause)***

Compared to standard care, blood flow rate reduction had uncertain effects on death (any cause) (Analysis 26.1: 1 study, 102 participants), as no events were reported.

***Cardiovascular death***

Compared to standard care, blood flow rate reduction had uncertain effects on cardiovascular death (Analysis 26.2: 1 study, 102 participants), as no events were reported.

No other primary or secondary outcomes were reported.

**Serotonin reuptake inhibitor versus placebo**

ASSertID 2015 compared serotonin reuptake inhibitor (sertraline) to placebo in people receiving HD during a follow-up of 6 months. The certainty of the evidence was very low.

***Death (any cause)***

Compared to placebo, serotonin reuptake inhibitor had uncertain effects on death (any cause) (Analysis 27.1 (1 study, 30 participants): RR 3.00, 95% CI 0.13 to 68.26; very low certainty evidence).

***Cardiovascular events***

Compared to placebo, serotonin reuptake inhibitor had uncertain effects on cardiovascular events (Analysis 27.2 (1 study, 30 participants): RR 3.00, 95% CI 0.13 to 68.26; very low certainty evidence).

***Depression***

Compared to placebo, serotonin reuptake inhibitor had uncertain effects on depression (Analysis 27.3 (1 study, 21 participants): BDI score; MD -0.60, 95% CI -5.48 to 4.28; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Beta-blockers versus angiotensin-converting enzyme inhibitors**

HDPAL 2014 compared beta-blockers (atenolol) to ACEi (lisinopril) in people receiving HD during a follow-up of 12 months. The certainty of the evidence was very low.

***Change in energy/fatigue***

Compared to ACEi, beta-blockers may increase change in energy/fatigue, but the evidence is very uncertain (Analysis 28.1 (1 study, 87 participants): KDQOL score; MD 4.00, 95% CI 2.79 to 5.21; very low certainty evidence).

***Change in overall health***

Compared to ACEi, beta-blockers may reduce change in overall health, but the evidence is very uncertain (Analysis 28.2 (1 study, 83 participants): KDQOL score; MD -2.20, 95% CI -3.55 to -0.85; very low certainty evidence).

***Change in general health***

Compared to ACEi, beta-blockers may increase change in general health, but the evidence is very uncertain (Analysis 28.3 (1 study, 88 participants): KDQOL score; MD 6.20, 95% CI 5.04 to 7.36; very low certainty evidence).

***Death (any cause)***

Compared to ACEi, beta-blockers had uncertain effects on death (any cause) (Analysis 28.4 (1 study, 200 participants): RR 1.00, 95% CI 0.26 to 3.89; very low certainty evidence).

***Cardiovascular death***

Compared to ACEi, beta-blockers had uncertain effects on cardiovascular death (Analysis 28.5 (1 study, 200 participants): RR 0.67, 95% CI 0.11 to 3.90; very low certainty evidence).

***Cardiovascular events***

Compared to ACEi, beta-blockers may reduce cardiovascular events, but the evidence is very uncertain (Analysis 28.6 (1 study, 200 participants): RR 0.57, 95% CI 0.33 to 0.99, very low certainty evidence).

***Access-related events***

Compared to ACEi, beta-blockers had uncertain effects on access-related events (Analysis 28.7 (1 study, 200 participants): RR 0.89, 95% CI 0.49 to 1.62; very low certainty evidence).

***Change in sleep quality***

Compared to ACEi, beta-blockers may reduce change in sleep quality, but the evidence is very uncertain (Analysis 28.8 (1 study, 87 participants): KDQOL score; MD -1.50, 95% CI -2.63 to -0.37; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Anabolic steroids versus placebo**

Two studies (Johansen 1999; Johansen 2006) compared anabolic steroids (nandrolone decanoate) to placebo in people receiving HD or PD during a median follow-up of 4.4 months. The certainty of the evidence was very low.

***Fatigue***

Compared to placebo, anabolic steroids had uncertain effects on fatigue (Analysis 29.1 (2 studies, 52 participants): POMS-F score; MD 1.24, 95% CI -3.66 to 6.13; $I^2$ = 76%; very low certainty evidence) in people receiving HD or PD. Moderate heterogeneity was observed between the studies.

***Change in fatigue***

Compared to placebo, anabolic steroids had uncertain effects on change in fatigue (Analysis 29.2 (1 study, 33 participants): POMS-F score; MD 2.00, 95% CI -1.74 to 5.74; very low certainty evidence) in people receiving HD.

***Death (any cause)***

Compared to placebo, anabolic steroids had uncertain effects on death (any cause) (Analysis 29.3 (2 studies, 68 participants): RR 0.35, 95% CI 0.04 to 3.23; $I^2$ = 0%, very low certainty evidence) in people receiving HD or PD.

No other primary or secondary outcomes were reported.

**Anabolic steroids versus exercise**

Johansen 2006 compared anabolic steroids (nandrolone decanoate) to exercise in people receiving HD during a follow-up of 2.7 months. The certainty of the evidence was very low.

***Fatigue***

Compared to exercise, anabolic steroids had uncertain effects on fatigue (Analysis 30.1 (1 study, 35 participants): POMS-F score; MD 3.00, 95% CI -0.02 to 6.02; very low certainty evidence).

***Change in fatigue***

Compared to exercise, anabolic steroids may increase change in fatigue, but the evidence is very uncertain (Analysis 30.2 (1 study, 35 participants): POMS-F score; MD 4.30, 95% CI 1.38 to 7.22; very low certainty evidence).

***Death (any cause)***

Compared to exercise, anabolic steroids had uncertain effects on death (any cause) (Analysis 30.3: 1 study, 39 participants), as no events were reported.

***Cardiovascular death***

Compared to exercise, anabolic steroids had uncertain effects on cardiovascular death (Analysis 30.4: 1 study, 39 participants), as no events were reported.

No other primary or secondary outcomes were reported.

**Anabolic steroids alone versus anabolic steroids plus exercise**

Johansen 2006 compared anabolic steroids (nandrolone decanoate) alone to anabolic steroids (nandrolone decanoate) plus exercise in people receiving HD during a follow-up of 2.7 months. The certainty of the evidence was very low.

***Fatigue***

Compared to anabolic steroids plus exercise, anabolic steroids alone may increase fatigue, but the evidence is very uncertain (Analysis 31.1 (1 study, 32 participants): POMS-F score; MD 4.60, 95% CI 1.06 to 8.14; very low certainty evidence).

***Change in fatigue***

Compared to anabolic steroids plus exercise, anabolic steroids alone may increase change in fatigue, but the evidence is very uncertain (Analysis 31.2 (1 study, 32 participants): POMS-F score; MD 4.00, 95% CI 1.34 to 6.66; very low certainty evidence).

***Death (any cause)***

Compared to anabolic steroids plus exercise, anabolic steroids alone had uncertain effects on death (any cause) (Analysis 31.3 (1 study, 39 participants): RR 0.35, 95% CI 0.02 to 8.10; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Anabolic steroids plus exercise versus placebo**

Johansen 2006 compared anabolic steroids (nandrolone decanoate) plus exercise to placebo in people receiving HD during a follow-up of 2.7 months. The certainty of the evidence was very low.

***Fatigue***

Compared to placebo, anabolic steroids plus exercise had uncertain effects on fatigue (Analysis 32.1 (1 study, 33 participants): POMS-F score; MD -1.00, 95% CI -4.26 to 2.26; very low certainty evidence).

***Change in fatigue***

Compared to placebo, anabolic steroids plus exercise had uncertain effects on change in fatigue (Analysis 32.2 (1 study, 33 participants): POMS-F score; MD -2.00, 95% CI -5.98 to 1.98; very low certainty evidence).

***Death (any cause)***

Compared to placebo, anabolic steroids plus exercise had uncertain effects on death (any cause) (Analysis 32.3 (1 study, 40 participants): RR 1.00, 95% CI 0.07 to 14.90; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Anabolic steroids plus exercise versus exercise alone**

Johansen 2006 compared anabolic steroids (nandrolone decanoate) plus exercise to exercise alone in people receiving HD during a follow-up of 2.7 months. The certainty of the evidence was very low.

***Fatigue***

Compared to exercise alone, anabolic steroids plus exercise had uncertain effects on fatigue (Analysis 33.1 (1 study, 35 participants): POMS-F score; MD -1.60, 95% CI -4.85 to 1.65; very low certainty evidence).

***Change in fatigue***

Compared to exercise alone, anabolic steroids plus exercise had uncertain effects on change in fatigue (Analysis 33.2 (1 study, 35 participants): POMS-F score; MD 0.30, 95% CI -2.91 to 3.51; very low certainty evidence).

***Death (any cause)***

Compared to exercise alone, anabolic steroids plus exercise had uncertain effects on death (any cause) (Analysis 33.3 (1 study, 40 participants): RR 3.00, 95% CI 0.13 to 69.52; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Glucose dialysate versus another type of glucose dialysate**

Raimann 2010 compared dialysates with 200 mg/dL of glucose (glucose-enriched dialysate) with 100 mg/dL of glucose in patients receiving HD during a follow-up of 0.7 months. The certainty of the evidence was very low.

***Death (any cause)***

Compared to 100 mg/dL glucose dialysate, glucose-enriched dialysate had uncertain effects on death (any cause) (Analysis 34.1: 1 study, 29 participants), as no events were reported.

***Cardiovascular events***

Compared to 100 mg/dL glucose dialysate, glucose-enriched dialysate had uncertain effects on cardiovascular events (Analysis 34.2: 1 study, 29 participants), as no events were reported.

No other primary or secondary outcomes were reported.

### Acupressure versus placebo or control

Seven studies (Bicer 2022; Cho 2004; Lin 2011; Sabouhi 2013; Su 2009; Tsay 2004a; Tsay 2004b) compared acupressure, including far-infrared rays (Lin 2011; Su 2009), acupressure without a specific definition (Cho 2004; Sabouhi 2013; Tsay 2004a), acupressure with an electrostimulation device (Bicer 2022), and acupressure or TEAS (Tsay 2004b) to placebo or control in people receiving HD, during a median follow-up of one month. Control included different types of intervention, according to the authors' definition (e.g. no intervention, standard care, heat path therapy). The certainty of the evidence was low or very low (Summary of findings 4).

#### *Fatigue*

Compared to placebo or control, acupressure may reduce fatigue (Analysis 35.1 (6 studies, 459 participants): PFS, revised PFS, or FI score; SMD -0.64, 95% CI -1.03 to -0.25; $I^2$ = 75%, low certainty evidence). Moderate heterogeneity was observed between the studies.

#### *Change in fatigue*

Compared to no intervention, acupressure may reduce change in fatigue, but the evidence is very uncertain (Analysis 35.2 (1 study, 64 participants): PFS score; MD -2.15, 95% CI -2.56 to -1.73; very low certainty evidence).

#### *Fatigue in the last week*

Compared to no intervention, acupressure had uncertain effects on fatigue in the last week (Analysis 35.3 (1 study, 61 participants): BFI score; MD -0.09, 95% CI -1.27 to 1.09; very low certainty evidence).

#### *Fatigue strength rate*

Compared to no intervention, acupressure had uncertain effects on fatigue strength rate (Analysis 35.4 (1 study, 61 participants): BFI score; MD -0.97, 95% CI -6.28 to 4.34; very low certainty evidence).

#### *Usual level of fatigue during the past 24 hours*

Compared to no intervention, acupressure had uncertain effects on the usual level of fatigue during the past 24 hours (Analysis 35.5 (1 study, 61 participants): BFI score; MD -0.26, 95% CI -5.53 to 5.01; very low certainty evidence).

#### *The worst level of fatigue during the past 24 hours*

Compared to no intervention, acupressure had uncertain effects on the worst level of fatigue during the past 24 hours (Analysis 35.6 (1 study, 61 participants): BFI score; MD -0.24, 95% CI -5.60 to 5.12; very low certainty evidence).

#### *Death (any cause)*

Compared to placebo or control, acupressure had uncertain effects on death (any cause) (Analysis 35.7: 2 studies, 169 participants), as no events were reported in the eligible studies.

#### *Cardiovascular death*

Compared to placebo or control, acupressure had uncertain effects on cardiovascular death (Analysis 35.8: 2 studies, 169 participants), as no events were reported in the eligible studies.

#### *Quality of life (overall)*

Compared to heat pad therapy, acupressure had uncertain effects on the overall QoL (Analysis 35.9 (1 study, 61 participants): World Health Organization Quality of Life-Brief Form (WHOQOL-BREF) score; MD -0.08, 95% CI -0.63 to 0.47; very low certainty evidence).

#### *Depression*

Compared to control, acupressure may reduce depression (Analysis 35.10 (3 studies, 199 participants): BDI score; MD -4.10, 95% CI -6.73 to -1.47; $I^2$ = 0%, low certainty evidence).

#### *Mood*

Compared to no intervention, acupressure had uncertain effects on mood (Analysis 35.11 (1 study, 61 participants): BFI score; MD -0.07, 95% CI -6.75 to 6.61; very low certainty evidence).

#### *Sleep quality*

Compared to usual care, acupressure had uncertain effects on sleep quality (Analysis 35.12 (2 studies, 141 participants): PSQI score; MD -1.17, 95% CI -2.59 to 0.24; $I^2$ = 5%, low certainty evidence).

No other primary or secondary outcomes were reported.

### Acupressure versus sham acupressure

Two studies (Sabouhi 2013; Tsay 2004a) compared acupressure with sham acupressure in people receiving HD during a median follow-up of 0.9 months. The certainty of the evidence was very low.

#### *Fatigue*

Compared to sham acupressure, acupressure had uncertain effects on fatigue (Analysis 36.1 (2 studies, 134 participants): PFS score; MD -0.71, 95% CI -1.95 to 0.52; $I^2$ = 87%, low certainty evidence). Substantial heterogeneity was observed between the studies.

#### *Change in fatigue*

Compared to sham acupressure, acupressure may reduce change in fatigue, but the evidence is very uncertain (Analysis 36.2 (1 study, 64 participants): PFS score; MD -1.59, 95% CI -2.00 to -1.17; very low certainty evidence).

#### *Death (any cause)*

Compared to sham acupressure, acupressure had uncertain effects on death (any cause) (Analysis 36.3: 1 study, 32 participants), as no events were reported.

#### *Cardiovascular death*

Compared to sham acupressure, acupressure had uncertain effects on cardiovascular death (Analysis 36.4: 1 study, 32 participants), as no events were reported.

#### *Depression*

Compared to sham acupressure, acupressure had uncertain effects on depression (Analysis 36.5 (1 study, 70 participants): BDI score; MD 2.17, 95% CI -2.93 to 7.27; very low certainty evidence).

***Sleep quality***

Compared to sham acupressure, acupressure had uncertain effects on sleep quality (Analysis 36.6 (1 study, 70 participants): PSQI score; MD 1.72, 95% CI -0.40 to 3.84; very low certainty evidence).

No other secondary outcomes were reported.

**Sham acupressure versus standard care**

Two studies (Sabouhi 2013; Tsay 2004a) compared sham acupressure to standard care in people receiving HD during a median follow-up of 0.9 months. The certainty of the evidence was very low.

***Fatigue***

Compared to standard care, sham acupressure may slightly reduce fatigue, but the evidence is very uncertain (Analysis 37.1 (2 studies, 135 participants): PFS score; MD -0.62, 95% CI -1.19, -0.05; $I^2$ = 44%; very low certainty evidence). Moderate heterogeneity was observed between the studies.

***Change in fatigue***

Compared to standard care, sham acupressure may slightly reduce change in fatigue, but the evidence is very uncertain (Analysis 37.2 (1 study, 64 participants): PFS score; MD -0.56, 95% CI -0.83 to -0.29; very low certainty evidence).

***Depression***

Compared to standard care, sham acupressure had uncertain effects on depression (Analysis 37.3 (1 study, 71 participants): BDI score; MD -3.41, 95% CI -8.71 to 1.89; very low certainty evidence).

***Sleep quality***

Compared to standard care, sham acupressure may reduce sleep quality, but the evidence is very uncertain (Analysis 37.4 (1 study, 71 participants): PSQI score; MD -2.22, 95% CI -4.11 to -0.33; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Acupressure versus another type of acupressure**

Tsay 2004b compared acupressure to another type of acupressure (TEAS) in people receiving HD during a follow-up of 1 month. The certainty of the evidence was very low.

***Fatigue***

Compared to TEAS, acupressure had uncertain effects on fatigue (Analysis 38.1 (1 study, 71 participants): PFS score; MD -0.09, 95% CI -0.84 to 0.66; very low certainty evidence).

***Death (any cause)***

Compared to TEAS, acupressure had uncertain effects on death (any cause) (Analysis 38.2: 1 study, 72 participants), as no events were reported.

***Cardiovascular death***

Compared to TEAS, acupressure had uncertain effects on cardiovascular death (Analysis 38.3: 1 study, 72 participants), as no events were reported.

***Depression***

Compared to TEAS, acupressure had uncertain effects on depression (Analysis 38.4 (1 study, 71 participants): BDI score; MD 0.90, 95% CI -2.92 to 4.72; very low certainty evidence).

***Sleep quality***

Compared to TEAS, acupressure had uncertain effects on sleep quality (Analysis 38.5 (1 study, 71 participants): PSQI score; MD 1.48, 95% CI -0.51 to 3.47; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Light therapy versus no intervention**

Schardong 2021 compared light therapy (photo-biomodulation therapy) to no intervention in people receiving HD during a follow-up of 1.8 months. The certainty of the evidence was very low.

***Death (any cause)***

Compared to no intervention, light therapy had uncertain effects on death (any cause) (Analysis 39.1: 1 study, 33 participants), as no events were reported.

***Cardiovascular death***

Compared to no intervention, light therapy had uncertain effects on cardiovascular death (Analysis 39.2: 1 study, 33 participants), as no events were reported.

***Quality of life (overall)***

Compared to no intervention, light therapy had uncertain effects on the overall QoL (Analysis 39.3 (1 study, 28 participants): Euro-Qol 5-dimensions (EQ-5D) health questionnaire; MD 0.05, 95% CI -0.05 to 0.16; very low certainty evidence).

No other primary or secondary outcomes were reported.

**Subgroup analyses**

Subgroup analyses did not provide substantively different results or were not possible due to few data and studies.

**Sensitivity analyses**

Sensitivity analyses did not provide substantively different results or were not possible due to few data and studies.

# DISCUSSION

## Summary of main results

We identified 94 studies (8191 randomised participants) evaluating interventions for fatigue in people with CKD requiring dialysis, including people receiving HD or PD. No studies were carried out in children. Risks of bias in the included studies were often unclear or high, leading to GRADE rated at low or very low certainty evidence.

Exercise, aromatherapy, massage and acupressure may improve fatigue compared to placebo, standard care or no intervention. A wide range of heterogenous interventions and fatigue-related outcomes were reported for exercise, aromatherapy, massage and acupressure, preventing us from pooling and analysing the data.

Due to the paucity of studies, the effects of other pharmacological and other non-pharmacological interventions on fatigue, including

non-physiological neutral amino acids, relaxation with or without music therapy, exercise with nandrolone, nutritional supplementation, CBT, ESAs, frequent HD sections, home BP monitoring, blood flow rate reduction, serotonin reuptake inhibitor, beta-blockers, anabolic steroids, glucose-enriched dialysate, or light therapy, were very uncertain.

The effects of pharmacological and non-pharmacological treatments on death, cardiovascular diseases, vascular access, QoL, depression, anxiety, hypertension or diabetes were sparse. No studies assessed tiredness, exhaustion or asthenia. Adverse events were rarely and inconsistently reported. Meta-analysis was not possible for the majority of the outcomes for these compared treatments due to single studies available for clinical outcomes.

### Overall completeness and applicability of evidence

In this review, we identified 94 studies comparing a broad range of interventions for fatigue in people receiving dialysis. Currently, evidence from existing studies is of low or very low certainty and is therefore not available to inform clinical care or policy. The majority of the included studies were performed in people on HD. No studies were conducted in children.

Most studies compared an intervention for fatigue with a placebo or control, and clinically important outcome data were rarely reported. A description of the interventions has been reported in Appendix 4. The majority of studies had a small sample size with a short duration, had methodological limitations, cross-over or quasi-RCT design, or were primarily designed to evaluate surrogate measures of effect. No outcome data were available for tiredness, exhaustion, or asthenia. Adverse events related to treatment were not systematically reported (see Appendix 5).

Future studies on interventions for treating fatigue in people undergoing HD and PD should evaluate outcomes as prioritised by patients, caregivers and health professionals (SONG-HD; SONG-PD) to better inform clinical practice and decision-making.

### Quality of the evidence

We used the standard risk of bias domains within the Cochrane tool together with GRADE methodology (GRADE 2008) to assess the certainty of study evidence. Since the certainty of evidence was low or very low for all outcomes, future studies might provide different results.

Some studies were at high or unclear risks of bias for most of the risk of bias domains assessment. The majority of studies did not report adequate blinding, attrition or selective reporting, and some received some funding from pharmaceutical companies. Relevant clinical outcomes were rarely available for many of the included studies.

Fatigue has been measured using different tools, and a high heterogeneity in the fatigue-related outcomes definition has been provided by authors, preventing our capability to pool the data. The variability in the reporting methods of some outcomes hamper data synthesis by meta-analysis. The limited number of studies prevented the exploration of other potential sources of heterogeneity in the analyses. Subgroup and sensitivity analysis could not be done to explore heterogeneity owing to insufficient data. Due to the limited number of studies, the assessment of adverse events was not possible. All studies reported SD or SE as an estimate of variance, and some of them provided data in descriptive or figure format only.

### Potential biases in the review process

This review was carried out using standard Cochrane methods. A highly sensitive search of the Cochrane Kidney Transplant specialised register was undertaken in October 2022, without language restriction and including grey literature. Each step was completed independently by at least two authors, including the selection of studies, data management, and risk of bias assessment to minimise the risks of misclassification and adjudication of evidence. Authors were contacted to collect further data as possible. Many studies did not report key outcomes in a format available for meta-analysis.

Potential biases identified in our review included:

1. The limited number of studies was a constraint on our ability to assess for potential reporting bias and selective outcome reporting
2. Fatigue was assessed using a broad range of measures and definitions
3. Poor quality studies could not be excluded due to the small number of included studies
4. Heterogeneity between treatment interventions was precluded due to the small number of data observations
5. The effects of interventions for fatigue on longer-term outcomes were uncertain, and the treatment endpoints were principally surrogate outcomes (e.g. laboratory parameters)
6. A large number of comparisons were identified that prevented pooling and meta-analysis of the data. In addition, the definitions of both the intervention and control groups were quite heterogeneous among the included studies
7. Some outcomes reported zero events, referred to a single study or both
8. Adverse events were rarely and inconsistently reported
9. Formal assessment for publication bias through visualisation of asymmetry in funnel plots could not be performed due to the limited number of studies available

### Agreements and disagreements with other studies or reviews

We believe this is the first large and comprehensive review that included both pharmacological and non-pharmacological interventions for fatigue in people receiving dialysis. However, some studies have examined the efficacy of either pharmacological or non-pharmacological interventions for fatigue in this population, but the number of meta-analyses published is still limited.

Astroth 2013 performed a systematic review of non-pharmaceutical interventions for fatigue in adults receiving HD. The data showed that non-pharmacological interventions (including infrared rays, exercise and acupressure) reduced fatigue in this setting. The main differences with our review included that Astroth 2013 excluded patients undergoing PD, children and non-English papers.

Picariello 2017 carried out a systematic review and meta-analysis to evaluate the efficacy of social-psychological interventions for the management of fatigue in CKD. Sixteen RCTs (1536 participants)

were included. Out of the 16 studies, only six reported social-psychological interventions improved fatigue in this setting, and data were not meta-analysed. However, they included adults with CKD stages 3-5, including people requiring KRT (HD, PD and kidney transplant recipients).

Melo 2020 conducted a systematic review of the effects of acupressure in CKD on QoL, sleep and fatigue. Only three out of nine studies (270 participants) focused on fatigue, showing a positive effect of this intervention on fatigue. However, they evaluated RCTs, including any CKD stages and excluded studies classified with a level of evidence lower than three by the Jadad scores. GRADE assessment was not performed.

Song 2018 conducted a systematic review and meta-analysis on the effects of exercise training compared to routine care in adult patients receiving HD. The treatment was not specifically provided for managing fatigue, but fatigue was reported as an outcome in three included studies (139 participants). Exercise training improved fatigue in HD. The main differences with our review were related to the inclusion and exclusion criteria, analyses were performed using a fixed model, and there was no information regarding the GRADE approach was provided.

Bouya 2018 performed a systematic review to assess the effect of aromatherapy on a broad range of complications of HD, including fatigue. Although the authors included 22 studies, only four addressed fatigue in this setting. Two out of four studies reported that lavender essence aromatherapy reduced fatigue in HD. Compared to our review, Bouya 2018 included both RCTs and observational studies and used the Jadad scale to assess the studies. GRADE assessment was not performed.

Johansen 2012 carried out a systematic review of the impact of ESAs on fatigue in adults receiving dialysis. This review included both RCTs and observational studies. Non-English papers were excluded. Although ESAs showed improvement in fatigue, the main differences with our review were related to the inclusion and exclusion criteria, which prevented our ability to compare their findings with our data.

## AUTHORS' CONCLUSIONS

### Implications for practice

Exercise, aromatherapy, massage and acupressure may improve fatigue compared to placebo, standard care or no intervention. Pharmacological and other non-pharmacological interventions had uncertain effects on fatigue or fatigue-related outcomes in people receiving dialysis. There is no evidence to inform decision-making in children. Evidence is largely lacking in PD. Adverse events were rarely and inconsistently reported.

### Implications for research

Future well-designed and adequately powered RCTs should be conducted to assess the benefits and harms of treatments to increase our confidence in the interventions for fatigue in people receiving HD or PD.

Further research is likely to change the estimated effects of interventions for fatigue and fatigue-related outcomes in people receiving dialysis. Evaluation of cost-effectiveness for interventions for fatigue would assist decision-making by policy-makers and health care providers in this setting.

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* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

**Ahmady 2019**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 14 days<br>• Study duration: December 2016 to August 2017 |
| Participants | Study characteristics<br>• Setting: single centre (Imam Reza Hospital based in Kermanshah)<br>• Country: Iran |

**Ahmady 2019** *(Continued)*

- Inclusion criteria: history of HD for at least 6 months; 18 to 65 years; ability to communicate verbally; not being allergic to the smells of lavender and orange; lack of respiratory diseases such as asthma; having a healthy sense of smell (through patient statements and nasal examination for no obstruction); being a non-candidate for kidney transplantation; not pregnant (for women); having no addiction
- Exclusion criteria: patients who were not interested in continuing the study and being absent for more than 3 consecutive sessions at the time of intervention

Baseline characteristics

- Number (analysed/randomised): intervention group 1 (30/30); intervention group 2 (30/30); control group (30/30)
- Mean age ± SD (years): overall (55.25 ± 11.79)
- Sex (M/F): intervention group 1 (16/14); intervention group 2 (16/14); control group (9/21)
- Dialysis type: HD
- Mean dialysis vintage ± SD (years): overall (4.1 ± 0.4)
- Comorbidities
  - CVD: not reported
  - Diabetes: intervention group 1 (12/18); intervention group 2 (8/22); control group (12/18)
  - Hypertension: not reported
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group 1<br>• Aromatherapy with 5 drops of lavender essential oil<br>Intervention group 2<br>• Aromatherapy with 5 drops of orange essential oil<br>Control group<br>• Placebo: 5 drops of distilling water<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>  ◦ Fatigue: FSS (Appendix 3)<br>• Death |
| Notes | Additional information<br>• Funding: Kermanshah University of Medical Sciences (Grant No. 95571)<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: IRCT201610244736N17<br>• A priori published protocol was reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

**Ahmady 2019** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Random block of numbers. Block randomisation was conducted as follows: the group of aromatherapy with lavender essential oil was given the code “A,” the group of aromatherapy with orange essential oil was given the code “B,” and the group of distilled water was given the code “C.” Then, six blocks of three were formed: ABC, ACB, BAC, BCA, CAB, and CBA. In order to select the groups, block BAC was randomly selected. Thus, on the first day (which was Saturday), 30 subjects were assigned to the group of aromatherapy with orange essential oil. On Sunday, 30 subjects were assigned to lavender essential oil group and finally on Monday, another 30 subjects were assigned to the control group."<br><br>Comment: random numbers are considered at low risk of bias |
| Allocation concealment (selection bias) | Low risk | Quote: "The names of subjects in each group were registered in the coming days. The statistical adviser of the study (second author) was responsible for determining the blocks, and the subjects were allocated into the study groups by the first author." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "There was no possibility of blinding subjects for the type of the assigned group." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. No other outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All participants completed the study. No lost to follow-up were reported |
| Selective reporting (reporting bias) | High risk | Protocol was published. It was reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue data were cumulated for 2 RCTs, all time points were not reported. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding did not influence the data analysis and conflicts of interest were not reported. No other source of bias were apparent |

**Akizawa 2002**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 4 weeks |

**Akizawa 2002** *(Continued)*

- Study duration: not reported

| | |
|---|---|
| Participants | Study characteristics<br>• Setting: not reported<br>• Country: Japan<br>• Inclusion criteria: undergoing maintenance HD 3 times/week (4 hours/dialysis session) and complicated orthostatic hypotension defined by SBP drop of ≥ 15 mm Hg after standing, as well as subjective symptoms of fatigability, malaise/weakness, dizziness and light-headed feeling<br>• Exclusion criteria: patients with narrow-angle glaucoma; severe hypertension; liver disorder; haemorrhagic complications; heart disease or peripheral vascular disorders<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group 1 (48/51); intervention group 2 (46/49); control group (47/49)<br>• Mean age ± SD (years): intervention group 1 (61.5 ± 11.0); intervention group 2 (63.5 ± 12.4); control group (61.1 ± 11.5)<br>• Sex (M/F): overall (71/78); intervention group 1 (30/21); intervention group 2 (22/27); control group (19/30)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): intervention group 1 (5.6 ± 20.2); intervention group 2 (6.1 ± 19.8); control group (6.9 ± 20.0)<br>• Comorbidities<br>  ○ CVD: not reported<br>  ○ Diabetes: intervention group 1 (27/51); intervention group 2 (19/49); control group (19/49)<br>  ○ Hypertension: not reported<br>  ○ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group 1<br>• L-DOPS (oral): 400 mg<br>Intervention group 2<br>• L-DOPS (oral): 200 mg<br>Control group<br>• Placebo (oral)<br>Co-interventions<br>• Concomitant use of antihypertensive or vasopressor drugs was permitted if they had been used prior to the initiation of the trial, but without a change of dose<br>• During HD, a minimum amount of fluid replacement was provided if patients developed hypertensive symptoms, and postural changes, such as lifting the lower extremities, were allowed as needed<br>• During the study period, HD conditions and dry weight were kept constant |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Changes in SBP and DBP: measured before and after standing (assessed during 4 times points while changes in BP after standing were assessed after 2 and 4 weeks) |

**Akizawa 2002** *(Continued)*

- Symptoms related to orthostatic hypotension questionnaire: fatigability, malaise/weakness, physical disturbing on standing up, dizziness on standing up, bad feeling, sleep disorder (Akizawa 2002)
- Light-headed feeling: recorded before and after HD
- Coldness of limbs: recorded before and after HD
- Adverse events: assessed until week 4
- Laboratory tests: including blood cell count, blood chemistry, chest X-ray and ECG (assessed before and after the trial)
- Pulse rate: recorded before and after HD

| | |
|---|---|
| Notes | Additional information<br>• Funding: Sumitomo Pharmaceuticals Co., Ltd provided L-DOPA<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not applicable<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "Double-blind design."<br><br>Comment: Although the author reported that the study used a double-blind design, information about blinding of participants and investigators was not clearly stated |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "Eight subjective symptoms related to orthostatic hypotension (fatigability, malaise/weakness, physical disturbing on standing up, dizziness on standing up, bad feeling, sleep disorder) were monitored through doctor's questions, based on notebooks kept by the patients. The severity of each symptom was separately assessed using a 4-point rating scale, i.e. severe (daily activities were greatly disturbed by the symptom), moderate (daily activities were disturbed by symptoms), mild (patients were aware of the symptoms, but daily activities were not disturbed), and asymptomatic (there was no symptom at all and patients were not bothered by any symptoms)."<br><br>Comment: Fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "Of the 149 patients, 5 were excluded from efficacy assessment due to missing blood pressure data, and 3 were also excluded because L-DOPS therapy was discontinued within 2 weeks of the trial. A total of 141 patients (400 mg group 48 patients, 200 mg group 46 patients, and placebo group 47 patients) were thus subjected to efficacy assessment."<br><br>Comment: 48/51 participants in intervention group 1 (400 mg L-DOPS), 46/49 participants in intervention group 2 (200 mg L-DOPS) and 47/49 participants in |

**Akizawa 2002** *(Continued)*

| | | |
|---|---|---|
| | | the control group (placebo) completed the study (> 5% lost to follow-up, whit differences between groups). In addition, some analyses were reported on a lower number of participants |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan was not reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was reported in a format that was not extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | High risk | There was no evidence of different baseline characteristics or different non-randomised co-interventions between groups. Funding (pharmaceutical company) could influence the data analysis, and conflicts of interest were not reported. |

**Amini 2016**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 8 weeks<br>• Study duration: 2016 (months not reported) |
| Participants | Study characteristics<br>• Setting: single-centre<br>• Country: Iran<br>• Inclusion criteria: signed the informed consent form to participate in the study; had a history of undergoing regular HD for at least 12 months; lack of suffering from severe neuromuscular diseases, depression, severe and unmanaged underlying diseases; lack of taking antidepressants and anti-anxiety and hypnotic medicines; lack of participating in exercise or non-pharmacological programs within the past 6 months; being able to perform interventional exercises<br>• Exclusion criteria: severe neuromuscular diseases, depression, severe and unmanaged underlying diseases; taking antidepressants and anti-anxiety and hypnotic medicines; participating in exercise or non-pharmacological programs within the past 6 months<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group 1 (not reported/33); intervention group 2 (not reported/32); control group (not reported/35)<br>• Mean age ± SD (years): intervention group 1 (56.12, SD not reported); intervention group 2 (54.31, SD not reported); control group (55.22, SD not reported)<br>• Sex (M/F): overall (64/36); intervention group 1 (22/11); intervention group 2 (21/11); control group (21/14)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): not reported<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported |

**Amini 2016** *(Continued)*

- Depression (clinician diagnosis): intervention group 1 (33/33); intervention group 2 (32/32); control group (35/35)

| | |
|---|---|
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group 1<br>• Progressive muscle relaxation: daily for 60 days<br>Intervention group 2<br>• Aerobic exercise: daily for 60 days<br>Control group<br>• No intervention<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Anxiety<br>  ○ General anxiety, state anxiety, trait anxiety: Spielberger (before the trial and after 8 weeks)<br>  ○ BAI: before the trial and after 8 weeks<br>• Fatigue<br>  ○ Piper fatigue scale: before the trial and after 8 weeks<br>  ○ Rhoten fatigue scale: before the trial and after 8 weeks<br>• Sleep quality: before the trial and after 8 weeks |
| Notes | Additional information<br>• Funding: not reported<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: ISSN 09751556<br>• A priori published protocol: the study protocol was approved by the Ethics Committee of the Shahrekord University of Medical Sciences<br>• Authors contacted but they did not reply |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "In this double-blind clinical trial."<br>Comment: Although author reported that the study used a double-blind design, information about blinding of participants and investigators were not clearly stated |

**Amini 2016** *(Continued)*

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|---|---|---|
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Quote: "Questionnaires of anxiety, sleep quality, and fatigue were completed by participants before and after the interventions."<br><br>Comment: Fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. Other subjective outcomes were assessed |
| Incomplete outcome data (attrition bias) All outcomes | High risk | The number of patients who completed the study was not clearly stated. It was unclear if there was evidence that the results were not biased by missing outcome data |
| Selective reporting (reporting bias) | High risk | Protocol was approved by the Ethics Committee of the Shahrekord University of Medical Sciences (not clear if it was published). Fatigue was reported in accordance with a pre-specified analysis plan, using multiple eligible outcome measurements (scales, time points). All outcomes that should be reported (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding and conflicts of interest were not reported |

**ASCEND 2016**

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|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 12 weeks<br>• Study duration: participants were enrolled between March 2015 and August 2017 and were followed through to November 2017 |
| Participants | Study characteristics<br>• Country: USA<br>• Setting: multicentre (41 centres in 3 sites: the University of Washington in Seattle, the University of Texas Southwestern in Dallas, and the University of New Mexico in Albuquerque)<br>• Inclusion criteria: ≥ 21 years; undergoing thrice-weekly maintenance HD for ≥ 3 months; able to speak and understand English; able to sign informed consent; BDI II score ≥ 15; current major depressive disorder or dysthymia on the MINI<br>• Exclusion criteria: unwilling or unable to participate; active suicidal intent; cognitive behavioural therapy within 3 months prior for depression or ongoing intensive psychotherapy (once weekly) for depression; current drug therapy with SSRI or SNRI at doses higher than listed in Appendix A, evidence of cognitive impairment on Mini-Cog, present or past psychosis or bipolar disorder I or II on the MINI, alcohol or substance abuse diagnosed on the MINI or history of such abuse in the past 3 months; life expectancy < 3 months, in the judgment of the site principal investigator; anticipated to receive living-related donor kidney transplantation within 3 months; pregnancy, lactation, or women of childbearing age not willing to use adequate birth control; clinical and/or laboratory evidence of chronic liver disease; history of significant active bleeding in the past 3 months, such as hospitalisation for GI bleeding, ongoing use of class I anti-arrhythmic medications (e.g. propafenone, flecainide), pimozide, |

**ASCEND 2016** *(Continued)*

monoamine oxidase inhibitors, reserpine, guanethidine, cimetidine, tricyclic antidepressants, triptans, tramadol, linezolid, tryptophan, and St John's wort; known hypersensitivity to sertraline

Baseline characteristics

- Number (analysed/randomised): intervention group 1 (60/60); intervention group 2 (60/60)
- Mean age ± SD (years): intervention group 1 (50 ± 13); intervention group 2 (53 ± 12)
- Sex (M/F): intervention group 1 (33/27); intervention group 2 (35/25)
- Dialysis type: HD
- Mean dialysis vintage ± SD (years): intervention group 1 (2.5 ± 4.4); intervention group 2 (2.7 ± 3.5)
- Comorbidities
  - CVD: not reported
  - Diabetes: intervention group 1 (35/60); intervention group 2 (38/60)
  - Hypertension: intervention group 1 (55/60); intervention group 2 (54/60)
  - Depression (clinician diagnosis): intervention group 1 (60/60); intervention group 2 (60/60)

Interventions

Intervention classification

- Non-pharmacological and pharmacological intervention
- Indication: study targeting fatigue

Intervention group 1

- CBT: 60-minute individual sessions (8 weekly sessions; then 2 sessions every other week)

Intervention group 2

- Flexible-dose sertraline: initial dose of 25 mg/day; dose escalation occurs every 2 weeks to a maximum of 200 mg/day, and the dose is held constant over the last 6 weeks

Co-interventions

- Not reported

Outcomes

Outcomes reported

- Depressive symptoms
  - BDI (Appendix 3): assessed at pre-screening, weeks 0, 6 and 12
  - Global Improvement Scale: assessed at weeks 0, 6 and 12
- Change from baseline in the depression symptoms
  - QIDS-C16-blind assessor (a cut-off ≥ 11 is used to identify depression): assessed at baseline, 6 and 12 weeks
  - QIDS-SR16-self-report: assessed at weeks 0, 2, 4, 6, 9 and 12)
- Major depressive disorder or dysthymia
  - MINI
- Anxiety
  - GAD-7 scale: assessed at weeks 0, 6 and 12
- Effect of disease on well-being
  - Sheehan Disability Scale
- Fatigue
  - SF-36
    - Energy: assessed at weeks 0, 6 and 12
    - Vitality: assessed at weeks 0, 6 and 12
- HRQoL
  - One-item Global Quality of Life Scale: assessed at weeks 0, 6 and 12
  - Satisfaction with Life Scale: assessed at weeks 0, 6 and 12
- Perceived social support
  - Multi-dimensional Scale of Perceived Social Support: assessed at weeks 0, 6 and 12
- Sleep

**ASCEND 2016** *(Continued)*

- PSQI: assessed at weeks 0, 6 and 12
- Physical activity
  - Single-item activity measure: assessed at weeks 0, 6 and 12
- Dialysis non-adherence: % treatments skipped or shortened by ≥ 10 min over 12-week intervention; assessed at weeks 0 and 12
- Dietary non-adherence: inter-dialytic weight gain as % of post-dialysis weight over the preceding 6 weeks: serum phosphorus during 3rd month
- Proportion of participants in each group willing to accept treatment for depression
  - Patient-reported outcomes and treatment adherence: assessed at baseline, 6 and 12 weeks
- Safety and tolerability measure
  - FIBSER scale: assessed at weeks 2, 4, 6, 9, and 12
- Adverse events
- Serious adverse events
- Blood test (Hb, potassium, phosphorus, albumin, PTH, Kt/V): assessed at 12 weeks

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| Notes | Additional information<br>• Funding: grant from the Patient-Centered Outcomes Research Institute (PCORI) (CER-1310-07253) and Dialysis Clinics, Inc. Support was also provided by the University of Texas Southwestern Medical Center O'Brien Kidney Research Core Center (NIDDK, P30DK079328), UT-STAR, NIH/NCATS Grant Number UL1RR024982, and the Veterans Affairs Puget Sound Health Care System<br>• Conflicts of interest/disclosures: "Ms. Diaz-Linhart reports personal fees from the University of Washington during the conduct of the study. Dr.Greene reports grants from the National Institutes of Health during the conduct of the study and personal fees from JanssenPharmaceuticals, Durect Corporation, and Pfizer and grants from AstraZeneca outside the submitted work. Dr.Trivedi reports personal fees from AcademyHealth, Acadia Pharmaceuticals, Alkermes, Akili Interactive, Allergan, AxsomeTherapeutics, Boehringer Ingelheim, Healthcare Global Village, Janssen Pharmaceuticals, Jazz Pharmaceuticals, LundbeckResearch USA, Medscape, Navitor, Otsuka America Pharmaceutical, Oxford Pharmagenesis, and Sage Therapeutics, and grants from the National Institute of Mental Health, National Institute on Drug Abuse, Cancer Prevention ResearchInstitute of Texas, and Janssen Pharmaceuticals, outside the submitted work. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M18-2229."<br>• Trial registration identification number: NCT02358343<br>• A priori published protocol was published |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomizations were performed through a Web portal by using computer-generated permuted blocks of various sizes."<br>Comment: Computer-generated is considered as low risk of bias |
| Allocation concealment (selection bias) | Low risk | Quote: "Randomizations were performed through a Web portal by using computer-generated permuted blocks of various sizes."<br>Comment: Web portal is considered as low risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "Open-label."<br>Comment: An open-label study is considered at high risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "An independent group charged with monitoring the safety of patients in the ASCEND trial, and the scientific integrity of the trial (unblinded)." |

**ASCEND 2016** *(Continued)*

| | | |
|---|---|---|
| | | Quote: "Randomized participants undergo blinded serial assessment of depressive symptoms every 6 weeks using the clinician-rated 16-item Quick Inventory of Depression Symptomatology (QIDS-C16) administered by research personnel blinded to intervention arm, via a Computer Assisted Telephone Interview (CATI)."<br><br>Comment: Fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used. It was not stated whether outcomes were assessed without knowledge of treatment allocation (it was stated that a blinded interviewer assessed the QIDS-C16, but no information was reported for the assessment of the fatigue questionnaire), and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. Other subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Quote from Merhotra 2019: "Of the 636 patients with a BDI-II score of 15 or above, 310 (49%) consented to screening and 184 were randomly assigned to the engagement (n = 92) or control (n = 92) group. Of these participants, 120 were randomly assigned to the CBT (n = 60) or sertraline (n = 60) group, 20 who declined treatment within or outside the study enrolled in the observation group, and 44 withdrew from the study."<br><br>Comment: Although some participants withdrew, all were included in the analysis |
| Selective reporting (reporting bias) | Low risk | Information about the protocol and the statistical analysis plan was reported. Multiple eligible outcome measurements (scales and time points) were assessed as pre-specified in the study protocol. Fatigue at the end of treatment was reported in a format that was not extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were reported |
| Other bias | High risk | Quote: "The funding organizations had no input in the analysis or interpretation of the data, the drafting of the manuscript, or the decision to submit the manuscript for publication."<br><br>Comment: Similar baseline characteristics between groups were reported. Funding was unlikely to influence the data analysis and reporting. However, conflicts of interest were reported |

**ASSertID 2015**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 6 months<br>• Study duration: not reported |
| Participants | Study characteristics<br>• Setting: multicentre (5 UK dialysis centres: the Lister Hospital in Stevenage, Hertfordshire, Southend Hospital in Essex, the Royal Free Hospital in London, and the Queen Elizabeth Hospital in Birmingham) |

**ASSertID 2015** *(Continued)*

- Country: UK
- Inclusion criteria: aged 18 or over; BDI at least 16 and MADRS at least 18 (mild to moderate depression); receiving HD treatment for a minimum of 3 months; patients who speak and read English
- Exclusion criteria: treatment for anxiety or depression during the previous 3 months with either antidepressants or formal psychological therapy; planned living donor transplant within the period of the trial; pregnancy or childbearing potential without adequate birth control; contraindicated coexistent drug therapy (sertraline SmPC), including triptans, antipsychotics, dopamine antagonists, tramadol, linezolid, warfarin; hepatic impairment - alanine transaminase more than twice the upper limit of normal and/or INR greater than 1.3; hepatitis; HIV/AIDS; Creutzfeldt-Jakob disease; diagnosis of a severe major depressive disorder and those judged to be at moderate to severe risk of self-harm who will be referred immediately for further psychiatric evaluation; other psychiatric conditions including substance dependency, psychosis, personality disorder, dementia or panic disorder, with the exception of other anxiety disorders

Baseline characteristics

- Number (analysed/randomised): intervention group (8/15); control group (13/15)
- Mean age ± SD (years): intervention group (61.7 ± 13.2); control group (56.4 ± 14.4)
- Sex (M/F): overall (23/7); intervention group (11/4); control group (12/3)
- Dialysis type: HD
- Mean dialysis vintage ± SD (years): not reported
- Comorbidities
  - CVD: not reported
  - Diabetes: intervention group (6/15); control group (7/15)
  - Hypertension: not reported
  - Depression (clinician diagnosis): intervention group (5/15); control group (5/15)

Interventions

Intervention classification

- Pharmacological intervention
- Indication: study targeting fatigue

Intervention group

- Sertraline hydrochloride: initial dose 50 mg with titration to 100 mg

Control group

- Placebo: microcrystalline cellulose and magnesium stearate

Co-interventions

- Not reported

Outcomes

Outcomes reported

- Fatigue outcome measures used: validation data available
- Fatigue
  - MFI-20 assessed at baseline and at 6 months (Appendix 3)
  - General fatigue
  - Mental fatigue
  - Physical fatigue
  - Reduced motivation
  - Reduced activity
- Depression symptoms
  - BDI-II: assessed at baseline and at 6 months
  - PHQ-9: assessed every month
  - Change in MADRS: assessed at baseline and at 2, 4 and 6 months
  - Change in BDI-II: assessed at baseline and at 6 months

**ASSertID 2015** *(Continued)*

- Clinical Global Impression
  - Severity scale: assessed at baseline and at 2, 4 and 6 months
  - Improvement scale: assessed at baseline and at 2, 4 and 6 months
- HRQoL
  - KDQoL: assessed at baseline and at 2, 4 and 6 months
  - EQ-5D: assessed at baseline and at 2, 4 and 6 months
- Adverse events: assessed every month
- Serious adverse events: assessed every month
- Biomedical and biochemical parameters: assessed every month
- Dialysis parameters: assessed every month
- Hospitalisation: assessed until end of treatment
- Withdrawal: assessed until end of treatment

| | |
|---|---|
| Notes | Additional information<br>• Funding: National Institute for Health Research programme, Research for Patient Benefit programme (PB-PG-0110-21073)<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: ISRCTN06146268<br>• A priori published protocol published FRiedli 2015 "A study of sertraline in dialysis (ASSertID): a protocol for a pilot randomised controlled trial of drug treatment for depression in patients undergoing haemodialysis" |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote from Friedli 2015 (protocol): "Randomisation will take place in blocks using pre-prepared codes for each centre. These will be incorporated into a protected web based randomisation programme prepared by Norwich CTU."<br><br>Comment: Sequence generation methods seemed to use a computer. No data were available to assess the possible imbalance between groups |
| Allocation concealment (selection bias) | Low risk | Quote from Friedli 2015 (protocol): "Randomisation will take place in blocks using pre-prepared codes for each centre. These will be incorporated into a protected web based randomisation programme prepared by Norwich CTU. Only the research psychiatrist will have authorised access to the online randomisation programme. Following randomisation the relevant pharmacy will be informed of the allocation (treatment A or B) by automatically generated email. The pharmacist will be blind to the allocation. The CTU will hold the patient-specific allocation data on a secure server. The CI and PI at each centre will have access to this data file only via a special log-in should the need arise to un-blind. No user identifiable data will stored in the randomisation database. Web traffic will be encrypted using standard secure sockets layer technology."<br><br>Comment: A web-based system is considered as low risk of bias. No data were available to assess the possible imbalance between groups |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote from Friedli 2017: "The patients, dispensing pharmacies, study psychiatrist, research nurses, all clinicians, trial manager, and study statistician were blind to the allocation of the study medication."<br><br>Comment: A double-blind study is considered as low risk of bias |
| Blinding of outcome assessment (detection bias) | High risk | Quote from Chilcot 2017: "Fatigue was assessed using the MFI-20." |

**ASSertID 2015** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | Comment: fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "Twenty-one (70%) patients completed the trial: eight (53%) in the sertraline group and 13 (87%) in the placebo group (P=0.05). In the sertraline group, there were six dropouts within the first 2 months. One patient died of cardiac arrest having taken one tablet. Three patients withdrew because of adverse events (one after 3 days with nausea, another after 12 days with headaches and dizziness, and the third due to insomnia after 23 days). The fifth patient withdrew because of concern about side effects, having taken no study medication. The sixth patient was admitted for a prolonged hospital stay with leg ulcers shortly after randomisation and subsequently withdrawn without having taken any study medication. At 3 months, a seventh patient withdrew because of sweating and palpitations. In the placebo group, one patient withdrew after the baseline interview because of concern about taking additional medication, and a second decided against continuing after 3 months. The number of dropouts due to adverse or severe adverse events was greater in the sertraline group."<br><br>Comment: overall, 21/30 participants completed the study (>5% lost to follow-up, differences between groups). Some reasons for discontinuations could be related to the treatment assigned |
| Selective reporting (reporting bias) | High risk | Protocol was published. Trial registration number reported that fatigue should be assessed using MFI-20 and SF-36 energy/fatigue sub scale, but data were reported only using MFI-20. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was reported in a format that was not extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | Similar baseline characteristics between groups were reported. Funding was unlikely to influence the data analysis and reporting and authors had no conflicts of interest |

**BA16285 2007**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 12 months in total (19 weeks core treatment period)<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Setting: multicentre (14 study centres)<br>• Country: USA |

**BA16285 2007** *(Continued)*

- Inclusion criteria: aged at least 18 years with CKD and CKD-related anaemia and receiving treatment with IV epoetin alfa; HD treatment >3 times/week for > 3 months before screening and receiving IV epoetin alfa maintenance therapy for > 3 months before screening; baseline Hb concentration of 10 to 13 g/dL, based on 3 measurements taken at screening and a difference of not more than 1.0 g/dL between the first and last measurements; adequate iron status (serum ferritin > 100 ng/mL and TSAT > 20% or hypochromic red cells < 10%
- Exclusion criteria: nonrenal causes of anaemia; presence of >1 condition known to cause an inadequate response to ESAs (including, but not limited to, acute infection or inflammation, bleeding requiring treatment within the 3 months before screening, severe hyperparathyroidism (iPTH, > 800 pg/mL), serum aluminium > 50 µg/L, haemoglobinopathy, haemolysis, vitamin B12 or folic acid deficiency); presence of severe disease (MI, severe or unstable coronary artery disease, stroke, and/or severe hepatic disease) within 3 months before study entry; blood transfusion within 3 months before study entry; thrombocyte count >500 × $10^3$ cells/µL; hypertension necessitating interruption of epoetin treatment in the 6 months before screening; and/or epilepsy diagnosed in the 6 months before screening; patients who did not comply with dialysis therapy; patients who had major elective surgery scheduled during the study or who had a life expectancy of < 6 months; women who were pregnant, possibly pregnant, or breastfeeding; patients with a known hypersensitivity to epoetin or polyethylene glycol; women of childbearing age were required to use an effective method of contraception throughout the study; patients with poorly controlled hypertension were not allowed to enter the extension period

Baseline characteristics

- Number (analysed/randomised): overall (79/91 - however, only 53/91 participants completed the extension study); intervention group 1 (not reported/46); intervention group 2 (not reported/45) - however, all participants were included in the ITT analyses
- Mean age ± SD (years): overall (58, SD not reported)
- Sex (M/F): intervention group 1 (32/14); treatment group 2 (28/17)
- Dialysis type: HD
- Mean dialysis vintage ± SD (years): not reported
- Comorbidities
  - CVD: not reported
  - Diabetes: not reported
  - Hypertension: not reported
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study reporting fatigue<br><br>Intervention group 1<br>• CERA: 0.25, 0.4 or 0.6 µg/150 IU once/week administration schedules<br><br>Intervention group 2<br>• CERA: 0.25, 0.4 or 0.6 µg/150 IU once every two weeks administration schedules<br><br>Co-interventions<br>• Patients received IV iron supplementation according to normal centre practice throughout the run-in, core, and extension treatment periods to maintain adequate iron status (TSAT at least 20% and serum ferritin at least 100 ng/mL) |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available (fatigue was reported as an adverse event)<br>• Adverse events: assessed until end of treatment<br>• Serious adverse events: assessed until end of treatment |

**BA16285 2007** *(Continued)*

- Change in Hb: assessed after 6 weeks until 12 months
- HCT concentration: assessed until 12 months every 4 weeks
- Laboratory assessments of iron parameters and blood chemistry (including CRP): assessed at -1, 6, 12, and 19 weeks of the core treatment period and at weeks 31, 43, and 55 of the extension period
- Anti-CERA antibodies: assessed at week -1, week4 once/week only, week 6 twice/week of the core treatment period, and week 43 of the extension period
- Vital signs (BP, heart rate) and weight: assessed every other week during the core treatment period and every 4 weeks during the extension period until 12 months
- iPTH, haptoglobin, vitamin B12, and folic acid: assessed at screening and week 43 of the extension period
- Adequacy of dialysis was assessed by calculating URR: assessed at 12 months
- Death: assessed until end of treatment
- MI: assessed until end of treatment

Notes

Additional information

- Funding: not reported
- Conflicts of interest/disclosures: Dr. Besarab serves as a consultant for Amgen Inc., Thousand Oaks, California; E Hoffmann-La Roche; and the major parenteral iron companies--American Regent, Inc., Shirley, New York; and Watson Pharmaceuticals, Inc., Corona, California--and has received honoraria from these companies for presentations at major nephrology meetings and for presentations relating to anaemia management and the pharmacokinetic/ pharmacodynamic aspects of erythropoiesis. Dr. Salifu has received research grants from Advanced Magnetics, Inc., Cambridge, Massachusetts; E Hoffmann- La Roche; and Novartis Pharmaceuticals Corporation, East Hanover, New Jersey. Dr. Lunde has conducted clinical research on behalf of Abbott Laboratories Inc., Abbott Park, Illinois; E Hoffmann- La Roche; Bristol-Myers Squibb Company, New York, New York; Dynavax Technologies Corp., Berkeley, California; Eli Lilly and Company, Indianapolis, Indiana; FibroGen, Inc., South San Francisco, California; Genzyme Corp., Cambridge, Massachusetts; GlaxoSmithKline, Research Triangle Park, North Carolina; Iomai Corp., Gaithersburg, Maryland; Merck & Co., Inc., Rahway, New Jersey; NICOX-PRA Sophia Antipolis Cedex, France;Novartis; Omnicare, Inc., Covington, Kentucky; Pfizer Laboratories, Groton, Connecticut; PharmaSeek, LLC, Madison, Wisconsin; PLIVA d.d., Zagreb, Croatia; Shire Pharmaceuticals, Wayne, Pennsylvania; The Sanofi-Aventis Group, Bridgewater, New Jersey; and Wyeth, Madison, New Jersey. Dr. Bansal has acted as a speaker/consultant for Merck, Novartis, and Pfizer; and has received research grants from Amgen, E Hoffmann-La Roche, Merck, and Pfizer. Dr. Fishbane has received research grants from Amgen, E Hoffmann-La Roche, and Watson; honoraria from Affymax, Inc., Palo Alto, California; Amgen; F. Hoffmann-La Roche; and Watson; consultancies with Amgen, E Hoffmann-La Roche, and Watson; and speakers' bureau or advisory board positions with Amgen, E Hoffmann-La Roche, Watson, and Wyeth
- Trial registration identification number: not reported
- A priori published protocol: The protocol was approved by the local ethics committees of the institutions taking part

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "This randomised, open-label, dose-finding study was conducted at 14 study centres across the United States."<br><br>Comment: Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias) | High risk | Quote: "This randomised, open-label, dose-finding study was conducted at 14 study centres across the United States." |

**BA16285 2007** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | Comment: An open-label study is considered as a high risk of bias. Participants experienced side effects that participants and/or investigators could know to be specific for one of the interventions |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "Adverse events (including fatigue) were recorded in the patients' case-report forms by the investigators throughout the study."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, fatigue was assessed as an adverse events and it was not stated whether it was assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant/investigators beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Quote: "A total of 91 patients entered the core period (mean age, 58 years; 66% male). Fifty-three patients continued into the extension period; 22 patients withdrew during this period (6 because of adverse e events, and 16 for other reasons). [...] Ten patients were withdrawn from the core treatment period. Four of these patients withdrew due to adverse events and 6, for other reasons (treatment refusal (2) and insufficient therapeutic response, kidney transplant, inadvertent concomitant administration of epoetin alfa, and anaemia not related to CRD (1 patient each)). All of these patients were included in the intention-to-treat (ITT) analysis and were also included in the per protocol (PP) analysis if they met the criteria for the latter. Twelve patients were separately excluded from the PP analysis, for a total PP population of 79 patients (28, 24, and 27 patients in groups A, B, and C, respectively). Fifty-three patients were entered into the extension phase of the study, 27 in the QW group and 26 in the Q2W group. Six patients withdrew because of adverse events, and 16, for other reasons (kidney transplant (4), site closure or transfer (4), treatment refusal (4), insufficient therapeutic response (2), elevated parathyroid hormone concentration (1), and positive pregnancy test (1))."<br><br>Comment: Although the authors stated that the analysis were performed according to ITT and PP, Figure 2 showed that not all participants completed the study. Reasons for discontinuations were reported |
| Selective reporting (reporting bias) | High risk | Protocol was approved by the local ethics committees of the institutions taking part into the study (not clear if it was published). Statistical analysis plan was not available. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was reported in a format that was not extractable per group. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | High risk | Baseline characteristics between groups were not reported. Funding was not reported but authors had conflicts of interest |

**Babamohammadi 2006**

***Study characteristics***

| | |
|---|---|
| Methods | Study design<br><br>• Parallel RCT<br><br>Study dates<br><br>• Duration of follow-up: 1 month |

**Babamohammadi 2006** *(Continued)*

- Time frame: not reported

| | |
|---|---|
| Participants | Study characteristics<br>• Setting: not reported<br>• Country: Iran<br>• Inclusion criteria: patients treated with HD from 2 to 8 years; patients had reading skill<br>• Exclusion criteria: patients afflicted by mental disease<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (not reported/19); control group (not reported/18)<br>• Mean age ± SD (years): intervention group (56.37 ± 15.38); control group (57.83 ± 16.64)<br>• Sex (M/F): intervention group (12/7); control group (11/7)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): intervention group (2.3 ± 2.0); control group (1.6 ± 2.1)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Home-care educational program<br>Control group<br>• No intervention<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Vital signs: SBP and DBP, weight, temperature and pulse<br>  ◦ Health assessment forms: assessed before and after the treatment<br>• Clinical signs: severity of nausea, vomiting, headache, bone pain, weakness and fatigue, itching and general condition<br>  ◦ Health assessment forms: assessed before and after the treatment<br>• Laboratory signs (BUN, creatinine, sodium, potassium, phosphorous and HCT): assessed before and after the treatment |
| Notes | Additional information<br>• Funding: not reported<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |
| ***Risk of bias*** | |

**Babamohammadi 2006** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "37 patients afflicted by chronic renal insufficiency were chosen and put into two categories randomly,"<br><br>Comment: Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "Demographic data questionnaire and health assessment form and rating scale (designed by researchers) were used to collect the data."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | It was not clear if outcome data were provided for all patients. it It was unclear if there was evidence that the results were not biased by missing outcome data |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan was not reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was not reported and authors had no conflicts of interest |

**Bagheri-Nesami 2016**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 4 weeks<br>• Time frame: not reported |

**Bagheri-Nesami 2016** *(Continued)*

| | |
|---|---|
| Participants | Study characteristics<br>• Setting: multicentre (2 hospitals affiliated with the Mazandaran University of Medical Sciences, Sari)<br>• Country: Iran<br>• Inclusion criteria: be willing to participate in the study; be treated with dialysis three times a week; be undergoing dialysis for at least six months; ≥ 18 years old; be conscious; have the ability to verbally communicate; have an uncompromised sense of smell<br>• Exclusion criteria: patients with a history of allergies and respiratory diseases; kidney transplant candidates; pregnant women; drug addicts<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (29/30); control group (30/30)<br>• Mean age ± SD (years): intervention group (62.31 ± 14.46); control group (59.33 ± 12.80)<br>• Sex (M/F): intervention group (17/12); control group (21/9)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): intervention group (3.54 ± 3.00); control group (3.49 ± 2.31)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: intervention group (3/29); control group (4/30)<br>  ◦ Hypertension: intervention group (8/29); control group (10/30)<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Inhalation of lavender essence (5%) 3 times/week<br>Control group<br>• Routine care<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ◦ FSS (Appendix 3)<br>  ■ Physical fatigue<br>  ■ Mental fatigue<br>  ■ Effect of fatigue on a person's social life |
| Notes | Additional information<br>• Funding: not reported<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: IRCT201407077494N9<br>• A priori published protocol was reported |
| ***Risk of bias*** | |

**Bagheri-Nesami 2016** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "The sample was randomly allocated in two groups using the Excel RANDBETWEEN function."<br><br>Comment: Sequence generation was performed using Excel RANDBETWEEN. No imbalance between intervention groups was apparent |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "Fatigue was measured using the Fatigue Severity Scale in both groups for a total of three times (before the intervention, and after the last intervention in the second and fourth weeks) by only one researcher who was blind to the treatment allocation."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was stated that the interviewer was blinded to the intervention. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Quote: "Only one patient from the experimental group was excluded because of an infection, resulting in 29 patients in the experimental group and 30 patients in the routine care group."<br><br>Comment: 29/30 participants in the intervention group and 30/30 participants in the control group completed the study (<5% lost to follow-up). Reasons for discontinuations seemed to be not related to the treatment allocation |
| Selective reporting (reporting bias) | High risk | Protocol was provided. Fatigue was reported in accordance with a pre-specified analysis plan, using multiple eligible outcome measurements (scales, time points). Fatigue at the end of treatment was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was not reported and authors had no conflicts of interest |

**Balouchi 2016**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Cross-over RCT<br>Study dates<br>• Duration of follow-up: 2 weeks (first phase) |

**Balouchi 2016** *(Continued)*

- Time frame: February 2015 to April 2016

| | |
|---|---|
| Participants | Study characteristics<br>• Setting: single centre (centre of Imam Khomeini Hospital in Zabol)<br>• Country: Iran<br>• Inclusion criteria: patients undergoing HD 3 times/week; having a history of HD treatments > 6 months; informed consent for the study; lack of acute stressful event in the past 6 months (death of loved one sand having an accident); lack of history of allergy to aromas; lack of proven problem in sense of smell (healthy olfactory sense that was evaluated by a physician); AKI<br>• Exclusion criteria: unwillingness to participate in the trial; kidney transplantation; hospitalisation in another ward except HD ward for other reasons (MI, CVC, dyspnoea)<br><br>Baseline characteristics<br>• Number (analysed/randomised): intervention group 1 (not reported/15); intervention group 2 (not reported/15)<br>• Mean age ± SD (years): overall (47 ± 14)<br>• Sex (M/F): overall (20/10)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): overall (4 ± 2)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br><br>Intervention group 1<br>• Inhalation of lavender extract (essential oil) on even and odd days of the week<br><br>Intervention group 2<br>• Inhalation of sweet orange extract (essential oil) on even and odd days of the week<br><br>Co-interventions<br>• Patients in both groups received routine care as well |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ◦ MFI-20: assessed at the beginning of the study, at the beginning of the second week and at the end of the second week (Appendix 3)<br>  ■ General fatigue<br>  ■ Physical fatigue<br>  ■ Mental fatigue<br>  ■ Decreased activity<br>  ■ Decreased motivation |
| Notes | Additional information<br>• Funding: this paper was obtained from student MSc thesis (number: Zbmu.1.Rec.1394.132), that approved in Zabol University of medical science |

**Balouchi 2016** *(Continued)*

- Conflicts of interest/disclosures: not reported
- Trial registration identification number: not reported
- A priori published protocol: not reported

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "Data were collected using a demographic questionnaire and the Multi-dimensional Fatigue Inventory (MFI-20)."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | The number of patients who completed the study was not clearly stated for the first phase. It was unclear if there was evidence that the results were not biased by missing outcome data |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was not reported in a format that was extractable for meta-analysis (cross-over study: data related to the first period were not reported). All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | No data were available to assess the possible imbalance between groups. Funding was unlikely to influence the data analysis and conflicts of interest were not reported |

**Barre 1988**

***Study characteristics***

| | |
|---|---|
| Methods | Study design<br><br>• Cross-over RCT<br><br>Study dates |

**Barre 1988** *(Continued)*

- Duration of follow-up: 2 months (first period) (each patient was randomly assigned a dialysate for 1 month period over 6 months)
- Time frame: not reported

| | |
|---|---|
| Participants | Study characteristics<br>• Setting: single centre<br>• Country: Canada<br>• Inclusion criteria: male patients undergoing HD<br>• Exclusion criteria: patients who took antihypertensive drugs<br>Baseline characteristics<br>• Number (analysed/randomised): overall (not reported/5)<br>• Age range: overall (46 to 62)<br>• Sex (M/F): overall (5/0)<br>• Dialysis type: HD<br>• Dialysis vintage (years, range): overall (2.1 to 10)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study reporting fatigue<br>Intervention group 1<br>• Dialysate containing 145 mEq/L of sodium for a 1-month period<br>Intervention group 2<br>• Dialysate containing 150 mEq/L of sodium for a 1-month period<br>Intervention group 3<br>• Dialysate containing 155 mEq/L of sodium for a 1-month period<br>Co-interventions<br>• All patients were taking a magnesium-containing phosphate binder (magaldrate)<br>• No changes were made in the dialysis therapy, diet, or medications |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available (fatigue was reported as an adverse event)<br>• Vital signs (arterial BP while seated, pulse, dry weight, interdialytic weight gain, predialysis MAP): assessed before and after dialysis<br>• Adverse events (including fatigue) (reported using a self-reported questionnaire for each dialysis): assessed for each dialysis<br>• Routine haematologic and biochemical data (change in serum sodium and magnesium levels): assessed before dialysis and at the end of each month |
| Notes | Additional information<br>• Funding: Erika (Rockleigh, Nj)<br>• Conflicts of interest/disclosures: not reported |

**Barre 1988** *(Continued)*

- Trial registration identification number: not applicable
- A priori published protocol: not reported

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Dialysis was performed in random sequence with dialysate sodium of 145, 150, or 155 mEq/L for 2 months at a time."<br><br>Comment: Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Quote: "The customise coded dialysis concentrates were provided by Erika (Rockleigh, Nj)."<br><br>Comment: The sponsor performed the allocation. Not sure if they were unaware of treatment assigned |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "A double blind prospective study was carried out in five stable men on chronic haemodialysis."<br><br>Comment: Although author reported that the study used a double-blind design, information about blinding of participants and investigators were not clearly stated |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "Each patient completed a questionnaire for each dialysis and was asked to report symptoms during and between dialysis. These included thirst, nausea, vomiting, headache, weakness, restless, fatigue, itchiness, crams, or any other symptoms."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, fatigue was assessed as an adverse event and it was not stated whether it was assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | The number of patients who completed the study was not clearly stated for the first phase. It was unclear if there was evidence that the results were not biased by missing outcome data |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was not reported in a format that was extractable for meta-analysis (cross-over study: data related to the first period were not reported). All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | High risk | No data were available to assess the possible imbalance between groups. Funding was likely to influence data analyses and interpretation and conflicts of interest were not reported |

**Bellinghieri 1983**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Cross-over RCT<br>Study dates<br>• Duration of follow-up: 8 weeks<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Setting: not reported<br>• Country: Italy<br>• Inclusion criteria: patients on HD 3 times/week (4 hours each dialysis); affected by an almost constant presence of cramps for at least 6 months during HD; experienced asthenia immediately afterwards and during the interval between one session and another<br>• Exclusion criteria: not reported<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (not reported/7); control group (not reported/7)<br>• Mean age ± SD (years): overall (49 ± 4)<br>• Sex (M/F): intervention group (4/3); control group (5/2)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): overall (1.9 ± 0.3)<br>• Comorbidities<br>  ○ CVD: not reported<br>  ○ Diabetes: not reported<br>  ○ Hypertension: not reported<br>  ○ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• L-carnitine (oral): 2 g/day<br>Control group<br>• Placebo<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Asthenia: evaluated every 15 days (Appendix 3)<br>• Cramps: evaluated every 15 days (Appendix 3)<br>• Blood samples for carnitine determination in muscle and serum (free carnitine, acetylcarnitine): assessed pre- and post-treatment<br>• Laboratory tests (red and white cells, HCT, calcium, potassium, triglyceride, cholesterol, lipoprotein): assessed pre and post-treatment |

**Bellinghieri 1983** *(Continued)*

- Death: assessed until the end of treatment

| | |
|---|---|
| Notes | Additional information<br>• Funding: Sigma-Tau, Pomezia<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not applicable<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "Double-blind study."<br><br>Comment: Although the author reported that the study used a double-blind design, information about blinding of participants and investigators were not clearly stated |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "Objective examination of asthenia consisted in making the patient flex the knees with the trunk in upright position for different intervals (exercise A) and walk repeatedly up band down three steps (exercise B). Asthenia was scored as slight if fatigue appeared at less than 60 sec of exercise A and at less than 30 ascents and descents during exercise B, intense at less than 15 sec of exercise A and at less than 10 ascents and descents of exercise B. Moderate degree of asthenia was between the two extremes. The exercises were performed immediately after and between haemodialysis. In the latter case the patients did the exercises at home and recorded the results."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. All outcomes that should be addressed (fatigue, cardiovascular disease, death and vascular access) were not reported. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | The number of patients who completed the study was not clearly stated for the first phase. It was unclear if there was evidence that the results were not biased by missing outcome data |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was not reported in a format that was extractable for meta-analysis (cross-over study: data related to the first period were not reported). All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |

**Bellinghieri 1983** *(Continued)*

| | | |
|---|---|---|
| Other bias | High risk | No data were available to assess the possible imbalance between groups. Funding (pharmaceutical company) could influenced the data analysis and conflicts of interest were not reported |

**Bicer 2022**

***Study characteristics***

| | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 4 weeks<br>• Time frame: June 2013 to September 2013 |
| Participants | Study characteristics<br>• Setting: multicentre (4 HD centres located in two cities)<br>• Country: Turkey<br>• Inclusion criteria: > 18 years; participated in HD program for an average of 4 hours, 3 times/week for at least 6 months; experienced hypotension during HD; could keep their fluid intake and diets constant during the study; capable of answering all of the questions, gained 2500 g or more between dialysis sessions, and agreed to participate in the study<br>• Exclusion criteria: did not experience hypotension problems during HD; cardiac pacemakers; pregnant; fistulas in both arms, psychiatric problems; suffered from nerve, soft tissue or vascular disease in their upper extremities<br>Baseline characteristics<br>• Number (analysed/randomised): overall (135/150); intervention group (67/not reported); control group (68/not reported)<br>• Mean age ± SD (years): intervention group (64.0 ± 11.6); control group (65.8 ± 12.1)<br>• Sex (M/F): intervention group (24/43); control group (30/38)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): intervention group (5.9 ± 4.5); control group (5.9 ± 3.9)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Acupressure with an electrostimulation device: 3 times/week for 1 month<br>Control group<br>• Placebo<br>Cointerventions |

**Bicer 2022** *(Continued)*

- Not reported

| | |
|---|---|
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>• PFS: baseline and at week 4<br>  ○ Behavioural/severity subscales assessing the effect and severity of fatigue on ADL<br>  ○ Affective subscale that includes emotional meaning attributed to fatigue<br>  ○ Sensory subscale reflecting psychological, physical, and emotional symptoms of fatigue<br>  ○ Cognitive/mood subscale reflecting the level of fatigue required to affect cognitive functions and mood<br>  ○ VAS: baseline and at week 4<br>• BP: baseline and at week 4<br>• Headache: during the study period<br>• Pain<br>  ○ VAS: baseline and at week 4<br>• BMI: baseline and at week 4<br>• Weight difference between predialysis and post-dialysis periods: baseline and at week 4<br>• Target UR and actual UR: baseline and at week 4<br>• Pulse rates: baseline and at week 4 |
| Notes | Additional information<br>• Funding: project code number TDK-2012-4135 by Erciyes University, Scientific Research Projects Unit<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "The patient data relating to the questionnaire, VAS pain (measurement of pain level), VAS fatigue, and Piper fatigue scale at the first follow-up (the first interview before acupressure) were collected by the researcher."<br><br>Comment: Fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |

**Bicer 2022** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "A total of 150 patients, meeting the inclusion criteria, were reached during the study. Five patients in the intervention group did not agree to participate in the study. Two of these patients experienced local pruritus in the area the device was applied, one patient developed a fistula problem, and two patients left the city during the follow-up. Additionally, three patients in the placebo group did not want to continue the study since two of these patients were receiving treatment in a hospital out of the city due to coronary angiography. Therefore, the study was completed with 135 patients."<br><br>Comment: 135/150 participants completed the study (> 5% loss to follow-up. Some reasons for discontinuation were provided, and some were related to the intervention |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan was not reported. It was reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue data at all time points were reported. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding did not influence the data analysis and conflicts of interest were not reported. No other source of bias were apparent |

**Biniaz 2015**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 8 weeks<br>• Time frame: October 2012 to January 2013 |
| Participants | Study characteristics<br>• Setting: multicentre (2 hospitals in an urban area of Iran)<br>• Country: Iran<br>• Inclusion criteria: > 18 years who attended regular HD 3 sessions/week; received HD ≥ 3 months; Hb > 80 g/L; did not take vitamin C from at least 3months before the study<br>• Exclusion criteria: active infection or active cancer<br>Baseline characteristics<br>• Number (analysed/randomised): overall (57/62); intervention group (30/not reported); control group (27/not reported)<br>• Mean age ± SD (years): intervention group (58.3 ± 11.5); control group (57.1 ± 10.7)<br>• Sex (M/F): intervention group (19/11); control group (16/11)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): intervention group (4.7 ± 4.5); control group (3.3 ± 2.6)<br>• Comorbidities<br>  ○ CVD: not reported<br>  ○ Diabetes: not reported |

**Biniaz 2015** *(Continued)*

- Hypertension: not reported
- Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Vitamin C supplementation (IV): 250 mg<br>Control group<br>• Placebo<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ○ MFI-20 questionnaire: at the start and end of study<br>  ■ General fatigue<br>  ■ Physical fatigue<br>  ■ Intellectual fatigue<br>• Hb: at the start and end of study<br>• HCT: at the start and end of study<br>• Ferritin: at the start and end of study<br>• Marital satisfaction score<br>  ○ ENRICH questionnaire: at the start and end of study |
| Notes | Additional information<br>• Funding: master's degree thesis supported by the Baqiyatallah University of Medical Sciences. This project was supported by a grant from the Nephrology and Urology Research Center of Baqiyatallah University of Medical Sciences<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "The samples were randomly distributed by a lottery method into two equal groups (simple random sampling)." |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "Double-blinded."<br>Comment: Although author reported that the study used a double-blind design, information about blinding of participants and investigators were not clearly stated |

**Biniaz 2015** *(Continued)*

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias) All outcomes | High risk | Quote: "Only 57 patients completed the study (30 persons in the intervention and 27 persons in the control group)."<br><br>Comment: 57/60 participants completed the study (> 5% loss to follow-up). Reasons for discontinuation were not provided and it was not clear if there was a difference between the two groups |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue was measured all time points. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding did not influence the data analysis and conflicts of interest were not reported. No other source of bias were apparent |

**BOLD 2020**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br><br>• Parallel RCT<br><br>Study dates<br><br>• Duration of follow-up: 4 months<br>• Time frame: recruitment started in March 2018 and ended August 2018, with the date of last follow-up in January 2019 |
| Participants | Study characteristics<br><br>• Setting: multicentre (San Francisco and Seattle)<br>• Country: USA<br>• Inclusion criteria: undergoing in-centre thrice weekly HD for treatment of ESKD; > 3 months since dialysis initiation; ability to obtain a brachial BP at dialysis and at home; >18 years<br>• Exclusion criteria: pregnant or breastfeeding (or anticipated pregnancy); incarcerated or institutionalised which may prohibit measurement of home BP, or participating in another intervention study that may affect BP; unmeasurable SBP (e.g. those with LV assist devices); chronic hypotension (defined as average pre-dialysis SBP < 100 mm Hg over last 2 weeks prior to screening off BP medications); life expectancy < 4 months; anticipated living donor kidney transplant within 4 months<br><br>Baseline characteristics<br><br>• Number (analysed/randomised): intervention group 1(25/25 - ITT); intervention group 2 (25/25 - ITT (24 participants completed)) |

**BOLD 2020** *(Continued)*

- Mean age ± SD (years): intervention group 1 (56.4 ± 13.1); intervention group 2 (56.9 ± 14.4)
- Sex (M/F): intervention group 1 (13/12); intervention group 2 (17/8)
- Dialysis type: HD
- Mean dialysis vintage ± SD (years): intervention group 1 (3.0 ± 2.2); intervention group 2 (3.0 ± 2.4)
- Comorbidities
  - CVD: not reported
  - Diabetes: not reported
  - Hypertension: not reported
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study reporting fatigue<br>Intervention group 1<br>• Home SBP<br>Intervention group 2<br>• Pre-dialysis SBP<br>Cointerventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Feasibility: how many eligible patients agreed to participate in the study after pre-screening (approach to enrol ratio)<br>• Adherence: percentage of participants in the home BP arm who were able to successfully perform home BP readings<br>• Hypertension<br>• Hypotension<br>• Intra-dialytic hypotension<br>• Other adverse events (including cramping, dizziness/lightheadedness)<br>• Self-reporting time to recovery<br>• Fatigue<br>• Preferred modality of home BP measurement transmission among the home BP participants<br>• Differences in dry weight target, actual observed pre-dialysis weight, and actual observed post-dialysis weight |
| Notes | Additional information<br>• Funding: National Institutes of Health, Satellite Healthcare and Northwest Kidney Centers<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: NCT03459807<br>• A priori published protocol was reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Participants were randomised using 1: 1 block randomisation, stratified by site." "Randomization was done by a computer algorithm, in random size blocks (e.g. 2, 4, or 6) stratified by recruitment site." |

**BOLD 2020** *(Continued)*

| | | |
|---|---|---|
| | | Comment: a sequence computer generation is considered as low risk of bias |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "This was a non-blinded 4-month, parallel group randomised controlled trial." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Quote: "Analysis followed the intent to treat principle." "Forty-nine of the 50 enrolled participants (98%) completed the study successfully (Figure 1). The sole participant who withdrew (from the pre-dialysis SBP treatment group) did so when she unexpectedly received a deceased donor kidney transplant."<br><br>Comment: 25/25 participants in intervention group 1 (home SBP) and 24/25 participants in intervention group 2 (pre-dialysis SBP) completed the study. There were differences between intervention groups (> 5% loss to follow-up). Reasons for discontinuations were provided, and they did not seem to be related to the treatment arm. However, ITT analysis was performed |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan was reported. Fatigue was not reported using multiple eligible outcome measurements (scales and time points). It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding did not influenced the data analysis and conflicts of interest were not reported. No other source of bias were apparent |

**Brass 2001**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Two parallel RCTs (study A + study B)<br>Study dates<br>• Duration of follow-up: 24 weeks<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Setting: multicentre (4 centres participated in study A and 12 centres participated in study B) |

**Brass 2001** *(Continued)*

- Country: USA
- Inclusion criteria: ESKD; HD treatment 3 times/week for at least 6 months; > 18 years; medical suitability to undergo graded ergometer exercise testing; ratio of acylcarnitine to carnitine concentrations > 0.40; Kt/V > 1.2 with less than 20% of variation during the previous 3 months
- Exclusion criteria: patients with claudication; medical condition that precluded safe performance of maximal exercise testing; inability to cooperate with exercise testing; the use of immunosuppressives, growth hormones, androgens, or anabolic steroids within the 3 months before study entry

Baseline characteristics

- Number (analysed/randomised)
  - Study A: intervention group (22/30, the ITT population was 28 participants); control group (27/30, ITT population was 28 participants)
  - Study B: intervention group 1 (32/not reported); intervention group 2 (30/not reported); intervention group 3 (32/not reported); control group (33/33)
- Mean age, range (years)
  - Study A (ITT population): intervention group (42, 19 to 76); control group (45, 23 to 64)
  - Study B: intervention group 1 (48, 27 to 76); intervention group 2 (48, 26 to 76); intervention group 3 (46, 25 to 79); control group (43, 24 to 67)
- Sex (M/F)
  - Study A (ITT population): treatment group (16/12); control group (16/12)
  - Study B: intervention group 1 (21/11); intervention group 2 (24/6); intervention group 3 (21/11); control group (20/13)
- Dialysis type: HD
- Mean dialysis vintage, range (years)
  - Study A (ITT population): intervention group (4.1, 0.6 to 23.1); control group (3.8, 0.8 to 23.6)
  - Study B: intervention group 1 (4.8, 0.7 to 16.0); intervention group 2 (7.2, 0.7 to 23.6); intervention group 3 (4.6, 0.8 to 17.5); control group (4.9, 0.6 to 20.4)
- Comorbidities
  - Study A
    - CVD: not reported
    - Diabetes: intervention group (3/28); control group (6/28)
    - Hypertension: not reported
    - Depression (clinician diagnosis): not reported
  - Study B
    - CVD: not reported
    - Diabetes: intervention group 1 (8/32); intervention group 2 (7/30); intervention group 3 (7/32); control group (4/33)
    - Hypertension: not reported
    - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br><br>• Pharmacological intervention<br>• Indication: study targeting fatigue<br><br>**Study A**<br><br>Intervention group<br><br>• L-carnitine (IV): 20 mg/kg at the conclusion of each thrice-weekly dialysis session for 24 weeks<br><br>Control group<br><br>• Placebo<br><br>**Study B**<br><br>Intervention group 1 |

**Brass 2001** *(Continued)*

- L-carnitine (IV): 10 mg/kg at the conclusion of each thrice-weekly dialysis session for 24 weeks

Intervention group 2

- L-carnitine (IV): 20 mg/kg at the conclusion of each thrice-weekly dialysis session for 24 weeks

Intervention group 3

- L-carnitine (IV): 40 mg/kg at the conclusion of each thrice-weekly dialysis session for 24 weeks

Control group

- Placebo

Co-interventions

- Not reported

Outcomes

Outcomes reported

- Fatigue outcome measures used: validation data available
- Change in exercise capacity
  - Maximal rate of oxygen consumption ($VO_{2max}$) using cycle ergometry: assessed at 12 and 24 weeks
  - ECG: assessed at 12 and 24 weeks
- Change in QoL
  - KDQ (Appendix 3): assessed at 12 and 24 weeks
    - Physical symptoms
    - Fatigue
    - Depression
    - Relationships with others
    - Frustration
- Adverse events: assessed until the end of treatment
- Serious adverse events: assessed until the end of treatment
- Change in laboratory values (HCT, Hb, lipid profile, liver function, predialysis chemistry, total carnitine, free carnitine, acylcarnitine concentrations, BUN, phosphate, creatinine): assessed every 4 weeks
- A/F ratio: assessed at baseline and after 24 weeks
- Kt/V: assessed at baseline and after 24 weeks
- Dry body weight: assessed at baseline and after 24 weeks
- Death: assessed until the end of treatment

Notes

Additional information

- Funding: Sigma Tau Pharmaceuticals, Inc, Gaithersburg, MD
- Conflicts of interest/disclosures: not reported
- Trial registration identification number: not applicable
- A priori published protocol: not reported

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Two placebo-controlled, double-blinded, randomised studies of carnitine supplementation were performed."<br><br>Comment: Sequence generation methods were not reported in sufficient detail to permit judgement |

**Brass 2001** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "Two placebo-controlled, double-blinded, randomised studies of carnitine supplementation were performed."<br><br>Comment: Although author reported that the study used a double-blind design, information about blinding of participants and investigators were not clearly stated |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "The Kidney Disease Questionnaire (KDQ) is a validated questionnaire for measuring quality of life in patients with ESRD. It was administered in English or Spanish by trained interviewers on non dialysis days. [...] A standardized chemistry panel was assessed during screening, at baseline, and after 12 and 24 weeks of treatment."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "Study A randomised 60 patients, 30 patients on each study arm. Four patients (2 patients from each group) were excluded from the intention-to-treat population because they withdrew before and post baseline exercise tests (2 patients received renal transplants, 1 patient relocated, and 1 patient withdrew after developing elevated serum transaminase levels). Within the intention-to-treat population (n = 56), 7 patients (1 patient, placebo; 6 patients, L-carnitine) withdrew before completing the 24-week protocol. Three patients received renal transplants, 1 patient withdrew consent, 1 patient became pregnant, 1 patient was unable to perform the exercise test, and 1 patient withdrew from the study after a serious adverse event unrelated to study drug. Study B randomised 133 patients. Six patients (all administered carnitine) did not have post baseline exercise assessments and were thus excluded from the intention-to-treat population (2 patients received renal transplants, 1 patient withdrew from the study, 1 patient experienced worsening of arthralgia, 1 patient died, and 1 patient withdrew because of ECG changes). Within the intention-to-treat population (n = 127), 9 patients (2 patients, placebo; 3 patients, 10 mg/kg of L-carnitine; 2 patients, 20 mg/kg of L-carnitine; 2 patients, 40 mg/kg of L-carnitine) failed to complete the full 24-week study. One patient had exercise-related problems, 1 patient was unable to exercise because of carpal tunnel syndrome, 4 patients received renal transplants, 1 patient withdrew because of back spasms, I patient refused the study drug because of abdominal pain, and 1 patient withdrew because of ECG changes."<br><br>Comment: 11/60 in the study A did not complete the study (> 5% lost to follow-up, with differences between groups). Reasons for discontinuations seemed to be not related to the treatment allocation. 15/133 in the study B did not complete the study (>5% lost to follow-up, with differences between groups). Reasons for discontinuations seemed to be not related to the treatment allocation |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue data were cumulated for 2 RCTs, all time points were not reported. All out- |

**Brass 2001** *(Continued)*

| | | |
|---|---|---|
| | | comes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | High risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding (pharmaceutical company) could influenced the data analysis and conflicts of interest were not reported |

**Canadian EPO 1990**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 6 months<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Setting: multicentre (13 hospitals in 8 Canadian university HD centres)<br>• Country: Canada<br>• Inclusion criteria: 18 to 75 years; medically stable on HD for > 3 months; HD 3 times/week in a hospital or self-care unit; Hb < 9.0 g/dL<br>• Exclusion criteria: anaemia was not caused by EPO deficiency; QoL or exercise capacity was affected by factors other than kidney failure; unable to perform a 6MWT; not be able to understand the questionnaires due to language or intellectual difficulties; unwilling or unable to give informed consent; history of DM; ischaemic heart disease; severe or uncontrolled hypertension; androgen or corticosteroid therapy<br>Baseline characteristics<br>• Number<br>  ◦ Completed the SIP/randomised: intervention group 1 (34/40); intervention group 2 (33/38); control group (32/40)<br>  ◦ Completed the KDQ/randomised; intervention group 1 (34/40); intervention group 2 (33/38); control group (31/40)<br>• Mean age ± SD (years): intervention group 1 (44 ± 16); intervention group 2 (43 ± 15); control group (48 ± 16)<br>• Sex (M/F): intervention group 1 (19/21); intervention group 2 (26/12); control group (25/15)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): intervention group 1 (4.6 ± 4.7); intervention group 2 (4.4 ± 5.1); control group (2.5 ± 3.1)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: intervention group 1 (0/40); intervention group 2 (0/38); control group (0/40)<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study targeting fatigue |

**Canadian EPO 1990** *(Continued)*

intervention group 1

- Epoetin alfa (IV): to achieve a target HB of 9.5–11.0 g/dL (low-target group), initial dose was 100 U/kg - outcomes were reported for intervention 1 + 2

Intervention group 2

- Epoetin alfa (IV): to achieve a target Hb of 11.5–13.0 g/dL (high-target group), initial dose was 100 U/kg - outcomes were reported for intervention 1 + 2

Control group

- Placebo (did not receive EPO alfa)

Co-interventions

- Not reported

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Outcomes

Outcomes reported

- Fatigue outcome measures used: validation data available
- Exercise capacity
  - Treadmill stress test (assessed at baseline, and 2, 4, and 6 months)
  - Time trade-off technique: score between 0 and 1, in which 1 represents perfect health and 0 a state in which the patient is indifferent between life and death (assessed at baseline, and 2 and 6 months)
  - 6MWT: assessed at baseline, and 2, 4, and 6 months
- HRQoL
  - KDQ: assessed at baseline, and 2, 4, and 6 months (Appendix 3)
  - Physical
  - Fatigue
  - Relationship
  - Frustration
  - Depression
- SIP: assessed at baseline, and 2, 4, and 6 months
  - Global
  - Physical
  - Ambulation
  - Body care and movement
  - Home management
  - Psychosocial
  - Communication
  - Work
  - Sleep and rest
  - Eating
  - Recreation and pastimes
  - Mobility
- Change in KDQ symptoms: assessed at baseline, and 2, 4, and 6 months
  - Energy
  - Weakness
  - Shortness of Breath
  - Fatigue
  - Depression
- Other problems associated with ESKD (sexuality): assessed at baseline, 2 and 6 months
- Change in Hb: from baseline to 2, 4 and 6 months
- Change in potassium, phosphorus, calcium, urea, creatinine, white cell count, platelet count: assessed at baseline, 2 and 6 months
- Change in functional capacity

**Canadian EPO 1990** *(Continued)*

- Minutes walked: assessed at baseline, 2 and 6 months
- Change in BP: assessed at baseline, 2 and 6 months
- Adverse events: assessed at baseline, 2 and 6 months
- Hypertension: assessed at baseline, 2 and 6 months
- Death: assessed at end of treatment

| | |
|---|---|
| Notes | Additional information<br>• Funding: Amgen Inc.<br>• Conflicts of interest/disclosures: T. J. M. were Amgen Inc. employees. The authors thank Ortho Pharmaceutical (Canada) who sponsored this study, and Johnson and Johnson Pharmaceutical Research and Development for providing the data for the reanalysis. The authors also thank Y. Mikyas (Amgen Inc.) for editorial support in preparation of this manuscript<br>• Trial registration identification number: not applicable<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote from Canadian EPO 1990: "Patients were stratified by hospital and randomised in blocks to receive placebo; erythropoietin at a dose adjusted to maintain the haemoglobin concentration at 95-110 g/l (low erythropoietin group); or erythropoietin at a dose adjusted to maintain the haemoglobin concentration at 115-130 g/l (high erythropoietin group)."<br><br>Comment: sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Quote from Canadian EPO 1990: "Patients were stratified by hospital."<br><br>Comment: method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote from Canadian EPO 1990: "To ensure that the study was double blind we established two teams of staff at each study centre. The unblinded team consisted of a doctor, a pharmacist, and a data clerk and was responsible for adjusting the dose of erythropoietin, prescribing iron supplements or transfusions, and sending haematological data to the coordinating centre. The blinded team consisted of nurses in the dialysis unit and our study group and all doctors in the dialysis unit other than those in the unblinded team; this team carried out routine clinical care and recorded adverse reactions and other clinical events but did not have access to the results of haematological tests or know the dose of erythropoietin or placebo that each patient was receiving."<br><br>Comment: a clear explanation of the double-blind study was provided |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote from Canadian EPO 1990: "The nurses in the study group administered tests to assess quality of life and exercise capacity."<br><br>Quote from Keown 2010: "Health-related quality of life was measured by the Kidney Disease Questionnaire (KDQ) and Sickness Impact Profile (SIP) between the placebo group and the combined Epoetin alfa-treated group."<br><br>Comment: the outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used (although nurses were part of the blinded team) it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influ- |

**Canadian EPO 1990** *(Continued)*

| | | |
|---|---|---|
| | | enced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Quote from Canadian EPO 1990: "Nineteen patients were withdrawn during the study: eight in the placebo group (because of transplantation (five), non-compliance (one), reaction to transfusion (one), seizure and death (one)); six in the low erythropoietin group (transplantation (two), hypertension (one), hypertension and seizure (one), subarachnoid haemorrhage and seizure (one), pregnancy (one)); and five in the high erythropoietin group (transplantation (three), hypertension (two)). Six patients were withdrawn before the follow-up at two months, and the 13 others were withdrawn before the follow-up at four months. The patient who became pregnant continued to receive erythropoietin but had a spontaneous miscarriage at 11- 1 2 weeks' gestation."<br><br>Quote from Muirhead 2008: "Analysis was conducted using ITT."<br><br>Comment: 11/78 in the two intervention groups and 8/40 in the placebo group did not completed the study. However, ITT analyses was performed |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | High risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding (pharmaceutical company) could influenced the data analysis and authors had conflicts of interest |

**Cecen 2021**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br>• Quasi-RCT<br>Study dates<br>• Duration of follow-up: 4 weeks<br>• Time frame: October 2018 to February 2019 |
| Participants | Study characteristics<br>• Setting: single centre (public hospital)<br>• Country: Turkey<br>• Inclusion criteria: receiving HD in the dialysis unit of a public hospital in Turkey; written consent to participate in the study; > 18 years; open to communication; able to speak and understand Turkish; receiving HD 3 times/week for ≥ 6 months; no loss of sensation, mass, fracture or ingrown toenail (onyxis); lower extremities free from pathological and tumoral disease; no symptoms of phlebitis, embolism and no bleeding disorder related to amputation, fracture, infection, wound, skin disease in patients > 65 years: SMMT score ≥ 24<br>• Exclusion criteria: not providing written consent to participate, < 18 years; HD twice/week for 6 months or less; loss of sensation, mass, fracture or ingrown toenail (onyxis) in patients > 65 years, SMMT score ≤ 23<br>Baseline characteristics |

**Cecen 2021** *(Continued)*

- Number (analysed/randomised): intervention group 1 (27/28); intervention group 2 (27/28); control group (28/28)
- Mean age ± SD (years): intervention group 1 (53.07 ± 18.13); intervention group 2 (59.96 ± 16.47); control group (55.36 ± 15.02)
- Sex (M/F): intervention group 1 (17/10); intervention group 2 (9/18); control group (13/15)
- Dialysis type: HD
- Mean dialysis vintage ± SD (years): intervention group 1 (5.5 ± 5.6); intervention group 2 (4.4 ± 3.9); control group (6.3 ± 4.7)
- Comorbidities
  - CVD: not reported
  - Diabetes: intervention group 1 (12/27); intervention group 2 (13/27); control group (7/28)
  - Hypertension: intervention group 1 (19/27); intervention group 2 (22/27); control group (19/28)
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group 1<br>• Hand massage<br>Intervention group 2<br>• Foot massage<br>Control group<br>• No intervention<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ○ 10-point VAS: baseline, weeks 2 and 4<br>• Mental health<br>  ○ SMMT (Appendix 3)<br>  ■ Time and space orientation<br>  ■ Recording memory<br>  ■ Attention<br>  ■ Recall<br>  ■ Language<br>• Hb<br>• HCT<br>• Ferritin<br>• BUN<br>• Creatinine<br>• Energy<br>  ○ 10-point VAS (baseline, weeks 2 and 4) |
| Notes | Additional information<br>• Funding: none<br>• Conflicts of interest/disclosures: none |

**Cecen 2021** *(Continued)*

- Trial registration identification number: not reported
- A priori published protocol: not reported

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | Since the study was a quasi-experimental trial, no random element was used in generating the allocation sequence or the sequence was predictable |
| Allocation concealment (selection bias) | High risk | Method of allocation concealment was not reported in sufficient detail to permit judgement. However, since the study was a quasi-experimental trial, there was a reason to suspect that the enrolling investigator or the participant had knowledge of the forthcoming allocation. No imbalance between intervention groups was apparent |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant/investigators beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Quote: "The patients involved in the preliminary application were included in the number of samples and new patients who met the criteria in each group of 28 patients were included in the groups by computerized randomisation and a total of 84 patients was reached. Since one patient from the hand massage group left the dialysis canter temporarily after the fifth massage session, and one patient from the foot massage group died after being taken to the intensive care prior to the fourth session, one patient from each group was excluded from the research. As a result, a total of 82 patients, including 27 patients in each of the hand massage and foot massage groups, and 28 patients in the control group, formed the sample of the research."<br><br>Comment: 54/56 participants in the intervention groups and 28/28 in the control group completed the study (< 5% loss to follow-up). Differences between subgroups were reported. Reasons for discontinuation were reported |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan was not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and authors had no conflicts of interest. The study seemed to be free from other source of bias |

### Chang 2010

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Quasi-RCT<br>Study dates<br>• Duration of follow-up: 8 weeks<br>• Time frame: August to November 2008 |
| Participants | Study characteristics<br>• Setting: multicentre (2 HD units in a medical centre in northern Taiwan)<br>• Country: Taiwan<br>• Inclusion criteria: patients were conscious; able to communicate; on HD for at least 3 months; had Kt/V > 1.1 for the last 3 months; HCT values > 27%; albumin levels > 3.7 g/dL; GOT and GPT values < 50 U/L; able to use a leg ergometer in bed without assistance<br>• Exclusion criteria: neuromuscular problems<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (36/44); control group (35/46)<br>• Mean age ± SD (years): intervention group (50.8 ± 10.72); control group (52.0 ± 8.7)<br>• Sex (M/F): intervention group (26/10); control group (24/11)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): intervention group (6.43 ± 3.91); control group (7.04 ± 4.16)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Intradialytic leg ergometry exercise<br>Control group<br>• Sedentary group<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Change in fatigue<br>  ◦ HD fatigue scale: assessed at baseline, and at 4 and 8 weeks (Appendix 3)<br>• Change in physical activity<br>  ◦ Bouchard's PAL: assessed at baseline, and at 4 and 8 weeks (Appendix 3)<br>• BP: assessed before, during and after exercise<br>• Heart rate: assessed before, during and after exercise |

**Chang 2010** *(Continued)*

- Peripheral oxygen saturation ($SpO_2$): assessed before, during and after exercise
- Cardiopulmonary response and signs of physical discomfort (fainting, chest pain or tightness, dyspnoea, nausea, vomiting, muscle or joint pain, or unsteady pedal speed): assessed before, during and after exercise

| | |
|---|---|
| Notes | Additional information<br>• Funding: Taipei Medical University and Shin Kong Memorial Hospital<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | High risk | Quote: "This was a quasi-experimental clinical trial in a medical centre with two haemodialyses units managed by the same medical and nursing team. The patients were assigned randomly to either unit. The experimental group was recruited from one unit and the control group from another, and participants were pair-matched based on age and gender."<br><br>Comment: Since the study was a quasi-experimental trial, no random element was used in generating the allocation sequence or the sequence was predictable |
| Allocation concealment (selection bias) | High risk | Method of allocation concealment was not reported in sufficient detail to permit judgement. However, since the study was a quasi-experimental trial, there was a reason to suspect that the enrolling investigator or the participant had knowledge of the forthcoming allocation. No imbalance between intervention groups was apparent |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "Subjects were interviewed by a research assistant to fill-out the fatigue scale and Bouchard's PAL on enrolment, during the fourth week and the eighth week of their haemodialysis visits. The research nurse is not a staff working in these haemodialysis units. She collected data independently and did not participate in patient care."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant/investigators beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed. It was not stated if the interviewer was blinded to the treatment allocation |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "From August to November 2008, there were 44 and 46 subjects in each unit who met the criteria and were invited to participate. Fourteen refused in the beginning as they were unwilling to participate. Five subjects dropped-out in later stages for various reasons (Figure 1). Thirty-six subjects (80%) in the experimental group and 35 patients (76%) in the control group completed the study." |

**Chang 2010** *(Continued)*

| | | |
|---|---|---|
| | | Comment: 36/44 participants in the intervention group and 35/46 participants in the control group completed the study (> 5% lost to follow-up with differences between groups). Reasons for discontinuations were not reported |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and authors had no conflicts of interest. The study seemed to be free from other source of bias |

**Chen 2008a**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 4 weeks<br>• Time frame: participants were recruited from July to August 2005. The trial was initiated on September 2005 and ended on October 2005 |
| Participants | Study characteristics<br>• Setting: single centre (the National Taiwan University Hospital)<br>• Country: Taiwan<br>• Inclusion criteria: undergoing PD > 3 months; ≥ 18 years; history of sleep disturbance > 3 months<br>• Exclusion criteria: active medical or unstable psychiatric condition and other documented symptoms of obstructive sleep apnoea and periodic limb movement disorders, such as restless legs syndrome<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (13/13); control group (13/13: 11/13 participants completed the study, but outcomes data were provided for all participants)<br>• Mean age ± SD (years): intervention group (51.9 ± 8.6); control group (48.7 ± 14.6)<br>• Sex (M/F): intervention group (8/5); control group (7/6)<br>• Dialysis type: PD<br>• Mean dialysis vintage ± SD (years): intervention group (3.1 ± 2.2); control group (3.7 ± 2.7)<br>• Comorbidities<br>  ○ CVD: not reported<br>  ○ Diabetes: intervention group (4/13); control group (1/13)<br>  ○ Hypertension: not reported<br>  ○ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group |

**Chen 2008a** *(Continued)*

- CBT

Control group

- Sleep hygiene education

Co-interventions

- All received conventional glucose-based lactate buffer PD solutions
- All participants received sleep hygiene education before the 4-week trial

Outcomes

Outcomes reported

- Fatigue outcome measures used: validation data available
- Change in sleep
  - PSQI: total score ranged from 0 to 21 points, with higher scores meaning poorer sleep quality (assessed before and after therapy)
    - Sleep quality
    - Sleep latency
    - Sleep duration
    - Sleep efficiency
    - Sleep disturbances
    - Use of sleep medication
    - Daytime dysfunction
- Change in fatigue
  - FSS: assessed before and after therapy (Appendix 3)
- Blood samples (Hb, albumin, calcium, phosphorus, BUN, creatinine, intact PTH): assessed before and after therapy
- Normalized protein catabolic rate: assessed before and after therapy
- Calcium-phosphate product: assessed before and after therapy
- Kt/V: assessed before and after therapy
- Residual renal function: assessed before and after therapy
- Changes in serum IL-6, IL-1beta, IL-18, and TNF-alfa levels: assessed before and after therapy
- Adverse events: assessed until the end of treatment

Notes

Additional information

- Funding: Ta-Tung Kidney Foundation and the Mrs Hsin-Chin Lee Kidney Research Fund
- Conflicts of interest/disclosures: none
- Trial registration identification number: NCT00155441
- A priori published protocol was reported

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "We randomly assigned participants by using computer generated randomised numbers with an allocation ratio of 1:1; to either the CBT group (13) or the control group (13). No stratification or blocking factors were used."<br><br>Comment: Computer generated randomised numbers is considered as low risk of bias. No imbalance between intervention groups was apparent |
| Allocation concealment (selection bias) | Unclear risk | Quote: "The sequence was concealed until the interventions were assigned. [...] The generation of allocation sequence and assignment of participants was performed by the project director." |

**Chen 2008a** *(Continued)*

| | | |
|---|---|---|
| | | Comment: It was not stated if the enrolling investigator (project director) had knowledge of the forthcoming allocation. No imbalance between intervention groups was apparent |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "This pilot study did not use a double-blind design, and participants were informed of their allocation sequence by telephone."<br><br>Comment: An open-label study is considered as high risk of bias. Interventions were different and participants and/or investigators were aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "Fatigue was assessed using a questionnaire. The 2 measurements were completed before and after the 4-week trial by all participants in both groups."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Quote:"Two participants in the control group withdrew after randomisation for personal considerations (1 person lived too far from the hospital, and the other needed to work in the night-time during the trial."<br><br>Comment: Although 2/13 participants withdrawal from the control group, Figure 1 and Table 4 showed that all patients were included in the analysis |
| Selective reporting (reporting bias) | High risk | Protocol was provided. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and authors had no conflicts of interest. The study seemed to be free from other source of bias |

**Chen 2011a**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 6 weeks<br>• Time frame: July to October 2009. The trial was initiated on November 2009 and ended on December 2009 |
| Participants | Study characteristics<br>• Setting: single centre (Far Eastern Memorial Hospital) |

**Chen 2011a** *(Continued)*

- Country: Taiwan
- Inclusion criteria: patients had been receiving maintenance HD for > 6 months; subjects who had a PSQI score of > 5 during enrolment screening; ≥ 18 years; a history of sleep disturbance for > 6 months
- Exclusion criteria: subjects with active medical psychiatric conditions and other documented symptoms of OSA (defined as Epworth Sleepiness Scale > 10 or typical symptoms) and periodic limb movement disorders, such as restless legs syndrome

Baseline characteristics

- Number (analysed/randomised): intervention group (37/40); control group (35/40)
- Mean age ± SD (years): intervention group (57 ± 9); control group (59 ± 11)
- Sex (M/F): intervention group (17/20); control group (13/22)
- Dialysis type: HD
- Mean dialysis vintage ± SD (years): intervention group (5.8 ± 4.0); control group (6.0 ± 5.0)
- Comorbidities
  - CVD: not reported
  - Diabetes: intervention group (12/37); control group (12/35)
  - Hypertension: intervention group (22/37); control group (22/35)
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• CBT: 3 times/week<br>Control group<br>• Sleep hygiene education<br>Co-interventions<br>• The study patients received 3.5 to 5 hours of HD 3 times/week with a blood flow rate of 250 to 300 mL/min and dialysate flow of 500 to 800 mL/min, using bicarbonate dialysate and reverse osmosis-purified water<br>• All of the participants used high-flux polysulfone membrane as the dialyser<br>• All participants received sleep hygiene education |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Sleep<br>  ○ PSQI: assessed at baseline and at 6 weeks<br>  ■ Sleep quality<br>  ■ Sleep latency<br>  ■ Sleep duration<br>  ■ Sleep efficiency<br>  ■ Sleep disturbances<br>  ■ Use of sleep medication<br>  ■ Daytime dysfunction<br>• Fatigue<br>  ○ FSS: assessed at baseline and at 6 weeks<br>  ○ Sleep efficiency<br>  ○ Sleep disturbances<br>  ○ Use of sleep medication |

**Chen 2011a** *(Continued)*

- Daytime dysfunction
- Depression
  - BDI: assessed at baseline and at 6 weeks
    - Depression
    - Cognitions
    - Physical symptoms
- Anxiety
  - BAI: assessed at baseline and at 6 weeks
- Changes in inflammation and oxidative stress (high-sensitive CRP, IL-1beta, IL-18, oxidized low-density lipoprotein levels): assessed at baseline and at 6 weeks
- Kt/V: assessed at baseline and at 6 weeks

| Notes | Additional information<br>• Funding: grants from the Far Eastern Memorial Hospital (FEMH-97-D-039) in Taiwan, Ta-Tung Kidney Foundation and to Hsin-Chin Lee Kidney Research Fund<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |
|---|---|

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "We randomised participants by computer-generated random numbers with an allocation ratio of 1:1; that is, either to the CBT group or to the control group."<br><br>Comment: Computer-generated randomised numbers is considered as low risk of bias. No imbalance between intervention groups was apparent |
| Allocation concealment (selection bias) | Unclear risk | Quote: "The generation of allocation sequence and assignment of participants was performed by the project director."<br><br>Comment: It was not stated if the enrolling investigator (project director) had knowledge of the forthcoming allocation. No imbalance between intervention groups was apparent |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "This study was an open-labelled design. Participants were informed of their allocation sequence by the nursing staff, and the sequence was concealed until the interventions were assigned."<br><br>Comment: An open-blinded study is considered as high risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "Fatigue was assessed using a questionnaire. The four measurements were completed before and after the 6-week trial by all of the participants in both groups."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias) | High risk | Quote: "After randomisation, three participants in the CBT group and five participants in the control group refused to participate and withdrew their in- |

**Chen 2011a** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | formed consent because of personal considerations. Therefore, a total of 72 subjects (37 in the CBT group and 35 in the control group) participated."<br><br>Comment: 37/40 participants in the intervention group and 35/40 participants in the control group completed the study (> 5% lost to follow-up, with differences between groups). Reasons for discontinuations seemed to be not related to the treatment allocation |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and authors had no conflicts of interest. The study seemed to be free from other source of bias |

**Cho 2004**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 4 weeks<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Setting: multicentre (2 HD clinics in major hospitals in Tainan, Chi Mei Medical Center)<br>• Country: Taiwan<br>• Inclusion criteria: HD patients with complaints of fatigue; ≥ 18 years; rational and able to communicate in Mandarin or Taiwanese; written consent to participate in the study; receiving routine HD treatment for at least 3 months<br>• Exclusion criteria: DSM IV psychiatric diagnoses: severe complications during dialysis; other severe diseases such as cancer<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (28/31); control group (30/31)<br>• Mean age ± SD (years): intervention group (45.1 ± 9.70); control group (53.7 ± 8.51)<br>• Sex (M/F): intervention group (8/20); control group (17/13)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): intervention group (4.95 ± 3.54); control group (4.72 ± 3.88)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classificaiton |

**Cho 2004** *(Continued)*

- Non-pharmacological intervention
- Indication: study targeting fatigue

Intervention group

- Acupressure

Control group

- No intervention

Co-interventions

- Not reported

| | |
|---|---|
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ○ Chinese version of the PFS assessed pre- and post-test<br>  ■ Behavioural/severity<br>  ■ Affective meaning<br>  ■ Sensory<br>  ■ Cognitive/mood<br>• Depression<br>  ○ Chinese version of the BDI: assessed pre- and post-test |
| Notes | Additional information<br>• Funding: not reported<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not applicable<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Patients were then assigned randomly to either experimental or the control group. [...] There were no differences in demographic data between the groups ($p > 0.05$). However, a significant difference in age ($p < 0.05$) was found between groups."<br><br>Comment: Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | It was not stated if the enrolling investigator (project director) had knowledge of the forthcoming allocation. Although there were some differences between groups, these differences did not suggest a problem with the randomisation process |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced report- |

**Cho 2004** *(Continued)*

| | | |
|---|---|---|
| | | ing. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, other subjective outcomes were reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "62 cases were recruited to this study and 3 cases in the experimental and 1 case in the control group dropped out. [...] The reasons for dropping out were relocation or being transferred to other dialysis centre."<br><br>Comment: 28/31 participants in the intervention group and 30/31 participants in the control group completed the study (> 5% lost to follow-up, with differences between group). Reasons for discontinuations seemed to be not related to the treatment allocation |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan was not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | Although there were some differences between groups, there was no substantial evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding and conflicts of interest were not reported |

**Chow 2010**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: intervention was performed for 6 weeks, follow-up was 12 weeks in total<br>• Time frame: 2005 (months not reported) |
| Participants | Study characteristics<br>• Setting: multicentre (2 local regional hospitals in Hong Kong)<br>• Country: Hong Kong<br>• Inclusion criteria: patients undergoing PD; able to access a telephone after discharge from the hospital<br>• Exclusion criteria: on intermittent PD or HD and those with planned admissions for special treatment procedures; patients with Tenckhoff catheters in situ for less than 3 months<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (43/50); control group (42/50)<br>• Mean age ± SD (years): intervention group (59.4 ± 13.97); control group (54.5 ± 12.8)<br>• Sex (M/F): intervention group (28/15); control group (24/18)<br>• Dialysis type: PD<br>• Mean dialysis vintage ± SD (years): intervention group (3.0 ± 2.6); control group (3.5 ± 2.6)<br>• Comorbidities<br>  ○ CVD: not reported<br>  ○ Diabetes: intervention group (19/43); control group (16/42)<br>  ○ Hypertension: not reported |

**Chow 2010** *(Continued)*

- Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Nurse-led case management programme for 6 weeks<br>Control group<br>• Routine hospital discharge service for 6 weeks<br>Co-interventions<br>• All the patients had received routine, intensive training prior to the start of the dialysis regimen |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• QoL<br>  ○ Chinese version of the KDQOL-SF: assessed before the intervention, at completion of the 6-week intervention and 6 weeks after completion of the programme<br>  ■ Symptoms/problems<br>  ■ Effects of kidney disease<br>  ■ Burden of kidney disease<br>  ■ Work status<br>  ■ Cognitive function<br>  ■ Quality of social interactions<br>  ■ Sexuality<br>  ■ Sleep<br>  ■ Social support<br>  ■ Dialysis staff encouragement<br>  ■ Patient satisfaction<br>  ○ Chinese version of the SF-36<br>  ■ Physical Function<br>  ■ Role-Physical<br>  ■ Role-Emotional<br>  ■ Social Function<br>  ■ Pain<br>  ○ General Health<br>  ○ Emotional well-being (mental health)<br>  ○ Energy/fatigue (vitality)<br>• Death: assessed until the end of treatment |
| Notes | Additional information<br>• Funding: Research Grants Council of Hong Kong (PolyU 5435/05H)<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

**Chow 2010** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "The study was a randomised controlled trial with a pre-test and post-test."<br><br>Comment: Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "The data were collected in 2005 at three time intervals using a structured self-report questionnaire. [...] Data collection was through face-to-face interview."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "The 100 patients who joined the study were randomly assigned to either the study or control group. There were 50 patients in each of the treatment arms. At week 12, 43 of the 50 study patients and 42 of the 50 controls had completed the follow-up questionnaires. A total of 85 patients completed the protocol and were included in the analysis (Figure 1)."<br><br>Comment: 43/50 participants in the intervention group and 42/50 participants in the control group completed the study (> 5% loss to follow-up). Reasons for discontinuations seemed to be not related to the treatment allocation |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and authors had no conflicts of interest. The study seemed to be free from other source of bias |

**Dashti-Khavidaki 2013**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br><br>• Cluster RCT<br><br>Study dates |

**Dashti-Khavidaki 2013** *(Continued)*

- Duration of follow-up: 6 months
- Time frame: October 2010 to October 2011

| | |
|---|---|
| Participants | Study characteristics<br>• Setting: single centre (HD ward of Imam Khomeini Hospital, affiliated to Tehran University of Medical Sciences)<br>• Country: Iran<br>• Inclusion criteria: aged 18 and 90 years; HD for at least 3 months; 3 times/week for 4 hours in each session using polysulfone membrane and bicarbonate buffer<br>• Exclusion criteria: positive history of dementia or other conditions that impair answering the questionnaire; unable to speak Persian<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (26/45); control group (34/47)<br>• Mean age ± SD (years): intervention group (55.4 ± 15.7); control group (48.6 ± 14.7)<br>• Sex (M/F): intervention group (14/12); control group (22/12)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): intervention group (7.75 ± 6.93); control group (5.7 ± 6.65)<br>• Comorbidities<br>  ○ CVD: not reported<br>  ○ Diabetes: not reported<br>  ○ Hypertension: not reported<br>  ○ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Pharmacist-led pharmaceutical care in addition to the standard care<br>Control group<br>• Standard care: brief medication review by nurses and monthly visits by nephrology fellow and attending physicians<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• QoL<br>  ○ SF-36: assessed at baseline and at 6 months<br>  ■ Physical function<br>  ■ Role-physical<br>  ■ Role-emotional<br>  ■ Social function<br>  ■ Pain<br>  ■ General health<br>  ■ Emotional well-being (mental health)<br>  ■ Energy/fatigue (vitality)<br>• Laboratory data (Hb and ferritin levels, TSAT, serum calcium, phosphate, intact PTH, albumin, LDL-cholesterol): assessed at baseline and at 6 months |

**Dashti-Khavidaki 2013** *(Continued)*

- Calcium-phosphate product: assessed at baseline and at 6 months
- Clinical data: assessed at baseline and at 6 months
- Death: assessed until the end of treatment
- Kidney transplant: assessed until the end of treatment
- Hospitalisation: assessed until the end of treatment

| | |
|---|---|
| Notes | Additional information<br>• Funding: This study was part of a Pharm. D thesis supported by Tehran University of Medical Sciences<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "SF-36 was completed by patients and was read for patients who were unable to read."<br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "Of these 92 patients, 45 and 47 patients assigned to the case and control groups respectively. Twenty-six patients in the case group and 34 subjects in the control group completed the study."<br>Comment: 26/45 participants in the intervention group and 34/47 participants in the control group completed the study (> 5% lost to follow-up, with differences between group). Reasons for discontinuations seemed to be not related to the treatment allocation |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to in- |

**Dashti-Khavidaki 2013** *(Continued)*

| | |
|---|---|
| | fluence the data analysis and authors had no conflicts of interest. The study seemed to be free from other source of bias |

**Duggal 2019**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 4 weeks<br>• Time frame: September 2017 to April 2018 |
| Participants | Study characteristics<br>• Setting: multicentre (18 centres)<br>• Country: USA<br>• Inclusion criteria: HD patients with recovery time 6 hours or more at baseline; aged 18 to 89 years; able to answer survey questions in English or Spanish, HD ≥ 3 times/week who reported post-dialysis fatigue ≥ 6 hours at baseline<br>• Exclusion criteria: Kt/V < 1.3 for those dialysing 3 times/week, or Kt/V < 2.1 for those dialysing 4 times/week so clearance targets could still be met despite blood flow rate reduction; pregnant, breastfeeding, or considering pregnancy; planned change in dialysis duration or timing, or if the primary nephrologist had a medical objection to the patient's involvement<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (44/52); control group (42/50)<br>• Mean age ± SD (years): intervention group (64.2 ± 13.1); control group (64.4 ± 11.9)<br>• Sex (M/F): intervention group (31/21); control group (34/26)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): intervention group (4.5 ± 3.6); control group (6.0 ± 6.7)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: intervention group (34/52); control group (31/50)<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study reporting fatigue<br>Intervention group<br>• Blood flow rate reduction of 100 mL/min to a minimum of 300 mL/min<br>Control group<br>• Standard care<br>Co-interventions<br>• Not reported |

**Duggal 2019** *(Continued)*

| | |
|---|---|
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data not available<br>• Reduction in dialysis recovery time<br>• Hospitalisation<br>• Fatigue<br>• QoL<br>  ○ LEVIL survey: baseline and weeks 1, 2, 3, 4 (Appendix 3)<br>  ■ Pain<br>  ■ Feeling washed out or drained<br>  ■ Sleep quality<br>  ■ Shortness of breath<br>  ■ Appetite<br>  ■ Well-being |
| Notes | Additional information<br>• Funding: Satellite Healthcare Research Fellowship award<br>• Conflicts of interest/disclosures: W.H., M.R., S.S., G.A., and B.S. are employees of Satellite Healthcare<br>• Trial registration identification number: not reported<br>• A priori published protocol: IRB Protocol SR064RT |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Patients were randomised in a 1:1 manner to intervention or control arms using a computer-generated sequence of randomly permuted blocks."<br>Comment: Comupter generation is considered at low risk of bias |
| Allocation concealment (selection bias) | Low risk | Quote: "The random allocation sequence was generated by statisticians who were not involved in the survey process." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "Single-blinded." "Patients were blinded to group assignment."<br>Comment: A single blinded study is considered as high risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | The outcomes were assessed with an appropriate measure, without differences between groups. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "There were 102 patients enrolled in the study. A total of 86 (84.3%) of those subjects completed the study. Of<br>those in the control group, 42 (84.0%) completed the study, and 44 (84.6%) of those in the intervention group<br>completed the study. Causes of discontinuation are noted."<br>Comment: 44/52 participants in the intervention group and 42/50 participants in the control group completed the study (> 5% lost to follow-up). There were differences between groups and reasons for discontinuation were provided |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were reported. Regarding fatigue, it was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was not reported in a format that was |

**Duggal 2019** *(Continued)*

| | | |
|---|---|---|
| | | not extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis. No other source of bias were apparent |

**Eroglu 2022**

***Study characteristics***

| | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 10 weeks<br>• Time frame: May 2019 to October 2019 |
| Participants | Study characteristics<br>• Setting: multicentre (2 dialysis clinics)<br>• Country: Turkey<br>• Inclusion criteria: ≥ 18 years; capable of communicating in Turkish; HD history of at least 3 months and actively receiving HD 2 or 3 times/week; reporting willingness to participate in this study<br>• Exclusion criteria: aggravated conditions who would not be able to continue with the study; other accompanying diseases that may directly affect the fatigue severity such as chronic obstructive pulmonary disease, advanced heart failure, asthma, and malignant tumours; diagnosed with anxiety or major depression by a psychiatrist; could not communicate in Turkish; used another complementary and integrative approach within the study period<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (30/31); control group (31/31)<br>• Mean age ± SD (years): intervention group (52.0 ± 15.16); control group (58.68 ± 14.57)<br>• Sex (M/F): intervention group (15/15); control group (20/11)<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: intervention group (6/30); control group (12/31)<br>  ◦ Hypertension: intervention group (17/30); control group (13/31)<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Benson relaxation technique combined with music therapy for 8 weeks<br>Control group<br>• No intervention for 8 weeks |

**Eroglu 2022** *(Continued)*

| | |
|---|---|
| | Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data not available<br>• Fatigue<br>  ○ PFS: assessed at baseline, weeks 4, 8, 10<br>  ■ Behavioural/severity<br>  ■ Affective<br>  ■ Sensory<br>  ■ Cognitive/mood<br>• Anxiety<br>  ○ HADS: assessed at baseline, weeks 4, 8, 10 (Appendix 3)<br>• Depression<br>  ○ HADS: assessed at baseline, weeks 4, 8, 10 |
| Notes | Additional information<br>• Funding: This study was a masters dissertation of H.E. and Z.G.M. was the advisor<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: NCT04299256<br>• A priori published protocol was reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "A blinded study could not be conducted as per the limitations of blinding for non-pharmacological tests." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Quote: "The second investigator randomly assigned all the participants to the intervention group (n = 31) and the control group (n = 31) in a 1:1 ratio using a random number table. After the allocation of all participants, 1 patient in the intervention group did not want to participate due to psychological/familial issues. Finally, the study was completed with a total of 61 patients, 30 in the intervention group and 31 in the control group."<br><br>Comment: 30/31 participants in the intervention group and 31/31 participants in the control group completed the study (< 5% loss to follow-up with slight |

**Eroglu 2022** *(Continued)*

| | | |
|---|---|---|
| | | differences between groups). Reasons for discontinuation were provided and they were not related to the intervention |
| Selective reporting (reporting bias) | High risk | Protocol was published. Fatigue was reported (Unruh 2013) in accordance with a pre-specified analysis plan, using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was not extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and authors had no conflicts of interest. No other source of bias were apparent |

**Fatigue-HD 2019**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 12 weeks<br>• Time frame: February 2019 to August 2019 |
| Participants | Study characteristics<br>• Setting: multicentre (6 dialysis clinics in Calgary)<br>• Country: Canada<br>• Inclusion criteria: aged ≥ 18 years; HD ≥ 3 months at the time of recruitment; were clinically and cognitively stable (able to provide informed consent) and scored an average of ≥ 4 on items 5, 7, 8 and 9 from the FSS, English-speaking<br>• Exclusion criteria: plan in place to discontinue in-centre HD within 6 months of recruitment; inadequate written and verbal English comprehension for study activities; if they resided in a long-term care facility or if they had a visual impairment that would preclude them from engaging with study materials<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (8/15); control group (14/15)<br>• Mean age ± SD (years): intervention group (60.0 ± 15.1); control group (64.8 ± 14.4)<br>• Sex (M/F): overall (18/12); intervention group (8/7); control group (10/5)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): not reported<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: intervention group (6/15); control group (9/15)<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): intervention group (6/15); control group (3/15) |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue |

**Fatigue-HD 2019** *(Continued)*

| | |
|---|---|
| | Intervention group<br>• PEP programme<br>Control group<br>• Education<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ○ FSS: assessed at week 1 and 12<br>  ○ MFIS: assessed at week 1 and 12 (Appendix 3)<br>• SONG-HD Fatigue (Appendix 3)<br>• Life participation<br>• COPM-Performance Scale: assessed at week 1 and 12 (Appendix 3)<br>• Fatigue management questionnaire: assessed at week 1 and 12 (Appendix 3)<br>• COPM-Satisfaction subscale: assessed at week 1 and 12<br>• NLI: assessed at week 1 and 12 (Appendix 3) |
| Notes | Additional information<br>• Funding: Canadian Institutes of Health Research (CIHR) Fellowship Program, and the Kidney Research Scientist Core Education andNational Training (KRESCENT) programme<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: NCT03825770<br>• A priori published protocol was reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Participants were randomised using a computer-generated random number sequence according to permuted blocked randomisation, stratified by dialysis unit."<br>Comment: A computer-generated random number sequence is considered as low risk of bias |
| Allocation concealment (selection bias) | Low risk | Quote: "We concealed allocation by having a research manager not otherwise involved with the study, provide treatment allocation to study coordinators over the phone." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "Participants were blinded to treatment allocation. It was not feasible to blind study coordinators, given the extensive training they received to learn to administer the intervention compared with the control."<br>Comment: A single blind study is considered as high risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote from the study protocol: "As the proposed study is small and its risks to participants are low, a Data and Safety Monitoring Board is not needed."<br>Comment: Fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allo- |

**Fatigue-HD 2019** *(Continued)*

| | | |
|---|---|---|
| | | cation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 8/15 participants in the intervention group and 14/15 participants in the control group completed the study (> 5% lost to follow-up). There were differences between treatment groups. Reasons for discontinuation were provided |
| Selective reporting (reporting bias) | High risk | Protocol was published. Fatigue was reported in accordance with a pre-specified analysis plan, using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was not extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and authors had no conflicts of interest. No other source of bias were apparent |

**Fatouros 2010**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br>• Cross-over RCT<br>Study dates<br>• Duration of follow-up: 8 weeks<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Setting: single centre<br>• Country: Greece<br>• Inclusion criteria: chronic therapy for at least 1 year before the study; 4-hours HD sessions 3 times/week (mean Kt/V at least 1.4) with standard bicarbonate dialysis using biocompatible membranes (low-flux polysulfone); Hb levels at least 11 g/dL (ESAs were administered to all patients); absence of antioxidant supplementation (vitamin E, statins, or any medication for the reduction of uric acid); adequate nourishment (total serum protein 6.8 ± 0.5 g/dL and serum albumin 4.3 ± 0.2 g/dL; no residual renal function; ability to perform stationary cycling; had not received any L-carnitine treatment in the previous 6 months<br>• Exclusion criteria: the presence of any active infectious/inflammatory disease (serum CRP levels at least 0.5 ± 0.4 mg/dL); uncontrolled hypertension and DM; diseases that might interfere with exercise capacity and/or be exacerbated by activity such as Ischaemic cardiopathy or symptoms related to coronary artery disease, anaemia (Hb levels < 11 g/dL, HCT < 33%), chronic lung disease, and orthopaedic disorders; use of steroids, immunosuppressives, and psychotropic agents; hospitalisation within 3 months before the study<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (not reported/6); control group (not reported/6)<br>• Mean age ± SD (years): overall (53.8 ± 2.3)<br>• Sex (M/F): intervention group (6/0); control group (6/0)<br>• Dialysis type: HD |

**Fatouros 2010** *(Continued)*

- Mean dialysis vintage ± SD (years): overall (7.08 ± 0.24)
- Comorbidities
  - CVD: not reported
  - Diabetes: not reported
  - Hypertension: not reported
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study reported fatigue (reported as time to fatigue)<br>Intervention group<br>• L-Carnitine (IV): 20 mg/kgof dry body weight<br>Control group<br>• Placebo: saline of an equal dose<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• $VO_{2peak}$, 12-lead ECG, perceived exertion, respiratory quotient, heart rate, time to exhaustion, brachial artery cuff pressure, exercise time to exhaustion: assessed before and after the first phase<br>• Heart rate: assessed before and after the first phase<br>• Blood samples (blood carnitine, lactate, malondialdehyde, protein carbonyls, reduced and oxidized glutathione, antioxidant capacity, catalase, glutathione peroxidase activity, uric acid): assessed before and after the first phase<br>• Fatigue (time to fatigue): time frame not clearly stated<br>• Nutrition evaluation (5-day diet recalls): assessed before and after the first phase<br>• Anthropometric profile (body weight, body mass index, percentage body fat): assessed before and after the first phase |
| Notes | Additional classification<br>• Funding: Democritus University Medical School. The funding sources played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication. The authors state that the results of the present study do not constitute endorsement by the American College of Sports Medicine<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |

**Fatouros 2010** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "Twelve haemodialysis patients received either L-carnitine (20 mg/kg$^{-1}$ IV) or placebo in a double-blind, placebo-controlled, counterbalanced, and cross-over design for 8 weeks."<br><br>Comment: Although the author reported that the study used a double-blind design, information about blinding of participants and investigators were not clearly stated |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "In their second visit, subjects returned their diet recall forms and underwent a progressive diagnostic test to exhaustion (GXT) on a stationary cycle ergometer to evaluate their peak oxygen consumption ($VO_2$ peak) while blood was collected before and immediately after testing."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Attrition was not reported in sufficient detail to permit judgment in the first phase of the study |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan was not reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was not reported in a format that was extractable for meta-analysis (cross-over study: data related to the first period were not reported). All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | No data were available to assess the possible imbalance between groups. Funding was unlikely to influence the data analysis and authors had no conflicts of interest |

**FHN DAILY 2007**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 12 months<br>• Time frame: patients were enrolled between March 2006 and May 2009 and the trials concluded in May 2010 |
| Participants | Study characteristics<br>• Setting: multicentre (2 clinical core consortiums headquartered at the Renal Research Institute in New York City and University of California San Francisco (later transferred to Stanford University; 10 clinical centres in the United States and Canada)<br>• Country: USA<br>• Inclusion criteria: patients undergoing HD 3 times/week; concomitant medical conditions; the ability to complete cardiac MRI; verbal communication ability in English or Spanish to permit completion of |

**FHN DAILY 2007** *(Continued)*

the quality of life interview; residential proximity to the dialysis units; achieved mean eKt/V at least 1.1 on at least two consecutive baseline sessions; patients aged 13 to 17 years were permitted

- Exclusion criteria: unable or unwilling to follow the study protocol for any reason (including mental incompetence); unable or unwilling to provide informed consent or sign the Institutional Review Board-approved consent form; requires HD > 3 times/week owing to medical comorbidity; currently pregnant, or planning to become pregnant within the duration of follow-up; currently on home HD; history of poor adherence to 3 times/week HD or PD; inability or unwillingness to come for in-centre HD 6 days/week, including inability to arrange adequate transportation;expected geographic unavailability at a participating HD unit for 42 consecutive weeks or 44 weeks total during follow-up; currently in an acute or chronic care hospital; contraindication to heparin, including allergy- or heparin-induced thrombocytopenia; expectation that native kidneys will recover; currently on daily or nocturnal HD or < 3 months as the patient discontinued daily or nocturnal HD; < 3 months as patient returned to HD after kidney transplantation or use of an alternative dialysis modality (such as PD); current use of investigational drugs or participation in another clinical trial; scheduled for living donor kidney transplant, change to PD, or plans to relocate to a non-study centre within the follow-up period; life expectancy < 6 months; medical history that might limit the patient's ability to take the trial treatments and complete the full duration of follow-up (including currently receiving chemo or radiotherapy for a malignant neoplastic disease other than localized non-melanoma skin cancer, active systemic infection (including tuberculosis, disseminated fungal infection, active AIDS), and cirrhosis with encephalopathy); medical conditions that would prevent the patient from receiving the cardiac MRI procedure (e.g. inability to remain still for the procedure, a metallic object in the body that is a contraindication to MRI such as cardiac pacemaker, cochlear implant, brain aneurysm clips, mechanical heart valves, recently placed artificial joints, and older vascular stents); inability to communicate verbally in English or Spanish; vascular access being used for HD is a non-tunnelled catheter; residual kidney function was urea clearance 3 mL/min/35 L urea volume

Baseline characteristics

- Number (analysed/randomised): intervention group (99/125); control group (84/120); however number of participants analysed varied based on the outcome (here is reported the lowest number of participants analysed, considering the outcomes of interest of the review)
- Mean age ± SD (years): intervention group (48.9 ± 13.6); control group (52.0 ± 14.1)
- Sex (M/F): intervention group (78/47); control group (73/47)
- Dialysis type: HD
- Median dialysis vintage. IQR (years): intervention group (3.85, 0.69 to 17.31)); control group (3.40, 0.58 to 12.94)
- Comorbidities
  - CVD: not reported
  - Diabetes: intervention group (50/125); control group (50/120)
  - Hypertension: intervention group (117/125); control group (111/120)
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study targeting fatigue<br><br>Intervention group<br>• Six times/week in-centre daily HD (1.5 to 2.75 hours/session)<br><br>Control group<br>• Conventional 3 times/week in-centre HD (2.5 to 4.5 hours/session)<br><br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported |

**FHN DAILY 2007** *(Continued)*

- Fatigue outcome measures used: validation data available
- Change during 12 months in LV mass
  - Cardiac magnetic resonance imaging: assessed until 12 months
- Death: assessed until the end of treatment
- Change in 12 months of the self-reported physical health
  - SF-36: assessed at baseline, 4 and 12 months
    - Physical Health Composite
    - Mental Health Composite
    - Physical functioning
    - Physical health problems
    - Pain
    - General health perceptions
    - Emotional well-being
    - Emotional health problem
    - Social functioning
    - Energy/fatigue
  - RAND Physical Health Composite: assessed at baseline, 4 and 12 months
- Short Physical Performance Battery (range from 1 to 12; higher values represent better physical function): assessed until 12 months
- HUI-3 Multi-attribute utility scale (range from 0 to 1; higher scores represent better health): assessed until 12 months
- Feeling Thermometer Scores (range from 0 to 100, with 100 representing best imaginable health state): assessed until 12 months
- Short Physical Performance Battery (range from 1 to 12; higher values represent better physical function): assessed until 12 months
- Depression
  - BDI: assessed at baseline, 4 and 12 months
- Cognitive function
  - Modified Mini-Mental Status (score ranges from 0 to 100; higher values represent better cognitive function): assessed at baseline, 4 and 12 months
    - Orientation
    - Attention
    - Calculation
    - Language
    - Short-term memory
- Executive function
  - Trial Making B score (10-minute limit) (ranges from 0 to 600 seconds; less time represents better executive control and less cognitive impairment): assessed at baseline, 4 and 12 months
- Trial Making B score (5-minute limit) (ranges from 0-300 seconds; less time represents better executive control and less cognitive impairment): assessed at baseline, 4 and 12 months
- Attention
  - Digit Symbol Substitution Test: assessed until 12 months
  - Trail-Making Test, Form A: assessed until 12 months
- Psychomotor speed
  - Grooved pegboard: assessed until 12 months
- Memory
  - Rey Auditory Verbal Learning Test, immediate and delayed recall: assessed until 12 months
  - Letter-Number Sequencing: assessed until 12 months
- Verbal fluency
  - Controlled Oral Word Association Test: assessed until 12 months
- Sleep and hour slept each night
- Sleep Problems Index (ranges from 0 to 100; higher values represent more problems): assessed at baseline, 4 and 12 months
- Caregiver burden

**FHN DAILY 2007** *(Continued)*

- Cousineau Caregiver Burden (ranges from 0 to 100; higher scores represent greater anxiety. Scores were calculated for only participants with unpaid caregivers): assessed at baseline, 4 and 12 months
- Laboratory results (pre-dialysis SCr, phosphate, urea nitrogen, albumin, interdialytic weight gain, extracellular fluid load, normalized protein catabolic rate, BMI, lean body mass by single frequency bioimpedance analysis, calcium, calcium-phosphate product, PTH, pre-dialysis Hb, iron, transferrin, ferritin): assessed at baseline 4 and 12 months
- Dialysis outcomes (target dry weight, prescribed treatment time): assessed at 12 months
- Safety (vascular access complication, iron losses, metabolic complication): assessed at 12 months
- Weekly average BP: assessed until 12 months
- Weekly average pre-dialysis pulse pressure: assessed until 12 months
- Proportion of patients with weekly average pre-dialysis SBP < 110 mm Hg: until 12 months
- Number of prescribed antihypertensive agents: assessed until 12 months
- Eritropoiesys: assessed at 12 months
- Hospitalisation, cardiovascular hospitalisation and total hospital days: assessed at 12 months
- Cost-effectiveness: assessed at 12 months
- End-diastolic, end-systolic, and stroke volumes; ejection fraction; cardiac output: assessed until 12 months
- Heart rate variability measures: assessed until 12 months
- Rate of intradialytic hypotension episodes: assessed until 12 months
- Phosphate binder dose, Vitamin D analogue dose: assessed until 12 months
- Hypertension: assessed until 12 months

| | |
|---|---|
| Notes | Additional information<br>• Funding: NIDDK, CMS, National Institutes of Health (NIH) Research Foundation, Fresenius Medical Care, Renal Research Institute, and Satellite Health Care. These trials were supported by NIDDK grantsU01DK066597 (Data Coordinating Center), 2U01DK066579 (Dr Levin), 3U01DK066481 (Dr Chertow), and 3U01DK066480 (Dr Rocco)<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: NCT00264758<br>• A priori published protocol: accessible at https://clinicalresearch.ccf.org/fhn/index.html |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote from Suri 2007: "Eligible subjects are then randomly assigned 1:1 to the frequent haemodialysis intervention or control arms, by a central, web-based program. Randomization is stratified by clinical centre and diabetic status, using permuted blocks."<br><br>Comment: A web-based program is considered as low risk of bias. No imbalance between intervention groups was apparent |
| Allocation concealment (selection bias) | Unclear risk | Quote from FHN Trial Group 2010: "Randomization was stratified according to clinical centre and diabetes status, with the use of randomly permuted blocks. Although treatment assignments could not be concealed, between group comparisons of the outcomes were concealed from the investigators throughout the course of the trial." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote from Kuella 2013: "Unblinded intervention."<br><br>Comment: An open-label study is considered as high risk of bias. Possible deviations from the intended intervention that arose from the trial context were not reported |

**FHN DAILY 2007** *(Continued)*

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Quote from Suri 2013: "A vascular access outcomes committee blinded to group allocation reviewed all access events to determine whether the event met the definition of repair or loss. [...] An independent outcomes committee blinded to group allocation reviewed these forms, discharge summaries, and supplementary chart information to determine whether each death or hospitalisation was access related or non–access related."<br><br>Quote from Suri 2014: "Patients also completed several questionnaires that were centrally administered by telephone before randomisation and 4 (F4) and 12 months (F12) after randomisation."<br><br>Quote from Ornt 2013: "An independent data and Safety Monitoring Board reviewed safety data and interim results."<br><br>Comment: An independent Data Safety Monitoring Board assessed the outcomes.The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was stated that outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may not have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely |
| Incomplete outcome data (attrition bias) All outcomes | High risk | Overall, attrition seemed to be > 5% of loss to follow-up with some difference between groups. Attrition was not reported in sufficient detail to permit judgment in the first phase of the study. Tamura 2010 reported that 239 participants were randomised but there were no data on the missing participants |
| Selective reporting (reporting bias) | Low risk | Protocol was published. Fatigue was reported (Unruh 2013) in accordance with a pre-specified analysis plan, using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was not extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Founding were unlikely to influence the data analysis and authors had no conflicts of interest |

**FHN NOCTURNAL 2007**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 12 months<br>• Time frame: patients were enrolled between March 2006 and May 2009 and the study concluded in May 2010 |
| Participants | Study characteristics<br>• Setting: multicentre (1 clinical core consortium headquartered at Wake Forest University in Winston-Salem, NC; 9 clinical centres in the USA and Canada)<br>• Country: USA |

**FHN NOCTURNAL 2007** *(Continued)*

- Inclusion criteria: adults undergoing HD 3 times/week; concomitant medical conditions; the ability to complete cardiac MRI; verbal communication ability in English or Spanish to permit completion of the QoL interview; residential proximity to the dialysis units; achieved mean eKt/V at least 1.1 on at least two consecutive baseline sessions
- Exclusion criteria: unable or unwilling to follow the study protocol for any reason (including mental incompetence); unable or unwilling to provide informed consent or sign the Institutional Review Board-approved consent form; requires
- HD > 3 times/week owing to medical comorbidity; currently pregnant, or planning to become pregnant within the duration of follow-up; currently on home HD; history of poor adherence to 3 times/week HD or PD; home environment unsuitable for performing home HD; expected inability to successfully complete the home nocturnal HD training protocol for any reason (e.g. both patient and caregiver are likely unable to be trained, or patient unable and no suitable caregiver exists); expected geographic unavailability at a participating HD unit for 42 consecutive weeks or 45 weeks total during follow-up; currently in an acute or chronic care hospital; contraindication to heparin, including allergy- or heparin-induced thrombocytopenia; expectation that native kidneys will recover; currently on daily or nocturnal HD or less than 3 months as the patient discontinued daily or nocturnal HD; less than 3 months as patient returned to HD after kidney transplantation or use of an alternative dialysis modality (such as PD); current use of investigational drugs or participation in another clinical trial; scheduled for living donor kidney transplant, change to PD, or plans to relocate to a non-study centre within the follow-up period; life expectancy less than 6 months; medical history that might limit the patient's ability to take the trial treatments and complete the full duration of follow-up (including currently receiving chemo or radiotherapy for a malignant neoplastic disease other than localized non-melanoma skin cancer, active systemic infection (including tuberculosis, disseminated fungal infection, active AIDS), and cirrhosis with encephalopathy); medical conditions that would prevent the patient from receiving the cardiac MRI procedure (e.g., inability to remain still for the procedure, a metallic object in the body that is a contraindication to MRI such as cardiac pacemaker, cochlear implant, brain aneurysm clips, mechanical heart valves, recently placed artificial joints, and older vascular stents); inability to communicate verbally in English or Spanish; vascular access being used for haemodialysis is a non-tunnelled catheter; eGFR 10 mL/min/1.73 $m^2$

Baseline characteristics

- Number (analysed/randomised): intervention group (34/45); control group (37/42); however numbers of participants analysed varied in base of the outcome (here is reported the lowest number of participants analysed, considering the outcomes of interest of the review)
- Mean age ± SD (years): intervention group (51.7 ± 14.4); control group (54.0 ± 12.9)
- Sex (M/F): intervention group (29/16); control group (28/14)
- Dialysis type: HD
- Median dialysis vintage. IQR (years): intervention group (1.32, 0.09 to 12.55)); control group (0.53, 0.10 to 6.00)
- Comorbidities
  - CVD: not reported
  - Diabetes: intervention group (19/45); control group (18/42)
  - Hypertension: intervention group (41/45); control group (39/42)
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study targeting fatigue<br><br>Intervention group<br>• 6-times/week home nocturnal HD(6-8 h/session)<br><br>Control group<br>• Conventional 3-times/week HD (2.5-5 h/session)<br><br>Co-interventions |

**FHN NOCTURNAL 2007** *(Continued)*

- Not reported

| | |
|---|---|
| Outcomes | Outcomes reported |

- Fatigue outcome measures used: validation data available
- Change during 12 months in LV mass
  - Cardiac magnetic resonance imaging: assessed until 12 months
- Death (assessed until the end of treatment)
- Change in 12 months of the self-reported physical health
  - SF-36: assessed at baseline, 4 and 12 months
    - Physical Health Composite
    - Mental Health Composite
    - Physical functioning
    - Physical health problems
    - Pain
    - General health perceptions
    - Emotional well-being
    - Emotional health problem
    - Social functioning
    - Energy/fatigue
  - RAND Physical Health Composite: assessed at baseline, 4 and 12 months
- Short Physical Performance Battery (range from 1 to 12; higher values represent better physical function): assessed until 12 months
- HUI-3 Multi-attribute utility scale (range from 0 to 1; higher scores represent better health): assessed until 12 months
- Feeling Thermometer Scores (range from 0 to 100, with 100 representing best imaginable health state): assessed until 12 months
- Short Physical Performance Battery (range from 1 to 12; higher values represent better physical function): assessed until 12 months
- Depression
  - BDI: assessed at baseline, 4 and 12 months
- Cognitive function
  - Modified Mini-Mental Status (score ranges from 0-100; higher values represent better cognitive function): assessed at baseline, 4 and 12 months
    - Orientation
    - Attention
    - Calculation
    - Language
    - Short-term memory
- Executive function
  - Trial Making B score (10-minute limit) (ranges from 0 to 600 seconds; less time represents better executive control and less cognitive impairment): assessed at baseline, 4 and 12 months
- Trial Making B score (5-minute limit) (ranges from 0-300 seconds; less time represents better executive control and less cognitive impairment): assessed at baseline, 4 and 12 months
- Attention
  - Digit Symbol Substitution Test: assessed until 12 months
  - Trail-Making Test, Form A: assessed until 12 months
- Psychomotor speed
  - Grooved pegboard: assessed until 12 months
- Memory
  - Rey Auditory Verbal Learning Test, immediate and delayed recall: assessed until 12 months
  - Letter-Number Sequencing: assessed until 12 months
- Verbal fluency
  - Controlled Oral Word Association Test: assessed until 12 months
- Sleep and hour slept each night

**FHN NOCTURNAL 2007** *(Continued)*

- Sleep Problems Index (ranges from 0 to 100; higher values represent more problems): assessed at baseline, 4 and 12 months
- Caregiver burden
- Cousineau Caregiver Burden (ranges from 0 to 100; higher scores represent greater anxiety. Scores were calculated for only participants with unpaid caregivers): assessed at baseline, 4 and 12 months
- Laboratory results (pre-dialysis SCr, phosphate, urea nitrogen, albumin, interdialytic weight gain, extracellular fluid load, normalized protein catabolic rate, BMI, lean body mass by single frequency bioimpedance analysis, calcium, calcium-phosphate product, PTH, pre-dialysis Hb, iron, transferrin, ferritin): assessed at baseline 4 and 12 months
- Dialysis outcomes (target dry weight, prescribed treatment time): assessed at 12 months
- Safety (vascular access complication, iron losses, metabolic complication): assessed at 12 months
- Weekly average BP: assessed until 12 months
- Weekly average pre-dialysis pulse pressure: assessed until 12 months
- Proportion of patients with weekly average pre-dialysis SBP < 110 mm Hg: until 12 months
- Number of prescribed antihypertensive agents: assessed until 12 months
- Eritropoiesys: assessed at 12 months
- Hospitalisation, cardiovascular hospitalisation and total hospital days: assessed at 12 months
- Cost-effectiveness: assessed at 12 months
- End-diastolic, end-systolic, and stroke volumes; ejection fraction; cardiac output: assessed until 12 months
- Heart rate variability measures: assessed until 12 months
- Rate of intradialytic hypotension episodes: assessed until 12 months
- Phosphate binder dose, Vitamin D analogue dose: assessed until 12 months
- Hypertension: assessed until 12 months

| | |
|---|---|
| Notes | Additional information<br>• Funding: NIDDK, CMS, National Institutes of Health (NIH) Research Foundation, Fresenius Medical Care, Renal Research Institute, and Satellite Health Care. These trials were supported by NIDDK grantsU01DK066597 (Data Coordinating Center), 2U01DK066579 (Dr Levin), 3U01DK066481 (Dr Chertow), and 3U01DK066480 (Dr Rocco)<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: NCT00271999<br>• A priori published protocol: accessible at https://clinicalresearch.ccf.org/fhn/index.html |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote from Suri 2007: "Eligible subjects are then randomly assigned 1:1 to the frequent HD intervention or control arms, by a central, web-based program. Randomization is stratified by clinical centre and diabetic status, using permuted blocks."<br><br>Comment: A web-based program is considered as low risk of bias. No imbalance between intervention groups was apparent |
| Allocation concealment (selection bias) | Unclear risk | Quote from FHN Trial Group 2010: "Randomization was stratified according to clinical centre and diabetes status, with the use of randomly permuted blocks. Although treatment assignments could not be concealed, between group comparisons of the outcomes were concealed from the investigators throughout the course of the trial." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote from Kuella 2013: "Unblinded intervention." |

**FHN NOCTURNAL 2007** *(Continued)*

| | | |
|---|---|---|
| | | Comment: An open-label study is considered as high risk of bias. Possible deviations from the intended intervention that arose from the trial context were not reported |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Quote from Suri 2013: "A vascular access outcomes committee blinded to group allocation reviewed all access events to determine whether the event met the definition of repair or loss. [...] An independent outcomes committee blinded to group allocation reviewed these forms, discharge summaries, and supplementary chart information to determine whether each death or hospitalisation was access related or non–access related."<br><br>Quote from Suri 2014: "Patients also completed several questionnaires that were centrally administered by telephone before randomisation and 4 (F4) and 12 months (F12) after randomisation."<br><br>Quote from Ornt 2013: "An independent data and Safety Monitoring Board reviewed safety data and interim results."<br><br>Comment: An independent Data Safety Monitoring Board assessed the outcomes.The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was stated that outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may not have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely |
| Incomplete outcome data (attrition bias) All outcomes | High risk | Overall, attrition seemed to be >5% of lost to follow-up with some difference between groups. Attrition was not reported in sufficient detail to permit judgment in the first phase of the study. Tamura 2010 reported that 84 participants were randomised but there were no data on the missing participants |
| Selective reporting (reporting bias) | Low risk | Protocol was published. Fatigue was reported (Unruh 2013) in accordance with a pre-specified analysis plan, using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was not extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Fundings were unlikely to influence the data analysis and authors had no conflicts of interest |

**Figueiredo 2018**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 16 weeks<br>• Time frame: January 2015 to December 2015 |
| Participants | Study characteristics<br>• Setting: not reported<br>• Country: Brazil |

**Figueiredo 2018** *(Continued)*

- Inclusion criteria: > 18 years; not receiving anti-inflammatory or antiallergic medication; under HD treatment 3 times/week for at least 3 months, and with arteriovenous fistula for HD access
- Exclusion criteria: any contraindication to physical exercise or inability to perform the functional tests

Baseline characteristics

- Number (analysed/randomised): intervention group 1 (10/11); intervention group 2 (10/13); intervention group 3 (11/13)
- Mean age (years) (SD not reported): intervention group 1 (52.8); intervention group 2 (49.5); intervention group 3 (45.2)
- Sex (M/F): intervention group 1 (7/4); intervention group 2 (10/3); intervention group 3 (9/4)
- Dialysis type: HD
- Mean dialysis vintage (years) (SD not reported): intervention group 1 (4.4); intervention group 2 (3.0); intervention group 3 (4.9)
- Comorbidities
  - CVD: not reported
  - Diabetes: intervention group 1 (2/11); intervention group 2 (2/13); intervention group 3 (3/13)
  - Hypertension: not reported
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group 1<br>• Inspiratory muscle training at 50% of MIP for 8 weeks<br>Intervention group 2<br>• Aerobic training low intensity for 8 weeks<br>Intervention group 3<br>• Combined training (inspiratory muscle training + aerobic training) for 8 weeks<br>Co-interventions<br>• The dialysis prescription and medication therapy remained unchanged during the study |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Functional capacity (incremental shuttle walk test): assessed at baseline, weeks 8 and 16<br>• MIP and lower limbs strength (sit-to-stand test of 30 seconds): assessed at baseline, weeks 8 and 16<br>• Plasma levels of IL-6, soluble tumour necrosis factor receptor 1 and 2, adiponectin, resistin and leptin, redox status parameters: assessed at baseline, weeks 8 and 16<br>• Anthropometric/physical parameters (weight, BMI, waist circumference and body fat percentage): assessed at baseline, weeks 8 and 16<br>• QoL<br>  ◦ KDQOL-SF: assessed at baseline, weeks 8 and 16 |
| Notes | • Funding: FundacËão de Amparo à Pesquisa do Estado de Minas Gerais, APQ-03093-15;<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: Registro Brasileiro de Ensaios clõÂnicos RBR-4hv9rs<br>• A priori published protocol was reported |
| ***Risk of bias*** | |

**Figueiredo 2018** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement. |
| Allocation concealment (selection bias) | Low risk | Quote: "Randomisation was performed using individual allocation codes placed within opaque, sealed envelopes by a person having no contact with the participants." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant/investigators beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. It was not stated if the monitoring group was blinded to the treatment assigned. However, objective and subjective outcomes were assessed. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Quote: "Intention-to-treat."<br><br>Comment: 10/11 participants in the intervention group 1 (IMT), 10/13 participants in the intervention group 2 (at), and 11/13 participants in the intervention group3 3 (combination) completed the study. However ITT was performed. |
| Selective reporting (reporting bias) | Low risk | Information about the protocol and the statistical analysis plan were reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was not extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were reported, but fatigue was not extractable. |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and authors had conflicts of interests. No other source of bias were apparent. |

**Foley 2000**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 48 weeks<br>• Time frame: May 1995 to December 1996 |
| Participants | Study characteristics |

**Foley 2000** *(Continued)*

- Setting: multicentre
- Country: Canada
- Inclusion criteria: > 17 years; maintenance HD > 3 months; LV hypertrophy (LV mass indexed to a body surface area > 131 g/m$^2$ in males and 100 g/m$^2$ in females) or LV dilation; a Hb between 9 and 11 g/dL in the month prior to randomisation; stable vascular access for the previous 3months; and life expectancy > 18 months
- Exclusion criteria: angina pectoris, MI, coronary artery bypass surgery, percutaneous transluminal angioplasty or congestive heart failure within the previous 12 months; active bleeding; uncorrected iron deficiency; valvular heart disease for which surgical intervention was planned within 1 year; and IV iron dextran intolerance

Baseline characteristics

- Number (analysed/randomised): intervention group 1 (68/73); intervention group 2 (66/73)
- Mean age ± SD (years): overall (61.5, SD not reported)
- Sex (M/F): intervention group 1 (44/29); intervention group 2 (47/26)
- Dialysis type: HD
- Dialysis vintage (years) (mean ± SD): not reported
- Comorbidities
  - CVD: not reported
  - Diabetes: not reported
  - Hypertension: not reported
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group 1<br>• Epoetin alpha (SC) to achieve Hb levels of 9.5 to 10.5 g/dL<br>Intervention group 2<br>• Epoetin alpha (SC) to achieve Hb levels of 13 to 14 g/dL<br>Co-interventions<br>• Epoetin alpha (SC) was administered in all patients<br>• Dosing guidelines were similar in the high- and low-target Hb groups |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Change in LV mass index in those with concentric LV hypertrophy: assessed from baseline to 48 weeks<br>• Change in cavity volume index in those with LV dilation: assessed from baseline to 48 weeks<br>• Pre-dialysis Hb: assessed every week for 24 weeks and then every 2 weeks<br>• BP: assessed every week for 24 weeks and then every 2 weeks<br>• TSAT: assessed every 2 weeks for 24 weeks and then every 4 weeks<br>• Serum chemistry (including Kt/V): assessed monthly<br>• ECG carried out on the day after a HD session, with the patients within 1 kg of dry weight): assessed at baseline and at 48 weeks<br>• HRQoL<br>  ◦ KDQ: assessed at baseline and at 12, 24, and 48 weeks (the assessment on week 12 was decided by investigator due to logistic difficulties)<br>  ▪ Fatigue<br>  ▪ Depression |

**Foley 2000** *(Continued)*

- Relationships with others
- Frustration
- Physical symptoms

- SF-36: assessed at baseline and at 12, 24, and 48 weeks (the assessment on week 12 was decided by investigator due to logistic difficulties)
  - Physical function
  - Social function
  - Physical role
  - Emotional role
  - Mental health
  - Energy
  - Pain
  - General health perception
- Health Utilities Index (Appendix 3): assessed at baseline and at 12, 24, and 48 weeks (the assessment on week 12 was decided by investigator due to logistic difficulties)
  - Sensation
  - Mobility
  - Emotion
  - Cognition
  - Self-care
  - Pain
  - Fertility

- Incidence of arteriovenous access thrombosis: assessed until the end of treatment
- Cardiac events (including ischaemic heart disease): assessed until the end of treatment
- Death: assessed until the end of treatment
- Hospitalisation (admissions and time spent in the hospital): evaluated over a mean duration of 309 days

| | |
|---|---|
| Notes | Additional information<br>• Funding: Janssen-Ortho Inc., Toronto, Canada. Dr. Foley and Dr. Parfrey designed and analysed this study<br>• Conflicts of interest/disclosures: Dr Foley and several of the other authors have received grant/research support, consultant positions, and/or speaker's bureau affiliations with Janssen Ortho, Amgen and Roche<br>• Trial registration identification number: not applicable<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote from Foley 2000: "This was a 48-week, open-label, randomised, controlled trial."<br><br>Comment: An open-label study was considered as high risk of bias |

**Foley 2000** *(Continued)*

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Quote: "A study monitoring group (R.N.F., P.S.P., and J.M.) at the coordinating centre in St. John's met weekly to review each patient's haemoglobin level, epoetin dose, iron saturation, and blood pressure level."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting (bot sure if the committee assessed also fatigue). Participant/investigators beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. It was not stated if the monitoring group was blinded to the treatment assigned. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias) All outcomes | High risk | Quote: "Follow-up studies were unavailable in 12 patients, 5 in the low target and 7 in the high target group. The reasons included transplantation (3), death (3), withdrawal of consent (3), Ischaemic heart disease (1) and other causes (1)."<br><br>Comment: 68/73 participants in the intervention group 1 (epoetin alpha to achieve HB of 9.5-10.5 g/dL) and 66/73 participants in the intervention group 2 (epoetin alpha to achieve Hb of 13-14 g/dL) completed the study (> 5% lost to follow-up, with differences between groups). Some reasons for discontinuations appeared to be related with the intervention. However, analyses were performed in 45 and 49 participants, respectively |
| Selective reporting (reporting bias) | Low risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was not extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were reported, but fatigue was not extractable |
| Other bias | High risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding (pharmaceutical company) could influenced the data analysis and authors had conflicts of interests |

**Fukuda 2015**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 12 weeks<br>• Time frame: March to August 2008 |
| Participants | Study characteristics<br>• Setting: multicentre (4 dialysis centres in the Osaka district in Japan)<br>• Country: Japan<br>• Inclusion criteria: 30 to 70 years; treated for ESKD for at least 1 year with afternoon HD 3 times/week; patients who had been taking vitamins before recruitment were included after a washout phase of at least 2 weeks<br>• Exclusion criteria: active malignant tumour; pregnancy; lactation |

**Fukuda 2015** *(Continued)*

Baseline characteristics

- Number (analysed/randomised): intervention group (87/103); control group (86/99)
- Mean age ± SD (years): intervention group (55.6 ± 10.0); control group (56.2 ± 8.9)
- Sex (M/F): intervention group (71/16); control group (72/15)
- Dialysis type: HD
- Mean dialysis vintage ± SD (years): intervention group (10.6 ± 8.26); control group (11.0 ± 7.74)
- Comorbidities
  - CVD: not reported
  - Diabetes: intervention group (21/87); control group (21/87)
  - Hypertension: not reported
  - Depression: not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study targeting fatigue<br><br>Intervention group<br>• Active treatment (containing vitamin B1, vitamin B2, niacin, vitamin B6, vitamin B12, folic acid, vitamin C, carnitine, coenzyme Q10, naive galacto-oligosaccharide, and zinc)<br><br>Control group<br>• Placebo<br><br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Changes in the acute and chronic fatigue<br>  ○ 4-point VAS: assessed at 0, 4, and 12 weeks<br>• Anxiety and depression<br>• Loss of attention and memory<br>• Pain<br>• Fatigue<br>• Overwork<br>• Autonomic imbalance<br>• Sleep problems<br>• Infection<br>• HRQoL<br>  ○ KDQOL-SF 36: assessed at 0, 4, and 12 weeks<br>  ■ Physical functioning<br>  ■ Role-physical<br>  ■ Bodily pain<br>  ■ Role-emotional<br>  ■ General health<br>  ■ Vitality<br>  ■ Social functioning<br>  ■ Mental health<br>  ■ Symptoms of the kidney-disease-specific (symptoms/problems, effects of kidney disease, burden of kidney disease, work status, cognitive function, sleep, quality of social interaction<br>  ■ Non-halted reported (social support, dialysis staff encouragement, patients satisfaction) |

**Fukuda 2015** *(Continued)*

- Serum ACTH
  - Immunoradiometric assay: assessed at weeks 0, 4, and 12
- Cortisol and α-melanocyte-stimulating hormone: assessed at weeks 0, 4, and 12
- Nonfasting blood (including lipid and inflammation parameters)
  - Radioimmunoassay: assessed at weeks 0, 4, and 12
- Human herpes virus 6 and 7 reactivation
  - Determined in saliva by polymerase chain reaction: assessed at weeks 0 and 12
- Numbers of viral DNA copies
  - Determined in saliva by polymerase chain reaction: assessed at weeks 0 and 12
- Autonomic function
  - Determined via measurement of beat-to-beat variation by using acceleration plethysmography
- Adverse events: assessed until the end of treatment
- Serious adverse events: assessed until the end of treatment
- Hospitalisation: assessed until the end of treatment
- Laboratory data (including white blood cell, Hb, platelets, albumin, AST, ALT, LDH, creatinine, sodium, potassium, calcium, phosphorous, iron, glucose, cholesterol, HDL, CRP; triglycerides): assessed at weeks 0, 4, and 12

Notes

Additional information

- Funding: this study was partly supported by grants from the Asahi Kasei Kuraray Medical Cooperation, 21st Century COE Program and Grant-in Aid for Scientific Research (C) (KAKENHI-24500826) by Ministry of Education, Culture, Sports, Science and Technology (Japan), and grants from Health Labour Sciences Research Grant (Comprehensive Research on Disability Health and Welfare [24163001]), Japan. Tsutomo Tabata, Mikio Okamura, Tomoyuki Yamanaka, Shigeki Okada, Sumio Hirata, Yasuyoshi Watanabe and Yosiki Nishizawa received research grants from the Asahi Kasei Kuraray Medical Cooperation, but the sponsors were not involved in the design, execution, analysis, or reporting of the results of this study
- Conflicts of interest/disclosures: nutritional drink and placebo products were prepared by the Asahi Kasei Kuraray Medical Corporation. Other authors declare no conflict of interests
- Trial registration identification number: UMIN 000001055
- A priori published protocol was published

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomisation by means of a computer-generated random number table (1:1) was to either the nutritional drink, or matching placebo in accordance with the minimization method with three factors (sex, age, each of four dialysis centre); one drink was taken by patients after each dialysis session under the supervision of a nurse."<br><br>Comment: Computer generation is considered as low-risk of bias. No imbalance between intervention groups was apparent |
| Allocation concealment (selection bias) | Unclear risk | Quote: "Originally assigned code numbers were kept in closed envelopes within the coordinating centre."<br><br>Comment: It was not reported if envelopes were numbered and opaque. No imbalance between intervention groups was apparent |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "The patients and attending physicians were blinded to the treatment. [...] All study investigators, medical staff, statistician and participants were blinded to the randomisation procedure and treatment assignments."<br><br>Comment: A double-blind study was considered as low risk of bias |

**Fukuda 2015** *(Continued)*

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Quote: "The safety of the intervention and scientific integrity of the study were supervised by an independent data and safety monitoring board located at the Center for Drug & Food Clinical Evaluation, Osaka City University Hospital, Osaka, Japan (coordinating centre)."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. It was not clearly stated if the independent data and safety monitoring was blinded to the treatment assigned. However, subjective and objective outcomes were reported. It was not stated if the independent data safety and monitoring board was blinded to the treatment allocation |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | Quote: "172 patients (86 in each group) completed the study. [...] One participant withdrew consent before the randomisation and a total of 202 patients [Inoue Hospital, Suita, Japan (n = 72); Ohno Memorial Hospital, Osaka, Japan (n = 54); Okada Clinic, Osaka, Japan (n = 31); Shirasagi Hospital, Osaka, Japan (n = 46)] were included in the trial and were randomly assigned to one of the two treatment arms. Of the 202 participants, six in the nutritional drink group and two in the placebo group did not receive allocation. Four participants in the nutritional group and two in the placebo group did not receive allocation because they withdrew consent. Two participants in the nutritional drink group did not receive allocation because of hospitalisation or changing the time of dialysis from afternoon to morning. Ten participants in each group discontinued intervention (in the nutritional group, 4 withdrew consent and 6 experienced adverse effects; in the placebo group, 1 withdrew consent, 1 was hospitalised, 5 experienced adverse effects, 2 changed the time of dialysis from afternoon to morning, and 1 had unknown reasons). Finally, 68 patients in Inoue Hospital, 43 in Ohno Memorial Hospital, 24 in Okada Clinic, and 39 in Shirasagi hospital completed the intervention. One patient was excluded from the final analysis because of changing the hospital visit date from a weekday to the weekend."<br><br>Comment: Figure 1 reported that no patients were lost to follow-up. However, 87/103 participants in the intervention group and 86/99 participants in the control group were analysed. 0/103 participants in the intervention group and 1/99 participants in the control group were excluded from the analyses (ITT) |
| Selective reporting (reporting bias) | High risk | Protocol was published. Fatigue was reported in accordance with a pre-specified analysis plan, using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was not involved in the design, execution, analysis, or reporting of the results of this study. The study seemed to be free from other source of bias |

**Grigoriou 2021**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br><br>• Cross-over RCT |

**Grigoriou 2021** *(Continued)*

| | |
|---|---|
| | Study dates<br>• Duration of follow-up: 9 months<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Country: Greece<br>• Setting: not reported<br>• Inclusion criteria: 18 to 70 years, HD patients both sexes who received regular HD treatment for at least 6 months; adequate dialysis delivery with Kt/V > 1.1; good compliance with dialysis treatment; serum albumin > 2.5 g/dL, Hb ≥ 11g/dL, sleep onset latency > 15 minutes or sleep efficiency < 85% or arousal index > 25<br>• Exclusion criteria: unable to give informed consent; opportunistic infection in the last 3 months; malignancy or infection requiring IV antibiotics within 2 months prior to enrolment; myo-skeletal contraindication to exercise requirement for systemic anticoagulation; participating or participated in an investigational drug or medical device study within 30 days or five half-lives, pregnant, breastfeeding or female of childbearing potential who does not agree to remain abstinent or to use an acceptable contraceptive regimen; lactate dehydrogenase > 300U/L, prolonged heart wave (QT) interval (as defined by corrected QT (QTc) > 460 msec in males and > 470 msec in females) on screening ECG, known current alcohol or drug abuse, known or suspected hypersensitivity to the study medication or any of its ingredients<br>• Number (analysed/randomised): overall (21/22)<br>• Mean age ± SD (years): overall (56 ± 19)<br>• Sex (M/F): overall (17/4)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): intervention group (10.6 ± 8.26); control group (11.0 ± 7.74)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression: not reported |
| Interventions | Intervention classificationn<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Intradialytic exercise training program<br>Control group<br>• Not participate in any type of systematic exercise training, standard HD<br>Co-interventions<br>• The patients underwent HD therapy 3 times/week using high flux polysulfone dialysers. The HD session lasted approximately 4 hours. An enoxaparin dose of 40 to 60 mg was administered IV before the beginning of each HD session. EPO therapy was given after the completion of HD session to normalize Hb within 12 to 14 g/dL |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ◦ Physical Fatigue will be assessed by hand grip, functional tests, cardiorespiratory max test: after 9 months |

**Grigoriou 2021** *(Continued)*

- Mental Fatigue will be assessed by questionnaires: after 9 months
- Cognitive Fatigue will be assessed by questionnaires: after 9 months

- Body composition: after 9 months
- Muscle functionality: after 9 months
- QoL aspects (assessed by questionnaires): after 9 months
- Sleep quality and quantity (assessed by questionnaires and a full night polysomnography): after 9 months
- Cardiac functionality: after 9 months
- Neurological Assessment: after 9 months

| | |
|---|---|
| Notes | Additional information<br>• Funding: University of Thessaly, Ministry of Development and Larissa University Hospital<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: NCT01721551<br>• A priori published protocol was reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "The order of the two scenarios was randomly applied in all patients using a computer random number generator."<br>Comment: A computer random number generator is considered as low risk of bias |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | It was not clear if outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. Fatigue was not clearly reported. However, other subjective outcome were reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Overall 21/22 participants completed the study. No information were reported to assess differences between groups |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan was reported. Fatigue was not clearly assessed and data were not reported in a format that was extractable for meta-analysis (cross-over study). All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | Baseline characteristics were not clearly reported. Funding was unlikely to influence the data analysis |

### Habibzadeh 2020

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 2 months<br>• Time frame: June 2016 to April 2017 |
| Participants | Study characteristics<br>• Country: Iran<br>• Setting: multicentre (Taleghani and Imam Khomeini in Urmia, Iran)<br>• Inclusion criteria: ESKD undergoing HD; willingness to participate in the study; at least 6 months on HD; no presence of infectious diseases (including all types of hepatitis); no recent severe psychological problem (e.g. psychosis or mania); lack of attendance in similar training courses (including massage courses); 18 and 85 years; male gender (due to the male being the interventionist to eliminate potential intervention biases and considering the cultural issues of Iran); attendance in dialysis sessions at least 3 times/week; at least elementary school education; no history of sensitivity, arthritis, rheumatoid arthritis or joint and orthopaedic problems; and lack of using sedative and analgesic and regenerative drugs<br>• Exclusion criteria: unwillingness to continue participation in the study; kidney transplantation during the study; onset of other illnesses; withdrawal from the HD program<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group 1 (30/30); intervention group 2 (30/30); intervention group 3 (30/30); control group (30/30)<br>• Mean age ± SD (years): overall (55.2 ± 12.7)<br>• Sex (M/F): intervention group 1 (30/0); intervention group 2 (30/0); intervention group 3 (30/0); control group (30/0)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): overall (4.70 ± 2.53)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression: not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group 1<br>• Foot massage with chamomile oil<br>Intervention group 2<br>• Foot massage with almond oil<br>Intervention group 3<br>• Foot massage with no oils<br>Control group |

**Habibzadeh 2020** *(Continued)*

- No intervention

Co-interventions

- Not reported

| | |
|---|---|
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ○ FSS (Appendix 3)<br>• QoL aspects<br>• KDQOL-SF (Appendix 3) |
| Notes | Additional information<br>• Funding: Master degree thesis of Osman Wosoi Dalavan by Urmia University of Medical Sciences<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: IRCT2016121731438N1<br>• A priori published protocol was reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Participants were randomly allocated into four groups (three intervention and one control group) by the first researcher. Numbers 1 through 120 were written on a small paper and placed in a basket; the participants were asked to take a number from the basket and classified based on this number (1 to 30 in the control group, 31 to 60 in the “Foot massage with chamomile oil group”, 61 to 90 in the “Foot massage with almond oil group” and 91 to the last in the “Foot massage without oil group”)." |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "Both participants and researcher were blind to participant allocation; however, due to noticeable differences in the oils used in foot massage, it was not possible to blind the researcher who performed the foot massage intervention and participants." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | It was not clear if fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, other subjective outcome were reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All participants completed the study and there were no lost to follow-up |
| Selective reporting (reporting bias) | High risk | Protocol was published. Fatigue was reported in accordance with a pre-specified analysis plan, using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |

**Habibzadeh 2020** *(Continued)*

| | | |
|---|---|---|
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was not involved in the design, execution, analysis, or reporting of the results of this study. The study seemed to be free from other source of bias |

**Hadadian 2016**

***Study characteristics***

| | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 5 weeks<br>• Time frame: February to July 2009 |
| Participants | Study characteristics<br>• Setting: multicentre (2 dialysis centres in major hospitals in Ahvaz-Iran Kermanshah (Imam Khomeini and Golestan hospitals), Iran)<br>• Country: Iran<br>• Inclusion criteria: ≥ 15 years; diagnosed with ESKD; had been treated with HD for at least 3 months and complained of fatigue<br>• Exclusion criteria: lower extremity amputation; pacemaker; complications requiring immediate medical intervention; under psychological medications; hospital admission for any other reason; needed a blood transfusion; surgery; having infection and bleeding<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (28/30); control group (28/30)<br>• Mean age ± SD (years): intervention group (48.15 ± 15.5); control group (56 ± 14.6)<br>• Sex (M/F): intervention group (20/8); control group (18/10)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): overall (2.75 ± 3.27); intervention group (2.13, SD not reported); control group (2.62, SD not reported)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• TEAS for 5 weeks<br>Control group<br>• Sham TEAS for 5 weeks<br>Co-interventions |

**Hadadian 2016** *(Continued)*

- Not reported

| | |
|---|---|
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ○ Chinese version of the BFI (Appendix 3): assessed at baseline and end of treatment<br>  ■ Fatigue in the last week<br>  ■ Fatigue right now<br>  ■ Usual level of fatigue during past 24 hours<br>  ■ Worst level of fatigue during past 24 hours<br>  ■ How during the past 24 hours, fatigue has interfered with general activity, mood, walking ability, normal work, relations with other people, enjoyment of life<br>  ■ General fatigue |
| Notes | Additional information<br>• Funding: Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not reported (this trial was non-registry in IRCT because the project was conducted in 2009, and in that time, the registration was optional for the universities)<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Fifty six patients who had undergone haemodialysis and meeting the inclusion criteria, were divided into two groups by simple random sampling."<br>Comment: Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "This study was done as a single-blind clinical trial. [...] TEAS group treated by acupuncture in real points, while, in the TEAS-Sham patients, based on the acupuncture expert opinion, the procedure was implemented for them in the false points, so that the patients were not aware of their grouping and blinded about it."<br>Comment: A single-blind study is considered as high risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "The questionnaires were filled up by the researcher before and after 10th session of intervention."<br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant/investigators beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. It was not stated if the interviewer was blinded to the treatment allocation |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "In this study 95 patients were screened, 72 patients met the inclusion criteria and 60 patients agreed and consented to the study. Four patients were excluded over the intervention: 2 in the TEAS group and 2 in the sham |

**Hadadian 2016** *(Continued)*

| | | |
|---|---|---|
| | | group. Finally, 56 cases including 28 cases in the TEAS group and 28 cases in the Sham group completed the research."<br><br>Comment: 28/30 participants in the intervention group and 28/30 participants in the control group completed the study (> 5% lost to follow-up, without differences between groups). Reasons for discontinuations were not reported |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis |

**Hadadian 2018**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 1 month<br>• Time frame: 2011 (months were not reported) |
| Participants | Study characteristics<br>• Setting: single centre (Imam Reza Hospital in Kermanshah)<br>• Country: Iran<br>• Inclusion criteria: receiving HD treatment for at least 6 months; willingness to participate in the study; ≥ 15 years; complete awareness of the situation; hearing and speaking ability as needed to learn the technique; and no psychological disease<br>• Exclusion criteria: lack of willingness to learn relaxation technique; failure to attend the training course; hospitalization for whatever reason; encountering physical or mental problems during the study<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (not reported/27); control group (not reported/38)<br>• Mean age ± SD (years): overall (52.66 ± 2.007)<br>• Sex (M/F): overall (28/37)<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification |

**Hadadian 2018** *(Continued)*

- Non-pharmacological intervention
- Indication: study targeting fatigue

Intervention group

- Progressive muscle relaxation

Control group

- No treatment

Co-interventions

- Not reported

| | |
|---|---|
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ○ BFI (Appendix 3) |
| Notes | Additional information<br>• Funding: Research and Technological department of the University<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | It was not clear how fatigue was assessed, although an appropriate measure was used. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant/investigators beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Not reported in sufficient detail to perform adjudication |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was not clearly reported. Fatigue was reported in a format that was not extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |

**Hadadian 2018** *(Continued)*

| | | |
|---|---|---|
| Other bias | Unclear risk | Baseline characteristics were not clearly reported. Funding was unlikely to influence the data analysis |

**Hasankhani 2013**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 30 days<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Setting: single centre (Bu-Ali Hospital in Ardabil, in Iran)<br>• Country: Iran<br>• Inclusion criteria: fatigue scores > 3; ability to communicate; ≥ 18 years; at least 3 months of dialysis and the lack of scarring; abnormal redness and swelling at the waist<br>• Exclusion criteria: fatigue score ≤ 3; suffered from acute diseases such as fevers, colds and infections; severe pain and heart disease, respiratory, liver, cancer and mental disorders such as depression or with surgery operation<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (not reported/30); control group (not reported/30)<br>• Mean age ± SD (years): not reported<br>• Sex (M/F): not reported<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Slow-stroke back massage<br>Control group<br>• Usual care<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported |

**Hasankhani 2013** *(Continued)*

- Fatigue outcome measures used: validation data available
- Fatigue
  - PFS (Appendix 3): assessed at starting, days 15 and 30
    - Behavioural
    - Emotional
    - Sensory
    - Cognitive

| | |
|---|---|
| Notes | Additional information<br>• Funding: Tabriz University of Medical Sciences<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Samples were selected at random."<br>Comment: Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "The control group in the past four weeks, they received usual care and they were not aware from massage therapy by the intervention group."<br>Comment: Not reported if investigators and all participants were aware on the treatment assigned. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | The number of patients who completed the study was not clearly stated. It was unclear if there was evidence that the results were not biased by missing outcome data |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was not reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | No data were available to assess the possible imbalance between groups. Funding was unlikely to influence the data analysis and reporting but conflicts of interest were not reported |

### Hassanzadeh 2018

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 4 weeks<br>• Time frame: June 2015 to April 2016 |
| Participants | Study characteristics<br>• Country: Iran<br>• Setting: not reported<br>• Inclusion criteria: 20 to 60 years; no history of major surgery stress-causing event within the last 6 months; lack of neuro-muscular disorders, mental disorders, malignant diseases or blood disorders; lack of smelling impairment or allergic rhinitis or respiratory problems, no smoking, using drugs and alcohol; allergy to lavender aroma by the statement of the patients; must sign the written informed consent; have an active profile; regularly refer to the selected HD centres at least for 12 weeks (3 sessions/week); have approved audio speech ability to answer the questions, and have a fatigue score of at least 4 based on BFI<br>• Exclusion criteria: kidney transplant and PD during the study, using sedatives or a non-drug-based method to reduce the level of fatigue during the study, death, changing the dialysis program, using perfumes during the study, and failure to follow the treatment program<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group 1 (not reported/35); intervention group 2 (not reported/35); control group (not reported/35)<br>• Mean age ± SD (years): intervention group 1 (42.66 ± 12.39); intervention group 2 (41.25 ± 12.55); control group (44.38 ± 11.54)<br>• Sex (M/F): intervention group 1 (19/16); intervention group 2 (16/19); control group (24/11)<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression: not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group 1<br>• Relaxation<br>Intervention group 2<br>• Lavender essential oil<br>Control group<br>• No intervention |

**Hassanzadeh 2018** *(Continued)*

| | |
|---|---|
| | Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue<br>  ◦ BFI (Appendix 3) |
| Notes | Additional information<br>• Funding: Zahedan University of Medical Sciences<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: IRCT2015050322067N1<br>• A priori published protocol was reported<br>• Authors contacted but they did not reply |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "The subjects were allocated into three groups randomly by lottery based on the days of week done. The two hospital-based research environments were divided based on morning and afternoon shifts and even and odd days. Then, every shift, the hospital and day were assigned randomly to one of the groups: A (relaxation techniques), B (aromatherapy), or C (control group). At first, each group was assigned a number and drew, in that order, another set of numbers to determine their lottery drawing order." |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. It was not clearly stated if the independent data and safety monitoring was blinded to the treatment assigned |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Not reported in sufficient detail to perform adjudication |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were reported. Fatigue was reported in accordance with a pre-specified analysis plan, using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the design, execution, analysis, or reporting of the results of this study |

**Hassanzadeh 2018** *(Continued)*

| | |
|---|---|
| | and authors had no conflicts of interest. The study seemed to be free from other source of bias |

**HDPAL 2014**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 12 months<br>• Time frame: August 2005 to September 2013 |
| Participants | Study characteristics<br>• Setting: single-centre (4 dialysis units affiliated with Indiana University)<br>• Country: USA<br>• Inclusion criteria: ≥ 18 years; ESKD treated with chronic HD dialysed 3 times/week for at least 3 months with hypertension and LV hypertrophy<br>• Exclusion criteria: patients with ongoing atrial fibrillation; BMI ≥ 40 kg/m$^2$; history of missing one or more HD treatments in the previous month; known drug abuse; severe chronic obstructive airway disease; stroke or MI within the previous 6 months or known contraindication to atenolol or lisinopril<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group 1 (58/100); intervention group 2 (46/100)<br>• Mean age ± SD (years): intervention group 1 (52.2 ± 11.7); intervention group 2 (53.1 ± 13.5)<br>• Sex (M/F): intervention group 1 (73/27); intervention group 2 (58/42)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): intervention group 1 (4.2 ± 4.4); intervention group 2 (3.9 ± 4.2)<br>• Comorbidities<br>  ◦ CVD: intervention group 1 (100/100); intervention group 2 (100/100)<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: intervention group 1 (100/100); intervention group 2 (100/100)<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study reporting fatigue<br>Intervention group 1<br>• Atenolol 25 mg 3 times/week, and the dose was doubled every 2 to 4 weeks up to a maximum dose of 100 mg<br>Intervention group 2<br>• Lisinopril 10 mg 3 times/week, and the dose was doubled every 2 to 4 weeks up to a maximum dose of 40 mg<br>Co-interventions<br>• All subjects were on thrice-weekly dialysis |

**HDPAL 2014** *(Continued)*

| | |
|---|---|
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available (fatigue was reported as an adverse event using a questionnaire)<br>• Adverse events (including fatigue, vascular access, hypertension and depression)<br>  ○ Questionnaire (20 questions were preceded by the following stem: 'Over the last week, how frequently have you found yourself bothered by the following symptoms?' The symptoms were as follows: fatigue or tiredness, chest pain, abdominal pain, cold hands or feet, dizziness on standing, muscle cramps, diarrhoea, nausea, vomiting, dry cough, upper respiratory infection or common cold, shortness of breath, headaches, persistent dizziness, numbness in hands or feet, decreased sex drive, decreased ability to have sex, drowsiness or sleepiness, depression or feeling sad and nightmares. The responses were constantly, frequently, sometimes, rarely or never. Never was coded as 0, rarely as 1, sometimes 2, frequently 3 and constantly as 4) (administered at baseline prior to any administration of the drug and subsequently at monthly intervals over the duration of the trial)<br>• Serious adverse events: assessed until the end of treatment<br>• Cardiovascular events (MI, stroke): assessed until the end of treatment<br>• Cardiovascular hospitalisation: assessed until the end of treatment<br>• All-cause hospitalisation: assessed until the end of treatment<br>• Cardiovascular death: assessed until the end of treatment<br>• Death: assessed until the end of treatment<br>• Pulse pressure: assessed at baseline, 3, 6 and 12 months<br>• Heart rate: assessed at baseline, 3, 6 and 12 months<br>• Change in aortic pulse wave: assessed at 6 months<br>• Change of left ventricular hypertrophy assessed at baseline, 6 and 12 months<br>  ○ ECG<br>• Post dialysis weights (monitored monthly): assessed at baseline, 3, 6 and 12 months<br>• HRQoL<br>  ○ KDQOL: assessed at the beginning and end of the trial<br>• BP (DBP and SBP) (recorded monthly twice daily): assessed at baseline, 3, 6 and 12 months<br>  ○ Self-inflating automatic oscillometry device |
| Notes | Additional information<br>• Funding: National Institutes of Health NIDDK 2R01-DK062030-10<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: NCT00582114<br>• A priori published protocol was reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote from Georgianos 2015: "Randomization was performed using a random permuted block design, and computer-generated random sequence was used for allocation concealment."<br><br>Comment: A computer-generated random sequence is considered as low risk of bias. No imbalance between intervention groups was apparent |
| Allocation concealment (selection bias) | Low risk | Quote from Agarwal 2014: "Subjects were randomised in a 1:1 ratio to either atenolol or lisinopril using concealed opaque envelopes, using a random permuted block design. A permuted block design was chosen to avoid imbalance in assignment to the study drugs over time. Random sequence was generated by a statistician using a computer program and study technicians opened these envelopes after confirming eligibility with the principal investigator." |

**HDPAL 2014** *(Continued)*

| | | |
|---|---|---|
| | | Comment: There was no reason to suspect that the statistician had knowledge of the forthcoming allocation. However, It was not reported if envelopes were numbered |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote from Agarwal 2014: "The Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril (HDPAL) was a randomised, open-label, parallel group, active control, single-centre trial that compared the safety and efficacy of ACE-inhibitor-based therapy with β- blocker-based treatment, each administered three times weekly after dialysis."<br><br>Comment: An open-label study is considered as high risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote from Agarwal 2016: "To accurately capture the adverse effects of atenolol and lisinopril in the HDPAL trial, we used a structured questionnaire."<br><br>Quote from Agarwal 2014: "An independent data and safety monitoring board reviewed the safety data and the study progress on an annual basis."<br><br>Comment: An independent data and safety monitoring board reviewed outcomes. The outcomes were assessed with an appropriate measure, without differences between groups (fatigue was reported as an adverse event). It was not stated if the independent data and safety monitoring was blinded to the treatment assigned. However, objective and subjective outcomes were assessed. It was not stated if the interviewer was blinded to the treatment allocation to evaluate fatigue |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote from supplementary Figure 1 in Agaewal 2014: "Reasons for removal by PI: Four subjects refused to perform home blood pressure monitoring repeatedly, one had pain with home BP measurements and one was excluded following a stroke. Reasons for withdrawal of consent was as follows. Atenolol: not feeling well, light-headed, BP too low, changed mind, wanted original medications, worry about BP, study medication made the subject sick Lisinopril: dizziness, headaches, high BP, fear of stroke, tired of taking BP, tired of participating (n= 4), no reason offered (n= 3), refused home BP monitoring, did not want study medication (n=2), wanted to go back on metoprolol."<br><br>Comment: As reported in Figure 1, 58/100 in the intervention group 1 (Atenolol) and 46/100 in the intervention group 2 (Lisinopril) completed the study (> 5% lost to follow-up, with differences between groups). Some reasons for discontinuations appeared to be related with the intervention |
| Selective reporting (reporting bias) | Low risk | Protocol was published. Fatigue was reported in accordance with a pre-specified analysis plan, using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was not extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were reported. Fatigue was reported but not extractable |
| Other bias | High risk | Quote from Agarwal 2014: "We terminated the trial on the unanimous recommendation of the independent data safety monitoring board which found a clear signal for cardiovascular safety on an annual monitoring meeting after complete randomisation. At their annual meeting, the committee also noted that the lisinopril group experienced an increase in the following: all-cause serious adverse events, all-cause hospitalisation rates, hypertension and hyperkalaemia."<br><br>Comment: There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and authors did not report conflicts of interest. However, the study was terminated early |

**Huang 2021**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 12 weeks<br>• Time frame: March to June 2017 |
| Participants | Study characteristics<br>• Setting: single-centre (HD department at a medical centre in northern Taiwan)<br>• Country: Taiwan<br>• Inclusion criteria: ≥ 20 years; ESKD; regular HD 3 times/week and up to 6 months or more; consciousness, can be used to communicate in Taiwanese and accept questionnaire interviews or self-filling questionnaire; no chest pain or shortness of breath symptoms; no lower extremity disability and ability to walk on their own; agree to take respiratory exercise intervention measures; have the intention to participate in this study and signed a consent form<br>• Exclusion criteria: unstable vital signs or serious heart disease (MI, unstable angina pectoris, cardiopulmonary disease); a complication occurs, such as aspiration pneumonia, history of arrhythmia, as well as taking heart rate medication; physician's advice is not suitable for exercise, such as bone and joint problems; temporary double vena cava catheter placed<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (40/43); control group 2 (43/43)<br>• Mean age ± SD (years): intervention group (53.70 ± 10.04); control group (61.19 ± 10.19)<br>• Sex (M/F): intervention group (29/11); control group (28/15)<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: intervention group (20/40); control group (28/43)<br>  ◦ Depression (clinician diagnosis): intervention group (14/40); control group (21/43) |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Breathing exercise week during HD for 15 to 20 minutes<br>Control group<br>• Usual care: routine nursing care during HD<br>Co-interventions<br>• Routine medications, medical treatment, and guidance regarding diet, daily activity and water restriction |
| Outcomes | Outcomes reported |

**Huang 2021** *(Continued)*

- Fatigue outcome measures used: validation data available
- Fatigue
  - HFS: assessed at baseline, 4, 8 and 12 weeks (Appendix 3)
- QoL
  - WHOQOL-BREF: assessed at baseline, 4, 8 and 12 weeks (Appendix 3)
- Vigour and motivation
- Mental ability
- Daily activities
- Distress and loss of control in mood
- Anxiety
  - HADS: assessed at baseline, 4, 8 and 12 weeks
  - Heart rate variability: after 3 months
- BP: after 3 months
- Oxygen saturation: after 3 months

| | |
|---|---|
| Notes | Additional information<br>• Funding: National Taipei University of Nursing and Health Sciences<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: NCT 03499054<br>• A priori published protocol was reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomly ordered permuted blocks of four were computer generated."<br><br>Comment: Computer generator is considered as low risk of bias |
| Allocation concealment (selection bias) | Low risk | Quote: "Randomization was performed offsite by a research team. To prevent possible bias, the study researchers involved in the recruitment process and intervention did not conduct randomisation. Resulting in the code names in order were placed in prepared, sealed, opaque envelopes with a series of numbers, which were later drawn for group assignment by one study researcher." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "Blinding participants of their group assignments were not feasible." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Fatigue assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, other subjective outcome were reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 40/43 participants in the intervention group and 43/43 participants in the control group completed the study (> 5% loss to follow-up). There were differences between treatment groups. Reason for discontinuation were provided |
| Selective reporting (reporting bias) | High risk | Protocol was published. Fatigue was reported using multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Information related to fatigue were not reported in suf- |

**Huang 2021** *(Continued)*

| | | |
|---|---|---|
| | | ficient detail to permit judgment. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and there were no conflicts of interest. No other source of bias were apparent |

**Jalalian 2015**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 2 months<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Setting: single centre (hospital of Tehran University of Medical Science)<br>• Country: Iran<br>• Inclusion criteria: maintenance HD patients<br>• Exclusion criteria: not reported<br>Baseline characteristics<br>• Number (analysed/randomised): overall (not reported/64)<br>• Mean age ± SD (years): not reported<br>• Sex (M/F): not reported<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Lavender and sweet orange essence<br>Control group<br>• No intervention<br>Co-interventions<br>• Not reported |

**Jalalian 2015** *(Continued)*

| | |
|---|---|
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ○ Rhoten fatigue scale: assessed before and after the treatment<br>• HRQoL<br>  ○ KDQOL-SF: assessed before and after the treatment |
| Notes | Additional information<br>• Funding: not reported<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported<br>• Abstract-only publication |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "Data were collected using demographic questionnaire, Rhoten Fatigue Scale and Kidney Disease Quality of Life Short Form (KDQOLSF)."<br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, other subjective outcome were reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | The number of patients who completed the study was not clearly stated. It was unclear if there was evidence that the results were not biased by missing outcome data |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Information related to fatigue were not reported in sufficient detail to permit judgment. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | No data were available to assess the possible imbalance between groups. Funding and conflicts of interest were not reported |

### Johansen 1999

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 6 months<br>• Time frame: April 1996 to July 1997 |
| Participants | Study characteristics<br>• Setting: single-centre (San Francisco General Hospital Medical Care outpatient dialysis unit)<br>• Country: USA<br>• Inclusion criteria: undergoing HD for at least 3 months; evidence of malnutrition; poor QoL as assessed by questionnaire; patients had to have two or more of the following to be considered for the assessment of malnutrition: albumin < 40 g/L, total cholesterol < 3.88 mmol/L (150 mg/dL), transferrin < 2 g/L, protein catabolic rate < 0.8 g/kg/day, predialysis serum urea nitrogen < 21.4 mmol/L (60 mg/dL), or insulin-like growth factor 1 < 300 ng/mL<br>• Exclusion criteria: received dialysis for fewer than 3 months or if they had other reasons for being in a catabolic state, such as HIV, knowing malignancy, corticosteroid treatment, surgery, or infection requiring IV antibiotics, within 3 months; participation in other studies; illicit drug use<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (12/14); control group (11/15)<br>  ○ HD/PD: intervention group (10/4); control group (10/5)<br>• Mean age ± SD (years): intervention group (44 ± 15); control group (50 ± 10)<br>  ○ HD: not reported<br>  ○ PD: not reported<br>• Sex (M/F): intervention group (11/3); control group (12/3)<br>  ○ HD: not reported<br>  ○ PD: not reported<br>• Dialysis type: HD/PD<br>• Mean dialysis vintage ± SD (years): intervention group (2.9 ± 2.7); control group (2.3 ± 2.0)<br>  ○ HD: not reported<br>  ○ PD: not reported<br>• Comorbidities<br>  ○ CVC: not reported<br>  ○ Diabetes: treatment group (5/14); control group (6/15)<br>  ■ HD: not reported<br>  ■ PD: not reported<br>  ○ Hypertension: not reported<br>  ○ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Nandrolone decanoate (IM): 100 mg once/week<br>Control group |

**Johansen 1999** *(Continued)*

- Placebo (IM): saline solution once/week

Co-interventions

- The same equipment was used for baseline, 3-month, and 6-month evaluation for all patients

Outcomes

Outcomes reported

- Fatigue outcome measures used: validation data available
- Change in body weight: assessed at baseline, 3 and 6 months
  - Electronic scale
- Change in body composition: assessed at baseline, 3 and 6 months
  - Electronic scale
- Change in lean body mass: assessed at baseline, 3 and 6 months
- Grip strength: assessed at baseline, 3 and 6 months
  - Handheld dynamometer
- Functional capacity
- Walking and stair-climbing times: assessed at baseline, 3 and 6 months
- Peak oxygen consumption ($VO_2$)
  - Treadmill performance: assessed at baseline, 3 and 6 months
- Laboratory results (SCr, albumin, total cholesterol, transferrin, total and free testosterone, luteinizing hormone, follicle-stimulating hormone, IGF-1, HCT, Hb): assessed monthly
- Heart rate
  - Treadmill performance: assessed at baseline, 3 and 6 months
- BP
  - Treadmill performance: assessed at baseline, 3 and 6 months
- Change Kt/V: assessed until the end of the study
- HRQoL
  - Questionnaire: assessed at baseline, 3 and 6 months
- Satisfaction
- Index of overall satisfaction: assessed at baseline, 3 and 6 months
- Eating dimension
  - Sickness impact profile: assessed at baseline, 3 and 6 months
- Fatigue
  - Profile of mood state: assessed at baseline, 3 and 6 months
- Anger/hostility components
  - Profile of mood state: assessed at baseline, 3 and 6 months
- Adverse events
  - Questionnaire: assessed at baseline, 3 and 6 months
- Sudden death: assessed until the end of treatment
- Hospitalisation: assessed until the end of treatment
- Severe hypertension: assessed until the end of treatment

Notes

Additional information

- Funding: grant RR-00083 from the National Center for Research Resources, Bethesda, Md, grant DK-45833 from the National Institute of Diabetes and Digestive and Kidney Disease, Bethesda, and a grant from the Bay Area Nutrition Center, Berkeley
- Conflicts of interest/disclosures: not reported
- Trial registration identification number: not applicable
- A priori published protocol: protocol was approved by the Committee on Human Research at the University of California, San Francisco

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

**Johansen 1999** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote; "Randomisation was computer-generated in block of 4."<br><br>Comment: Computer-generation is considered as low risk of bias. No imbalance between intervention groups was apparent |
| Allocation concealment (selection bias) | Low risk | Quote: "Assignments were made sequentially by a research pharmacist who dispensed medication but was not otherwise involved in the study."<br><br>Quote: "Esternal research pharmacist seemed to ensure allocation concealment. No imbalance between intervention groups was apparent." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "Dialysis staff, patients, and investigators were blinded through the study to treatment assigned."<br><br>Comment: A double-blind trial is considered as low risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "Quality of life was assessed by and instrument administered by personal interview."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "25 subjects completed the 6-month protocol and 23 of these (12 in the nandrolone group and 11 in the placebo group) had all measurements made. Two subjects completed the study but were unable to have final measurements taken because of medical instability. Three subjects were withdrawn from the placebo group because of elevated transaminase, hematoma at the study drug injection site, ans sudden death. One subject in the nandrolone group was withdrawn after developing angina."<br><br>Comment: 12/14 participants in the intervention group and 11/15 participants in the control group completed and reported all measurements of the study (> 5% lost to follow-up, with differences between groups). Reasons for discontinuations seemed to be related to the treatment allocation |
| Selective reporting (reporting bias) | High risk | Protocol was approved by the Committee on Human Research at the University of California. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and conflicts of interest were not reported |

**Johansen 2006**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br><br>• Parallel RCT |

**Johansen 2006** *(Continued)*

| | |
|---|---|
| | Study dates<br>• Duration of follow-up: 12 weeks<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Setting: single-centre (San Francisco General Hospital Medical Care outpatient dialysis unit)<br>• Country: USA<br>• Inclusion criteria: men and women undergoing maintenance HD 3 times/week; adequate dialysis delivery with Kt/V 1.2 and good compliance with dialysis treatment (i.e. not missing more than 2 dialysis treatments in the month before enrolment)<br>• Exclusion criteria: dialysis for < 3 months; reasons to be in a catabolic state (including HIV with opportunistic infection in the past 3 months, malignancy, or infection that required intravenous antibiotics within 2 months before enrolment); unable to give informed consent; active IV drug users; thigh dialysis graft; contraindications to resistance exercise training such as MI within 6 months, active angina, uncompensated congestive heart failure, or orthopaedic or musculoskeletal limitations<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group 1 (16/19); intervention group 2 (16/20); control group 1 (17/20); control group 2 (19/20)<br>• Mean age ± SD (years): intervention group 1 (55.7 ± 13.4); intervention group 2 (55.5 ± 12.5); control group 1 (56.8 ± 13.8); control group 2(54.4 ± 13.6)<br>• Sex (M/F): intervention group 1 (10/9); intervention group 2 (13/7); control group 1 (12/8); control group 2 (14/6)<br>• Dialysis type: HD<br>• Median dialysis vintage, IQR (years): overall (not reported); intervention group 1 (3.33, 0.25 to 24); intervention group 2 (1.17, 0.33 to 12.67); control group 1 (2.13, 0.25 to 13)); control group 2 (2.75, 0.29 to 9)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: intervention group 1 (10/19); intervention group 2 (9/20); control group 1 (8/20); control group 2 (12/20)<br>  ◦ Hypertension: intervention group 1 (18/19); intervention group 2 (20/20); control group 1 (17/20); control group 2 (18/20)<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Pharmacological and non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group 1<br>• Nandrolone decanoate: 100 mg (0.5 mL) for women and 200 mg (1 mL) for men, 3 times/week<br>Intervention group 2<br>• Nandrolone decanoate: 100 mg for women and 200 mg for men, 3 times/week + lower extremity resistance exercise training<br>Control group 1<br>• Placebo<br>Control group 2<br>• Placebo + lower extremity resistance exercise training<br>Co-interventions |

**Johansen 2006** *(Continued)*

- Not reported

| | |
|---|---|
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Change in body weight: assessed at baseline and 3 months<br>• Change in body composition: assessed at baseline and 3 months<br>• Change in lean body mass<br>  ○ Dual-energy X-ray absorptiometry: assessed at baseline and 3 months<br>• Change in quadriceps muscle cross-sectional area<br>  ○ Magnetic resonance imaging: assessed at baseline and 3 months<br>• Change in knee extensor muscle strength<br>• Computerized dynamometer: assessed at baseline and 3 months<br>• Physical performance: assessed at baseline and 3 months<br>  ○ Gait speed<br>  ○ Stairs<br>  ○ Sit and stand<br>• Self-reported physical functioning<br>  ○ Physical functioning of the SF-36 (asks individuals to characterize their degree of limitation in performing 10 activities as not limited at all, limited a little, or limited a lot): assessed at baseline and 3 months<br>  ○ Human Activity Profile (94 activities and patients are asked to report whether they still do the activity, no longer do the activity, or never did the activity): assessed at baseline and 3 months<br>• Physical activity<br>  ○ Threedimensional accelerometers: assessed at baseline and 3 months<br>  ■ Human Activity Profile Maximum Activity Score<br>  ■ Human Activity Profile Adjusted Activity Score<br>• Laboratory results (pre-dialysis SCr): assessed at baseline and 3 months<br>• Hip abduction<br>• Magnetic resonance imaging: assessed at baseline and 3 months<br>• Isokinetic knee extension at 90 degrees/s (Nm)<br>  ○ Magnetic resonance imaging (assessed at baseline, 3 months)<br>• Isokinetic knee extension at 120 degrees/s (Nm)<br>  ○ Magnetic resonance imaging: assessed at baseline and 3 months<br>• Hip flexion: assessed at baseline and 3 months<br>• MRI: assessed at baseline and 3 months<br>• Fatigue and change in fatigue<br>  ○ Profile of Mood State: assessed at baseline and 3 months<br>• Anger/hostility components<br>  ○ Profile of Mood State: assessed at baseline and 3 months<br>• HRQoL and change in QoL<br>  ○ Physical Functioning SF-36: assessed at baseline and 3 months<br>• Adverse events: assessed until the end of treatment<br>• Death: assessed until the end of treatment |
| Notes | Additional information<br>• Funding: grant from the National Institute of Diabetes and Digestive and Kidney Diseases (DK-56182). Study drug and matching placebo were kindly provided by Organon, Inc., Roseland, NJ<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |

***Risk of bias***

**Johansen 2006** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Participants were randomly assigned to treatment groups in a 1:1:1:1 manner by the research pharmacist using variable block sizes, which were not known to investigators until the completion of the study."<br><br>Comment: Sequence generation methods were not reported in sufficient detail to permit judgement. No imbalance between intervention groups was apparent |
| Allocation concealment (selection bias) | Low risk | Quote: "Nandrolone decanoate and a placebo that was identical in appearance to the active drug were prepared and supplied to the research pharmacy by Organon, Inc. (Roseland, NJ)."<br><br>Quote: "Participants were randomly assigned to treatment groups in a 1:1:1:1 manner by the research pharmacist using variable block sizes, which were not known to investigators until the completion of the study."<br><br>Comment: Esternal research pharmacist seemed to ensure allocation concealment. No imbalance between intervention groups was apparent |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "Interventions included double-blinded weekly nandrolone decanoate (100 mg for women; 200 mg for men) or placebo injections."<br><br>Comment: Although author reported that the study used a double-blind design, information about blinding of participants and investigators were not clearly stated |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "Eighty haemodialysis patients were enrolled in the study, and 79 were randomly assigned. [...] Sixty-eight patients completed the study. Reasons for non completion are shown in Figure 1. Six participants discontinued study drug (four who were receiving placebo and two who were receiving nandrolone) before the end of the treatment period, only two of whom discontinued all study participation. Therefore, results for the four patients who discontinued study drug but were still available for follow-up measures are included in analyses. Those who received placebo discontinued because of an itchy reaction at the injection site, a nonspecific feeling that the drug was having adverse effects, abdominal pain and liver function test abnormalities, and discovery of a history of prostate cancer. Those who received nandrolone discontinued because of interference with sexual function (after five doses) and fear of possible adverse effects (after three doses)."<br><br>Comment: 16/19 participants in the intervention group 1 (nandrolone), 16/20 participants in the intervention group 2 (nandrolone + lower extremity resistance exercise training), 17/20 participants in the control group 1 (placebo) and 19/20 participants in the control group 2 (placebo + lower extremity resistance exercise training) completed and reported all measurements of the study (> 5% lost to follow-up, with differences between groups). Reasons for discontinuations seemed to be related to the treatment allocation. |

**Johansen 2006** *(Continued)*

| | | |
|---|---|---|
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue at the end of treatment was not reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | High risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Pharmaceutical company who provided the drugs could influenced the data analysis and authors did not report conflicts of interest |

**Kaplin Serin 2020**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 6 weeks<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Setting: multicentre (2 dialysis units)<br>• Country: Turkey<br>• Inclusion criteria: to continue treatment in the dialysis unit; to receive HD treatment for longer than 6 months; ≥ 18 years; be able to read and write basic Turkish text to understand the questionnaires; no difficulties in communication and no mental disorders as confirmed by hospital psychologists; to agree to participate and to practice relaxation exercises<br>• Exclusion criteria: not reported<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (48/48); control group (48/48)<br>• Mean age ± SD (years): intervention group (39.1 ± 15.3); control group (49.8 ± 14.1)<br>• Sex (M/F): intervention group (36/12); control group (27/21)<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: intervention group (6/48); control group (13/48)<br>  ◦ Hypertension: intervention group (13/48); control group (16/48)<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Progressive relaxation exercises<br>Control group |

**Kaplin Serin 2020** *(Continued)*

| | |
|---|---|
| | • No intervention<br><br>Co-interventions<br><br>• Not reported |
| Outcomes | Outcomes reported<br><br>• Fatigue outcome measures used: validation data available<br>• Pain<br>  ○ VAS (Appendix 3)<br>• Fatigue<br>  ○ PFS (Appendix 3)<br>• QoL<br>  ○ SF-36 scale (Appendix 3) |
| Notes | Additional information<br><br>• Funding: MSc thesis from Gaziantep University of Turkey<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "The data were collected by the researchers through face-to-face interviews with the patients."<br><br>Comment: Fatigue was assessed with an appropriate measure, without differences between groups. Objective measures were used. However, objective and subjective outcomes were assessed. It was not stated if the interviewer was blinded to the treatment allocation |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All participants completed the study and there were no lost to follow-up |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis |

**Karadag 2019**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 30 days<br>• Time frame: March and December 2017 |
| Participants | Study characteristics<br>• Setting: multicentre (unit of Gaziantep University Sahinbey Research and Application Hospital located in a province in southeastern Turkey)<br>• Country: Turkey<br>• Inclusion criteria: receiving HD regularly for at least 6 months; being capable of communicating and having no problems of hearing and speech; 18 and 65 years; no smelling problem, no history of eczema, asthma, herbal allergy; no allergy to lavender; not diagnosed with psychiatric disorder; participating in the study voluntarily<br>• Exclusion criteria: not reported<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (30/30); control group (30/30)<br>• Mean age ± SD (years): intervention group (55.76 ± 13.23); control group (46.43 ± 14.23)<br>• Sex (M/F): intervention group (13/17); control group (11/19)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): intervention group (4.5 ± 4.4); control group (3.7 ± 3.8)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Lavender oil<br>Control group<br>• No intervention<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ◦ FSS (Appendix 3)<br>• Anxiety |

**Karadag 2019** *(Continued)*

- BAI (Appendix 3)

| | |
|---|---|
| Notes | Additional information<br>• Funding: not reported<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All participants were included into the analysis. There were no lost to follow-up |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was not reported |

**Konstadinidou-ND 2002**

***Study characteristics***

| | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 6 months |

**Konstadinidou-ND 2002** *(Continued)*

- Time frame: not reported

| | |
|---|---|
| Participants | Study characteristics<br>• Setting: single centre (Renal Unit of AHEPA Hospital)<br>• Country: Greece<br>• Inclusion criteria: regular HD with an artificial kidney for at least 6 months for 3 sessions/week of 4 hours each<br>• Exclusion criteria: unstable hypertension; congestive heart failure (grade > II according to NYHA); cardiac arrhythmias (at least III according to Lown); recent MI or unstable angina; persistent hyperkalaemia before dialysis; DM; active liver disease; bone disease that puts the patient at risk of a fracture; arthritic or orthopaedic problems limiting exercise; peripheral vascular disease; undisciplined patients<br><br>Baseline characteristics<br>• Number (analysed/randomised): intervention group 1 (16/21); intervention group 2 (10/12); intervention group 3 (10/12); control group (12/13)<br>• Mean age ± SD (years): intervention group 1 (46.4 ± 13.9); intervention group 2 (48.3 ± 12.1); intervention group 3 (51.4 ± 12.5); control group (50.2 ± 7.9)<br>• Sex (M/F): intervention group 1 (11/5); intervention group 2 (8/2); intervention group 3 (8/2); control group (4/8)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): intervention group 1 (6.5 ± 5.2); intervention group 2 (6 ± 5.5); intervention group 3 (5.2 ± 3.1); control group (6.6 ± 7.2)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: intervention group 1 (0/21); intervention group 2 (0/12); intervention group 3 (0/12); control group (0/13)<br>  ◦ Hypertension: intervention group 1 (10/16); intervention group 2 (6/10); intervention group 3 (6/10); control group (8/12)<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue endpoints (data on fatigue were not reported)<br><br>Intervention group 1<br>• Supervised aerobic and strengthening training on the non-dialysis days, 3 times/week<br><br>Intervention group 2<br>• Supervised exercise program during HD, 3 times/week<br><br>Intervention group 3<br>• Moderate unsupervised moderate exercise program at home, 3 times/week<br><br>Control group<br>• Usual lifestyle<br><br>Co-interventions<br>• To exclude any impact of the changes in the status of anaemia on the aerobic capacity of patients, we tried to keep the Hb/HCT level stable for all kidney patients (optimum level Hb/HCT ratio was considered 11/33) throughout the study by increasing or decreasing the dose of EPO, whenever necessary<br>• All patients were on stable medical therapy during the study |

**Konstadinidou-ND 2002** *(Continued)*

- Dialysis procedure was kept stable throughout the 6-month period program (by using the same model of filter and constant composition of the dialysis solution, and by keeping the HD session time constant throughout this period)

| | |
|---|---|
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Physical assessment: assessed at the beginning and the end of the study<br>• Laboratory tests: assessed at the beginning and the end of the study<br>• Lactic acid<br>  ○ Photometer: assessed at the beginning and the end of the study<br>• Resting ECG: assessed at the beginning and the end of the study<br>• BP<br>  ○ Mercury sphygmomanometer: was monitored until the end of the study<br>• ECG: assessed at the beginning and the end of the study<br>• Oxygen consumption ($VO_2$)<br>  ○ Spiroergometric: assessed at the beginning and the end of the study<br>• Anaerobic threshold ($VO_2AT$)<br>  ○ Spiroergometric: assessed at the beginning and the end of the study<br>• Respiratory exchange ration<br>  ○ Spiroergometric: assessed at the beginning and the end of the study<br>• Total exercise time<br>  ○ Spiroergometric: assessed at the beginning and the end of the study<br>• Pulmonary ventilation<br>  ○ Spiroergometric: assessed at the beginning and the end of the study<br>  ○ Spirometry: assessed at the beginning and the end of the study<br>• Heart rate<br>  ○ Spiroergometric: assessed at the beginning and the end of the study<br>• Severe hypertension or hypotension: assessed until the end of treatment<br>• > 2.5 mm ST segment shift in ECG: during the test it was monitored and recorded every 3 min<br>• Adverse events (including severe arrhythmias): assessed until the end of treatment<br>• Death: assessed until the end of treatment<br>• Fatigue (leg fatigue)<br>  ○ Modified Bruce treadmill exercise test: assessed at the beginning and the end of the study |
| Notes | Additional information<br>• Funding: not reported<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not applicable<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias) | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |

**Konstadinidou-ND 2002** *(Continued)*
All outcomes

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "Treadmill exercise test to fatigue endpoints. [...] To measure lactic acid, blood samples were taken from the right ear before and 4 min after the end of the exercise test. Lactic acid measurement was carried out in a photometer."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. Objective measures were used. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "However, during the study 5 patients from Group A, 1 from Group B, 2 from C voluntarily withdrew, while 1 patient from Group B and 1 from D died of causes unrelated to exercise. Finally, 48 patients on HD completed the entire study. [...] Group A had a higher dropout rate (23.8%) and the reasons were lack of time, transportation difficulties and medical reasons unrelated to exercise. The dropout rate in both Groups B and C was 16.7% and the reason for withdrawal was an acute illness."<br><br>Comment: 16/21 participants in intervention group 1 (supervised aerobic training), 10/12 participants in intervention group 2 (supervised exercise program), 10/12 participants in intervention group 3 (unsupervised moderate exercise) and 12/13 participants in the control group (usual lifestyle) completed the study (> 5% lost to follow-up, with differences between groups). Reasons for discontinuations seemed to be not related to the treatment allocation |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported. |
| Other bias | Unclear risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding and conflicts of interest were not reported |

**Krase 2022**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 7 months<br>• Time frame: October 2016 to May 2018 |
| Participants | Study characteristics<br>• Setting: multicentre (2 dialysis centres in Greece)<br>• Country: Greece<br>• Inclusion criteria: clinically stable patients who had received regular HD treatment for at least 3 months, with adequate dialysis delivery (Kt/V > 1.2) and good compliance of dialysis treatment (standard schedule of 3 dialysis/week for 4 hours; absence of any complications related to dialysis, such as hypertension, nausea, dizziness, and muscle cramps, cardiac arrhythmias, hypoglycaemia, muscle pain), serum albumin > 3.0 g/dL, haemoglobin ≥ 11 g/ dL and treated with HuEPO |

**Krase 2022** *(Continued)*

- Exclusion criteria: in a catabolic state (e.g. hyperthyroidism); active vasculitis; malignancies; pregnant; HIV; opportunistic infections; myoskeletal contraindication to exercise; requirement for systemic anticoagulation; participant or participated in an investigational drug or medical device study within 30 days or 5 half-lives or inflammations, that required IV antibiotics within 3 months prior to enrolment; diabetics receiving insulin therapy; NYHA grade IV heart failure; mental incapacity to consent

Baseline characteristics

- Number (analysed/randomised): intervention group (21/24); control group (23/24)
- Mean age ± SD (years): intervention group (66.04 ± 15.35); control group (68.26 ± 11.07)
- Sex (M/F): intervention group (16/5); control group (10/13)
- Dialysis type: HD
- Mean dialysis vintage ± SD (years): intervention group (7.29 ± 4.0); control group (5.39 ± 5.55)
- Comorbidities
  - CVD: not reported
  - Diabetes: not reported
  - Hypertension: not reported
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Aerobic intradialytic exercise training<br>Control group<br>• No intervention<br>Co-interventions<br>• Four hours of dialysis treatment with EPO |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ○ Questionnaire (name was not clearly reported)<br>• Vastus lateralis architecture (using ultrasonography)<br>• Functional capacity: assessed up to 7 months<br>  ○ 6MWT<br>  ○ 5 repetitions sit-to-stand, sit-to-stand 60 sec, handgrip strength<br>• Maximal aerobic power: assessed up to 7 months<br>  ○ Åstrand test<br>• QoL: assessed up to 7 months<br>  ○ SF-36 (Appendix 3)<br>  ■ Vitality<br>  ■ Physical functioning<br>  ■ Bodily pain<br>  ■ General health<br>  ■ Perceptions physical role functioning<br>  ■ Emotional role functioning<br>  ■ Social role functioning<br>  ■ Mental health<br>• Change in body heat storage: assessed up to 7 months |

**Krase 2022** *(Continued)*

- Change in insulin resistance: assessed up to 7 months
- Change in muscle size: assessed up to 7 months
- Change in daily physical activity: assessed up to 7 months

| | |
|---|---|
| Notes | Additional information<br>• Funding: European Union's Horizon 2020 programme (Grant agreement No. 645710). Also supported by the European Union Horizon 2020 Research and Innovation Programme"H2020 MSCAS-RISE-Muscle Stress Relief" (Grant agreement No. 645648)<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: NCT03905551<br>• A priori published protocol was reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Patients enrolled by a research assistant assigned into the study while the order that the patients assigned to the first scenario was randomly using a computer random number generator." |
| Allocation concealment (selection bias) | Low risk | Quote: "Patients enrolled by a research assistant assigned into the study while the order that the patients assigned to the first scenario was randomly using a computer random number generator."<br>Comment: Although it was not clear if research assistant was aware of treatment allocation, the use of computer seemed to prevent bias in allocation concealment |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. Fatigue was not clearly reported. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 21/24 participants in the intervention group and 23/24 participants in the control group completed the study (> 5% lost to follow-up). There were differences between groups. Reasons for discontinuation were provided |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was not reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence data analysis and interpretation. No other source of bias were apparent |

**Lazarus 2020**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 8 weeks<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Setting: single centre<br>• Country: India<br>• Inclusion criteria: 20 to 80 years; diagnosed with CKD and undergoing HD<br>• Exclusion criteria: not reported<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (100/100); control group (100/100)<br>• Mean age ± SD (years): not reported<br>• Sex (M/F): not reported<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ○ CVD: not reported<br>  ○ Diabetes: not reported<br>  ○ Hypertension: not reported<br>  ○ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Olive-oil massage<br>Control group<br>• No intervention<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ○ FSS (Appendix 3) |
| Notes | Additional information<br>• Funding: none<br>• Conflicts of interest/disclosures: none |

**Lazarus 2020** *(Continued)*

- Trial registration identification number: not reported
- A priori published protocol: not reported

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "In a randomised double blind placebo controlled study."<br>Comment: Although the study was reported as a double blind study, it was not reported if participants and investigators were blinded to the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All participants completed the study. There was no lost to follow-up |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported with multiple eligible outcome measurements (scales and time points). It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | Baseline characteristics were not clearly reported. There were neither funding nor conflict of interests |

**Leski 1979**

***Study characteristics***

| | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 4 weeks<br>• Time frame: not reported |
| Participants | Study characteristics |

**Leski 1979** *(Continued)*

- Setting: single centre
- Country: Switzerland
- Inclusion criteria: HD patients
- Exclusion criteria: not reported

Baseline characteristics

- Number (analysed/randomised): overall (not reported/10)
- Mean age ± SD (years): overall (53.1 ± 9.0)
- Sex (M/F): overall (5/5)
- Dialysis type: HD
- Mean dialysis vintage ± SD (years): overall (3.2 ± 2.3)
- Comorbidities
  - CVD: not reported
  - Diabetes: not reported
  - Hypertension: not reported
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Dialysis sessions with dialysate containing glucose 400 mg/100 mL<br>Control group<br>• Dialysis sessions with dialysate of the same composition but without glucose<br>Co-interventions<br>• Every patient had 3 dialysis sessions/week |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ◦ Questionnaire (evaluated on a 3-point system, 0, +, + +): assessed post dialysis<br>  ◦ Glycaemia: assessed in all samples during the study period<br>• Immunoreactive insulin: measured in 44/120 sessions<br>• BP: monitoring during the study period<br>• Body weight: monitoring during the study period<br>• Headache<br>  ◦ Questionnaire (evaluated on a 3-point system, 0, +, + +): assessed during and after dialysis<br>• Leg cramps<br>  ◦ Questionnaire (evaluated on a 3-point system, 0, +, + +): assessed during and after dialysis<br>• Adverse events (hypotension): assessed until the end of treatment<br>• Laboratory results (cholesterol, triglycerides, BUN, plasma creatinine, sodium, potassium): assessed pre and post dialysis |
| Notes | Additional information<br>• Funding: not reported<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not applicable<br>• A priori published protocol: not reported |

**Leski 1979** *(Continued)*

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "Each patient was interrogated in a standardized fashion by the same person (Th. N.) during each dialysis concerning the preceding one. [...] The questionnaire was evaluated on a three-point system, 0, +, + +, headache during and after dialysis, fatigue and leg cramps."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | The number of patients who completed the study was not clearly stated. It was unclear if there was evidence that the results were not biased by missing outcome data |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was not reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | No data were available to assess the possible imbalance between groups. Funding and conflicts of interest were not reported |

**Li 2014b**

***Study characteristics***

| | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 12 weeks<br>• Time frame: 2010 to 2012 (months were not reported) |

**Li 2014b** *(Continued)*

| | |
|---|---|
| Participants | Study characteristics<br>• Setting: multicentre (renal units of two local regional hospitals in Guangdong province, China)<br>• Country: China<br>• Inclusion criteria: Mandarin-speaking; able to communicate; access a telephone after discharge; agreed to participate<br>• Exclusion criteria: receiving intermittent PD or HD; planned admissions for special treatment procedures; patients with Tenckhoff catheters in situ < 3 months; psychosis or dementia; dying or unable to communicate; transferred to another unit during their stay in hospital<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (69/80); control group (66/80)<br>• Mean age ± SD (years): intervention group (57.4 ± 12.8); control group (55.2 ± 11.9)<br>• Sex (M/F): intervention group (42/27); control group (37/29)<br>• Dialysis type: PD<br>• Mean dialysis vintage ± SD (years): intervention group (3.2 ± 2.4); control group (3.5 ± 2.2)<br>• Comorbidities<br>  ○ CVD: not reported<br>  ○ Diabetes: intervention group (33/69); control group (27/66)<br>  ○ Hypertension: not reported<br>  ○ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Post-discharge nurse-led telephone support for 6 weeks<br>Control group<br>• Routine hospital discharge care<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• HRQoL<br>  ○ Chinese version of the KDQOL-SF: assessed at baseline before discharge, 6 and 12 weeks after discharge<br>  ■ Symptom/problem<br>  ■ Effect on kidney disease<br>  ■ Burden of kidney disease<br>  ■ Cognitive function<br>  ■ Quality of social interaction<br>  ■ Sexual function<br>  ■ Work status<br>  ■ Social support<br>  ■ Staff encouragement<br>  ■ Physical functioning<br>  ■ Role-physical<br>  ■ Patient satisfaction |

**Li 2014b** *(Continued)*

- Energy/fatigue
- Sleep
- Pain
- General health perception
- Emotional well-being
- Role-emotional
- Social function
- Overall health

- Blood chemistry (blood urea, creatinine, sodium, potassium, phosphate, albumin): assessed at baseline before discharge, 6 and 12 weeks after discharge
- Complication control: assessed at baseline before discharge, 6 and 12 weeks after discharge
- Readmission: assessed at baseline before discharge, 6 and 12 weeks after discharge
- Clinic visit rates: assessed at baseline before discharge, 6 and 12 weeks after discharge
- Adverse events: assessed until the end of treatment
- Hospitalisation: assessed until the end of treatment
- Death: assessed until the end of treatment

| | |
|---|---|
| Notes | Additional information<br>• Funding: supported by Outstanding young talents training project of Guangdong Province (Grant No. LYM11035) and the Guangdong Natural Science Foundation, China (Grant No. S2011040005590)<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "The patients were assigned to the study or control group using fifty sets of computer-generated random numbers."<br><br>Comment: Computer generation is considered as low risk of bias. No imbalance between intervention groups was apparent |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "The 160 patients who joined the study were randomly assigned to either the study or control group. There were 80 patients in each of the treatment arms. At week 12, 69 of the 80 (86.3%) study patients and 66 of the 80 (82.5%) controls had completed the follow-up questionnaires. A total of 135 patients completed the protocol and were included in the analysis (Figure 1)." |

**Li 2014b** *(Continued)*

| | | |
|---|---|---|
| | | Comment: 69/80 participants in the intervention group and 66/80 participants in the control group completed the study (> 5% lost to follow-up, without differences between groups). Reasons for discontinuations seemed to be not related to the treatment allocation |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and authors had no conflicts of interest. The study seemed to be free from other source of bias |

**Lillevang 1990**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 8 weeks<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Setting: not reported<br>• Country: Denmark<br>• Inclusion criteria: HD for at least 3 months and Hb < 5.6 mmol/L (the average value based on at least 3 measurements within the last 3 weeks before inclusion in the study)<br>• Exclusion criteria: < 18 years; pregnancy or nursing women; serum ferritin < 150 µg/L; malignant disease; BP > 160/90 mm Hg (the average value, based on measurements performed during the last 12 dialysis sessions); participation in other clinical studies; blood transfusion within the last 3 weeks; deferoxamine treatment within the last 3 months; or anaemia due to other diseases but renal<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (9/9); control group (7/10) (it was reported that "one patient chose to not want to participate" but it was not clear in which group he was)<br>• Mean age, range (years): intervention group (49.1, 25 to 70); control group (43.4, 22 to 57)<br>• Sex (M/F): treatment group (7/2); control group (6/4)<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Pharmacological intervention |

**Lillevang 1990** *(Continued)*

- Indication: study targeting fatigue

Intervention group

- rHu-EPO: 50 IU/kg IV 3 times/week (EPO 5000 IE/mL, diluted in a buffer solution)

Control group

- Placebo (buffer solution)

Co-interventions

- Not reported

Outcomes

Outcomes reported

- Fatigue outcome measures used: validation data available
- Change in laboratory results (B-Hb, erythrocytes, mean erythrocyte cell volume, mean erythrocyte cell HCT, S-transferrin, S-haptoglobin, vitamin B12, S-iron, S-ferritin, reticulocytes, leucocytes and differentiation, thrombocytes, S-potassium, S-sodium, S-carbamide, S-creatinine, ALAT, S-bilirubin (total), S-gamma-glutamyl transferase, S-alkaline phosphatase, S-calcium, S-phosphate, B-glucose, S-protein and bleeding time measurement a.m. Ivy): assessed at weeks 0, 4 and 8
- BP (SBP and DBP): assessed until the end of the study
- Weight: assessed until the end of the study
- Adverse events: assessed until the end of the study
- HRQoL
  - Questionnaire (name not reported) (13 symptoms had a score between 0 to 10 was then calculated (0 to 130 points)): assessed at 0 and 8 weeks
    - Perception of severity
    - Frequency
    - Duration
    - Sleep disorders
    - Medication
    - Daily life
    - QoL
    - Fatigue
    - Cramps
    - Rashed
    - Shortness of breath
    - Headache
    - Joint pain
    - Muscle fatigue/weakness
    - Nausea
    - Emesis
    - Angina pectoris
    - Dizziness
    - Palpitation

Notes

Additional information

- Funding: not reported
- Conflicts of interest/disclosures: not reported
- Trial registration identification number: not applicable
- A priori published protocol: not reported
- Not English

**Lillevang 1990** *(Continued)*

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "The design of the study was a double blinded, placebo-controlled study with a duration of eights weeks."<br><br>Comment: Although author reported that the study used a double-blind design, information about blinding of participants and investigators were not clearly stated |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "In order to investigate the effect of the treatment methods on the patients' quality of life, a structured interview was performed before and after the study, where the interviewer (the same person for all patients), based upon the patients answers given, calculated a score for the most common complaints that can be seen among haemodialysis patients. [...] Neither the patient, nor the interviewer, saw the results from week 0 during the week 8 interview."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "19 adult haemodialysis patients in stable phase. The study was sent to and accepted by the regional ethical research committee. One patient chose to not want to participate. [...] All patients in the EPO-group completed their study. In the placebo group, three patients had to be excluded due to need of blood transfusion at week 3 (2) and week 5 (1)."<br><br>Comment: 9/9 participants in the intervention group and 7/10 participants in the control group completed the study (> 5% lost to follow-up, with differences between groups) |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | No sufficient data were available to assess the possible imbalance between groups. Funding and conflicts of interest were not reported |

**Lin 2011**

***Study characteristics***

**Lin 2011** *(Continued)*

| | |
|---|---|
| Methods | Study design<br>• Quasi-RCT<br>Study dates<br>• Duration of follow-up: 2 months<br>• Time frame: January to March 2007 |
| Participants | Study characteristics<br>• Setting: single-centre (HD centre in Taipei)<br>• Country: Taiwan<br>• Inclusion criteria: 18 and 65 years; HD > 3 months and they were needled on acupoints for 3 to 5 hours/sitting, 3 times/week; weight gain < 6% between 2 successive HD sessions; sensitivity of their skin to temperature is intact; no infection or hospitalisation for at least one month during the pre-study assessment period; willing to participate in this research after an explanation and they must submit their letter of consent to this effect<br>• Exclusion criteria: not reported<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (36/36); control group (25/25)<br>• Mean age ± SD (years): not reported<br>• Sex (M/F): intervention group (16/20); control group (15/10)<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Far-infrared irradiation (acupuncture)<br>Control group<br>• No intervention<br>Co-interventions: not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ◦ Taiwan version of BFI (Appendix 3): assessed before and after the treatment<br>• Usual level of fatigue during the past 24 hours<br>• Worst level of fatigue during the past 24 hours<br>• Fatigue in the last week<br>• Fatigue strength rate<br>• Disturbance of life<br>• General activity |

**Lin 2011** *(Continued)*

- Mood
- Walking ability
- Normal work
- Relations with other people
- Enjoyment of life
- Meridian equipment
  - Ryodoraku instrument: assessed before and after the treatment
    - Small intestine meridian
    - Large intestine meridian
- Laboratory results (Hb, albumin, BUN, creatinine): assessed before and after the treatment

| | |
|---|---|
| Notes | Additional information<br>• Funding: not reported<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Prior to the intervention process, the selected patients were randomly divided by computer into two groups."<br><br>Comment: The study was a quasi-experimental study. Computer generation is considered as low risk of bias. No imbalance between intervention groups was apparent |
| Allocation concealment (selection bias) | High risk | Method of allocation concealment was not reported in sufficient detail to permit judgement. However the study used a quasi-experimental design |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "To minimize participants' misunderstanding of the Brief Fatigue Inventory-Taiwan Form (BFI-T), the data were collected mainly via a face-to-face survey interview. The participants were allowed to ask any questions about the study at any stage."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant/investigators beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. Other outcomes were objective |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All participants completed the study and were included into the analyses |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for |

**Lin 2011** *(Continued)*

| | | |
|---|---|---|
| | | meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding and conflicts of interest were not reported |

**Linde 2001**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 48 to 76 weeks (the study duration was extended from 48 weeks to 76 weeks in Sweden (48 study centres) due to a slower increase in Hb values than anticipated. Since the withdrawal rate was high, results at week 48 are presented for many variables)<br>• Time frame: 1995 to 1996 (the months were not reported) |
| Participants | Study characteristics<br>• Setting: multicentre (62 hospital centres: Sweden (48), Norway (8), Finland (5) and Iceland (1))<br>• Country: multinational (Sweden, Norway, Finland, Iceland)<br>• Inclusion criteria: renal anaemia; stratified into 3 groups: pre-dialysis, HD and PD patients; pre-dialysis patients (SCr 300 mmol/L or CrCl < 30 mL/min) were not expected to become dialysis-dependent within 1 year; Hb values in the subnormal range (90 to 120 g/L) for at least 3 months with or without epoetin therapy prior to entering the study<br>• Exclusion criteria: anaemia from causes other than CKD; DBP repeatedly at least 100 mmHg; uncontrolled diabetes (HbA1c > 10%); clinically relevant abnormal liver function; severe secondary hyperparathyroidism (cystic bone disease, PTH >3 00 ng/L); clinical signs of aluminium intoxication (serum aluminium > 100 mg/L) or treatment with desferrioxamine; uncontrolled overhydration in Hb patients (requiring repeatedly ultrafiltration of at least 4 L); active infection, inflammation or malignancy<br>◦ An amendment added new exclusion criteria: angina pectoris and/or congestive heart failure corresponding to NYHA classes III and IV; history of a coronary-artery by-pass grafting and/or percutaneous transluminal coronary angioplasty < 2 years ago; history of transmural MI < 3 years ago; permanent atrial fibrillation or uncontrolled arterial hypertension<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (73/180); control group (83/164)<br>◦ HD: intervention group (63/157); control group (71/136)<br>◦ PD: intervention group (10/23); control group (12/28)<br>• Mean age ± SD (years)<br>◦ HD: intervention group (65 ± 12); control group (64 ± 15)<br>◦ PD: intervention group (60 ± 9); control group (60 ± 13)<br>• Sex (M/F): intervention group (125/55); control group (106/53)<br>◦ HD: intervention group (108/49); control group (92/44)<br>◦ PD: intervention group (17/6); control group (14/9)<br>• Dialysis type: HD, PD<br>• Dialysis vintage (years) (mean ± SD)<br>◦ HD: intervention group (2.6 ± 3.3); control group (3.0 ± 3.9)<br>◦ PD: treatment group (1.1 ± 1); control group (2.4 ± 4.4)<br>• Comorbidities<br>◦ CVD: not reported |

**Linde 2001** *(Continued)*

- Diabetes: intervention group (33/180); control group (33/159)
  - HD: intervention group (28/157); control group (27/136)
  - PD: intervention group (5/23); control group (6/28)
- Hypertension: not reported
- Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br><br>• Pharmacological intervention<br>• Indication: study targeting fatigue<br><br>Intervention group<br><br>• Epo alfa (SC): to reach normal Hb 135 to 150 g/L in females and 145 to 160 g/L in males<br>  ○ Patients randomised to N-Hb not already receiving epoetin initially received 50 U/kg of epoetin alfa 3 times/week. For patients already receiving epoetin, the initial dose increment was 50%. The dose was increased by 25% if reticulocytes had not increased by at least 75% after 2 weeks of treatment. Epoetin alfa was increased by a further 25%, if the increase in Hb was < 10 g/L after 4 weeks. The dose was then adjusted every 2 weeks, aiming at a monthly increase in Hb of 10 to 15 g/L to reach the target Hb level within 3 months<br><br>Control group<br><br>• Subnormal Hb of 90 to 120 g/L with or without epoetin alfa<br><br>Co-interventions<br><br>• Patients received iron supplementation with oral iron sulphate or IV iron sucrose to keep TSAT > 20% and serum ferritin levels between 400 to 800 mg/L during the correction phase and > 250 mg/L during the maintenance phase |
| Outcomes | Outcomes reported<br><br>• Fatigue outcome measures used: validation data available<br>• Change in HRQoL<br>  ○ KDQ: assessed at baseline and at week 48<br>  ■ Physical symptoms<br>  ■ Fatigue<br>  ■ Depression<br>  ■ Frustration<br>  ■ Relations with others<br>• Self-Image Scales: assessed at baseline and at week 48<br>• Leicester Uremic Symptoms Scale: assessed at baseline and at week 48<br>• ESKD-DL scales: assessed at baseline and at week 48<br>• VAS: assessed at baseline and at week 48<br>• Adverse events: assessed until the end of treatment<br>• Vascular access: assessed until the end of the study<br>• Serious adverse events: assessed until the end of treatment<br>• Vital signs (including SBP, DBP): assessed weekly until the end of the study<br>• Progression rate of CKD<br>  ○ Endogenous CrCL (24 hours urine collection) in pre-dialysis patients: assessed at weeks 0 and 48<br>  ○ Iohexol clearance in pre-dialysis patients: assessed at weeks 0 and 48<br>  ○ Cr-EDTA clearance in pre-dialysis patients: assessed at weeks 0 and 48<br>• All-cause death (included sepsis, infection, uraemia NUD and malignancy): assessed until 48 weeks<br>• Laboratory results (TSAT, serum ferritin, creatinine, Hb, GFR): assessed at week 0 and 48<br>• Epo alfa dose: assessed at weeks 0 and 48<br>• Iron sucrose dose: assessed at weeks 1 to 4 and 45 to 48 |

**Linde 2001** *(Continued)*

- Fraction functioning grafts: assessed at days 1, 7, 14 and months 3 and 6
- Hospitalisation: assessed until the end of treatment
- Cardiovascular death: included MI, atherosclerotic disease of the coronary arteries, aorta and peripheral arteries, congestive heart failure, sudden death and cerebrovascular disease): assessed until the end of treatment
- ESKD (for pre-dialysis patients): assessed until the end of the study
- Transplant: assessed at 6 months
- Transplant acute rejection: assessed at 6 months

| | |
|---|---|
| Notes | Additional information<br>• Funding: not reported<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not applicable<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote from Furuland 2003: "This was a multicenter, randomised, open-label trial in patients with renal anaemia."<br>Comment: An open-label study is considered as high risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote from Furuland 2003: "Thrombovascular events and vascular access thrombosis were recorded and categorized centrally by one coordinator based on a WHO classification."<br>Comment: Some outcomes were recorded centrally (not sure that it was valid also for fatigue). The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | As reported in table 2, overall 73/180 participants in the intervention group and 83/164 participants in the control group completed the study (> 5% lost to follow-up, with differences between groups). Some reasons for discontinuations (adverse events) seemed to be related to the treatment allocation |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |

**Linde 2001** *(Continued)*

| | | |
|---|---|---|
| Other bias | Unclear risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding and conflicts of interest were not reported |

**Mohajeranirad 2021**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 6 weeks<br>• Time frame: February 2020 to May 2020 |
| Participants | Study characteristics<br>• Setting: single-centre (Arak Hami Dialysis Center)<br>• Country: Iran<br>• Inclusion criteria: > 18 years; history of HD for at least 3 months; no consumption of herbal supplements for at least 3 months before study<br>• Exclusion criteria: allergies to herbal capsules during the study; changes in diet and physical activity levels during the intervention; unwillingness to cooperate in the study; candidate for a kidney transplant<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (25/27); control group (25/27)<br>• Mean age ± SD (years): intervention group (60.64 ± 2.88); control group (64.84 ± 2.54)<br>• Sex (M/F): intervention group (12/13); control group (11/14)<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Helichrysum Psudoplicatum supplementation capsule 250 mg/day<br>Control group<br>• Placebo capsule<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported |

**Mohajeranirad 2021** *(Continued)*

- Fatigue outcome measures used: validation data available
- Fatigue
  - FSS (Appendix 3); a total score of < 36 means no fatigue, and ≥ 36 means the presence of fatigue
- Pruritus intensity
  - NRS: patients scored from 0 (no itch) to 10 (worst imaginable itch)
- QoL
  - ItchyQoL (Appendix 3)
- Anorexia
  - SNAQ (Appendix 3)
- Laboratory parameters (urea, creatinine, albumin and Hb)

| | |
|---|---|
| Notes | Additional information<br>• Funding: Arak University of Medical Sciences (Grant number: 6086)<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: IRCT20180610040049N2<br>• A priori published protocol: the protocol received Ethical approval |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "In a randomised double blind placebo controlled study."<br>Comment: Although the study was reported as a double blind study, it was not reported if participants and investigators were blinded to the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "54 participants were selected and randomly assigned into two groups: intervention and placebo. During the study, four patients dropped out of the interventional and placebo group due to personal reasons. Finally, 50 patients [interventional (n=25) and placebo (n=25)] completed the trial and included in the analysis."<br>Comment: 25/27 participants in the intervention group and 25/27 participants in the control group completed the study (>5% lost to follow-up). Reasons for discontinuation were not reported |
| Selective reporting (reporting bias) | High risk | Protocol was reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |

**Mohajeranirad 2021** *(Continued)*

| | | |
|---|---|---|
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence data analysis and interpretation. No other source of bias were apparent |

**Mohamed 2013**

***Study characteristics***

| | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 12 weeks<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Setting: multicentre (2 tertiary care hospitals affiliated with an academic centre)<br>• Country: not reported<br>• Inclusion criteria: patients ≥ 18 years with type 2 diabetes undergoing HD<br>• Exclusion criteria: not reported<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group 1 (not reported/15); intervention group 2 (not reported/19)<br>• Median age, IQR (years): intervention group 1 (73, 45 to 88); intervention group 2 (65, 35 to 95)<br>• Sex (M/F): intervention group 1 (9/6); intervention group 2 (11/8)<br>• Dialysis type: HD<br>• Median dialysis vintage, IQR (years): intervention group 1 (2.83, 1.0 to 6.58); intervention group 2 (1.42, 0.42 to 8.0)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: intervention group 1 (15/15); intervention group 2 (19/19)<br>  ◦ Hypertension: not reported<br>  ◦ Depression: not reported |
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study reporting fatigue<br>Intervention group 1<br>• Higher dialysate glucose concentration baths: 11 mmol/L<br>Intervention group 2<br>• Standard dialysate glucose concentration baths: 5.5 mmol/L<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported |

**Mohamed 2013** *(Continued)*

- Fatigue outcome measures used: validation data available
- HbA1c: assessed at baseline and at week 12
- HRQoL
  - RAND SF-36 (including fatigue assessment): assessed at baseline and at week 12
    - General component
    - Social function

| | |
|---|---|
| Notes | Additional information<br>• Funding: not reported<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported<br>• Abstract |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "Participants were randomised in an open-label fashion."<br>Comment: An open-label study was considered as high risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "One patient withdrew in the third week from the higher DGC group."<br>Comment: The number of patients who completed the study was not clearly stated. It was unclear if there was evidence that the results were not biased by missing outcome data |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Outcomes information were not reported in sufficient detail to permit judgment. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | No data were available to assess the possible imbalance between groups. Funding and conflicts of interest were not reported |

**Mohamed 2014**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Quasi-RCT<br>Study dates<br>• Duration of follow-up: 3 months<br>• Time frame: November to December 2013 |
| Participants | Study characteristics<br>• Setting: single-centre (Hemodialysis Unit at Public Fayoum Hospital, Ministry of Health)<br>• Country: Egypt<br>• Inclusion criteria: recently diagnosed with kidney failure and requiring HD at least 3 months; patients had to be sedentary for 6 months or more; ≥ 18 years; able to communicate<br>• Exclusion criteria: acute heart and lung disease; acute infectious diseases; Hb < 10 g/dL; physical or mental disability preventing the proper performance of the protocol<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (40/40); control group (40/40)<br>• Mean age ± SD (years): not reported<br>• Sex (M/F): intervention group (18/22); control group (20/20)<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ○ CVD: not reported<br>  ○ Diabetes: not reported<br>  ○ Hypertension: not reported<br>  ○ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Educational nursing intervention protocol for 2 weeks<br>Control group<br>• Standard nursing instruction and routine hospital care<br>Co-interventions<br>• All adult patients were scheduled for HD |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ○ PFS (Appendix 3): assessed pre and post-test and after 3 months<br>  ■ Behavioural<br>  ■ Affective<br>  ■ Sensory<br>  ■ Cognitive/mood |

**Mohamed 2014** *(Continued)*

- General knowledge in CKD and HD
  - Structured Knowledge Questionnaires Sheet (40 questions; each right answer got one score, while no answer take zero score): assessed pre and post-test and after 3 months
    - General information about CKD
    - General information about HD
    - Clinical manifestation
    - Diagnostic evaluation
    - Knowledge about nutrition
    - Self–care measures
    - Knowledge about complication
- Laboratory results (Hb, sodium, potassium, blood urea, creatinine): assessed pre- and post-test and after 3 months

| | |
|---|---|
| Notes | Additional information<br>• Funding: not reported<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "The patient assessment sheet was filled by the researcher through personal interview."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant/investigators beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed. It was not stated if the interviewer was blinded to the treatment allocation |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Table 3 reported that all participants completed the study. However, it was not clearly stated if some participants discontinued |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |

**Mohamed 2014** *(Continued)*

| | | |
|---|---|---|
| Other bias | Unclear risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding and conflicts of interest were not reported |

**Mohammadpourhodki 2021**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 4 weeks<br>• Time frame: April to July 2019 |
| Participants | Study characteristics<br>• Setting: single-centre (HD Unit)<br>• Country: Iran<br>• Inclusion criteria: ability to verbally communicate; 18 to 65 years; history of dialysis for at least 3 months; receiving 3 sessions of HD/week; no allergy to Lavender and Citrus Aurantium; no experience with massage or aromatherapy; not candidate for kidney transplantation at the time of the study; no history of substance abuse; no serious complication in the lower extremities such as diabetic foot ulcer, peripheral neuropathy, and vascular problems based on the physician's examination<br>• Exclusion criteria: withdrawal of dialysis during the study for any reason (such as travel, migration, kidney transplant, and patient death)<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group 1 (35/35); intervention group 2 (35/35); control group (35/35)<br>• Mean age ± SD (years): intervention group 1 (50.58 ± 14.05); intervention group 2 (50.42 ± 17.44); control group (57.60 ± 16.40)<br>• Sex (M/F): intervention group 1 (25/10); intervention group 2 (23/12); control group (20/15)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): overall (3.4 ± 2.0)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group 1<br>• Lavender essential oil<br>Intervention group 2<br>• Citrus Aurantium essential oil |

**Mohammadpourhodki 2021** *(Continued)*

| | |
|---|---|
| | Control group<br>• No intervention<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>• FSS (Appendix 3)<br>• QoL<br>  ○ SF-36 (Appendix 3)<br>  ■ Physical and social function<br>  ■ Emotional role<br>  ■ Bodily pain<br>  ■ General health<br>  ■ Vitality<br>  ■ Mental health<br>• Sleep<br>  ○ PSQI |
| Notes | Additional information<br>• Funding: none<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: IRCT20180711040432N2<br>• A priori published protocol was reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Block randomisation."<br>Comment: Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "Not blinded." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant/investigators beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias) | Low risk | All participants completed the study. There were no lost to-follow-up |

**Mohammadpourhodki 2021** *(Continued)*

All outcomes

| | | |
|---|---|---|
| Selective reporting (reporting bias) | High risk | Protocol was published. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. There was no source of funding or conflict of interests. No other source of bias were apparent |

**Motedayen 2014**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT (author reported that the study was a controlled trial)<br>Study dates<br>• Duration of follow-up: 2 months<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Setting: multicentre (Baqiyatallah Hospital and Labbafinejad Hospital, Tehran)<br>• Country: Iran<br>• Inclusion criteria: undergoing HD 3 times/week for at least 3 months who were capable of learning during the exercises<br>• Exclusion criteria: patients participating in the regular exercise program in the preceding 6 months; medical prohibition from the exercise; history of ischaemic heart disease; third-degree congestive heart failure; unstable angina; kidney transplant; high BP (≥ 180/110 mm Hg); low BP (≤ 90 mm Hg); reluctance to continue participating in the exercises<br>Baseline characteristics<br>• Number (analysed/randomised): overall (66/75); intervention group (33/not reported); control group (33/not reported)<br>• Mean age ± SD (years): overall (56.75 ± 11.91)<br>• Sex (M/F): intervention group (22/11); control group (16/17)<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Intradialytic physical and mental exercises for 2 months |

**Motedayen 2014** *(Continued)*

| | |
|---|---|
| | Control group<br>• No intervention<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ○ FSS (Appendix 3): assessed at baseline, and at months 1 and 2<br>• Death: assessed until the end of treatment |
| Notes | Additional information<br>• Funding: This paper was derived from the thesis and approved by Nursing School Board of Examiners in Baqiyatallah University of Medical Sciences. The special thanks go to Baqiyatallah Hospital Nephrology and Urology Research Center for its financial support<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "The Fatigue Severity Scale (FSS) questionnaire was completed by the subjects prior to the study and at the end of the first and the second months."<br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. Other objective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "Initially, 75 patients were assigned to the experimental and control groups; nine patients were excluded from the study because of death, transplantation, transportation from the health centre, or refusing to do the exercises regularly due to fatigue, boredom, and sleeplessness on the night before dialysis. Therefore, the findings of the study were extracted from the information of two 33-patient groups."<br>Comment: Overall, 66/75 participants completed the study (>5% lost to follow-up; possible differences between groups were not reported). Reasons for discontinuations seemed to be not related to the treatment allocation |

**Motedayen 2014** *(Continued)*

| | | |
|---|---|---|
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and conflicts of interest was not reported |

**Muz 2017**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 1 month<br>• Time frame: August 2014 to February 2015 |
| Participants | Study characteristics<br>• Setting: multicentre (5 HD centres settled in two provinces in Turkey)<br>• Country: Turkey<br>• Inclusion criteria: ≥ 18 years; no eye or hearing disabilities; voluntary participation in the study; HD for 3 months; continue dialysis in the same unit/centre, undergo HD treatment for 3 sessions/week; not to take any sleeping pill before aromatherapy and during the course of the study; have average or severe fatigue symptoms (VAS fatigue score should be 3 or more); have a score of 5 or more for PSQI; speak Turkish<br>• Exclusion criteria: any respiratory system disease; any allergy to essential oils used; any obstacle to smell; use of other integrative medicine applications during treatment<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (27/41); control group (35/39)<br>• Mean age ± SD (years): intervention group (52.26 ± 14.50); control group (59.26 ± 12.43)<br>• Sex (M/F): intervention group (18/9); control group (16/19)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): intervention group (6.29 ± 3.91); control group (6.24 ± 5.27)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Treatment group<br>• Inhalation of sweet orange and lavender oil every day |

**Muz 2017** *(Continued)*

| | |
|---|---|
| | Control group<br>• No intervention<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Sleep quality<br>  ○ PSQI (Appendix 3): assessed at baseline and after 1 month<br>  ■ Daytime sleepiness dysfunction<br>  ■ Subjective sleep quality<br>  ■ Sleep latency<br>  ■ Sleep duration<br>  ■ Habitual sleep efficiency<br>  ■ Sleep disturbance<br>  ■ Global sleep quality<br>• Fatigue<br>  ○ 10-point VAS: assessed at baseline, every week for 1 month<br>  ○ PFS (Appendix 3): assessed at baseline, every week for 1 month<br>• Behavioural/severity<br>• Affective meaning<br>• Sensory<br>• Cognitive mood<br>• Laboratory results (Hb, HCT, albumin, urea, CrCl): assessed at baseline at the end of the study<br>• Hospitalisation: assessed until the end of the treatment |
| Notes | Additional information<br>• Funding: supported in part by a grant from the Erciyes University Scientific Research Projects Coordination Unit (no. TDK-2014-5222)<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Random selection of samples was performed."<br>Comment: Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "Visual Analogue Scale (VAS) score, Piper fatigue scale, and Pittsburgh Sleep Quality Index (PSQI) were determined via face-to-face interview and patient documents. In the first week (the first follow-up), second week (second |

**Muz 2017** *(Continued)*

| | | |
|---|---|---|
| | | follow-up), and third week (third follow-up), Visual Analogue Scale (VAS) score and Piper fatigue scale were obtained by the researcher."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant/investigators beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Figure 1 reported the number of participants who did not complete the follow-up. 27/41 participants in the intervention group and 35/39 participants in the control group completed the study (> 5% lost to follow-up, with differences between groups) |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and authors had no conflicts of interest. The study seemed to be free from other source of bias |

**Ozdemir 2013**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 1 week<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Setting: multicentre (HD units of two institutions in the city of Gaziantep located in the Southeastern Anatolia region of Turkey)<br>• Country: Turkey<br>• Inclusion criteria: ≥ 18 years; full consciousness and orientation; did not have any communication problems; HD 3 times/week for at least 6 months; marked level of severity of fatigue, pain and cramp as at least 1 in VAS; volunteered to participate in the research<br>• Exclusion criteria: patients with open foot wound; suspicious fracture; burn; deep vein thrombosis; peripheral neuropathy<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (not reported/40); control group (not reported/40)<br>• Mean age ± SD (years): intervention group (43.1 ± 15.8); control group (54.0 ± 12.8)<br>• Sex (M/F): intervention group (13/27); control group (17/23) |

**Ozdemir 2013** *(Continued)*

- Dialysis type: HD
- Dialysis vintage (years) (mean ± SD): not reported
- Comorbidities
  - CVD: not reported
  - Diabetes: not reported
  - Hypertension: not reported
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Foot reflexology for 30 minutes, 3 times/week for 1 week<br>Control group<br>• No intervention<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ○ PFS (Appendix 3) (assessed at baseline and after 1 week)<br>  ■ Behavioural/severity<br>  ■ Affective meaning<br>  ■ Sensory<br>  ■ Cognitive/mood<br>• Pain<br>  ○ 10-point VAS (Appendix 3): assessed at baseline and after 1 week<br>• Cramps<br>  ○ 10-point VAS (Appendix 3): assessed at baseline and after 1 week<br>• Laboratory results (Hb, HCT, albumin, URR): assessed at baseline and after 1 week<br>• Kt/V: assessed at baseline and after 1 week |
| Notes | Additional information<br>• Funding: not reported<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomization was performed by MedCalc software to give equal chance to each intervention group."<br>Comment: Computer-generation is considered as low risk of bias. No imbalance between intervention groups was apparent |

**Ozdemir 2013** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "The data of the intervention and control groups were collected by using the questionnaire, Piper Fatigue Scale and Visual Analogue Scale (VAS)."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | The number of patients who completed the study was not clearly stated. It was unclear if there was evidence that the results were not biased by missing outcome data |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding and conflicts of interest were not reported |

**Parfrey 2005**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 96 weeks<br>• Time frame: February 2000 to June 2001. The last patient completed the study in May 2003 |
| Participants | Study characteristics<br>• Setting: multicentre (95 centres)<br>• Country: multinational (10 countries, Europe (Australia, Belgium, Canada, France, Germany, Greece, Hungary, Poland, Spain, UK)<br>• Inclusion criteria: ≥ 18 years; maintenance HD started within the previous 3 to 18 months without symptomatic cardiac disease; predialysis Hb between 8 and 12 g/dL; LV volume index < 100 mL/$m^2$; and predialysis DBP < 100 mm Hg<br>• Exclusion criteria: clinical evidence or history of symptomatic cardiac failure or ischaemic heart disease; daily prednisone dose > 10 mg; medical conditions likely to reduce epoetin responsiveness, |

**Parfrey 2005** *(Continued)*

including uncorrected iron deficiency; concurrent malignancy; blood transfusion in the preceding month; therapy with cytotoxic agents; seizure in the preceding year; hypersensitivity to IV iron; current pregnancy or breastfeeding

Baseline characteristics

- Number (analysed/randomised): intervention group 1 (164/300); intervention group 2 (160/296)
- Mean age ± SD (years): intervention group 1 (49.4 ± 15.2); intervention group 2 (52.2 ± 15.6)
- Sex (M/F): intervention group 1 (180/120); intervention group 2 (178/118)
- Dialysis type: HD
- Mean dialysis vintage ± SD (years): intervention group 1 (0.9 ± 0.4); intervention group 2 (0.8 ± 0.4)
- Comorbidities
  - CVD: not reported
  - Diabetes: not reported
  - Hypertension: not reported
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group 1<br>• SC or IV epoetin alfa to reach low target Hb (9.5 to 11.5 g/dL), for 96 weeks<br>Intervention group 2<br>• SC or IV epoetin alfa to reach high target Hb (13.5 to 14.5 g/dL), for 96 weeks<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• HRQoL<br>  ◦ KDQoL (Appendix 3): assessed at weeks 0, 24, 36, 48, 60, 72, 84, and 96<br>• Energy/fatigue<br>• Burden of kidney disease<br>• Cognitive function<br>• Symptoms/problems<br>• Sexual function<br>• Sleep<br>• Social support<br>• Work status<br>• Dialysis staff encouragement<br>• Patient satisfaction rating<br>• Overall health rating<br>• Physical functioning<br>• Role limitations - physical<br>• Pain<br>• General health<br>• Emotional well-being<br>• Role limitation - emotional<br>• Social function |

**Parfrey 2005** *(Continued)*

- Quality of social interaction
- Vitality
- SF-36 (Appendix 3): assessed at weeks 0, 24, 36, 48, 60, 72, 84, and 96
- Death: assessed until the end of treatment
- Laboratory results (BMI, URR, TSAT, albumin, serum concentrations of N terminal pro–B type natriuretic peptide, cardiac troponin T, CRP, IL-6): assessed every week
- Hb: assessed weekly for 24 weeks and biweekly thereafter
- Vital signs (SBP, DBP): assessed every week
- Adverse events: classified by the World Health Adverse Reactions Terminology (Appendix 3)
- Transfusion rate: assessed at weeks 0, 24, 36, 48, 60, 72, 84, and 96
- Time to first transfusion: assessed at weeks 0, 24, 36, 48, 60, 72, 84, and 96
- LV cavity volumes
  - ECG: assessed at 24, 48 and 96 weeks
- LV mass index: assessed at 24, 48 and 96 weeks
- Rates of de novo heart failure (defined as dyspnoea): assessed at 24, 48 and 96 weeks
- Change in functional capacity
  - 6MWT performance: assessed at weeks 0, 24, 48, and 96
- Fatigue
  - FACIT-fatigue: assessed at weeks 0, 24, 36, 48, 60, 72, 84, and 96

| | |
|---|---|
| Notes | Additional information<br>• Funding: Johnson&Johnson Pharmaceutical Research and Development. The study sponsor identified the participating centres, monitored the data collection, and entered the data in a central database<br>• Conflicts of interest/disclosures: P.S.P. has received research support and has been an academic advisor to companies that make erythropoietin products: Ortho Biotech, Amgen, and Roche. R.N.F. has received research support and honoraria from Ortho Biotech and honoraria from Affymax, Amgen, Ortho Biotech, and Roche. B.M.C. has received research support and honoraria from Ortho Biotech. P.S.P. declares that he had full access to all of the data in the study and had final responsibility for the decision to submit for publication<br>• Trial registration identification number: not applicable (trial was performed before 2005)<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote from Foley 2008: "The study was centrally coordinated from St. John's, Canada for Canadian patients and Manchester, England for European patients. Randomization was performed at the coordinating centres with an interactive voice randomisation telephone system using permuted blocks stratified by concurrent epoetin use and sex."<br><br>Comment: The interactive voice system is likely to be a computer. No imbalance between intervention groups was apparent |
| Allocation concealment (selection bias) | Low risk | Quote from Foley 2008: "The study was centrally coordinated from St. John's, Canada for Canadian patients and Manchester, England for European patients. Randomization was performed at the coordinating centres with an interactive voice randomisation telephone system using permuted blocks stratified by concurrent epoetin use and sex."<br><br>Comment: An interactive voice system is considered as low risk of bias. No imbalance between intervention groups was apparent |

**Parfrey 2005** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote from Foley 2009: "Patients and attending physicians were masked to treatment assignment. [...] Local investigators and the dialysis unit were also masked to treatment assignment."<br><br>Quote from Parfley 2005: "A randomised, double-blind design was used with patients and outcome assessors but not treating physicians, who were blinded to assigned haemoglobin target."<br><br>Comment: A double-blind trial is considered as low risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote from Foley 2009: "Quality of life was assessed using the KDQoL questionnaire, with prespecified outcomes being Energy/Fatigue scores, and Quality of Social Interaction Scores."<br><br>Quote from Foley 2009: "Independent Data Monitoring Committee Members."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting (not sure that the Independent Data Monitoring Committee Members assessed fatigue). Participant/investigators beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. It was not stated if the independent data monitoring was blinded to the treatment assigned. However, objective and subjective outcomes were assessed. It was not stated if the interviewer was blinded to the treatment allocation |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Quote from Parfley 2005: "324 (54%) patients remained in the study for 96 weeks, 160 (54%) in the higher and 164 (55%) in the lower target groups. The reasons for study exit— renal transplantation (n 133, 67 in the higher and 66 in the lower target group), adverse events (n 76, 39 and 37), patient choice (n 28, 9 and 19), loss to follow-up (n 2, 1 and 1), and other (n 36, 21 and 15)—were similar in the two target groups."<br><br>Comment: 164/300 participants in intervention group 1 (epoetin alfa to reach low target haemoglobin) and 160/296 participants in intervention group 2 (epoetin alfa to reach high target Hb) completed the study (> 5% lost to follow-up, without differences between groups). Reasons for discontinuations (adverse events) seemed to be related to the treatment allocation. However, all outcomes have been reported on the ITT population |
| Selective reporting (reporting bias) | Low risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were reported |
| Other bias | High risk | Quote from Foley 2009: "Baseline characteristics were similar except for the older age of high target subjects (52.2 versus 49.4 years)."<br><br>Comment: There was no substantial evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding (pharmaceutical company) could influence the data analysis and authors reported conflicts of interest |

**PEDAL 2020**

***Study characteristics***

| | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 6 months<br>• Time frame: June 2015 to June 2019 |
| Participants | Study characteristics<br>• Setting: multicentre (12 dialysis units)<br>• Country: UK<br>• Inclusion criteria: prevalent CKD stage 5 patients receiving maintenance HD therapy for > 3 months; male or female, aged > 18 years; able to provide written informed consent<br>• Exclusion criteria: dialysis < 6 months; dialysis withdrawal was being considered; likely to receive a live-donor transplant or transfer to PD in the period of time; within 3 months of initiation of HD; deemed to be clinically unstable by their treating physician; bilateral lower limb amputations; dementia or severe cognitive impairment; unable to give informed consent; psychiatric disorders (who are not treated and stable); pregnant<br>Baseline characteristics<br>• Number (analysed/randomised): overall (379 participants were randomised, but 335 attended the baseline visit: 243/335); intervention group (116/175); control group (127/160)<br>• Mean age ± SD (years): overall (59.4 ± 14.7)<br>• Sex (M/F): intervention group (108/67); control group (101/59)<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ◦ CVD: intervention group (70/175); control group (40/160)<br>  ◦ Diabetes: intervention group (75/175); control group (65/160)<br>  ◦ Hypertension: intervention group (141/175); control group (131/160)<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Intradialytic exercise training<br>Control group<br>• No intervention<br>Co-interventions<br>• Usual HD care |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• HRQoL<br>• KDQOL-SF (Appendix 3)<br>• EQ-5D-5L: assessed at baseline and end of treatment |

**PEDAL 2020** *(Continued)*

- Peak aerobic capacity
  - International Physical Activity Questionnaire: assessed at baseline and end of treatment
- Physical fitness
  - International Physical Activity Questionnaire: assessed at baseline and end of treatment
- Habitual physical activity levels
  - Duke's Activity Status Index: assessed at baseline and end of treatment
- Falls
  - Tinetti Falls Efficacy Scale: assessed at baseline and end of treatment
- Symptom burden assessments
  - EQ-5D: assessed at baseline and end of treatment
- Arterial stiffness (pulse wave velocity)
- Anthropometric measures
- BP
- Laboratory parameters (Hb, serum phosphate, PTH)
- Adverse events
- Hospitalizations
- Cost-effectiveness

| Notes | Additional information |
|---|---|

- Funding: The National Institute for Health Research (grant number: NIHR-HTA 12/ 23/09)
- Conflicts of interest/disclosures: none.
- Trial registration identification number: ISRCTN N83508514; NCT02222402
- A priori published protocol was published

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote from Greenword 2020: "Randomization was conducted via a centrally controlled web based randomisation system, run by the Glasgow Clinical Trials Unit (GCTU). To ensure balanced assignment across critical variables, a minimization algorithm was employed, taking into account baseline age, gender and diabetes status." |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote from Greenword 2020: " It was impossible to blind the 'treating' physiotherapy assistants or the participants, and thus the study implemented a blinded outcome assessment and analysis." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote from Greenword 2020: "This was a prospective, pragmatic multicenter RCT with blinded outcome assessment."<br><br>Fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote from Greenword 2021: "In total, the trial recruited 379 participants. A total of 335 participants attended a baseline study visit: 175 participants who were randomised to the exercise intervention and 160 participants who were |

**PEDAL 2020** *(Continued)*

| | | |
|---|---|---|
| | | randomised to usual care. Participants were informed of group allocation only after completing all baseline assessments. Fifty-nine patients allocated to the exercise intervention and 60 participants allocated to usual care did not complete the 6-month assessment. In total, seven participants died during the study: three participants from the intervention group and four participants from the usual-care group. In the intervention group, 40 participants were withdrawn and 16 did not attend for the final 6-month assessment. In the usual-care group, 15 participants were withdrawn and 14 participants did not attend the 6-month assessment."<br><br>Comment: 116/175 participants in the intervention group and 127/160 participants in the control group (no intervention) completed the study (> 5% lost to follow-up, with differences between groups). Reasons for discontinuations were reported |
| Selective reporting (reporting bias) | Low risk | Protocol was published. Fatigue was reported in accordance with a pre-specified analysis plan, using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. However, objective and subjective outcomes were assessed. All outcomes that should be addressed (fatigue, CVD, and death) were reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and authors had no conflicts of interest. The study seemed to be free from other source of bias |

**Pellizzaro 2013**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 10 weeks<br>• Time frame: June to September 2009 |
| Participants | Study characteristics<br>• Setting: single centre (dialysis unit of Santa Casa de Misericórdia, Porto Alegre, Rio Grande do Sul)<br>• Country: Brazil<br>• Inclusion criteria: 18 and 70 years; dialysis > 3 months; agree to participate by signing an informed consent form<br>• Exclusion criteria: unstable angina; uncontrolled cardiac arrhythmia; decompensated heart failure; SBP > 200 mm Hg; DBP > 120 mm Hg; acute pericarditis or myocarditis; decompensated DM (fasting serum glucose > 300 mg/dL); severe untreated mitral or aortic insufficiency/stenosis; severe lung conditions; acute systemic infection; severe bone disease; lower limb amputations; cognitive disorders; unable to perform the proposed tests due to disabling musculoskeletal, bone, or joint disorders<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group 1 (11/15); intervention group 2 (14/15); control group (14/15)<br>• Mean age ± SD (years): intervention group 1 (43 ± 13.8); intervention group 2 (48.9 ± 10.1); control group (51.9 ± 11.6)<br>• Sex (M/F): intervention group 1 (8/3); intervention group 2 (7/7); control group (8/6) |

**Pellizzaro 2013** *(Continued)*

- Dialysis type: HD
- Median dialysis vintage, IQR (years): intervention group 1 (5, 2 to 11); intervention group 2 (4.5, 0.9 to 10); control group (4.5, 1 to 6.5)
- Comorbidities
  - CVD: not reported
  - Diabetes: not reported
  - Hypertension: not reported
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group 1<br>• Respiratory muscle training for 10 weeks<br>Intervention group 2<br>• Peripheral muscle training for 10 weeks<br>Control group<br>• No intervention<br>Co-interventions<br>• All patients performed HD 3 times/week with a Tina machine (Baxter), with capillary filter size 10 L (Gambro). The standard prescription for the HD was blood flow rate at 300 mL/min, dialysate flow rate at 700 mL/min, and total dialysis session length of 4 hours<br>• Vascular access was through an arteriovenous fistula in all patients |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• HRQoL<br>• KDQOL-SF (Appendix 3): assessed before and after 70 days<br>• Energy/fatigue<br>• Pain<br>• Sleep<br>• Symptoms/problems<br>• Change in maximal inspiratory pressure (PImax)<br>  ◦ Respiratory pressure metre: assessed before and at the end of the test<br>• Change in maximal expiratory pressure (PEmax)<br>  ◦ Respiratory pressure metre: assessed before and at the end of the test<br>• Forced vital capacity<br>  ◦ Spirometry: assessed before and at the end of the test<br>• Change in functional capacity<br>  ◦ 6MWT: assessed before and at the end of the test<br>• Kt/Vsp: assessed before and after training<br>• Subjective effort perception<br>  ◦ Borg scale: assessed before and at the end of the test<br>• Death: assessed until the end of treatment<br>• Vital signs (BP, heart rate, respiratory rate, peripheral oxygen saturation ($SpO_2$))<br>  ◦ Pulse oximeter: assessed before and after training<br>• Laboratory results (CRP, HCT, Hb, serum levels of urea, creatinine, potassium, phosphorus, albumin): assessed before and after 70 days |

**Pellizzaro 2013** *(Continued)*

| | |
|---|---|
| Notes | Additional information<br>• Funding: Research Funding of Hospital de Clínicas de Porto Alegre (FIPE/HCPA)<br>• Conflicts of interest/disclosures: none. The authors alone are responsible for the content and writing of the article<br>• Trial registration identification number: not reported<br>• A priori published protocol: protocol number 3087/09 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Randomisation was made by dividing the subjects into three blocks of 15 each, five in each group."<br>Comment: Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "Of the 45 patients initially included, six did not complete the study protocol due to non-compliance (n = 5) or death (n = 1) and were not included in the analysis."<br>Comment: 11/15 participants in the intervention group 1 (respiratory muscle training), 14/15 participants in the intervention group 2 (peripheral muscle training), and 14/15 participants in the control group (no treatment) completed the study (> 5% lost to follow-up, with differences between groups). Reasons for discontinuations seemed to be not related to the treatment allocation |
| Selective reporting (reporting bias) | High risk | Protocol was published. Fatigue was reported in accordance with a pre-specified analysis plan, using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. However, objective and subjective outcomes were assessed. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and authors had no conflicts of interest. The study seemed to be free from other source of bias |

**Picariello 2018**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 3 months<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Country: UK<br>• Setting: multicentre (two National Health Service sites in England)<br>• Inclusion criteria: > 18 years; confirmed ESKD diagnosis; experiencing clinical levels of fatigue defined as scoring > 18 on the CFQ, when using the continuous scoring; full verbal and written proficiency in English; receiving in-centre HD; length of time on dialysis > 90 days; willing and able to take part in the study and intervention. All participants reported fatigue at baseline<br>• Exclusion criteria: no informed consent or refused to be randomised; cognitive impairments, severe mental health disorder (e.g. psychosis and bipolar disorder); do not have full verbal and written proficiency in English; currently receiving psychotherapy; currently participating in any other intervention trial; failing on dialysis; approaching end of life (supportive care/palliative care pathway), have a fatigue (CFQ) score below the cut-off at the pre-randomisation assessment (spontaneous improvement after screening)<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (11/12); control group (7/12)<br>• Mean age ± SD (years): intervention group (59.8 ± 17.8); control group (53.0 ± 18.0)<br>• Sex (M/F): intervention group (8/4); control group (4/8)<br>• Dialysis type: HD<br>• Dialysis vintage (years): not reported<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• CBT for fatigue (BReF intervention), 4 to 6 weeks, depending on each participant's needs<br>Control group<br>• Waiting-list control<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available |

**Picariello 2018** *(Continued)*

- Renal fatigue
- Fatigue severity
  - CFQ: assessed at baseline and after 3 months
- Fatigue-related functional impairment
  - Work and Social Adjustment Scale: assessed at baseline and after 3 months
- Sleep quality
  - PSQI: assessed at baseline and after 3 months
- Depression
  - Patient Health Questionnaire-9: assessed at baseline and after 3 months
- Anxiety
  - Generalised Anxiety Disorder-7: assessed at baseline and after 3 months
- Changes in fatigue perceptions
  - Brief Illness Perception Questionnaire: assessed at baseline and after 3 months
- Cognitive and behavioural responses to fatigue
  - Cognitive and Behavioural Responses to Symptoms Questionnaire: assessed at baseline and after 3 months
- Sleep hygiene behaviours
  - Sleep Hygiene Index: assessed at baseline and after 3 months
- Physical activity
  - International Physical Activity Questionnaire–short form: assessed at baseline and after 3 months

| | |
|---|---|
| Notes | Additional information<br>• Funding: PhD project funded by a Biomedical Research Studentship to Miss Federica Picariello from the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: ISRCTN91238019<br>• A priori published protocol was published<br>• Authors contacted and they reported no death |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomisation was stratified by centre and randomly varying block sizes were used to maintain balance of numbers in each arm across the period of recruitment while maintaining allocation concealment. King's College London's Independent Randomisation Service was used. Because the randomisation sequence was automated in real time, the allocation sequence was concealed from researchers." |
| Allocation concealment (selection bias) | Low risk | Quote: "Randomisation was stratified by centre and randomly varying block sizes were used to maintain balance of numbers in each arm across the period of recruitment while maintaining allocation concealment. King's College London's Independent Randomisation Service was used. Because the randomisation sequence was automated in real time, the allocation sequence was concealed from researchers." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "The nature of the trial meant participants were unblinded to their allocations." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "Follow-up measures were completed independently by participants via post. An independent researcher, who was not involved in the intervention development or delivery, assisted seven participants with the completion of |

**Picariello 2018** *(Continued)*

| | | |
|---|---|---|
| | | the follow-up measures. The statistician (SN) remained blind to treatment allocation until after the analyses were conducted."<br><br>Comment: Fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed. It was not stated if the interviewer was blinded to the treatment allocation |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "Eighteen participants completed the follow-up measures at T1."<br><br>Comment: 11/12 participants in the intervention group and 7/12 participants in the control group completed the study (> 5% lost to follow-up, with differences between groups). Reasons for discontinuations were not reported |
| Selective reporting (reporting bias) | High risk | Information about the protocol were reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of intervention was reported in a format that was not extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | Quote: "The authors alone are responsible for the content and writing of the article."<br><br>Comment: There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and reporting and authors had no conflicts of interest |

**Raimann 2010**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br>• Cross-over RCT<br>Study dates<br>• Duration of follow-up: 3 weeks<br>• Time frame: April to June 2008 |
| Participants | Study characteristics<br>• Setting: multicentre (2 dialysis centres of the Renal Research Institute in New York City)<br>• Country: USA<br>• Inclusion criteria: diabetic and nondiabetic patients in HD; ≥ 18 years; HD vintage > 30 days<br>• Exclusion criteria: receiving HD other than 3 times/week; history of infection, antibiotic treatment or hospitalisation during the preceding month<br>Baseline characteristics<br>• Number (analysed/randomised): overall (29/29) |

**Raimann 2010** *(Continued)*

- Mean age ± SD (years): overall (54 ± 13)
- Sex (M/F): overall (15/14)
- Dialysis type: HD
- Mean dialysis vintage ± SD (years): overall (5 ± 4)
- Comorbidities
  - CVD: not reported
  - Diabetes: intervention group 1 (6/8); intervention group 2 (8/21)
  - Hypertension: not reported
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group 1<br>• Dialysate glucose: 100 mg/dL<br>Intervention group 2<br>• Dialysate glucose: 200 mg/dL<br>Co-interventions<br>• No food was provided during the study treatments, and subjects were asked to refrain from eating |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Laboratory results (potassium, phosphorous, glucose, insulin, HCT): measured at 0, 30, 60, 120, 180, 240 min<br>• Adverse events (including hypoglycaemia, cardiac arrhythmias): assessed at the end of treatment<br>• BP (especially SBP)<br>  ○ OIscillometric method: measured at 0, 30, 60, 120, 180, 240 min<br>  ○ ECG: assessed at each treatment<br>  ○ Holter: assessed at each treatment<br>• Interdialytic weight gain<br>• Fatigue<br>  ○ FSS (Appendix 3): after 3 weeks<br>  ■ Motivation<br>  ■ Exercise<br>  ■ Physical functioning<br>  ■ Duties and responsibilities<br>  ■ Social life<br>  ■ Subjective perception of fatigue |
| Notes | Additional information<br>• Funding: none<br>• Conflicts of interest/disclosures: J.A.D.-B. is an employee of Fresenius Medical Care North America, P.K. and N.W.L. own stocks of Fresenius Medical Care (the author reported no conflicts of interest)<br>• Trial registration identification number: NCT00618033<br>• A priori published protocol: approved by the Institutional Review Board of Beth Israel Medical Center, New York City, NY |
| ***Risk of bias*** | |

**Raimann 2010** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "Chronic haemodialysis patients participated in this randomised, single masked, controlled crossover trial. [...] Throughout the entire study, patients were masked to dialysate glucose levels"<br><br>Comment: A single-blind study is considered as high risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All participants completed the study. No patients were loss to follow-up |
| Selective reporting (reporting bias) | High risk | The study protocol was approved by the Institutional Review Board of Beth Israel Medical Center. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was not reported in a format that was extractable for meta-analysis (cross-over study: data related to the first period were not reported). All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | No data were available to assess the possible imbalance between groups. There was no funding and the authors did not have conflicts of interest |

**Reilly-Spong 2015**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 6 months (but after kidney transplantation (2, 6 and 12 months) will be analysed for efficacy, as reported in Reilly-Spong 2015)<br>• Time frame: January 2010 to March 2012. Follow-up for post-transplant outcomes ended June 2014 |
| Participants | Study characteristics<br>• Setting: multicentre (university transplant centre and dialysis clinics)<br>• Country: USA |

**Reilly-Spong 2015** *(Continued)*

- Inclusion criteria: adults with progressive kidney disease eligible for kidney or kidney-pancreas transplant; ≥ 18 years; able to read and write in English; interested in attending the workshops; able to use a telephone for teleconferences
- Exclusion criteria: prior transplant; prior MBSR or regular meditation practice; serious mental health concerns (suicidally, psychotic disorder, or substance abuse identified on screening by a psychologist); hospitalised or medically unstable (e.g. recent stroke); kidney transplant scheduled within the next 3 months

Baseline characteristics

- Number (analysed/randomised): intervention group (15/18); control group (14/19)
  - HD: intervention group (not reported/11); control group (not reported/13)
  - PD: intervention group (not reported/4); control group (not reported/1)
- Mean age ± SD (years): not reported for patients with GFR < 15 mL/min/1.73 $m^2$
- Sex (M/F): not reported for patients with GFR < 15 mL/min/1.73 $m^2$
- Dialysis vintage (years) (mean ± SD): not reported
- Comorbidities
  - CVD: not reported for patients with GFR < 15 mL/min/1.73 $m^2$
  - Diabetes: not reported for patients with GFR < 15 mL/min/1.73 $m^2$
  - Hypertension: not reported for patients with GFR < 15 mL/min/1.73 $m^2$
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Telephone-adapted MBSR: an 8-week program of meditation and yoga<br>Control group<br>• Telephone-based support group: psychosocial interventions<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Anxiety<br>  ○ STAI (Appendix 3): assessed at baseline, 2 and 6 months<br>• Depression<br>  ○ CES-D (Appendix 3): assessed at baseline, 2 and 6 months<br>• Sleep<br>  ○ PSQI (Appendix 3): assessed at baseline, 2 and 6 months<br>  ■ Sleep quality<br>  ■ Sleep medications<br>  ■ Daytime dysfunction<br>• Pain<br>  ○ SF-12v2 (Appendix 3): assessed at baseline, 2 and 6 months<br>  ■ Physical Component Score<br>  ■ Mental Component Score<br>• Fatigue<br>  ○ PROMIS-Fatigue Short Form v1.0 (Appendix 3): assessed at baseline, 2 and 6 months<br>• HRQoL<br>  ○ SF-12v2 (Appendix 3): assessed at baseline, 2 and 6 months |

**Reilly-Spong 2015** *(Continued)*

- Physical Component Score
- Mental Component Score

- Helpfulness of mindfulness practice to cope with stress: assessed at baseline, 2 and 6 months
- VAS
- Mindful state
  - MAAS (15 items): assessed at baseline, 2 and 6 months
- Worry measured
  - Penn State Worry Questionnaire (16 items): assessed at baseline, 2 and 6 months
- Stress
- Perceived Stress Scale (14 items): assessed at baseline, 2 and 6 months
- Kidney disease in daily life and the burden of kidney disease
  - KDQOL-SF: assessed at baseline, 2 and 6 months
  - Impact Subscale (4 items): assessed at baseline, 2 and 6 months
  - Burden Subscale (8 items): assessed at baseline, 2 and 6 months
- Salivary cortisol measurements
  - Actigraphy: assessed at baseline, 2 and 6 months

| Notes | Additional information |
|---|---|

- Funding: National Institutes of Health (grant DK013083), National Institute of Diabetes and Digestive and Kidney Diseases Award P01 DK013083 and National Center for Advancing Translational Sciences of the National Institutes of Health Award Number UL1TR000114
- Conflicts of interest/disclosures: none
- Trial registration identification number: NCT01254214
- A priori published protocol was reported. The Journeys trial was approved by the University of Minnesota Institutional Review Board (IRB 0907S70361)

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote from Reilly-Sponge 2015: "Randomisation schedules were computer-generated using SAS, and designed using small randomly permuted blocks to promote balance within strata across treatment arms."<br><br>Comment: Computer-generated is considered as low risk of bias |
| Allocation concealment (selection bias) | Low risk | Quote from Reilly-Sponge 2015: "The randomisation schedule was generated by the study statistician who was masked with respect to variables other than stratification variables."<br><br>Comment: The statistician should ensure concealment and it was assessed as low risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote from Gross 2017: "We conducted a randomised, active-controlled, open-label trial to test whether a Mindfulness-based Stress Reduction (MBSR) program delivered in a novel workshop-teleconference format would reduce symptoms and improve health-related quality of life in patients awaiting kidney transplantation."<br><br>Comment: An open-label study is considered as high risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote from Gross 2017: "Participants completed self-report questionnaires at baseline, post-intervention, and after 6-months."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment |

**Reilly-Spong 2015** *(Continued)*

| | | |
|---|---|---|
| | | allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | The number of patients who completed the study with GFR < 15 mL/min/1.73 $m^2$ was not clearly stated. It was unclear if there was evidence that the results were not biased by missing outcome data |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was reported in a format that was not extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and reporting and authors had no conflicts of interest |

**Roshanravan 2016**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 4 weeks<br>• Time frame: 2013 (months were not reported) |
| Participants | Study characteristics<br>• Setting: multicentre (Imam-Ali and Mehreiran clinic in Bojnurd)<br>• Country: Iran<br>• Inclusion criteria: ≥ 18 years; dialysis for at least 3 months; HD 3 times/week and 4 hours each time; no history of limb amputation or wounds in massage zone; no history of chronic or disabling disease (cancers, COPD, heart failure, rheumatoid arthritis and SLE); no physically handicapped and psychotic disorders that makes patients unable to cure themselves individually<br>• Exclusion criteria: kidney transplantation or PD; haemodynamic complication in most dialysis sessions; death or refusal to be in the study<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (26/27); control group 1 (25/27); control group 2 (27/27)<br>• Mean age ± SD (years): overall (48.91 ± 15.46)<br>• Sex (M/F): intervention group (14/12); control group 1 (13/12); control group 2 (14/13)<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported |

**Roshanravan 2016** *(Continued)*

- Hypertension: not reported
- Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Foot reflexology<br>Control group 1<br>• Sham foot reflexology without pressing certain parts of the foot<br>Control group 2<br>• Routine care (no intervention)<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ◦ PFS (Appendix 3): assessed before and after the treatment<br>  ▪ Behavioural/intensity<br>  ▪ Emotional<br>  ▪ Sensory<br>  ▪ Cognitive/mood<br>• Death: assessed until the end of treatment<br>• Hospitalisation: assessed until the end of treatment |
| Notes | Additional information<br>• Funding: this article is the result of a master's degree in intensive care thesis and a proposal approved by the Nursing Research Center. Thereby we thank Deputy of Research and technology of Golestan University of medical sciences for their financial support<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: IRCT201307077821N5<br>• A priori published protocol were reported. The study was approved by the Golestan medical university Ethics Committee (no clearly stated if this information was related to the protocol)<br>• Not English |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias) | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |

**Roshanravan 2016** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | |
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Quote: "Patients filled the questionnaire when their dialysis has been completed and have been disconnected from the dialysis machine."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias) All outcomes | High risk | 26/27 participants in the intervention group (foot reflexology), 25/27 participants in the control group 1 (sham) and 27/27 participants in the control group 2 (no treatment) completed the study (> 5% lost to follow-up, with differences between groups). Reasons for discontinuations were not reported |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and conflicts of interest were not reported |

**Sabouhi 2013**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br><br>• Parallel RCT<br><br>Study dates<br><br>• Duration of follow-up: 4 weeks<br>• Time frame: not reported |
| Participants | Study characteristics<br><br>• Setting: multicentre (3 HD centres of Nour, Alzahra, and Shariati, hospitals)<br>• Country: Iran<br>• Inclusion criteria: ≥ 18 years; diagnosis of EKSD; undergoing HD at least for 3 months; chief complaint of fatigue and having fatigue score ≥ 5 based on fatigue severity VAS; lack of any wound or fracture; being in complete psychological and mental health to attend the study and fill the questionnaire; and not having undergone complementary medicine treatment in the past 3 months of the study<br>• Exclusion criteria: absence for 2 sessions of acupressure intervention; lack of interest in continuing the study<br><br>Baseline characteristics<br><br>• Number (analysed/randomised): intervention group (not reported/32); control group 1 (not reported/32); control group 2 (not reported/32) |

**Sabouhi 2013** *(Continued)*

- Mean age ± SD (years): intervention group (53.4 ± 13.9); control group 1 (55.4 ± 11.5); control group 2 (54.3 ± 13.4)
- Sex (M/F): intervention group (18/14); control group 1 (18/14); control group 2 (18/14)
- Dialysis type: HD
- Dialysis vintage (years) (mean ± SD): not reported
- Comorbidities
  - CVD: not reported
  - Diabetes: not reported
  - Hypertension: not reported
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Acupressure for 4 weeks<br>Control group 1<br>• Sham: acupressure was performed as mentioned above with a distance of 1 cm away from the actual intervention site for 4 weeks<br>Control group 2<br>• Routine unit care (no intervention)<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue and its change<br>  ○ PFS (Appendix 3): assessed at weeks 0 and 4<br>  ■ Behavioural<br>  ■ Emotional<br>  ■ Sensory<br>  ■ Cognitive<br>  ○ FSS with a 10-point VAS (Appendix 3): assessed at weeks 0 and 4 |
| Notes | Additional information<br>• Funding: Research Deputy of School of Nursing and Midwifery, Isfahan University of Medical Sciences (thesis approved by Isfahan University of Medical Sciences, project number 390303)<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "After random subjects' allocation through minimization method, 32 subjects were assigned to each group of the study, placebo and control." |

**Sabouhi 2013** *(Continued)*

| | | |
|---|---|---|
| | | Comment: Minimization method is considered as low risk of bias. No imbalance between intervention groups was apparent |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported in sufficient detail to permit judgment. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | The number of patients who completed the study was not clearly stated. It was unclear if there was evidence that the results were not biased by missing outcome data |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and reporting and authors had no conflicts of interest. The study seemed to be free from other sources of bias |

**Sajadi 2016**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br>• Cross-over RCT<br>Study dates<br>• Duration of follow-up: 1 week<br>• Time frame: August to October 2014 |
| Participants | Study characteristics<br>• Setting: single centre (HD unit of Vlieasr Hospital in Arak)<br>• Country: Iran<br>• Inclusion criteria: ≥ 18 years; afflicted to some degrees of fatigue (mild, moderate, and severe); referring consistently and regularly 3 times/week for receiving HD; receiving HD for at least 6 months; having haemodynamic stability; being able to listen and speak; having an acceptable level of alertness for responding to questions<br>• Exclusion criteria: dependence on narcotics; chronic anaemia (Hb < 8 g/dL) |

**Sajadi 2016** *(Continued)*

| | |
|---|---|
| | Baseline characteristics<br>• Number (analysed/randomised): intervention group 1 (not reported/23); intervention group 2 (not reported/23)<br>• Mean age ± SD (years): overall (58.46 ± 13.46)<br>• Sex (M/F): intervention group 1 (9/14); intervention group 2 (16/7)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): overall (3.55 ± 3.90)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group 1<br>• Cold dialysis solution temperature of 35.5°C<br>Intervention group 2<br>• Dialysis solution temperature of 37°C (conventional temperature solution)<br>Co-interventions<br>• Each group received 3 sessions of HD, each time for 4 hours |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ◦ PFS (Appendix 3): assessed at weeks 0 and 1<br>  ▪ Behavioural<br>  ▪ Emotional<br>  ▪ Sensory<br>  ▪ Temperamental/cognitive<br>• Vital signs (BP, heartbeat)<br>  ◦ Digital arm-fit stethoscope: assessed before, during, and after dialysis<br>• Armpit temperature<br>  ◦ Mercury-filled thermometer: assessed before and after dialysis |
| Notes | Additional information<br>• Funding: This article is part of a Master's of Science thesis approved by Arak University of Medical Sciences (project number, 2019); Arak University of Medical Sciences supporting the study by a research grant<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: IRCT2014082518928N1<br>• A priori published protocol was reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

**Sajadi 2016** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "The participants were allocated into 2 groups through simple random sampling method."<br><br>Comment: Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "In a double-blinded cross-over clinical trial, 46 participants were recruited from a haemodialysis unit in Iran."<br><br>Comment: Although author reported that the study used a double-blind design, information about blinding of participants and investigators were not clearly stated |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "A self-reported questionnaire was used to collect data. [...] The researcher read and completed it for illiterate patients."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. Other objective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | The number of patients who completed the study was not clearly stated for the first period. It was unclear if there was evidence that the results were not biased by missing outcome data |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was not reported in a format that was extractable for meta-analysis (cross-over study: data related to the first period were not clearly reported). All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | Baseline characteristics between groups were not reported in sufficient detail. Funding was unlikely to influence the data analysis and reporting and authors had no conflicts of interest |

**Salehi 2020**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br><br>• Parallel RCT<br><br>Study dates<br><br>• Duration of follow-up: 4 months<br>• Time frame: not reported |
| Participants | Study characteristics |

**Salehi 2020** *(Continued)*

- Setting: single centre (HD units of Shafa Hospital and Jawad Al Aemeh Center, affiliated with Kerman University of Medical Sciences)
- Country: Iran
- Inclusion criteria: ≥ 18 years; receiving HD for at least 3 months; without problems in their legs
- Exclusion criteria: contraindication of exercise according to doctors' perspective; diabetic foot; PTH > 1000 ng/L; not exercising for more than 3 sessions

Baseline characteristics

- Number (analysed/randomised): intervention group (20/27); control group (17/27)
- Mean age ± SD (years): intervention group (57.8 ± 9.17); control group (54.65 ± 10.02)
- Sex (M/F): intervention group (13/7); control group (13/4)
- Dialysis type: HD
- Mean dialysis vintage ± SD (years): intervention group (3.6 ± 3.2); control group (3.1 ± 1.7)
- Comorbidities
  - CVD: not reported
  - Diabetes: not reported
  - Hypertension: not reported
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Mini-bikes for 20 min twice/week for 3 months<br>Control group<br>• No intervention for 3 months<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Death<br>• Fatigue<br>  ◦ MFI-20 (Appendix 3)<br>  ▪ Fatigue<br>  ▪ Physical fatigue<br>  ▪ Decline in activity<br>  ▪ Decline in motivation<br>  ▪ Mental fatigue |
| Notes | Additional information<br>• Funding: none<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: IRCT20180314039100N1<br>• A priori published protocol was reported |
| ***Risk of bias*** | |

**Salehi 2020** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, subjective and objective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 20/27 participants in the intervention group and 17/27 participants in the control group completed the study (> 5% lost to follow-up). There were differences between groups. Reasons for discontinuation were reported |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were reported. Fatigue was assessed using multiple eligible outcome measurements (scales and time points). Fatigue at the end of treatment was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. There was no source of funding or conflict of interests. No other source of bias were apparent |

**Sang 1997**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 6 weeks<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Setting: single centre (dialysis unit of University Hospital of Alberta, Edmonton)<br>• Country: Canada<br>• Inclusion criteria: adult patients undergoing HD<br>• Exclusion criteria: not reported<br>Baseline characteristics |

**Sang 1997** *(Continued)*

- Number (analysed/randomised): overall (23/29)
- Mean age ± SD (years): overall (59 ± 14)
- Sex (M/F): overall (18/5)
- Dialysis type: HD
- Mean dialysis vintage ± SD (years): overall (4 ± 5)
- Co-morbidities
  - CVD: not reported
  - Diabetes: not reported
  - Hypertension: not reported
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br><br>• Pharmacological intervention<br>• Indication: study targeting fatigue<br><br>Intervention group 1<br><br>• Protocol A: standard dialysis (steady dialysate sodium of 140 mEq/L)<br><br>Intervention group 2<br><br>• Protocol B: linear sodium ramping during dialysis (initial dialysate sodium of 155 mEq/L, continuous decline to 140 mEq/L by the end of the dialysis)<br><br>Intervention group 3<br><br>• Protocol C: stepwise ramping sodium (dialysate sodium of 155 mEq/L for the first 3 hours and 140 mEq/L for the last hour of dialysis)<br><br>Cointerventions<br><br>• All patients underwent 4-hour HD with the blood flow set to achieve an approximate Kt/V of 1.4<br>• All dialyses were performed with hollow-fibre cellulose membrane filters, bicarbonate dialysate, and systemic heparin |
| Outcomes | Outcomes reported<br><br>• Fatigue outcome measures used: validation data available<br>• Adverse events (including hypertension and fatigue)<br>  ◦ Questionnaire: patients rated thirst, cramps, and headaches from a scale of 1 = absent to 5 = severe. Each symptom could thus score between 0 and 30 for a 2-week period. Fatigue was scored as present or absent. The sum of each side effect was calculated and compared for each 2-week period and separately for the 12 hours immediately following the dialysis session as well as the next day<br>• Vital signs (SBP, DBP, pulse rate): assessed every hour<br>• Interrdialitic weight gain: assessed during each treatment<br>• Laboratory results: sodium, urea, creatinine, and HCT levels were monitored weekly, both before and after the dialysis, and albumin, calcium, potassium, and phosphate levels were examined before dialysis each week<br>• Total ultrafiltration: the timeframe of this outcome was not clearly reported, it was probably assessed during each treatment<br>• Assessment of dialysis<br>  ◦ Analogue scale questionnaire (1 = the worst, intolerable dialysis and 5 = excellent dialysis, with 3 being a normal dialysis session): immediately after the dialysis session, the mean score for each 2-week period was calculated |
| Notes | Additional information<br><br>• Funding: not reported<br>• Conflicts of interest/disclosures: not reported |

**Sang 1997** *(Continued)*

- Trial registration identification number: not applicable
- A priori published protocol: not reported

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "The patients were blinded as to what sodium concentration was used in the dialysate. [...] There were eight protocol violations; two occurred during standard haemodialysis, one during linear ramping, and five during stepwise ramping. Data for the eight haemodialysis sessions were excluded in the analysis."<br><br>Comment: Authors reported that patients were blinded. However, interventions were different and investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "Six of the 29 patients did not complete the protocol and were not included in the analysis, apart from the reason for discontinuation. [...] Six patients stopped their treatments because of thirst. When they stopped, they were evenly distributed with two in each protocol."<br><br>Comment: Overall, 23/29 participants completed the study (> 5% lost to follow-up, difference between groups could not be assessed). Reasons for discontinuations seemed to be related to the treatment allocation |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was not reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | Baseline characteristics between groups were not reported. Funding and conflicts of interest were not reported |

**Schardong 2021**

***Study characteristics***

| | |
|---|---|
| Methods | Study design |

**Schardong 2021** *(Continued)*

- Parallel RCT

Study dates

- Duration of follow-up: 8 weeks
- Time frame: October 2017 to September 2018

| | |
|---|---|
| Participants | Study characteristics<br>• Setting: single centre (HD outpatient of Santa Clara hospital at ISCMPA)<br>• Country: Brazil<br>• Inclusion criteria: CKF on HD for ≥ 3 months, of both sexes; 18 and 80 years; URR ≥ 65% and weekly dialysis frequency of 3 times/week were included in the study<br>• Exclusion criteria: cognitive dysfunction that prevented performing the evaluations; inability to understand the informed consent form; epidermal lesions at the site of PBM application, patients with active carcinoma, stroke sequelae, recent acute MI (2 months); uncontrolled hypertension (SBP > 230 mm Hg and DBP > 120 mm Hg); IV grade heart failure according to the NYHA or decompensated; unstable angina; deep venous thrombosis in the lower limb; incapacitating osteoarticular or musculoskeletal disease, uncontrolled diabetes (glycaemia > 300 mg/dL), febrile state and/or infectious disease, and smokers<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (14/17); control group (14/16)<br>• Mean age ± SD (years): intervention group (53.0 ± 17); control group (58.1 ± 16.9)<br>• Sex (M/F): intervention group (9/5); control group (7/7)<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: intervention group (2/14); control group (4/14)<br>  ◦ Hypertension: intervention group (13/14); control group (13/14)<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Photobiomodulation therapy<br>Control group<br>• No intervention<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Vital signs<br>• Adverse events<br>• Muscle strength<br>• Muscle structure<br>• Functional capacity<br>  ◦ 6MWT |

**Schardong 2021** *(Continued)*

- Pain
  - 10-point VAS (Appendix 3)
- Fatigue
  - 10-point VAS (Appendix 3)
- HRQoL
  - EQ-5D (Appendix 3)
    - Mobility
    - Personal care
    - Habitual activities
    - Pain/discomfort
    - Anxiety/depression
  - KDQOL-SF (Appendix 3)

| | |
|---|---|
| Notes | Additional information<br>• Funding: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) – Financial code 001<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: NCT03250715<br>• A priori published protocol was reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomization occurred through the www.random.org website." |
| Allocation concealment (selection bias) | Low risk | Quote: "The sequence of numbers was generated by a researcher “blinded” to the study, and it was kept confidential until the beginning of the intervention to guarantee the concealment of the allocation." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "All analyses were conducted by a researcher blind to the study procedures (randomisation, evaluations, and intervention)."<br><br>Comment: Fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, subjective and objective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "Thirty-six patients with CKF on HD were evaluated for eligibility and possible admission into the study. Twenty-eight met the inclusion criteria and finalized the protocol."<br><br>Comment: 14/17 participants in the intervention group and 14/16 participants in the control group completed the study (> 5% lost to follow-up). There were differences between groups. Reasons for discontinuation were reported |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were reported. Fatigue was assessed using multiple eligible outcome measurements (scales |

**Schardong 2021** *(Continued)*

| | | |
|---|---|---|
| | | and time points). Fatigue at the end of treatment was reported in a format that was not extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence data analysis and interpretation. No other source of bias were apparent |

**Schmitz 2016**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br>• Cross-over RCT<br>Study dates<br>• Duration of follow-up: 4 weeks<br>• Time frame: November 2011 to February 2013 |
| Participants | Study characteristics<br>• Setting: multicentre (4 dialysis centres)<br>• Country: Germany<br>• Inclusion criteria: patients on stable dialysis and medication prescription<br>• Exclusion criteria: patients with a planned hospital stay and catheter as vascular access<br>Baseline characteristics<br>• Number (analysed/randomised): overall (92/95)<br>  ○ HDF post-dilution: overall (not reported/44)<br>  ○ HDF pre-dilution: overall (not reported/26)<br>  ○ haemodialysis: overall (not reported/25)<br>• Mean age ± SD (years): overall (67.3 ± 14.1)<br>  ○ HDF post-dilution: overall (not reported)<br>  ○ HDF pre-dilution: overall (not reported)<br>  ○ haemodialysis: overall (not reported)<br>• Sex (M/F): overall (54/38)<br>  ○ HDF post-dilution: overall (not reported)<br>  ○ HDF pre-dilution: overall (not reported)<br>  ○ haemodialysis: overall (not reported)<br>• Dialysis type: HDF post-dilution, HDF pre-dilution, HD<br>• Mean dialysis vintage ± SD (years): overall (4.51 ± 3.97)<br>  ○ HDF post-dilution: overall (not reported)<br>  ○ HDF pre-dilution: overall (not reported)<br>  ○ haemodialysis: overall (not reported)<br>• Comorbidities<br>  ○ CVD: not reported<br>  ○ Diabetes: not reported<br>  ○ Hypertension: not reported<br>  ○ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification |

**Schmitz 2016** *(Continued)*

- Pharmacological intervention
- Indication: study reporting fatigue

Intervention group 1

- Citrate dialysate

Intervention group 2

- Standard dialysate

Co-interventions

- Not reported

| | |
|---|---|
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available (fatigue was reported as an adverse event)<br>• Laboratory results (calcium, pH, acid-base status, including pre and post-treatment bicarbonate): assessed before and after each dialysis session<br>• Vital signs (BP, heart rate): assessed before and after each dialysis session<br>• Intra-dialytic events and Kt/V<br>  ○ Online Clearance Monitoring: recorded after each dialysis session<br>• Adverse events (including fatigue, clotting and vascular access problems): assessed until the end of treatment<br>• Dialysis efficacy (i.e. dose and removal ratios of urea, creatinine, phosphate and β-2-microglobulin): the timeframe of this outcome was not clearly reported<br>• Other laboratory results (PTH, alkaline phosphatase, electrolytes, calcium, magnesium, Hb, CRP, potassium): assessed during the first dialysis in the fourth week<br>• Death: assessed until the end of treatment |
| Notes | Additional information<br>• Funding: Fresenius Medical Care<br>• Conflicts of interest/disclosures: O.L. received travel grants for scientific congresses from Fresenius Medical Care. B.F. received reimbursement for the conduct of clinical studies from Baxter, Amgen, Medice and B. Braun. J.K.-J. is an employee of Fresenius Medical Care. Other authors declare no conflicts of interest<br>• Trial registration identification number: NCT01532297<br>• A priori published protocol were reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Each patient was treated for 4 weeks with standard dialysate (standard phase) and 4 weeks with citrate dialysate (citrate phase) in the sequence determined by the computer-generated randomisation scheme. A centralized fax randomisation in a 1:1 ratio with stratification for centre and dialysis modality was carried out."<br><br>Comment: A computer-generated randomisation scheme is considered as low risk of bias. No data were available to assess the possible imbalance between groups |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |

**Schmitz 2016** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used (fatigue was assessed as an adverse event), it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "Of the 95 patients enrolled (HDF post-dilution: 44, HDF pre-dilution: 26, HD: 25), 7 terminated the study prematurely for reasons not associated with the study protocol, e.g. kidney transplantation or death due to an exacerbation of concomitant diseases. Three of them were completely excluded from the analysis because they were withdrawn before the first study treatment, so the full analysis set (FAS) constituted of 92 patients."<br><br>Comment: Overall, 92/95 participants were reported in the analysis. However, Figure 1 showed that only 48/95 participants were assessed per protocol analysis. Tables 2, 3 and 5 reported data for 90 participants in the standard dialysate phase |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was not reported in a format that was extractable for meta-analysis (cross-over study: data related to the first period were not clearly reported). All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | High risk | Baseline characteristics between groups were not reported. Funding (pharmaceutical company) could influence the data analysis and some authors had conflicts of interest |

**Semeniuk 2000**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br>• Cross-over RCT<br>Study dates<br>• Duration of follow-up: 12 weeks (first period)<br>• Time frame: November 1997 to June 1998 |
| Participants | Study characteristics<br>• Setting: single-centre<br>• Country: Canada |

**Semeniuk 2000** *(Continued)*

- Inclusion criteria: ≥ 18 years undergoing HD; had been on dialysis for a minimum of 1 year, had at least 2 of the following symptoms: intradialytic hypotension, muscle cramping, lack of energy, muscle weakness or myopathy, cardiomyopathy, or lack of responsiveness to EPO
- Exclusion criteria: mentally incompetent to complete a QoL questionnaire

Baseline characteristics

- Number (analysed/randomised): overall (10/16)
- Mean age ± SD (years): overall (66.9 ± 15.9)
- Sex (M/F): overall (5/11)
- Dialysis type: HD
- Dialysis vintage (years) (mean ± SD): not reported
- Comorbidities
  - CVD: not reported
  - Diabetes: not reported
  - Hypertension: not reported
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• IV L-carnitine 20 mg/kg<br>Control group<br>• Placebo (normal saline)<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data not available<br>• Changes in health-related quality of life<br>  ○ KDQ (Appendix 3): baseline, 6 and 12 weeks<br>• Fatigue<br>  ○ KDQ (Appendix 3): baseline, 6 and 12 weeks<br>• Adverse events (including intradialytic hypertension and cramping)<br>• BP<br>• Death<br>• Nutritional intake: baseline, 6 and 12 weeks<br>• Adequacy of dialysis: baseline, 6 and 12 weeks<br>• Laboratory parameters: baseline, 6 and 12 weeks<br>  ○ Urea<br>  ○ Creatinine<br>  ○ Iron<br>  ○ Hb<br>  ○ Albumin |
| Notes | Additional information<br>• Funding: Sigma Tau<br>• Conflicts of interest/disclosures: not reported |

**Semeniuk 2000** *(Continued)*

- Trial registration identification number: not applicable
- A priori published protocol: not reported

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Patients were randomised using a table of random numbers." |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Quote: "Double-blind."<br><br>Comment: Although author reported that the study used a double-blind design, information about blinding of participants and investigators were not clearly stated |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Fatigue was assessed with an appropriate measure, without differences between groups. However, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Not reported in sufficient detail at the end of the first phase to perform adjudication |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. It was not reported if fatigue was assessed using multiple eligible outcome measurements (scales and time points) were pre-specified for the first period of the study. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was not reported in a format that was extractable for meta-analysis (cross-over study: data related to the first period were not clearly reported). All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | High risk | Baseline characteristics between groups were not reported. Funding (pharmaceutical company) could influence the data analysis and interpretation |

**Shahdadi 2016**

***Study characteristics***

| | |
|---|---|
| Methods | Study design<br><br>• Parallel RCT<br><br>Study dates<br><br>• Duration of follow-up: 3 weeks<br>• Time frame: 2015 (months were not reported) |

**Shahdadi 2016** *(Continued)*

| | |
|---|---|
| Participants | Study characteristics<br>• Setting: single centre (Imam Khomeini Hospital dialysis centre in the city of Zabolin)<br>• Country: Iran<br>• Inclusion criteria: ≥ 18 years; history of at least 6 months of dialysis; willingness to participate in research; being on the list of weekly dialysis and carrying out HD 3 times/week and 4 to 32 hours each time; no history of reflexology in the last 6 months; having full consciousness; listening and speaking acceptable ability to answer the questions; the lack of chronic pain and diabetes; having a degree of fatigue; a minimum score of fatigue between (10 to 39) based on questionnaires fatigue severity<br>• Exclusion criteria: death of the patient; mental and sensory disorders; perform a kidney transplant during the study; patient revised in collaboration with researchers during the study and not to be pleased to be working<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (26/26); control group (26/26)<br>• Mean age ± SD (years): intervention group (47.42 ± 12.51); control group (47.04 ± 10.57)<br>• Sex (M/F): intervention group (21/5); control group (15/11)<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ○ CVD: not reported<br>  ○ Diabetes: not reported<br>  ○ Hypertension: not reported<br>  ○ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Slow stroke back massage<br>Control group<br>• No treatment<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ○ FSS (Appendix 3): assessed at weeks 0 and 3 |
| Notes | Additional information<br>• Funding: not reported<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

**Shahdadi 2016** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "The subjects were randomly divided into two groups."<br><br>Comment: Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "The data collecting tool was included Individual demography and fatigue severity questionnaire."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | All participants completed the study. However, it was not stated if some patients discontinued |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding and conflicts of interest were not reported |

**Singer 2010**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br><br>• Parallel RCT<br><br>Study dates<br><br>• Duration of follow-up: 3 months<br>• Time frame: not reported |
| Participants | Study characteristics<br><br>• Setting: single centre (Canberra Hospital)<br>• Country: Australia |

**Singer 2010** *(Continued)*

- Inclusion criteria: subjects were either receiving 3 times/week maintenance HD therapy or receiving maintenance PD therapy (defined as having a PD catheter in situ that was being used or planned to be used within 2 months of enrolment)
- Exclusion criteria: unable to give informed consent; concurrently enrolled in another clinical intervention trial; < 18 years; who were clinically unstable; having a life expectancy < 3 months; using ascorbate supplements within previous 2 weeks; not willing to abstain from non-study ascorbate supplements for the duration of the study; who lacked fluency in English or who had previous diagnosis of primary hyperoxaluria

Baseline characteristics

- Number (analysed/randomised): intervention group (not reported/37); control group (not reported/38)
  - haemodialysis: intervention group (not reported/32); control group (not reported/33)
  - peritoneal dialysis: intervention group (not reported/5); control group (not reported/5)
- Mean age ± SD (years): not reported for dialysis participants
- Sex (M/F): not reported for dialysis participants
- Dialysis type: HD, PD
- Median dialysis vintage, IQR (years): intervention group (1, 0 to 3.25); control group (2, 0.14 to 3.7)
  - HD: not reported
  - PD: not reported
- Comorbidities
  - CVD: not reported
  - Diabetes: not reported
  - Hypertension: not reported
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Ascorbic acid (Vitamin C) 250 mg, 3 times/week<br>Control group<br>• Placebo (lactose), 3 times/week<br>Co-interventions<br>• All participants received conventional dialysis |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Effect of ascorbate supplementation<br>  ○ KDQOL-SF (Appendix 3): assessed at 3 months<br>  ■ Muscle soreness<br>  ■ Itchy skin<br>  ■ Dyspnoea<br>  ■ Fatigue<br>  ■ Symptom score<br>  ■ Cognitive score<br>• Bacteraemia: assessed until the end of treatment<br>• Residual kidney function (residual GFR in PD): assessed at 3 months<br>  ○ Renal Unit databases<br>  ■ eGFR |

**Singer 2010** *(Continued)*

- Ascorbate levels
  - High-performance liquid chromatography: assessed at 3 months
    - Plasma ascorbate
- Cardiovascular instability (a fall in BP during dialysis necessitating either a fluid bolus, slowing of ultrafiltration or Trendelenburg positioning): assessed at 3 months
- Pre-printed sheet placed in dialysis notes, with confirmation from the clinical record
- Adverse events
  - Open-ended question: assessed at 3 months
    - Nausea
    - Worsening of diarrhoea

| Notes | Additional information |
|---|---|

- Funding: the Canberra Hospital Private Practice Fund and the Canberra Hospital Renal Unit
- Conflicts of interest/disclosures: none
- Trial registration identification number: ACTRN12608000016336
- A priori published protocol was reported

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomisation was by computer-generated random number with subjects stratified according to diabetic status and by the need for maintenance dialysis treatment."<br><br>Comment: A computer-generated randomisation scheme is considered as low risk of bias |
| Allocation concealment (selection bias) | Low risk | Quote: "Study drugs were compounded and packaged by an external pharmacy."<br><br>Comment: External pharmacy performed the allocation concealment |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "The study design was a prospective, single-centre, double-blind, randomised, placebo-controlled trial. [...] Both the subjects and investigators were blinded as to allocation until after the final subject had completed the study, and all follow-up data had been collected."<br><br>Comment: A double-blind trial is considered as low risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote; "The Kidney Dialysis Quality of Life-Short Form (KDQOL-SF) symptom and cognitive sub scales were administered either face to face or by telephone by a single research assistant."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "Baseline ascorbate levels were not available in three subjects. This was due to mishandling of the samples in two subjects and one subject refusing venesection. A further one subject withdrew from the study after randomisation and collection of an ascorbate level, but before completing other baseline data. Data for all subjects were included until their exit from the study." |

**Singer 2010** *(Continued)*

| | | |
|---|---|---|
| | | Comment: As reported in Figure 1, 48/49 participants in the intervention group and 48/51 participants in the control group completed the follow-up period. 49/49 participants in the intervention group and 49/51 participants in the control group completed the analysis. However, data on participants undergoing dialysis were not reported in sufficient detail to permit judgment |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was not reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and authors did not have conflicts of interest |

**Singh 2003**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Cross-over RCT<br>Study dates<br>• Duration of follow-up: 3 weeks<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Setting: not reported<br>• Country: India<br>• Inclusion criteria: ESKD patients on maintenance HD > 1 month<br>• Exclusion criteria: pulmonary or cardiac disorders; acute or chronic infective disorders or patients on immunosuppressant drugs<br>Baseline characteristics<br>• Number (analysed/randomised): overall (not reported/24)<br>• Mean age ± SD (years): overall (41 ± 13)<br>• Sex (M/F): overall (18/2)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD(years): overall (0.3 ± 0.16)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study reporting fatigue |

**Singh 2003** *(Continued)*

| | |
|---|---|
| | Intervention group 1<br>• Cuprophan low flux dialyser membranes<br>Intervention group 2<br>• Polysulfone low flux dialyser membranes<br>Co-interventions<br>• Biweekly dialysis schedule of 4 hours sessions |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available (fatigue was reported as an adverse event)<br>• IL-1 beta<br>  ○ ELISA kits: assessed at 0, 15, 240 min<br>• TNFa<br>  ○ ELISA kits: assessed at 0, 15, 240 min<br>• Interdailysis symptoms: monitored in a total of 240 dialysis sessions<br>  ○ Nausea<br>  ○ Vomiting<br>  ○ Chest pain<br>  ○ Fever<br>  ○ Chills<br>  ○ Breathlessness<br>  ○ Cramps<br>  ○ Back pain<br>  ○ Itching<br>  ○ Restlessness<br>  ○ Fatigue<br>  ○ Hypotension |
| Notes | Additional information<br>• Funding: not reported<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not applicable<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and investigators/participants could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | For fatigue, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant be- |

**Singh 2003** *(Continued)*

| | | |
|---|---|---|
| | | liefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | The number of patients who completed the study was not clearly stated. It was unclear if there was evidence that the results were not biased by missing outcome data |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was not reported in a format that was extractable for meta-analysis (cross-over study: data related to the first period were not clearly reported). All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | Baseline characteristics between groups were not reported. Funding and conflicts of interest were not reported |

**Singh 2008a**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Cross-over RCT<br>Study dates<br>• Duration of follow-up: 7 days<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Setting: multicentre<br>• Country: USA<br>• Inclusion criteria: ≥ 18 years; informed consent; Hb between 9.0 g/dL and 12.5 g/dL (90 to 125 g/L); serum ferritin level of ≤ 600 ng/mL (µg/L); TSAT ≤ 50%; negative serum pregnancy test result or not of childbearing potential; patients undergoing dialysis for at least 90 days<br>• Exclusion criteria: history of parenteral or oral iron therapy within 7 days; blood transfusion within 2 weeks; major surgery within 30 days; active infection; history of malignancy; cause of anaemia other than iron deficiency; allergy to iron products or to 2 or more drugs; and those who were breast-feeding<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (not reported/145); control group (not reported/158)<br>  ○ HD: not reported<br>  ○ PD: not reported<br>• Mean age ± SD (years): not reported for dialysis participants<br>• Sex (M/F): not reported for dialysis participants<br>• Dialysis type: HD, PD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ○ CVD: not reported<br>  ○ Diabetes: not reported |

**Singh 2008a** *(Continued)*

- Hypertension: not reported
- Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study reporting fatigue<br>Intervention group<br>• Ferumoxytol (IV) 510 mg (17 mL)<br>Control group<br>• Sterile saline placebo (IV) 0.9% (17 mL)<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available (fatigue was reported as an adverse event)<br>• Averse events (including fatigue and infection)<br>  ○ Direct questioning of study patients: assessed at baseline and 7 days<br>• Serious adverse events: assessed at baseline and 7 days<br>  ○ Death<br>  ○ Life-threatening event<br>  ○ Hospitalisation<br>  ○ Persistent or significant disability<br>  ○ Congenital anomaly<br>• Changes from baseline in laboratory tests: assessed at baseline and 7 days<br>• Changes from baseline in vital signs: assessed at baseline and 7 days<br>  ○ BP |
| Notes | • Funding: National Institute of Health Grant T32-DK007527-23 and AMAG Pharmaceuticals Inc<br>• Conflicts of interest/disclosures: Drs Kausz and Brenner are employees of AMAG Pharmaceuticals, and Dr Singh is a member of the Clinical Studies Steering Committee of AMAG Pharmaceuticals Inc. Dr Singh receives research support from Amgen, Johnson and Johnson, AMAG, Roche, andWatson. He is on the speakers bureau for Johnson and Johnson and Watson. He has received consulting income from AMAG, Johnson and Johnson, and Amgen<br>• Trial registration identification number: NCT00255450<br>• A priori published protocol was reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Eligible patients were randomly assigned in a 1:1 ratio (simple block randomisation) to either ferumoxytol or placebo by using a telephone-based system (ClinPhone Interactive Voice Response System, East Windsor, NJ)."<br>Comment: The interactive voice systems could be considered as a computer |
| Allocation concealment (selection bias) | Low risk | Quote: "Eligible patients were randomly assigned in a 1:1 ratio (simple block randomisation) to either ferumoxytol or placebo by using a telephone-based system (ClinPhone Interactive Voice Response System, East Windsor, NJ)."<br>Comment: Interactive system voice is considering as low risk of bias |

**Singh 2008a** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "Patients, investigators, and study coordinators were blinded, with the exception of 1 individual at each site designated the Test Article Administrator, who administered study treatments."<br><br>Comment: A double-blind trial is considered as low risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "The blinded investigators and study coordinators, but not the Test Article Administrator, were involved in the assessment and attribution of adverse events. [...] All laboratory tests were performed at a central laboratory. [...] Relatedness of AEs to treatment was determined by the blinded site investigators. [...] Direct questioning of study patients regarding adverse events."<br><br>Comment: Blinded investigators and study coordinators were involved in the assessment and attribution of adverse events (including fatigue) |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | The number of patients who completed the study was not clearly stated. It was unclear if there was evidence that the results were not biased by missing outcome data |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was not reported in a format that was extractable for meta-analysis (cross-over study: data related to the first period were not clearly reported). All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | High risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Government funding was unlikely to influence the data analysis but the pharmaceutical company could influence the data analysis and authors had conflicts of interest |

**Sklar 1998**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br><br>• Cross-over RCT<br><br>Study dates<br><br>• Duration of follow-up: 1 week<br>• Time frame: not reported |
| Participants | Study characteristics<br><br>• Setting: multicentre (Department of Medicine, United Health Services Hospitals, Binghamton; State University of New York, Health Science Center at Syracuse, Syracuse, NY; and the Guthrie Research Institute, Sayre, PA)<br>• Country: USA<br>• Inclusion criteria: patients receiving maintenance HD treatments affected by post-dialysis fatigue<br>• Exclusion criteria: not reported<br><br>Baseline characteristics |

**Sklar 1998** *(Continued)*

- Number (analysed/randomised): intervention group 1 (8/not reported); intervention group 2 (8/not reported)
- Mean age ± SD (years): overall (61 ± 12)
- Sex (M/F): overall (9/7)
- Dialysis type: HD
- Dialysis vintage (years) (mean ± SD): not reported
- Comorbidities
  - CVD: not reported
  - Diabetes: not reported
  - Hypertension: not reported
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group 1<br>• Cuprophan low flux dialyser membranes<br>Intervention group 2<br>• Polymethylmethacrylate low-flux dialyser membranes<br>Co-interventions<br>• Each patient was dialysed 3 times/week on a Baxter SPS 550 machine |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• TNF alfa (pre and post-dialysis): assessed during the first and last dialysis treatments<br>• Change in the body weight (pre and post-dialysis): assessed during the first and last dialysis treatments<br>• SBP (pre and post-dialysis): assessed during the first and last dialysis treatments<br>• Change in osmolarity (pre and post-dialysis): assessed during the first and last dialysis treatments<br>• Fatigue score<br>  ◦ 6-hour logs of sleep (fatigue scores were calculated as the sum of the hours of sleep and the hours of fatigue experienced by patients for up to 6 hours after each dialysis treatment): assessed until the end of treatment<br>  ◦ Fatigue index questionnaire (each domain rated from 1 to 5): assessed during the first and last dialysis treatments<br>  ■ Intensity<br>  ■ Duration<br>  ■ Frequency |
| Notes | Additional information<br>• Funding: Donald Guthrie Foundation for Research and Education, Sayre, PA, and the Arthur T. Cantwell Foundation, Coudersport, PA<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not applicable<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

**Sklar 1998** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "Patients were blinded with respect to the type of membrane used during all dialysis treatments throughout the study."<br><br>Comment: Not reported if investigators were blind. However, interventions were different and investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "Levels of post dialysis fatigue were determined by analysis of 6-hour logs of sleep and perception of fatigue recorded by patients after each of these dialysis treatments. At the completion of the study, the patients submitted their log sheets to one of the investigators."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. Other objective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "Five patients were not included in the data analysis because they were individuals who destabilized medically (2) or submitted incomplete log sheets (3)."<br><br>Comment: Overall, 16/21 participants completed the study (> 5% lost to follow-up, difference between groups could not be assessed). Reasons for discontinuations seemed to be not related to the treatment allocation |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was not reported in a format that was extractable for meta-analysis (cross-over study: data related to the first period were not clearly reported). All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | Baseline characteristics between groups were not reported. Funding was unlikely to influence the data analysis and conflicts of interest were not reported |

**Sklar 1999**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br><br>• Cross-over RCT<br><br>Study dates<br><br>• Duration of follow-up: 2 cycles<br>• Time frame: February to June 1998 |

**Sklar 1999** *(Continued)*

| | |
|---|---|
| Participants | Study characteristic<br>• Setting: single centre (Wilson Memorial Regional Medical Center, Johnson City, NY, located in upstate NY)<br>• Country: USA<br>• Inclusion criteria: patients receiving maintenance HD treatments 3 times/week for at least 3 months affected by post-dialysis fatigue (fatigue index > 4)<br>• Exclusion criteria: medically unstable; mentally incompetent<br>Baseline characteristics<br>• Number (analysed/randomised): overall (12/17)<br>• Age (range) (years): overall (48 to 60)<br>• Sex (M/F): overall (9/3)<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group 1<br>• Hypernatric HD with 150 to 155 mEq/L sodium bath, two cycles<br>Intervention group 2<br>• Routine dialysis with 135 to 140 mEq/L sodium bath, two cycles<br>Intervention group 3<br>• Isolated ultrafiltration, two cycles<br>Intervention group 4<br>• Isolated diffusion, two cycles<br>Control group 1<br>• Sham procedures with isolated membrane, two cycles<br>Control group 2<br>• Sham procedures without recirculation exposure to a dialysis membrane, two cycles<br>Co-interventions<br>• Each patient was dialysed 3 times/week on a Baxter SPS 550 machine<br>• Each subject was dialysed with their usual membrane, either a low-flux polymethyl methacrylate or cuprophan membrane |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Change in serum electrolyte (potassium) and urea nitrogen level: assessed pre and post-dialysis |

**Sklar 1999** *(Continued)*

- Change in the body weight: assessed pre and post-dialysis
- SBP: assessed pre and post-dialysis
- Change in osmolarity: assessed pre and post-dialysis
- Death: assessed until the end of treatment
- Intradialytic symptoms
  - Questionnaire: assessed during each treatment
    - Headache
    - Cramps
    - Nausea
    - Dizziness
- Fatigue index questionnaire (Appendix 3): assessed at the beginning and the end of treatment
  - Intensity
  - Duration
  - Frequency

| Notes | Additional information |
|---|---|

- Funding: United Health Services Hospitals, Binghamton, NY
- Conflicts of interest/disclosures: not reported
- Trial registration identification number: not applicable
- A priori published protocol: not reported

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "The order of procedures was determined from a random numbers table."<br><br>Comment: Random numbers table is considered as low risk of bias |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "The order of procedures was determined from a random numbers table and performed in single-blinded fashion, with weight scales and dialysis machines hidden from the view of the patients."<br><br>Comment: A single-blind study is considered as high risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "Each patient recorded hourly fatigue scores during the entire study period on a fatigue intensity."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "Of the 17 patients entered onto the study, 5 patients dropped out early: 2 patients could not tolerate the dietary restrictions and 3 patients required surgical procedures, of which 1 patient died of complications. The remaining 12 patients were able to complete at least one of each type of treatment over the two cycles, with only 2 patients unable to undergo all procedures in the second cycle; 1 patient could not undergo the sham procedures because of |

**Sklar 1999** *(Continued)*

| | | |
|---|---|---|
| | | progressive intolerance to fluid restrictions and 1 patient developed exacerbation of chronic obstructive lung disease and could not tolerate isolated diffusion and recirculation."<br><br>Comment: Overall, 12/17 participants completed the study (> 5% lost to follow-up, difference between groups could not be assessed). Some reasons for discontinuations seemed to be related to the treatment allocation |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was not reported in a format that was extractable for meta-analysis (cross-over study: data related to the first period were not clearly reported). All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | Baseline characteristics between groups were not reported. Funding was unlikely to influence the data analysis and conflicts of interests were not reported |

**SOCIABLE 2017**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 8 months<br>• Time frame: not reported |
| Participants | • Setting: multicentre (2 centres in Baltimore)<br>• Country: USA<br>• Inclusion criteria: ≥ 60 years; English speaking; treated with in-centre HD for at least 6 months at a facility in Baltimore, MD; and with limitations in physical function (difficulty in at least 1 of the following: bathing, dressing, walking across a room, grooming [referring to things done personally to ensure a clean and neat appearance], getting on or off the toilet, and getting on or off the bed) and low SES (less than high school education, unemployment, and/or household income < $25,000/year)<br>• Exclusion criteria: inability to understand the informed consent process and give consent via signed written consent form<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (6/6); control group (3/6)<br>• Mean age ± SD (years): intervention group (69.5 ± 4.6); control group (68.6 ± 7.8)<br>• Sex (M/F): intervention group (4/2); control group (3/3)<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ○ CVD: not reported<br>  ○ Diabetes: not reported<br>  ○ Hypertension: not reported<br>  ○ Depression (clinician diagnosis): not reported |

**SOCIABLE 2017** *(Continued)*

| | |
|---|---|
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study reporting fatigue<br>Intervention group<br>• SOCIABLE (Seniors Optimizing Community Integration to Advance Better Living with ESRD) services<br>Control group<br>• Usual care (patients receive SOCIABLE 6 months after the trial)<br>Cointerventions<br>• Patients received a group of services called CAPABLE, which include home visits from a nurse and an occupational therapist, and a handyman for repairs if you need them and help with improving social support |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Disability<br>  ○ Disability score for ADLs (Appendix 3): baseline, 4 and 8 months<br>  ■ Bathing<br>  ■ Dressing<br>  ■ Walking<br>  ■ Grooming<br>  ■ How difficult each one is to do<br>  ○ Lawton Instrumental ADLs (Appendix 3)<br>  ■ Hopping<br>  ■ Light housekeeping<br>  ■ Managing finances<br>• Death<br>• Pain<br>• Depression<br>• Physical function (energy, walking)<br>• Tiredness<br>• Satisfaction<br>  ○ Social Support and Satisfaction score (baseline and at 5 months)<br>• Social network<br>  ○ Social Network score (baseline and at 5 months) |
| Notes | Additional information<br>• Funding: Johns Hopkins University<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: NCT03055273<br>• A priori published protocol was reported<br>• Abstract but some information was reported in clinicaltrials.gov<br>• Authors contacted: they said that the full information were reported in Crews DC, Delaney AM, Walker Taylor JL, Cudjoe TKM, Nkimbeng M, Roberts L, Savage J, Evelyn-Gustave A, Roth J, Han D, Boyér LL, Thorpe RJ Jr, Roth DL, Gitlin LN, Szanton SL. Pilot Intervention Addressing Social Support and Functioning of Low Socioeconomic Status Older Adults With ESRD: The Seniors Optimizing Community Integration to Advance Better Living with ESRD (SOCIABLE) Study. Kidney Med. 2019 Jan 24;1(1):13-20<br>• Fatigue was addressed by therapist: it was reported "Although there is currently no standardized outcome measure for fatigue in HD patients, approaches such as our study, which address both the person and their environment, might offer a means to meaningfully reduce symptoms. Energyconserva- |

**SOCIABLE 2017** *(Continued)*

tion techniques, such as those taught by our occupational therapist, might be particularly impact for HD patients."

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement. No imbalance between intervention groups was apparent |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement. No imbalance between intervention groups was apparent |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote from the study suggested by authors: "Single blind study".<br><br>Comment: A single blind is considered as high risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote from the study suggested by authors: "Our outcome assessor was masked to randomisation assignment."<br><br>Comment: Fatigue was not clearly reported, although the therapy helped people in addressing fatigue during their activities. However, subjective measures were used. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 9/12 participants completed the study (> 5% loss to follow-up). Reasons were not provided |
| Selective reporting (reporting bias) | High risk | Information about the protocol were reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was not reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding did not influence the data analysis and authors did not have conflicts of interest |

**Soliman 2015**

***Study characteristics***

| | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 8 weeks<br>• Time frame: June 2014 to November 2014 |
| Participants | Study characteristics |

**Soliman 2015** *(Continued)*

- Setting: single centre
- Country: Egypt
- Inclusion criteria: male and female; > 18 years; minimum HD vintage of 3 months, stable on HD; no recent hospitalisation; no acute or chronic medical conditions that would make exercise training potentially hazardous or primary outcomes impossible to assess; receiving HD 3 times/week, for 3 or 4 hours/session, having no problems in arteriovenous fistulas, adequate dialysis therapy (Kt/V > 1.2); high-flux dialysis membrane was in use only those patients who used bicarbonate solution were included; unintentional low dietary protein intake < 1 g/kg of ideal weight/day for at least 2 months, unintentional low dietary energy intake < 30 kcal/kg of ideal weight/day for at least 2 months
- Exclusion criteria: uncontrolled hypertension; congestive heart failure; arrhythmia requiring treatment; unstable angina; major valvular heart disease; MI, significant arteriosclerosis; risk of fracture; musculoskeletal disorders; change in the resting ECG; severe aortic stenosis; suspected or known dissecting aneurysm; myocarditis; participation in another trial; inadequate dialysis Kt/V < 1.2; Hb < 10 g/dL unstable on dialysis

Baseline characteristics

- Number (analysed/randomised): intervention group (18/23); control group (12/17)
- Age (years): not reported
- Sex (M/F): intervention group (8/10); control group (6/6)
- Dialysis type: HD
- Dialysis vintage (years) (mean ± SD): not reported
- Comorbidities
  - CVD: not reported
  - Diabetes: not reported
  - Hypertension: not reported
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Range of motion exercise<br>Control group<br>• No intervention<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ◦ IFS (Appendix 3): baseline, 1 and 2 months<br>• Serum electrolyte level, including phosphate and potassium, and calcium: baseline, 1 and 2 months<br>• Hb: baseline, 1 and 2 months<br>• BP: baseline, 1 and 2 months<br>• Other laboratory parameters (urea, creatinine): baseline, 1 and 2 months |
| Notes | Additional information<br>• Funding: not reported<br>• Conflicts of interest/disclosures: none |

**Soliman 2015** *(Continued)*

- Trial registration identification number: not reported
- A priori published protocol was not reported

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement. No imbalance between intervention groups was apparent |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement. No imbalance between intervention groups was apparent |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and investigators/participants could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Fatigue was assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "40 met the inclusion criteria and agreed to participate within the proposed study, 10 patients were excluded from the study due to death, transplantation or refusing to try to do exercise regularly due to fatigue. Of those, 30 patients completed the study, 18 in experimental group and twelve in control group."<br><br>Comment: 18/23 participants in the intervention group and 12/17 participants in the control group completed the study (> 5% lost to follow-up). There were differences between groups. Reasons for discontinuation were provided |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was not reported |

**Su 2009**

***Study characteristics***

| | |
|---|---|
| Methods | Study design<br><br>• Parallel RCT<br><br>Study dates<br><br>• Duration of follow-up: 12 weeks |

**Su 2009** *(Continued)*

- Time frame: December 2006 to February 2007

| | |
|---|---|
| Participants | Study characteristics<br>• Setting: single centre (Taiwan University Hospital)<br>• Country: Taiwan<br>• Inclusion criteria: 18 to 80 years; receiving 3, 3–5 hour HD sessions/week at the time of the study; received HD for at least 6 months<br>• Exclusion criteria: hospitalised for any other reasons beside HD treatment; pregnant; had pacemaker<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (31/34); control group (30/35)<br>• Mean age ± SD (years): intervention group (61.07 ± 13.87); control group (58.57 ± 12.61)<br>• Sex (M/F): intervention group (16/15); control group (17/13)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): intervention group (5.7 ± 6.1); control group (4.9 ± 5.1)<br>• Comorbidities<br>  ○ CVD: not reported<br>  ○ Diabetes: intervention group (13/31); control group (6/30)<br>  ○ Hypertension: not reported<br>  ○ Depression (clinician diagnosis): not reported |
| Interventions | Intervention clasification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Far infrared ray stimulation on acupoints<br>Control group<br>• Heat pad therapy<br>Co-interventions<br>• Dialysis session |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Heart rate variability analyser (assessed at 0, 4th, 8th, and 12th weeks)<br>  ○ Mean heart rate<br>  ○ Standard Deviation of Normal to Normal (SDNN) (> 30)<br>  ○ Root Mean Square of the Successive Differences (RMSSD) (> 20)<br>  ○ PSI (10 to 50, lower is better)<br>  ○ Frequency domain analysis<br>  ■ Total power<br>  ■ High frequency (0.15 to 0.40 Hz) (HF)<br>  ■ Low frequency (0.05 to 0.15 Hz) (LF)<br>  ■ Very low frequency (< 0.05Hz) (VLF)<br>  ■ LF/HF ratio (0.5 to 2.0)<br>  ■ ANS activity (enhancement is better)<br>  ■ ANS balance status (SNS: PNS = 3:2 or 2:3)<br>  ■ Fatigue index (LF, < 0.05 Hz)<br>  ■ Stress index (< 50) |

**Su 2009** *(Continued)*

- Stress resistance (enhancement is better)

- Changes in quality of life (assessed before and after treatment)
  - Taiwanese version of the WHOQOL-BREF: assessed at week 0 and week 12
    - Overall QoL
    - General health
    - Physical
    - Psychological
    - Environmental
    - HRQoL
    - Satisfaction
    - Social relations

| | |
|---|---|
| Notes | Additional information<br>• Funding: not reported<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "A randomised sample of 69 patients block in 4 was originally chosen."<br>Comment: Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and investigators/participants could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "During the study, 3 patients from the experimental group and 5 from the control group left for undisclosed reasons. Hence, the final count was 31 patients for Far infrared ray therapy and 30 patients for heat pad therapy."<br>Comment: 31/34 participants in the intervention group and 30/35 participants in the control group completed the study (> 5% lost to follow-up, with difference between group). Reasons for discontinuations were reported |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for |

**Su 2009** *(Continued)*

| | | |
|---|---|---|
| | | meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, death and vascular access) were not reported |
| Other bias | Unclear risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding and conflicts of interest were not reported |

**Suzuki 2018**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 8 weeks<br>• Time frame: October 2013 to September 2015 |
| Participants | Study characteristics<br>• Setting: single centre (Jikei University Katsushika Medical Center in Japan)<br>• Country: Japan<br>• Inclusion criteria: ≥ 20 years; dialysis duration for a minimum of 2 months with adequate dialysis delivery; stable medical condition<br>• Exclusion criteria: severe or symptomatic cardiovascular disease; orthopaedic complaints interfering with physical function test; severe dementia; implanted medical devices contraindicating MRI scans<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (13/15); control group (13/14)<br>• Mean age ± SD (years): intervention group (66.2 ± 12.8); control group (65.± 1 8.1)<br>• Sex (M/F): intervention group (14/1); control group (13/1)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): intervention group (2.3 ± 2.0); control group (2.5 ± 2.0)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: intervention group (7/13); control group (10/13)<br>  ◦ Hypertension: intervention group (11/13); control group (13/13)<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Electrical muscle stimulation<br>Control group<br>• No intervention<br>Co-interventions |

**Suzuki 2018** *(Continued)*

| | |
|---|---|
| | • Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Isometric knee extensor strength<br>• Physical function<br>  ○ Timed up-and-go test<br>• HRQoL<br>  ○ SF-8: assessed at baseline and end of treatment<br>• Laboratory parameters (albumin, Hb, lipids, IGF-1): assessed at baseline and end of treatment<br>• BP: assessed at baseline and end of treatment)<br>• Dry weight: assessed at baseline and end of treatment<br>• Adverse events |
| Notes | Additional information<br>• Funding: This study received no external funding<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: UMIN000012061<br>• A priori published protocol was reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "A total of 29 HD patients were eligible for inclusion in the study and were randomly assigned to either the EMS or the control (no training) group by simple random allocation (drawing lots)."<br><br>Comment: Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | Quote: "This was a prospective, open-label, randomised controlled trial."<br><br>Comment: An open-label study is considered as high risk of bias |
| Blinding of outcome assessment (detection bias) All outcomes | High risk | The outcomes (including vitality) were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias) All outcomes | High risk | Quote: "The EMS group included 14 men and 1 woman, while the control group included 13 men and 1 woman. Thirteen (86.7%) participants in the EMS group completed EMS training. The reasons for failure to complete training were hospitalisation before intervention (n51) and dropout due to discomfort of the wet electrode bands (n51). Likewise, 13 (92.9%) participants in the control group completed the protocol. One participant in the control group with- |

**Suzuki 2018** *(Continued)*

| | | |
|---|---|---|
| | | drew consent to join the study. The final analyses included 13 patients in each group."<br><br>Comment: 13/15 participants in the intervention group and 13/14 participants in the control group completed the study (> 5% lost to follow-up, with difference between group). Reasons for discontinuations were reported |
| Selective reporting (reporting bias) | High risk | Information about the protocol were reported. Vitality was reported using multiple eligible outcome measurements (scales, time points). Vitality was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and authors did not have conflicts of interest. No other source of bias were apparent |

**SWIFT 2020**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Study design<br>• Cluster RCT<br>Study dates<br>• Duration of follow-up: 12 months<br>• Time frame: April 2021 to September 2023 |
| Participants | Study characteristics<br>• Setting: multicentre (4 units)<br>• Country: Australia<br>• Inclusion criteria: HD; ≥ 18 years; willing and able to adhere to all trial requirements and able to provide informed consent<br>• Exclusion criteria: < 18 years; unable to provide informed consent<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (not reported/109); control group (not reported/117)<br>• Mean age ± SD (years): overall (62, SD not reported)<br>• Sex (M/F): not reported<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study reporting fatigue |

**SWIFT 2020** *(Continued)*

| | |
|---|---|
| | Intervention group<br>• Regular symptom monitoring with feedback to people receiving HD and their clinicians<br>Control group<br>• Usual care<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Symptoms severity<br>  ○ IPOS-Renal (Appendix 3): baseline, 3 months, 6 months, 9 months, 12 months. The IPOS-Renal is a 15-symptom checklist measures self-reported:<br>  ■ Pain<br>  ■ Shortness of breath<br>  ■ Weakness<br>  ■ Nausea<br>  ■ Vomiting<br>  ■ Poor appetite<br>  ■ Constipation<br>  ■ Sore mouth<br>  ■ Drowsiness<br>  ■ Poor mobility<br>  ■ Itching<br>  ■ Difficulty sleeping<br>  ■ Restless legs<br>  ■ Skin changes<br>  ■ Diarrhoea<br>• HRQoL<br>  ○ HRQoL and EQ-5D-5L questionnaire (intervention group): baseline, 6 months, 12 months<br>  ○ HRQoL alone (control group): baseline, 6 months, 12 months<br>• Death<br>• Healthcare utilisation<br>• Cost-effectiveness<br>• Withdrawal from dialysis: up to 12 months<br>• Fatigue<br>  ○ SONG-HD fatigue score: baseline, 6 months, 12 months<br>• HD duration, frequency and adequacy: up to 12 months<br>• Hospitalisations: up to 12 months |
| Notes | Additional information<br>• Funding: Australian NHMRC Project Grant #1159051; KHA Project Grant KHA2018-RM; NHMRC TRIP Fellowship#1150989 RM; BEAT-CKD NHMRC Program Grant #1159051, NHMRC Investigator Grant #1196033, Queensland AdvancingClinical Research Fellowship Grant<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: ACTRN12620001061921<br>• A priori published protocol was reported<br>• Abstract |
| ***Risk of bias*** | |

**SWIFT 2020** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "The randomisation takes place, on a state-by-state basis using the method of minimisation as they agree to participate. The randomisation was stratified based upon location (state), metropolitan or regional, private or public unit or prior or current use of the IPOS-Renal questionnaire for symptom monitoring within each centre and cluster size." |
| Allocation concealment (selection bias) | Low risk | Quote: "The trial statistician concealed until the site initiation visit. Access to the allocations is limited to the CI (RLM), the trial statistician (CB), the CTC trial operations coordinator (PW) and ANZDATA Registry Manager (Ms. Kylie Hurst) to minimise risk of inadvertently influencing sites or prematurely revealing allocation." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "Blinding to allocation is not possible within clusters due to the nature of the intervention; however, all staff compiling and analysing outcome data will be blinded to allocation."<br><br>Comment: Interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "Blinding to allocation is not possible within clusters due to the nature of the intervention; however, all staff compiling and analysing outcome data will be blinded to allocation."<br><br>Comment: Fatigue was assessed with an appropriate measure. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. Other subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Not reported in sufficient detail to perform adjudication |
| Selective reporting (reporting bias) | High risk | Information about the protocol were reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was reported in a format that was not extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | Quote: "The study sponsor and the study founders (Australian NHMRC, Kidney Health Australia), did not have any role or ultimate authority in study design; collection, management, analysis, interpretation of data, writing of the report, or the decision to submit the report for publication."<br><br>Comment: Baseline characteristics were not reported. Funding did not influence the data analysis and authors did not have conflicts of interest |

**Thomas 2017**

***Study characteristics***

**Thomas 2017** *(Continued)*

| | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 8 weeks<br>• Time frame: March to July 2016 |
| Participants | Study characteristics<br>• Setting: single centre (Jewish General Hospital HD unit, Montreal)<br>• Country: Canada<br>• Inclusion criteria: patients on HD who speak English or French and had depression and/or anxiety symptoms as indicated by scores of ≥ 6 on the PHQ-9 and/or GAD-7 scales<br>• Exclusion criteria: significant cognitive impairment (determined by an abnormal score on the Mini-Cog); current psychosis; or acute suicidal ideation with intent<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (17/21); control group (15/20)<br>• Mean age ± SD (years): intervention group (66 ± 13); control group (64 ± 14)<br>• Sex (M/F): intervention group (14/7); control group (13/7)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): intervention group (5 ± 7); control group (3 ± 3)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: intervention group (11/21); control group (15/20)<br>  ◦ Hypertension: intervention group (16/21); control group (16/20)<br>  ◦ Depression (clinician diagnosis): intervention group (21/21); control group (20/20) |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study reporting fatigue<br>Intervention group<br>• Mindfulness meditation<br>Control group<br>• Treatment-as-usual without intervention<br>Co-interventions<br>• Both control and intervention groups received Psychoeducational literature on anxiety and depression |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available (fatigue was reported as an adverse event)<br>• Proportion of participants screened as eligible who enrolled: assessed at 8 weeks<br>• Proportion of participants who completed the 8-week trial in the intervention arm (completed ≥ 13 sessions and stayed with the intervention until week 8): assessed at 8 weeks<br>• Patient's satisfaction of the intervention provided<br>  ◦ "How much they enjoyed" each mindfulness practice (scale of 1 to 10, estimated their frequency of independent meditative practice over the last week, and assess the improvement in "courage", "hope", "dignity", "self-confidence"): assessed at 8 weeks<br>  ◦ Adverse events: assessed at 8 weeks: (including fatigue post-dialysis) |

**Thomas 2017** *(Continued)*

- Intervention tolerability
  - 10-point Likert scale: assessed at 8 weeks
- Change in depression
  - PHQ-9 (Appendix 3): assessed during 8-week follow-up
- Change in anxiety
  - GAD-7 (Appendix 3): assessed during 8-week follow-up
  - Hospitalisation: assessed at 8 weeks

| Notes | Additional information |
|---|---|

- Funding: Hoffman-La Roche Ltd and Lundbeck Canada Inc. S.R. is supported by the Canadian Institute of Health Research Fellowship Award and Fonds de Recherche Santé Québec Chercheur- Boursier Clinicien Junior Investigator Award. This study was also supported by charitable donations to the Jewish General Hospital Division of Geriatric Psychiatry
- Conflicts of interest/disclosures: none
- Trial registration identification number: NCT02686333
- A priori published protocol was reported

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "The interventionists randomised the participant codes to the intervention group or the control group, using a simple 1:1 computer-generated sequence."<br><br>Comment: A computer-generated sequence is considered as low risk of bias. No imbalance between intervention groups was apparent |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and investigators/participants could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "Participants completed questionnaires with an independent assessor who then assigned each of them an anonymous code.The interventionists, who were not involved in the recruitment process and patient assessment, randomised the participant codes to the intervention group or the control group, using a simple 1:1 computer-generated sequence." [...] "This study was a randomised, controlled, assessor-blinded trial conducted in an urban haemodialysis unit. Both the assessor and the statistical associate were blinded to randomisation allocation."<br><br>Comment: Fatigue was assessed as an adverse event. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. Other subjective outcomes were assessed. Not sure if the outcome assessment was blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "Of missed sessions, 55% were due to logistic issues (switches in the location or time of assigned haemodialysis shifts) and 45% were due to refusals (most common reasons given were “too tired” or “too ill” on the given day). Five patients dropped out early in treatment (<2 sessions) for “feeling too medically ill” (n=1), “feeling already improved” (n=1), and “lack of interest” (n=3). One patient stopped after five sessions when they were transferred to home peritoneal dialysis therapy." |

**Thomas 2017** *(Continued)*

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|---|---|---|
| | | Comment: 17/21 participants in the intervention group and 15/20 participants in the control group participants completed the study (> 5% lost to follow-up, with difference between groups). Reasons for discontinuations seemed to be not related to the treatment allocation |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Fatigue at the end of treatment was not reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | High risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding (pharmaceutical company) could influence the data analysis and authors did not have conflicts of interest |

**Tsai 2016**

***Study characteristics***

| | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 4 weeks<br>• Time frame: March 2014 to January 2017 |
| Participants | Study characteristics<br>• Setting: single centre (units of the nephrology department affiliated with the Kaohsiung Chang Gung Memorial Hospital in Taiwan)<br>• Country: Taiwan<br>• Inclusion criteria: patients met the KDOQI guidelines for intradialytic hypotension; pre-HD SBP of 100 mm Hg and less or a decrease in SBP > 20 mm Hg, accompanied by at least one of the following: diaphoresis, nausea, vomiting, cramps, headache or dizziness; aged 20 to 75 years; were on maintenance HD for at least 3 months; had suffered intradialytic hypotension in at least 15% of their dialysis sessions during the past 2 months; were willing to sign the consent form were included<br>• Exclusion criteria: severe disorders of the heart, brain, liver, or haematopoietic system; active malignancy; mental disorders; pregnancy or lactation; or had experienced hypersensitivity skin reactions to herbal acupoint therapy<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (14/18); control group (13/14)<br>• Mean age ± SD (years): intervention group (62.29 ± 4.80); control group (59.46 ± 9.38)<br>• Sex (M/F): intervention group (6/8); control group (2/11)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): intervention group (15.00 ± 6.88); control group (10.31 ± 6.96,)<br>• Comorbidities<br>  ◦ CVD: intervention group (3/14); control group (2/13)<br>  ◦ Diabetes: intervention group (3/14); control group (4/13)<br>  ◦ Hypertension: not reported |

**Tsai 2016** *(Continued)*

- Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Herbal acupoint therapy<br>Control group<br>• Sham herbal acupoint treatment<br>Co-interventions<br>• The same dialyser was used for each patient during the entire study period |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Frequency of intradialytic hypotension: assessed at 0 and 4 weeks<br>• Episodes and number of nursing interventions: assessed at 0 and 4 weeks<br>• Pre, nadir and post-dialysis BP: assessed at 0 and 4 weeks<br>• Change in fatigue: assessed at the 0 and 4 weeks<br>  ○ 10-point VAS: scores of 1 to 3 represent mild levels, scores of 4 to 6 represent moderate levels, and scores of 7 to 10 represent severe levels<br>• Recovery time from fatigue after dialysis<br>  ○ Rated as within minutes (0), when arriving home (1), at bedtime (2), the next morning (3), and by next HD (4): assessed at 0 and 4 weeks<br>• Blood chemistry: assessed at the 0th and 4th week<br>  ○ Hb<br>  ○ White blood cell<br>  ○ BUN<br>  ○ Potassium<br>  ○ Calcium<br>  ○ Potassium<br>  ○ Albumin<br>  ○ HCT<br>• Treatment failure: assessed at the 0th and 4th week<br>• Dry weight: assessed at the 0th and 4th week<br>• Dialysis adequacy: assessed at the 0th and 4th week<br>• Ultrafiltration goal decrease: assessed at the 0th and 4th week<br>• Volume of study fluid used: assessed at the 0th and 4th week<br>• Early discontinuation of dialysis: assessed at the 0th and 4th week<br>• Adverse events: assessed at the 0th and 4th week<br>  ○ Case report form |
| Notes | Additional information<br>• Funding: Chang Gung Memorial Hospital with grant number CMRPG 8D0341 and CMU under the Aim for Top University Plan of the Taiwan Ministry of Education<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: NCT02210377<br>• A priori published protocol: research protocol was published and approved by the Institutional Review Board of Chang Gung Memorial Hospital (CGMH) (IRB no. 102-4749A3 and 104-3156C) |

**Tsai 2016** *(Continued)*

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote from Tsai 2016: "Participants were randomly and equally allocated to either the herbal acupoint therapy (HAT) or placebo group by computer-generated randomisation."<br><br>Quote from Tsai 2016 protocol: "Randomisation will be generated by a computerised random number function in Microsoft Excel, and the patients, programme assessors and statisticians will be unaware of the group to which they have been assigned. A block randomisation procedure (based on age, comorbidities such as cardiovascular disease and diabetes mellitus) will be employed to ensure that group allocation is equal and that the characteristics of the trial participants are similar."<br><br>Comment: A computer-generated sequence with random numbers is considered as low risk of bias. No imbalance between intervention groups was apparent |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote from Tsai 2016: "All patients, program assessors, outcome assessors, and statisticians were blind to the group allocations until the end of the clinical trial."<br><br>Comment: A double blind study is considered as low risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote from Tsai 2016: "Patient subjective assessments of the degree of fatigue and recovery time from fatigue after dialysis in both groups. [...] All patients, program assessors, outcome assessors, and statisticians were blind to the group allocations until the end of the clinical trial."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was stated that outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment that may have influenced reporting. However, objective and subjective outcomes were assessed. Overall the outcome assessment was blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote from Tsai 2016: "In all, 27 patients (84%) completed the entire study. [...] These patients were randomly divided into a group receiving HAT therapy (18 patients) and a group receiving sham-HAT therapy (14 patients), and 5 patients (15.6%) dropped out before week 2. The remainder of the patients provided complete data at follow-up."<br><br>Comment: As reported in Figure 1, 14/18 participants in the intervention group and 13/14 participants in the control group participants completed the study (> 5% lost to follow-up, with difference between groups). Reasons for discontinuations seemed to be not related to the treatment allocation (discontinuation for disease progression and withdrawal in the intervention group and withdrawal in the control group |
| Selective reporting (reporting bias) | High risk | Protocol was published and approved by the Institutional Review Board of Chang Gung Memorial Hospital. Fatigue was reported in accordance with a pre-specified analysis plan, using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |

**Tsai 2016** *(Continued)*

| | | |
|---|---|---|
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and authors did not have conflicts of interest. The study seemed to be free from other sources of bias |

**Tsay 2004a**

***Study characteristics***

| | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 4 weeks<br>• Time frame: over a 6-month period (year and months not reported) |
| Participants | Study characteristics<br>• Setting: multicentre (4 dialysis centres in major hospitals, Taiwan)<br>• Country: Taiwan<br>• Inclusion criteria: ≥ 18 years; diagnosed with ESKD; HD for at least 3 months; and complained of fatigue<br>• Exclusion criteria: patients with a lower extremity amputation; comorbid diagnoses of psychiatric disorders; congestive heart failure; chronic obstructive pulmonary disease; insulin-dependent diabetes; neuromuscular disease; systemic lupus erythematosus; rheumatoid arthritis; cancer; regular steroid therapy; or was using antihypertensive medications<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (35/35); control group 1 (35/35); control group 2 (36/36)<br>• Mean age ± SD (years): intervention group (57.23 ± 10.93); control group 1 (60.49 ± 12.21); control group 2 (56.81 ± 13.30)<br>• Sex (M/F): overall (36/70)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): intervention group (3.6 ± 3.2); control group 1 (5.0 ± 4.3); control group 2 (3.8 ± 3.4)<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): intervention group (35/35); control group 1 (35/35); control group 2 (36/36) |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Acupressure plus usual care, for 4 weeks<br>Control group 1<br>• Placebo, sham acupressure plus usual care, for 4 weeks |

**Tsay 2004a** *(Continued)*

| | |
|---|---|
| | Control group 2<br>• Usual care<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ○ PFS (Appendix 3): (assessed pre-treatment and a week following treatment<br>  ■ Behavioural/severity<br>  ■ Sensory<br>  ■ Cognitive/mood<br>  ■ Affective meaning<br>  ○ 10-point VAS for fatigue (Appendix 3): assessed pre-treatment and a week following treatment<br>• Sleep quality<br>• PSQI (Appendix 3): assessed post-test only<br>  ○ Sleep quality<br>  ○ Sleep latency<br>  ○ Sleep duration<br>  ○ Sleep efficiency<br>  ○ Sleep disturbances<br>  ○ Sleep sufficiency<br>  ○ Use of sleeping medications<br>• Depression<br>  ○ BDI (Appendix 3): assessed post-test only |
| Notes | Additional information<br>• Funding: National Science Counsel of Taiwan provided funding (NSC 90-2314-B-227-004)<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: no applicable<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "This prospective, randomised controlled trial with a pre-test, post-test design was carried out over a 6-month period."<br>Comment: Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allo- |

**Tsay 2004a** *(Continued)*

| | | |
|---|---|---|
| | | cation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. Other subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | All participants completed the study. However, it was not stated if some participants discontinued |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and conflicts of interest was not reported |

**Tsay 2004b**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 1 month<br>• Time frame: over a 4-month period (year and months not reported) |
| Participants | Study characteristics<br>• Setting: multicentre (4 dialysis centres in major hospitals in northern Taiwan)<br>• Country: Taiwan<br>• Inclusion criteria: ≥ 18 years; diagnosis with ESKD and treatment with HD for at least 3 months; complaints of fatigue symptoms; PSQI scores of at least 5 points; andBDI scores of 10 points or higher<br>• Exclusion criteria: lower-extremity amputations; co-morbid diagnoses of psychiatric disorders; congestive heart failure; COPD; insulin-dependent diabetes; neuromuscular disease; systemic lupus erythematosus; rheumatoid arthritis; cancer; regular steroid therapy; or use of anti-hypertension medications<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group 1 (35/36); intervention group 2 (36/36); control group (35/36)<br>• Mean age ± SD (years): overall (58.16 ± 12.1)<br>• Sex (M/F): overall (36/70)<br>• Dialysis type: HD<br>• Mean dialysis vintage ± SD (years): overall (4.2 ± 3.7)<br>• Comorbidities<br>  ○ CVD: not reported<br>  ○ Diabetes: not reported<br>  ○ Hypertension: not reported<br>  ○ Depression (clinician diagnosis): not reported |

**Tsay 2004b** *(Continued)*

| | |
|---|---|
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group 1<br>• Acupressure for 4 weeks<br>Intervention group 2<br>• TEAS for 4 weeks<br>Control group<br>• Routine unit care<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ○ PFS (Appendix 3): assessed baseline, during the intervention and post-intervention<br>  ■ Behavioural/severity<br>  ■ Sensory<br>  ■ Cognitive/mood<br>  ■ Affective meaning<br>• Sleep quality<br>  ○ PSQI (Appendix 3): assessed baseline, during the intervention and post-treatment<br>  ■ Sleep quality<br>  ■ Sleep latency<br>  ■ Sleep duration<br>  ■ Sleep efficiency<br>  ■ Sleep disturbances<br>  ■ Sleep sufficiency<br>  ■ Use of sleeping medications<br>  ○ Quality of sleep was also assessed routinely by asking patients to rate their perception of sleep quality using a rating of 0 (poor sleep quality) to 10 (fitful rest or sleep): assessed routinely during the study period<br>• Depression<br>  ○ BDI (Appendix 3): assessed baseline, during the intervention and post-treatment |
| Notes | Additional information<br>• Funding: National Science Counsel of Taiwan<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not applicable<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "The study was a randomised controlled trial." |

**Tsay 2004b** *(Continued)*

| | | |
|---|---|---|
| | | Comment: Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "Pre-dialysis fatigue was assessed routinely by asking patients to rate their perception of fatigue using a rating of 0 to 10, 0 indicating no fatigue and 10 indicating severe fatigue."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. Other subjective outcomes were reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Quote: "108 patients agreed and consented to the study. One hundred and six patients completed the study. Two patients were dropped over the 1-month intervention: 1 in the acupressure group and 1 in the control group. One patient was lost for medical reasons, while the other patient relocated."<br><br>Comment: 35/36 participants in the intervention group 1 (acupressure), 36/36 participants in the intervention group 2 (Transcutaneous Electrical Acupoint Stimulation) and 35/36 participants in the control group (routine unit care) completed the study (< 5% lost to follow-up, without difference between groups). Reasons for discontinuations seemed to be not related to the treatment allocation |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and conflicts of interest was not reported |

**Unal 2016**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br><br>• Parallel RCT<br><br>Study dates<br><br>• Duration of follow-up: 4 weeks<br>• Time frame: January 2014 to February 2015 |

**Unal 2016** *(Continued)*

| | |
|---|---|
| Participants | Study characteristics<br>• Setting: single centre (a private dialysis clinic in Turkey)<br>• Country: Turkey<br>• Inclusion criteria: 18 and 60 years; HD twice/week; did not have any communication problems<br>• Exclusion criteria: skin lesions; open foot wounds; malignant diseases; thrombosis; bleeding disorders<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group 1 (35/36); intervention group 2 (35/37); control group (35/37)<br>• Mean age ± SD (years): intervention group 1 (51.74 ± 12.29); intervention group 2 (53.89 ± 13.18); control group (57.37 ± 13.12)<br>• Sex (M/F): intervention group 1 (19/16); intervention group 2 (16/19); control group (20/15)<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ◦ CVD: treatment group 1 (not reported): not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group 1<br>• Foot reflexology<br>Intervention group 2<br>• Back massage<br>Control group<br>• Control (no intervention)<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ◦ Turkish version of 10-point VAS (18 items): assessed pre- and post-intervention<br>  ■ Fatigue<br>  ■ Energy<br>• Sleep quality<br>  ◦ PSQI (Appendix 3): assessed pre- and post-intervention<br>  ■ Sleep quality<br>  ■ Sleep latency<br>  ■ Sleep duration<br>  ■ Sleep efficiency<br>  ■ Sleep disturbances<br>  ■ Sleep sufficiency |

**Unal 2016** *(Continued)*

- Use of sleeping medications

| | |
|---|---|
| Notes | Additional information<br>• Funding: doctoral thesis of Kevser Sevgi Unal by Ataturk University Institute of Health Sciences<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "The Visual Analogue Scale (VAS) for Fatigue and the Pittsburg Sleep Quality Index (PSQI) were administered to the patients as a pretest immediately before they were taken to haemodialysis."<br><br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. Other subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "From the 110 patients, a total of 105 patients (35 patients per group) reached the end of the study, with one patient in the foot reflexology group and two patients in the back massage group having withdrawn from the study, and two patients in the control group having left the dialysis centre."<br><br>Comment: 35/36 participants in the intervention group 1 (foot reflexology), 35/37 participants in the intervention group 2 (back massage) and 35/37 participants in the control group (control) completed the study (> 5% lost to follow-up, with difference between groups) |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Low risk | There was no evidence of difference in the baseline characteristics, or different non-randomised co-interventions between groups. Funding was unlikely to influence the data analysis and authors had no conflicts of interest. The study seemed to be free from other sources of bias |

**Varaei 2020**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 16 weeks<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Setting: multicentre (3 teaching hospitals affiliated to Tehran University of Medical Sciences, Tehran, Iran)<br>• Country: Iran<br>• Inclusion criteria: > 18 years; minimal HD history of 1 year; 3 HD sessions/week; healthy olfactory function and no history of allergic rhinitis or respiratory disorders; no allergy to aromatic herbs; no participation in aromatherapy or massage therapy programs during the last 6 months before the study; not to take any sleeping pill before aromatherapy and during the course of the study; no history of foot amputation or active skin lesion in the feet; no addiction to opioids; no affliction by debilitating chronic physical conditions such as cardiac, respiratory, liver, or mental disorders according to patients' medical records<br>• Exclusion criteria: death during the study; kidney transplantation during the study<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group 1 (32/32); intervention group 2 (32/32); control group (32/32)<br>• Mean age ± SD (years): not reported<br>• Sex (M/F): not reported<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ◦ CVD: not reported<br>  ◦ Diabetes: not reported<br>  ◦ Hypertension: not reported<br>  ◦ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group 1<br>• Inhalation aromatherapy with lavender essence oil<br>Intervention group 2<br>• Massage aromatherapy with sweet orange essence oil<br>Control group<br>• No intervention<br>Co-interventions<br>• Dialysis routine care |

**Varaei 2020** *(Continued)*

| | |
|---|---|
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Fatigue<br>  ○ Rhoten fatigue 10-point VAS scale: assessed at baseline, week 8 and 16<br>• BP |
| Notes | Additional information<br>• Funding: The Tehran Faculty of Nursing and Midwifery and Tehran University of Medical Sciences, Tehran<br>• Conflicts of interest/disclosures: none<br>• Trial registration identification number: IRCT2014101819564N1<br>• A priori published protocol was reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "This was a three-group single-blind randomised controlled trial."<br>Comment: A single blind study is considered as high risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "The biostatistician who analysed the study data was blind to the interventions."<br>Comment: Fatigue assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. Other subjective outcomes were assessed. However, the outcome assessment was blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All participants completed the study and there was no lost to follow-up |
| Selective reporting (reporting bias) | High risk | Information about the protocol were reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | Baseline characteristics were not clearly reported. Funding was unlikely to influence the data analysis and authors had no conflicts of interest |

**VENOUS 2020**

| ***Study characteristics*** | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 12 months<br>• Time frame: not reported |
| Participants | Study characteristics<br>• Setting: not reported<br>• Country: Japan<br>• Inclusion criteria: dialysis patients > 70 years<br>• Exclusion criteria: hypoalbuminaemia as less than 3.0 g/dL; history of cardiovascular events 3 months prior to the entry; independence; > 90 years<br>Baseline characteristics<br>• Number (analysed/randomised): intervention group (15/28); control group (14/26)<br>• Mean age ± SD (years): not reported<br>• Sex (M/F): not reported<br>• Dialysis type: not reported<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ○ CVD: intervention group (0/28); control group (0/26)<br>  ○ Diabetes: not reported<br>  ○ Hypertension: not reported<br>  ○ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Pharmacological intervention<br>• Indication: study reporting fatigue<br>Intervention group<br>• Anti-thrombotic polymethyl-methacrylate membrane<br>Control group<br>• Placebo<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Nutritional status<br>  ○ Malnutrition inflammation score: every 3 months, up to 12 months<br>• Normalised protein catabolic rate: every 3 months, up to 12 months<br>• Creatinine generation rate: every 3 months, up to 12 months<br>• Patients symptoms as a QoL (arthralgia, skin itchiness, irritable sense, fatigue, headache, dialysis-related hypotension, leg cramps, and post-dialytic bed-free time): every 3 months, up to 12 months |

**VENOUS 2020** *(Continued)*

| | |
|---|---|
| Notes | Additional information<br>• Funding: not reported<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not reported<br>• A priori published protocol: not reported<br>• Abstract |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | It was unclear if fatigue was assessed with an appropriate measure. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. Other subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "11 patients in the NF group and 10 patients in the PS group were dropped out from the study. The reasons of the discontinuation were hypoalbuminaemia (1), increased bete-2 microglobulin, social reasons (2), dead (1), unknown reason (5) in NF group, and modality change (2), unknown reason (8). Finally, 15 patients in NF and 14 patients terminated the study, however, 2 patients with the data deficit in each group were excluded." |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported in a format that was not extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | No data were available to assess the possible imbalance between groups. Funding and conflicts of interest were not reported |

**Vishnevskii 2014**

***Study characteristics***

| | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates |

**Vishnevskii 2014** *(Continued)*

- Duration of follow-up: 4 weeks
- Time frame: not reported

| | |
|---|---|
| Participants | Study characteristics<br>• Setting: not reported<br>• Country: not reported<br>• Inclusion criteria: haemodialysis patients<br>• Exclusion criteria: not reported<br>Baseline characteristics<br>• Number (analysed/randomised): overall (not reported/24)<br>• Mean age ± SD (years): not reported<br>• Sex (M/F): overall (not reported): not reported<br>• Dialysis type: HD<br>• Dialysis vintage (years) (mean ± SD): not reported<br>• Comorbidities<br>  ○ CVD: not reported<br>  ○ Diabetes: not reported<br>  ○ Hypertension: not reported<br>  ○ Depression (clinician diagnosis): not reported |
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Transcutaneous electrical muscle stimulation<br>Control group<br>• No intervention<br>Co-interventions<br>• Not reported |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Pre- and post-dialysis blood test (assessed at the start of the protocol until the last week)<br>• Disadaptative symptoms (dyspnoea) (the timeframe for the assessment of this outcome was not clearly reported)<br>• Distance walked<br>  ○ 6MWT: assessed at the start of the protocol until the last week<br>• Changes of Kt/V: the timeframe for the assessment of this outcome was not clearly reported<br>• Changes in laboratory results (URR, creatinine, phosphate, urea): the timeframe for the assessment of this outcome was not clearly reported<br>• Fatigue<br>  ○ Borg scale: assessed before and after the test, until the last week<br>• Breathless<br>  ○ Borg scale: assessed before and after the test, until the last week |
| Notes | Additional information<br>• Funding: not reported |

**Vishnevskii 2014** *(Continued)*

- Conflicts of interest/disclosures: not reported
- Trial registration identification number: not reported
- A priori published protocol: not reported
- Abstract

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Sequence generation methods were not reported in sufficient detail to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was not reported in sufficient detail to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not reported. However, interventions were different and participants and/or investigators could be aware of the treatment assigned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Not reported. The outcomes were assessed with an appropriate measure, without differences between groups. It was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | The number of patients who completed the study was not clearly stated. It was unclear if there was evidence that the results were not biased by missing outcome data |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. It was not reported if multiple eligible outcome measurements (scales and time points) were pre-specified. It was unclear if the reported approach to analysing this outcome was pre-specified or influenced by the results. Outcomes information were not reported in sufficient detail to permit judgment. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |
| Other bias | Unclear risk | No data were available to assess the possible imbalance between groups. Funding and conflicts of interest were not reported |

**Yurtkuran 2007**

***Study characteristics***

| | |
|---|---|
| Methods | Study design<br>• Parallel RCT<br>Study dates<br>• Duration of follow-up: 3 months<br>• Time frame: 2004 (months not reported) |
| Participants | Study characteristics |

**Yurtkuran 2007** *(Continued)*

- Setting: single centre (HD unit of the Nephrology Department, Uludag University Faculty of Medicine)
- Country: Turkey
- Inclusion criteria: dialysis for at least 6 months (4 hours/day and 3 times/week); had no unstable hypertension, arrhythmia or cardiac angina after 10 min of fast pedalling
- Exclusion criteria: use of analgesic or nonsteroid anti-inflammatory drugs; an average musculoskeletal pain score of at least 2 on a scale of 0 to 10 (VAS) in the previous month; ischaemic cardiac pain, arrhythmia or unstable hypertension after 10 min fast pedalling; unstable angina; congestive heart failure (grade II); significant cardiac valve disease and conduction abnormalities according to the screening ECG; cerebrovascular disease; electrolyte imbalance; persistent hyperkalaemia before dialysis; DM; active liver disease; arthritic or orthopaedic problems limiting exercise; peripheral vascular disease; undisciplined patients

Baseline characteristics

- Number (analysed/randomised): intervention group (19/20); control group (18/20)
- Mean age ± SD (years): intervention group (38 ± 14.2); control group (41 ± 9.97)
- Sex (M/F): intervention group (9/11); control group (7/13)
- Dialysis type: HD
- Mean dialysis vintage ± SD (years): intervention group (1.8 ± 1.0); control group (1.7 ± 1.2)
- Comorbidities
  - CVD: not reported
  - Diabetes: not reported
  - Hypertension: not reported
  - Depression (clinician diagnosis): not reported

| | |
|---|---|
| Interventions | Intervention classification<br>• Non-pharmacological intervention<br>• Indication: study targeting fatigue<br>Intervention group<br>• Yoga-based exercise for 3 months<br>Control group<br>• No intervention<br>Co-interventions<br>• All the patients in the yoga and control groups were given active range of motion exercises to do for 10 min at home |
| Outcomes | Outcomes reported<br>• Fatigue outcome measures used: validation data available<br>• Pain and its change<br>  ○ VAS: assessed before and after the study period<br>• Fatigue and its change<br>  ○ VAS: assessed before and after the study period<br>• Sleep disturbance and its change<br>  ○ VAS: assessed before and after the study period<br>• Grip strength and its change: assessed before and after the study period<br>• Laboratory results and their change (urea, creatinine, calcium, alkaline phosphatase, phosphorus, cholesterol, HDL-cholesterol, triglyceride, erythrocyte, HCT): assessed before and after the study period<br>• Adverse events: assessed until the end of treatment<br>• Vital signs (heart rate, BP) |

**Yurtkuran 2007** *(Continued)*

- Stethoscope and a sphygmomanometer: assessed at the end of the HD procedure and exercise sessions

| | |
|---|---|
| Notes | Addtional information<br>• Funding: not reported<br>• Conflicts of interest/disclosures: not reported<br>• Trial registration identification number: not applicable (trial was performed before 2005)<br>• A priori published protocol: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "In the single-blind study, simple randomisation was done by a physician using a computer-generated table of random numbers, and 40 participants were allocated to two groups."<br>Comment: A computer-generated table of random numbers is considered as low risk of bias. No imbalance between intervention groups was apparent |
| Allocation concealment (selection bias) | Unclear risk | Quote: "The procedure was concealed from the evaluating physician."<br>Comment: Method of allocation concealment was not reported in sufficient detail to permit judgement. No imbalance between intervention groups was apparent |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: "In the single-blind study, simple randomisation was done by a physician using a computer-generated table of random numbers, and 40 participants were allocated to two groups."<br>Comment: A single-blind study is considered as high risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "Clinical and laboratory variables were evaluated in the intervention and control groups. The physician who did the examination was blind to the allocation."<br>Comment: The outcomes were assessed with an appropriate measure, without differences between groups. However, subjective measures were used, it was not stated whether outcomes were assessed without knowledge of treatment allocation, and knowledge of treatment assignment may have influenced reporting. Participant/investigators beliefs about the superiority/inferiority of either intervention could have influenced their assessment of the outcome, but there was no evidence that this was likely. However, objective and subjective outcomes were assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Quote: "Three of the 40 patients who met the inclusion criteria were dropped, as they missed three sessions in a 3-month-period and adhered poorly to the exercise instructions. Thus, 19 patients in the exercise group and 18 patients in the control group were left."<br>Comment: 19/20 participants in the intervention group and 18/20 participants in the control group completed the study (> 5% lost to follow-up, with differences between groups). Reasons for discontinuations were not reported |
| Selective reporting (reporting bias) | High risk | Information about the protocol and the statistical analysis plan were not reported. Fatigue was reported using multiple eligible outcome measurements (scales, time points). Fatigue was reported in a format that was extractable for meta-analysis. All outcomes that should be addressed (fatigue, cardiovascular disease, and death) were not reported |

**Yurtkuran 2007** *(Continued)*

| | | |
|---|---|---|
| Other bias | Unclear risk | There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups. Funding and conflicts of interest were not reported |

6MWT: 6-minute walk test; ACTH: adrenocorticotropic hormone; ADL: activity of daily living; AKI: acute kidney injury; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; BFI: Brief Fatigue Inventory; BMI: body mass index; BP: blood pressure; BUN: blood urea nitrogen; CBT: Cognitive Behavioural Therapy; CERA: Continuous Erythropoietin Receptor Activator; CES-D: Center for Epidemiologic Studies Depression Scale; CFQ: Chalder Fatigue Questionnaire; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CrCl: creatinine clearance; CRP: C-reactive protein; CVC: central venous catheter; CVD: cardiovascular disease; COPM: DBP: diastolic blood pressure; DM: diabetes mellitus; DSM: Diagnostic and Statistical Manual of Mental Disorders; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; EPO: erythropoietin; EQ-5D (-5L): EuroQol 5-dimensions (5-level); EAS: erythropoiesis-stimulating agents; ESKD: end-stage kidney disease; FACIT: Functional Assessment of Chronic Illness Therapy; FIBSER: Frequency, Intensity and Burden of Side Effects Rating Scale; FSS: Fatigue Severity Scale; GAD-7: Generalized Anxiety Disorder; GI: gastrointestinal; GOT: glutamic oxaloacetic transaminase; GPT: glutamic pyruvic transaminase; HADS: Hospital Anxiety and Depression Scale; Hb: haemoglobin; HCT: haematocrit; HD: haemodialysis; HDL: high-density lipoprotein; HFS: haemodialysis fatique scale; HIV: human immunodeficiency virus; HRQoL: Health-related quality of life; IFS: Iowa Fatigue Scale; IL: interleukin; IM: intramuscular injection; IPOS-Renal: Integrated Palliative Outcome Scale-Renal; IQR: interquartile range; ItchyQoL: QoL questionnaire fo patients with pruritus; ITT: intention to treat; IV: intravenous; KDOQI: Kidney Disease Outcomes Quality Initiative; KDQ: kidney disease questionnaire; KDQoL(SF): Kidney Disease Quality of life (Short Form); Kt/V: dialyser urea clearance adequacy; L-DOPS: L-threo-3,4-dihydroxyphenylserine; LDH: lactate dehydrogenase;; LEVIL: London Evaluation of Illness; LDL- low-density lipoprotein; LV: left ventricular; M/F: male/female; MAAS: Mindful Attention Awareness Scale; MADSR: Montgomery–Asberg Depression Rating Scale; MAP: mean arterial pressure; MBSR: Mindfulness Based Stress Reduction; MFI-20: Multidimensional fatigue inventory; MFIS: Modified Fatigue Impact Scale; MI: myocardial infarction; MINI: Mini International Neuropsychiatric Interview; Mini-Cog: mini cognitive; MIP: maximal inspiratory pressure; MRI: magnetic resonance imaging; NRS: numerical rating scale; NYHA: New York Heart Association; OSA: obstructive sleep apnea; PAL: physical activity log; PD: peritoneal dialysis; PEP: Personal Energy Planning; PFS: Piper Fatigue Scale; PHQ-9: Patient Health Questionnaire-9; PSQI: Pittsburgh Sleep Quality Index; PTH: parathyroid hormone; QIDS-16: Quick Inventory of Depression Symptomatology; QoL: quality of life; RCT: randomised controlled trial; rHuEPO: recombinant human erythropoietin; RNLI: Reintegration to Normal Living Index; SBP: systolic blood pressure; SC: subcutaneous; SCr: serum creatinine; SD: standard deviation; SF-8: 8-item Short Form Health Survey; SF-12: 12-item Short Form Health Survey; SF-36: 36-Item Short Form Health Survey; SIP: sickness impact profile; SMMT: Standardized Mini Mental Test; SNAG: Simplified Nutritional Appetite Questionnaire; SNRI: serotonin-norepinephrine reuptake inhibitor; SONG: Standardised Outcomes in Nephrology; SSRI: selective serotonin reuptake inhibitor; STAI: State-Trait Anxiety Inventory; TEAS: Trans Cutaneous Electrical Acupoint Stimulation; TSAT: transferrin saturation; UR: ultrafiltration rate; URR: urea reduction ratio; VAS: visual analogue scale; WHOQOL-BREF: WHO quality of life - brief form

## Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| CHAIR 2015 | Fatigue was not a primary or secondary outcome (chair stand exercise versus passive stretch exercise) |
| Churchill 1987 | Fatigue was not a primary or secondary outcome (dialysis reuse versus single use) |
| Dashti-Khavidaki 2011 | Fatigue was not a primary or secondary outcome (clonazepam versus zolpidem) |
| Eglence 2013 | Not RCT: all participants in the intervention group came from a Turkish HD centre, and all participants in the control group came from another Turkish HD centre |
| Gram 1998 | Fatigue was not a primary or secondary outcome (growth hormone versus placebo) |
| Heshmati Far 2015 | Fatigue was not a primary or secondary outcome (Benson relaxation technique versus control) |
| Heshmatifar 2015 | Fatigue was not a primary or secondary outcome (Benson relaxation technique versus usual care) |
| Laupacis 1992 | Not RCT |

| Study | Reason for exclusion |
|---|---|
| Macagnan 2019 | Fatigue was not a primary or secondary outcome (photo-biomodulation therapy versus placebo) |
| Nakamoto 2008 | Fatigue was not a primary or secondary outcome (Juzen-taiho-to (TJ-48) versus placebo) |
| Sharp 2005 | Fatigue was not a primary or secondary outcome (immediate CBT versus deferred-treatment) |
| Shimizu 1983 | Fatigue was not a primary or secondary outcome (high sodium + bicarbonate concentrate group versus high sodium + acetate concentrate group versus low sodium + bicarbonate concentrate group versus low sodium + acetate concentrate) |
| Siami 1991 | Fatigue was not a primary or secondary outcome (IV L-carnitine versus placebo) |
| Tawney 2000 | Fatigue was not a primary or secondary outcome (physical rehabilitation program versus usual care) |
| TREAT 2005 | Wrong population: CKD patients who not required dialysis |
| Tsai 2015 | Fatigue was not a primary or secondary outcome (nurse-led breathing training program versus waiting list) |

CBT: cognitive behavioural therapy; CKD: chronic kidney disease; HD: haemodialysis; IV: intravenous; RCT: randomised controlled trial

### Characteristics of studies awaiting classification *[ordered by study ID]*

**NCT00440869**

| | |
|---|---|
| Methods | • Study design: RCT<br>• Duration of follow-up: 6 days |
| Participants | • Country: USA<br>• Setting: not reported<br><br>Inclusion criteria<br><br>• > 18 years<br>• Undergoing HD for 3 months or more or healthy control without kidney disease<br><br>Exclusion criteria<br><br>• Inability to give informed consent<br>• Diagnosis of DM<br>• Musculoskeletal contraindications to exercise<br>• Infection requiring IV antibiotics within 2 months<br>• Hospitalisation within 2 months<br>• Ingestion of antioxidant supplements within 1 month<br>• Requirement for systemic anticoagulation<br>• eGFR < 60 mL/min/1.73 $m^2$ for healthy controls |
| Interventions | Treatment group<br><br>• N-acetylcysteine 600 mg<br><br>Control group<br><br>• Placebo |

| NCT00440869 *(Continued)* | |
|---|---|
| | Co-interventions<br>• Not reported |
| Outcomes | Planned outcomes<br>• Change in quadriceps muscle endurance during intermittent submaximal contractions<br>• Change in exercise-induced markers of oxidative stress |
| Notes | Additional information<br>• ClinicalTrials.gov Identifier: NCT00440869<br>• Funding: National Institute of Diabetes and Digestive and Kidney Diseases<br>• Recruitment status: completed<br>• Study completed: started in February 2007 and completed in December 2009<br>• No study results are available |

DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HD: haemodialysis; IV: intravenous; RCT: randomised controlled trial

**Characteristics of ongoing studies** *[ordered by study ID]*

| ACTRN12617000420347 | |
|---|---|
| Study name | Evaluating the effectiveness of practicing yoga during haemodialysis for fatigue in patients with end stage kidney disease |
| Methods | Study design<br>• RCT<br>• Duration of follow-up: 12 weeks |
| Participants | Study characteristics<br>• Country: Australia<br>• Setting: multicentre (2 dialysis facilities in Brisbane, Queensland)<br>• Inclusion criteria<br>  ◦ 18 and 80 years, who have been received for a period of greater than 90 days prior to trial entry<br>  ◦ In-centre patients with a HD prescription of 3 sessions/week<br>  ◦ Patients with an arterial venous fistula or graft<br>  ◦ Patients who are haemodynamically stable, meaning no medical intervention has been needed for hypotensive episodes and use of saline at least 2 weeks prior to trial entry<br>  ◦ Receive a global fatigue score of -4 on the BFI scale<br>  ◦ Must be competent to understand the research procedures, and provide written informed consent<br>  ◦ Not currently practicing yoga<br>• Exclusion criteria<br>  ◦ ESKD patients who dialyse at home<br>  ◦ ESKD patients who are treated with peritoneal dialysis<br>  ◦ HD patients with catheters, including cuffed tunnelled and non-cuffed non-tunnelled catheters<br>  ◦ HD patients with concomitant conditions that in the opinion of the Chief Investigator may adversely affect the safety and efficacy of the intradialytic yoga intervention, or severely limit the patient's ability to complete the study |
| Interventions | Intervention group<br>• Intradialytic yoga for 3 sessions/week over 12 weeks |

**ACTRN12617000420347** *(Continued)*

| | |
|---|---|
| | Control group<br>• Usual care<br>Co-interventions<br>• Not reported |
| Outcomes | Planned outcomes<br>• Change in symptoms of fatigue<br>  ○ CFQ: after 12 weeks<br>• Change in symptoms of post-dialysis fatigue recorded by participants<br>  ○ Post Dialysis Fatigue Diary: after 12 weeks<br>• Change in HRQoL<br>  ○ KDQoL-SF: after 12 weeks<br>• Change in potassium level: after 12 weeks<br>• Change in level of phosphate: after 12 weeks<br>• Change in interdialytic fluid gain: after 12 weeks<br>• Changes in biochemical markers (BP, CRP, urea, TSAT, ferritin, creatinine, ALP, intact PTH, albumin, erythrocyte count, HCT, Kt/V, electrolyte): after 12 weeks<br>• Feasibility and acceptability and dropout rate<br>• Participants' beliefs about the treatment intervention<br>  ○ CEQ: after 12 weeks<br>• Adherence to the intervention measured as frequency and duration: after 12 weeks<br>• Qualitative feedback from caregivers<br>• Adverse events (vascular access dysfunction, hypotensive/hypertensive episodes, muscles cramps, musculoskeletal injuries, cardiovascular events, hospitalisation, deaths): after 12 weeks |
| Starting date | July 2017 |
| Contact information | Kylie Barr<br>Phone: +61 409 992 262<br>Email: k.barr@westernsydney.edu.au |
| Notes | ClinicalTrials.gov Identifier: ACTRN12617000420347. Funding: none. Recruitment status: completed |

**ACTRN12618000724279**

| | |
|---|---|
| Study name | Evaluation of the effectiveness of home-base physical training in patients undergoing haemodialysis |
| Methods | Study design<br>• RCT<br>• Duration of follow-up: 6 months |
| Participants | Study characteristics<br>• Country: Poland<br>• Setting: not reported<br>• Inclusion criteria<br>  ○ Adults suffering from ESKD, treated by HD for at least 3 months |

**ACTRN12618000724279** *(Continued)*

- No contraindications to physical training
- Giving informed written consent

- Exclusion criteria
  - Lack of logical contact

| | |
|---|---|
| Interventions | Intervention group<br>• Home-based physical training with recommended frequency 3 times/week on days without dialysis treatment. Every training session lasts 30 minutes (3 times at 10-minute intervals)<br>Control group<br>• Non-training group<br>Co-interventions<br>• Not reported |
| Outcomes | Planned outcomes<br>• Fatigue<br>  ◦ Borg scale (Rate of Perceived Exertion scale) (≤ 3 on 0-10 scale): after 6 months<br>  ◦ FACIT Fatigue Scale: after 6 months<br>• Assessment of exercise tolerance: after 6 months<br>• Functional fitness<br>  ◦ Fullerton Test: after 6 months<br>• Quality of life<br>  ◦ KDQOL-SF TM: after 6 months<br>• Physical function<br>  ◦ 6MWT: after 6 months<br>• Peripheral BP: after 6 months<br>• Physical activity<br>  ◦ IPAQ: after 6 months<br>• BIA: after 6 months<br>• Independence in activities of daily living<br>  ◦ Katz index: after 6 months<br>• Independence of instrumental activities of daily living<br>  ◦ Lawton Index: after 6 months<br>• Hand grip strength: after 6 months<br>• Lower extremities strength<br>  ◦ Sit to Stand to Sit Test: after 6 months<br>• Change in rheologic properties of blood composite of AI- aggregation of RBC index: after 6 months<br>• EI- elongation of RBC index: after 6 months<br>• Change in biochemical profile composite of tNO3, fibrinogen and Irisin: after 6 months<br>• Haematological parameters (Hb, HCT, erythrocytes leukocyte count platelet count): after 6 months<br>• Assessment of heart structure and function (mitral valve medium and maximum pressure gradient, E/A ratio, right ventricular systolic pressure, left ventricular end-systolic and end-systolic diameter, intra-ventricular septal thickness (IVS) during systole and diastole, left ventricular posterior wall during systole and diastole, left and right atrial size: after 6 months<br>• Levels of calcium, phosphorous, potassium, sodium, albumin, urea, creatinine: after 6 months |
| Starting date | August 2015 |
| Contact information | Katarzyna Chojak-Fijalka<br>Phone: +48 683 11 24 |

| | |
|---|---|
| **ACTRN12618000724279** *(Continued)* | Email: katarzyna.chojak@awf.krakow.pl |
| Notes | ClinicalTrials.gov Identifier: ACTRN12618000724279. Funding: University of Physical Education in Cracow. Recruitment status: completed |

**ACTRN12620000408987**

| | |
|---|---|
| Study name | Structured exercise prograM to reduce Fatigue In patients receiving dialysis: a preference-stratified adaptive Trial (M-FIT) |
| Methods | Study design<br>• RCT<br>• Duration of follow-up: 36 weeks (12 weeks treatment + additional 24 weeks follow-up) |
| Participants | Study characteristics<br>• Country: Australia<br>• Setting: multicentre<br>• Inclusion criteria<br>  ○ On maintenance HD or PD (> 3 months) with a life expectancy of > 12 months<br>  ○ ≥ 18 years<br>  ○ Willing to participate and provide informed consent<br>  ○ Able to speak, read and write English<br>  ○ Access to a smartphone or tablet with Internet access<br>  ○ Ability to carry out movements at intensity level 1 of all 3 exercise prescriptions and the stretches in the control arm (as assessed by the site exercise professional)<br>• Exclusion criteria<br>  ○ Known cardiovascular disease that places the participant at an unacceptable risk of untoward events occurring during exercise training (as deemed by the treating physician)<br>  ○ Have received or are expected to receive a kidney transplant within 12 months<br>  ○ Currently meeting the physical activity guidelines as assessed by Active Australia Survey/National Health survey (150 min/week of moderate-intensity aerobic (cardio) activity and 2 sessions/week of resistance training) |
| Interventions | Intervention group 1<br>• Walking (3 non-consecutive days/week, (~60 min/session); will complete a series of stretches after their walking sessions)<br>Intervention group 2<br>• Resistance training (3 non-consecutive days/week (~60 min/session); consists of a core set of 8 exercises, option to include 2 exercises to facilitate individualisation of exercise prescription, includes warm-up and cool-down stretches. e.g. sit to stand, wall push up, standing horizontal TheraBand row, etc)<br>Intervention group 3<br>• Combination of aerobic (cardio) and resistance training (3 non-consecutive days/week (~60 minutes/session); e.g. aerobic/cardio: walking, cycling etc e.g. resistance: sit to stand, wall push ups etc, which are home-based exercises delivered through a mobile application)<br>Control group<br>• Same process as the exercise arms; however, access on the M-FIT application will be restricted to a low-intensity stretching routine only (no access to exercise sessions or videos). They will be |

**ACTRN12620000408987** *(Continued)*

| | |
|---|---|
| | doing 3 non-consecutive days of stretches e.g. shoulder stretch, hip flexor stretch etc for about 10 mins at home, via the app and complete trial outcome assessment questionnaires<br><br>Co-interventions<br><br>• Not reported |
| Outcomes | Planned outcomes<br><br>• Fatigue<br>  ○ Pittsburgh Fatigability Scale questionnaires: baseline, 4, 8, 12, 36 weeks<br>  ○ FACIT-Fatigue: SONG-HD Fatigue: baseline, 4, 8, 12, 36 weeks<br>  ○ FACIT Fatigue Scale: baseline, 4, 8, 12 weeks<br>• Physical activity<br>  ○ Wrist-worn activity monitor (ActiGraph): baseline, at week 12 and week 36<br>• Neuromuscular fitness: baseline, at week 12 and week 36<br>• Heart rate: at week 12 and week 36<br>• Death<br>• Vascular access: up to 36 weeks<br>• PD infections: up to 36 weeks<br>• Technique survival: up to 36 weeks<br>• Exercise adherence<br>  ○ Study-specific self-report questionnaires to be completed for every exercise session: up to 12 weeks<br>• Hospitalisation: up to 36 weeks<br>• HRQoL<br>  ○ EQ-5D-5: baseline, 4, 8, 12, 36 weeks<br>• Cost-effectiveness and cost-utility: up to 36 weeks<br>• Frailty<br>  ○ Fried Frailty Index: baseline, at week 12 and week 36<br>• Mood<br>  ○ HADS: baseline, 4, 8, 12, 36 weeks<br>• Social participation<br>  ○ Ability to Participate in Social Roles and Activities (PROMIS-SF) questionnaire: baseline, 4, 8, 12, 36 weeks<br>• BMI: baseline, 12, 36 weeks<br>• Exercise capacity<br>  ○ 6MWT: baseline, 12, 36 weeks<br>• Balance<br>  ○ Tinetti balance test (score): baseline, 12, 36 weeks<br>• Sleep<br>  ○ Wrist-worn activity monitor (ActiGraph): baseline, at week 12 and week 36<br>• Process evaluation (for patients and staff)<br>  ○ Qualitative semi-structured interviews: immediately post-intervention and another 12 months post-intervention<br>• Usability of the M-FIT mobile application<br>  ○ Modified system usability scale (mSUS): at week 36 |
| Starting date | March 2020 |
| Contact information | Allison Jaure<br><br>Phone: +61 2 9845 1467<br><br>Email: allison.jaure@sydney.edu.au |

**ACTRN12620000408987** *(Continued)*

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|---|---|
| Notes | ClinicalTrials.gov Identifier: ACTRN12620000408987. Funding: Australian Department of Health. Recruitment status: Not yet recruiting |

**Burrai 2019a**

| | |
|---|---|
| Study name | Effects of virtual reality in patients undergoing dialysis study protocol |
| Methods | Study design<br>• RCT<br>• Duration of follow-up: 1 month |
| Participants | Study characteristics<br>• Country: Italy<br>• Setting: multicentre<br>• Inclusion criteria<br>  ○ > 18 years<br>  ○ In treatment with 3 weekly HD sessions<br>  ○ HD duration ≥ 3 hours<br>  ○ No acoustic deficit<br>  ○ No visual impairment<br>  ○ Patient-oriented in time and space<br>• Informed consent<br>• Exclusion criteria<br>  ○ Use of antipsychotic drugs<br>  ○ Not in possession of smartphones or in possession of smartphones without an Internet connection |
| Interventions | Intervention group<br>• Virtual reality<br>Control group<br>• Standard care |
| Outcomes | Planned outcomes<br>• Stressors<br>  ○ Hemodialysis Stressor Scale (Appendix 3)<br>• Anxiety<br>  ○ STAI-Y1 (Appendix 3): at each HD session for 1 month<br>• Fatigue<br>  ○ 10-point VAS (Appendix 3): at each HD session for 1 month<br>• Pain<br>  ○ 10-point VAS (Appendix 3)<br>• Pruritus: at each HD session for 1 month<br>• Arterial pressure: at each HD session for 1 month<br>• Heart rate: at each HD session for 1 month<br>• Respiration rate: at each HD session for 1 month<br>• Duration of the session: at each HD session for 1 month<br>• Adverse events<br>• Withdrawn |

**Burrai 2019a** *(Continued)*

| | |
|---|---|
| Starting date | Not reported |
| Contact information | Francesco Burrai<br>Phone: not reported<br>Email: francesco.burrai@atssardegna.it |
| Notes | ClinicalTrials.gov Identifier: not reported. Funding: not reported. Recruitment status: not reported |

**Cardoso 2019**

| | |
|---|---|
| Study name | Effects of continuous moderate exercise with partial blood flow restriction during hemodialysis: A protocol for a randomized clinical trial |
| Methods | Study design<br>• RCT<br>• Duration of follow-up: 13 weeks |
| Participants | Study characteristics<br>• Country: Brazil<br>• Setting: single centre hospital São Francisco de Paula in Pelotas, Southern Brazil<br>• Inclusion criteria<br>  ◦ > 18 years<br>  ◦ In treatment with HD<br>• Exclusion criteria:<br>  ◦ Diagnosis of coronary artery disease, presence of active infection or cancer<br>  ◦ Presence of musculoskeletal limitations preventing exercise performance<br>  ◦ Cognitive alterations making it impossible to understand the instructions of the exercises<br>  ◦ SBP to 180 mm Hg or DBP 105 mm Hg at rest; resting heart rate to 120 bpm |
| Interventions | Intervention group 1<br>• Moderate exercise with blood flow restriction<br>Intervention group 2<br>• Moderate exercise without blood flow restriction<br>Control group<br>• No exercise<br>Co-interventions<br>• Not reported |
| Outcomes | Planned outcomes<br>• Muscle thickness<br>  ◦ 6MWT<br>• IL-6, IL-10<br>• CRP<br>• Superoxide dismutase activity<br>• Glutathione peroxidase activity |

**Cardoso 2019** *(Continued)*

- TNF-alfa
- Strength
- HRQoL
  - KDQOL-SF

| | |
|---|---|
| Starting date | Not reported |
| Contact information | Rodrigo Kohn Cardoso<br>Phone: not reported<br>Email: rafaelorcy@gmail.com |
| Notes | ClinicalTrials.gov Identifier: RBR-8T2P2M. Funding: not reported. Conflict of interests: none. Recruitment status: not reported |

**CONVINCE 2020**

| | |
|---|---|
| Study name | Benefits and harms of high-dose haemodiafiltration versus high-flux haemodialysis: the comparison of high-dose haemodiafiltration with high-flux haemodialysis (CONVINCE) trial protocol |
| Methods | Study design<br>• Parallel RCT<br>• Duration of follow-up: 3 years |
| Participants | Study characteristics<br>• Setting: multicentre<br>• Country: Europe<br>• Inclusion criteria<br>  ○ Signed and dated written Informed Consent Form obtained from the participant or his/her guardian or in accordance with local regulations<br>  ○ ≥ 18 years<br>  ○ Diagnosed with ESKD<br>  ○ On HD treatment for ≥ 3 months<br>  ○ Likely to achieve high-dose HDF (≥ 23 L, in post-dilution mode), according to the protocol<br>  ○ Willing to have a dialysis session with a duration of ≥ 4 hours, 3 times/week<br>  ○ Understands study procedures and is able to comply<br>• Exclusion criteria<br>  ○ Severe participant non-compliance defined as severe non-adherence to the dialysis procedure and accompanying prescriptions, especially frequency and duration of dialysis treatment<br>  ○ Life expectancy < 3 months<br>  ○ HDF treatment < 90 days before screening<br>  ○ Anticipated living donor kidney transplantation < 6 months after screening<br>  ○ Evidence of any other diseases or medical conditions that may interfere with the planned treatment, affect participant compliance or place the participant at high risk for treatment-related complications<br>  ○ Participation in any other study will be discussed with and decided by the Executive Board<br>  ○ Unavailable ≥ 3 months during the study conduct for study visits |
| Interventions | Intervention group 1<br>• High-dose HDF |

**CONVINCE 2020** *(Continued)*

Intervention group 2

- Continuation of conventional high-flux HD

Co-interventions

- BP-modifying medication used for managing co-morbid conditions and complications of CKD, including diabetes, Ischaemic heart disease and heart failure, as part of usual care
- ESAs, iron preparations, drugs for treatment of hyperkalaemia, phosphate binders, vitamin D and vitamin D analogues, PTH antagonists and extracorporeal anticoagulants might be applied, as these are considered part of routine clinical care

Outcomes

Planned outcomes

- All-cause death
- Cardiovascular events
- All-cause and infection-related hospitalisations
- HRQoL
  - EQ-5D-5L
  - Modified KDQOL symptom checklist
  - Health transition items (2 items of the SF-36)
  - PROMIS Physical Function 4-item short form (part of the PROMIS Profile-29)
- Cost-effectiveness
- Adverse events
- Acute coronary syndrome
- Myocardial infarction (STEMI/NSTEMI)
- Unstable angina pectoris
- Congestive heart failure
- Coronary artery bypass graft
- Percutaneous transluminal coronary angioplasty and/or stenting
- Transient ischaemic attack
- Cerebral vascular accident
- Therapeutic carotid procedure (endarterectomy and/or stenting)
- Vascular intervention of peripheral arterial ischemias (revascularization, percutaneous transluminal angioplasty and/or stenting using physician reporting based on standard consensus definitions)
- Anxiety
  - PROMIS Anxiety 4-item short form (part of the PROMIS Profile-29)
- Depression
  - PROMIS Depression 4-item short form (part of the PROMIS Profile-29)
- Life participation
  - PROMIS Ability to participate in social roles and activities 4-item short form (part of the PROMIS Profile-29)
- Sleep
  - PROMIS Sleep disturbance 4-item short form (part of the PROMIS Profile-29)
- Stress
  - Perceived Stress Questionnaire 5-item short form
- Self-Efficacy
  - 5-item sub-set of the General Self-Efficacy Scale
  - MOS Social Support Scale 4-item short form
- Pain
  - PROMIS Pain Interference 4-item short form (part of the PROMIS Profile-29)
  - PROMIS Pain Intensity one item (part of the PROMIS Profile-29)
- Fatigue
  - PROMIS Fatigue 6-item customised short form
- Cognitive impairment

**CONVINCE 2020** *(Continued)*

| | |
|---|---|
| | ○ PROMIS Cognitive Abilities 4-item customised short form |
| Starting date | Not reported |
| Contact information | Peter J Blankestijn<br>Phone: not reported<br>Email: P.J.Blankestijn@umcutrecht.nl |
| Notes | Netherlands National Trial Register (NTR 7138). Funding: European Union's Horizon 2020 research and innovation programme under grant agreement No 754803. Recruitment status: recruiting |

**CTRI/2018/02/012021**

| | |
|---|---|
| Study name | The effectiveness of Intradialytic exercise on fatigue and quality of sleep among patients undergoing hemodialysis |
| Methods | Study design<br>• RCT<br>• Duration of follow-up: not reported |
| Participants | Study characteristics<br>• Country: not reported<br>• Setting: not reported<br>• Inclusion criteria<br>○ Adults HD patients<br>• Exclusion criteria<br>○ Not reported |
| Interventions | Intervention group<br>• Intradialytic exercise<br>Control group<br>• No intervention |
| Outcomes | Planned outcomes<br>• Fatigue<br>• Sleep quality |
| Starting date | Not reported. The trial was posted on 2018 |
| Contact information | PD Rai<br>Phone: not reported<br>Email: not reported |
| Notes | Only RIS.txt file was available to extract data. ClinicalTrials.gov Identifier: CTRI/2018/02/012021. Funding: not reported. Recruitment status: not reported |

**Hamad 2021**

| | |
|---|---|
| Study name | Effect of plantar electrical nerve stimulation during routine hemodialysis process on the daily physical activity in adults with diabetes and end stage renal disease-a randomized double blinded controlled trial |
| Methods | Study design<br>• RCT<br>• Duration of follow-up: 12 weeks |
| Participants | Study characteristics<br>• Country: not reported<br>• Setting: not reported<br>• Inclusion criteria<br>  ○ Adults with diabetes and kidney failure undergoing HD<br>• Exclusion criteria<br>  ○ Not reported |
| Interventions | Intervention group<br>• Plantar electrical nerve stimulation<br>Control group<br>• Identical but non-functional device for the same period<br>Co-interventions<br>• Not reported |
| Outcomes | Planned outcomes<br>• Daily life physical activity (e.g. cumulative postures including sitting, standing, lying, and walking; walking characteristics including step count, number of unbroken walking bout, and postural transitions including sit to stand and stand to sit) (at baseline and at 12 weeks) |
| Starting date | Not reported |
| Contact information | Mishra, R. K.<br>Phone: not reported<br>Email: not reported |
| Notes | ClinicalTrials.gov Identifier: not reported. Funding: not reported. Fatigue was not clearly reported and this study would be evaluated in the following update |

**NCT01620580**

| | |
|---|---|
| Study name | Symptom management program for hemodialysis patients |
| Methods | Study design<br>• RCT<br>• Duration of follow-up: 8 weeks |
| Participants | Study characteristics |

**NCT01620580** *(Continued)*

- Country: USA
- Setting: not reported
- Inclusion criteria
  - ≥ 18 years
  - HD 3 times/week
  - Received HD for ≥ 6 months
  - Read and write English
  - Have telephone service
- Exclusion criteria
  - History of dementia
  - AIDS
  - Active cancer
  - Inability to give informed consent

| | |
|---|---|
| Interventions | Intervention group<br>• Self-management strategies with 15-minute discussion<br>Control group<br>• Dietary information (4 units)<br>Co-interventions<br>• Not reported |
| Outcomes | Planned outcomes<br>• Itching: after 8 weeks<br>• Tiredness: after 8 weeks<br>• Numbness: after 8 weeks<br>• Sleep disturbance (difficulty falling asleep and difficulty staying asleep): after 8 weeks<br>• Adherence to treatment diary improved social functioning, physical functioning and emotional status: after 8 weeks<br>• Feasibility of implementing self-management intervention: after 5 weeks |
| Starting date | September 2011 |
| Contact information | Francess V Danquah<br>Phone: not reported<br>Email: not reported |
| Notes | ClinicalTrials.gov Identifier: NCT01620580. Funding: The University of Texas Health Science Center, Houston. Recruitment status: completed |

**NCT02361268**

| | |
|---|---|
| Study name | End-Stage Renal Disease Intra-dialysis Lifestyle Education study (END-IDLE) |
| Methods | Study design<br>• RCT<br>• Duration of follow-up: 24 weeks (intervention performed for 12 weeks) |

**NCT02361268** *(Continued)*

| | |
|---|---|
| Participants | Study characteristics<br>• Country: USA<br>• Setting: not reported<br>• Inclusion criteria<br>  ○ Maintenance HD for ≥ 3 months<br>  ○ Adequately dialysed (Kt/V ≥ 1.2 measured within last 3 months)<br>  ○ Expected to remain in present HD shift for next 4 months<br>  ○ Expected to remain on HD for at least 6 months<br>  ○ ≥ 18 years<br>• Exclusion criteria<br>  ○ Acute or chronic medical conditions that would make intra-dialysis yoga potentially hazardous<br>  ○ Unstable cardiac disease e.g. angina, life-threatening arrhythmia<br>  ○ Chronic lung disease that prevents gentle exercise or deep breathing exercises<br>  ○ Active cerebrovascular diseaseMajor depression<br>  ○ Chronic symptoms of nausea, vomiting, or diarrhoea<br>  ○ Current participation in exercise or mind-body program/practice<br>  ○ Cognitive impairment (MME ≤ 24) measured at baseline testing visit |
| Interventions | Intervention group 1<br>• Intradialysis yoga for 12 weeks, 15 to 60 minutes of yoga during dialysis.<br>Intervention group 2<br>• Educational program for 12 weeks (12 modules)<br>Co-interventions<br>• Not reported |
| Outcomes | Planned outcomes<br>• Change in Physical Component Summary<br>  ○ KDQOL-SF (Appendix 3): after 24 weeks<br>• Chronic illness therapy fatigue<br>  ○ Functional Assessment of Chronic Illness Therapy-Fatigue: after 24 weeks<br>• Profile of Mood States: after 24 weeks<br>• Depression<br>  ○ Center for Epidemiological Studies Depression: after 24 weeks<br>• Patient satisfaction with dialysis treatment: after 24 weeks<br>• Sleep<br>  ○ PSQI: after 24 weeks<br>• Self-efficacy for self-management (assessed by questionnaire): after 24 weeks<br>• 6MWT: after 24 weeks<br>• BP: after 12 weeks<br>• Endothelial function: after 12 weeks<br>• Arterial stiffness: after 12 weeks<br>• Autonomic tone (including baroreflex and heart rate variability): after 12 weeks |
| Starting date | July 2015 |
| Contact information | Gurjeet S Birdee<br>Phone: not reported<br>Email: not reported |

**NCT02361268** *(Continued)*

| | |
|---|---|
| Notes | ClinicalTrials.gov Identifier: NCT02361268. Funding: Vanderbilt University Medical Center and National Center for Complementary and Integrative Health (NCCIH). Recruitment status: completed |

**Quintiliano 2019**

| | |
|---|---|
| Study name | Transcranial direct current stimulation in management of pain, mood, functionality, and quality of life in patients undergoing hemodialysis: a study protocol for a double-blind controlled randomized trial |
| Methods | Study design<br>• RCT<br>• Duration of follow-up: 4 weeks |
| Participants | Study characteristics<br>• Country: Brazil<br>• Setting: single centre<br>• Inclusion criteria<br>  ◦ Male or female aged 18 to 75 years undergoing HD with ESKD (CKD 5D2) for > 3 months, (4 hours/session)<br>  ◦ Pain-related with a score of more than 4 (range of scores from 1 to 10) in a visual analogue scale (VAS) for > 3 months<br>  ◦ Have physical capacity to do physical evaluation and be capable of consenting to treatment and understanding study explanations and questionnaires<br>  ◦ Provide informed consent<br>• Exclusion criteria<br>  ◦ Electrical implants in the body<br>  ◦ History of epilepsy or convulsion<br>  ◦ Clinically contraindicated to receive tDCS, such as having metal embedded in their scalp or brain<br>  ◦ Psychiatric illness<br>  ◦ Pregnant women<br>  ◦ Signs of severe disease and/or indication of hospitalisation, including instability, infection, acute myocardial infarction, and stroke |
| Interventions | Intervention group 1<br>• Motor cortex (M1)<br>Intervention group 2<br>• Dorsolateral prefrontal cortex (DLPFC)<br>Control group<br>• Sham group<br>Co-interventions<br>Not reported |
| Outcomes | Planned outcomes<br>• Pain: baseline, week 1 and 4<br>• Depression: baseline, week 1 and 4<br>• Functionality: baseline, week 1 and 4 |

**Quintiliano 2019** *(Continued)*

| | |
|---|---|
| | • QoL: baseline, week 1 and 4 |
| Starting date | Not reported. Trial was registered on 2018 |
| Contact information | Artur Quintiliano<br>Phone: not reported<br>Email: artur_bezerra@hotmail.com |
| Notes | Brazilian Clinical Trials Registry/Registro Brasileiro de Ensaios Clínicos (ensaiosclinicos.gov.br), 1111–1216-0137. Funding: funded by the authors. Recruitment status: not reported |

**Sharma 2022**

| | |
|---|---|
| Study name | Energy conservation education intervention for people with end-stage kidney disease receiving haemodialysis (EVEREST): protocol for a cluster randomised control trial |
| Methods | Study design<br>• Cluster RCT<br>• Duration of follow-up: 12 weeks |
| Participants | Study characteristics<br>• Country: Nepal<br>• Setting: single centre<br>• Inclusion criteria<br>  ○ Participants diagnosed with kidney failure and undergoing HD for ≥ 3 months<br>  ○ ≥ 18 years<br>  ○ Able to speak and understand Nepali language and willing to participate<br>• Exclusion criteria<br>  ○ Earlier grades of CKD or not dependent on HD<br>  ○ Those acutely ill, diagnosed with cognitive impairment and those who are not willing to participate |
| Interventions | Intervention group<br>• Individual face-to-face educational intervention session<br>Control group<br>• Usual care<br>Co-interventions<br>• Not reported |
| Outcomes | Planned outcomes<br>• Fatigue: baseline, 4, 8, 12 weeks<br>• Other CKD symptoms: baseline, 4, 8, 12 weeks<br>• Occupational performance: baseline, 4, 8, 12 weeks<br>• QoL SF-36 questionnaire: baseline, 4, 8, 12 weeks |
| Starting date | Not reported |

**Sharma 2022** *(Continued)*

| | |
|---|---|
| Contact information | Sita Sharma<br>Phone: not reported<br>Email: sita.sharma@griffithuni.edu.au |
| Notes | Trials registration number NCT04360408. Funding: none. Recruitment status: not reported |

**SLEEP-HD 2021**

| | |
|---|---|
| Study name | Tailoring of cognitive behavior therapy for insomnia for patients with kidney failure undergoing hemodialysis: The sleep-HD study |
| Methods | Study design<br>• Cluster RCT<br>• Duration of follow-up: not reported |
| Participants | Study characteristics<br>• Country: not reported<br>• Setting: multicentre<br>• Inclusion criteria<br>  ○ Undergoing 3 times/week maintenance HD for > 3 months and have baseline Insomnia Severity Index scores > 10 with sleep disturbances > 3 nights/week for > 3 months<br>• Exclusion criteria<br>  ○ Not reported |
| Interventions | Intervention group 1<br>• CBT performing in 6 weekly sessions<br>Intervention group 2<br>• Trazodone<br>Placebo group<br>• Placebo<br>Co-interventions<br>• Not reported |
| Outcomes | Planned outcomes<br>• Fatigue was not clearly stated<br>• Sleep outcomes |
| Starting date | Not reported |
| Contact information | McCurry, S.<br>Phone: not reported<br>Email: not reported |
| Notes | Trials registration number not reported. Funding: not reported. Recruitment status: not reported |

**TACcare 2018**

| | |
|---|---|
| Study name | Rationale and design of technology assisted stepped collaborative care intervention to improve patient-centered outcomes in hemodialysis patients (TACcare trial) |
| Methods | Study design<br>• RCT<br>• Duration of follow-up: 12 months |
| Participants | Study characteristics<br>• Country: USA<br>• Setting: multicentre (Pennsylvania and New Mexico)<br>• Inclusion criteria<br>  ○ ≥ 18 years<br>  ○ Undergoing 3 times/week maintenance HD for over 3 months<br>  ○ English or Spanish-speaking<br>  ○ Ability to provide informed signed consent<br>  ○ No evidence of thought disorder, delusions, or active suicidal intent observed or reported<br>• Exclusion criteria<br>  ○ Evidence of thought disorder, delusions or active suicidal intent – observed or reported<br>  ○ Active substance abuse<br>  ○ Too ill or cognitively impaired to participate based on clinicians' judgement<br>  ○ Anticipated life expectancy < 1 year<br>  ○ Unable or unwilling to adhere to study protocol<br>  ○ Participating in another clinical trial or taking an investigational drug<br>  ○ Scheduled for living donor kidney transplant within the next 6 months<br>  ○ Relocating to another dialysis unit within 6 months |
| Interventions | Intervention group<br>• CBT (TACcare or technology-delivered health education) for 12 weeks<br>Control group<br>• No intervention for 12 weeks<br>Co-interventions<br>• Not reported |
| Outcomes | Planned outcomes<br>• QoL<br>• Depression<br>  ○ PHQ-9: baseline and 12 weeks<br>  ○ BDI-II: baseline and 12 weeks<br>• Pain<br>  ○ 10-point VAS: baseline and 12 weeks<br>  ○ BPI Short form: baseline and 12 weeks<br>• Fatigue<br>  ○ 10-point VAS: baseline and 12 weeks<br>  ○ FACIT Fatigue: baseline and 12 weeks<br>• Inflammatory biomarker levels<br>• Adherence to fluid restriction: baseline, 3, 6 and 12 months<br>• Adherence to HD treatments: baseline, 3, 6 and 12 months |

**TACcare 2018** *(Continued)*

| | |
|---|---|
| | • Adherence to medications<br>  ○ MAQ Morisky Green Levine: baseline, 3, 6 and 12 months<br>• Adverse events |
| Starting date | February 2018 |
| Contact information | Manisha Jhamb<br>Phone: 412-647-7062<br>Email: jhambm@upmc.edu |
| Notes | Trial Registeration Numbrer: NCT03440853. Funding: University of Pittsburgh. Recruitment status: recruiting |

**van der Borg 2016**

| | |
|---|---|
| Study name | Protocol of a mixed method, randomized controlled study to assess the efficacy of a psychosocial intervention to reduce fatigue in patients with End-Stage Renal Disease (ESRD) |
| Methods | Study design<br>• RCT<br>• Duration of follow-up: 9 months |
| Participants | Study characteristics<br>• Country: the Netherlands<br>• Setting: not reported<br>• Inclusion criteria<br>  ○ Dialysis patients (either HD or PD at home, a hospital or a dialysis centre)<br>  ○ ≥ 18 years<br>  ○ Male or female experiencing (severe) fatigue (score CIS scale ≥ 35)<br>  ○ Being able to walk/move for at least 10 min with or without a supporting device such as a walking stick; having a sufficient understanding of the Dutch language in order to participate in counselling (group) interviews and fill out the questionnaires adequately<br>• Exclusion criteria<br>  ○ Dialysis during the night (since it is assumed that patients on day dialysis experience more severe fatigue compared to patients on night dialysis)<br>  ○ Participation in other studies or treatments aimed at reducing fatigue<br>  ○ Treatment by a psychologist or psychiatrist (for severe psychiatric problems such as depression, psychosis, personality disorders or schizophrenia)<br>  ○ Alcohol or drug addiction |
| Interventions | Intervention group<br>• Psychosocial counselling sessions led by a social worker (8 modules) + usual treatment<br>Control group<br>• Usual care<br>Co-interventions<br>• Not reported |
| Outcomes | Planned outcomes |

**van der Borg 2016** *(Continued)*

- Fatigue severity
  - CIS-fatigue questionnaire: assessed at baseline, post-intervention/16 weeks, and at 3 and 6-month follow-up
- Quality of life (kidney disease specific)
  - KDQOL: assessed at baseline, post-intervention/16 weeks, and at 3 and 6-month follow-up
    - Coping style
    - Illness cognitions/perceptions
    - Catastrophizing thoughts
    - Depression
    - Social support
    - Overall perceptions
- Implementation process
  - Interviews and focus groups (qualitative approach): assessed at baseline, post-intervention/16 weeks, and at 3 and 6-month follow-up
- Patients' and social workers' expectations and experiences
  - Interviews and focus groups (qualitative approach): assessed post-intervention
- Medical parameters: assessed at baseline, post-intervention/16 weeks, and at 3 and 6-month follow-up
- Adverse events: assessed post-intervention

| | |
|---|---|
| Starting date | Not reported. Trial was registered on August 2015 |
| Contact information | Wieke E. van der Borg<br>Phone: not reported<br>Email: not reported |
| Notes | The Netherlands National Trial Register (NTR): NTR5366. Funding: Dutch Kidney Foundation. Recruitment status: not reported |

**van der Veen 2021**

| | |
|---|---|
| Study name | A clinical approach of intradialytic creatine supplementation in dialysis-dependent CKD patients: a rationale and study design |
| Methods | Study design<br>• RCT<br>• Duration of follow-up: 6 weeks |
| Participants | Study characteristics<br>• Country: not reported<br>• Setting: not reported<br>• Inclusion criteria<br>  ○ ≥ 18 years<br>  ○ Undergoing maintenance HD<br>• Exclusion criteria<br>  ○ Not reported |
| Interventions | Intervention group 1<br>• Intradialytic creatine supplementation (0.5 mM)<br>Intervention group 2 |

**van der Veen 2021** *(Continued)*

| | |
|---|---|
| | • Intradialytic creatine supplementation (1.0 mM)<br>Intervention group 3<br>• Intradialytic creatine supplementation (1.5 mM)<br>Intervention group 4<br>• Intradialytic creatine supplementation (2.0 mM)<br>Placebo group<br>• Placebo<br>Co-interventions<br>• Not reported |
| Outcomes | Planned outcomes<br>• Plasma creatine concentration and intra-erythrocytic creatine concentration<br>• Handgrip strength<br>• Dialysate excretion of creatinine as a measure of muscle mass<br>• Body composition measured with bioelectrical impedance analysis |
| Starting date | Not reported |
| Contact information | Van Der Veen, Y.<br>Phone: not reported<br>Email: not reported |
| Notes | Trial Registeration Numbrer: not reported. Funding: not reported. Recruitment status: not reported |

6-minute walking test; AIDS: acquired immunodeficiency syndrome; ALP: alkaline phosphatase; BDI: Beck Depression Inventory; BFI: Brief Fatigue Inventory; BIA: Bioelectrical Impedance Analysis; BMI: body mass index; BP: blood pressure; BPI: Brief Pain Inventory; CBT: Cognitive-behavior therapy; CEQ: Credibility Expectancy Questionnaire; CFQ: Chalder Fatigue Questionnair; CIS: Checklist Individual Strength; CKD: chronic kidney disease; CRP: C-reactive protein; DBP: diastolic blood pressure; ESA: erythropoiesis stimulating agents; ESKD: end-stage kidney disease; FACIT: Functional Assessment of Chronic Illness Therapy; HADS: Hospital Anxiety and Depression Scale; Hb: haemoglobin; HCT: haematocrit; HDF: haemodiafiltration; HRQoL: health-related quality of life; IPAQ: International Physical Activity Questionnaire; KDQoL-SF: Kidney Disease and Quality of Life Short form; Kt/V: dialyser urea clearance adequacy; MAQ: Medication Adherence Questionnaire; PD: peritoneal dialysis; PHQ-9: Patient Health Questionnaire-9; PSQI: Pittsburgh Sleep Quality Index; PTH: parathyroid hormone; QoL: quality of life; RBC: red blood cells; RCT: randomised controlled trial; SBP: systolic blood pressure; SF-36: 36-Item Short Form Health Survey; SONG-HD: Standard Outcomes in Nephrology-Haemodialysis; TSAT: transferrin saturation; VAS: visual analogue scale

## DATA AND ANALYSES

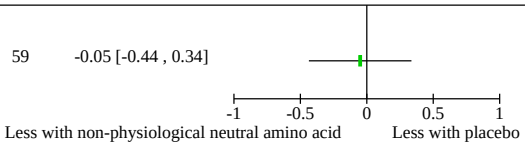
### Comparison 1. Non-physiological neutral amino acid versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.1 Fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 1.1.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.2 Change in fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 1.2.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 1.3 Number with improvement of fatigue | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.3.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.4 Number with aggravation of fatigue | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.4.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.5 Death (any cause) | 3 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 1.5.1 Haemodialysis | 3 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 1.6 Cardiovascular death | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 1.6.1 Haemodialysis | 2 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 1.7 Quality of life (overall) | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 1.7.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 1.8 Change in quality of life | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 1.8.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 1.9 Depresssion | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 1.9.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 1.10 Change in depression | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 1.10.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 1.11 Hypertension | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.11.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

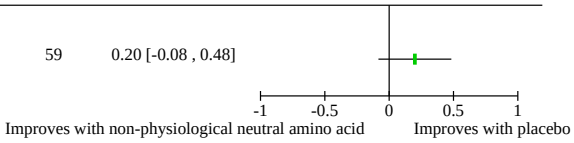
### Analysis 1.1. Comparison 1: Non-physiological neutral amino acid versus placebo, Outcome 1: Fatigue

| Study or Subgroup | Non-physiological neutral amino acid Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.1.1 Haemodialysis** | | | | | | | | |
| Brass 2001 | 5.09 | 1.28 | 121 | 5.14 | 1.22 | 59 | -0.05 [-0.44 , 0.34] | |



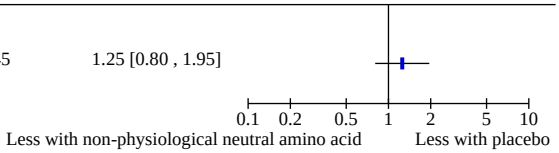

### Analysis 1.2. Comparison 1: Non-physiological neutral amino acid versus placebo, Outcome 2: Change in fatigue

| Study or Subgroup | Non-physiological neutral amino acid Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.2.1 Haemodialysis** | | | | | | | | |
| Brass 2001 | 0.44 | 0.95 | 121 | 0.24 | 0.89 | 59 | 0.20 [-0.08 , 0.48] | |



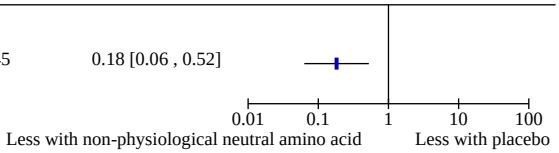

### Analysis 1.3. Comparison 1: Non-physiological neutral amino acid versus placebo, Outcome 3: Number with improvement of fatigue

| Study or Subgroup | Non-physiological neutral amino acid Events | Total | Placebo Events | Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.3.1 Haemodialysis** | | | | | | |
| Akizawa 2002 | 36 | 76 | 17 | 45 | 1.25 [0.80 , 1.95] | |



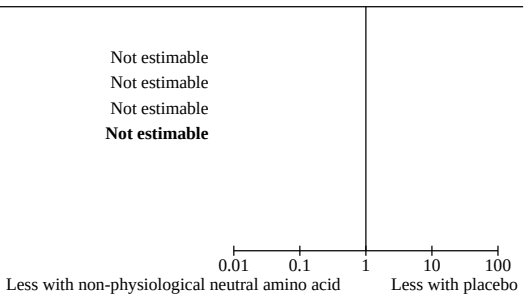

### Analysis 1.4. Comparison 1: Non-physiological neutral amino acid versus placebo, Outcome 4: Number with aggravation of fatigue

| Study or Subgroup | Non-physiological neutral amino acid Events | Total | Placebo Events | Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.4.1 Haemodialysis** | | | | | | |
| Akizawa 2002 | 4 | 76 | 13 | 45 | 0.18 [0.06 , 0.52] | |



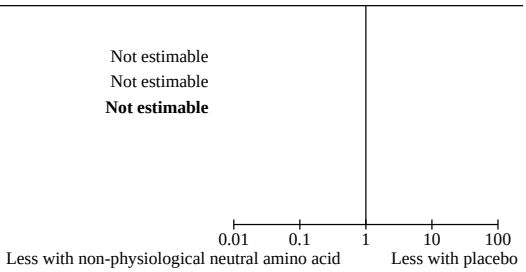
## Analysis 1.5. Comparison 1: Non-physiological neutral amino acid versus placebo, Outcome 5: Death (any cause)

| Study or Subgroup | Non-physiological neutral amino acid Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.5.1 Haemodialysis** | | | | | | |
| Bellinghieri 1983 | 0 | 7 | 0 | 7 | | Not estimable |
| Brass 2001 | 0 | 130 | 0 | 63 | | Not estimable |
| Akizawa 2002 | 0 | 100 | 0 | 49 | | Not estimable |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



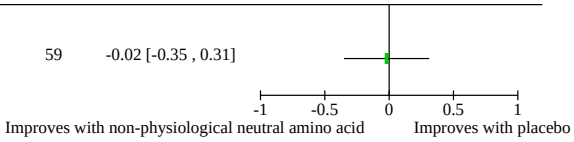

## Analysis 1.6. Comparison 1: Non-physiological neutral amino acid versus placebo, Outcome 6: Cardiovascular death

| Study or Subgroup | Non-physiological neutral amino acid Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.6.1 Haemodialysis** | | | | | | |
| Bellinghieri 1983 | 0 | 7 | 0 | 7 | | Not estimable |
| Akizawa 2002 | 0 | 100 | 0 | 49 | | Not estimable |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



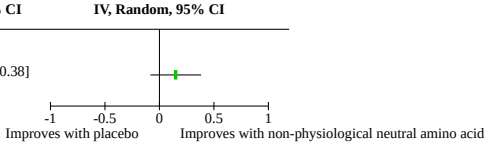

## Analysis 1.7. Comparison 1: Non-physiological neutral amino acid versus placebo, Outcome 7: Quality of life (overall)

| Study or Subgroup | Non-physiological neutral amino acid Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **1.7.1 Haemodialysis** | | | | | | | |
| Brass 2001 | 5.27 | 1.03 | 121 | 5.29 | 1.08 | 59 | -0.02 [-0.35 , 0.31] |

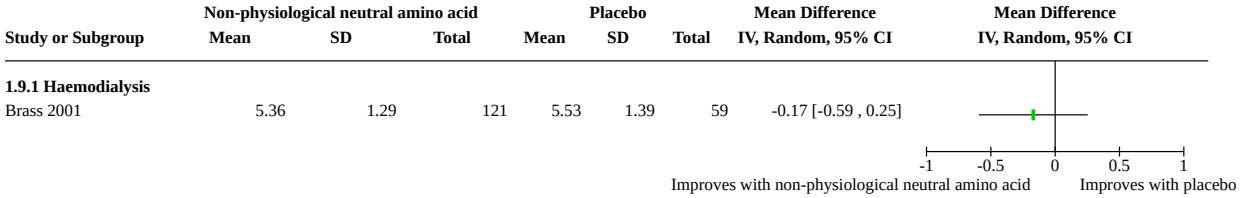



## Analysis 1.8. Comparison 1: Non-physiological neutral amino acid versus placebo, Outcome 8: Change in quality of life

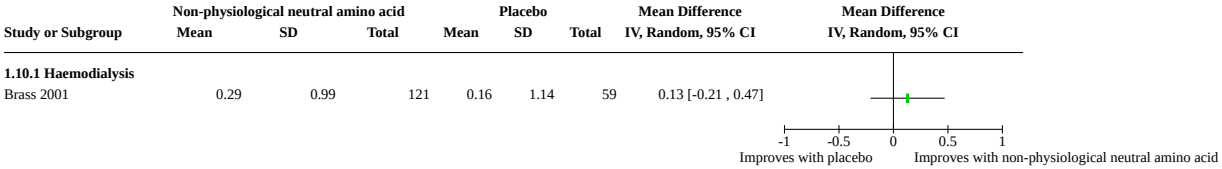
| Study or Subgroup | Non-physiological neutral amino acid Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **1.8.1 Haemodialysis** | | | | | | | |
| Brass 2001 | 0.44 | 0.76 | 121 | 0.29 | 0.74 | 59 | 0.15 [-0.08 , 0.38] |



### Analysis 1.9. Comparison 1: Non-physiological neutral amino acid versus placebo, Outcome 9: Depresssion




### Analysis 1.10. Comparison 1: Non-physiological neutral amino acid versus placebo, Outcome 10: Change in depression



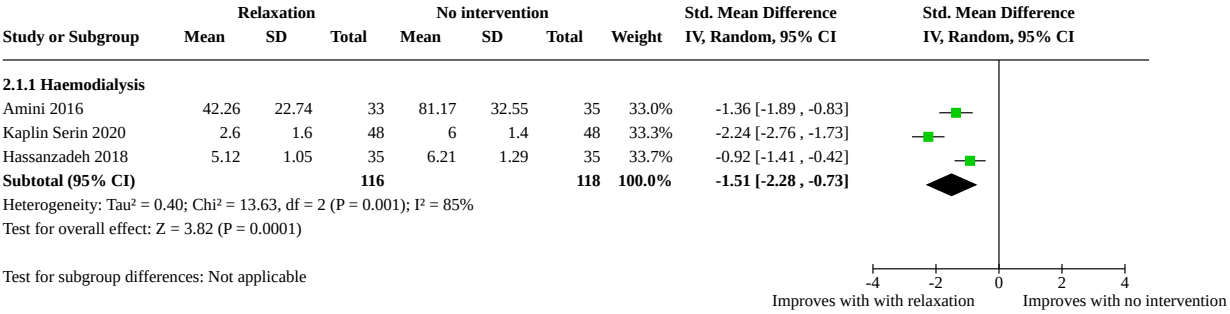

### Analysis 1.11. Comparison 1: Non-physiological neutral amino acid versus placebo, Outcome 11: Hypertension


## Comparison 2. Relaxation versus no intervention

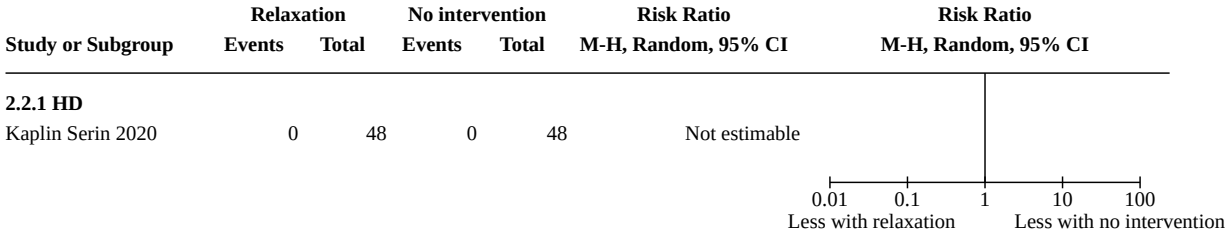
| Outcome or sub-group title | No. of studies | No. of partici-pants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.1 Fatigue | 3 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 2.1.1 Haemodialysis | 3 | 234 | Std. Mean Difference (IV, Random, 95% CI) | -1.51 [-2.28, -0.73] |
| 2.2 Death (any cause) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2.2.1 HD | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2.3 Cardiovascular death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2.3.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2.4 Anxiety | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 2.4.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

| Outcome or sub-group title | No. of studies | No. of partici-pants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.5 Sleep quality | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 2.5.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

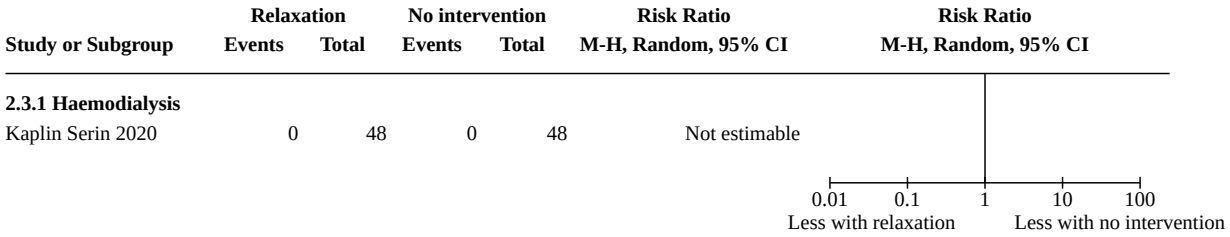
### Analysis 2.1. Comparison 2: Relaxation versus no intervention, Outcome 1: Fatigue



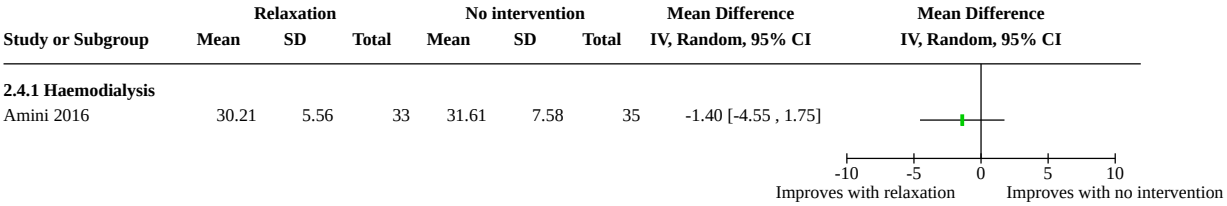

### Analysis 2.2. Comparison 2: Relaxation versus no intervention, Outcome 2: Death (any cause)



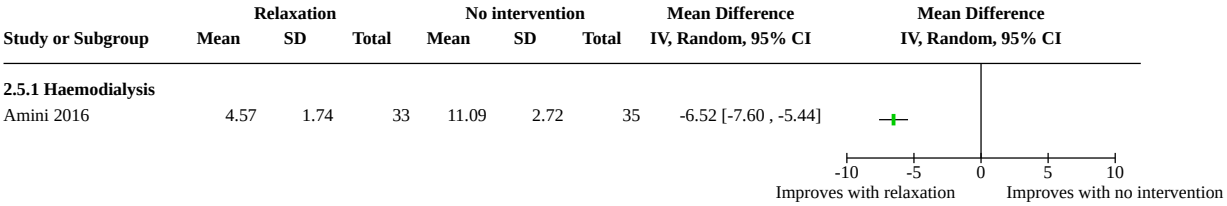

### Analysis 2.3. Comparison 2: Relaxation versus no intervention, Outcome 3: Cardiovascular death



### Analysis 2.4. Comparison 2: Relaxation versus no intervention, Outcome 4: Anxiety



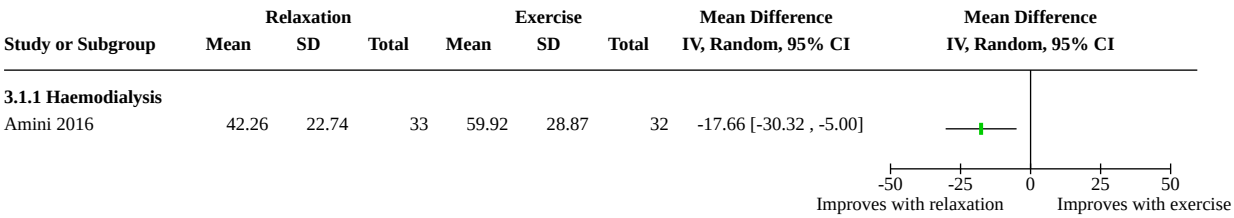

### Analysis 2.5. Comparison 2: Relaxation versus no intervention, Outcome 5: Sleep quality




## Comparison 3. Relaxation versus exercise

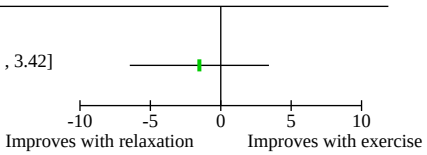
| Outcome or sub-group title | No. of studies | No. of partici-pants | Statistical method | Effect size |
|---|---|---|---|---|
| 3.1 Fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 3.1.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 3.2 Anxiety | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 3.2.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 3.3 Sleep quality | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 3.3.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

### Analysis 3.1. Comparison 3: Relaxation versus exercise, Outcome 1: Fatigue



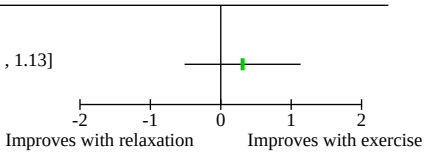
### Analysis 3.2. Comparison 3: Relaxation versus exercise, Outcome 2: Anxiety

| Study or Subgroup | Relaxation Mean | Relaxation SD | Relaxation Total | Exercise Mean | Exercise SD | Exercise Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **3.2.1 Haemodialysis** | | | | | | | |
| Amini 2016 | 30.21 | 5.56 | 33 | 31.73 | 13.17 | 32 | -1.52 [-6.46 , 3.42] |




### Analysis 3.3. Comparison 3: Relaxation versus exercise, Outcome 3: Sleep quality

| Study or Subgroup | Relaxation Mean | Relaxation SD | Relaxation Total | Exercise Mean | Exercise SD | Exercise Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **3.3.1 Haemodialysis** | | | | | | | |
| Amini 2016 | 4.57 | 1.74 | 33 | 4.26 | 1.65 | 32 | 0.31 [-0.51 , 1.13] |

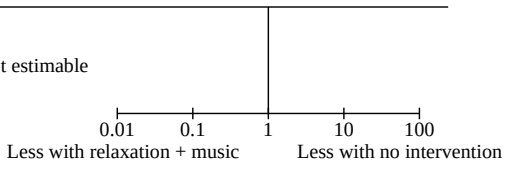



## Comparison 4. Relaxation + music versus no intervention

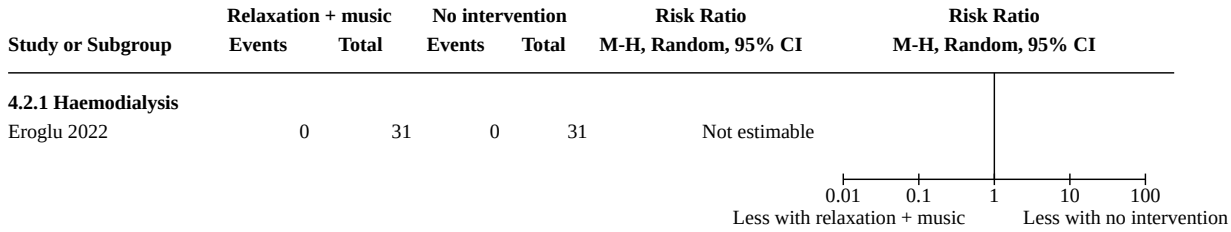
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 4.1 Death (any cause) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 4.1.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 4.2 Cardiovascular death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 4.2.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

### Analysis 4.1. Comparison 4: Relaxation + music versus no intervention, Outcome 1: Death (any cause)

| Study or Subgroup | Relaxation + music Events | Relaxation + music Total | No intervention Events | No intervention Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **4.1.1 Haemodialysis** | | | | | |
| Eroglu 2022 | 0 | 31 | 0 | 31 | Not estimable |



### Analysis 4.2. Comparison 4: Relaxation + music versus no intervention, Outcome 2: Cardiovascular death

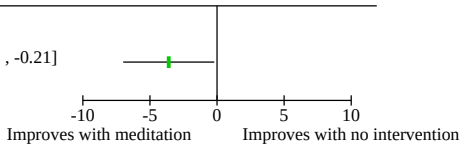



## Comparison 5. Meditation versus no intervention

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 5.1 Fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 5.1.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 5.2 Death (any cause) | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 5.2.1 Haemodialysis | 2 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 5.3 Cardiovascular death | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 5.3.1 Haemodialysis | 2 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 5.4 Depression | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 5.4.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 5.5 Change in depression | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 5.5.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 5.6 Anxiety | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 5.6.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 5.7 Change in anxiety | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 5.7.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 5.8 Sleep disturbance | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 5.8.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

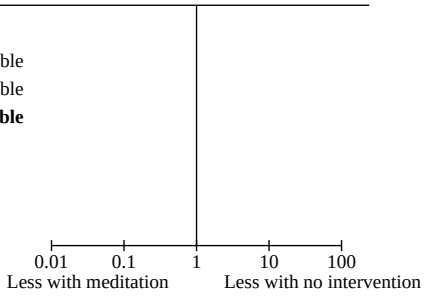
### Analysis 5.1. Comparison 5: Meditation versus no intervention, Outcome 1: Fatigue

| Study or Subgroup | Meditation Mean | SD | Total | No intervention Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **5.1.1 Haemodialysis** | | | | | | | |
| Yurtkuran 2007 | 3.3 | 1.5 | 19 | 6.9 | 7.2 | 18 | -3.60 [-6.99 , -0.21] |



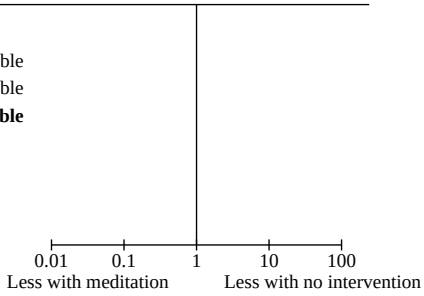

### Analysis 5.2. Comparison 5: Meditation versus no intervention, Outcome 2: Death (any cause)

| Study or Subgroup | Meditation Events | Total | No intervention Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **5.2.1 Haemodialysis** | | | | | | |
| Thomas 2017 | 0 | 21 | 0 | 20 | | Not estimable |
| Yurtkuran 2007 | 0 | 20 | 0 | 20 | | Not estimable |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



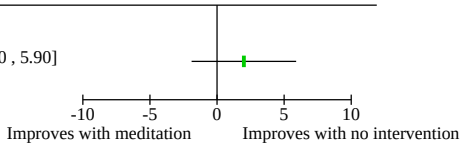

### Analysis 5.3. Comparison 5: Meditation versus no intervention, Outcome 3: Cardiovascular death

| Study or Subgroup | Meditation Events | Total | No intervention Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **5.3.1 Haemodialysis** | | | | | | |
| Thomas 2017 | 0 | 21 | 0 | 20 | | Not estimable |
| Yurtkuran 2007 | 0 | 20 | 0 | 20 | | Not estimable |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



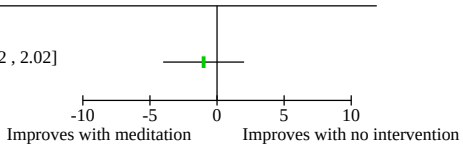

### Analysis 5.4. Comparison 5: Meditation versus no intervention, Outcome 4: Depression

| Study or Subgroup | Meditation Mean | SD | Total | No intervention Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **5.4.1 Haemodialysis** | | | | | | | |
| Thomas 2017 | 10.3 | 5 | 17 | 8.3 | 6.1 | 15 | 2.00 [-1.90 , 5.90] |



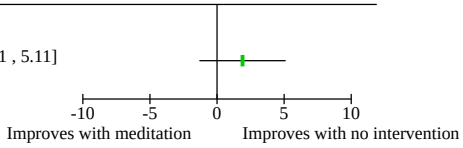
### Analysis 5.5. Comparison 5: Meditation versus no intervention, Outcome 5: Change in depression

| Study or Subgroup | Meditation Mean | Meditation SD | Meditation Total | No intervention Mean | No intervention SD | No intervention Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **5.5.1 Haemodialysis** | | | | | | | | |
| Thomas 2017 | -3 | 3.9 | 17 | -2 | 4.7 | 15 | -1.00 [-4.02 , 2.02] | |



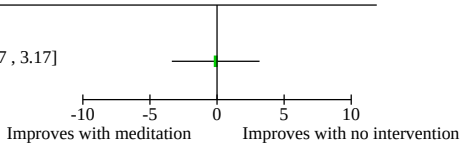

### Analysis 5.6. Comparison 5: Meditation versus no intervention, Outcome 6: Anxiety

| Study or Subgroup | Meditation Mean | Meditation SD | Meditation Total | No intervention Mean | No intervention SD | No intervention Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **5.6.1 Haemodialysis** | | | | | | | | |
| Thomas 2017 | 6 | 4.3 | 17 | 4.1 | 4.9 | 15 | 1.90 [-1.31 , 5.11] | |



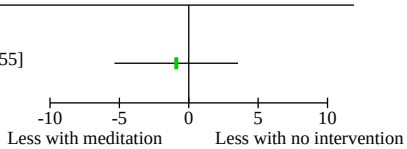

### Analysis 5.7. Comparison 5: Meditation versus no intervention, Outcome 7: Change in anxiety

| Study or Subgroup | Meditation Mean | Meditation SD | Meditation Total | No intervention Mean | No intervention SD | No intervention Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **5.7.1 Haemodialysis** | | | | | | | | |
| Thomas 2017 | -0.9 | 4.6 | 17 | -0.8 | 4.8 | 15 | -0.10 [-3.37 , 3.17] | |




### Analysis 5.8. Comparison 5: Meditation versus no intervention, Outcome 8: Sleep disturbance

| Study or Subgroup | Meditation Mean | Meditation SD | Meditation Total | No intervention Mean | No intervention SD | No intervention Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **5.8.1 Haemodialysis** | | | | | | | | |
| Yurtkuran 2007 | 3.4 | 5.2 | 19 | 4.3 | 8.2 | 18 | -0.90 [-5.35 , 3.55] | |



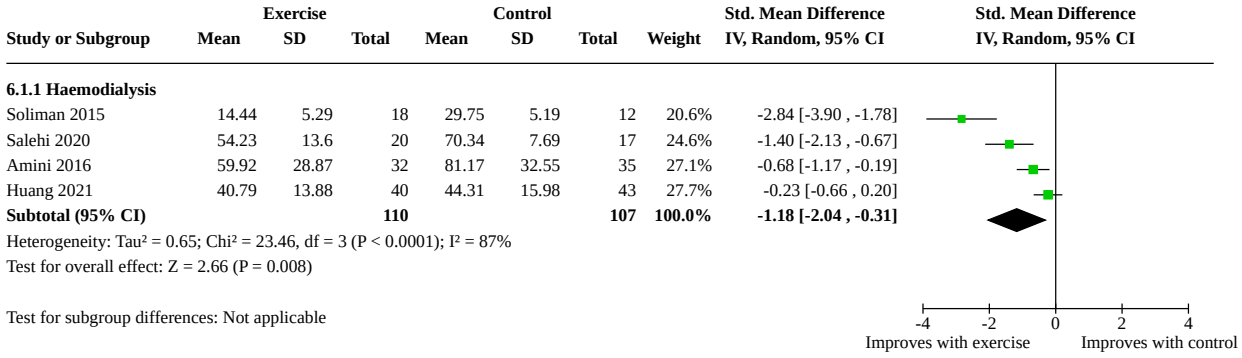

## Comparison 6. Exercise versus control

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 6.1 Fatigue | 4 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 6.1.1 Haemodialysis | 4 | 217 | Std. Mean Difference (IV, Random, 95% CI) | -1.18 [-2.04, -0.31] |

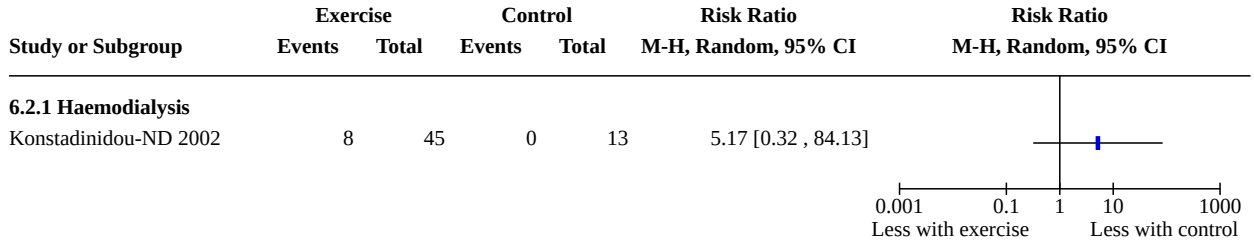
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 6.2 Number reporting fatigue | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 6.2.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 6.3 Change in fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 6.3.1 HD | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 6.4 General fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 6.4.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 6.5 Physical fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 6.5.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 6.6 Mental fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 6.6.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 6.7 Number with moderate fatigue | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 6.7.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 6.8 Number with severe fatigue | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 6.8.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 6.9 Vitality | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 6.9.1 HD | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 6.10 Energy/fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 6.10.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 6.11 Death (any cause) | 8 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 6.11.1 Haemodialysis | 8 | 739 | Risk Ratio (M-H, Random, 95% CI) | 0.87 [0.43, 1.76] |
| 6.12 Cardiovascular death | 5 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 6.12.1 Haemodialysis | 5 | 587 | Risk Ratio (M-H, Random, 95% CI) | 0.61 [0.10, 3.62] |
| 6.13 Quality of life (overall) | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 6.13.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 6.14 General health | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 6.14.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 6.15 Anxiety | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 6.15.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 6.16 Cardiovascular events | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 6.16.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

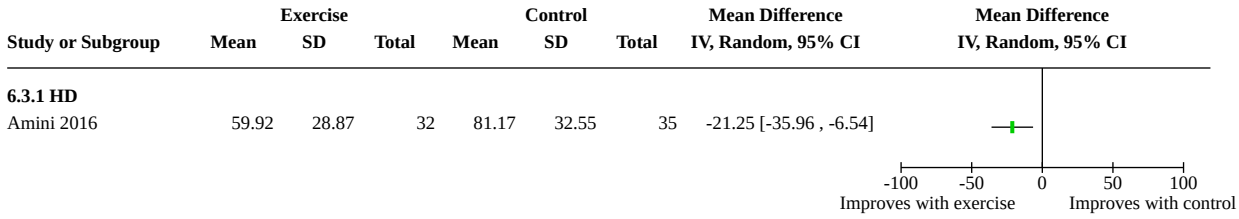
## Analysis 6.1. Comparison 6: Exercise versus control, Outcome 1: Fatigue




## Analysis 6.2. Comparison 6: Exercise versus control, Outcome 2: Number reporting fatigue

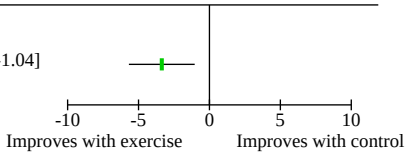



## Analysis 6.3. Comparison 6: Exercise versus control, Outcome 3: Change in fatigue



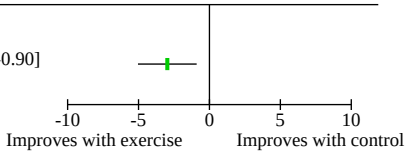
### Analysis 6.4. Comparison 6: Exercise versus control, Outcome 4: General fatigue

| Study or Subgroup | Exercise Mean | Exercise SD | Exercise Total | Control Mean | Control SD | Control Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **6.4.1 Haemodialysis** | | | | | | | | |
| Salehi 2020 | 10.83 | 4.38 | 20 | 14.19 | 2.74 | 17 | -3.36 [-5.68 , -1.04] | |



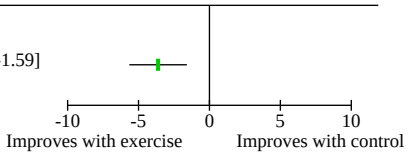

### Analysis 6.5. Comparison 6: Exercise versus control, Outcome 5: Physical fatigue

| Study or Subgroup | Exercise Mean | Exercise SD | Exercise Total | Control Mean | Control SD | Control Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **6.5.1 Haemodialysis** | | | | | | | | |
| Salehi 2020 | 12.78 | 4.22 | 20 | 15.75 | 1.95 | 17 | -2.97 [-5.04 , -0.90] | |



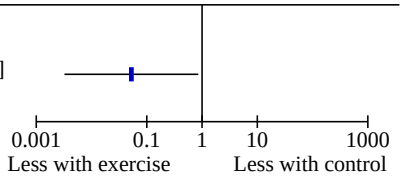

### Analysis 6.6. Comparison 6: Exercise versus control, Outcome 6: Mental fatigue

| Study or Subgroup | Exercise Mean | Exercise SD | Exercise Total | Control Mean | Control SD | Control Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **6.6.1 Haemodialysis** | | | | | | | | |
| Salehi 2020 | 8.44 | 2.28 | 20 | 12.06 | 3.71 | 17 | -3.62 [-5.65 , -1.59] | |



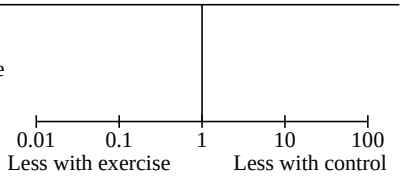

### Analysis 6.7. Comparison 6: Exercise versus control, Outcome 7: Number with moderate fatigue

| Study or Subgroup | Exercise Events | Exercise Total | Control Events | Control Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **6.7.1 Haemodialysis** | | | | | | |
| Soliman 2015 | 0 | 18 | 6 | 12 | 0.05 [0.00 , 0.86] | |



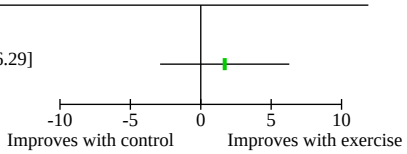
### Analysis 6.8. Comparison 6: Exercise versus control, Outcome 8: Number with severe fatigue

| Study or Subgroup | Exercise Events | Exercise Total | Control Events | Control Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **6.8.1 Haemodialysis** | | | | | |
| Soliman 2015 | 0 | 18 | 0 | 12 | Not estimable |



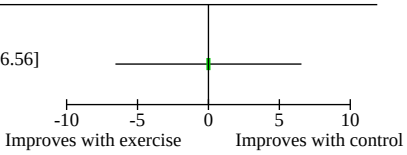

### Analysis 6.9. Comparison 6: Exercise versus control, Outcome 9: Vitality

| Study or Subgroup | Exercise Mean | Exercise SD | Exercise Total | Control Mean | Control SD | Control Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **6.9.1 HD** | | | | | | | |
| Suzuki 2018 | 53.1 | 5.5 | 13 | 51.4 | 6.4 | 13 | 1.70 [-2.89 , 6.29] |




### Analysis 6.10. Comparison 6: Exercise versus control, Outcome 10: Energy/fatigue

| Study or Subgroup | Exercise Mean | Exercise SD | Exercise Total | Control Mean | Control SD | Control Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **6.10.1 Haemodialysis** | | | | | | | |
| PEDAL 2020 | 41.4 | 26.4 | 114 | 41.4 | 24.9 | 122 | 0.00 [-6.56 , 6.56] |



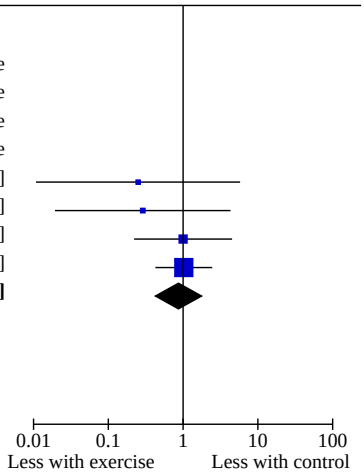

### Analysis 6.11. Comparison 6: Exercise versus control, Outcome 11: Death (any cause)

| Study or Subgroup | Exercise Events | Exercise Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **6.11.1 Haemodialysis** | | | | | | |
| Krase 2022 | 0 | 24 | 0 | 24 | | Not estimable |
| Chang 2010 | 0 | 44 | 0 | 46 | | Not estimable |
| Huang 2021 | 0 | 43 | 0 | 43 | | Not estimable |
| Suzuki 2018 | 0 | 15 | 0 | 14 | | Not estimable |
| Soliman 2015 | 0 | 23 | 1 | 17 | 5.1% | 0.25 [0.01 , 5.79] |
| Konstadinidou-ND 2002 | 1 | 45 | 1 | 13 | 6.9% | 0.29 [0.02 , 4.31] |
| Salehi 2020 | 3 | 27 | 3 | 27 | 22.1% | 1.00 [0.22 , 4.52] |
| PEDAL 2020 | 10 | 174 | 9 | 160 | 65.9% | 1.02 [0.43 , 2.45] |
| **Subtotal (95% CI)** | | **395** | | **344** | **100.0%** | **0.87 [0.43 , 1.76]** |
| Total events: | 14 | | 14 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 1.41, df = 3 (P = 0.70); I² = 0%

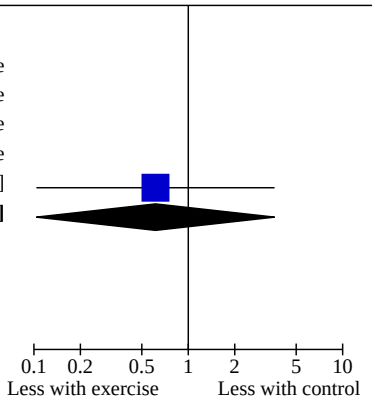
Test for overall effect: Z = 0.39 (P = 0.69)

Test for subgroup differences: Not applicable



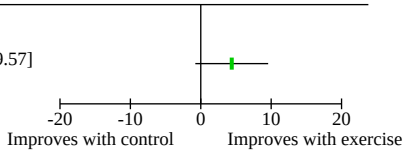
### Analysis 6.12. Comparison 6: Exercise versus control, Outcome 12: Cardiovascular death

| Study or Subgroup | Exercise Events | Exercise Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **6.12.1 Haemodialysis** | | | | | | |
| Krase 2022 | 0 | 24 | 0 | 24 | | Not estimable |
| Chang 2010 | 0 | 44 | 0 | 46 | | Not estimable |
| Huang 2021 | 0 | 43 | 0 | 43 | | Not estimable |
| Suzuki 2018 | 0 | 15 | 0 | 14 | | Not estimable |
| PEDAL 2020 | 2 | 174 | 3 | 160 | 100.0% | 0.61 [0.10 , 3.62] |
| **Subtotal (95% CI)** | | **300** | | **287** | **100.0%** | **0.61 [0.10 , 3.62]** |
| Total events: | 2 | | 3 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.54 (P = 0.59) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



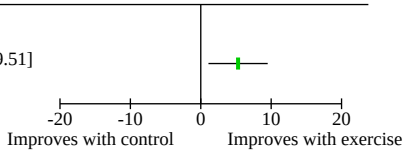

### Analysis 6.13. Comparison 6: Exercise versus control, Outcome 13: Quality of life (overall)

| Study or Subgroup | Exercise Mean | Exercise SD | Exercise Total | Control Mean | Control SD | Control Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **6.13.1 Haemodialysis** | | | | | | | |
| PEDAL 2020 | 63.7 | 19.3 | 111 | 59.3 | 20.9 | 121 | 4.40 [-0.77 , 9.57] |



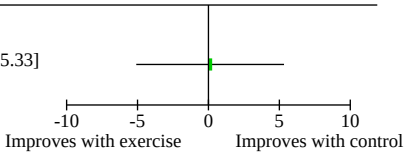

### Analysis 6.14. Comparison 6: Exercise versus control, Outcome 14: General health

| Study or Subgroup | Exercise Mean | Exercise SD | Exercise Total | Control Mean | Control SD | Control Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **6.14.1 Haemodialysis** | | | | | | | |
| Suzuki 2018 | 53.5 | 4.2 | 13 | 48.2 | 6.5 | 13 | 5.30 [1.09 , 9.51] |



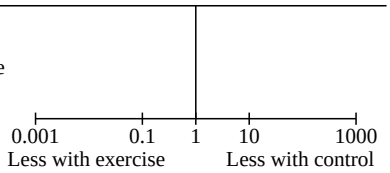

### Analysis 6.15. Comparison 6: Exercise versus control, Outcome 15: Anxiety

| Study or Subgroup | Exercise Mean | Exercise SD | Exercise Total | Control Mean | Control SD | Control Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **6.15.1 Haemodialysis** | | | | | | | |
| Amini 2016 | 31.73 | 13.17 | 32 | 31.61 | 7.58 | 35 | 0.12 [-5.09 , 5.33] |



### Analysis 6.16. Comparison 6: Exercise versus control, Outcome 16: Cardiovascular events

| Study or Subgroup | Exercise Events | Exercise Total | Control Events | Control Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **6.16.1 Haemodialysis** | | | | | |
| Konstadinidou-ND 2002 | 0 | 45 | 0 | 13 | Not estimable |

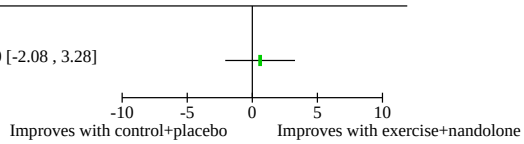



## Comparison 7. Exercise with nandrolone versus control with nandrolone placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 7.1 Fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 7.1.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 7.2 Change in fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 7.2.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 7.3 Death (any cause) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 7.3.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

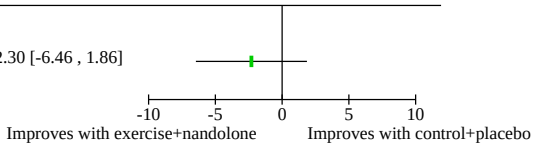
### Analysis 7.1. Comparison 7: Exercise with nandrolone versus control with nandrolone placebo, Outcome 1: Fatigue

| Study or Subgroup | Exercise+nandolone Mean | SD | Total | Control+placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **7.1.1 Haemodialysis** | | | | | | | |
| Johansen 2006 | 7.8 | 4.2 | 19 | 7.2 | 4 | 17 | 0.60 [-2.08 , 3.28] |

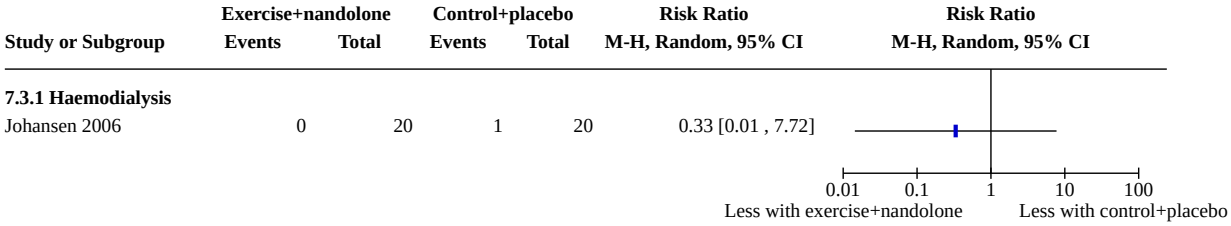



### Analysis 7.2. Comparison 7: Exercise with nandrolone versus control with nandrolone placebo, Outcome 2: Change in fatigue

| Study or Subgroup | Exercise+nandolone Mean | SD | Total | Control+placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **7.2.1 Haemodialysis** | | | | | | | |
| Johansen 2006 | -3.2 | 5.4 | 19 | -0.9 | 7.1 | 17 | -2.30 [-6.46 , 1.86] |



### Analysis 7.3. Comparison 7: Exercise with nandrolone versus control with nandrolone placebo, Outcome 3: Death (any cause)




## Comparison 8. Exercise (inspiratory muscle training) versus exercise (aerobic training)

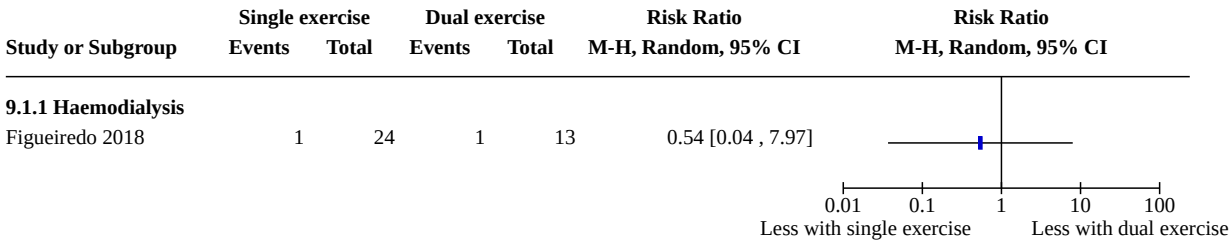
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 8.1 Death (any cause) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 8.1.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

### Analysis 8.1. Comparison 8: Exercise (inspiratory muscle training) versus exercise (aerobic training), Outcome 1: Death (any cause)


## Comparison 9. Single versus combined exercise

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 9.1 Death (any cause) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 9.1.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

**Analysis 9.1. Comparison 9: Single versus combined exercise, Outcome 1: Death (any cause)**

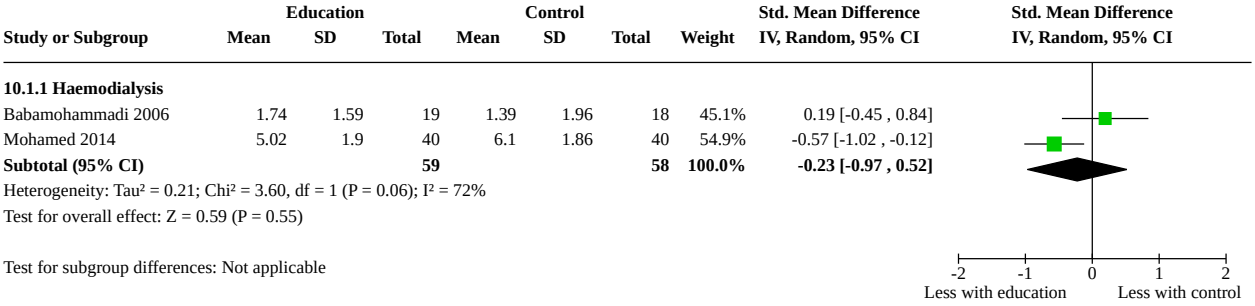



## Comparison 10. Education versus control

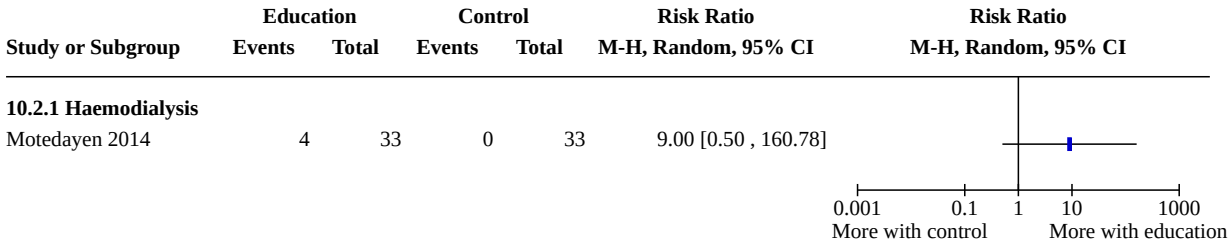
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 10.1 Fatigue | 2 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 10.1.1 Haemodialysis | 2 | 117 | Std. Mean Difference (IV, Random, 95% CI) | -0.23 [-0.97, 0.52] |
| 10.2 Remission of fatigue symptoms | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 10.2.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 10.3 Medium fatigue symptoms | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 10.3.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 10.4 Severe fatigue symptoms | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 10.4.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 10.5 Weakness | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 10.5.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 10.6 Energy/fatigue | 2 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 10.6.1 Peritoneal dialysis | 2 | 220 | Mean Difference (IV, Random, 95% CI) | 4.50 [-0.55, 9.54] |
| 10.7 Death (any cause) | 5 | 314 | Risk Ratio (M-H, Random, 95% CI) | 0.94 [0.25, 3.57] |
| 10.7.1 Peritoneal dialysis | 1 | 100 | Risk Ratio (M-H, Random, 95% CI) | 3.00 [0.13, 71.92] |
| 10.7.2 Haemodialysis | 4 | 214 | Risk Ratio (M-H, Random, 95% CI) | 0.61 [0.08, 4.74] |
| 10.8 Cardiovascular death | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 10.8.1 Haemodialysis | 2 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 10.9 Quality of life (overall) | 2 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 10.9.1 Peritoneal dialysis | 2 | 220 | Mean Difference (IV, Random, 95% CI) | 1.86 [-2.96, 6.69] |
| 10.10 Sleep (overall) | 2 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 10.10.1 Peritoneal dialysis | 2 | 220 | Mean Difference (IV, Random, 95% CI) | 7.46 [2.04, 12.87] |

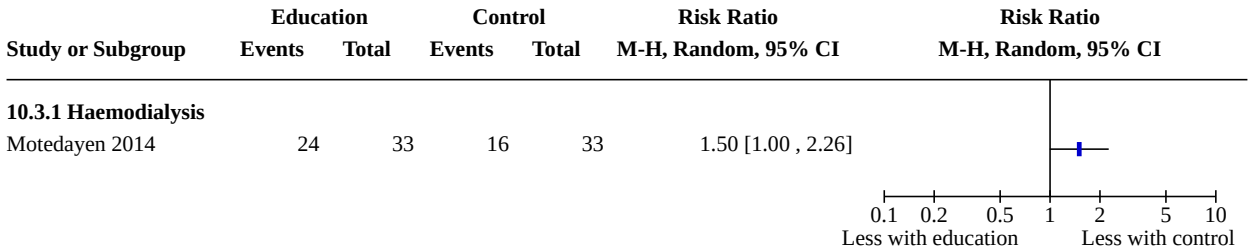
### Analysis 10.1. Comparison 10: Education versus control, Outcome 1: Fatigue




### Analysis 10.2. Comparison 10: Education versus control, Outcome 2: Remission of fatigue symptoms

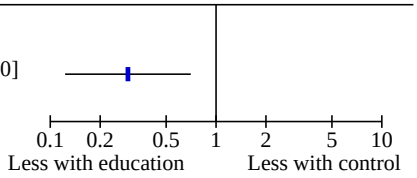



### Analysis 10.3. Comparison 10: Education versus control, Outcome 3: Medium fatigue symptoms



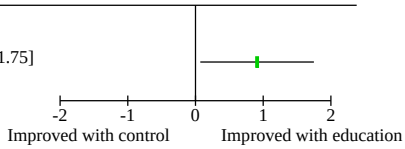
## Analysis 10.4. Comparison 10: Education versus control, Outcome 4: Severe fatigue symptoms

| Study or Subgroup | Education Events | Education Total | Control Events | Control Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **10.4.1 Haemodialysis** | | | | | |
| Motedayen 2014 | 5 | 33 | 17 | 33 | 0.29 [0.12 , 0.70] |



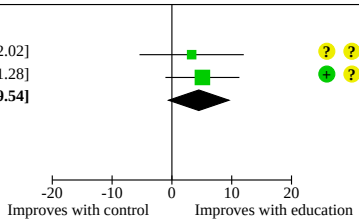

## Analysis 10.5. Comparison 10: Education versus control, Outcome 5: Weakness

| Study or Subgroup | Education Mean | Education SD | Education Total | Control Mean | Control SD | Control Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **10.5.1 Haemodialysis** | | | | | | | |
| Babamohammadi 2006 | 1.58 | 1.5 | 19 | 0.67 | 1.08 | 18 | 0.91 [0.07 , 1.75] |




## Analysis 10.6. Comparison 10: Education versus control, Outcome 6: Energy/fatigue

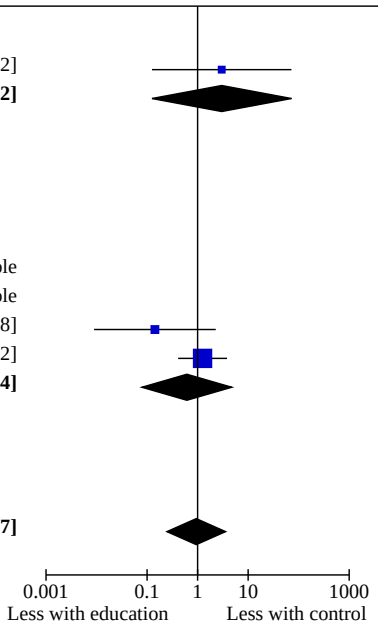
| Study or Subgroup | Education Mean | Education SD | Education Total | Control Mean | Control SD | Control Total | Weight | Mean Difference IV, Random, 95% CI | Risk of Bias A B C D E F G |
|---|---|---|---|---|---|---|---|---|---|
| **10.6.1 Peritoneal dialysis** | | | | | | | | | |
| Chow 2010 | 43.7 | 18.6 | 43 | 40.4 | 22.2 | 42 | 33.5% | 3.30 [-5.42 , 12.02] | ? ? − − − − + |
| Li 2014b | 48.4 | 17.7 | 69 | 43.3 | 18.9 | 66 | 66.5% | 5.10 [-1.08 , 11.28] | + ? − − − − + |
| **Subtotal (95% CI)** | | | **112** | | | **108** | **100.0%** | **4.50 [-0.55 , 9.54]** | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0% | | | | | | | | | |
| Test for overall effect: Z = 1.75 (P = 0.08) | | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | | |




**Risk of bias legend**
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

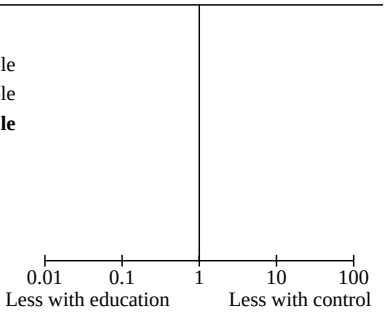
## Analysis 10.7. Comparison 10: Education versus control, Outcome 7: Death (any cause)

| Study or Subgroup | Education Events | Education Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **10.7.1 Peritoneal dialysis** | | | | | | |
| Chow 2010 | 1 | 50 | 0 | 50 | 15.4% | 3.00 [0.13 , 71.92] |
| **Subtotal (95% CI)** | | **50** | | **50** | **15.4%** | **3.00 [0.13 , 71.92]** |
| Total events: | 1 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.68 (P = 0.50) | | | | | | |
| **10.7.2 Haemodialysis** | | | | | | |
| Mohamed 2014 | 0 | 40 | 0 | 40 | | Not estimable |
| Fatigue-HD 2019 | 0 | 15 | 0 | 15 | | Not estimable |
| SOCIABLE 2017 | 0 | 6 | 3 | 6 | 19.4% | 0.14 [0.01 , 2.28] |
| Dashti-Khavidaki 2013 | 6 | 45 | 5 | 47 | 65.2% | 1.25 [0.41 , 3.82] |
| **Subtotal (95% CI)** | | **106** | | **108** | **84.6%** | **0.61 [0.08 , 4.74]** |
| Total events: | 6 | | 8 | | | |
| Heterogeneity: Tau² = 1.30; Chi² = 2.12, df = 1 (P = 0.15); I² = 53% | | | | | | |
| Test for overall effect: Z = 0.47 (P = 0.64) | | | | | | |
| **Total (95% CI)** | | **156** | | **158** | **100.0%** | **0.94 [0.25 , 3.57]** |
| Total events: | 7 | | 8 | | | |
| Heterogeneity: Tau² = 0.39; Chi² = 2.57, df = 2 (P = 0.28); I² = 22% | | | | | | |
| Test for overall effect: Z = 0.09 (P = 0.93) | | | | | | |
| Test for subgroup differences: Chi² = 0.68, df = 1 (P = 0.41), I² = 0% | | | | | | |



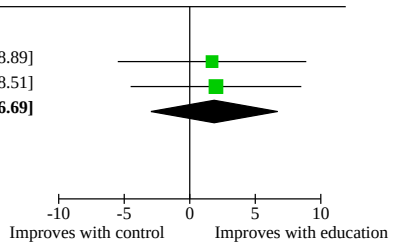

## Analysis 10.8. Comparison 10: Education versus control, Outcome 8: Cardiovascular death

| Study or Subgroup | Education Events | Education Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **10.8.1 Haemodialysis** | | | | | | |
| Mohamed 2014 | 0 | 40 | 0 | 40 | | Not estimable |
| Fatigue-HD 2019 | 0 | 15 | 0 | 15 | | Not estimable |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |

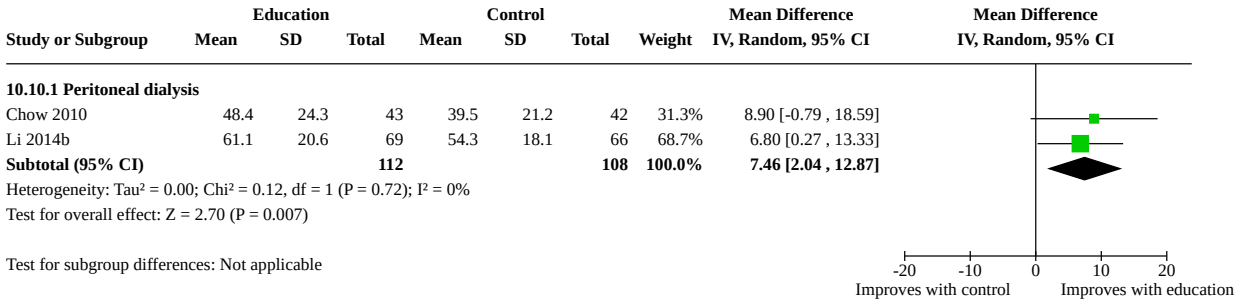



## Analysis 10.9. Comparison 10: Education versus control, Outcome 9: Quality of life (overall)

| Study or Subgroup | Education Mean | Education SD | Education Total | Control Mean | Control SD | Control Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **10.9.1 Peritoneal dialysis** | | | | | | | | |
| Chow 2010 | 45.8 | 19.6 | 43 | 44.1 | 13.8 | 42 | 45.0% | 1.70 [-5.49 , 8.89] |
| Li 2014b | 49.2 | 19.4 | 69 | 47.2 | 19.2 | 66 | 55.0% | 2.00 [-4.51 , 8.51] |
| **Subtotal (95% CI)** | | | **112** | | | **108** | **100.0%** | **1.86 [-2.96 , 6.69]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 0.76 (P = 0.45) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |



### Analysis 10.10. Comparison 10: Education versus control, Outcome 10: Sleep (overall)

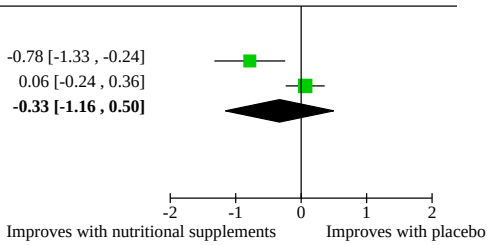



## Comparison 11. Nutritional supplements versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 11.1 Fatigue | 2 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 11.1.1 Haemodialysis | 2 | 230 | Std. Mean Difference (IV, Random, 95% CI) | -0.33 [-1.16, 0.50] |
| 11.2 Vitality | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 11.2.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 11.3 General health | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 11.3.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 11.4 Death (any cause) | 1 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 11.4.1 Haemodialysis | 1 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 11.4.2 Peritoneal dialysis | 1 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 11.5 Cardiovascular death | 1 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 11.5.1 Haemodialysis | 1 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 11.5.2 Peritoneal dialysis | 1 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 11.6 Sleep problems | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 11.6.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

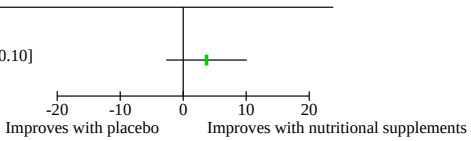
## Analysis 11.1. Comparison 11: Nutritional supplements versus placebo, Outcome 1: Fatigue

| Study or Subgroup | Nutritional supplements Mean | SD | Total | Placebo Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **11.1.1 Haemodialysis** | | | | | | | | |
| Biniaz 2015 | 49.8 | 13.5 | 30 | 61.6 | 16.2 | 27 | 46.3% | -0.78 [-1.33 , -0.24] |
| Fukuda 2015 | 5.59 | 4.56 | 87 | 5.31 | 4.52 | 86 | 53.7% | 0.06 [-0.24 , 0.36] |
| **Subtotal (95% CI)** | | | **117** | | | **113** | **100.0%** | **-0.33 [-1.16 , 0.50]** |
| Heterogeneity: Tau² = 0.31; Chi² = 7.20, df = 1 (P = 0.007); I² = 86% | | | | | | | | |
| Test for overall effect: Z = 0.78 (P = 0.43) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |



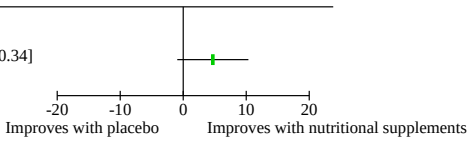

## Analysis 11.2. Comparison 11: Nutritional supplements versus placebo, Outcome 2: Vitality

| Study or Subgroup | Nutritional supplements Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **11.2.1 Haemodialysis** | | | | | | | |
| Fukuda 2015 | 62.2 | 22.4 | 87 | 58.5 | 20.5 | 86 | 3.70 [-2.70 , 10.10] |



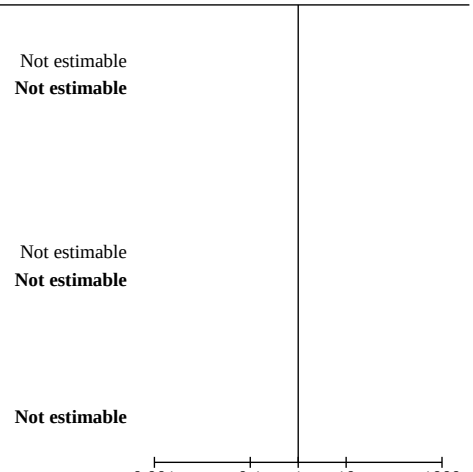

## Analysis 11.3. Comparison 11: Nutritional supplements versus placebo, Outcome 3: General health

| Study or Subgroup | Nutritional supplements Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **11.3.1 Haemodialysis** | | | | | | | |
| Fukuda 2015 | 48.5 | 16.6 | 87 | 43.8 | 21 | 86 | 4.70 [-0.94 , 10.34] |



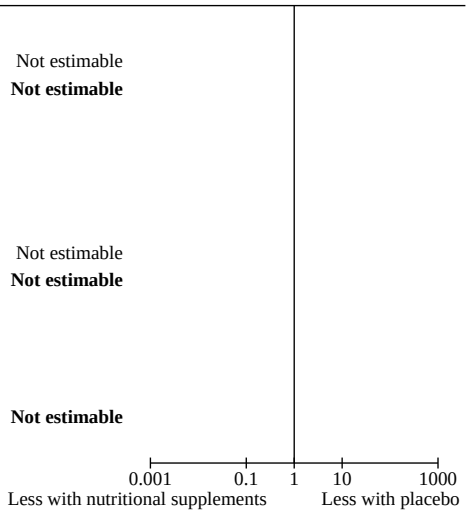

## Analysis 11.4. Comparison 11: Nutritional supplements versus placebo, Outcome 4: Death (any cause)

| Study or Subgroup | Nutritional supplements Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **11.4.1 Haemodialysis** | | | | | | |
| Singer 2010 | 0 | 32 | 0 | 33 | | Not estimable |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **11.4.2 Peritoneal dialysis** | | | | | | |
| Singer 2010 | 0 | 5 | 0 | 5 | | Not estimable |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **Total (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



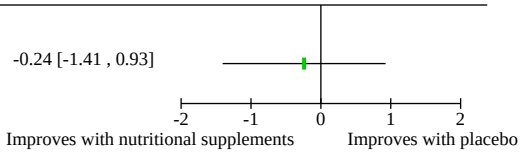
### Analysis 11.5. Comparison 11: Nutritional supplements versus placebo, Outcome 5: Cardiovascular death

| Study or Subgroup | Nutritional supplements Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **11.5.1 Haemodialysis** | | | | | | |
| Singer 2010 | 0 | 32 | 0 | 33 | | Not estimable |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **11.5.2 Peritoneal dialysis** | | | | | | |
| Singer 2010 | 0 | 5 | 0 | 5 | | Not estimable |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **Total (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |




### Analysis 11.6. Comparison 11: Nutritional supplements versus placebo, Outcome 6: Sleep problems

| Study or Subgroup | Nutritional supplements Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **11.6.1 Haemodialysis** | | | | | | | |
| Fukuda 2015 | 3.98 | 3.77 | 87 | 4.22 | 4.05 | 86 | -0.24 [-1.41 , 0.93] |

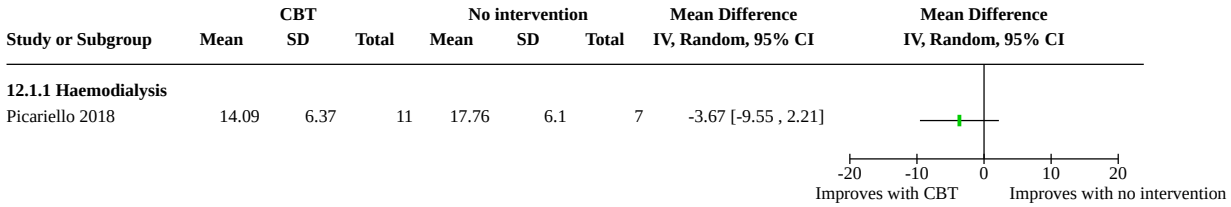



## Comparison 12. Cognitive behavioural therapy versus no intervention

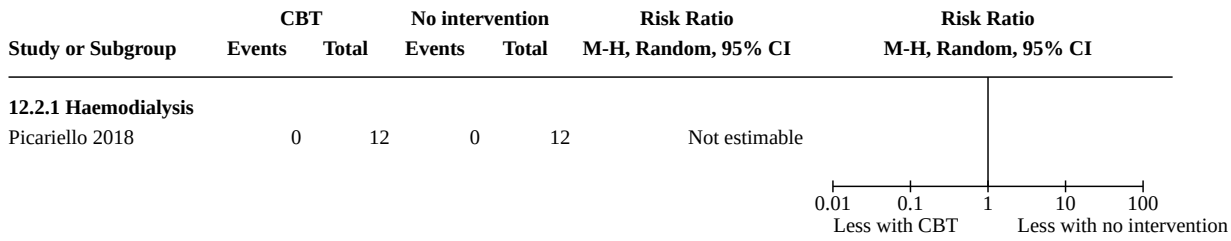
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 12.1 Fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 12.1.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 12.2 Death (any cause) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 12.2.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 12.3 Cardiovascular death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 12.3.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 12.4 Depression | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 12.4.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 12.5 Anxiety | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 12.5.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 12.6 Sleep quality | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 12.6.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

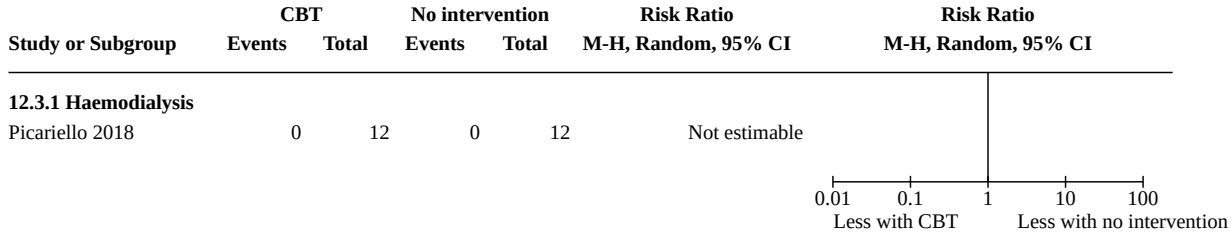
**Analysis 12.1. Comparison 12: Cognitive behavioural therapy versus no intervention, Outcome 1: Fatigue**



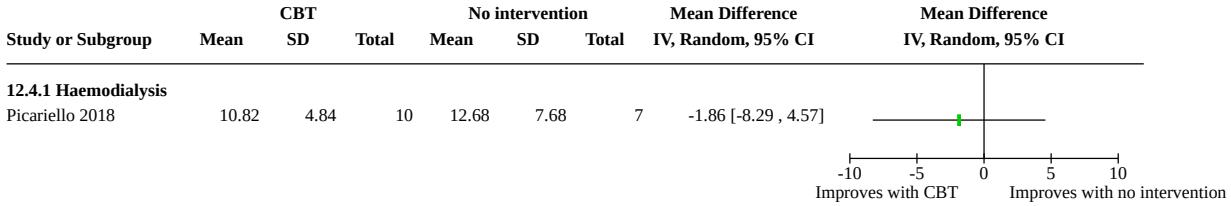

**Analysis 12.2. Comparison 12: Cognitive behavioural therapy versus no intervention, Outcome 2: Death (any cause)**



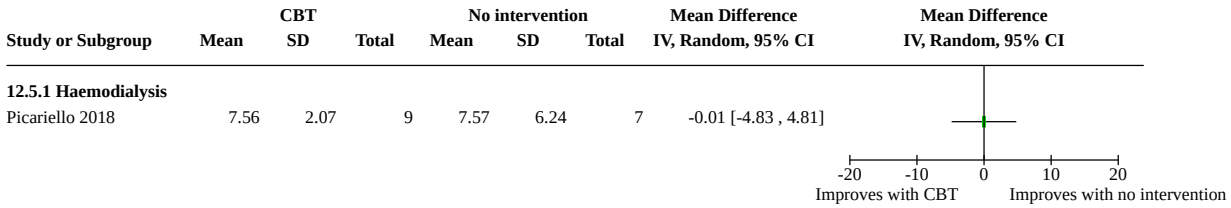

**Analysis 12.3. Comparison 12: Cognitive behavioural therapy versus no intervention, Outcome 3: Cardiovascular death**



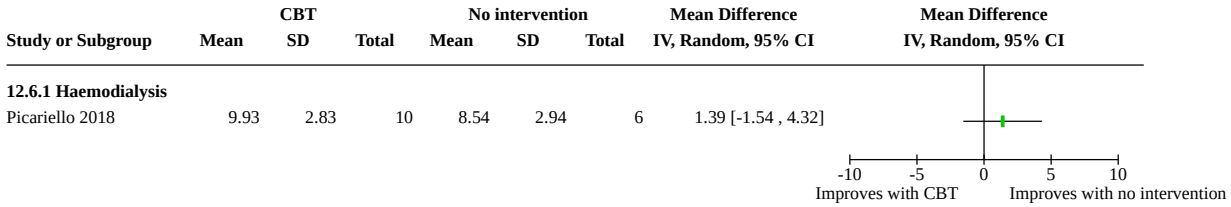
### Analysis 12.4. Comparison 12: Cognitive behavioural therapy versus no intervention, Outcome 4: Depression




### Analysis 12.5. Comparison 12: Cognitive behavioural therapy versus no intervention, Outcome 5: Anxiety




### Analysis 12.6. Comparison 12: Cognitive behavioural therapy versus no intervention, Outcome 6: Sleep quality



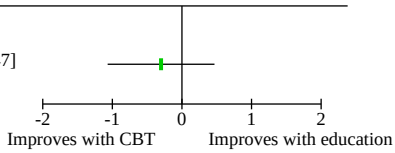

### Comparison 13. Cognitive behavioural therapy versus education

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 13.1 Fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 13.1.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 13.2 Number with decline in fatigue | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 13.2.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 13.3 Death (any cause) | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 13.3.1 Haemodialysis | 2 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 13.4 Cardiovascular death | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 13.4.1 Haemodialysis | 2 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 13.5 Depression | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 13.5.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 13.6 Number with decline in depression | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 13.6.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 13.7 Anxiety | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 13.7.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 13.8 Number with decline in anxiety | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 13.8.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 13.9 Sleep (overall) | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 13.9.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

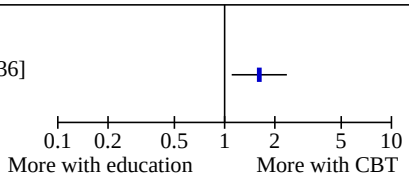
**Analysis 13.1. Comparison 13: Cognitive behavioural therapy versus education, Outcome 1: Fatigue**

| Study or Subgroup | CBT Mean | CBT SD | CBT Total | Education Mean | Education SD | Education Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **13.1.1 Haemodialysis** | | | | | | | | |
| Chen 2011a | 3.9 | 1.5 | 37 | 4.2 | 1.8 | 35 | -0.30 [-1.07 , 0.47] | |



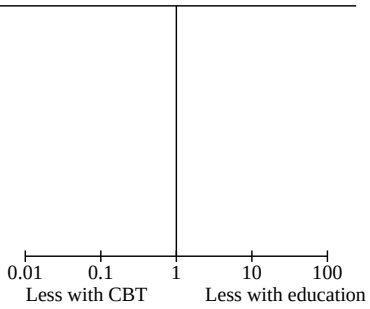

**Analysis 13.2. Comparison 13: Cognitive behavioural therapy versus education, Outcome 2: Number with decline in fatigue**

| Study or Subgroup | CBT Events | CBT Total | Education Events | Education Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **13.2.1 Haemodialysis** | | | | | | |
| Chen 2011a | 29 | 37 | 17 | 35 | 1.61 [1.10 , 2.36] | |



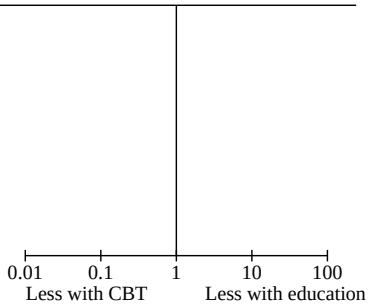
### Analysis 13.3. Comparison 13: Cognitive behavioural therapy versus education, Outcome 3: Death (any cause)

| Study or Subgroup | CBT Events | CBT Total | Education Events | Education Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **13.3.1 Haemodialysis** | | | | | | |
| Chen 2011a | 0 | 40 | 0 | 40 | | Not estimable |
| Chen 2008a | 0 | 13 | 0 | 13 | | Not estimable |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



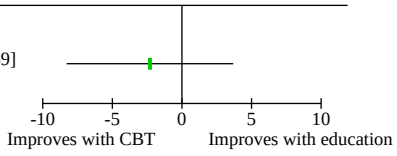

### Analysis 13.4. Comparison 13: Cognitive behavioural therapy versus education, Outcome 4: Cardiovascular death

| Study or Subgroup | CBT Events | CBT Total | Education Events | Education Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **13.4.1 Haemodialysis** | | | | | | |
| Chen 2011a | 0 | 40 | 0 | 40 | | Not estimable |
| Chen 2008a | 0 | 13 | 0 | 13 | | Not estimable |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



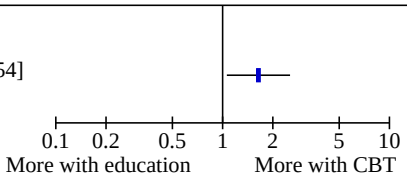

### Analysis 13.5. Comparison 13: Cognitive behavioural therapy versus education, Outcome 5: Depression

| Study or Subgroup | CBT Mean | CBT SD | CBT Total | Education Mean | Education SD | Education Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **13.5.1 Haemodialysis** | | | | | | | |
| Chen 2011a | 13.8 | 11.5 | 37 | 16.1 | 14.2 | 35 | -2.30 [-8.29 , 3.69] |

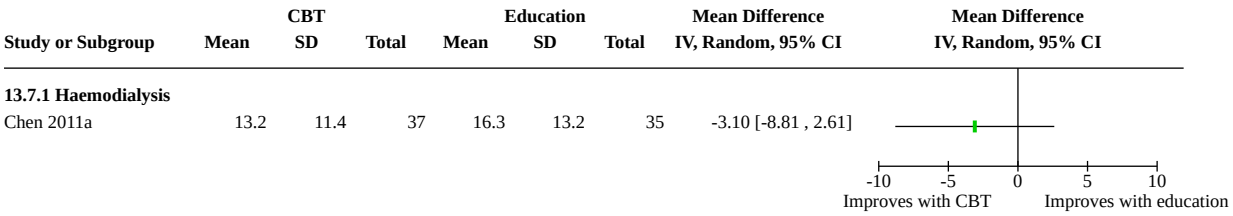



### Analysis 13.6. Comparison 13: Cognitive behavioural therapy versus education, Outcome 6: Number with decline in depression

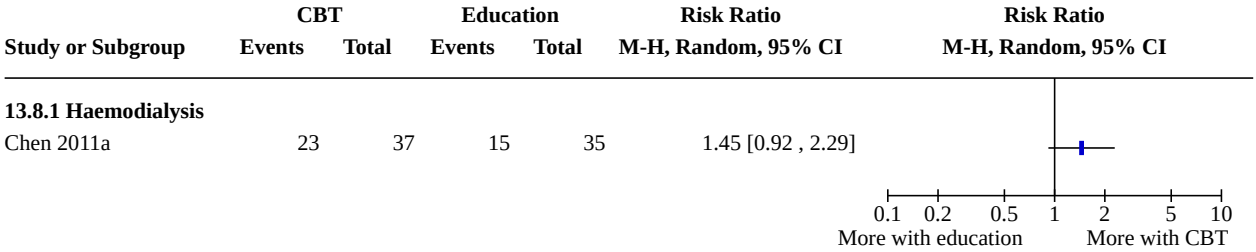
| Study or Subgroup | CBT Events | CBT Total | Education Events | Education Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **13.6.1 Haemodialysis** | | | | | |
| Chen 2011a | 26 | 37 | 15 | 35 | 1.64 [1.06 , 2.54] |



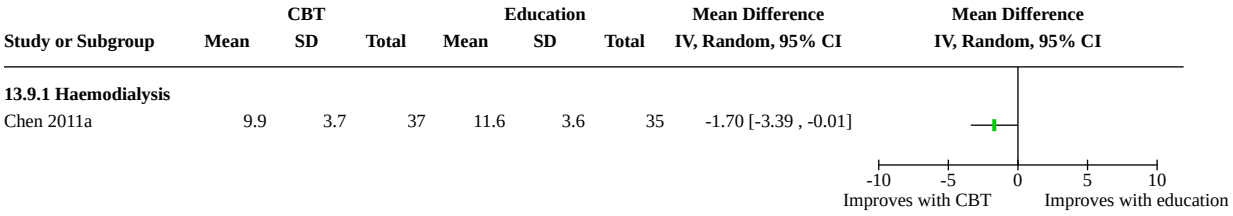
### Analysis 13.7. Comparison 13: Cognitive behavioural therapy versus education, Outcome 7: Anxiety




### Analysis 13.8. Comparison 13: Cognitive behavioural therapy versus education, Outcome 8: Number with decline in anxiety



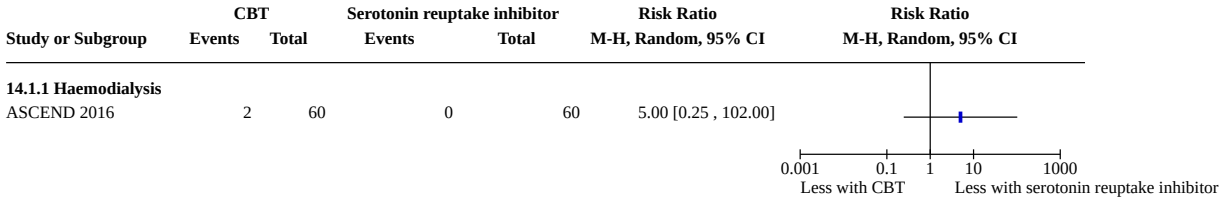

### Analysis 13.9. Comparison 13: Cognitive behavioural therapy versus education, Outcome 9: Sleep (overall)




## Comparison 14. Cognitive behavioural therapy versus serotonin reuptake inhibitor

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 14.1 Death (any cause) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 14.1.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

**Analysis 14.1. Comparison 14: Cognitive behavioural therapy versus serotonin reuptake inhibitor, Outcome 1: Death (any cause)**




## Comparison 15. Aromatherapy versus placebo or standard care

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 15.1 Fatigue | 7 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 15.1.1 Haemodialysis | 7 | 542 | Std. Mean Difference (IV, Random, 95% CI) | -1.23 [-1.96, -0.50] |
| 15.2 Change in fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 15.2.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 15.3 Vitality | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 15.3.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 15.4 Death (any cause) | 6 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 15.4.1 Haemodialysis | 6 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 15.5 Cardiovascular death | 6 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 15.5.1 Haemodialysis | 6 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 15.6 Quality of life (overall) | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 15.6.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 15.7 Global sleep quality | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 15.7.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 15.8 Change in global sleep quality | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

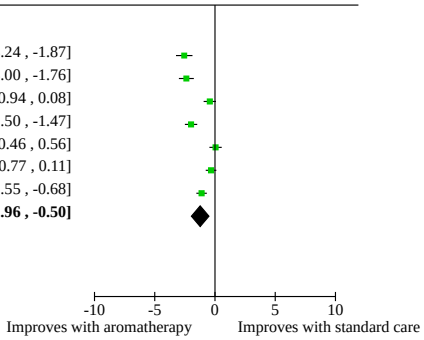
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 15.8.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 15.9 Sleep disturbance | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 15.9.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 15.10 Change in sleep disturbance | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 15.10.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

## Analysis 15.1. Comparison 15: Aromatherapy versus placebo or standard care, Outcome 1: Fatigue

| Study or Subgroup | Aromatherapy Mean | SD | Total | Placebo/standard care Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **15.1.1 Haemodialysis** | | | | | | | | |
| Muz 2017 | 3.09 | 2.01 | 27 | 7.38 | 1.33 | 35 | 13.6% | -2.55 [-3.24 , -1.87] |
| Hassanzadeh 2018 | 3.64 | 0.79 | 35 | 6.21 | 1.29 | 35 | 13.9% | -2.38 [-3.00 , -1.76] |
| Karadag 2019 | 35.23 | 5.21 | 30 | 38.46 | 9.12 | 30 | 14.4% | -0.43 [-0.94 , 0.08] |
| Varaei 2020 | 4.57 | 1.22 | 64 | 7.06 | 1.29 | 32 | 14.4% | -1.99 [-2.50 , -1.47] |
| Bagheri-Nesami 2016 | 42.61 | 18.5788 | 29 | 41.7 | 18.5678 | 30 | 14.4% | 0.05 [-0.46 , 0.56] |
| Ahmady 2019 | 31.67 | 3.77 | 60 | 34.7 | 15.09 | 30 | 14.6% | -0.33 [-0.77 , 0.11] |
| Mohammadpourhodki 2021 | 35.3 | 4.04 | 70 | 45.1 | 14.1 | 35 | 14.7% | -1.11 [-1.55 , -0.68] |
| **Subtotal (95% CI)** | | | **315** | | | **227** | **100.0%** | **-1.23 [-1.96 , -0.50]** |

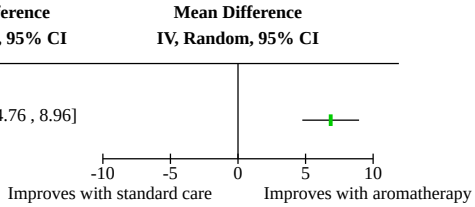
Heterogeneity: Tau² = 0.89; Chi² = 82.83, df = 6 (P < 0.00001); I² = 93%
Test for overall effect: Z = 3.32 (P = 0.0009)

Test for subgroup differences: Not applicable



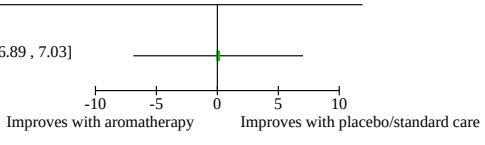

## Analysis 15.2. Comparison 15: Aromatherapy versus placebo or standard care, Outcome 2: Change in fatigue

| Study or Subgroup | Aromatherapy Mean | SD | Total | Placebo/standard care Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **15.2.1 Haemodialysis** | | | | | | | |
| Karadag 2019 | 6 | 4.57 | 30 | -0.86 | 3.68 | 30 | 6.86 [4.76 , 8.96] |



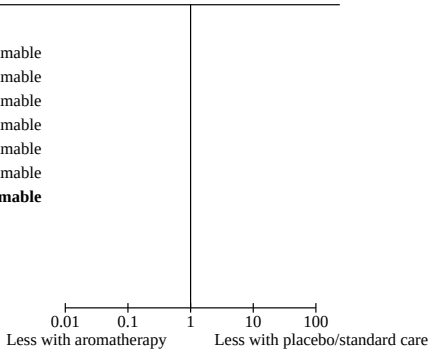

## Analysis 15.3. Comparison 15: Aromatherapy versus placebo or standard care, Outcome 3: Vitality

| Study or Subgroup | Aromatherapy Mean | SD | Total | Placebo/standard care Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **15.3.1 Haemodialysis** | | | | | | | |
| Mohammadpourhodki 2021 | 60.6 | 4.71 | 70 | 60.53 | 20.75 | 35 | 0.07 [-6.89 , 7.03] |



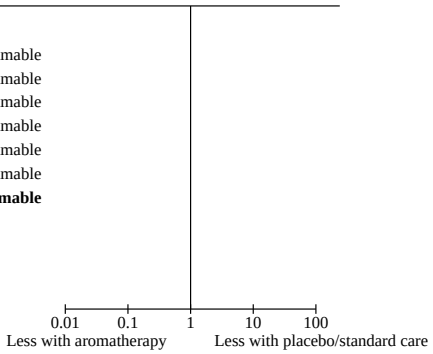
## Analysis 15.4. Comparison 15: Aromatherapy versus placebo or standard care, Outcome 4: Death (any cause)

| Study or Subgroup | Aromatherapy Events | Aromatherapy Total | Placebo/standard care Events | Placebo/standard care Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **15.4.1 Haemodialysis** | | | | | | |
| Bagheri-Nesami 2016 | 0 | 30 | 0 | 30 | | Not estimable |
| Muz 2017 | 0 | 27 | 0 | 35 | | Not estimable |
| Ahmady 2019 | 0 | 60 | 0 | 30 | | Not estimable |
| Karadag 2019 | 0 | 30 | 0 | 30 | | Not estimable |
| Mohammadpourhodki 2021 | 0 | 70 | 0 | 35 | | Not estimable |
| Varaei 2020 | 0 | 64 | 0 | 32 | | Not estimable |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



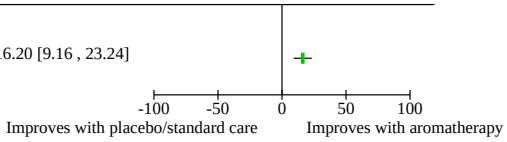

## Analysis 15.5. Comparison 15: Aromatherapy versus placebo or standard care, Outcome 5: Cardiovascular death

| Study or Subgroup | Aromatherapy Events | Aromatherapy Total | Placebo/standard care Events | Placebo/standard care Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **15.5.1 Haemodialysis** | | | | | | |
| Bagheri-Nesami 2016 | 0 | 30 | 0 | 30 | | Not estimable |
| Muz 2017 | 0 | 27 | 0 | 35 | | Not estimable |
| Ahmady 2019 | 0 | 60 | 0 | 30 | | Not estimable |
| Karadag 2019 | 0 | 30 | 0 | 30 | | Not estimable |
| Mohammadpourhodki 2021 | 0 | 70 | 0 | 35 | | Not estimable |
| Varaei 2020 | 0 | 64 | 0 | 32 | | Not estimable |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



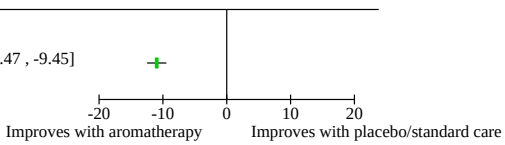

## Analysis 15.6. Comparison 15: Aromatherapy versus placebo or standard care, Outcome 6: Quality of life (overall)

| Study or Subgroup | Aromatherapy Mean | Aromatherapy SD | Aromatherapy Total | Placebo/standard care Mean | Placebo/standard care SD | Placebo/standard care Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **15.6.1 Haemodialysis** | | | | | | | |
| Mohammadpourhodki 2021 | 63.8 | 4.6 | 70 | 47.6 | 21 | 35 | 16.20 [9.16 , 23.24] |

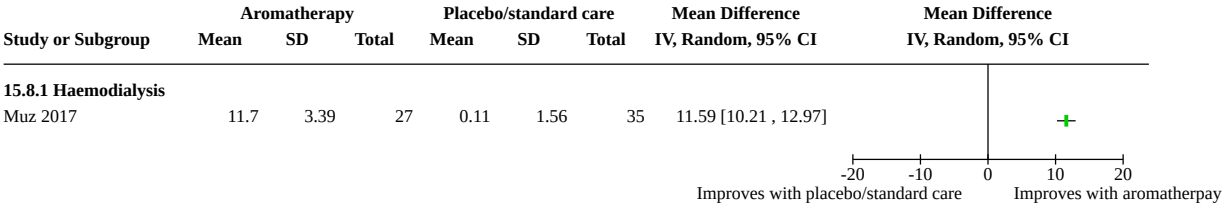



## Analysis 15.7. Comparison 15: Aromatherapy versus placebo or standard care, Outcome 7: Global sleep quality

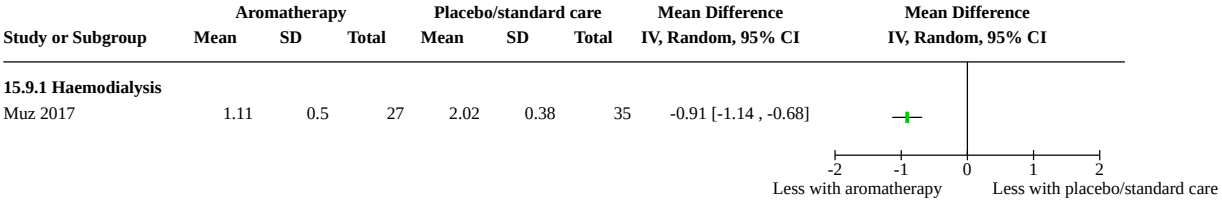
| Study or Subgroup | Aromatherapy Mean | Aromatherapy SD | Aromatherapy Total | Placebo/standard care Mean | Placebo/standard care SD | Placebo/standard care Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **15.7.1 Haemodialysis** | | | | | | | |
| Muz 2017 | 4.66 | 3.66 | 27 | 15.62 | 1.81 | 35 | -10.96 [-12.47 , -9.45] |



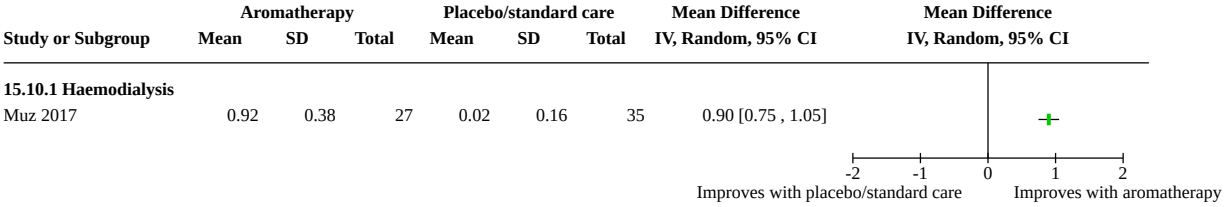
### Analysis 15.8. Comparison 15: Aromatherapy versus placebo or standard care, Outcome 8: Change in global sleep quality




### Analysis 15.9. Comparison 15: Aromatherapy versus placebo or standard care, Outcome 9: Sleep disturbance




### Analysis 15.10. Comparison 15: Aromatherapy versus placebo or standard care, Outcome 10: Change in sleep disturbance




## Comparison 16. Aromatherapy (lavender extract) versus aromatherapy (orange extract)

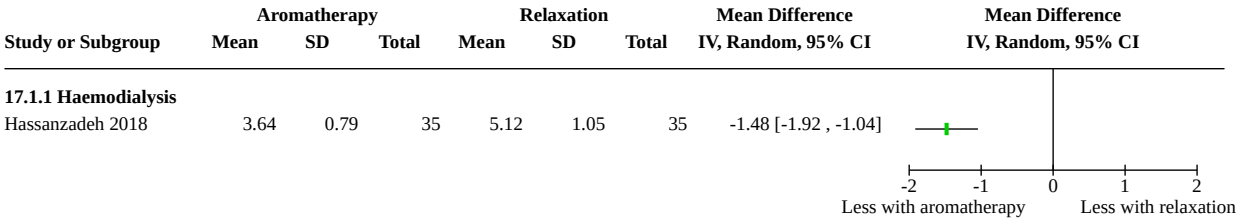
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 16.1 Fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 16.1.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

### Analysis 16.1. Comparison 16: Aromatherapy (lavender extract) versus aromatherapy (orange extract), Outcome 1: Fatigue


## Comparison 17. Aromatherapy versus relaxation

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 17.1 Fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 17.1.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

### Analysis 17.1. Comparison 17: Aromatherapy versus relaxation, Outcome 1: Fatigue




## Comparison 18. Massage versus no intervention

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 18.1 Fatigue | 7 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 18.1.1 Haemodialysis | 7 | 657 | Std. Mean Difference (IV, Random, 95% CI) | -1.06 [-1.47, -0.65] |
| 18.2 Change in fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 18.2.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 18.3 Number with severe fatigue | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 18.3.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 18.4 Energy | 2 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 18.4.1 Haemodialysis | 2 | 152 | Mean Difference (IV, Random, 95% CI) | 4.87 [1.69, 8.06] |
| 18.5 Death (any cause) | 3 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 18.5.1 Haemodialysis | 3 | 404 | Risk Ratio (M-H, Random, 95% CI) | 1.53 [0.06, 36.31] |
| 18.6 Cardiovascular death | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 18.6.1 Haemodialysis | 2 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 18.7 Quality of life (overall) | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 18.7.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 18.8 Change in quality of life | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 18.8.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 18.9 Sleep (overall) | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 18.9.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

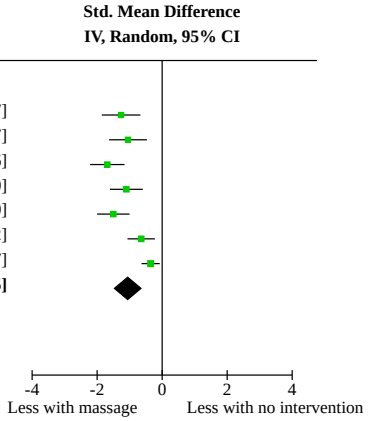
## Analysis 18.1. Comparison 18: Massage versus no intervention, Outcome 1: Fatigue

| Study or Subgroup | Massage Mean | Massage SD | Massage Total | No intervention Mean | No intervention SD | No intervention Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **18.1.1 Haemodialysis** | | | | | | | | |
| Roshanravan 2016 | 3.8 | 1.27 | 26 | 5.19 | 0.87 | 27 | 13.0% | -1.26 [-1.86 , -0.67] |
| Shahdadi 2016 | 37.65 | 11.51 | 26 | 48.92 | 9.52 | 26 | 13.2% | -1.05 [-1.63 , -0.47] |
| Cecen 2021 | 60 | 4.7 | 54 | 77.14 | 16.02 | 28 | 13.8% | -1.69 [-2.21 , -1.16] |
| Unal 2016 | 58.51 | 18.8 | 35 | 80.74 | 21.1 | 35 | 14.1% | -1.10 [-1.60 , -0.60] |
| Ozdemir 2013 | 3.3 | 1.4 | 40 | 5.5 | 1.5 | 40 | 14.2% | -1.50 [-2.00 , -1.00] |
| Habibzadeh 2020 | 4.77 | 1.13 | 90 | 5.51 | 1.17 | 30 | 15.1% | -0.65 [-1.07 , -0.22] |
| Lazarus 2020 | 4.39 | 2.37 | 100 | 5.17 | 2 | 100 | 16.6% | -0.35 [-0.63 , -0.07] |
| **Subtotal (95% CI)** | | | **371** | | | **286** | **100.0%** | **-1.06 [-1.47 , -0.65]** |

Heterogeneity: Tau² = 0.24; Chi² = 32.40, df = 6 (P < 0.0001); I² = 81%

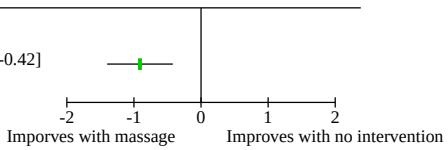
Test for overall effect: Z = 5.10 (P < 0.00001)

Test for subgroup differences: Not applicable



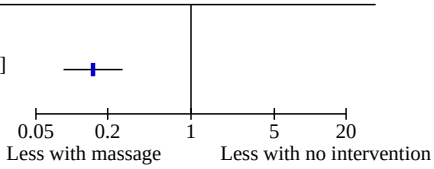
## Analysis 18.2. Comparison 18: Massage versus no intervention, Outcome 2: Change in fatigue

| Study or Subgroup | Massage Mean | Massage SD | Massage Total | No intervention Mean | No intervention SD | No intervention Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **18.2.1 Haemodialysis** | | | | | | | |
| Habibzadeh 2020 | -0.93 | 1.07 | 90 | -0.02 | 1.22 | 30 | -0.91 [-1.40 , -0.42] |



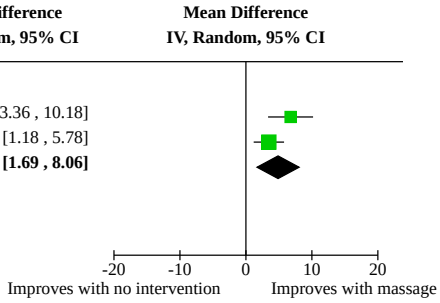

## Analysis 18.3. Comparison 18: Massage versus no intervention, Outcome 3: Number with severe fatigue

| Study or Subgroup | Massage Events | Massage Total | No intervention Events | No intervention Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **18.3.1 Haemodialysis** | | | | | |
| Lazarus 2020 | 11 | 100 | 73 | 100 | 0.15 [0.09 , 0.27] |



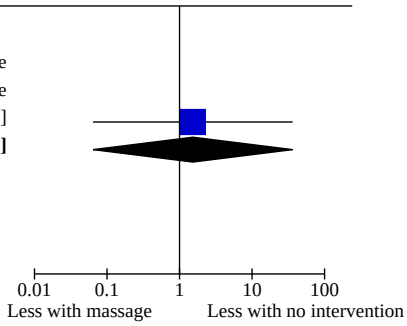

## Analysis 18.4. Comparison 18: Massage versus no intervention, Outcome 4: Energy

| Study or Subgroup | Massage Mean | Massage SD | Massage Total | No intervention Mean | No intervention SD | No intervention Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **18.4.1 Haemodialysis** | | | | | | | | |
| Unal 2016 | 28.74 | 6.6 | 35 | 21.97 | 7.9 | 35 | 42.4% | 6.77 [3.36 , 10.18] |
| Cecen 2021 | 22.41 | 2.71 | 54 | 18.93 | 5.9 | 28 | 57.6% | 3.48 [1.18 , 5.78] |
| **Subtotal (95% CI)** | | | **89** | | | **63** | **100.0%** | **4.87 [1.69 , 8.06]** |
| Heterogeneity: Tau² = 3.21; Chi² = 2.46, df = 1 (P = 0.12); I² = 59% | | | | | | | | |
| Test for overall effect: Z = 3.00 (P = 0.003) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |



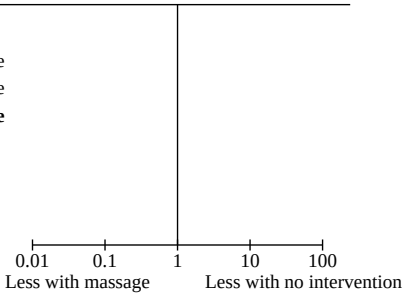

## Analysis 18.5. Comparison 18: Massage versus no intervention, Outcome 5: Death (any cause)

| Study or Subgroup | Massage Events | Massage Total | No intervention Events | No intervention Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **18.5.1 Haemodialysis** | | | | | | |
| Habibzadeh 2020 | 0 | 90 | 0 | 30 | | Not estimable |
| Lazarus 2020 | 0 | 100 | 0 | 100 | | Not estimable |
| Cecen 2021 | 1 | 56 | 0 | 28 | 100.0% | 1.53 [0.06 , 36.31] |
| **Subtotal (95% CI)** | | **246** | | **158** | **100.0%** | **1.53 [0.06 , 36.31]** |
| Total events: | 1 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.26 (P = 0.79) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



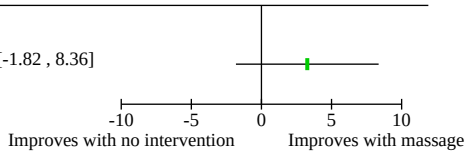
### Analysis 18.6. Comparison 18: Massage versus no intervention, Outcome 6: Cardiovascular death

| Study or Subgroup | Massage Events | Massage Total | No intervention Events | No intervention Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **18.6.1 Haemodialysis** | | | | | | |
| Habibzadeh 2020 | 0 | 90 | 0 | 30 | | Not estimable |
| Lazarus 2020 | 0 | 100 | 0 | 100 | | Not estimable |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



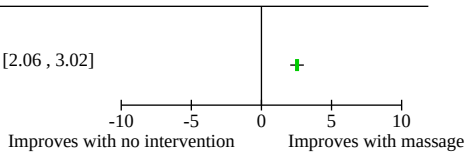

### Analysis 18.7. Comparison 18: Massage versus no intervention, Outcome 7: Quality of life (overall)

| Study or Subgroup | Massage Mean | Massage SD | Massage Total | No intervention Mean | No intervention SD | No intervention Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **18.7.1 Haemodialysis** | | | | | | | |
| Habibzadeh 2020 | 52.07 | 3.56 | 90 | 48.8 | 14.07 | 30 | 3.27 [-1.82 , 8.36] |



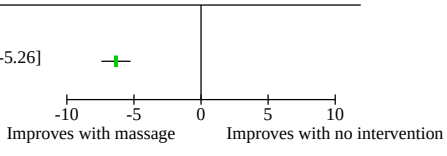

### Analysis 18.8. Comparison 18: Massage versus no intervention, Outcome 8: Change in quality of life

| Study or Subgroup | Massage Mean | Massage SD | Massage Total | No intervention Mean | No intervention SD | No intervention Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **18.8.1 Haemodialysis** | | | | | | | |
| Habibzadeh 2020 | 2.65 | 1.37 | 90 | 0.11 | 1.1 | 30 | 2.54 [2.06 , 3.02] |




### Analysis 18.9. Comparison 18: Massage versus no intervention, Outcome 9: Sleep (overall)

| Study or Subgroup | Massage Mean | Massage SD | Massage Total | No intervention Mean | No intervention SD | No intervention Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **18.9.1 Haemodialysis** | | | | | | | |
| Unal 2016 | 5.54 | 2.15 | 35 | 11.88 | 2.47 | 35 | -6.34 [-7.42 , -5.26] |

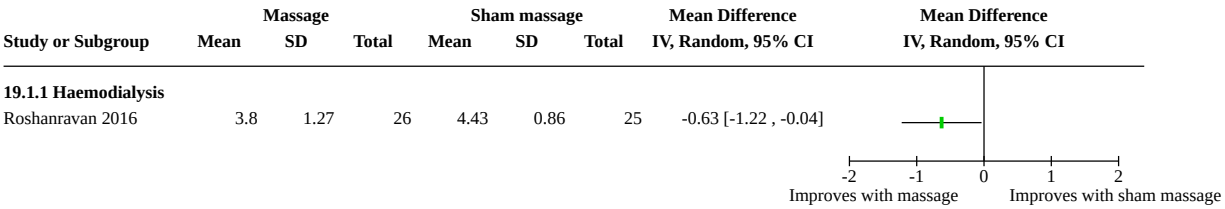



## Comparison 19. Massage versus sham massage

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 19.1 Fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 19.1.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

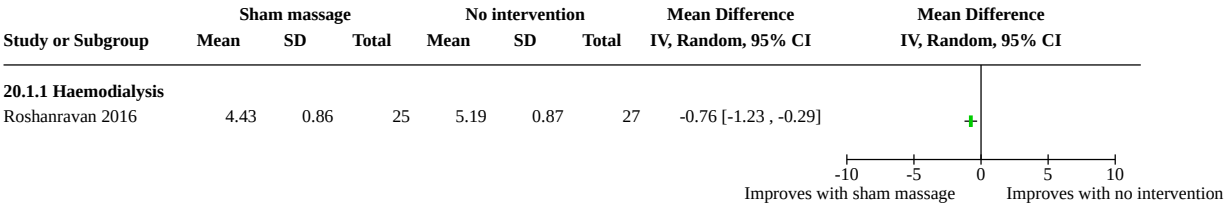
### Analysis 19.1. Comparison 19: Massage versus sham massage, Outcome 1: Fatigue




## Comparison 20. Sham massage versus no intervention

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 20.1 Fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 20.1.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

### Analysis 20.1. Comparison 20: Sham massage versus no intervention, Outcome 1: Fatigue




## Comparison 21. Massage versus massage

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 21.1 Fatigue | 2 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 21.1.1 Haemodialysis | 2 | 160 | Std. Mean Difference (IV, Random, 95% CI) | -0.77 [-1.10, -0.43] |
| 21.2 Change in fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 21.2.1 HD | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 21.3 Energy | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

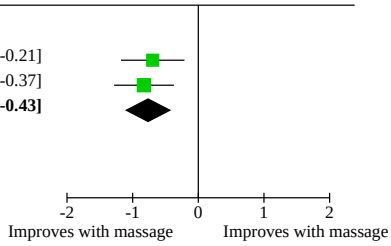
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 21.3.1 HD | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 21.4 All-cause death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 21.4.1 HD | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 21.5 Cardiovascular death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 21.5.1 HD | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 21.6 Quality of life (overall) | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 21.6.1 HD | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 21.7 Change in quality of life | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 21.7.1 HD | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 21.8 Sleep (overall) | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 21.8.1 HD | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

### Analysis 21.1. Comparison 21: Massage versus massage, Outcome 1: Fatigue

| Study or Subgroup | Massage Mean | Massage SD | Massage Total | Massage Mean | Massage SD | Massage Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **21.1.1 Haemodialysis** | | | | | | | | |
| Unal 2016 | 58.51 | 18.8 | 35 | 70.77 | 16 | 35 | 47.0% | -0.69 [-1.18 , -0.21] |
| Habibzadeh 2020 | 4.55 | 1.14 | 60 | 5.51 | 1.17 | 30 | 53.0% | -0.83 [-1.28 , -0.37] |
| **Subtotal (95% CI)** | | | **95** | | | **65** | **100.0%** | **-0.77 [-1.10 , -0.43]** |

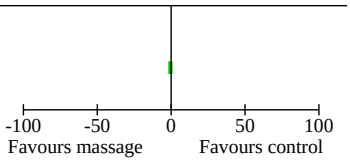
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.69); I² = 0% 
Test for overall effect: Z = 4.52 (P < 0.00001)

Test for subgroup differences: Not applicable



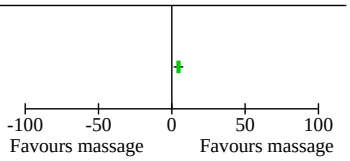

### Analysis 21.2. Comparison 21: Massage versus massage, Outcome 2: Change in fatigue

| Study or Subgroup | Massage Mean | Massage SD | Massage Total | Massage Mean | Massage SD | Massage Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **21.2.1 HD** | | | | | | | |
| Habibzadeh 2020 | -1.1 | 1.11 | 60 | -0.6 | 0.99 | 30 | -0.50 [-0.95 , -0.05] |



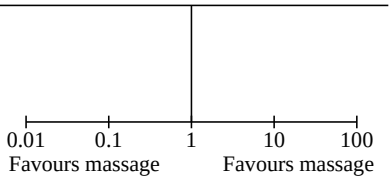
### Analysis 21.3. Comparison 21: Massage versus massage, Outcome 3: Energy

| Study or Subgroup | Massage Mean | Massage SD | Massage Total | Massage Mean | Massage SD | Massage Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **21.3.1 HD** | | | | | | | | |
| Unal 2016 | 28.74 | 6.6 | 35 | 24.2 | 7.3 | 35 | 4.54 [1.28 , 7.80] | |



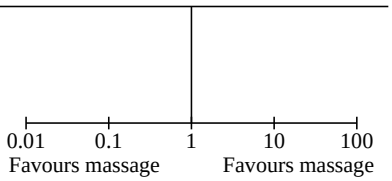

### Analysis 21.4. Comparison 21: Massage versus massage, Outcome 4: All-cause death

| Study or Subgroup | Massage Events | Massage Total | Massage Events | Massage Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **21.4.1 HD** | | | | | | |
| Habibzadeh 2020 | 0 | 60 | 0 | 30 | Not estimable | |



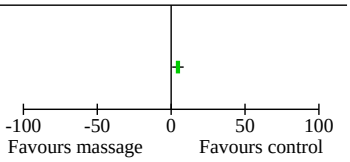

### Analysis 21.5. Comparison 21: Massage versus massage, Outcome 5: Cardiovascular death

| Study or Subgroup | Massage Events | Massage Total | Massage Events | Massage Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **21.5.1 HD** | | | | | | |
| Habibzadeh 2020 | 0 | 60 | 0 | 30 | Not estimable | |

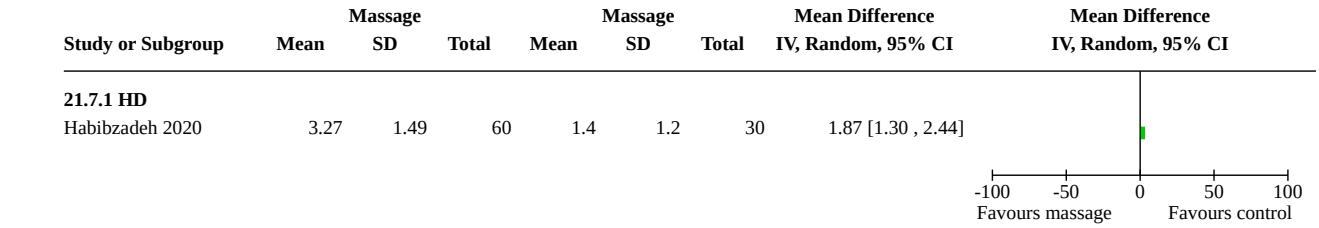



### Analysis 21.6. Comparison 21: Massage versus massage, Outcome 6: Quality of life (overall)

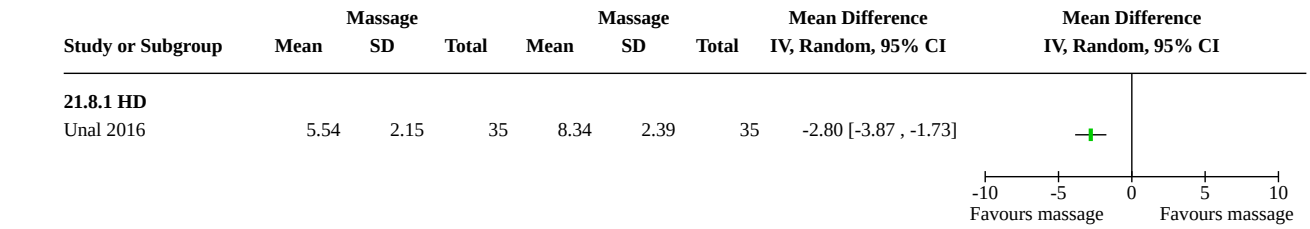
| Study or Subgroup | Massage Mean | Massage SD | Massage Total | Massage Mean | Massage SD | Massage Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **21.6.1 HD** | | | | | | | | |
| Habibzadeh 2020 | 53.6 | 3.56 | 60 | 49 | 10.5 | 30 | 4.60 [0.74 , 8.46] | |



### Analysis 21.7. Comparison 21: Massage versus massage, Outcome 7: Change in quality of life




### Analysis 21.8. Comparison 21: Massage versus massage, Outcome 8: Sleep (overall)

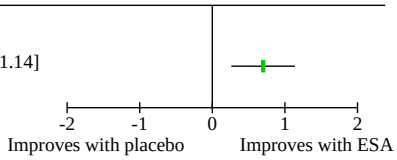



## Comparison 22. Erythropoietin stimulating agents versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 22.1 Fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 22.1.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 22.2 Weakness | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 22.2.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 22.3 Energy | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 22.3.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 22.4 Death (any cause) | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 22.4.1 Haemodialysis | 2 | 137 | Risk Ratio (M-H, Random, 95% CI) | 0.17 [0.01, 4.15] |
| 22.5 Cardiovascular death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 22.5.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 22.6 Depression | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 22.6.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 22.7 Clotting of vascular access | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 22.7.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

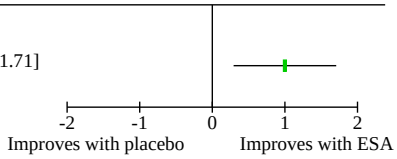
### Analysis 22.1. Comparison 22: Erythropoietin stimulating agents versus placebo, Outcome 1: Fatigue

| Study or Subgroup | ESA Mean | ESA SD | ESA Total | Placebo Mean | Placebo SD | Placebo Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **22.1.1 Haemodialysis** | | | | | | | | |
| Canadian EPO 1990 | 5.2 | 0.8185 | 67 | 4.5 | 1.1314 | 32 | 0.70 [0.26 , 1.14] | |



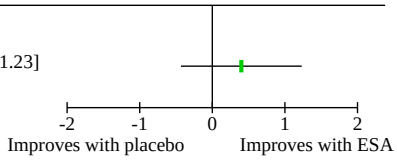

### Analysis 22.2. Comparison 22: Erythropoietin stimulating agents versus placebo, Outcome 2: Weakness

| Study or Subgroup | ESA Mean | ESA SD | ESA Total | Placebo Mean | Placebo SD | Placebo Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **22.2.1 Haemodialysis** | | | | | | | | |
| Canadian EPO 1990 | 5.3 | 1.6371 | 67 | 4.3 | 1.6971 | 32 | 1.00 [0.29 , 1.71] | |



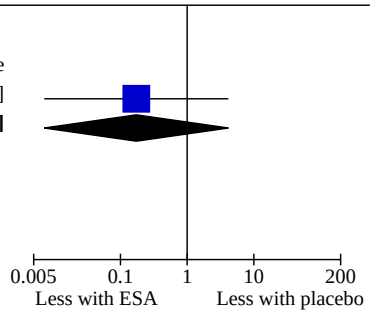

### Analysis 22.3. Comparison 22: Erythropoietin stimulating agents versus placebo, Outcome 3: Energy

| Study or Subgroup | ESA Mean | ESA SD | ESA Total | Placebo Mean | Placebo SD | Placebo Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **22.3.1 Haemodialysis** | | | | | | | | |
| Canadian EPO 1990 | 4.8 | 2.4556 | 67 | 4.4 | 1.6971 | 32 | 0.40 [-0.43 , 1.23] | |



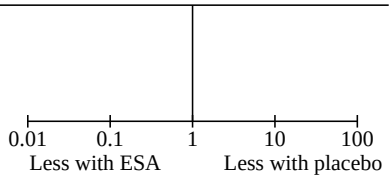

### Analysis 22.4. Comparison 22: Erythropoietin stimulating agents versus placebo, Outcome 4: Death (any cause)

| Study or Subgroup | ESA Events | ESA Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **22.4.1 Haemodialysis** | | | | | | | |
| Lillevang 1990 | 0 | 9 | 0 | 10 | | Not estimable | |
| Canadian EPO 1990 | 0 | 78 | 1 | 40 | 100.0% | 0.17 [0.01 , 4.15] | |
| **Subtotal (95% CI)** | | **87** | | **50** | **100.0%** | **0.17 [0.01 , 4.15]** | |
| Total events: | 0 | | 1 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z = 1.08 (P = 0.28) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |



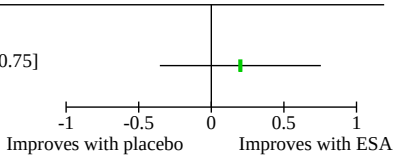
**Analysis 22.5. Comparison 22: Erythropoietin stimulating agents versus placebo, Outcome 5: Cardiovascular death**

| Study or Subgroup | ESA Events | ESA Total | Placebo Events | Placebo Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **22.5.1 Haemodialysis** | | | | | |
| Lillevang 1990 | 0 | 9 | 0 | 10 | Not estimable |



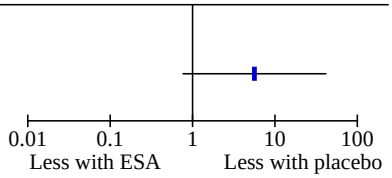

**Analysis 22.6. Comparison 22: Erythropoietin stimulating agents versus placebo, Outcome 6: Depression**

| Study or Subgroup | ESA Mean | ESA SD | ESA Total | Placebo Mean | Placebo SD | Placebo Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **22.6.1 Haemodialysis** | | | | | | | |
| Canadian EPO 1990 | 5.3 | 1.6371 | 67 | 5.1 | 1.1314 | 32 | 0.20 [-0.35 , 0.75] |




**Analysis 22.7. Comparison 22: Erythropoietin stimulating agents versus placebo, Outcome 7: Clotting of vascular access**

| Study or Subgroup | ESA Events | ESA Total | Placebo Events | Placebo Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **22.7.1 Haemodialysis** | | | | | |
| Canadian EPO 1990 | 11 | 78 | 1 | 40 | 5.64 [0.75 , 42.16] |




**Comparison 23. Erythropoietin stimulating agents: normal versus high haemoglobin target**

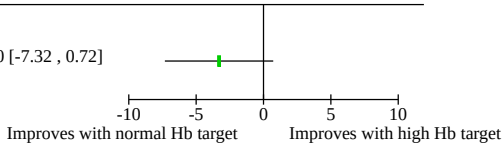
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 23.1 Fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 23.1.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 23.2 Change in fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 23.2.1 Haemoglobin | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 23.3 Vitality | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 23.3.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 23.4 Change in vitality | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 23.4.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 23.5 Death (any cause) | 3 | 1086 | Risk Ratio (M-H, Random, 95% CI) | 1.05 [0.71, 1.56] |
| 23.5.1 Haemodialysis | 3 | 1035 | Risk Ratio (M-H, Random, 95% CI) | 1.11 [0.73, 1.68] |
| 23.5.2 Peritoneal dialysis | 1 | 51 | Risk Ratio (M-H, Random, 95% CI) | 0.61 [0.17, 2.17] |
| 23.6 Cardiovascular death | 1 | 344 | Risk Ratio (M-H, Random, 95% CI) | 1.30 [0.68, 2.48] |
| 23.6.1 Haemodialysis | 1 | 293 | Risk Ratio (M-H, Random, 95% CI) | 1.56 [0.75, 3.26] |
| 23.6.2 Peritoneal dialysis | 1 | 51 | Risk Ratio (M-H, Random, 95% CI) | 0.73 [0.19, 2.74] |
| 23.7 Cardiovascular events (angina pectoris, myocardial infarction, pulmonary oedema or cardiac failure) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 23.7.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 23.8 Arteriovenous access thrombosis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 23.8.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 23.9 Hypertension | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 23.9.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 23.10 Myocardial infarction | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 23.10.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 23.11 Congestive heart failure | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 23.11.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 23.12 Permanent catheter thrombosis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 23.12.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 23.13 Arterious graft loss | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 23.13.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 23.14 Arterious fistula thrombosis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 23.14.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 23.15 Arterious fistula loss | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 23.15.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 23.16 Permanent catheter loss | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 23.16.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

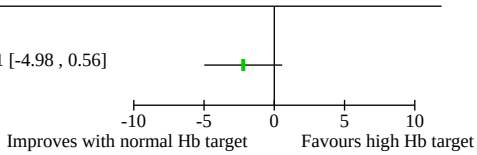
### Analysis 23.1. Comparison 23: Erythropoietin stimulating agents: normal versus high haemoglobin target, Outcome 1: Fatigue

| Study or Subgroup | Normal Hb target Mean | SD | Total | High Hb target Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **23.1.1 Haemodialysis** | | | | | | | | |
| Parfrey 2005 | 64.8 | 23.8822 | 291 | 68.1 | 25.5881 | 291 | -3.30 [-7.32 , 0.72] | |



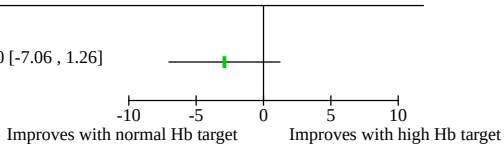

### Analysis 23.2. Comparison 23: Erythropoietin stimulating agents: normal versus high haemoglobin target, Outcome 2: Change in fatigue

| Study or Subgroup | Normal Hb target Mean | SD | Total | High Hb target Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **23.2.1 Haemoglobin** | | | | | | | | |
| Parfrey 2005 | -3.21 | 17.0587 | 291 | -1 | 17.0587 | 291 | -2.21 [-4.98 , 0.56] | |



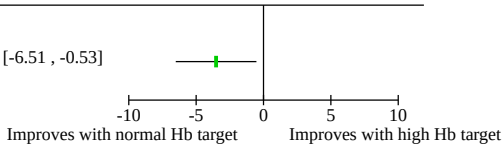

### Analysis 23.3. Comparison 23: Erythropoietin stimulating agents: normal versus high haemoglobin target, Outcome 3: Vitality

| Study or Subgroup | Normal Hb target Mean | SD | Total | High Hb target Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **23.3.1 Haemodialysis** | | | | | | | | |
| Parfrey 2005 | 52.4 | 25.1893 | 282 | 55.3 | 25.1893 | 282 | -2.90 [-7.06 , 1.26] | |



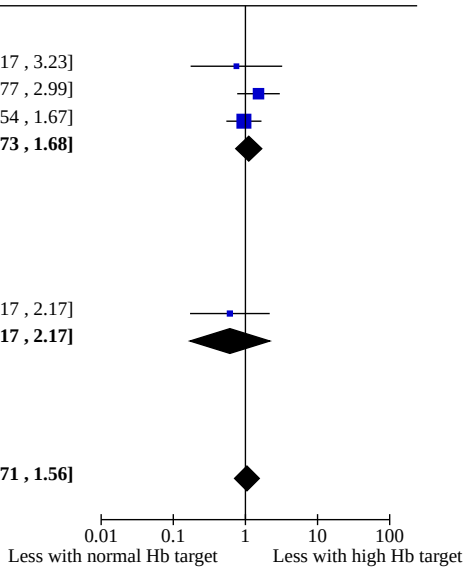
## Analysis 23.4. Comparison 23: Erythropoietin stimulating agents: normal versus high haemoglobin target, Outcome 4: Change in vitality

| Study or Subgroup | Normal Hb target Mean | SD | Total | High Hb target Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **23.4.1 Haemodialysis** | | | | | | | | |
| Parfrey 2005 | -2.31 | 18.1363 | 282 | 1.21 | 18.1363 | 282 | -3.52 [-6.51 , -0.53] | |



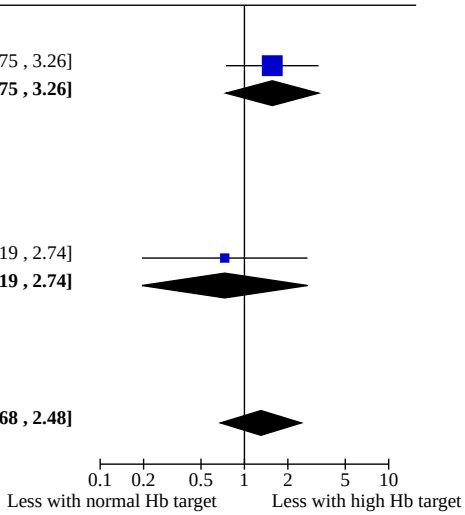

## Analysis 23.5. Comparison 23: Erythropoietin stimulating agents: normal versus high haemoglobin target, Outcome 5: Death (any cause)

| Study or Subgroup | Normal Hb target Events | Total | High Hb target Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **23.5.1 Haemodialysis** | | | | | | | |
| Foley 2000 | 3 | 73 | 4 | 73 | 7.3% | 0.75 [0.17 , 3.23] | |
| Parfrey 2005 | 20 | 300 | 13 | 296 | 33.6% | 1.52 [0.77 , 2.99] | |
| Linde 2001 | 22 | 157 | 20 | 136 | 49.5% | 0.95 [0.54 , 1.67] | |
| **Subtotal (95% CI)** | | **530** | | **505** | **90.4%** | **1.11 [0.73 , 1.68]** | |
| Total events: | 45 | | 37 | | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 1.38, df = 2 (P = 0.50); I² = 0% | | | | | | | |
| Test for overall effect: Z = 0.50 (P = 0.62) | | | | | | | |
| **23.5.2 Peritoneal dialysis** | | | | | | | |
| Linde 2001 | 3 | 23 | 6 | 28 | 9.6% | 0.61 [0.17 , 2.17] | |
| **Subtotal (95% CI)** | | **23** | | **28** | **9.6%** | **0.61 [0.17 , 2.17]** | |
| Total events: | 3 | | 6 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z = 0.77 (P = 0.44) | | | | | | | |
| **Total (95% CI)** | | **553** | | **533** | **100.0%** | **1.05 [0.71 , 1.56]** | |
| Total events: | 48 | | 43 | | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 2.16, df = 3 (P = 0.54); I² = 0% | | | | | | | |
| Test for overall effect: Z = 0.24 (P = 0.81) | | | | | | | |
| Test for subgroup differences: Chi² = 0.78, df = 1 (P = 0.38), I² = 0% | | | | | | | |



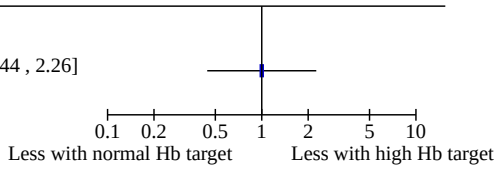
## Analysis 23.6. Comparison 23: Erythropoietin stimulating agents: normal versus high haemoglobin target, Outcome 6: Cardiovascular death

| Study or Subgroup | Normal Hb target Events | Total | High Hb target Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **23.6.1 Haemodialysis** | | | | | | |
| Linde 2001 | 18 | 157 | 10 | 136 | 76.2% | 1.56 [0.75 , 3.26] |
| **Subtotal (95% CI)** | | **157** | | **136** | **76.2%** | **1.56 [0.75 , 3.26]** |
| Total events: | 18 | | 10 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.18 (P = 0.24) | | | | | | |
| **23.6.2 Peritoneal dialysis** | | | | | | |
| Linde 2001 | 3 | 23 | 5 | 28 | 23.8% | 0.73 [0.19 , 2.74] |
| **Subtotal (95% CI)** | | **23** | | **28** | **23.8%** | **0.73 [0.19 , 2.74]** |
| Total events: | 3 | | 5 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.47 (P = 0.64) | | | | | | |
| **Total (95% CI)** | | **180** | | **164** | **100.0%** | **1.30 [0.68 , 2.48]** |
| Total events: | 21 | | 15 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.97, df = 1 (P = 0.33); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.80 (P = 0.42) | | | | | | |
| Test for subgroup differences: Chi² = 0.96, df = 1 (P = 0.33), I² = 0% | | | | | | |



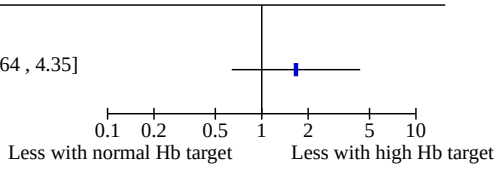

## Analysis 23.7. Comparison 23: Erythropoietin stimulating agents: normal versus high haemoglobin target, Outcome 7: Cardiovascular events (angina pectoris, myocardial infarction, pulmonary oedema or cardiac failure)

| Study or Subgroup | Normal Hb target Events | Total | High Hb target Events | Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **23.7.1 Haemodialysis** | | | | | |
| Foley 2000 | 10 | 73 | 10 | 73 | 1.00 [0.44 , 2.26] |



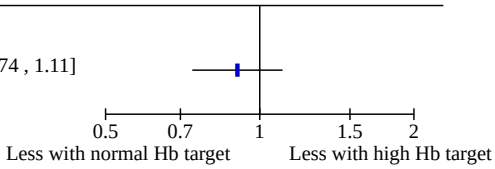

## Analysis 23.8. Comparison 23: Erythropoietin stimulating agents: normal versus high haemoglobin target, Outcome 8: Arteriovenous access thrombosis

| Study or Subgroup | Normal Hb target Events | Total | High Hb target Events | Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **23.8.1 Haemodialysis** | | | | | |
| Foley 2000 | 10 | 73 | 6 | 73 | 1.67 [0.64 , 4.35] |



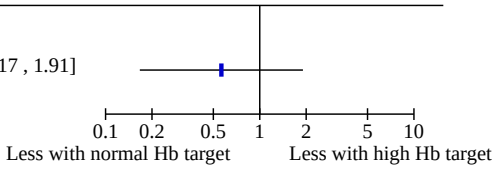
### Analysis 23.9. Comparison 23: Erythropoietin stimulating agents: normal versus high haemoglobin target, Outcome 9: Hypertension

| Study or Subgroup | Normal Hb target Events | Total | High Hb target Events | Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **23.9.1 Haemodialysis** | | | | | |
| Parfrey 2005 | 110 | 300 | 120 | 296 | 0.90 [0.74 , 1.11] |



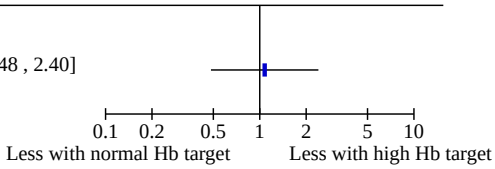

### Analysis 23.10. Comparison 23: Erythropoietin stimulating agents: normal versus high haemoglobin target, Outcome 10: Myocardial infarction

| Study or Subgroup | Normal Hb target Events | Total | High Hb target Events | Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **23.10.1 Haemodialysis** | | | | | |
| Parfrey 2005 | 4 | 300 | 7 | 296 | 0.56 [0.17 , 1.91] |



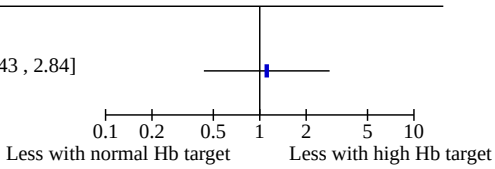

### Analysis 23.11. Comparison 23: Erythropoietin stimulating agents: normal versus high haemoglobin target, Outcome 11: Congestive heart failure

| Study or Subgroup | Normal Hb target Events | Total | High Hb target Events | Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **23.11.1 Haemodialysis** | | | | | |
| Parfrey 2005 | 12 | 300 | 11 | 296 | 1.08 [0.48 , 2.40] |



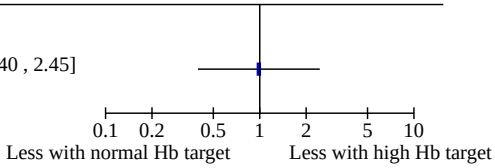

### Analysis 23.12. Comparison 23: Erythropoietin stimulating agents: normal versus high haemoglobin target, Outcome 12: Permanent catheter thrombosis

| Study or Subgroup | Normal Hb target Events | Total | High Hb target Events | Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **23.12.1 Haemodialysis** | | | | | |
| Parfrey 2005 | 9 | 300 | 8 | 296 | 1.11 [0.43 , 2.84] |



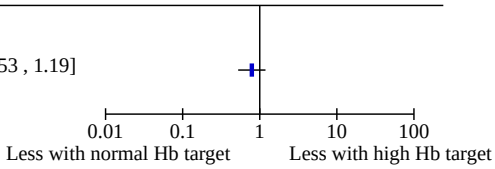
### Analysis 23.13. Comparison 23: Erythropoietin stimulating agents: normal versus high haemoglobin target, Outcome 13: Arterious graft loss

| Study or Subgroup | Normal Hb target Events | Total | High Hb target Events | Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **23.13.1 Haemodialysis** | | | | | | |
| Parfrey 2005 | 9 | 300 | 9 | 296 | 0.99 [0.40 , 2.45] | |



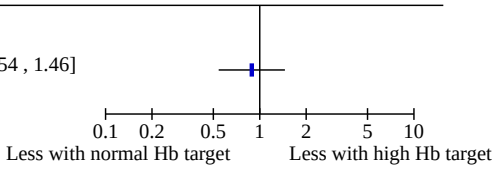

### Analysis 23.14. Comparison 23: Erythropoietin stimulating agents: normal versus high haemoglobin target, Outcome 14: Arterious fistula thrombosis

| Study or Subgroup | Normal Hb target Events | Total | High Hb target Events | Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **23.14.1 Haemodialysis** | | | | | | |
| Parfrey 2005 | 36 | 300 | 45 | 296 | 0.79 [0.53 , 1.19] | |



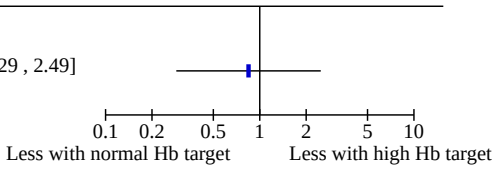

### Analysis 23.15. Comparison 23: Erythropoietin stimulating agents: normal versus high haemoglobin target, Outcome 15: Arterious fistula loss

| Study or Subgroup | Normal Hb target Events | Total | High Hb target Events | Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **23.15.1 Haemodialysis** | | | | | | |
| Parfrey 2005 | 27 | 300 | 30 | 296 | 0.89 [0.54 , 1.46] | |




### Analysis 23.16. Comparison 23: Erythropoietin stimulating agents: normal versus high haemoglobin target, Outcome 16: Permanent catheter loss

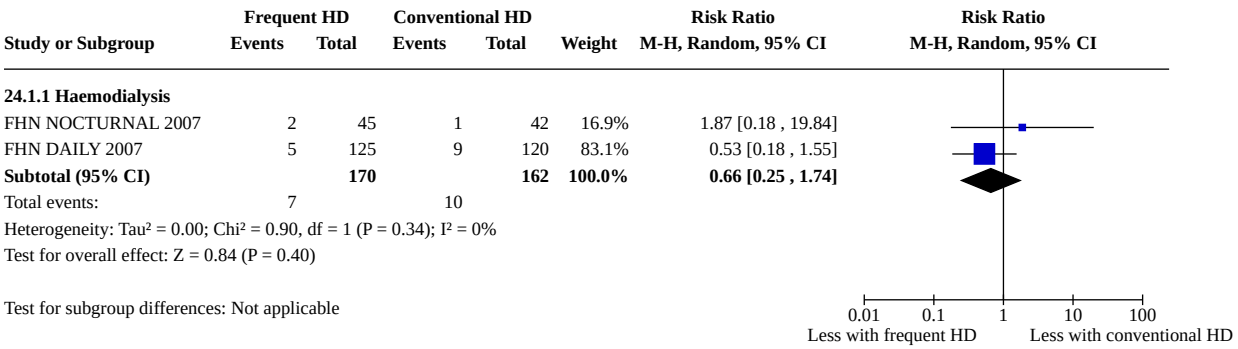
| Study or Subgroup | Normal Hb target Events | Total | High Hb target Events | Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **23.16.1 Haemodialysis** | | | | | | |
| Parfrey 2005 | 6 | 300 | 7 | 296 | 0.85 [0.29 , 2.49] | |



**Comparison 24. Frequent versus conventional haemodialysis**

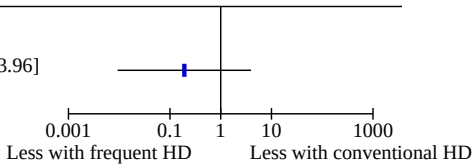
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 24.1 Death (any cause) | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 24.1.1 Haemodialysis | 2 | 332 | Risk Ratio (M-H, Random, 95% CI) | 0.66 [0.25, 1.74] |
| 24.2 Cardiovascular death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 24.2.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 24.3 Depression | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 24.3.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 24.4 Vascular access outcomes (repair, loss, or access-related hospitalisation) | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 24.4.1 Haemodialysis | 2 | 332 | Risk Ratio (M-H, Random, 95% CI) | 1.53 [1.13, 2.07] |
| 24.5 Access loss | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 24.5.1 Haemodialysis | 2 | 332 | Risk Ratio (M-H, Random, 95% CI) | 1.21 [0.72, 2.03] |
| 24.6 Access stenosis | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 24.6.1 Haemodialysis | 2 | 332 | Risk Ratio (M-H, Random, 95% CI) | 1.10 [0.37, 3.25] |
| 24.7 Access thrombosis | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 24.7.1 Haemodialysis | 2 | 332 | Risk Ratio (M-H, Random, 95% CI) | 1.53 [0.28, 8.51] |

**Analysis 24.1. Comparison 24: Frequent versus conventional haemodialysis, Outcome 1: Death (any cause)**



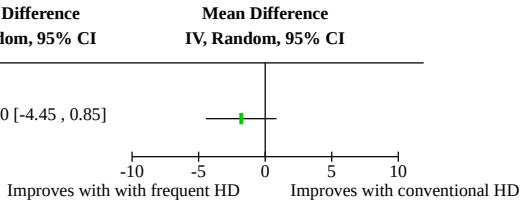
## Analysis 24.2. Comparison 24: Frequent versus conventional haemodialysis, Outcome 2: Cardiovascular death

| Study or Subgroup | Frequent HD Events | Frequent HD Total | Conventional HD Events | Conventional HD Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **24.2.1 Haemodialysis** | | | | | |
| FHN DAILY 2007 | 0 | 125 | 2 | 120 | 0.19 [0.01 , 3.96] |



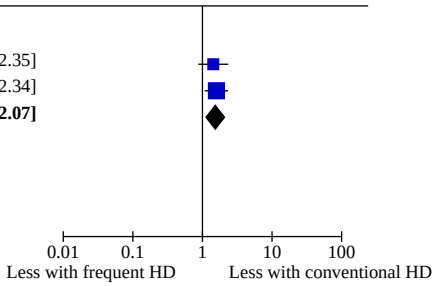

## Analysis 24.3. Comparison 24: Frequent versus conventional haemodialysis, Outcome 3: Depression

| Study or Subgroup | Frequent HD Mean | Frequent HD SD | Frequent HD Total | Conventional HD Mean | Conventional HD SD | Conventional HD Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **24.3.1 Haemodialysis** | | | | | | | |
| FHN DAILY 2007 | 10.4 | 8.5 | 101 | 12.2 | 9.9 | 88 | -1.80 [-4.45 , 0.85] |



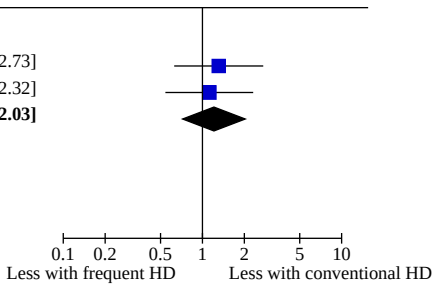

## Analysis 24.4. Comparison 24: Frequent versus conventional haemodialysis, Outcome 4: Vascular access outcomes (repair, loss, or access-related hospitalisation)

| Study or Subgroup | Frequent HD Events | Frequent HD Total | Conventional HD Events | Conventional HD Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **24.4.1 Haemodialysis** | | | | | | |
| FHN NOCTURNAL 2007 | 23 | 45 | 15 | 42 | 37.8% | 1.43 [0.87 , 2.35] |
| FHN DAILY 2007 | 48 | 125 | 29 | 120 | 62.2% | 1.59 [1.08 , 2.34] |
| **Subtotal (95% CI)** | | **170** | | **162** | **100.0%** | **1.53 [1.13 , 2.07]** |
| Total events: | 71 | | 44 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0% | | | | | | |
| Test for overall effect: Z = 2.72 (P = 0.007) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |




## Analysis 24.5. Comparison 24: Frequent versus conventional haemodialysis, Outcome 5: Access loss

| Study or Subgroup | Frequent HD Events | Frequent HD Total | Conventional HD Events | Conventional HD Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **24.5.1 Haemodialysis** | | | | | | |
| FHN DAILY 2007 | 15 | 125 | 11 | 120 | 49.3% | 1.31 [0.63 , 2.73] |
| FHN NOCTURNAL 2007 | 12 | 45 | 10 | 42 | 50.7% | 1.12 [0.54 , 2.32] |
| **Subtotal (95% CI)** | | **170** | | **162** | **100.0%** | **1.21 [0.72 , 2.03]** |
| Total events: | 27 | | 21 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.77); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.72 (P = 0.47) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |

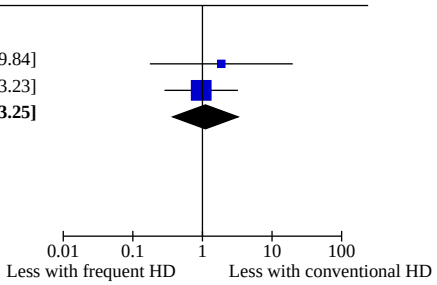


### Analysis 24.6. Comparison 24: Frequent versus conventional haemodialysis, Outcome 6: Access stenosis

| Study or Subgroup | Frequent HD Events | Frequent HD Total | Conventional HD Events | Conventional HD Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **24.6.1 Haemodialysis** | | | | | | |
| FHN NOCTURNAL 2007 | 2 | 45 | 1 | 42 | 20.9% | 1.87 [0.18 , 19.84] |
| FHN DAILY 2007 | 5 | 125 | 5 | 120 | 79.1% | 0.96 [0.29 , 3.23] |
| **Subtotal (95% CI)** | | **170** | | **162** | **100.0%** | **1.10 [0.37 , 3.25]** |
| Total events: | 7 | | 6 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.18 (P = 0.86)

Test for subgroup differences: Not applicable

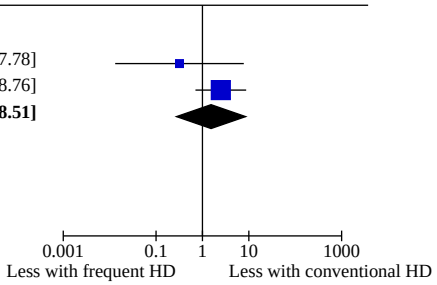



### Analysis 24.7. Comparison 24: Frequent versus conventional haemodialysis, Outcome 7: Access thrombosis

| Study or Subgroup | Frequent HD Events | Frequent HD Total | Conventional HD Events | Conventional HD Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **24.7.1 Haemodialysis** | | | | | | |
| FHN DAILY 2007 | 0 | 125 | 1 | 120 | 23.6% | 0.32 [0.01 , 7.78] |
| FHN NOCTURNAL 2007 | 8 | 45 | 3 | 42 | 76.4% | 2.49 [0.71 , 8.76] |
| **Subtotal (95% CI)** | | **170** | | **162** | **100.0%** | **1.53 [0.28 , 8.51]** |
| Total events: | 8 | | 4 | | | |

Heterogeneity: Tau² = 0.59; Chi² = 1.38, df = 1 (P = 0.24); I² = 28%
Test for overall effect: Z = 0.49 (P = 0.62)

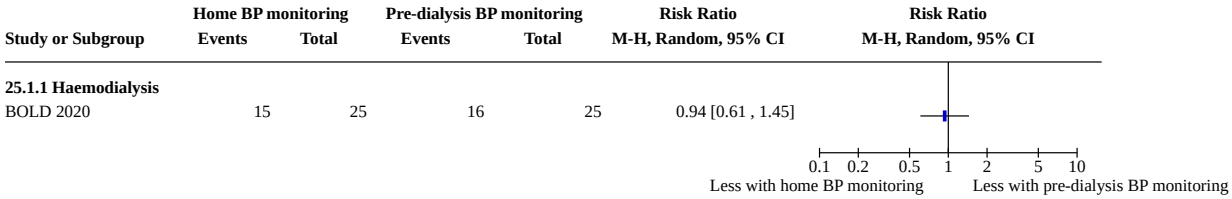
Test for subgroup differences: Not applicable



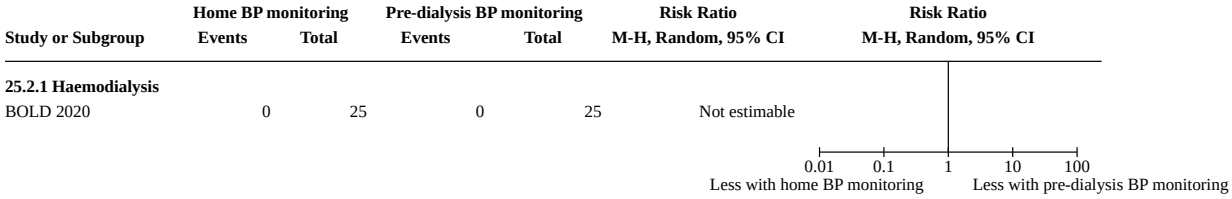

## Comparison 25. Home versus pre-dialysis blood pressure monitoring

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 25.1 Number reporting fatigue | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 25.1.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 25.2 Death (any cause) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 25.2.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 25.3 Cardiovascular death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 25.3.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

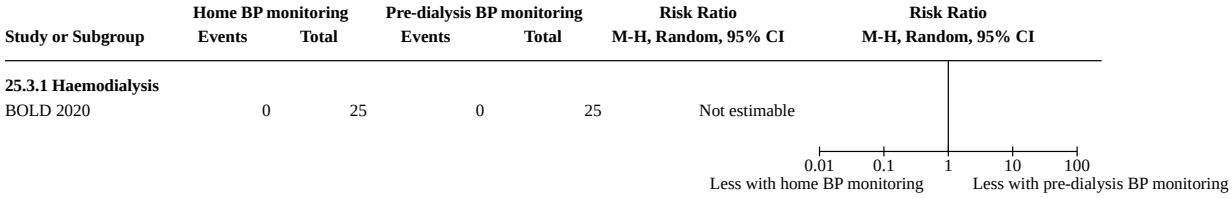
### Analysis 25.1. Comparison 25: Home versus pre-dialysis blood pressure monitoring, Outcome 1: Number reporting fatigue




### Analysis 25.2. Comparison 25: Home versus pre-dialysis blood pressure monitoring, Outcome 2: Death (any cause)




### Analysis 25.3. Comparison 25: Home versus pre-dialysis blood pressure monitoring, Outcome 3: Cardiovascular death

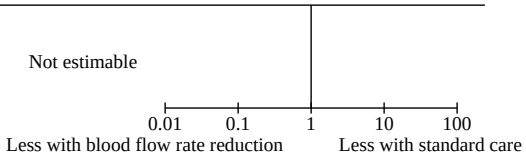



## Comparison 26. Blood flow rate reduction versus standard care

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 26.1 Death (any cause) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 26.1.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 26.2 Cardiovascular death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 26.2.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

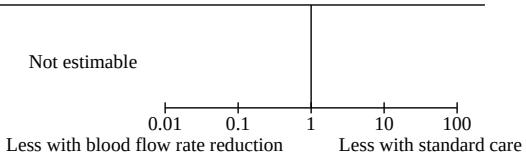
### Analysis 26.1. Comparison 26: Blood flow rate reduction versus standard care, Outcome 1: Death (any cause)

| Study or Subgroup | Blood flow rate reduction Events | Total | Standard care Events | Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **26.1.1 Haemodialysis** | | | | | | |
| Duggal 2019 | 0 | 52 | 0 | 50 | Not estimable | |




### Analysis 26.2. Comparison 26: Blood flow rate reduction versus standard care, Outcome 2: Cardiovascular death

| Study or Subgroup | Blood flow rate reduction Events | Total | Standard care Events | Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **26.2.1 Haemodialysis** | | | | | | |
| Duggal 2019 | 0 | 52 | 0 | 50 | Not estimable | |

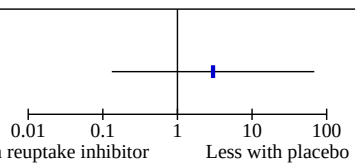



## Comparison 27. Serotonin reuptake inhibitor versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 27.1 Death (any cause) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 27.1.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 27.2 Cardiovascular death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 27.2.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 27.3 Depression | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 27.3.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

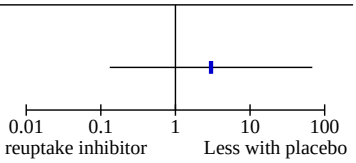
### Analysis 27.1. Comparison 27: Serotonin reuptake inhibitor versus placebo, Outcome 1: Death (any cause)

| Study or Subgroup | Serotonin reuptake inhibitor Events | Total | Placebo Events | Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **27.1.1 Haemodialysis** | | | | | | |
| ASSertID 2015 | 1 | 15 | 0 | 15 | 3.00 [0.13 , 68.26] | |



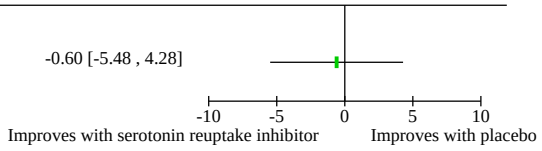
### Analysis 27.2. Comparison 27: Serotonin reuptake inhibitor versus placebo, Outcome 2: Cardiovascular death

| Study or Subgroup | Serotonin reuptake inhibitor Events | Total | Placebo Events | Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **27.2.1 Haemodialysis** | | | | | |
| ASSertID 2015 | 1 | 15 | 0 | 15 | 3.00 [0.13 , 68.26] |




### Analysis 27.3. Comparison 27: Serotonin reuptake inhibitor versus placebo, Outcome 3: Depression

| Study or Subgroup | Serotonin reuptake inhibitor Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **27.3.1 Haemodialysis** | | | | | | | |
| ASSertID 2015 | 10.3 | 5.8 | 8 | 10.9 | 5.1 | 13 | -0.60 [-5.48 , 4.28] |



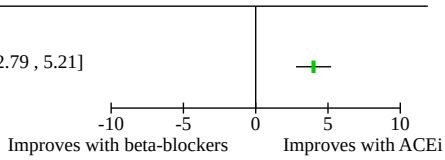

### Comparison 28. Beta-blockers versus angiotensin-converting enzyme inhibitors

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 28.1 Change in energy/fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 28.1.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 28.2 Change in overall health (QoL) | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 28.2.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 28.3 Change in general health (QoL) | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 28.3.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 28.4 Death (any cause) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 28.4.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 28.5 Cardiovascular death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 28.5.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 28.6 Cardiovascular events | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 28.6.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 28.7 Access-related events | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 28.7.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 28.8 Change in sleep quality | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 28.8.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

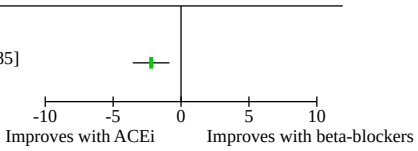
**Analysis 28.1. Comparison 28: Beta-blockers versus angiotensin-converting enzyme inhibitors, Outcome 1: Change in energy/fatigue**

| | Beta-blockers | | | ACEi | | | Mean Difference | Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | IV, Random, 95% CI | IV, Random, 95% CI |
| **28.1.1 Haemodialysis** | | | | | | | | |
| HDPAL 2014 | 6.3 | 2.6 | 51 | 2.3 | 3 | 36 | 4.00 [2.79 , 5.21] | |



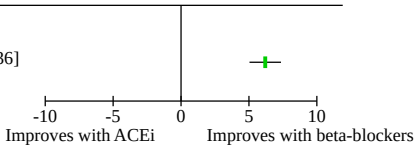

**Analysis 28.2. Comparison 28: Beta-blockers versus angiotensin-converting enzyme inhibitors, Outcome 2: Change in overall health (QoL)**

| | Beta-blockers | | | ACEi | | | Mean Difference | Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | IV, Random, 95% CI | IV, Random, 95% CI |
| **28.2.1 Haemodialysis** | | | | | | | | |
| HDPAL 2014 | -1.8 | 2.8 | 48 | 0.4 | 3.3 | 35 | -2.20 [-3.55 , -0.85] | |



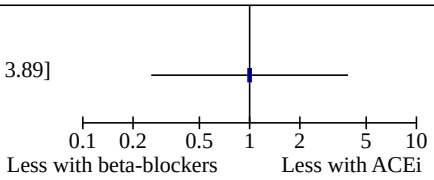

**Analysis 28.3. Comparison 28: Beta-blockers versus angiotensin-converting enzyme inhibitors, Outcome 3: Change in general health (QoL)**

| | Beta-blockers | | | ACEi | | | Mean Difference | Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | IV, Random, 95% CI | IV, Random, 95% CI |
| **28.3.1 Haemodialysis** | | | | | | | | |
| HDPAL 2014 | 3.3 | 2.5 | 51 | -2.9 | 2.9 | 37 | 6.20 [5.04 , 7.36] | |



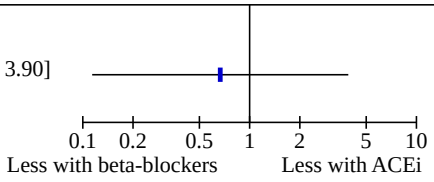
### Analysis 28.4. Comparison 28: Beta-blockers versus angiotensin-converting enzyme inhibitors, Outcome 4: Death (any cause)

| Study or Subgroup | Beta-blockers Events | Total | ACEi Events | Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **28.4.1 Haemodialysis** | | | | | | |
| HDPAL 2014 | 4 | 100 | 4 | 100 | 1.00 [0.26 , 3.89] | |



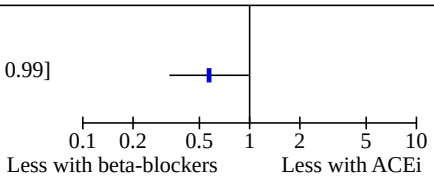

### Analysis 28.5. Comparison 28: Beta-blockers versus angiotensin-converting enzyme inhibitors, Outcome 5: Cardiovascular death

| Study or Subgroup | Beta-blockers Events | Total | ACEi Events | Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **28.5.1 Haemodialysis** | | | | | | |
| HDPAL 2014 | 2 | 100 | 3 | 100 | 0.67 [0.11 , 3.90] | |



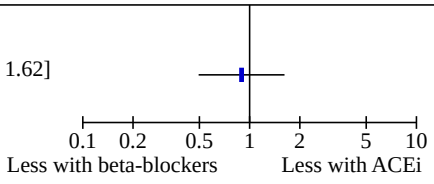

### Analysis 28.6. Comparison 28: Beta-blockers versus angiotensin-converting enzyme inhibitors, Outcome 6: Cardiovascular events

| Study or Subgroup | Beta-blockers Events | Total | ACEi Events | Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **28.6.1 Haemodialysis** | | | | | | |
| HDPAL 2014 | 16 | 100 | 28 | 100 | 0.57 [0.33 , 0.99] | |

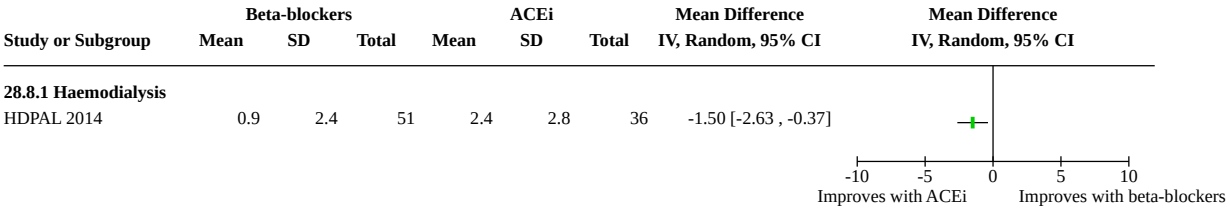



### Analysis 28.7. Comparison 28: Beta-blockers versus angiotensin-converting enzyme inhibitors, Outcome 7: Access-related events

| Study or Subgroup | Beta-blockers Events | Total | ACEi Events | Total | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **28.7.1 Haemodialysis** | | | | | | |
| HDPAL 2014 | 17 | 100 | 19 | 100 | 0.89 [0.49 , 1.62] | |



**Analysis 28.8. Comparison 28: Beta-blockers versus angiotensin-converting enzyme inhibitors, Outcome 8: Change in sleep quality**

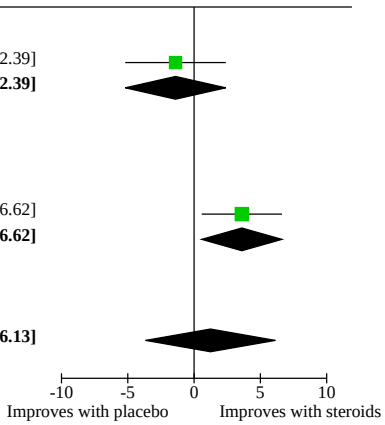



## Comparison 29. Anabolic steroids versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 29.1 Fatigue | 2 | 52 | Mean Difference (IV, Random, 95% CI) | 1.24 [-3.66, 6.13] |
| 29.1.1 Haemodialysis and peritoneal dialysis | 1 | 19 | Mean Difference (IV, Random, 95% CI) | -1.40 [-5.19, 2.39] |
| 29.1.2 Haemodialysis | 1 | 33 | Mean Difference (IV, Random, 95% CI) | 3.60 [0.58, 6.62] |
| 29.2 Change in fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 29.2.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 29.3 Death (any cause) | 2 | 68 | Risk Ratio (M-H, Random, 95% CI) | 0.35 [0.04, 3.23] |
| 29.3.1 Haemodialysis and peritoneal dialysis | 1 | 29 | Risk Ratio (M-H, Random, 95% CI) | 0.36 [0.02, 8.07] |
| 29.3.2 Haemodialysis | 1 | 39 | Risk Ratio (M-H, Random, 95% CI) | 0.35 [0.02, 8.10] |

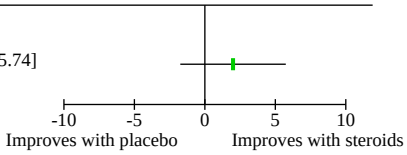
## Analysis 29.1. Comparison 29: Anabolic steroids versus placebo, Outcome 1: Fatigue

| Study or Subgroup | Steroids Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **29.1.1 Haemodialysis and peritoneal dialysis** | | | | | | | | |
| Johansen 1999 | 3.1 | 4.5 | 11 | 4.5 | 3.9 | 8 | 47.3% | -1.40 [-5.19 , 2.39] |
| **Subtotal (95% CI)** | | | **11** | | | **8** | **47.3%** | **-1.40 [-5.19 , 2.39]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.72 (P = 0.47) | | | | | | | | |
| **29.1.2 Haemodialysis** | | | | | | | | |
| Johansen 2006 | 10.8 | 4.8 | 16 | 7.2 | 4 | 17 | 52.7% | 3.60 [0.58 , 6.62] |
| **Subtotal (95% CI)** | | | **16** | | | **17** | **52.7%** | **3.60 [0.58 , 6.62]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 2.33 (P = 0.02) | | | | | | | | |
| **Total (95% CI)** | | | **27** | | | **25** | **100.0%** | **1.24 [-3.66 , 6.13]** |
| Heterogeneity: Tau² = 9.44; Chi² = 4.08, df = 1 (P = 0.04); I² = 76% | | | | | | | | |
| Test for overall effect: Z = 0.50 (P = 0.62) | | | | | | | | |
| Test for subgroup differences: Chi² = 4.08, df = 1 (P = 0.04), I² = 75.5% | | | | | | | | |



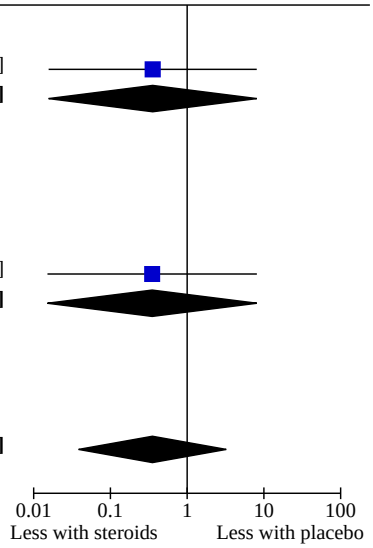

## Analysis 29.2. Comparison 29: Anabolic steroids versus placebo, Outcome 2: Change in fatigue

| Study or Subgroup | Steroids Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **29.2.1 Haemodialysis** | | | | | | | |
| Johansen 2006 | 1.1 | 3.3 | 16 | -0.9 | 7.1 | 17 | 2.00 [-1.74 , 5.74] |




## Analysis 29.3. Comparison 29: Anabolic steroids versus placebo, Outcome 3: Death (any cause)

| Study or Subgroup | Steroids Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **29.3.1 Haemodialysis and peritoneal dialysis** | | | | | | |
| Johansen 1999 | 0 | 14 | 1 | 15 | 50.3% | 0.36 [0.02 , 8.07] |
| **Subtotal (95% CI)** | | **14** | | **15** | **50.3%** | **0.36 [0.02 , 8.07]** |
| Total events: | 0 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.65 (P = 0.52) | | | | | | |
| **29.3.2 Haemodialysis** | | | | | | |
| Johansen 2006 | 0 | 19 | 1 | 20 | 49.7% | 0.35 [0.02 , 8.10] |
| **Subtotal (95% CI)** | | **19** | | **20** | **49.7%** | **0.35 [0.02 , 8.10]** |
| Total events: | 0 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.65 (P = 0.51) | | | | | | |
| **Total (95% CI)** | | **33** | | **35** | **100.0%** | **0.35 [0.04 , 3.23]** |
| Total events: | 0 | | 2 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.92 (P = 0.36) | | | | | | |
| Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0% | | | | | | |

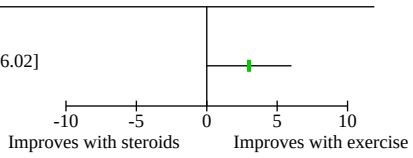


## Comparison 30. Anabolic steroids versus exercise

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 30.1 Fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 30.1.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 30.2 Change in fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 30.2.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 30.3 Death (any cause) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 30.3.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 30.4 Cardiovascular death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 30.4.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

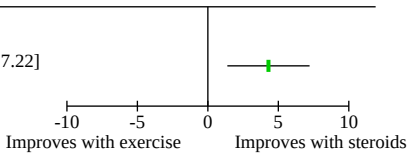
### Analysis 30.1. Comparison 30: Anabolic steroids versus exercise, Outcome 1: Fatigue

| | Steroids | | | Exercise | | | Mean Difference | Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | IV, Random, 95% CI | IV, Random, 95% CI |
| **30.1.1 Haemodialysis** | | | | | | | | |
| Johansen 2006 | 10.8 | 4.8 | 16 | 7.8 | 4.2 | 19 | 3.00 [-0.02 , 6.02] | |



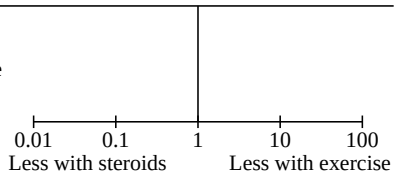

### Analysis 30.2. Comparison 30: Anabolic steroids versus exercise, Outcome 2: Change in fatigue

| | Steroids | | | Exercise | | | Mean Difference | Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | IV, Random, 95% CI | IV, Random, 95% CI |
| **30.2.1 Haemodialysis** | | | | | | | | |
| Johansen 2006 | 1.1 | 3.3 | 16 | -3.2 | 5.4 | 19 | 4.30 [1.38 , 7.22] | |



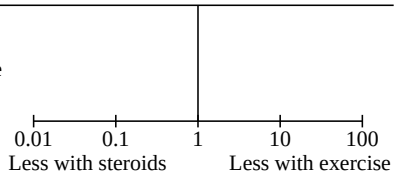
### Analysis 30.3. Comparison 30: Anabolic steroids versus exercise, Outcome 3: Death (any cause)

| Study or Subgroup | Steroids Events | Steroids Total | Exercise Events | Exercise Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **30.3.1 Haemodialysis** | | | | | |
| Johansen 2006 | 0 | 19 | 0 | 20 | Not estimable |




### Analysis 30.4. Comparison 30: Anabolic steroids versus exercise, Outcome 4: Cardiovascular death

| Study or Subgroup | Steroids Events | Steroids Total | Exercise Events | Exercise Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **30.4.1 Haemodialysis** | | | | | |
| Johansen 2006 | 0 | 19 | 0 | 20 | Not estimable |

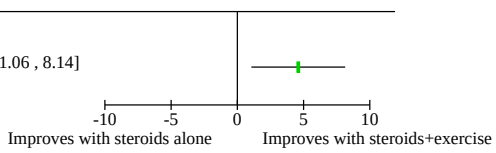



## Comparison 31. Anabolic steroids alone versus anabolic steroids + exercise

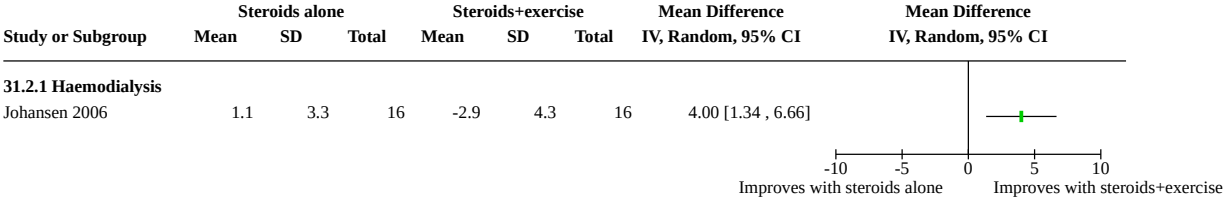
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 31.1 Fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 31.1.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 31.2 Change in fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 31.2.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 31.3 Death (any cause) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 31.3.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

### Analysis 31.1. Comparison 31: Anabolic steroids alone versus anabolic steroids + exercise, Outcome 1: Fatigue

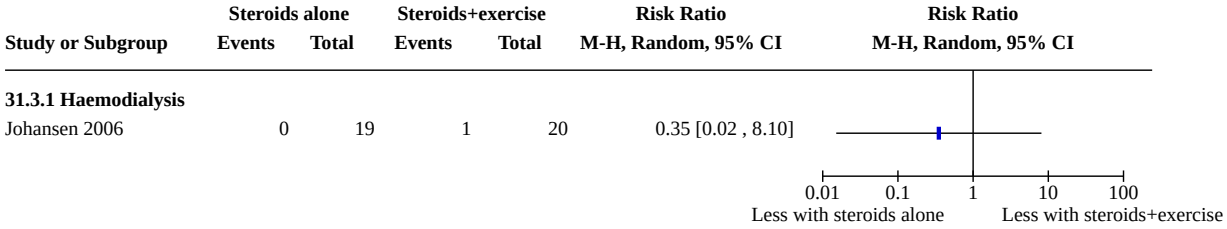
| Study or Subgroup | Steroids alone Mean | SD | Total | Steroids+exercise Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **31.1.1 Haemodialysis** | | | | | | | |
| Johansen 2006 | 10.8 | 4.8 | 16 | 6.2 | 5.4 | 16 | 4.60 [1.06 , 8.14] |



### Analysis 31.2. Comparison 31: Anabolic steroids alone versus anabolic steroids + exercise, Outcome 2: Change in fatigue



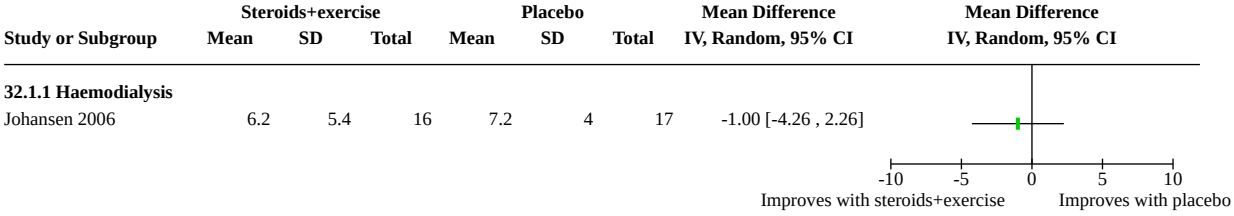

### Analysis 31.3. Comparison 31: Anabolic steroids alone versus anabolic steroids + exercise, Outcome 3: Death (any cause)




## Comparison 32. Anabolic steroids + exercise versus placebo

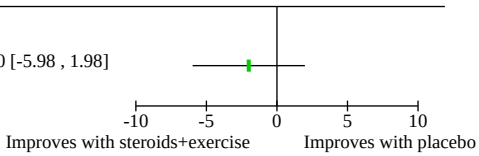
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 32.1 Fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 32.1.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 32.2 Change in fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 32.2.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 32.3 Death (any cause) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 32.3.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

### Analysis 32.1. Comparison 32: Anabolic steroids + exercise versus placebo, Outcome 1: Fatigue



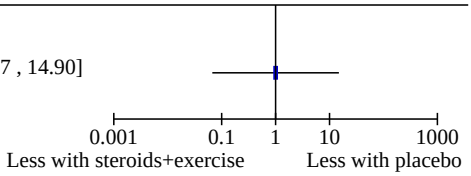
### Analysis 32.2. Comparison 32: Anabolic steroids + exercise versus placebo, Outcome 2: Change in fatigue

| Study or Subgroup | Steroids+exercise Mean | SD | Total | Placebo Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **32.2.1 Haemodialysis** | | | | | | | |
| Johansen 2006 | -2.9 | 4.3 | 16 | -0.9 | 7.1 | 17 | -2.00 [-5.98 , 1.98] |




### Analysis 32.3. Comparison 32: Anabolic steroids + exercise versus placebo, Outcome 3: Death (any cause)

| Study or Subgroup | Steroids+exercise Events | Total | Placebo Events | Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **32.3.1 Haemodialysis** | | | | | |
| Johansen 2006 | 1 | 20 | 1 | 20 | 1.00 [0.07 , 14.90] |

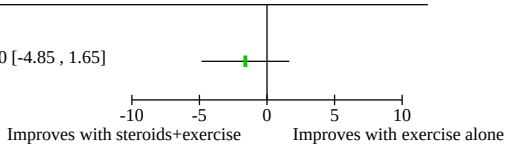



## Comparison 33. Anabolic steroids + exercise versus exercise alone

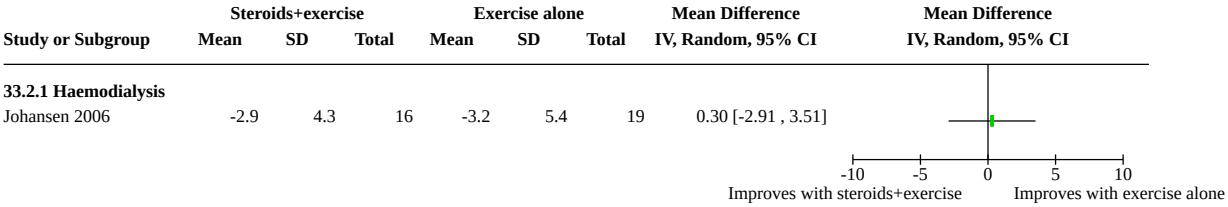
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 33.1 Fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 33.1.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 33.2 Change in fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 33.2.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 33.3 Death (any cause) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 33.3.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

### Analysis 33.1. Comparison 33: Anabolic steroids + exercise versus exercise alone, Outcome 1: Fatigue

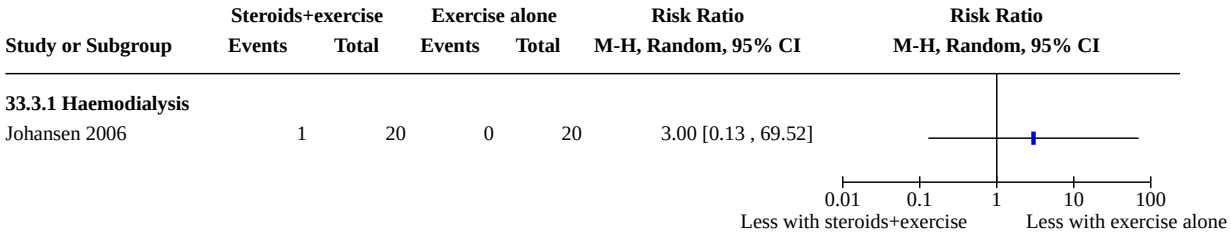
| Study or Subgroup | Steroids+exercise Mean | SD | Total | Exercise alone Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **33.1.1 Haemodialysis** | | | | | | | |
| Johansen 2006 | 6.2 | 5.4 | 16 | 7.8 | 4.2 | 19 | -1.60 [-4.85 , 1.65] |



### Analysis 33.2. Comparison 33: Anabolic steroids + exercise versus exercise alone, Outcome 2: Change in fatigue



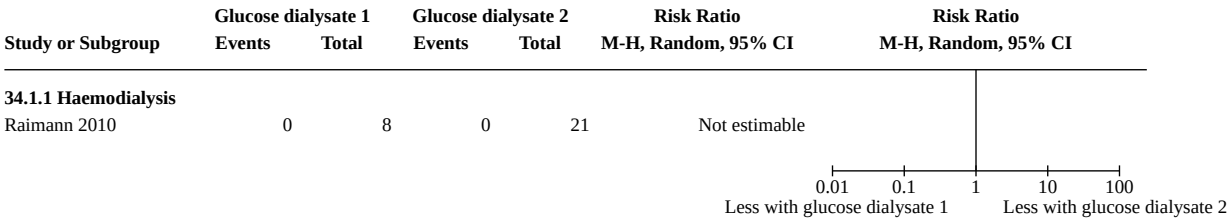

### Analysis 33.3. Comparison 33: Anabolic steroids + exercise versus exercise alone, Outcome 3: Death (any cause)



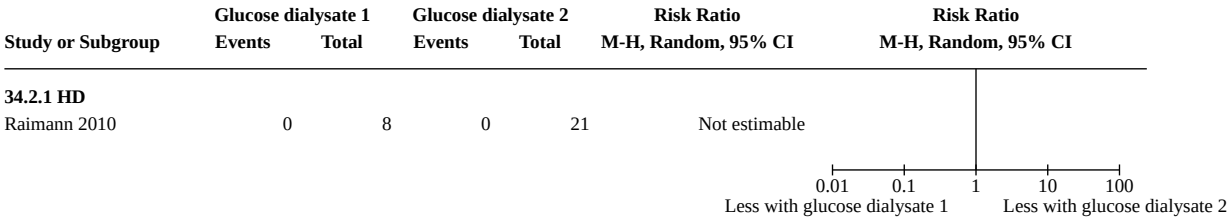

## Comparison 34. Glucose dialysate versus another glucose dialysate

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 34.1 Death (any cause) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 34.1.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 34.2 Cardiovascular death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 34.2.1 HD | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

### Analysis 34.1. Comparison 34: Glucose dialysate versus another glucose dialysate, Outcome 1: Death (any cause)



### Analysis 34.2. Comparison 34: Glucose dialysate versus another glucose dialysate, Outcome 2: Cardiovascular death




### Comparison 35. Acupressure versus placebo or control

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 35.1 Fatigue | 6 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 35.1.1 Haemodialysis | 6 | 459 | Std. Mean Difference (IV, Random, 95% CI) | -0.64 [-1.03, -0.25] |
| 35.2 Change in fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 35.2.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 35.3 Fatigue in the last week | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 35.3.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 35.4 Fatigue strength rate | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 35.4.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 35.5 Usual level of fatigue during past 24 hours | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 35.5.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 35.6 Worst level of fatigue during past 24 hours | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 35.6.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 35.7 Death (any cause) | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 35.7.1 Haemodialysis | 2 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 35.8 Cardiovascular death | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 35.8.1 Haemodialysis | 2 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 35.9 Quality of life (overall) | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 35.9.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

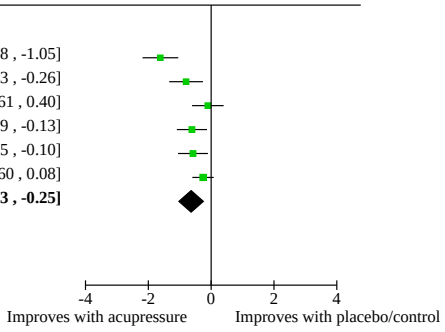
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 35.10 Depression | 3 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 35.10.1 Haemodialysis | 3 | 199 | Mean Difference (IV, Random, 95% CI) | -4.10 [-6.73, -1.47] |
| 35.11 Mood | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 35.11.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 35.12 Sleep quality | 2 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 35.12.1 Haemodialysis | 2 | 141 | Mean Difference (IV, Random, 95% CI) | -1.17 [-2.59, 0.24] |

### Analysis 35.1. Comparison 35: Acupressure versus placebo or control, Outcome 1: Fatigue

| Study or Subgroup | Acupressure Mean | SD | Total | Placebo/control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **35.1.1 Haemodialysis** | | | | | | | | |
| Sabouhi 2013 | 4.6 | 0.975 | 32 | 6.3 | 1.1 | 32 | 15.2% | -1.62 [-2.18 , -1.05] |
| Cho 2004 | 3.4 | 1.5 | 28 | 4.7 | 1.7 | 30 | 15.7% | -0.80 [-1.33 , -0.26] |
| Su 2009 | 121.71 | 32.68 | 31 | 125.1 | 30.9 | 30 | 16.3% | -0.11 [-0.61 , 0.40] |
| Tsay 2004b | 4.61 | 1.72 | 35 | 5.7 | 1.8 | 35 | 16.7% | -0.61 [-1.09 , -0.13] |
| Tsay 2004a | 4.66 | 1.77 | 35 | 5.71 | 1.82 | 36 | 16.8% | -0.58 [-1.05 , -0.10] |
| Bicer 2022 | 5.84 | 1.47 | 67 | 6.18 | 1.12 | 68 | 19.2% | -0.26 [-0.60 , 0.08] |
| **Subtotal (95% CI)** | | | **228** | | | **231** | **100.0%** | **-0.64 [-1.03 , -0.25]** |

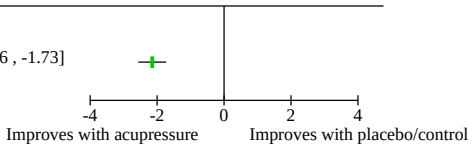
Heterogeneity: Tau² = 0.18; Chi² = 20.22, df = 5 (P = 0.001); I² = 75%
Test for overall effect: Z = 3.21 (P = 0.001)

Test for subgroup differences: Not applicable



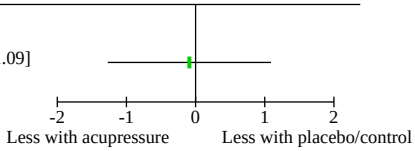

### Analysis 35.2. Comparison 35: Acupressure versus placebo or control, Outcome 2: Change in fatigue

| Study or Subgroup | Acupressure Mean | SD | Total | Placebo/control Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **35.2.1 Haemodialysis** | | | | | | | |
| Sabouhi 2013 | -2.07 | 1.07 | 32 | 0.075 | 0.542 | 32 | -2.15 [-2.56 , -1.73] |



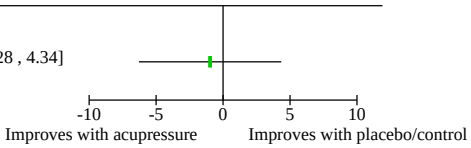

### Analysis 35.3. Comparison 35: Acupressure versus placebo or control, Outcome 3: Fatigue in the last week

| Study or Subgroup | Acupressure Mean | SD | Total | Placebo/control Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **35.3.1 Haemodialysis** | | | | | | | |
| Lin 2011 | 1.19 | 2.4 | 36 | 1.28 | 2.25 | 25 | -0.09 [-1.27 , 1.09] |



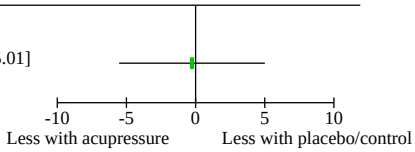
## Analysis 35.4. Comparison 35: Acupressure versus placebo or control, Outcome 4: Fatigue strength rate

| Study or Subgroup | Acupressure Mean | SD | Total | Placebo/control Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **35.4.1 Haemodialysis** | | | | | | | | |
| Lin 2011 | 3.63 | 10.98 | 36 | 4.6 | 10 | 25 | -0.97 [-6.28 , 4.34] | |



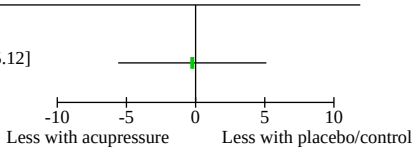

## Analysis 35.5. Comparison 35: Acupressure versus placebo or control, Outcome 5: Usual level of fatigue during past 24 hours

| Study or Subgroup | Acupressure Mean | SD | Total | Placebo/control Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **35.5.1 Haemodialysis** | | | | | | | | |
| Lin 2011 | 3.94 | 9.6 | 36 | 4.2 | 10.8 | 25 | -0.26 [-5.53 , 5.01] | |



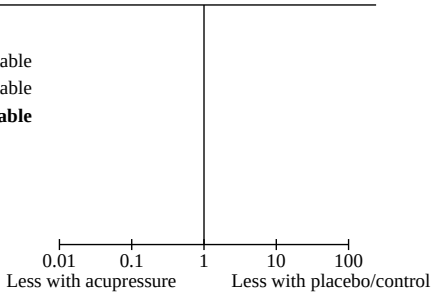

## Analysis 35.6. Comparison 35: Acupressure versus placebo or control, Outcome 6: Worst level of fatigue during past 24 hours

| Study or Subgroup | Acupressure Mean | SD | Total | Placebo/control Mean | SD | Total | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **35.6.1 Haemodialysis** | | | | | | | | |
| Lin 2011 | 4.16 | 9.3 | 36 | 4.4 | 11.25 | 25 | -0.24 [-5.60 , 5.12] | |




## Analysis 35.7. Comparison 35: Acupressure versus placebo or control, Outcome 7: Death (any cause)

| Study or Subgroup | Acupressure Events | Total | Placebo/control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **35.7.1 Haemodialysis** | | | | | | | |
| Lin 2011 | 0 | 36 | 0 | 25 | | Not estimable | |
| Tsay 2004b | 0 | 72 | 0 | 36 | | Not estimable | |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** | |
| Total events: | 0 | | 0 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |

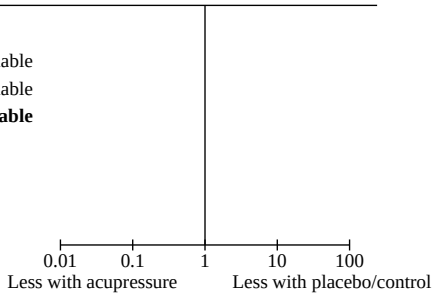


## Analysis 35.8. Comparison 35: Acupressure versus placebo or control, Outcome 8: Cardiovascular death

| Study or Subgroup | Acupressure Events | Acupressure Total | Placebo/control Events | Placebo/control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **35.8.1 Haemodialysis** | | | | | | |
| Lin 2011 | 0 | 36 | 0 | 25 | | Not estimable |
| Tsay 2004b | 0 | 72 | 0 | 36 | | Not estimable |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |

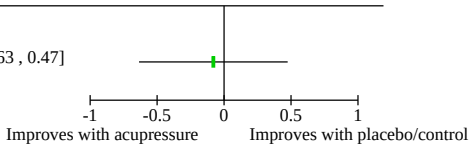
Heterogeneity: Not applicable
Test for overall effect: Not applicable

Test for subgroup differences: Not applicable




## Analysis 35.9. Comparison 35: Acupressure versus placebo or control, Outcome 9: Quality of life (overall)

| Study or Subgroup | Acupressure Mean | Acupressure SD | Acupressure Total | Placebo/control Mean | Placebo/control SD | Placebo/control Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **35.9.1 Haemodialysis** | | | | | | | |
| Su 2009 | 3.42 | 0.89 | 31 | 3.5 | 1.28 | 30 | -0.08 [-0.63 , 0.47] |

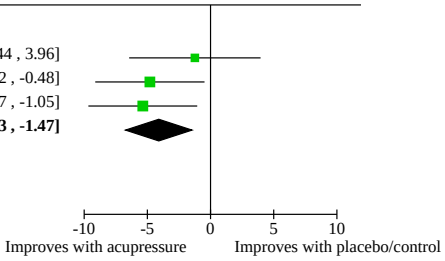



## Analysis 35.10. Comparison 35: Acupressure versus placebo or control, Outcome 10: Depression

| Study or Subgroup | Acupressure Mean | Acupressure SD | Acupressure Total | Placebo/control Mean | Placebo/control SD | Placebo/control Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **35.10.1 Haemodialysis** | | | | | | | | |
| Tsay 2004a | 20.37 | 10.65 | 35 | 21.61 | 11.69 | 36 | 25.6% | -1.24 [-6.44 , 3.96] |
| Cho 2004 | 10.1 | 9.3 | 28 | 14.9 | 7.3 | 30 | 37.1% | -4.80 [-9.12 , -0.48] |
| Tsay 2004b | 13.52 | 8.82 | 35 | 18.88 | 9.55 | 35 | 37.3% | -5.36 [-9.67 , -1.05] |
| **Subtotal (95% CI)** | | | **98** | | | **101** | **100.0%** | **-4.10 [-6.73 , -1.47]** |

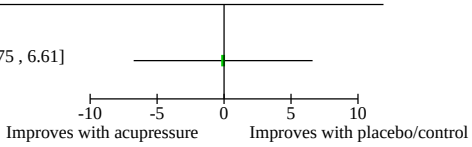
Heterogeneity: Tau² = 0.00; Chi² = 1.59, df = 2 (P = 0.45); I² = 0%
Test for overall effect: Z = 3.05 (P = 0.002)

Test for subgroup differences: Not applicable

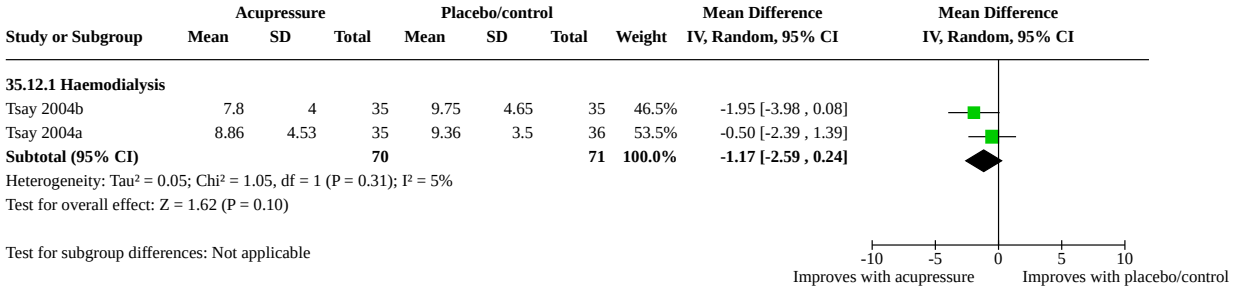



## Analysis 35.11. Comparison 35: Acupressure versus placebo or control, Outcome 11: Mood

| Study or Subgroup | Acupressure Mean | Acupressure SD | Acupressure Total | Placebo/control Mean | Placebo/control SD | Placebo/control Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **35.11.1 Haemodialysis** | | | | | | | |
| Lin 2011 | 3.61 | 12.48 | 36 | 3.68 | 13.5 | 25 | -0.07 [-6.75 , 6.61] |



### Analysis 35.12. Comparison 35: Acupressure versus placebo or control, Outcome 12: Sleep quality




## Comparison 36. Acupressure versus sham acupressure

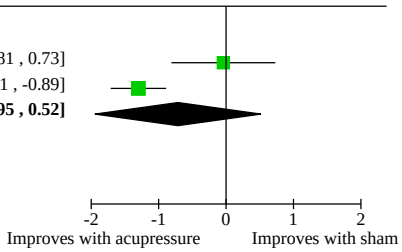
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 36.1 Fatigue | 2 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 36.1.1 Haemodialysis | 2 | 134 | Mean Difference (IV, Random, 95% CI) | -0.71 [-1.95, 0.52] |
| 36.2 Change in fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 36.2.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 36.3 Death (any cause) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 36.3.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 36.4 Cardiovascular death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 36.4.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 36.5 Depression | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 36.5.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 36.6 Sleep quality | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 36.6.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

## Analysis 36.1. Comparison 36: Acupressure versus sham acupressure, Outcome 1: Fatigue

| Study or Subgroup | Acupressure Mean | SD | Total | Sham Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **36.1.1 Haemodialysis** | | | | | | | | |
| Tsay 2004a | 4.66 | 1.77 | 35 | 4.7 | 1.51 | 35 | 46.5% | -0.04 [-0.81 , 0.73] |
| Sabouhi 2013 | 4.6 | 0.975 | 32 | 5.9 | 0.675 | 32 | 53.5% | -1.30 [-1.71 , -0.89] |
| **Subtotal (95% CI)** | | | **67** | | | **67** | **100.0%** | **-0.71 [-1.95 , 0.52]** |

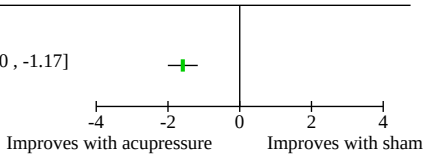
Heterogeneity: Tau² = 0.69; Chi² = 7.99, df = 1 (P = 0.005); I² = 87%
Test for overall effect: Z = 1.14 (P = 0.26)

Test for subgroup differences: Not applicable



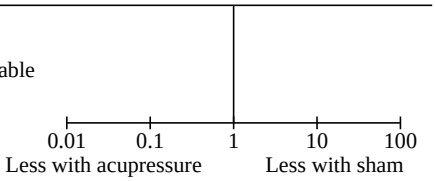

## Analysis 36.2. Comparison 36: Acupressure versus sham acupressure, Outcome 2: Change in fatigue

| Study or Subgroup | Acupressure Mean | SD | Total | Sham Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **36.2.1 Haemodialysis** | | | | | | | |
| Sabouhi 2013 | -2.07 | 1.07 | 32 | -0.483 | 0.55 | 32 | -1.59 [-2.00 , -1.17] |



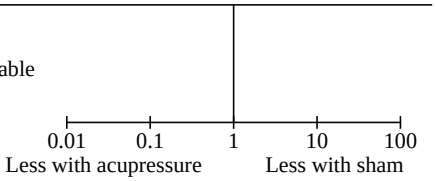

## Analysis 36.3. Comparison 36: Acupressure versus sham acupressure, Outcome 3: Death (any cause)

| Study or Subgroup | Acupressure Events | Total | Sham Events | Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **36.3.1 Haemodialysis** | | | | | |
| Tsai 2016 | 0 | 18 | 0 | 14 | Not estimable |



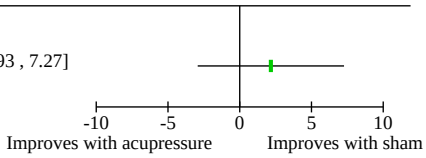

## Analysis 36.4. Comparison 36: Acupressure versus sham acupressure, Outcome 4: Cardiovascular death

| Study or Subgroup | Acupressure Events | Total | Sham Events | Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **36.4.1 Haemodialysis** | | | | | |
| Tsai 2016 | 0 | 18 | 0 | 14 | Not estimable |



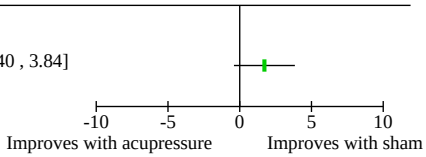
### Analysis 36.5. Comparison 36: Acupressure versus sham acupressure, Outcome 5: Depression

| Study or Subgroup | Acupressure Mean | SD | Total | Sham Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **36.5.1 Haemodialysis** | | | | | | | |
| Tsay 2004a | 20.37 | 10.65 | 35 | 18.2 | 11.11 | 35 | 2.17 [-2.93 , 7.27] |




### Analysis 36.6. Comparison 36: Acupressure versus sham acupressure, Outcome 6: Sleep quality

| Study or Subgroup | Acupressure Mean | SD | Total | Sham Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **36.6.1 Haemodialysis** | | | | | | | |
| Tsay 2004a | 8.86 | 4.53 | 35 | 7.14 | 4.53 | 35 | 1.72 [-0.40 , 3.84] |




## Comparison 37. Sham acupressure versus standard care

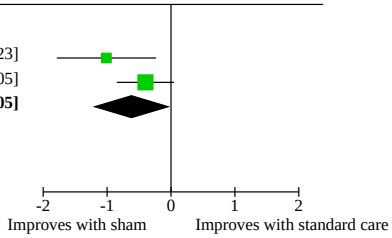
| Outcome or subgroup title | No. of studies | No. of partici-pants | Statistical method | Effect size |
|---|---|---|---|---|
| 37.1 Fatigue | 2 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 37.1.1 Haemodialysis | 2 | 135 | Mean Difference (IV, Random, 95% CI) | -0.62 [-1.19, -0.05] |
| 37.2 Change in fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 37.2.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 37.3 Depression | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 37.3.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 37.4 Sleep quality | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 37.4.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

### Analysis 37.1. Comparison 37: Sham acupressure versus standard care, Outcome 1: Fatigue

| Study or Subgroup | Sham Mean | Sham SD | Sham Total | Standard care Mean | Standard care SD | Standard care Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **37.1.1 Haemodialysis** | | | | | | | | |
| Tsay 2004a | 4.7 | 1.51 | 35 | 5.71 | 1.82 | 36 | 35.9% | -1.01 [-1.79 , -0.23] |
| Sabouhi 2013 | 5.9 | 0.675 | 32 | 6.3 | 1.1 | 32 | 64.1% | -0.40 [-0.85 , 0.05] |
| **Subtotal (95% CI)** | | | **67** | | | **68** | **100.0%** | **-0.62 [-1.19 , -0.05]** |

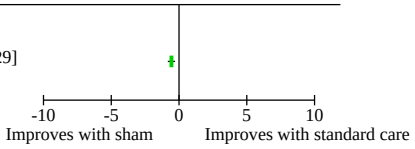
Heterogeneity: Tau² = 0.08; Chi² = 1.78, df = 1 (P = 0.18); I² = 44%
Test for overall effect: Z = 2.12 (P = 0.03)

Test for subgroup differences: Not applicable



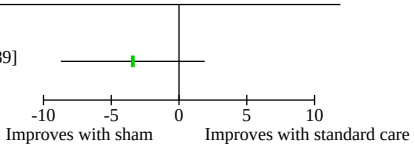

### Analysis 37.2. Comparison 37: Sham acupressure versus standard care, Outcome 2: Change in fatigue

| Study or Subgroup | Sham Mean | Sham SD | Sham Total | Standard care Mean | Standard care SD | Standard care Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **37.2.1 Haemodialysis** | | | | | | | |
| Sabouhi 2013 | -0.483 | 0.55 | 32 | 0.075 | 0.542 | 32 | -0.56 [-0.83 , -0.29] |



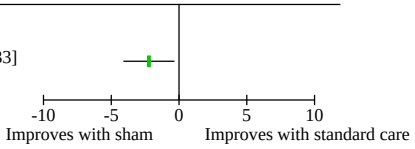

### Analysis 37.3. Comparison 37: Sham acupressure versus standard care, Outcome 3: Depression

| Study or Subgroup | Sham Mean | Sham SD | Sham Total | Standard care Mean | Standard care SD | Standard care Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **37.3.1 Haemodialysis** | | | | | | | |
| Tsay 2004a | 18.2 | 11.11 | 35 | 21.61 | 11.69 | 36 | -3.41 [-8.71 , 1.89] |




### Analysis 37.4. Comparison 37: Sham acupressure versus standard care, Outcome 4: Sleep quality

| Study or Subgroup | Sham Mean | Sham SD | Sham Total | Standard care Mean | Standard care SD | Standard care Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **37.4.1 Haemodialysis** | | | | | | | |
| Tsay 2004a | 7.14 | 4.53 | 35 | 9.36 | 3.5 | 36 | -2.22 [-4.11 , -0.33] |



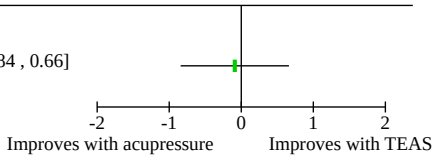

## Comparison 38. Acupressure versus transcutaneous electrical acupoint stimulation

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 38.1 Fatigue | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 38.1.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 38.2 Death (any cause) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 38.2.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 38.3 Cardiovascular death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 38.3.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 38.4 Depression | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 38.4.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 38.5 Sleep quality | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 38.5.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

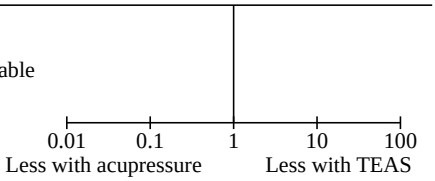
**Analysis 38.1. Comparison 38: Acupressure versus transcutaneous electrical acupoint stimulation, Outcome 1: Fatigue**

| Study or Subgroup | Acupressure Mean | SD | Total | TEAS Mean | SD | Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **38.1.1 Haemodialysis** | | | | | | | |
| Tsay 2004b | 4.61 | 1.72 | 35 | 4.7 | 1.5 | 36 | -0.09 [-0.84 , 0.66] |



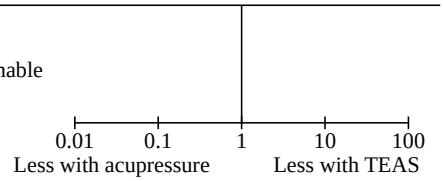

**Analysis 38.2. Comparison 38: Acupressure versus transcutaneous electrical acupoint stimulation, Outcome 2: Death (any cause)**

| Study or Subgroup | Acupressure Events | Total | TEAS Events | Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **38.2.1 Haemodialysis** | | | | | |
| Tsay 2004b | 0 | 36 | 0 | 36 | Not estimable |



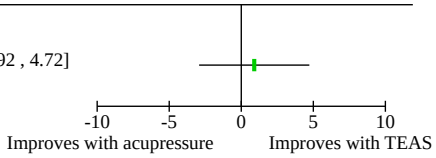
### Analysis 38.3. Comparison 38: Acupressure versus transcutaneous electrical acupoint stimulation, Outcome 3: Cardiovascular death

| Study or Subgroup | Acupressure Events | Acupressure Total | TEAS Events | TEAS Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **38.3.1 Haemodialysis** | | | | | |
| Tsay 2004b | 0 | 36 | 0 | 36 | Not estimable |



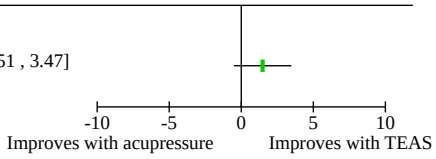

### Analysis 38.4. Comparison 38: Acupressure versus transcutaneous electrical acupoint stimulation, Outcome 4: Depression

| Study or Subgroup | Acupressure Mean | Acupressure SD | Acupressure Total | TEAS Mean | TEAS SD | TEAS Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **38.4.1 Haemodialysis** | | | | | | | |
| Tsay 2004b | 13.52 | 8.82 | 35 | 12.62 | 7.55 | 36 | 0.90 [-2.92 , 4.72] |




### Analysis 38.5. Comparison 38: Acupressure versus transcutaneous electrical acupoint stimulation, Outcome 5: Sleep quality

| Study or Subgroup | Acupressure Mean | Acupressure SD | Acupressure Total | TEAS Mean | TEAS SD | TEAS Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **38.5.1 Haemodialysis** | | | | | | | |
| Tsay 2004b | 7.8 | 4 | 35 | 6.32 | 4.55 | 36 | 1.48 [-0.51 , 3.47] |

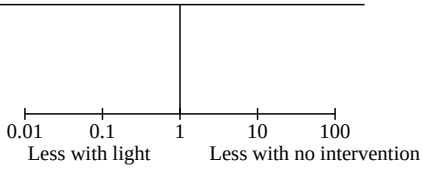



## Comparison 39. Light versus no intervention

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 39.1 Death (any cause) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 39.1.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 39.2 Cadiovascular death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 39.2.1 Haemodialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 39.3 Quality of life (overall) | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 39.3.1 Haemodialysis | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |

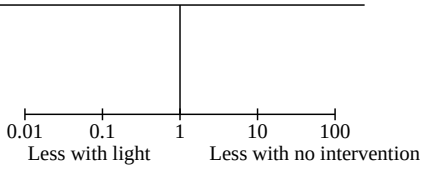
### Analysis 39.1. Comparison 39: Light versus no intervention, Outcome 1: Death (any cause)

| Study or Subgroup | Light Events | Light Total | No intervention Events | No intervention Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **39.1.1 Haemodialysis** | | | | | |
| Schardong 2021 | 0 | 17 | 0 | 16 | Not estimable |



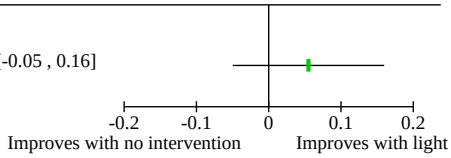

### Analysis 39.2. Comparison 39: Light versus no intervention, Outcome 2: Cadiovascular death

| Study or Subgroup | Light Events | Light Total | No intervention Events | No intervention Total | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **39.2.1 Haemodialysis** | | | | | |
| Schardong 2021 | 0 | 17 | 0 | 16 | Not estimable |




### Analysis 39.3. Comparison 39: Light versus no intervention, Outcome 3: Quality of life (overall)

| Study or Subgroup | Light Mean | Light SD | Light Total | No intervention Mean | No intervention SD | No intervention Total | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **39.3.1 Haemodialysis** | | | | | | | |
| Schardong 2021 | 0.713 | 0.16 | 14 | 0.658 | 0.12 | 14 | 0.05 [-0.05 , 0.16] |




## APPENDICES

### Appendix 1. Electronic search strategies

| Database | Search terms |
|---|---|
| CENTRAL | 1. MeSH descriptor: [Mental Fatigue] this term only<br>2. fatigue:ti,ab,kw (Word variations have been searched)<br>3. "lassitude":ti,ab,kw (Word variations have been searched)<br>4. tired or tiredness:ti,ab,kw (Word variations have been searched)<br>5. weary or weariness:ti,ab,kw (Word variations have been searched)<br>6. exhaustion:ti,ab,kw (Word variations have been searched)<br>7. {or #1-#6}<br>8. MeSH descriptor: [Renal Dialysis] explode all trees<br>9. MeSH descriptor: [Hemofiltration] explode all trees<br>10. MeSH descriptor: [Kidney Failure, Chronic] this term only |

*(Continued)*

| | |
|---|---|
| | 11."dialysis":ti,ab,kw (Word variations have been searched)<br>12.hemodialysis or haemodialysis:ti,ab,kw (Word variations have been searched)<br>13.hemofiltration or haemofiltration:ti,ab,kw (Word variations have been searched)<br>14.hemodiafiltration or haemodiafiltration:ti,ab,kw (Word variations have been searched)<br>15."end-stage kidney" or "end-stage renal" or "endstage kidney" or "endstage renal":ti,ab,kw (Word variations have been searched)<br>16.eskd or eskf or esrd or esrf:ti,ab,kw (Word variations have been searched)<br>17.MeSH descriptor: [Peritoneal Dialysis] explode all trees<br>18.peritoneal dialysis:ti.ab.kw (Word variations have been searched)<br>19.(CAPD or CCPD or APD): ti,ab,kw (Word variations have been searched)<br>20.{or #8-#19}<br>21.{and #7, #20} |
| MEDLINE | 1. Fatigue/<br>2. fatigue.tw.<br>3. lassitude.tw.<br>4. (tiredness or tired).tw.<br>5. (weary or weariness).tw.<br>6. exhaustion.tw<br>7. weakness.tw<br>8. or/1-7<br>9. Renal Replacement Therapy/<br>10.Renal Dialysis/<br>11.Hemodiafiltration/<br>12.Hemodialysis, home/<br>13.exp Hemofiltration/<br>14.dialysis.tw.<br>15.(hemodialysis or haemodialysis).tw.<br>16.(hemofiltration or haemofiltration).tw.<br>17.(hemodiafiltration or haemodiafiltration).tw.<br>18.exp Peritoneal Dialysis/<br>19.peritoneal dialysis.tw<br>20.(CAPD or CCPD or APD).tw.<br>21.or/9-20<br>22.and/8,21 |
| EMBASE | 1. fatigue/ or exhaustion/ or lassitude/<br>2. fatigue.tw.<br>3. lassitude.tw.<br>4. (tiredness or tired).tw.<br>5. (weary or weariness).tw.<br>6. exhaustion.tw.<br>7. weakness.tw.<br>8. or/1-7<br>9. exp renal replacement therapy/<br>10.extended daily dialysis/<br>11.hemodialysis/<br>12.home dialysis/<br>13.hemofiltration/<br>14.hemodiafiltration/<br>15.dialysis.tw.<br>16.(hemodialysis or haemodialysis).tw. |

(Continued)

17.(hemofiltration or haemofiltration).tw.
18.(hemodiafiltration or haemodiafiltration).tw.
19.renal replacement therapy-dependent renal disease/
20.Peritoneal Dialysis/
21.Continuous Ambulatory Peritoneal Dialysis/
22.peritoneal dialysis.tw.
23.(CAPD or CCPD or APD).tw.
24.peritoneal dialysis fluid/
25.peritoneal dialysis catheter/
26.or/9-25
27.and/8,26

## Appendix 2. Risk of bias assessment tool

| Potential source of bias | Assessment criteria |
|---|---|
| **Random sequence generation**<br><br>Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence | *Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random). |
| | *High risk of bias:* Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention. |
| | *Unclear:* Insufficient information about the sequence generation process to permit judgement. |
| **Allocation concealment**<br><br>Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment | *Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes). |
| | *High risk of bias:* Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure. |
| | *Unclear*: Randomisation stated but no information on method used is available. |
| **Blinding of participants and personnel**<br><br>Performance bias due to knowledge of the allocated interventions by participants and personnel during the study | *Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken. |
| | *High risk of bias*: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding. |
| | *Unclear*: Insufficient information to permit judgement |
| **Blinding of outcome assessment** | *Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken. |

*(Continued)*

| | |
|---|---|
| Detection bias due to knowledge of the allocated interventions by outcome assessors. | *High risk of bias:* No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding. |
| | *Unclear:* Insufficient information to permit judgement |
| **Incomplete outcome data**<br><br>Attrition bias due to amount, nature or handling of incomplete outcome data. | *Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods. |
| | *High risk of bias:* Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation. |
| | *Unclear:* Insufficient information to permit judgement |
| **Selective reporting**<br><br>Reporting bias due to selective outcome reporting | *Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon). |
| | *High risk of bias:* Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study. |
| | *Unclear:* Insufficient information to permit judgement |
| **Other bias**<br><br>Bias due to problems not covered elsewhere in the table | *Low risk of bias:* The study appears to be free of other sources of bias. |
| | *High risk of bias:* Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem. |
| | *Unclear:* Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias. |

## Appendix 3. Outcome definitions

| Outcome | Definition |
|---|---|

(Continued)

| | |
|---|---|
| ADL: Activities of Daily Living | Eight questions: they range from 0, meaning they have no difficulty, to 2, which means they can not do it even with help |
| Asthenia | Scored as slight if fatigue appeared at less than 60 sec of exercise A and at less than 30 ascents and descents during exercise B, intense at less than 15 sec of exercise A and at less than 10 ascents and descents of exercise B. Moderate degree of asthenia was between the two extremes |
| BAI: Beck Anxiety Inventory | 21 questions about how the subject has been feeling in the last week expressed as common symptoms of anxiety. Each question has the same set of four possible answer choices (0 (never) and 3 (critically)). The total score ranges from 0 to 63 points, with higher scores meaning more anxiety |
| BDI: Beck Depression Inventory | 21-question multiple-choice self-report inventory for measuring the severity of depression. The total score ranges from 0 to 63 points, with higher total scores indicating more severe depressive symptoms |
| BFI: Brief Fatigue Inventory | Checklist with 10 questions so that the first question asks if the respondents had felt fatigue over the last week. Other questions ask about level of fatigue felt by the respondent at the time, normal and highest level of fatigue over the past 24 h, and the effects of fatigue on their general activity, mood, ability to walk, communicate with others, and enjoying life. The questions are designed based on an 11-point scale (0-10) so that 'zero' is the best possible condition and 10 is the worst. Eventually, total fatigue level of the patient is calculated as the total score of the questions 2-10 (9 questions) divided by nine |
| Bouchard's PAL | Activities are categorized into 9 levels, with 1 as the least intense (0.26 kcal/kg/15 min) and 9 as the highest intensity (1.96 kcal/kg/15 min |
| CES-D: Center for Epidemiologic Studies Depression Scale | Scores ≥ 16 indicate clinically meaningful symptoms |
| COPM: Canadian Occupational Performance Measure | Individuals asked to rate, on a 10-point Likert scale, his/her performance in each of three self-selected priority activities of everyday living. Higher scores out of 10 indicate better performance/satisfaction with performance |
| Cramps | Frequency, severity, site, and duration of the cramps were recorded and scored as slight when they lasted less than 5 mm; moderate 5 to 10 mm; intense more than 10 mm |
| ENRICH questionnaire | One of these 10 items assessed sexual satisfaction. The total score was the sum of positive and negative items and ranged from 10 to 50 |
| EQ-5D: EuroQol-5 dimension health questionnaire | Number 1 indicates the best state of health (perfect health) and 0 the worst state of health (death) |
| Fatigue Management Questionnaire | Individuals asked to rate various aspects of their fatigue management (e.g. overall impact on life participation; satisfaction; self-efficacy), out of 10, on 5-point Likert-scale questions. Scores are then summed and averaged for each of two subscales (Performance Subscale and Satisfaction Subscale), with higher scores out of 10 indicating better fatigue management) |
| Fatigue score | HD patients fatigue scale developed by Chung and Kao: fatigue was measured on a five-point rating scale inquiring about 25 essential symptoms of fatigue, with 5 indicating the most fatigue and 1 the least |
| FI: Fatigue Index questionnaire | Each domain rated from 1 to 5, recorded hourly during the entire study period on a fatigue intensity form as follows: 0, none; 1, mild (noticeable but without effect); 2, moderate (felt sluggish); 3, severe (required rest); or 4, overwhelming (slept). The maximal fatigue score recorded within 6 hours after dialysis or at similar time periods on non-dialysis days (baseline) was used to rate the level of fatigue for the period in question |

*(Continued)*

| | |
|---|---|
| FSS: Fatigue Severity Score | Nine questions, which questions 1–4 and 6 focus on the quality of fatigue, questions 5–7 and 9 are about physical and mental fatigue and their effects on the social life of individuals, and question 8 measures the severity of fatigue. The score range for each question is between 1 and 7, with a score of 1 for absolute disagreement and a score of 7 for absolute agreement. The total score range of the questionnaire is between 7 and 63, so a score of 36 or higher is an indication of fatigue. Hence, higher scores are indicative of higher fatigue |
| GAD: Generalized Anxiety Disorder | Brief 7-item self-report scale on the basis of Diagnostic and Statistical Manual of Mental Disorders-IV criteria for generalized anxiety disorder, with items scored from 0 (not at all) to 3 (nearly every day) |
| HADS: Hospital Anxiety and Depression Scale | 14-item self-report screening scale that comprises 7 items for each of the Anxiety and Depression subscales. The questionnaire assesses symptoms over the preceding week. Each item is scored on a 4-point Likert scale, giving maximum subscale scores of 21 for depression and anxiety |
| HFS: Haemodialysis Fatigue scale | 26 items; it used a 4-point scoring, from rarely or never happening) to often happening (3). A higher score means worse fatigue |
| HSS: Haemodialysis Stressor Scale | 5-point Likert-type scale (always: 5,mostly: 4, sometimes: 3, rarely: 2, and never). The Physiological Hemodialysis Stressor subscale score ranges between 6 and 30, and the Psychosocial Hemodialysis Stressor subscale score varies between 23 and 115. The total HSS score can range from 29 to 145. The higher the scores, the higher the perceived stress levels are |
| Health Utilities Index | This is an interval scale that can vary in theory between 0 (death) and 1 (perfect health) |
| IFS: Iowa Fatigue Scale | Eleven questions determined the level of fatigue (four questions were in cognitive aspects, a pair of questions were about physical fatigue, three questions were about energy rate and pair of questions were about work output). Fatigue score range was from 11 to 55. Score indicated the minimum fatigue rate, and 55 was maximum rate |
| IPOS-Renal: Integrated Palliative Outcome Scale-Renal | All symptoms cores are reported on a 0 to 4 scale (0=not at all, 1=slightly, 2=moderately, 3=severely, 4=overwhelmingly bothered) and indicate the effect of the symptom on the respondent over the past week |
| ItchyQoL: QoL questionnaire fo patients with pruritus | Consists of 27 questions. The answers to each question consist of five levels: never, rarely, sometimes, often, and always, which are scored from 1 to 5, respectively |
| KDQ: Kidney Disease Questionnaire | Follows a 7-point Likert-type scale (7 = no problem, 1 = a severe problem) with higher scores indicating better health-related quality of life. A clinically meaningful difference in KDQ score was a 0.5 point change, and a mean change of 1.0 represented a large clinical change |
| KDQOL-SF: Kidney Disease Quality of Life-Short Form | 43 items related to the quality of life in relation to kidney patients, with 36 items related to general health. Specific dimensions of the questionnaire include: symptoms and the list of problems (12 items), the effect of kidney disease (8 items), the burden of kidney disease (4 items), job performance (2 items), cognitive function (3 items), the quality of social relationships (3 items), sexual function (2 items), sleep (4 items), social support (2 items), medical) staff support (2 items), and general health status (1 item). 22 Different questions have different answer options. As to scoring, each question is scored in a scale ranging from 0 (worst health) to 100 (best health) |
| LEVIL: London Evaluation of Illness | Subject responses were rated from 0 (worst symptoms) to 100 (no symptoms |
| MFI-20: Multidimensional Fatigue Inventory | Each dimension includes four items, and responses are score based on a 5-point Likert scale from strongly agree to strongly disagree. Higher scores indicate greater fatigue. Total score of each dimension ranges between 4 and 20, and the total fatigue score ranges between 20 and 100. Scores of 20-41 indicate mild fatigue, scores of 48-74 indicate moderate fatigue, and scores of 75-100 indicate severe fatigue |

*(Continued)*

| | |
|---|---|
| MFIS: Modified Fatigue Impact Scale | A 21-item Likert-based scale that assesses the effects of fatigue on physical, cognitive and psychosocial functioning. Scores are summed to produce an overall score out of 84, with higher scores indicating worse fatigue impact |
| PHQ-9: Patient Health Questionnaire-9 | Brief 9-item self-report scale on the basis of the Diagnostic and Statistical Manual of Mental Disorders-IV criteria for major depressive disorder, in which each item is scored from 0 (not at all) to 3 (nearly every day) |
| PFS: Piper Fatigue Scale | Includes a total of 27 items and evaluates subjective perception of the patients on fatigue under four subscales. Responses for each item were scored between 0-10 points. The total fatigue score was obtained by summing the points of 22 items, then dividing the sum into the number of items. High scores signify a high level of perceived fatigue |
| PROMIS-Fatique Short Form | Seven items about energy or exhaustion |
| PSQI: Pittsburgh Sleep Quality Index | Scale comprised 18 items and 7 component scores. Every component was evaluated from 0 to 3. The total of these component points yielded the total score of the scale, which ranged from 0 to 21. A high score (5 or above) indicated poor sleep quality. Sleep quality classified as good (0–4) and poor (5–21) |
| RNLI: Reintegration to Normal Living Index | Assesses the degree to which individuals who have experienced traumatic or incapacitating illness achieve reintegration into normal activities, using 11 declarative statements each accompanied by a 10-point visual analogue scale. Scores are then added to produce an overall score out of 110, with higher scores indicating better reintegration to normal living |
| SF-12: 12-item Short Form Health Survey | Higher Mental Component Scores and Physical Component scores indicate better HRQoL |
| SF-36: 36-item Short Form Health Survey | Eight subscales include physical function, role limitation due to physical problems, social function, role limitation due to emotional problems, mental health, fitness/fatigue, pain, and understanding of general health. By calculating the scores obtained from the subscales, 2 main scale scores are obtained; physical and mental scales. Each subscale score ranges from 0 to 100. The physical and mental scale scores are also between 0 and 100. Zero indicates the worst and 100 indicates the best health condition |
| SMMT: Standardized Mini Mental Test | Covers five main areas and consists of 11 items, takes approximately 10 min to complete. The highest score obtainable from the SMMT is 30. In the SMMT, a score of 24–30 points is considered normal, 20–23 is considered to indicate light/mild dementia, 10–19 to indicate intermediate/mid-stage dementia, and 0–9 to indicate advanced dementia |
| SNAG: Simplified Nutritional Appetite Questionnaire | Maximum score of 20 and a score < 14 indicates poor appetite |
| SONG-HDF: Standardised Outcomes in Nephrology-Haemodialysis Fatigue | Assesses the severity of fatigue, and its impact on daily living, in people on maintenance haemodialysis using 3 Likert-style questions. Scores are summed to produce a total score out of 9, with higher scores indicating worse fatigue |
| STAI / STAI-Y1: State-Trait Anxiety Inventory | Composed of 20 items concerning state anxiety. 4-point Likert scale: 1 = “not at all”; 2 = “a little”; 3 = “enough”; and 4 = “very much.” The final score is obtained by sum of the responses to the individual items and can vary from a minimum of 20 to a maximum of 80. A higher score indicates a greater level of anxiety in the subject) with scores ≥ 40 indicating elevated anxiety |
| Symptoms related to orthostatic hypotension questionnaire | Assessed using a 4-point rating scale; severe (daily activities were greatly disturbed by the symptom), moderate (daily activities were disturbed by symptoms), mild (patients were aware of the symptoms, but daily activities were not disturbed), and asymptomatic (there was no symptom at all and patients were not bothered by any symptoms). The improvement for each symptom or the global improvement rating was assessed using a 6-point rating scale (marked improvement (4 or higher), moderate improvement (3 or 2 and if patients have no new symptoms), slight improve- |

(Continued)

| | |
|---|---|
| | ment (2 or 1 and if patients have no new symptoms), no changes (±1, 0), aggravation (-2 or less, or if patients develop new symptoms), asymptomatic (if patients have no new symptoms) |
| VAS: Visual Analogue Scale | Numbers were placed at equal intervals on a horizontal line. The presence of the worst value was rated the highest point (e.g. 10 on a 10-point scale)<br><br>Example: 1-3 mild; 4-6 moderate; 7-10 severe |
| WHOQOL-BREF: WHO Quality of Life - brief form | 26 items; it used a 5-point Likert scale. Items 3, 4 and 26 are scored in reverse. A higher score represents better quality of life |
| World Health Adverse Reactions Terminology | *Haemorrhage:* epistaxis, gastric ulcer haemorrhagic, gastrointestinal haemorrhage, haematoma, haematuria, haemoptysis, nose haemorrhage, rectal haemorrhage, haemothorax, oral haemorrhage, peptic ulcer haemorrhagic, vaginal haemorrhage, and cystitis haemorrhagic<br><br>*Infection*: fever, herpes zoster, infection, bacterial infection, fungal infection, influenza-like symptoms, peritonitis, pneumonia, sinusitis, and tooth caries<br><br>*Vascular access problems*: arteriovenous fistula loss or thrombosis, device-related complications, permanent dialysis catheter loss, and thrombosis<br><br>*Surgical intervention*<br><br>*Anaemia and related symptoms*: anaemia, asthenia, fatigue, and malaise<br><br>*Cardiovascular:* blood pressure fluctuation, cardiac failure, chest pain, coronary artery disorder, dizziness, hypertension, hypotension, myocardial infarction, non-site-specific vascular disorder, palpitations, pericarditis, peripheral gangrene, pulmonary oedema, and vascular disorder<br><br>*Respiratory:* coughing, cyanosis, dyspnoea, and atrial fibrillation<br><br>*Gastrointestinal:* abdominal pain, anorexia, ascites, ulcerative colitis, diarrhoea, gastric ulcer, hepatic cirrhosis, intestinal obstruction, nausea, oesophagitis, and vomiting<br><br>*Musculoskeletal:* arthralgia, arthritis, arthropathy, back pain, bone disorder, fall, fracture pathologic, injury, leg pain, myalgia, skeletal pain, and ankylosing spondylitis<br><br>*Skin*: folliculitis, pruritus, purpura, rash, skin disorder, and skin ulceration<br><br>*Neurologic:* cerebellar infarction, cerebral atrophy, cerebrovascular disorder, coma, confusion, gait abnormal, headache, hearing decreased, insomnia, ischial neuralgia, somnolence, and abnormal vision<br><br>*Miscellaneous:* acidosis, allergic reaction, anxiety, aggravated diabetes mellitus, dysuria, hydronephrosis, hyperkalaemia, hyperparathyroidism, hypoglycaemia, nail disorder, non-site-specific embolism, thrombosis, oedema, generalized oedema, peripheral oedema, pain, renal cyst, thrombocytopenia, thrombosis, transplant rejection, Wegener's granulomatosis, weight decrease |

## Appendix 4. TIDieR framework of interventions descriptions for included studies

| Study ID | Intervention | Control | Aim | What | How | Who, where, when | Tailoring/modification | How well: planned | How well: actual |
|---|---|---|---|---|---|---|---|---|---|
| Ahmady 2019 | **Aromatherapy** | **Control** | To assess the effects of aromatherapy on fatigue in HD | Participants received aromatherapy with lavender, aromatherapy with orange essential oil or were assigned to the control group | Five drops of each essence were poured on a cotton ball and pinned to the patient's collar for 30 min. In the control group, five drops of distilled water were used | 14 interventions were provided both in the hospital and at home | - | Patients were trained to perform the interventions at home, and a reminder was sent to them by the first author every morning at 8 o'clock via text messages | All participants completed the study |
| Akizawa 2002 | **L-DOPS (400 or 200 mg)** | **Placebo** | To assess the effect of L-DOPS on post-dialysis orthostatic hypotension in HD | Different doses of L-DOPS were compared to placebo | L-DOPS was administered 30 min before the start of HD | The treatment was provided in the clinic for 4 weeks | - | - | 141/149 participants completed the study |
| Amini 2016 | **1) Relaxation**<br>**2) Exercise** | **Control** | To investigate the effect of aerobic exercise or PMR on anxiety, fatigue, and sleep in HD | PMR group received a CD; aerobic exercises were performed at a certain time of the day | The PMR group used the CD and contract and relax the muscles. The aerobic exercise group did predetermined exercise | Both interventions were performed daily for 60 days. PMR was performed at home before going to sleep, exercises were performed in the clinic with the researcher, for 8 weeks | The defective performance of the patients was corrected | A checklist of the exercises was delivered. The researcher supervised and followed up through telephone call or in person | - |
| ASCEND 2016 | **Sertraline** | **CBT** | To evaluate the efficacy of CBT versus sertra- | CBT or sertraline therapy | The CBT group scheduled for 10 sessions of 60 min. Sertraline start- | The session were conducted over 12 weeks, and | The sertraline group had | - | 120/120 participants |

(Continued)

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | line for treating depression in HD | | ed with 25 mg/day during the first week and increased to 50 mg/day in the second week. The goal of the titration phase was to achieve a dose of 200 mg | were conducted face-to-face by trained therapists during HD | dosage titrated every 2 weeks for the first 6 weeks and then maintained for 6 weeks in accordance with measurement-based care | | completed the study |
| ASSertID 2015 | **Sertraline** | **Placebo** | To test MFI questionnaire in HD patients with depression | Sertraline or placebo was administered | - | Research psychiatrist assessed all patients for 6 months | - | - | - |
| BA16285 2007 | **CERA once/ week** | **CERA once every 2 weeks** | To determine the optimal dose and tolerability for IV CERA in HD patients with CKD | Participants taken IV CERA, administered at 3 different doses (0.25 µg/150 IU, 0.4 µg/150 IU, or 0.6 µg/150 IU) and were switched to once/week or once every 2 weeks | - | The follow-up was 12 months | After the first 6 weeks, dose adjustments were allowed every 3 weeks in the once/ week group, and every 4 weeks in the once every 2 weeks group. Dose adjustments were also permitted for safe- | - | 53/91 participants completed the study |

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| | | | | | | | ty at any point during the study | | |
| Babamohammadi 2006 | **Home-care educational program** | **Control** | To assess the effects of a confined program of home-care on the health status in HD | Educational program on kidneys, HD, fistula care, diet and daily consumption of drugs was performed | Home-care contained four visits/month (1 session/week before day of the HD schedule) | Researchers and nurses supported the educational sessions (1/week) for 1 month | - | Researchers answered to patient and family questions, reviewed of before session and provided final evaluation plan | - |
| Bagheri-Nesami 2016 | **Aromathera-py** | **Control** | To examine the efficacy of lavender essential oil for the alleviation of fatigue in HD | The intervention group inhaled lavender essence 5% | A cotton ball soaked in 3 drops of essential oil was attached and patients were asked to breathe slowly | The intervention group inhaled lavender essence 5% for 10 min, 3 times/week for 4 weeks in the clinic | - | - | 59/60 participants completed the study |
| Balouchi 2016 | **Aromathera-py** | **Aromathera-py** | To examine the effects of inhaling lavender and orange extracts in HD | Patients inhaled either lavender or orange extract | Patients were instructed to pour a drop of essential oil on a gauze and pin it to their shirt and rest the night after dialysis | The intervention was performed 3 times/week for 2 weeks at home | - | - | - |
| Barre 1988 | **Low dialysate sodium** | **High dialysate sodium** | To assess if higher dialysate sodium increase, thirst, hypertension, weight gain and oedema in HD | Dialysate (145, 150 or 155 mEq/L) of sodium was performed to all patients | - | Intervention was performed in the clinic for 1 month period each time (overall 2 months of the same treatment) | - | - | - |
| Bellinghieri 1983 | **L-carnitine** | **Placebo** | To evaluate the effect of L-carnitine on serum and muscle car- | L-carnitine (2 g/day orally) was divided in two administrations | - | - | - | - | - |

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| | | | nitine levels in HD | | | | | | |
| Bicer 2022 | **Acupressure** | **Placebo** | To determine the effect of acupressure on blood pressure, headache, and fatigue level in HD | Participants were randomised to acupressure or placebo | An electrostimulation device was attached to the Neiguan acupuncture point. In the placebo group, the device was attached on the wrist to the same acupuncture point but without battery | 12-session body acupressure, performed by electrostimulation device operated during each dialysis session 3 times/week for 1 month | - | The researcher participated in an "Acupressure and Aromatherapy Course," including a 24-hour theoretical and applied training in this skill | 135/150 participants completed the study |
| Biniaz 2015 | **Nutritional supplementation** | **Placebo** | To assess the effects of vitamin C on fatigue in HD | Participants were randomised to vitamin C or placebo | The intervention group received vitamin C. The control group, placebo saline was injected | 250 mg of vitamin C was injected intravenously immediately at the end of each HD session 3 times/week for 8 weeks | - | - | 57/62 participants completed the study |
| BOLD 2020 | **Home SBP** | **Pre-dialysis SBP** | To assess the effect of home SBP or pre-dialysis SBP in HD | Participants were randomised to home SBP or pre-dialysis SBP | In the home BP arm participants measured their BPs twice/day. Participants were trained by research staff on proper techniques for home BP measurement. In the other arm SBP readings were taken immediately prior to the start of each HD treatment | Participants were instructed by research staff to take their home BP the day after the dialysis session. Participants were asked to only take 2 BP readings over a 2-week period to not be burdensome. In the other arm, the staff took readings over 2 weeks (6 readings) | - | They received in-person visits at their HD sessions or phone calls by the local study team at least weekly to remind them to take their home BPs. Participants shared the readings with the study team | 49/50 participants completed the study. However ITT was performed |

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| | | | | | | | | using text messaging, phone call, in-person or paper log | |
| Brass 2001 | **L-carnitine** | **Placebo** | To assess if L-carnitine increases plasmatic carnitine, maximal exercise capacity, and improve QoL in HD (2 RCTs) | **Study A**: L-carnitine 20 mg/kg<br><br>**Study B**: L-carnitine 10, 20, 40 mg/kg | - | Both RCTs were performed after dialysis for 24 weeks | - | - | 56/60 participants completed the study A<br><br>127/133 participants completed the study B |
| Canadian EPO 1990 | **EPO alfa** | **Placebo** | To ascertain the impact of EPO treatment on anaemia symptoms in HD | Patients in the treatment groups received IV EPO alfa | EPO was injected IV as a 10 mL bolus at the end of each session of dialysis (3 times/week), for 6 months in the clinic | - | The dose was subsequently adjusted to achieve the target Hb concentration | Standard encouragement was given during both exercise tests | 99/118 participants completed the study |
| Cecen 2021 | **Massage** | **Control** | To examine the effect of hand massage and foot massage on fatigue in HD | Patients were randomised to hand or foot massage or control | The patients in the massage groups used liquid vaseline using repeated patting and kneading movements. The control group did not received the intervention | Massage groups received the intervention 3 times/week for 4 weeks. The control group continued to receive HD and nursing care | - | - | 82/84 participants completed the study |
| Chang 2010 | **Exercise** | **Control** | To assess the effect of leg ergometry exercise on fatigue and physical activity in HD | The ergometer was placed on the bed for patients to pedal while supine for dialysis | Warm-up by stepping for 5 min. The first exercise session was for 10 min, the second for 20 min and then for 30 min | The leg ergometry exercise was performed in the bed within the first hour of each HD session for 30 min for 8 weeks, in the clinic | Patients were permitted to rest or request to train at a lower intensity if | - | 71/90 participants completed the study |

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| | | | | | | | they were stressed | | |
| Chen 2008a | **CBT** | **Education** | To assess the effectiveness of CBT, evaluating changes in sleep quality and inflammatory cytokines in PD | The intervention group received CBT and sleep hygiene education, whereas the control group received only sleep hygiene education | The intervention group received 4 CBT sessions. The sleep-focused intervention involved the cognitive, sleep, stimulus control, relaxation, and educational components | A psychiatrist performed 4 x 1-hour-weekly treatment sessions of CBT for 4 weeks in the clinic | - | - | All participants were included into the analyses |
| Chen 2011a | **CBT** | **Education** | To validate the efficacy of CBT on sleep, fatigue, depression, anxiety, inflammation and oxidative stress in HD | The intervention group received 30 min of CBT and sleep hygiene education. The control group received sleep problem consultations | CBT included a psychiatrist-oriented, video-assisted CBT program, and group discussion and education | Two psychiatrists performed the intervention 3 times/week for a 6-week period in the clinic, and gave consultations to the control group at least once/week | Control group received consultations from psychiatrists as long as the participants needed during the trial | - | 72/80 participants completed the study |
| Cho 2004 | **Acupressure** | **Control** | To assess the difference in fatigue and depression between acupressure therapy or usual care in HD | The intervention consisted in pressing and rubbing the fingers pads for 5 sec and then releasing for 1 sec | Every acupoint was pressed for 3 min for a total of 12 min, and then the two lower limbs were massaged for 3 min | The researcher performed the intervention for 12 min 3 days/week for 4 months, in the clinic | - | The precision of acupoints was confirmed if subjects' treatment area felt sore, numb, heavy, distended and/or warm during the massage. 2 experts, who confirmed the 100% ac- | 58/62 participants completed the study |

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| | | | | | | | | curacy and agreement, evaluated the accuracy of acupoint | |
| Chow 2010 | **Nurse-led case management programme** | **Control** | To examine the effectiveness of a nurse-led case management programme in improving the QoL in PD | Intervention group received a discharge planning protocol and a telephone follow-up. Control group received routine discharge care | The discharge planning included participation of patients in discussing the discharge plan and an assessment of the patient's physical, social, cognitive and emotional needs | Nurse managers contacted patients by telephone weekly for six consecutive weeks (20-30 min of call), when the patients was outside the clinic | Patients could contact the case manager as needed should they require further assistance, or could call the 24-hour hotline service if the case manager was not available at any time | The content of the call was guided by the protocol. The nurse checked and reinforced the patient's behaviours in achieving the objectives, identifying new and potential complications | 85/100 participants completed the study |
| Dashti-Khavidaki 2013 | **Pharmaceutical care** | **Control** | To assess the impact of pharmaceutical care on HRQoL in HD | Intervention group received pharmaceutical care, control group received standard care | Patients were educated about their disease, medications lifestyle modification, and their nutrition | Patients in the case group were visited weekly by clinical pharmacist, for 6 months | The pharmacist interviewed patients and his/her caregiver to evaluate patient's medication adherence | Two booklets regarding correct drug administration and nutrition for HD were given to the patients | 60/92 participants completed the study |
| Duggal 2019 | **Blood flow rate reduced** | **Control** | To assess the effects of blood | Participants were randomised to | Subjects in the intervention arm had their blood flow rate reduced by 100 | Intervention was provided for 4 | - | - | 86/102 participants |

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| | | | flow rate reduced in HD | blood flow rate reduced or usual care | mL/min or to a minimum blood flow rate of 300 mL/min, whichever was higher. Patients in the control arm continued usual care | weeks in the clinic | | | completed the study |
| Eroglu 2022 | **Relaxation + music** | **Control** | To investigate the effects of the BRT combined with music therapy on fatigue, anxiety, and depression levels in HD | Participants were randomised to relaxation + music therapy or no treatment | Small groups of 10-12 subjects performed the intervention. The PI demonstrated deep breathing techniques step by step. Then, the PI opened the music piece and gave BRT comments in a slightly lower voice. The control group received regular care | The PI delivered a training booklet in the intervention group. The intervention was performed in the clinic twice a week for 8 weeks (20 min each) | - | The PI was trained with the BRT protocol and in music therapy | 61/62 participants completed the study |
| Fatigue-HD 2019 | **Education** | **Control** | To assess the effects of PEP programme on fatigue in HD | Participants randomised to the treatment arm completed the tailored, 7–9 weeks PEP programme. The control arm reviewed info on the website | The PEP programme is a 2-part intervention that teaches participants how to use energy management strategies to improve participation in three self-selected life activities. The control arm reviewed general information about kidney disease management from the Kidney School online learning modules with a trained study coordinator | The intervention group performed a web-supported 7–9 weeks energy management programme in the clinic. | The intervention was a tailored programme. | Study coordinators received in-person training from a trained therapist prior to administering the intervention. Study coordinators monitored and encouraged participant adherence to the treatment protocol | 22/30 participants completed the study |
| Fatouros 2010 | **L-carnitine** | **Placebo** | To examine the effect of L-carnitine supplementation on exercise per- | L-carnitine or placebo was administered intravenously | - | Intervention was administered 3 times/week for 8 week in the clinic | - | - | - |

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| | | | formance and blood redox status in HD | after each dialysis session | | | | | |
| FHN DAILY 2007 | **HD 6 times/ week** | **Control** | To conduct randomised controlled clinical trials in daily HD | Intervention group conducted 6 times/ week HD, compared with conventional 3 times/week HD | - | The interventions were performed in the clinic (3 or 6 times/week) for 12 months | - | - | Numbers of participants analysed varied in base of the outcome |
| FHN NOCTURNAL 2007 | **Nocturnal HD 6 times/ week** | **Control** | To conduct randomised controlled clinical trials in nocturnal HD | Intervention group conducted 6 times/ week nocturnal HD, compared with conventional 3 times/ week nocturnal HD | - | The interventions were performed in the clinic (3 or 6 times/week) for 12 months | - | - | Numbers of participants analysed varied in base of the outcome |
| Figueiredo 2018 | **1) Exercise: inspiratory muscle training (IMT)**<br><br>**2) Exercise: aerobic training (AT)** | **Exercise (combination therapy)** | To assess the effect of IMT, AT or both in HD | Patients were randomised to ITM, AT or combination therapy | The IMT group performed 3 sets of 15 deep inspirations at the equipment mouthpiece and rested for 60 sec. The AT was performed by cycle ergometer (5-min warm-up, 30 min of cycling, and a 5 min cooling-down period).<br><br>In the combination therapy sessions, IMT was performed immediately before AT and, in the AT group, the participants performed sets of inspirations with IMT devices, but without resistance to inspiration | All interventions were intradialytic, and they were performed during the first 2 hours of dialysis, 3 times/week for 8 weeks or 24 sessions | - | ITM: MIP was reevaluated every 6 sessions for load adjustment<br><br>AT: During exercise, patients were asked every 5 min about the fatigue score, and the cycle ergometer load was adjusted to achieve a fatigue score between 3-5 points in the | 31/37 participants completed the study |

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| Foley 2000 | **EPO alpha (Hb target 9.5 to 10.6 g/dL)** | **EPO alpha (Hb target 13 to 14 g/dL)** | To assess the effects of a normal Hb target in HD patients who are at an earlier phase of their cardiac disease | Patients were randomised to receive epoetin alpha either to reach low or high target Hb | - | The intervention was performed in the clinic for 48 weeks | When the Hb level was below target levels, the epoetin dose was increased by 25%; when the Hb was above target levels, the epoetin dose was decreased by 25% | - | 134/146 participants completed the study |
| Fukuda 2015 | **Nutritional supplementation** | **Placebo** | To examine the effects of nutritional supplementation on fatigue, QoL, and immune dysfunction in HD | Patients received active treatment or placebo | One bottle of "AMP01" or placebo was administered | Treatments were administered after each dialysis session (3 times/week) for 12 weeks | - | - | 172/202 participants completed the study |
| Grigoriou 2021 | **Exercise** | **Control** | To investigate whether a single bout of hybrid intradialytic exercise affects left-ventricular function in HD | All participants completed two different HD trials on 2 different days, separated by 1 week: (1) standard HD and (2) HD including a single bout of hybrid intradialytic exercise (aerobic and resistance) | Hybrid intradialytic training included the usual intradialytic cycling followed by resistance training using elastic bands and dumbbells | Patients were instructed to cycle between 50 and 55 rpm for 45 min in the clinic | - | - | 21/22 participants completed the study |

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| Habibzadeh 2020 | **Massage** | **Control** | To explore the impact of foot massage with chamomile oil and almond oil on the severity of fatigue and QoL in HD | Participants were randomised to massage with chamomile oil, almond oil, no oils or no treatment by the trained researcher | The foot massage was performed on the thenar and thumb by briefly pressing as rotationally, from the heel to the toes, with 3 mL of oil<br><br>In the control group, there was no intervention and the participants were only monitored | All massages were performed for 20 min, 3 times/week for 8 weeks | - | The trained researcher, who learned foot massage techniques from a traditional medicine practitioner and received a certificate of foot massage at a recognized Iranian Traditional Medicine Association | All participants completed the study |
| Hadadian 2016 | **Acupressure** | **Sham acupressure** | To evaluate the effects of TEAS on fatigue in HD | TEAS group treated by acupuncture in real points<br><br>Sham group procedure was performed on false points | The sham TEAS treatment followed the same protocol as the TEAS treatment except for the positioning of the points electro-stimulation | The intervention was limited to 5 min of TEAS (50 sec/acupoint) 6 acupoints bilaterally for 10 sessions, 2-3 times/week for 5 weeks in the clinic | - | Three acupoints were selected for TEAS treatment after consultation with acupuncturists. The device guideline and its instruction brochure were provided | 56/60 participants completed the study |
| Hadadian 2018 | **Relaxation** | **Control** | To determine the effect of progressive muscle relaxation technique on fatigue in HD | Participants were randomised to progressive muscle relaxation technique or no treatment | A CD containing the first and second steps was placed on the test group. After being assured of the person's learning, he was asked to do 2 relaxation sessions/day, according to the program set at | Each relaxation step lasts about 15 min. The entire test group performed relaxation exercises for 30 days at home according to the schedule | - | The researcher also regularly monitored the process of doing work by attending a dialy- | 65 participants were randomised but the number of patients analysed were not |

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| | | | | | home, so that one should be aware of the frequency of relaxation before bedtime.<br><br>In the control group, no intervention was performed | | | sis session and telephone follow-up of patients at home. Also, the researcher's telephone number was provided to patients to resolve the patient's ambiguity | clearly stated |
| Hasankhani 2013 | **Massage** | **Control** | To study the effect of back massage on fatigue in HD | The intervention group received back massage by slow-stroke method. The control group received usual care | The patients in the intervention group were sited and small rotational movements with the thumb on the neck was performed | The intervention was provided 3 times/week, on dialysis, for 10 min, within 4 weeks | - | - | - |
| Hassanzadeh 2018 | **1) Relaxation**<br><br>**2) Aromatherapy** | **Control** | To assess the effects of relaxation, aromatherapy compared to control on fatigue in HD | Participants were randomised to Benson muscle relaxation techniques, 5% lavender essential oil or standard care alone | Two drops of 5% lavender essential oil inoculated in sweet almond oil was added on a cotton ball and pinned to the subjects' collar<br><br>In the Benson relaxation techniques group the intervention was applied in the dialysis ward and at home for 15-20 min twice/day for 4 weeks by themselves<br><br>The control group only received regular healthcare actions | The patients were trained how to perform the intervention procedure in individual interventions groups in 3, 20-min sessions, before, during and after the HD. This was followed in the dialysis ward and at home twice/day for 4 weeks | In the lavender essential oil group, the intervention was carried out by the patients in the morning after waking and before bed at night. For those that did not perform | The audio file and training pamphlet of relaxation and aromatherapy methods also were given to the patients for better learning at home. Authors followed up patients in HD wards directly and in their | - |

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| | | | | | | | the intervention in the morning, it was performed during dialysis after the patient's condition was stabilised | home by phone | |
| HDPAL 2014 | **Atenolol** | **Lisinopril** | To develop a tool to evaluate symptoms and examine the relationship between the change in symptoms with BP control in HD | Patients received atenolol or lisinopril | - | Both treatments were administered 3 times/week after dialysis for 12 months | If BP control was not possible felodipine or amlodipine 10 mg (once/day) was added, followed by other antihypertensive therapies in the following order: doxazosin, minoxidil and guanfacine. If ambulatory BP was ≥ 155 mm Hg SBP or ≥ 95 mm Hg DBP patients, the maximum dose of the drug | - | 133/200 participants completed the questionnaire that reported fatigue |

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| | | | | | | | was used: for lisinopril 40 mg or for atenolol 100 mg | | |
| Huang 2021 | **Exercise** | **Control** | To assess the effects of exercise on fatigue in HD | Participants were randomised to breathing-based leg exercises during HD or not intervention | The breathing-based leg exercises program comprised abdominal breathing and low intensity leg exercise, including leg lifts, quadriceps femoris contraction and knee flexion. The control group performed standard care | The intervention lasted for 15 min at one time, 3 times/week for 12 weeks in the clinic by researchers | - | A video was delivered until the exercise could be performed correctly. The safety of the program was evaluate considering oxyhaemoglobin saturation | 83/86 participants completed the study |
| Jalalian 2015 | **Aromathera-py** | **Aromathera-py** | To examine the effects of inhaling lavender and orange extracts in HD | Patients inhaled either lavender or orange extract | 2 drops of lavender essence with fresh orange was poured on a 2x2 gauze and pinned to the patients' collar | Subjects breathed normally for 15-20 min, 3 times/week for 8 weeks | - | - | - |
| Johansen 1999 | **Nandrolone decanoate** | **Placebo** | To assess the effect of nandrolone decanoate on lean body mass, functional status, and QoL in HD and PD | Patients received nandrolone decanoate or placebo | - | Nandrolone decanoate or placebo was administered by intramuscular injection once a week for 6 months by the staff, in the clinic | Monthly liver function test were checked. Dose was also reduced for signs of virilization | - | 23/29 participants completed all the measurements |
| Johansen 2006 | **1) Nandrolone decanoate** | **1) Placebo with exercise** | To compare changes in LBM, muscle size and strength, | Participants were randomised to nandrolone | Training started with two sets of 10 repetitions. Patients were sited and performed 5 maximal leg ex- | Exercise was performed by nurses under the supervision of study | When patients could perform three | Investigators received a package | 68/79 participants completed the study |

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| | **with exercise**<br><br>**2) Nandrolone decanoate without exercise** | **2) Placebo without exercise** | physical performance, and self-reported functioning in HD | with or without exercise training, and placebo with or without exercise training | tension repetitions at 90 degrees and 15 repetitions at 120 degrees | personnel 3 times/week, for 12 weeks, in the clinic | sets with correct technique, the weight was increased | with 12 vials of study drug or placebo and a card with exercise group assignment from the pharmacy after each participant was assigned | |
| Kaplin Serin 2020 | **Relaxation** | **No intervention** | To compare changes in LBM, muscle size and strength, physical performance, and self-reported functioning in HD | Participants were randomised to nandrolone with or without exercise training, and placebo with or without exercise training | Training started with two sets of 10 repetitions. Patients were sited and performed 5 maximal leg extension repetitions at 90 degrees and 15 repetitions at 120 degrees | Exercise was performed by nurses under the supervision of study personnel 3 times/week, for 12 weeks, in the clinic | When patients could perform three sets with correct technique, the weight was increased | Investigators received a package with 12 vials of study drug or placebo and a card with exercise group assignment from the pharmacy after each participant was assigned | 68/79 participants completed the study. |
| Karadag 2019 | **Aromatherapy** | **Control** | To assess the effect of aromatherapy on fatigue and anxiety in HD | Participants were randomised to lavender oil or no intervention | The patients inhaled 2% lavender oil before HD. 2 drops of lavender oil were dropped on a 2 × 2 cm gauze dressing, placed on the chest area of the patients' clothes, for a duration of 20 min, with direction to patients to breathe normally | The intervention group inhaled lavender oil during the dialysis for 30 days (2 or 3 times/week). No application was made to the control group. | - | - | All participants completed the study |

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| Konstadinidou-ND 2002 | **Exercise** | **Control** | To compare the effects of 3 modes of exercise training on cardiorespiratory fitness in HD. | Patients were randomised to receive exercise during non-HD days, during HD, at home or conduct usual lifestyle | Group A followed exercise on the non-HD days (10 min warm-up, 30 min exercise). Group B followed exercise during HD (5 min warm-up, active cycling, 5 min cool-down). Group C followed an unsupervised exercise at home, using a cycle-ergometer and followed instructions. All exercises were performed for 60 min | The treatments were performed in the clinic or outside the clinic under the supervision of a sports physician and the 2 physical education teachers, 3 times/week for 6 months | The intensity of exercise was prescribed on an individual basis | The patients were divided into subgroups to keep a high frequency of patient–therapist contact. Doctors kept close contact with patients who performed exercise at home, visiting them monthly and answering questions | 48/58 participants completed the study. |
| Krase 2022 | **EPO** | **Placebo** | To assess the effect of EPO on fatigue in HD | Participants were randomised to EPO or placebo | - | - | - | - | - |
| Lazarus 2020 | **Massage** | **Control** | To determine the effect of olive oil massage therapy on fatigue in HD | Participants were randomised to olive oil massage or no treatment | The massages were all performed manually and used the classic techniques of effleurage and kneading with constant touch and pressure. The control group continues to receive routine care | The intervention group were given a lower back and lower leg massage using olive oil at the beginning, and after every hour, of their HD using olive oil for a period of 8 weeks | - | - | All participants completed the study |
| Leski 1979 | **Dialysate containing glucose** | **Dialysate without glucose** | To evaluate the effect of a glucose-enriched dialysate in HD | 12 dialysis sessions sequentially were performed used either a dialysate | - | The intervention was performed by medical staff in the clinic | - | - | - |

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| | | | | containing glucose 400 mg/100 mL or a dialysate without glucose | | | | | |
| Li 2014b | **Nurse led telephone support** | **Control** | To test the effectiveness of post-discharge nurse-led telephone support in PD | Control group received routine discharge care; intervention group received nurse led telephone support | Control group received doctor support, a telephone hotline service, self-help printed materials. Intervention group received a discharge planning protocol and a post-discharge nurse-led telephone support. After discharge, nurse called patients | intervention was performed at home for 6 weeks | An individualized education program was conducted by the nurse prior to discharge to consolidate learning experiences and clarify misconceptions | The content of each telephone call was guided by the protocol and the specific problems identified. The telephone conversations were audio taped to ensure consistency of the interventions | 135/160 participants completed the study |
| Lillevang 1990 | **EPO** | **Placebo** | To investigate HD patients' own perception of their quality of life, before and after EPO-treatment | Patients were randomised to EPO or placebo | - | The intervention was provided at the end of HD in the clinic from the medical staff | - | - | 18/19 participants completed the study |
| Lin 2011 | **Acupressure** | **Control** | The aim of this study is to evaluate the effects of far-infrared (FIR) rays on the meridian in HD. | The intervention group received acupressure treatment: the control group received no intervention | The acupoint was kept in place by a piece, and fixed onto the four acupoints. The patients in the experimental group were trained to administer this FIR acupoint treatment on every point | FIR irradiation on each acupoint for 30 min, thrice weekly by the patient | - | An explanatory note was provided. To minimize participants' misunderstanding of the BFI-T, the data were collected via interview | All participants completed the study |

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| | | | | | | | | and they could ask questions | |
| Linde 2001 | **EPO alpha to achieve normal-HB target** | **Subnormal-HB target with or without ESA** | To examine if normalization of Hb with EPO alfa improves QoL and is safe in pre-dialysis, HD and PD | Participants were randomised to EPO alfa to reach normal Hb of 135–160 g/L or subnormal HB of 90–120 g/L with or without EPO alfa | - | The intervention was performed by the clinical staff in the clinic for 48-76 weeks | - | - | 210/416 participants completed the study |
| Mohajeranirad 2021 | **Nutritional supplementation** | **Placebo** | To assess the effects of psudoplicatum capsules on pruritus, fatigue, quality of life in HD | Participants were randomised to psudoplicatum capsules or placebo | Patients in the intervention group were given 250mg H. psudoplicatum and patients in the control group were given 250 mg placebo | The intervention was performed for 6 weeks, 3 times/day | - | - | 50/54 participants completed the study |
| Mohamed 2013 | **Higher dialysate glucose concentration** | **Standard dialysate glucose concentration** | To assess quality of life among HD patients randomised to two different dialysate glucose concentration baths | Higher (11 mmol/L) or standard dialysate glucose concentration baths (5.5 mmol/L) were provided | - | Treatments were performed for 12 weeks in the clinic | - | - | All participants completed the study |
| Mohamed 2014 | **Education** | **Control** | To evaluate the effectiveness of an educational intervention on fatigue in HD | The intervention provided instruction to enhance the patient's knowledge about CKD, coping, nutrition and exercises. Controls received instruction | 4 interventional session of 30 - 45 minutes with lectures, discussions, booklet and demonstration. The control group received the usual care recommended by the nephrologists' in relation with healthy lifestyle | The intervention consisted in 4 sessions over 2 weeks | - | - | - |

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| Mohammadpourhodki 2021 | **Aromatherapy (massage)** | **Placebo** | To evaluate the effect of aromatherapy on quality of life in HD | The intervention groups received aromatherapy massage with lavender essential oil or Citrus Aurantium essential oil for 4 weeks. For the control group, only foot massage was performed | Effleurage massage method was conducted using approximately 10 to 15 mL of 1.5% of oil | The intervention was performed 3 times/week by trained nurses one hour after the beginning of the HD in the clinic (20 min/session) | Aromatherapy massage was performed by trained female and male nurses for female and male patients, respectively | - | All participants completed the study |
| Motedayen 2014 | **Exercise** | **Control** | To investigate the effect of intradialytic physical and mental exercises on fatigue in HD | The experimental group participated in a intradialytic training program | Each session began whit positive thinking. Then the patients were encouraged to do stretching and flexibility movements in the muscles and taking a deep breath with soft music | The intervention was performed twice/week for 2 months (20 min), by a senior expert in the clinic | Each patient was initially questioned about their limitations to design a personalised exercise program. The exercises would be stopped in case of problems | - | 66/75 participants completed the study |
| Muz 2017 | **Aromatherapy** | **Control** | To determine the effect of aromatherapy practiced by inhalation on the sleep quality and fatigue in HD | Sweet orange and lavender oil inhalation was performed. | Lavender and sweet orange oils were dropped to a gauze bandage, which was placed 5 cm away from under the nose and patients smelled for 2 min. Education about aromatherapy was provided | The researcher trained patients. The patients performed intervention before sleeping every day for a month | | Aromatherapy was prepared by the research with the aid of an expert. A message was sent to patient's phone daily to remind to | 62/80 participants completed the study |

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| | | | | | | | | apply aromatherapy. Issues were solved | |
| Ozdemir 2013 | **Acupressure** | **Control** | To evaluate the effect of reflexology on fatigue, pain and cramp in HD | The intervention group received foot reflexology treatment | Reflexology was applied 15 min for each foot. Relaxing techniques at the beginning at the end of the session was performed. Feet were positioned at the chest level of the researchers. | Reflexology application was performed by a researcher for 1 week in 3 sessions (30 min each), in the clinic | Pressure force was adjusted according to the patient's physical appearance and age | - | - |
| Parfrey 2005 | **EPO alpha (Hb target 9.5 to 11.5 g/dL)** | **EPO alpha (Hb target 13.5 to 14.5 g/dL)** | To compare the impact of higher versus lower Hb targets on fatigue and QoL in HD | Participants were randomised to receive EPO alfa to reach low target (9.5 to 11.5 g/dL) or high target (13.5 to 14.5 g/dL) Hb | After random treatment assignment, patients assigned to the low target remained on their pre-study epoetin dose. Patients with the higher target received a 25% dose escalation, or an initial dose of 150 units/Kg/week if naive to epoetin | In both groups, when haemoglobin levels deviated from target, epoetin doses were changed by 25% of the previous dose or 25 units per kilogram. | - | - | 324/596 participants completed the study |
| PEDAL 2020 | **Exercise** | **Control** | To assess the effect of exercise on QoL in HD | Participants were randomised to exercise or no treatment | The intervention consisted of using a modified cycle ergometer to perform aerobic exercise in a semirecumbent position. Twice/week, after the aerobic cycling exercise, participants completed lower extremity muscular conditioning exercises | The intervention was performed, 3 times per week during the first 2 hours of HD. | The prescribed individualized training intensity was derived from a peak aerobic capacity (VO2peak) assessment. New exercise intensity ranges | - | 234/335 participants who did the baseline visit completed the study |

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| | | | | | | | were established at the 3-month follow-up assessment point | | |
| Pellizzaro 2013 | **Exercise** | **Control** | To study respiratory and peripheral muscle training, and changes in functional, biochemical, and inflammatory parameters in HD | The respiratory training program consisted of training the inspiratory muscles, while the peripheral muscle program trained the knee extensor muscles | The RMT group performed three sets of 15 inspirations at the equipment mouthpiece and rested for 60 sec. The PMT group performed 3 sets of 15 knee extension repetitions, resting for 60 sec in between. The control group did not perform any intervention | The training was performed for 10 weeks (30 sessions) in the sitting position, in the clinic | The exercise load was changed throughout the training according to 50% of PImax or according to 1MR found at 30 days. | In order to estimate the optimal distance to be walked, walked distance prediction formulas were used according to gender | 39/45 participants completed the study |
| Picariello 2018 | **CBT** | **Control** | To evaluate the feasibility and acceptability of the CBT for fatigue in HD | CBT versus waiting-list control arm | The CBT targets individuals fatigue thoughts, emotions, and behaviours by identifying and managing unhelpful thoughts in relation to fatigue. The control group received usual renal care and a manual | The CBT was performed by a therapist (3-5 sessions: first and last sessions face-to-face for 1-hour, remaining over the phone for 30 min) | Tailored CBT-based self-management intervention | - | 18/24 participants completed the study |
| Raimann 2010 | **Dialysate with low-dose glucose** | **Dialysate with high-dose glucose** | To investigate fatigue using 100 mg/dL versus 200 mg/dL dialysate glucose in HD | Participants were randomised either to 100 or 200 mg/dL dialysate glucose | - | The intervention was provided from 3 weeks in the clinic | - | - | 29/29 participants completed the study |
| Reily-Spong 2015 | **Meditation** | **Control** | To assess if yoga improve HD and PD patients to cope with pain and dis- | Patient received yoga exercise training and psychosocial support or | Yoga poses and homework were performed in the intervention group. Support performed six one-hour teleconferences | A certified yoga teacher led all sessions performed the exercise for 8 weeks | - | Each weekly teleconference included discussions. | Not reported only for patient in HD and PD |

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| | | | tress following transplant surgery | only psychosocial support | | in the clinic and at home | | Telephone conference calls were selected to reduce travel time | |
| Roshanravan 2016 | **Acupressure** | **1) Control**<br>**2) Placebo** | To assess the effect of foot reflexology on fatigue in HD | Participants were randomised to foot reflexology, placebo or control group | The patients in intervention group received foot reflexology for 20 min, and simple foot reflexology without pressing certain parts of the foot was done in placebo group. The patients in control group received only routine care | The researcher and a female co-researcher performed the reflexology in the clinic, 3 times/week and for 4 weeks. | The duration of reflective massage depends on patients age and some other factors and varies from 5 to 30 min | - | 78/81 participants completed the study |
| Sabouhi 2013 | **Acupressure** | **1) Control**<br>**2) Placebo** | To investigate the effectiveness of acupressure on fatigue in HD | Intervention and placebo groups received acupressure or sham acupressure. Control group received usual care | This intervention was carried out in both legs, hands, and the waist. | Researchers provided 6 acupoints with massage for 20 min/day, 3 days/week for 4 weeks, in the clinic. | - | Determination of acupoints was made based on the second supervisor's guidance on the acupoints standard location | - |
| Sajadi 2016 | **Cold dialysis** | **Warm dialysis** | The purpose of this study was to explore the effect of cold dialysis on fatigue in HD | Patients received 3 sessions of HD with a 37°C or 35.5°C solution | - | The intervention was performed 3 times/week for 1 week from the medical staff in the clinic | - | The weighing scale for patients, dialysis machines, and barometer were calibrated by a technician to assured precision | - |

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| Salehi 2020 | **Exercise** | **Control** | To assess the effect of exercise on fatigue in HD | Patients were randomised to bike exercise or no treatment | The intervention was performed using the electric exercise bike. The researcher placed the bike on the bed, fixed the patient's feet to the pedals using adhesive straps | The exercise program was conducted twice a week for 12 weeks during HD (20 min). | If the participant had a blood pressure of 180/110 mmHg and higher, systolic pressure lower than 90 mm Hg, chest pain, shortness of breath, or high body temperature (> 37.8 C) before or during dialysis, the exercise would be discontinued | Participants were instructed on how to exercise and verbal encouragement was provided to them during exercise | 37/54 participants completed the study |
| Sang 1997 | **Steady dialysate sodium** | **1) Linear sodium ramping**<br>**2) Stepwise sodium ramping** | Patients were randomised to steady, linear or stepwise ramping sodium in HD | Steady (140 mEq/L), linear (from 155 mEq/L to 140 mEq/L) and stepwise ramping sodium (155 mEq/L for 3 hours and 140 mEq/L for the last hour of dialysis) were performed | - | All patients underwent 6 weeks of experimental treatment in the clinic, performed by the staff | - | Stopping HD or changing the protocol was considered as protocol failure | 23/29 participants completed the study |
| Schardong 2021 | **Laser** | **Control** | To evaluate the chronic effect of photo-biomodulation (PBM) on | Participants were randomised to PBM or standard care | The control group did not receive any physical therapy intervention. | The intervention group received 24 sessions of PBM during HD | - | - | 28/33 participants completed the study |

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| | | | the functional capacity in HD | | PBM was applied at 6 points demarcated in the quadriceps and 2 points in the gastrocnemius muscle | | | | |
| Schmitz 2016 | **Citrate dialysate** | **Standard citrate** | To investigate the effect of citrate dialysate in patients on different dialysis modalities | Patients were randomised to citrate dialysate or standard citrate | - | The treatment was provided in the clinic from the staff for 4 weeks | - | - | 92/95 were included into the analysis. All participants completed the analysis |
| Semeniuk 2000 | **Nutritional supplements** | **Placebo** | To investigate the effect of L-carnitine on fatigue in HD | Patients were randomised to L-carnitine or placebo | - | Patients were randomised to L-carnitine or placebo for 12 weeks and then they were crossed-over | - | - | 10/12 participants completed the study |
| Shahdadi 2016 | **Massage** | **Control** | To assess the effect of slow stroke back massage on fatigue in HD | Patients were randomised to slow stroke back massage or control group | Massage was performed in sitting position. Movements is per formed several times | 2 sessions/week (6 in total) was performed by a nurse for 10 min, for 3 weeks in the clinic | - | - | All participants completed the study |
| Singer 2010 | **Nutritional supplementation** | **Placebo** | To determine the effect of ascorbate on cardiovascular stability in dialysis | Patients were randomised to ascorbic acid or placebo | - | The intervention was performed for 3 months | - | - | Not clearly reported for people in HD and PD |
| Singh 2003 | **Dialyser** | **Dialyser** | To ascertain the effect of membrane on TNF-alfa and fatigue in HD | Patients were randomised to polysulfone or cuprophan membrane | - | The intervention was performed for 3 weeks in the clinic | - | - | Not clearly reported at the end of the first phase |

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| Singh 2008a | **Iron replacement product** | **Placebo** | To assess the safety of ferumoxytol in HD | Patients were randomised to ferumoxytol or placebo | Ferumoxytol or placebo on day 0 was administered as a rapid IV push over 17 sec. | The intervention was performed for 1 week in the clinic | - | - | Not clearly reported at the end of the first phase |
| Sklar 1998 | **Dialyzer** | **Dialyzer** | To compare low flux polysulfone and cuprophan membrane on cytokine and intradialytic symptoms in HD | Patients were randomised to poly methylmethacrylate or cuprophan membrane | - | The intervention was performed for 1 week in the clinic by medical staff and investigators | - | - | Not clearly reported at the end of the first phase |
| Sklar 1999 | **Dialysis procedures** | **Sham dialysis procedures** | To assess the fatigue response to isolated aspects of the dialysis procedure | Patients were randomised to hypernatremic HD, routine dialysis, isolated ultrafiltration, isolated diffusion, sham procedures with isolated membrane, and sham procedures without recirculation exposure to a dialysis membrane | Hypernatremia HD was performed with 150-155-mEq/L sodium bath, routine dialysis with 135-140-mEq/L sodium bath. No further information was reported for other dialysis procedures | The intervention was performed in the clinic, 2 cycles each | Patients receiving treatments without ultrafiltration who complained dyspnoea and/or excessive weight gain were switched to regular HD | Patients were seen at the completion of their treatments and called at home the next day by the investigators | Not clearly reported at the end of the first phase |
| SOCIABLE 2017 | **Education** | **Control** | To assess the effect of SOCIABLE services in HD | SOCIABLE services gave emphasis on supporting the social function and the physical and everyday living function | SOCIABLE services support function among older adults with ESKD. The occupational therapist taught energy conservation techniques and supplied assistive devices so the individual could get dressed without fatigue | SOCIABLE services involve a nurse, and occupational therapist and a handyman. Participants will receive 10 home visits plus minor home repairs and assistive devices over | - | The nurse wrote a letter to the primary care provider and nephrologist summarizing the participant's goal | 9/12 participants completed the study |

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| | | | | | | a 4-month period of time | | achievements | |
| Soliman 2015 | **Exercise** | **Control** | To determine the impact of Intradialytic exercise on fatigue in HD | Participants were randomised to Range of Motion (ROM) exercise or no treatment | ROM exercises performed to all joint of upper and lower limb excluded body part connected to dialysis machine and paid attention to other limb involved in exercise to avoid disconnection | ROM exercise was prescribed for 15 min/day, 3 times/week, during HD | ROM exercises lasted for 15 min, in the first 2 hours of dialysis according to patients tolerance and stopped next 2 hours of HD | Pre-demonstration and post-description of the exercise technique, the patients demonstrated in 3 training sessions and received the booklet | 30/40 participants completed the study |
| Su 2009 | **Acupressure** | **Heat** | To determine the impact of far infrared ray stimulation treatment in HD | The intervention group performed far infrared ray stimulation on acupoints, the control group performed heat pad therapy | In both groups were applied acupoints or heat | Each participant received three 30 min intervals of either acupressure treatment or heat at 40◦C/week for 12 weeks in the clinic | - | - | 61/69 participants completed the study |
| Suzuki 2018 | **Exercise** | **Control** | To evaluate the effects of intradialytic electrical muscle stimulation (EMS) in HD | Participants were randomised to EMS or no treatment | Silicone-rubber electrode bands, 5.5 cm in width, were wrapped around the waist. An anode was set at the distal femurs and a cathode at the waist and ankles to stimulate the gluteal and upper- and lower-leg muscle groups | EMS training of the lower extremities was performed within the first 2 hours of the HD session. The training was conducted 3 times/week for 8 weeks using a handheld muscle stimulator | For each training session, the stimulus intensity was individually adjusted by a rehabilitation physician to the highest level attainable, not | - | 26/29 participants completed the study |

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| | | | | | | | exceeding the patients' perceived discomfort | | |
| SWIFT 2020 | **Education** | **Control** | To assess if regular symptom monitoring with feedback in HD can improve QoL | Symptom monitoring WIth Feedback Trial (SWIFT) versus usual care | Participants in the intervention arm will complete the IPOS-Renal at baseline up to 12 months | IPOS-Renal results will be emailed to the centre nurse unit manager or delegate, and the participant's treating nephrologist | If a participant does not have their own email address, they can nominate the address of a family member or close friend | - | - |
| Thomas 2017 | **Meditation** | **Control** | To determine the feasibility, tolerability and enrolment rates and to examine whether the intervention reduced depression and anxiety in HD | The intervention group received individual chairside meditation intervention. The control group received treatment as usual in the HD setting | The intervention consisted of meditative practices (body scan, guided meditation, silent meditation, gentle arm movements). Before and after each session patients performed a 1–2 min to explore their experience | The expert interventionists provided the intervention for 8 weeks, 10–15 min, 3 times/week in the clinic. Patients were pushed to practice at home | The intervention was practiced in alternating fashion, on the basis of patient preference. | Interventionists received qualitative subjective comments from participants, and asked for overall feedback after each session. | 32/41 participants completed the study |
| Tsai 2016 | **Acupressure** | **Sham acupressure** | The evaluate the efficacy and safety of herbal acupoint therapy for intradialytic hypotension in HD | Patients were randomised to acupressure or sham acupressure | The patches were applied before the HD. The patches were placed on 3 points and each acupoint was covered with gauze for 4 hours | Four hours of treatment was administered for 3 times/week for 4 weeks, in the clinic | - | Participants were supervised by nurses to prevent them from touching the patches during each session | 27/32 participants completed the study |

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| Tsay 2004a | **Acupressure** | **1) Sham acupressure**<br>**2) Control** | The purpose of the study is to investigate the effectiveness of acupressure on fatigue in HD | Patients were randomised to receive acupressure (plus usual care), sham acupressure (plus usual care) or usual care alone | Acupressure group received acupressure massage (3 min of massage to relax and 12 min of acupoints), the placebo group received a massage at locations with no acupoints. Control group received usual care only | The researcher and her assistants provided massage 3 times/week for 4 weeks, 15 min each, in the clinic | - | The precision of the acupoint was confirmed if subjects felt sore during the massage. Two experts, evaluated the accuracy of acupoints selection for this study | All participants were included into the analyses |
| Tsay 2004b | **1) Acupressure**<br>**2) TEAS** | **Control** | To test the effectiveness of acupressure and TEAS on fatigue, sleep and depression in HD | Patients were randomised to receive acupressure, TEAS (using paired skin electrodes) or routine unit care | Patients in the acupressure and TEAS groups received treatment, whereas patients in the control group only received routine unit care. Subjects in the treatment groups were instructed not to massage any acupoints | The researcher and her assistants provided acupressure and TEAS for 15 min of treatment 3 times/week for 1 month, in the clinic | - | The precision of the acupoint was confirmed if subjects felt sore during the massage. Two experts, evaluated the accuracy of acupoints selection for this study | 106/108 participants completed the study |
| Unal 2016 | **Massage** | **Control** | To examine the effectiveness of foot reflexology and back massage on sleep and fatigue in HD | Patients were randomised to foot reflexology, the back massage or control group | The foot reflexology group placed in either sitting or lying position and begins with relaxation exercises. In the back massage group patients were lying down. In both groups, 3 to 5 drops of baby oil were applied | A researcher provided the interventions, twice/week, 30 min each, for 4 weeks in the clinic | - | - | 105/110 participants completed the study |

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| Varaei 2020 | **1) Aromatherapy (inhalation)**<br><br>**2) Aromatherapy (massage)** | **Control** | To assess the effect of aromatherapy on fatigue in HD | The three groups of this study were lavender and sweet orange inhalation aromatherapy group, lavender and sweet orange aromatherapy massage group, and a control group | One drop of lavender and one drop of sweet orange essential oils were poured on a 2 × 2 cm gauze and it was attached to the shirt collar of each eligible patient for 20 min. The patient was asked to breathe gently. Patients in the control group received neither inhalation aromatherapy nor aromatherapy massage | This intervention was implemented for all patients in the inhalation aromatherapy group 3 times/week for 8 consecutive weeks. | A massage therapist (a female therapist for female patients and a male one for male patients) stood at the bottom of the patient's bed and held patient's foot in her/his own hands | - | All participants completed the study |
| VENOUS 2020 | **Anti-thrombotic polymethyl-methacrylate** | **Placebo** | To examine the effects of anti-thrombotic polymethyl-methacrylate on nutritional status in dialysis | Patients were randomised to anti-thrombotic polymethyl-methacrylate or placebo | - | - | - | - | 25/54 participants completed the study |
| Vishnevskii 2014 | **Transcutaneous Electrical Muscle Stimulation** | **Control** | To evaluate the Transcutaneous Electrical Muscle Stimulation capability in improvement of the efficiency and physical ability in HD | Patients were randomised to intervention or control group | The intervention group received muscle stimulation of the lower extremities (3 times each session for 30 min). The control group remained on previous dialysis regimen | The intervention group received the treatment during HD sessions for 4 weeks, 3 times/week | - | - | - |
| Yurtkuran 2007 | **Exercise (yoga)** | **Control** | To evaluate the effects of a yoga-based exercise program on pain, fatigue, | The intervention group performed yoga exercises, the control group | The exercises were done in the standing, sitting and lying positions. The rhythm consisted of 6-sec expiration and stretch- | Yoga-based exercises were by an instructor for 30 min/day twice a week | Modifications of various postures were | Each patient in the yoga group was provided with | 37/40 participants completed the study |

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| | sleep, and biochemical markers in HD. | did not attend the yoga class | ing/4-sec inspiration and relaxing; 10 repetitions were done for every movement. Every session ended with relaxation | for 3 months, in the clinic. Both groups performed exercises at home for 10 minutes | based on participant abilities/tolerance | an illustrated booklet explaining the poses. The home-based exercises was explained by a physiotherapist. We kept contact with all patients to answer questions |

Footnotes:

BP: blood pressure; BRT: Benson relaxation technique; CBT: cognitive-behavioural therapy; CERA: Continuous Erythropoietin Receptor Activator; CKD: chronic kidney disease; DBP: diastolic blood pressure; EPO alfa: epoetin alfa; Hb: haemoglobin; HD: haemodialysis; HRQoL: health-related quality of life; IV: intravenous; L-DOPS: L-threo-3,4-dihydroxyphenylserine; PD: peritoneal dialysis; PEP: Personal Energy Planning; PMR: progressive muscle relaxation; QoL: quality of life; RCT: randomised controlled trial; SBP: systolic blood pressure; TEAS: Transcutaneous Electrical Acupoint Stimulation

## Appendix 5. Studies reporting adverse events

| Study ID | Intervention | Control | Adverse events in the intervention arm | Adverse events in the control arm | Comments |
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| Akizawa 2002 | **L-DOPS (400 or 200 mg)** | **Placebo** | Overall, 5/100 patients in the treatment group reported headache, increased blood pressure, urinary retention, facial hot flushed, bad feeling, drug eruption, but number of patients who reported each adverse event was not reported | Feeling irritated (1), insomnia (1) | Quote: "Adverse events occurred in 3/51 patients in the 400 mg group (5.9%; i.e.,headache, increased blood pressure, urinary retention), 2/49 patients in the 200 mg group (4.1%; i.e., headache, increased blood pressure, facial hot flushed, bad feeling, drug eruption), and 1/49 patients in the placebo group (2.0%; i.e., feeling irritated, insomnia)." |
| ASCEND 2016 | **Sertraline** | **CBT** | Death 0/60, hospitalisation/other 9/60, major bleeding 1/60, cardiac 3/60, gastrointestinal 1/60, infection 2/60, other 2/60 | Death 2/60, hospitalisation/other 14/60, major bleeding 2/60, cardiac 4/60, gastrointestinal 1/60, infection 2/60, other 8/60 | Quote: "Serious adverse events occurred in both treatment groups: 13 in 11 patients in the CBT group and 18 in 14 patients in the sertraline group. Non-serious adverse events were more frequent in the sertraline (56 events in 25 patients) than the CBT (17 events in 12 patients) group." |
| ASSertID 2015 | **Sertraline** | **Placebo** | Adverse events and/or serious adverse events (9/15); cardiovascular death (1/15) | Adverse events and/or serious adverse events (9/15); cardiovascular death (0/15) | Quote: "Eighteen patients experienced adverse events (24) and/ or SAEs (13), nine in each randomized group. Infections (8) and nausea (4) were the most commonly reported adverse events. With regard to the SAEs, there was one death that was possibly related to the study medication as mentioned above, six SAEs that were unlikely to be related, and six SAEs that were not related to the study medication." "In the sertraline group, there were six dropouts within the first 2 months. One patient died of cardiac arrest having taken one tablet. Three patients withdrew because of adverse events (one after 3 days with nausea, another after 12 days with headaches and dizziness, |

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| | | | | | and the third due to insomnia after 23 days). The fifth patient withdrew because of concern about side effects, having taken no study medication. The sixth patient was admitted for a prolonged hospital stay with leg ulcers shortly after randomisation and subsequently withdrawn without having taken any study medication. At 3 months, a seventh patient withdrew because of sweating and palpitations. In the placebo group, one patient withdrew after the baseline interview because of concern about taking additional medication, and a second decided against continuing after 3 months." |
| BA16285 2007 | **C.E.R.A. (once/week)** | **C.E.R.A. (once every 2 weeks)** | Adverse events were reported for all study participants without distinction between groups (fatigue, anaemia, headache, vomiting, dizziness, diarrhoea, upper respiratory tract infection, nausea, dyspnoea, kidney transplantation, chest pain, muscle cramp or spasm, pyrexia, constipation, pruritus, rectal cancer, accelerated hypertension, cerebrovascular accident, death, acute myocardial infarction and multiple organ failure, chronic renal failure) | Adverse events were reported for all study participants without distinction between groups (fatigue, anaemia, headache, vomiting, dizziness, diarrhoea, upper respiratory tract infection, nausea, dyspnoea, kidney transplantation, chest pain, muscle cramp or spasm, pyrexia, constipation, pruritus, rectal cancer, accelerated hypertension, cerebrovascular accident, death, acute myocardial infarction and multiple organ failure, chronic renal failure) | Quote: "During the core study period, 4 AEs led to premature withdrawal (worsening anaemia [2 patients in group A and 1 in group C] and kidney transplant [1 in group A]). All cases of anaemia were considered to be related to study medication, whereas the kidney transplant was not. There were 5 withdrawals because of AEs in the extension period (pruritus, chest pain, rectal cancer, accelerated hypertension, and cerebrovascular accident [1 patient each]). In addition, dialysis was discontinued in 1 patient (at the request of her family), who was subsequently withdrawn from the study. The investigator classified this as an AE of chronic renal failure. All AEs leading to withdrawal in the extension period were considered to be unrelated to the study medication with the exception of accelerated hypertension (1 patient), which was classified as an SAE. Nineteen patients experienced an SAE during the core period, and 22, during the extension period. Two |

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| | | | | | patients died during the extension period of the study (acute myocardial infarction and multiple organ failure); these deaths were deemed as SAEs. Neither death was considered related to treatment." |
| Barre 1988 | **Low dialysate sodium** | **High dialysate sodium** | In general, adverse events were reported for all study participants without clear distinction between groups (fatigue, thirst, cramps, back pain, stomach-ache, irritability, nausea, vomiting, headache, weakness, restlessness, itchiness, or any other symptoms) | In general, adverse events were reported for all study participants without clear distinction between groups (fatigue, thirst, cramps, back pain, stomach-ache, irritability, nausea, vomiting, headache, weakness, restlessness, itchiness, or any other symptoms) | Quote: "One patients accounted for 52% of symptoms during dialysis and 58% of symptoms between dialyses. As noted, thirst was significantly less frequent with a sodium dialysate of 150 mEq/L, whereas headache was more frequent with the same dialysate. Fatigue during dialysis was more frequent with sodium dialysate of 145 mEq/L, whereas other symptoms, including cramps, back pain, stomachache, and irritability, were less frequent with a sodium dialysate of 155 mEq/L. Symptoms between dialyses, including thirst and headache, were more frequent with dialysate sodium of 155 mEq/L but were only present in two patients." |
| Bicer 2022 | **Acupressure** | **Placebo** | 70.1% of the patients in the intervention group experienced hypotension | 0.9% of the patients in the placebo group experienced hypotension | Quote:" The procedure-related side effects did not develop in all the patients included in the study and no patients felt unwell during or after the procedure." |
| BOLD 2020 | **Home SBP** | **Pre-dialysis SBP** | Post-dialysis SBP<90 mmHg 2/25, post-dialysis SBP>200 mmHg 3/25, syncope 1/25, fall 3/25, flash pulmonary oedema 0/25, cramping 13/25, dizziness 10/25, light-headedness 14/25, hypotension 21/25. | Post-dialysis SBP<90 mmHg 0/25, post-dialysis SBP>200 mmHg 2/25, syncope 1/25, fall 6/25, flash pulmonary oedema 0/25, cramping 18/25, dizziness 14/25, light-headedness 12/25, hypotension 18/25. | Quote: "The proportion of dialysis treatments with either excessively low or high pre or post dialysis SBP was small and similar in the two treatment groups. The rates of syncope, falls and flash pulmonary edema were also comparable between treatment groups." |
| Brass 2001 | **L-carnitine** | **Placebo** | In general, adverse events were reported for all study participants without clear distinction between | In general, adverse events were reported for all study participants without clear distinction between | Quote: "The most commonly reported adverse events were flu syndrome, injection-site reaction, pain, pharyngitis, headache, and |

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| | | | groups (flu syndrome, injection-site reaction, pain, pharyngitis, headache, hypertension).<br><br>The intervention group reported serious adverse events (data included study A and B): body injection site reaction (4/130), infection (2/130), chest pain (3/130), abdominal pain (2/130), fever (1/130), accidental injury (1/130), neck pain (1/130), tachycardia (3/130), atrial fibrillation (1/130), hypertension (1/130), hypotension (1/130), aortic stenosis (1/130), colitis (1/130), vomiting (2/130), parathyroid disease (1/130), hyperkalaemia (2/130), hypervolaemia (1/130), lung oedema (1/130), pneumonia (1/130), skin carcinoma (1/130), amblyopia (1/130), urogenital kidney failure (8/130) | groups (flu syndrome, injection-site reaction, pain, pharyngitis, headache, hypertension).<br><br>The control group reported serious adverse events (data included study A and B): body injection site reaction (6/63), infection (4/63), chest pain (0/63), abdominal pain (0/63), fever (0/63), accidental injury (0/63), neck pain (0/63), tachycardia (0/63), atrial fibrillation (0/63), hypertension (0/63), hypotension (0/63), aortic stenosis (0/63), colitis (0/63), vomiting (0/63), parathyroid disease (0/63), hyperkalaemia (0/63), hypervolaemia (0/63), lung oedema (0/63), pneumonia (0/63), skin carcinoma (0/63), amblyopia (0/63), urogenital kidney failure (3/63) | hypertension and showed no difference in frequency between L-carnitine and placebo. Several serious adverse events occurred during the course of the study, with no differences between active and placebo groups. No serious adverse event was believed by the investigators to be certainly or probably drug related and they were consistent with the population's underlying disease and maintenance haemodialysis treatment."<br><br>Table 7 reported "events that occurred only in placebo groups were not listed". |
| Canadian EPO 1990 | **EPO alfa** | **Placebo** | Adverse events for both intervention groups were reported: seizure (2/78), clotting of vascular access (11/78), clotting of tubing in dialysis machine (8/78), pain in chest (13/78), epistaxis or haemorrhage (10/78), abnormal sense of taste (11/78), headache (26/78), redness of eyes (5/78), flu-like symptoms (18/78), aches in bone or muscle (20/78). | Adverse events in the control group were reported: seizure (1/40), clotting of vascular access (1/40), clotting of tubing in dialysis machine (4/40), pain in chest (6/40), epistaxis or haemorrhage (7/40), abnormal sense of taste (6/40), headache (19/40), redness of eyes (0/40), flu-like symptoms (12/40), aches in bone or muscle (9/40). | Table V reported in the Canadian EPO 1990. |
| Chang 2010 | **Exercise** | **Control** | Adverse events were not reported in the intervention group | All adverse events were not reported in the control group. However, authors reported that a muscle/joint pain (1/35) | Quote: "There were three early terminations due to a Borg score of 15 (1), muscle/joint pain (1), and unsteady pedal speed (1). All occurred among the sedentary subjects." |

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| | | | | led to early termination | |
| Chen 2008a | **CBT** | **Education** | One participant with underlying stable major depression experienced a minor episode, but it was not reported in which treatment group he was allocated.<br><br>1/13 participants in the intervention group experienced morning dyspnoea | One participant with underlying stable major depression experienced a minor episode, but it was not reported in which treatment group he was allocated.<br><br>Other adverse events were not reported in the control group | Quote: "One participant with underlying stable major depression experienced a minor episode because of cessation of antidepressant therapy. One participant in the CBT group experienced 1 episode of morning dyspnoea after a large meal during the last week of this 4-week trial." |
| Chen 2011a | **CBT** | **Education** | There were no adverse events in the intervention group | There were no adverse events in the control group | Quote: "No adverse events were reported during the intervention." |
| Eroglu 2022 | **Relaxation + music** | **Control** | No information was reported in detail | No information was reported in detail | Quote: "Moreover, no participants dropped out owing to unexpected adverse effects of BRT combined with music therapy." |
| Fatouros 2010 | **L-carnitine** | **Placebo** | No adverse events were reported in the intervention group | No adverse events were reported in the control group | Quote: "No adverse clinical effect related to L-carnitine supplementation was reported." |
| FHN DAILY 2007 | **Frequent HD** | **Conventional HD** | Death 5/125, all hospitalisation 109/125, all interventions related to vascular access 95/125, hypokalaemia 13/125, hyperphosphataemia 15/125 | Death 9/120, all hospitalisation 114/120, all interventions related to vascular access 65/120, hypokalaemia 6/120, hyperphosphataemia 9/120 | Quote from FHN trial 2010: "Adverse events were reported in table 4." |
| Foley 2000 | **EPO alpha (Hb target 9.5-10.6 g/dL)** | **EPO alpha (Hb target 13-14 g/dL)** | Arteriovenous access thrombosis and cardiac events were reported in the low target Hb group but the number of patients was not reported. During the study period 3/73 participants died in the low target Hb group | Arteriovenous access thrombosis and cardiac events were reported in the high target Hb group but the number of patients was not reported. During the study period 4/73 participants died in the high target Hb group | Quote: "The comparative incidence of arteriovenous access thrombosis, cardiac events, and death." |
| Fukuda 2015 | **Nutritional supplementation** | **Placebo** | Adverse events in the intervention group were reported: increased blood pressure (1/103), dizziness (1/103), insomnia (1/103), nausea (1/103), diarrhoea | Adverse events in the control group were reported: increased glucose level (1/99), felt sick (2/99), stomach discomfort (1/99), hospitalisation (2/99). | Quote: "In the nutritional drink group, one participant reported increased blood pressure, one complained of dizziness, one complained of insomnia, one reported nausea, and two had diarrhoea. One par- |

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| | | | (2/103), sudden hearing loss (1/103). One participant in each group had cramp in the lower leg | One participant in each group had cramp in the lower leg | ticipant in each group had cramp in the lower leg. In the placebo group, one participant reported increased glucose level, two felt sick, and one complained of stomach discomfort. One participant developed sudden hearing loss and was prescribed any vitamins. Two participants were hospitalised in the placebo group. The safety monitoring board confirmed no serious adverse events, and hospitalisation was determined relating to the study intervention." |
| Grigoriou 2021 | **Exercise** | **Control** | Not reported in sufficient detail | Not reported in sufficient detail | Quote: "All participants completed both scenarios without any adverse effects or significant complaints." |
| HDPAL 2014 | **Atenolol** | **Lisinopril** | A questionnaire assessed the following adverse events: fatigue or tiredness, chest pain, abdominal pain, cold hands or feet, dizziness on standing, muscle cramps, diarrhoea, nausea, vomiting, dry cough, upper respiratory infection or common cold, shortness of breath, headaches, persistent dizziness, numbness in hands or feet, decreased sex drive, decreased ability to have sex, drowsiness or sleepiness, depression or feeling sad and nightmares. However, data were not reported considering the treatment assigned (for only 133 patients who completed the questionnaire).<br><br>Adverse events in the intervention group were reported: overall serious adverse events (58/100), all-cause hospitalisation (37/100), infections (24/100), access-re- | A questionnaire assessed the following adverse events: fatigue or tiredness, chest pain, abdominal pain, cold hands or feet, dizziness on standing, muscle cramps, diarrhoea, nausea, vomiting, dry cough, upper respiratory infection or common cold, shortness of breath, headaches, persistent dizziness, numbness in hands or feet, decreased sex drive, decreased ability to have sex, drowsiness or sleepiness, depression or feeling sad and nightmares. However, data were not reported considering the treatment assigned (for only 133 patients who completed the questionnaire).<br><br>Adverse events in the control group were reported: overall serious adverse events (70/100), all-cause hospitalisation (59/100), infections (20/100), access-re- | Quote from Agarwal 2016: "The symptoms were as follows: fatigue or tiredness, chest pain, abdominal pain, cold hands or feet, dizziness on standing, muscle cramps, diarrhoea, nausea, vomiting, dry cough, upper respiratory infection or common cold, shortness of breath, headaches, persistent dizziness, numbness in hands or feet, decreased sex drive, decreased ability to have sex, drowsiness or sleepiness, depression or feeling sad and nightmares."<br><br>Quote from Agarwal 2014;"Table 3 shows the serious adverse events between groups over the course of the trial." |

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| | | | lated (17/100), central nervous system (3/100), cancer-related complications (2/100), cardiovascular event (16/100), angina (0/100), arrhythmia (2/100), cardiac arrest (0/100), congestive heart failure (5/100), myocardial infarction (2/100), peripheral vascular disease (1/100), revascularization (3/100), stroke (2/100), valve replacement surgery (1/100), cardiovascular death (2/100), non-cardiovascular death (2/100), fractures (7/100), parathyroidectomy (3/100), biliary-related (1/100), bowel-related (3/100), falls (6/100), gastrointestinal bleeding (2/100), hypertensive crisis (3/100), hyperglycaemia (1/100), hyperkalaemia (3/100), hypoglycaemia (2/100), hypotension with hospitalisation (6/100), miscellaneous (12/100) | lated (19/100), central nervous system (3/100), cancer-related complications (2/100), cardiovascular event (28/100), angina (2/100), arrhythmia (3/100), cardiac arrest (2/100), congestive heart failure (10/100), myocardial infarction (3/100), peripheral vascular disease (5/100), revascularization (4/100), stroke (2/100), valve replacement surgery (1/100), cardiovascular death (3/100), non-cardiovascular death (1/100), fractures (1/100), parathyroidectomy (1/100), biliary-related (2/100), bowel-related (5/100), falls (3/100), gastrointestinal bleeding (5/100), hypertensive crisis (10/100), hyperglycaemia (3/100), hyperkalaemia (10/100), hypoglycaemia (4/100), hypotension with hospitalisation (5/100), miscellaneous (18/100) | |
| Johansen 1999 | **Nandrolone decanoate** | **Placebo** | Adverse events in the intervention group were reported: hematoma (1/14), reduction in testicular size (1/14), amenorrhoea (1/14), acne (1/14), hypertension (3/14) | Adverse events in the control group were reported: hematoma (1/15), skin rash (2/15), hypertension (3/15) | Quote:"Reason for inability to undergo treadmill included coronary artery disease (7 subjects), severe hypertension (2 subjects), hospitalisation (3 subjects), study drop-out (2 subjects), valvular heart disease, amputation, arthritis, abdominal hernia, and diabetic foot ulcer (1 subject). [...] The study was generally well tolerated, but minor adverse events occurred. Two subject (one in each arm) developed hematoma. One nandrolone recipient complained of a reduction in testicular size that resolved with dose reduction.two men (both in the placebo group) complained of skin rash. Of the 3 women who received nandrolone, 2 re- |

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| | | | | | quired dose reduction for amenorrhoea and acne, respectively. [...] Six subjects (3 in each group) required increase in antihypertensive medication dosages." |
| Johansen 2006 | **Nandrolone decanoate with or without exercise** | **Placebo with or without exercise** | Adverse events in both intervention groups were reported: interference with sexual function (1/39) | Adverse events in the both control groups were reported: death (1/40), not feeling well (1/40), abdominal pain (1/40), itchy reaction (1/40) | Quote: "Those who received placebo discontinued because of an itchy reaction at the injection site, a nonspecific feeling that the drug was having adverse effects, abdominal pain and liver function test abnormalities, and discovery of a history of prostate cancer. Those who received nandrolone discontinued because of interference with sexual function (after five doses) and fear of possible adverse effects (after three doses)." |
| Konstadinidou-ND 2002 | **Exercise** | **Control** | Adverse events in both intervention groups were reported: death (1/36) | Adverse events in the control group were reported: death (1/12) | Quote:"However, during the study 5 patients from Group A, 1 from Group B, 2 from C voluntarily withdrew, while 1 patient from Group B and 1 from D died of causes unrelated to exercise." |
| Krase 2022 | **Exercise** | **Control** | No detailed information was reported | No detailed information was reported | Quote: "Exercise was well tolerated by all patients, and no adverse reactions were reported." |
| Leski 1979 | **Dialysate containing glucose** | **Dialysate without glucose** | The study assessed fatigue, headache and leg cramps using a questionnaire: number of patients who reported these adverse events after dialysis was not reported. Hypotension was recorded but the author did not report information neither on the intervention group allocation nor on the number of cases | The study assessed fatigue, headache and leg cramps using a questionnaire: number of patients who reported these adverse events after dialysis was not reported. Hypotension was recorded but the author did not report information neither on the intervention group allocation nor on the number of cases | Quote: "Headache diminished in frequency during the sessions after the sessions. Fatigue during dialysis was not significantly altered, however post-dialysis fatigue dropped significantly. The episodes of hypotension decreased in number, but not significantly. The same was the case for cramps." |
| Li 2014b | **Nurse led telephone support** | **Control** | As reported in figure 1, death was reported in the intervention group but the number of patients was not reported. | As reported in figure 1, death was reported in the control group but the number of patients was not reported. | Quote: "The presence of edema, existence of peritonitis, catheter infections, exit-site condition and weight gain were observed as the complication control of the participants within 42 |

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| | | | No data were clearly reported for oedema, peritonitis, catheter infections, exit-site condition in the intervention group | No data were clearly reported for oedema, peritonitis, catheter infections, exit-site condition in the control group | days (6 weeks) and 84 days (12 weeks) post-discharge." |
| Lillevang 1990 | **EPO** | **Placebo** | Adverse events in the intervention group were reported: skeletal pain (1/9), abdominal pain (1/10) | Adverse events in the control group were reported: bodily distress (1/9), leg cramps (1/10) | Quote:"During the study period, the following adverse effects was registered (defined as new complaints from the patients, independent of the patients perception of relationship with the treatment): in the treatment group, there was one case of skeletal pain and one case of abdominal pain; in the placebo group, there was one case of “bodily distress” and one case of leg cramps." |
| Linde 2001 | **EPO alpha to achieve normal-Hb target** | **Subnormal-Hb target with or without ESA** | Overall, in the intervention group there were the following adverse events: death (25/180), adverse events (29/180).<br>Specifically:<br>• HD: death (22/157), adverse events (26/157)<br>• PD: death (3/23), adverse events (3/23)<br>5 participants had sepsis<br>Data related to predialysis patient were not reported because they were out of our scope | Overall, in the control group there were the following adverse events: death (26/164), adverse events (14/164).<br>Specifically:<br>• HD: death (20/136), adverse events (14/136)<br>• PD: death (6/28), adverse events (0/28)<br>7 participants had sepsis<br>Data related to predialysis patient were not reported because they were out of our scope | Quote from Furuland 2003: "In a multivariate logistic regression analysis of SAE the number of patients with at least one SAE was 110 and 97 in the N-Hb and S-Hb groups, respectively. [...] Five patients in the N-Hb group and seven in the S-Hb group had sepsis." |
| Mohammadpourhodki 2021 | **Aromatherapy** | **Placebo** | None known | None known | Quote: "None of patients included in the intervention groups reported side effects or local or general complications." |
| Muz 2017 | **Aromatherapy** | **Control** | As reported in figure 1, participants in the intervention group reported: nausea and vomiting (1/41), in- | No adverse events were reported for the control group in figure 1. | No relevant quotations were reported |

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| | | | crease of blood pressure (2/41). | | |
| Parfrey 2005 | **ESA (normal Hb target)** | **ESA (high Hb target)** | Adverse events in the intervention group 1 were reported: any (281/300), hypertension (110/300), hypotension (105/300), platelet/bleeding/clotting arteriovenous fistula thrombosis (23/300), hematoma (36/300), arteriovenous fistula loss (26/300), vomiting (52/300), diarrhoea (53/300), nausea (53/300), abdominal pain (46/300), upper respiratory tract infection (69/300), dyspnoea (42/300), cough (36/300), pharyngitis (31/300), myalgia (85/300), skeletal pain (64/300), arthralgia (43/300), headache (64/300), dizziness (40/300), skin disorder (39/300), pruritus (33/300), infection (32/300), urinary tract infection (27/300), hyperparathyroidism (30/300), pain (47/300), back pain (40/300), fever (42/300), influenza (37/300), device complication (27/300), surgery (39/300), arteriovenous fistula thrombosis (36/300), non-site-specific embolism thrombosis (12/300), permanent catheter thrombosis (9/300), cerebrovascular disorder (4/300), peripheral ischaemia (7/300), angina pectoris (8/300), myocardial infarction (4/300), chest pain (7/300), permanent catheter loss (6/300), arteriovenous fistula loss (27/300), arteriovenous graft loss (9/300), tachycardia | Adverse events in the intervention group 2 were reported: any (284/296), hypertension (120/296), hypotension (85/296), platelet/bleeding/clotting arteriovenous fistula thrombosis (30/296), hematoma (45/296), arteriovenous fistula loss (30/296), vomiting (54/296), diarrhoea (50/296), nausea (47/296), abdominal pain (45/296), upper respiratory tract infection (72/296), dyspnoea (35/296), cough (35/296), pharyngitis (29/296), myalgia (81/296), skeletal pain (39/296), arthralgia (36/296), headache (86/296), dizziness (16/296), skin disorder (41/296), pruritus (23/296), infection (34/296), urinary tract infection (29/296), hyperparathyroidism (19/296), pain (41/296), back pain (35/296), fever (30/296), influenza (30/296), device complication (42/296), surgery (20/296), arteriovenous fistula thrombosis (45/296), non-site-specific embolism thrombosis (14/296), permanent catheter thrombosis (8/296), cerebrovascular disorder (12/296), peripheral ischaemia (8/296), angina pectoris (9/296), myocardial infarction (7/296), chest pain (4/296), permanent catheter loss (7/296), arteriovenous fistula loss (30/296), arteriovenous graft loss (9/296), tachycardia | Quote from Parfrey 2005: "Treatment-emergent adverse events that occurred in at least 10% of patients; vascular, access loss, and cardiac events that occurred in at least 2% of patients; and death in lower and higher target groups. " |

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| | | | (15/300), palpitations (9/300), atrial fibrillation (7/300), bradycardia (5/300), pulmonary oedema (16/300), cardiac failure (6/300), pulmonary oedema or heart failure (19/300), death (20/300) | (22/296), palpitations (6/296), atrial fibrillation (6/296), bradycardia (7/296), pulmonary oedema (9/296), cardiac failure (2/296), pulmonary oedema or heart failure (11/296), death (13/296) | |
| PEDAL 2020 | **Exercise** | **Control** | Greenwood 2021 reported: serious adverse events 69/175, blood and lymphatic system disorders 2/175, cardiac disorders 9/175, congenital disorders 0/175, gastrointestinal disorders 10/175, hepatobiliary disorders 2/175, infections and infestations 29/175, injury 15/175, metabolism and nutritional disorders 13/175, musculoskeletal and connective tissue disorders 3/175, cancer 1/175, nervous system disorders 5/175, psychiatric disorders 3/175, renal and urinary disorders 0/175, respiratory disorders 10/175, reproductive disorders 1/175, skin and subcutaneous tissue disorders 1/175, surgical procedures 24/175, vascular disorders 4/175 | Greenwood 2021 reported: serious adverse events 56/160, blood and lymphatic system disorders 0/160, cardiac disorders 6/160, congenital disorders 1/160, gastrointestinal disorders 4/160, hepatobiliary disorders 1/160, infections and infestations 18/160, injury 12/160, metabolism and nutritional disorders 4/160, musculoskeletal and connective tissue disorders 1/160, cancer 0/160, nervous system disorders 3/160, psychiatric disorders 1/160, renal and urinary disorders 1/160, respiratory disorders 3/160, reproductive disorders 1/160, skin and subcutaneous tissue disorders 0/160, surgical procedures 13/160, vascular disorders 6/160 | Quote from Greenwood 2021: "The number of patients with harms (serious adverse events) was similar in the intervention group (n = 69) and control group (n = 56)." |
| Picariello 2018 | **CBT** | **Control** | Admission to hospital 1/18 | Admission to hospital 2/7 | Quote: "No trial adverse events occurred." |
| Reilly-Spong 2015 | **Meditation** | **Control** | There were no adverse events in the intervention group | There were no adverse events in the control group | Quote from Reilly-Spong 2015: "No adverse effects related to the interventions were reported." |
| Salehi 2020 | **Exercise** | **Control** | None known | None known | Quote: "None of the patients suffered from such complications and all participated without interruption." |
| Sang 1997 | **Steady dialysate sodium** | **Linear sodium ramping** | Adverse events (hypotension, cramps, fatigue, thirsty and to- | Adverse events (fatigue, thirsty and total symptoms) were | Quote: "The number of symptomatic or asymptomatic hypotensive episodes |

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| | | **Stepwise sodium ramping** | tal symptoms) were recorded as score in all treatment groups. Other adverse events were not clearly stated | recorded as score in all treatment groups. Other adverse events were not clearly stated | and the time of occurrence of a hypotensive episode were recorded. [...] It was noted when the patient complained of angina, cramps, nausea, or headaches, or vomited. [...] Thirst, fatigue, dizziness and total symptoms were also recorded." |
| Schardong 2021 | **Laser** | **Control** | Not reported in sufficient detail | Not reported in sufficient detail | Quote: "Regarding the safety of this therapy, no changes were observed in patients' vital signs and adverse effects during laser applications, as well as in the interval between them." |
| Schmitz 2016 | **Citrate dialysate** | **Standard citrate** | Adverse events (including death) were not clearly reported per group in the first phase on the study period | Adverse events (including death) were not clearly reported per group in the first phase on the study period | Quote: "The events such as cramps and hypotension were more frequent with citrate dialysate. [...] The most common adverse events during standard dialysate use were infections and vascular disorders. During the citrate dialysate phase, the most frequent events were general disorders like fatigue, followed by infections and musculoskeletal disorders, e.g. muscle spasm or pain." |
| Semeniuk 2000 | **Nutritional supplementation** | **Placebo** | Not reported in sufficient detail | Not reported in sufficient detail | Some adverse events were reported (gastrointestinal and cardiovascular adverse events, hypotension). However, no data were clearly reported for the first phase of the cross-over study. |
| Singer 2010 | **Vitamin C** | **Placebo** | Adverse events in the intervention group were reported:<br><br>acute coronary syndrome (0/37). Other adverse events (including commence dialysis, bacteraemia and dialysis access thrombosis) were not clearly stated | Adverse events in the control group were reported:<br><br>acute coronary syndrome (0/38). Other adverse events (including commence dialysis, bacteraemia and dialysis access thrombosis) were not clearly stated | Quote: "During the study, there were no episodes of acute coronary syndrome, and two subjects commenced dialysis, both to the PD modality. There were too few bacteraemia (two in ascorbate group and one in placebo group) and dialysis access thromboses (one in ascorbate group) to analyse differences between the groups." |
| Singh 2003 | **Dialyser** | **Dialyser** | Adverse events were not clearly reported per group in the first | Adverse events were not clearly reported per group in the first | Quote: "Among clinical symptoms nausea was the most common symptom, |

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| | | | phase on the study period | phase on the study period | which occurred in 62% sessions on cuprophan, and 54% on polysulfone membrane, the difference was not significant. Vomiting, chest pain, fever, chills, and breathlessness occurred significantly more during dialysis with cuprophan membrane as compared with polysulfone. Cramps, back pain, itching, restlessness, post dialysis fatigue, and hypotension did not significantly differ." |
| Singh 2008a | **Iron replacement product** | **Placebo** | Adverse events (including death) were not clearly reported per group in the first phase on the study period | Adverse events (including death) were not clearly reported per group in the first phase on the study period | No relevant quotations were reported. |
| Sklar 1999 | **Dialysis procedures** | **Sham dialysis procedures** | Adverse events (including death) were not clearly reported per group in the first phase on the study period | Adverse events (including death) were not clearly reported per group in the first phase on the study period | No relevant quotations were reported. |
| Suzuki 2018 | **Exercise** | **Control** | Cramps 1/13, muscle pain 3/13 | Cramps 0/13, muscle pain 0/13 | Quote: "In the EMS group, leg cramps occurred in one patient during EMS but rapidly faded without treatment. Muscle pain was reported by three patients after EMS but spontaneously healed within a few days." |
| Thomas 2017 | **Meditation** | **Control** | There were no adverse events in the intervention group | There were no adverse events in the control group | Quote: "No adverse events were observed." |
| Tsai 2016 | **Acupressure** | **Sham acupressure** | Adverse events in the intervention group were reported:<br><br>localized erythema (2/14), pruritus (2/14), infection (0/14).<br><br>There were no serious adverse events in the intervention group | There were neither adverse events nor serious adverse events in the control group | Quote: "No serious adverse events were reported. In the intervention group, we observed localized erythema below the non-woven adhesive plaster after early treatment in two patients, who withdrew during the study due to an intolerable pruritus reaction. No patient was found to have an infection. No adverse events were reported for patients in the sham group." |

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| Yurtkuran 2007 | **Exercise** | **Control** | There were no adverse events in the intervention group | There were no adverse events in the control group | Quote: "No side-effects were seen". |

Footnotes:

L-DOPS: L-threo-3,4-dihydroxyphenylserine; C.E.R.A.: Continuous Erythropoietin Receptor Activator; EPO alfa: epoetin alfa; CBT: cognitive-behavioral therapy

## HISTORY

Protocol first published: Issue 8, 2018

## CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: Angela Ju, Allison Jaure, Valeria Saglimbene, Mark Unruh, Jonathan Craig, Giovanni Strippoli
2. Study selection: Patrizia Natale, Angela Ju, Valeria Saglimbene
3. Extract data from studies: Patrizia Natale, Valeria Saglimbene
4. Enter data into RevMan: Patrizia Natale
5. Carry out the analysis: Patrizia Natale, Allison Jaure
6. Interpret the analysis: Patrizia Natale, Angela Ju, Giovanni Strippoli, Jonathan Craig, Valeria Saglibene, Mark Unruh, Giovanni Stallone, Allison Jaure
7. Draft the final review: Patrizia Natale, Allison Jaure
8. Disagreement resolution: Allison Jaure, Jonathan Craig, Giovanni Strippoli

## DECLARATIONS OF INTEREST

Patrizia Natale: no relevant interests were disclosed

Angela Ju: no relevant interests were disclosed

Giovanni FM Strippoli: no relevant interests were disclosed

Jonathan C Craig: no relevant interests were disclosed

Valeria M Saglimbene: no relevant interests were disclosed

Mark L Unruh: no relevant interests were disclosed

Giovanni Stallone: no relevant interests were disclosed

Allison Jaure: no relevant interests were disclosed

## SOURCES OF SUPPORT

### Internal sources

- No sources of support provided

### External sources

- No sources of support provided

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have clarified our objectives as follows: "This review aims to evaluate the effects of any pharmacological and non-pharmacological interventions on fatigue in people with chronic kidney disease requiring dialysis, such as haemodialysis and peritoneal dialysis, including any setting (e.g. dialysis performed in the clinic or at home) and frequency."

We have clarified the inclusion criteria of the population of interest as follows: "Patients of any age with ESKD on any form of dialysis. The dialysis treatment could be performed both in the clinic and at home. Any frequency of the dialysis treatment was included."

We have clarified our interventions as follows: "We considered any intervention affecting levels of self-reported fatigue in patients on dialysis." In addition, we have added hypoxia-inducible factors in the type of pharmacological interventions.

We have added sleep and mood to the secondary outcomes.

## INDEX TERMS

### Medical Subject Headings (MeSH)

*Cardiovascular Diseases; Fatigue [etiology] [therapy]; Kidney; Quality of Life; Randomized Controlled Trials as Topic; Renal Dialysis; *Renal Insufficiency

### MeSH check words

Humans