Cochrane Library

Cochrane Database of Systematic Reviews

Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease (Review)

Jones S, Man WDC, Gao W, Higginson IJ, Wilcock A, Maddocks M

Jones S, Man WDC, Gao W, Higginson IJ, Wilcock A, Maddocks M.
Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease.
Cochrane Database of Systematic Reviews 2016, Issue 10. Art. No.: CD009419.
DOI: 10.1002/14651858.CD009419.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease

Sarah Jones[1,2], William D-C Man[1,2], Wei Gao[3], Irene J Higginson[3], Andrew Wilcock[4], Matthew Maddocks[5]

[1]NIHR Respiratory Biomedical Research Unit, Royal Brompton & Harefield NHS Foundation Trust and Imperial College, London, UK. [2]Harefield Pulmonary Rehabilitation Unit, Harefield Hospital, Middlesex, UK. [3]Department of Palliative Care, Policy and Rehabilitation, Cicely Saunders Institute, King's College London, London, UK. [4]Hayward House Macmillan Specialist Palliative Care Unit, University of Nottingham, Nottingham, UK. [5]Department of Palliative Care, Policy and Rehabilitation, Cicely Saunders Institute, King's College London, London, UK

Contact address: Matthew Maddocks, Department of Palliative Care, Policy and Rehabilitation, Cicely Saunders Institute, King's College London, Denmark Hill, London, SE5 9PJ, UK. matthew.maddocks@kcl.ac.uk.

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 10, 2016.

Citation: Jones S, Man WDC, Gao W, Higginson IJ, Wilcock A, Maddocks M. Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease. *Cochrane Database of Systematic Reviews* 2016, Issue 10. Art. No.: CD009419. DOI: 10.1002/14651858.CD009419.pub3.

ABSTRACT

Background

This review is an update of a previously published review in the Cochrane Database of Systematic Reviews Issue 1, 2013 on Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease.

Patients with advanced progressive disease often experience muscle weakness, which can impact adversely on their ability to be independent and their quality of life. In those patients who are unable or unwilling to undertake whole-body exercise, neuromuscular electrical stimulation (NMES) may be an alternative treatment to enhance lower limb muscle strength. Programmes of NMES appear to be acceptable to patients and have led to improvements in muscle function, exercise capacity, and quality of life. However, estimates regarding the effectiveness of NMES based on individual studies lack power and precision.

Objectives

Primary objective: to evaluate the effectiveness of NMES on quadriceps muscle strength in adults with advanced disease. Secondary objectives: to examine the safety and acceptability of NMES, and its effect on peripheral muscle function (strength or endurance), muscle mass, exercise capacity, breathlessness, and health-related quality of life.

Search methods

We identified studies from searches of the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), and Database of Abstracts of Reviews of Effects (DARE) (the Cochrane Library), MEDLINE (OVID), Embase (OVID), CINAHL (EBSCO), and PsycINFO (OVID) databases to January 2016; citation searches, conference proceedings, and previous systematic reviews.

Selection criteria

We included randomised controlled trials in adults with advanced chronic respiratory disease, chronic heart failure, cancer, or HIV/AIDS comparing a programme of NMES as a sole or adjunct intervention to no treatment, placebo NMES, or an active control. We imposed no language restriction.

Data collection and analysis

Two review authors independently extracted data on study design, participants, interventions, and outcomes. We assessed risk of bias using the Cochrane 'Risk of bias' tool. We calculated mean differences (MD) or standardised mean differences (SMD) between intervention and control groups for outcomes with sufficient data; for other outcomes we described findings from individual studies. We assessed the evidence using GRADE and created a 'Summary of findings' table.

Main results

Eighteen studies (20 reports) involving a total of 933 participants with COPD, chronic respiratory disease, chronic heart failure, and/or thoracic cancer met the inclusion criteria for this update, an additional seven studies since the previous version of this review. All but one study that compared NMES to resistance training compared a programme of NMES to no treatment or placebo NMES. Most studies were conducted in a single centre and had a risk of bias arising from a lack of participant or assessor blinding and small study size. The quality of the evidence using GRADE comparing NMES to control was low for quadriceps muscle strength, moderate for occurrence of adverse events, and very low to low for all other secondary outcomes. We downgraded the quality of evidence ratings predominantly due to inconsistency among study findings and imprecision regarding estimates of effect. The included studies reported no serious adverse events and a low incidence of muscle soreness following NMES.

NMES led to a statistically significant improvement in quadriceps muscle strength as compared to the control (12 studies; 781 participants; SMD 0.53, 95% confidence interval (CI) 0.19 to 0.87), equating to a difference of approximately 1.1 kg. An increase in muscle mass was also observed following NMES, though the observable effect appeared dependent on the assessment modality used (eight studies, 314 participants). Across tests of exercise performance, mean differences compared to control were statistically significant for the 6-minute walk test (seven studies; 317 participants; 35 m, 95% CI 14 to 56), but not for the incremental shuttle walk test (three studies; 434 participants; 9 m, 95% CI -35 to 52), endurance shuttle walk test (four studies; 452 participants; 64 m, 95% CI -18 to 146), or for cardiopulmonary exercise testing with cycle ergometry (six studies; 141 participants; 45 mL/minute, 95% CI -7 to 97). Limited data were available for other secondary outcomes, and we could not determine the most beneficial type of NMES programme.

Authors' conclusions

The overall conclusions have not changed from the last publication of this review, although we have included more data, new analyses, and an assessment of the quality of the evidence using the GRADE approach. NMES may be an effective treatment for muscle weakness in adults with advanced progressive disease, and could be considered as an exercise treatment for use within rehabilitation programmes. Further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate. We recommend further research to understand the role of NMES as a component of, and in relation to, existing rehabilitation approaches. For example, studies may consider examining NMES as an adjuvant treatment to enhance the strengthening effect of programmes, or support patients with muscle weakness who have difficulty engaging with existing services.

PLAIN LANGUAGE SUMMARY

Muscle stimulation for weakness in adults with advanced disease

Background

Individual studies suggest that neuromuscular electrical stimulation, or NMES, may help improve the muscle weakness that people often experience as a consequence of a progressive disease. NMES uses a lightweight stimulator unit and skin electrodes to produce a controlled and comfortable muscle contraction. Being a passive form of exercise, NMES allows patients to exercise their leg muscles at home whilst seated. This may be particularly helpful for people who are unable to take part in more strenuous forms of exercise, for example because of shortness of breath or fatigue.

Key results

In this review update we considered 18 clinical studies comparing NMES to either no exercise, placebo NMES, or weight training in groups of people with advanced chronic respiratory disease, chronic heart failure, and/or cancer of the lungs. NMES appeared to be more effective than the control conditions at improving thigh muscle strength. We also observed a positive effect on this outcome when precise measures were used to assess muscle bulk. The evidence for an effect of NMES on ability to exercise was inconclusive. Further research is required to understand how NMES can be used within broader rehabilitation approaches that combine exercise with education and behaviours to reduce the impact of muscle weakness on daily life, for example becoming more physically active.

Quality of the evidence

We rated the quality of the evidence from studies using four levels: very low, low, moderate, or high. Very low-quality evidence means that we are very uncertain about the results. High-quality evidence means that we are very confident in the results. Overall, the quality of the evidence was low for the effect on thigh muscle strength and very low to moderate for the effects on other outcomes. There were problems with the design of some studies; often people taking part or assessors knew if they were receiving or testing NMES. In addition, the results for many outcomes were inconsistent or imprecise.

Implications for practice and research

This review suggests that NMES is a potentially effective treatment for muscle weakness in people with progressive diseases such as cancer, advanced chronic respiratory disease, and chronic heart failure, though the quality of the evidence is low. NMES might be considered for use within rehabilitation programmes. It was not possible to compare the effects of NMES to other forms of exercise, for example weight training, because the majority of studies compared NMES to a control group that received no treatment or a sham treatment. Further research is needed to understand the effect of NMES on the ability to exercise and quality of life.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Neuromuscular electrical stimulation (NMES) versus control for adults with advanced disease for muscle weakness

NMES for adults with advanced disease for muscle weakness

Patient or population: adults with advanced disease for muscle weakness
Settings: hospital, community, or home settings
Intervention: NMES

Control: no intervention (7 studies), placebo NMES (8 studies), or resistance training (1 study)

Outcomes	Illustrative comparative risks* (95% CI)		No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk		
	Control	NMES		
Quadriceps muscle strength Handheld or fixed dynamometry Follow-up: median 6 weeks	The mean change was 0.43 standard deviations from baseline.	The mean change in the intervention groups was **0.53 standard deviations higher** (ranging from 0.19 to 0.87 standard deviations higher).	781 (12 studies)	⊕⊕⊖⊖ **low** [1,2]
Safety Serious adverse events Follow-up: median 6 weeks	No serious adverse events related to control interventions reported.	**No serious adverse events** related to NMES reported.	933 (18 studies)	⊕⊕⊕⊖ **moderate** [3]
Safety Adverse events: Muscle discomfort Follow-up: median 6 weeks	0/415 (0%) participants reported muscle discomfort following control interventions.	19/518 (**3.7%**) participants **reported muscle discomfort** following NMES.	933 (18 studies)	⊕⊕⊕⊖ **moderate** [3]
Muscle mass Anthropometry, DEXA, ultrasound, computed tomography Follow-up: 4 to 9 weeks	The mean change in muscle mass ranged from 0.04 to 0.49 standard deviations from baseline across the different assessment modalities used.	The mean change in muscle mass ranged from **0.09 to 1.01 standard deviations higher** across the different assessment modalities used.	314 (8 studies)	⊕⊖⊖⊖ **very low** [4,5,6,7]
Exercise performance - walking distance 6MWT, ISWT, ESWT Follow-up: median 6 weeks	The mean change in distance walked was 21, 36, and 37 metres from baseline across the different walking tests used.	The mean change in distance walked was **35, 9, and 64 metres further** across the different walking tests used.	788 (13 studies)	⊕⊖⊖⊖ **very low** [2,7,8,9]
Exercise performance - peak oxygen uptake Follow-up: median 6 weeks	The mean change in peak oxygen uptake was -0.4 mL/min from baseline.	The mean exercise performance - peak oxygen uptake in the intervention groups was **44.8 mL/min higher** (95% CI 7.3 lower to 97.0 higher)	109 (4 studies)	⊕⊕⊖⊖ **low** [7,9]

*The basis for the **assumed risk** is the mean change from baseline in the control groups. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

6MWT: 6-minute walk test; **CI:** confidence interval; **DEXA:** dual energy X-ray absorptiometry; **ESWT:** endurance shuttle walk test; **ISWT:** incremental shuttle walk test

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]Downgraded once: the lower 95% CI for the estimate of effect was below what would be considered a small effect (standardised mean difference 0.2).
[2]Downgraded once: statistical tests indicated a high degree of heterogeneity; I^2 values > 0.5.
[3]Downgraded once: small population size and limitations in reporting of safety data collection.
[4]Downgraded once: the estimate of effect for this outcome was inconsistent across different assessment modalities.
[5]Downgraded once: either study participants or outcome assessors were not blinded, but the outcome being assessed was non-volitional.
[6]Downgraded once: findings derived from computed tomography were from a single study.
[7]Downgraded once: wide variance of point estimates, and inconsistency regarding the direction of an effect or whether or not there is an effect.
[8]Downgraded once: the lower 95% CI for the effect estimate for the 6MWT was below the established minimally important difference.
[9]Downgraded once: either study participants or outcome assessors were not blinded, and the outcome being assessed was volitional.

BACKGROUND

This review is an update of a previously published review in the Cochrane Database of Systematic Reviews Issue 1, 2013 on Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease.

Description of the condition

Patients with progressive diseases such as cancer or chronic obstructive pulmonary disease (COPD) frequently develop muscle weakness as a consequence of the disease and its treatment. Patients often adopt sedentary lifestyles due to limiting symptoms that can lead to lower limb weakness, which precipitates a downward spiral of disability. Other aetiological factors for skeletal muscle dysfunction, dependent on the disease, include low-grade systemic inflammation, nutritional insufficiency, and/or an imbalance between anabolic and catabolic hormones (Donaldson 2012). Muscle weakness impacts adversely on levels of physical function, independence, and quality of life (Dodson 2011; Man 2009; Strassburg 2005). Evidence concerning its impact is strongest in COPD, where lower limb muscle dysfunction has been shown to directly influence exercise performance and, independent of lung disease severity, predict healthcare utilisation, in Greening 2015, and mortality (Donaldson 2012). Aerobic and resistance exercise, when performed regularly, can improve muscle function and the related clinical consequences (Bausewein 2008; Cramp 2008; Lacasse 2006). However, the reach of supervised programmes is limited by issues around time, scheduling, and travel. Whole-body exercises are also not always accessible to patients who experience a high symptom burden, or who become breathless at low levels of exertion (Fischer 2009; Gysels 2007; Maddocks 2009b).

Description of the intervention

In patients who are unable or unwilling to perform conventional exercise, neuromuscular electrical stimulation (NMES) may be an alternative method of enhancing lower limb muscle strength. NMES uses a lightweight, battery-powered stimulator unit which, via self adhesive electrodes, produces a controlled and comfortable contraction and relaxation of the underlying muscles (Dehail 2008). NMES can be used to produce a muscle contraction equivalent to 20% to 40% of a maximum voluntary contraction (Maffiuletti 2010), and therefore fulfils the American College of Sports Medicine's broader definition of exercise as "a planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness" (Thompson 2010). NMES of the quadriceps muscles can be self administered at home, unsupervised, and carries a low metabolic load, thus providing an acceptable therapy to patients living with a high symptom burden (Sillen 2014b). As a passive treatment, it potentially demands less change in lifestyle than other forms of exercise (Ambrosino 2004).

How the intervention might work

Studies in people with cardio-respiratory disease have examined NMES alone and occasionally as an adjunct to other forms of exercise training. A typical programme consists of 30 to 60 minutes of stimulation, generally of the quadriceps with or without additional lower limb muscles, for example calves, hamstrings, or glutei, three to five times each week, for four to eight weeks (Dehail 2008; Roig 2009; Sillen 2009). Programmes appear to be well tolerated, to lead to similar changes in muscle biochemistry as other forms of exercise (Dal Corso 2007; Gondin 2011; Nuhr 2004), and are associated with improvements in muscle function, exercise capacity, and components of quality of life, for example exertional breathlessness (Maddocks 2009a; Neder 2002; Nuhr 2004; Vivodtzev 2006).

Why it is important to do this review

Despite these promising findings, clinical studies of NMES have generally been small and of variable methodological quality. Furthermore, where findings are pooled they tend to be disease specific, so overall estimates of effect for NMES lack power and precision. This updated review aimed to provide a comprehensive synthesis of the evidence base regarding the use of NMES for muscle weakness in adults with advanced disease.

OBJECTIVES

Primary objective: to evaluate the effectiveness of NMES on quadriceps muscle strength in adults with advanced disease. Secondary objectives: to examine the safety and acceptability of NMES, and its effect on peripheral muscle function (strength or endurance), muscle mass, exercise capacity, breathlessness, and health-related quality of life.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) with a parallel, single-stage, or cross-over design, including studies using minimisation, or with a quasi-randomised allocation in cases where allocation concealment was described.

Types of participants

Participants were adults with advanced diseases where muscle loss and weakness is common, that is cancer, COPD, chronic heart failure (CHF), or HIV/AIDS (Evans 2008; Muscaritoli 2010). The inclusion criteria for advanced disease were as follows. Participants with cancer should have locally advanced or metastatic disease and should not be receiving or scheduled for anticancer treatment with curative intent. Participants with COPD should have a forced expiratory volume in one second (FEV_1) of less than 50% predicted and be categorised as stage III or IV by Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric criteria (GOLD 2005). Participants with CHF should have New York Heart Association stage III or IV disease (NYHA 1994), and participants with AIDS should be categorised as clinical stage 3 or 4 by the World Health Organization (WHO) criteria (WHO 2007). The cutoff point for including individual participant groups was 50%, that is at least half of the study population must fall within the definitions outlined above. Participants may be studied in any setting. We did not include studies relating to participants with conditions not regarded as progressive, refractory to treatment and advanced, or applying NMES in the presence of recognised contra-indications, for example local malignancy.

Types of interventions

We included studies examining a programme of NMES (more than one session) offered as a sole intervention or as an adjuvant to another form of exercise. Stimulation could be applied to the quadriceps with or without additional lower limb muscle groups,

for example hamstrings, gastrocnemius, glutei. We expected programmes to vary in terms of stimulation frequency (Hz), pulse type and width (μs), duty cycle (the proportion of time the intervention is 'active', usually expressed as a percentage), session length (min), and frequency (sessions/week) and overall programme duration (weeks). We did not include studies examining the acute effects of NMES following a single session. We used no restrictions on the site of stimulation or parameters used. Interventions could be compared to either an inactive control (e.g. no treatment, placebo, or sham NMES), or an active control such as an alternative form of exercise.

Types of outcome measures

Primary outcomes

1. Quadriceps muscle strength assessed immediately following a programme of NMES.

Secondary outcomes

1. Adherence to prescribed programmes.
2. Occurrence of adverse events.
3. Muscle strength, endurance, and mass.
4. Exercise performance.
5. Breathlessness.
6. Health-related quality of life.

Search methods for identification of studies

Electronic searches

The search for the original review was performed on 1 July 2012. The search period for this update was from 1 July 2012 to 6 January 2016. We searched the following electronic databases for this update:

- Cochrane Central Register of Controlled Trials (CENTRAL) Issue 12 of 12, 2015 (the Cochrane Library);
- Cochrane Database of Systematic Reviews (CDSR) Issue 12 of 12, 2015 (the Cochrane Library);
- *Database of Abstracts of Reviews of Effects (DARE), Issue 1 of 4, 2015 (the Cochrane Library);
- MEDLINE (OVID) July 2012 to 5 January 2016;
- Embase (OVID) July 2012 to 5 January 2016;
- CINAHL (EBSCO) July 2012 to 5 January 2016;
- PsycINFO (OVID) 2012 to December week 5 2015;
- British Nursing Index July 2012 to 5 January 2016;
- Web of Science July 2012 to 5 January 2016.

*DARE has not been updated since March 2015. See Appendix 1 for details of the search strategies.

Searching other resources

In the original review we checked reference lists of identified articles and articles citing all retrieved studies, relevant editorials, and reviews (Ambrosino 2004; Ambrosino 2008; Dehail 2008; Dourado 2004; Larsen 2004; Roig 2009; Sillen 2009; Vivodtzev 2009), websites (www.ifess.org, www.srr.org.uk, www.electrotherapy.org), and textbooks (Baker 2000; Robertson 2006; Skinner 2005) for further studies.

For this update, we searched the metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct), ClinicalTrials.gov (www.clinicaltrials.gov), and the WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) on 6 January 2016 to identify additional completed or ongoing studies. We reviewed the electrotherapy database (www.electrotherapy.org), bibliographies of any randomised trials, and review articles identified, and contacted the authors and known experts in the field to identify additional published or unpublished data. We also made contact with corresponding authors of retrieved studies and researchers known to be active in this topic area to learn of any unpublished data or grey literature arising from meetings or conference proceedings. We used no language restriction in the selection of studies.

Data collection and analysis

Selection of studies

We merged studies identified by the search strategy, removed any duplicates, and two review authors (SJ, MM) independently assessed the titles and abstracts for relevance. We reviewed abstracts of potentially eligible studies, and where any reference was made to NMES we obtained full texts. In cases where abstracts were not available and the study could not be excluded on the basis of its title, we obtained full texts. Two review authors (SJ, MM) independently assessed the full texts of potentially relevant studies for compliance with the review eligibility criteria. Review authors resolved any disagreements by discussion. Where required, we made requests to study authors for further information until a consensus regarding study eligibility was reached.

Data extraction and management

We (SJ, WG, AW, MM) extracted data from included studies to summarise study methods and bias (study design, sequence generation, allocation sequence concealment, blinding), participants (number, age, sex, ethnicity, diagnosis, disease severity, setting), and interventions (target muscle group(s), programme frequency, pulse type and width, duty cycle, session length and frequency, and overall programme duration). We recorded adherence to the prescribed programme (either self reported or objective) and the occurrence of any adverse events.

Outcome data collected at baseline, and immediately following a NMES programme or at first follow-up, included:

- quadriceps muscle strength, either isometric or isotonic, generally assessed using myometry and a measure of force (e.g. in kilograms (kg) or Newton metres (Nm));
- other muscle strength or muscle endurance, with endurance generally assessed as time or number of repetitions to a specified decline in muscle performance;
- muscle mass, generally assessed by anthropometry or imaging as volume (cm^3) or cross-sectional area, typically measured at the midpoint of the muscle (cm^2);
- maximal and submaximal exercise capacity, generally assessed by a walking or cycling test and a measure of oxygen uptake (mL/min) or performance, e.g. distance walked in metres (m);
- breathlessness, generally assessed according to intensity on a numerical or categorical scale, with a higher score representing more severe breathlessness;

- health-related quality of life, generally assessed on a numerical or categorical scale with a higher score representing a better quality of life.

Two review authors independently extracted data and resolved any disagreements by discussion until a consensus was reached.

Assessment of risk of bias in included studies

Two review authors (SJ, MM or WG) independently assessed each study for risk of bias using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We obtained information to aid this assessment from study reports, protocols, published comments, and personal contact with study authors. Thereafter, we made a judgement as to the level of risk of bias for that domain. We assessed the following for each study.

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table, computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated).
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomisation, consecutively numbered, sealed, opaque envelopes); unclear risk of bias (method not clearly stated).
- Blinding of participants and personnel (checking for possible performance bias). We assessed the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We assessed methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how this was achieved). We considered studies that were not double-blind to have a high risk of bias.
- Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study had a clear statement that outcome assessors were unaware of treatment allocation, and ideally described how this was achieved); unclear risk of bias (study stated that outcome assessors were blind to treatment allocation but lacked a clear statement on how this was achieved). We would often but not always exclude studies where outcome assessment was not blinded; if included, we considered them as having a high risk of bias.
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk (less than 10% of participants did not complete the study and/or ‘baseline observation carried forward’ analysis was used); unclear risk of bias (used 'last observation carried forward' analysis); high risk of bias (used 'completer' analysis).
- Selective reporting (checking for possible reporting bias). We assessed studies for selective outcome reporting using the following judgements: low risk of bias (study protocol available and all prespecified primary outcomes of interest adequately reported or study protocol not available but all expected primary outcomes of interest adequately reported or all primary outcomes numerically reported with point estimates and measures of variance for all time points); unclear risk of bias (insufficient information provided to permit a judgement of low/high risk of bias); or high risk of bias (incomplete reporting of prespecified primary outcomes or point estimates and measures of variance for one or more primary outcome not reported numerically (e.g. graphically only) or one or more primary outcomes reported using measurements, analysis methods, or subsets of data that were not prespecified or one or more reported primary outcomes were not prespecified or results for a primary outcome expected to have been reported were excluded).
- In this updated review we also considered study size (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (equal to or more than 200 participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (fewer than 50 participants per treatment arm).

Measures of treatment effect

The key comparison of interest for any meta-analysis was NMES versus any study control intervention, including no treatment, placebo, or an active comparator. We presented treatment effect sizes using appropriate metrics. We analysed outcomes as continuous data when possible. We expressed the size of treatment effect using the mean difference (MD) (where all studies utilised the same measurement scale) or the standardised mean difference (SMD) (where studies used different scales). In order to aid interpretation of the pooled effect size for quadriceps strength, our primary outcome, we back-transformed the SMD value to a kilogram format on the basis of the mean standard deviation (SD) from trials using this measurement scale. We plotted the results of each study's available data as point estimates with corresponding 95% confidence intervals (CIs) using forest plots. If included trials demonstrated clinical homogeneity, we performed meta-analysis using an inverse variable fixed-effect model to estimate the overall direction, size, and consistency of a strengthening effect on the quadriceps muscles from NMES immediately postprogramme. If included trials demonstrated clinical heterogeneity we used a random-effects model. For outcomes where we considered meta-analysis not appropriate, we described the findings from individual studies.

Unit of analysis issues

All included trials randomised participants at the individual participant level. We planned to include data from all study groups when participants had been allocated to one of multiple NMES groups, using the same control group data for both comparisons. We planned to enter cross-over trials into a meta-analysis when it was clear that data were free from carry-over effects, and to combine the results of cross-over trials with those of parallel trials by imputing the postprogramme between-group correlation coefficient from an included trial, if individual participant data were available. However, as we did not identify any cross-over trials that met the inclusion criteria of this review, issues concerning them did not arise.

Dealing with missing data

In cases where there were missing data or insufficient data to perform meta-analysis, we attempted to contact the study authors of included studies. If study authors only presented data in graphical form, we did not attempt to extract the data from the figures.

Assessment of heterogeneity

We evaluated the included trials for clinical homogeneity regarding study population, NMES and control interventions, timing of follow-up, and outcome measurement. For trials that were sufficiently clinically homogenous to pool, we formally explored heterogeneity using the Chi^2 test to investigate the statistical significance of any heterogeneity, and the I^2 statistic to estimate the amount of heterogeneity across trial conditions and its impact on the meta-analysis (Higgins 2002; Higgins 2003). If considerable (I^2 greater than 50%) or substantial clinical heterogeneity (I^2 greater than 75%) was confirmed, we performed a random-effects model or separate fixed-effect model calculation to estimate a strengthening effect from NMES for each subgroup.

Assessment of reporting biases

We considered the possible influence of small-study/publication biases on review findings as part of our 'Risk of bias' assessment and GRADE assessments of the quality of the evidence. Where sufficient data are available, we may include visual or statistical analyses of reporting bias in future updates of this Cochrane review.

Data synthesis

We grouped extracted data according to intervention, comparator, and outcome. Regarding interventions, we pooled data from studies that investigated NMES as single therapy and alongside other treatments together. For multi-arm studies with multiple NMES interventions, we considered each intervention separately. Regarding comparators, we pooled data across trials with a no-treatment, placebo, and active comparator together. We reported the outcome of the 'Risk of bias' assessment but included all data in our analyses. Where we found inadequate data to support statistical pooling, we described a narrative synthesis of the overall evidence.

Quality of the evidence

Two review authors (SJ, MM) independently rated the quality of the evidence for each outcome using the GRADE system to rank the quality of the evidence employing GRADEpro GDT (GRADEpro GDT 2015). The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the body of evidence for each outcome. The GRADE system uses the following criteria for assigning grade of evidence.

- High: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low: 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: any estimate of effect is very uncertain.

We decreased grade if:

- serious (-1) or very serious (-2) limitation to study quality;
- important inconsistency (-1);
- some (-1) or major (-2) uncertainty about directness;
- imprecise or sparse data (-1);
- high probability of reporting bias (-1).

We included a 'Summary of findings' table to present the main findings. In particular, we included key information concerning the quality of the evidence, the magnitude of effect of the interventions examined, and the sum of available data on quadriceps muscle strength, adverse events, muscle mass, and exercise performance.

Subgroup analysis and investigation of heterogeneity

For outcomes where sufficient data were available, we used descriptive comparisons to consider differences between programmes that involved stimulating the quadriceps alone or in combination with one or more additional muscle groups, for programmes up to or over six weeks overall duration, and in populations with and without COPD, as the aetiology driving muscle dysfunction may be expected to be different.

Sensitivity analysis

To examine the robustness of the primary analysis of an effect on quadriceps muscle strength, we completed sensitivity analyses after removing studies where participants or outcome assessors were not blinded to the study treatment allocation, and studies in which NMES was compared to an active intervention such as resistance training.

RESULTS

Description of studies

We included a total of 18 studies in this update, adding seven new studies since the previous version (Akar 2015; Greening 2014; Maddocks 2013; Maddocks 2016a; Sillen 2014a; Tasdemir 2015; Vieira 2014).

Results of the search

Our initial search for the previous review yielded 11 eligible studies (Figure 1) across patient groups with COPD (Abdellaoui 2011; Bourjeily-Habr 2002; Dal Corso 2007; Nápolis 2011; Neder 2002; Vivodtzev 2006; Vivodtzev 2012; Zanotti 2003), chronic heart failure (Nuhr 2004; Quittan 2001), and thoracic cancer (Maddocks 2009a).

Figure 1. Study flow diagram.

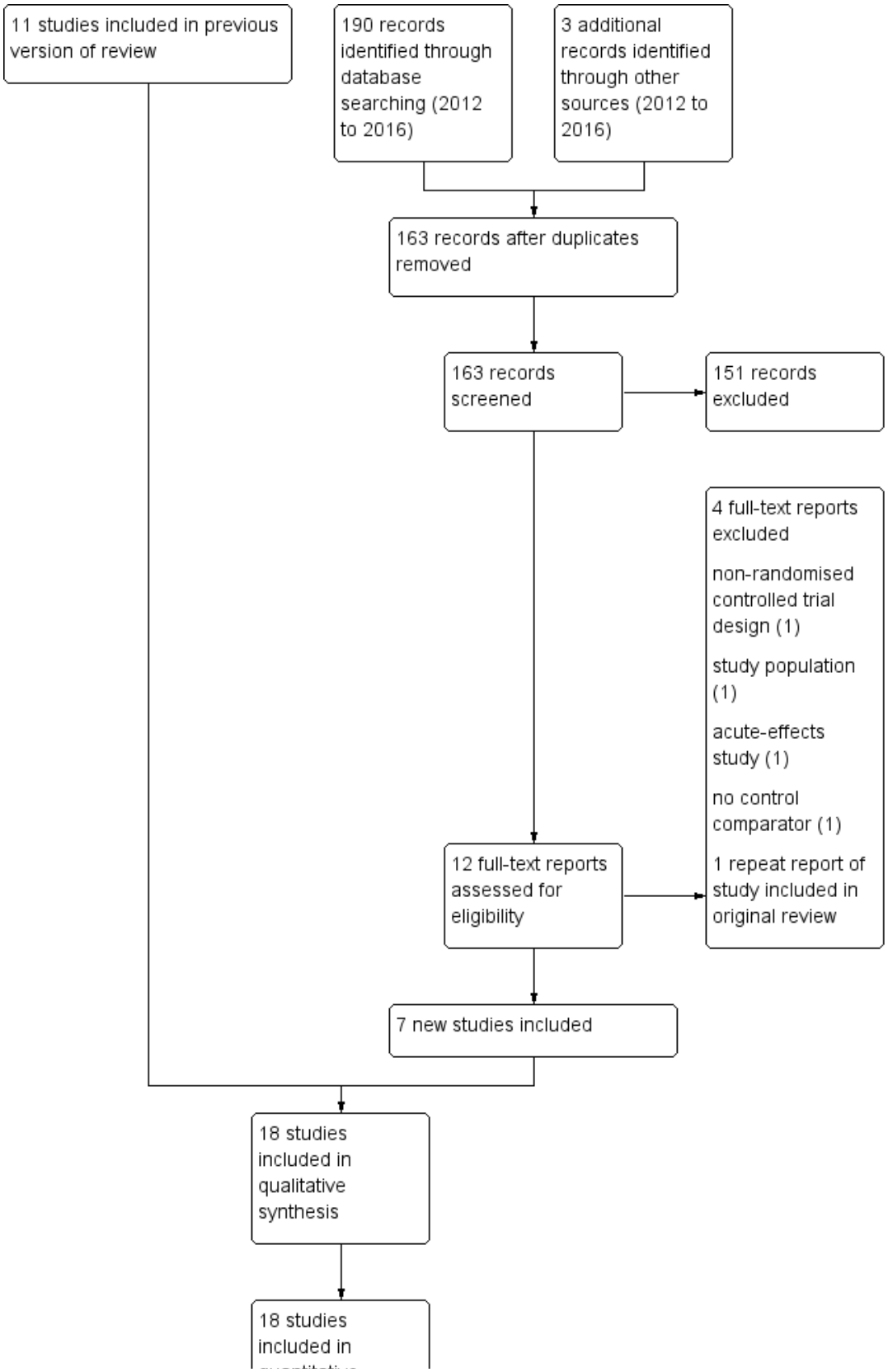
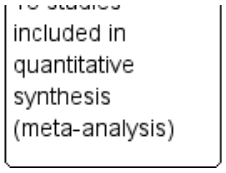


Figure 1. (Continued)



Searches for this update yielded 163 separate new citations, and we retrieved 12 full texts (Figure 1). Seven studies met the eligibility criteria across patient groups with COPD (Akar 2015; Maddocks 2016a; Sillen 2014a; Tasdemir 2015; Vieira 2014), chronic respiratory disease (Greening 2014), and thoracic cancer (Maddocks 2013). Five studies were two-arm RCTs. Two studies were three-arm RCTs (Akar 2015; Sillen 2014a), and we considered data on both NMES interventions studied for meta-analyses. We identified no new studies that recruited participants with HIV/AIDS.

Included studies

Participants

Overall, the 18 included studies related to 933 participants with four different conditions: COPD: 13 studies, 403 participants (Abdellaoui 2011; Akar 2015; Bourjeily-Habr 2002; Dal Corso 2007; Maddocks 2016a; Nápolis 2011; Neder 2002; Sillen 2014a; Tasdemir 2015; Vieira 2014; Vivodtzev 2006; Vivodtzev 2012; Zanotti 2003); chronic respiratory disease: 1 study, 389 participants (Greening 2014); chronic heart failure: 2 studies, 76 participants (Nuhr 2004; Quittan 2001); and thoracic cancer: 2 studies, 65 participants (Maddocks 2009a; Maddocks 2013). The mean age of participants ranged from 53 to 71 years, and overall there was a male preponderance (n = 505/54%). Some studies targeted patients with predetermined body mass index (Abdellaoui 2011; Vivodtzev 2006), muscle weakness (Sillen 2014a; Vivodtzev 2006), or level of breathlessness (Dal Corso 2007; Greening 2014; Nápolis 2011; Neder 2002; Sillen 2014a; Vieira 2014), whilst others had broad inclusion criteria (e.g. Bourjeily-Habr 2002; Nuhr 2004). Common exclusion criteria included locomotor or neurological conditions that would affect ability to exercise, or features that could restrict the use of NMES, such as an implantable cardiac pacemaker. For more detailed information including eligibility criteria, see the Characteristics of included studies table.

Interventions and controls

NMES interventions were offered at home after an initial period of teaching, with the exception of five studies with interventions offered following a period of acute critical illness, which were offered to inpatients (Abdellaoui 2011; Akar 2015; Greening 2014; Vivodtzev 2006; Zanotti 2003). All programmes targeted the quadriceps either alone or with additional muscle groups including the hamstrings (Abdellaoui 2011; Bourjeily-Habr 2002; Nuhr 2004; Quittan 2001), calves (Bourjeily-Habr 2002; Sillen 2014a; Vivodtzev 2012), glutei (Zanotti 2003), and deltoids (Akar 2015). NMES was offered alone in all but seven studies, where NMES was offered as part of a more comprehensive rehabilitation programme (Akar 2015; Greening 2014; Sillen 2014a; Tasdemir 2015; Vieira 2014; Vivodtzev 2006; Zanotti 2003).

Stimulation parameters and programme characteristics varied considerably among studies, with median (range) values of: stimulation frequency 50 (15 to 75) Hz, pulse duration 400 (200 to 700) µs, target duty cycle 33 (13 to 75) %, session length 30 (18 to 240) minutes, session frequency 5 (2 to 7) times each week, and programme duration 6 (4 to 11) weeks. In all studies, stimulation amplitude was reported to be set to elicit a visible or palpable muscle contraction within the participant's tolerance and increased over the course of the programme. Five studies reported initial training amplitudes (range 10 to 57 maximum amplitude) (Abdellaoui 2011; Akar 2015; Bourjeily-Habr 2002; Dal Corso 2007; Maddocks 2016a), which are of limited value without knowledge of the (variable) assumed skin resistance of the stimulation unit used. Where the level of contraction was expressed according to participants' maximum voluntary contraction, starting values ranged from 25% to 30% (Nuhr 2004; Quittan 2001).

Outcome measures

Thirteen studies assessed quadriceps muscle strength using fixed, in Bourjeily-Habr 2002, Dal Corso 2007, Greening 2014, Maddocks 2009a, Maddocks 2013, Maddocks 2016a, Nápolis 2011, Neder 2002, Quittan 2001, Sillen 2014a, Vivodtzev 2006, Vivodtzev 2012, or hand-held, in Abdellaoui 2011, dynamometry. Two studies assessed peripheral muscle strength globally using a physician-rated categorical scale (Akar 2015; Zanotti 2003), and one study used one-repetition maximum by free weights (Tasdemir 2015).

Strength assessments for other stimulated muscle groups were limited to the hamstrings (Bourjeily-Habr 2002; Quittan 2001). Four studies used fatigue-inducing constant load protocols were used to examine quadriceps endurance (Neder 2002; Quittan 2001; Sillen 2014a; Vivodtzev 2012). Body composition assessments used to assess the mass of peripheral muscles, usually of the thigh, included anthropometry (Vieira 2014; Vivodtzev 2006), dual energy X-ray absorptiometry (DEXA) (Dal Corso 2007; Maddocks 2013), ultrasonography (Maddocks 2016a), and computed tomography (Quittan 2001; Vivodtzev 2012). Maximal and submaximal exercise capacity were assessed using cycle ergometry cardiopulmonary exercise testing (Nápolis 2011; Neder 2002; Nuhr 2004; Sillen 2014a; Vieira 2014), 6-minute walk test (6MWT) (Abdellaoui 2011; Dal Corso 2007; Maddocks 2016a; Nápolis 2011; Nuhr 2004; Sillen 2014a; Vieira 2014; Vivodtzev 2006), incremental shuttle walk test (ISWT) (Bourjeily-Habr 2002; Greening 2014; Tasdemir 2015), or endurance shuttle walk test (ESWT) (Greening 2014; Maddocks 2009a; Tasdemir 2015; Vivodtzev 2012).

Other objective measures included performance in various lower limb functional tasks: sit to stand (Quittan 2001; Tasdemir 2015), the number of days for participants on an intensive care unit to be transferred from bed to chair (Akar 2015; Zanotti 2003), and physical activity level assessed using an accelerometer (Maddocks 2009a; Maddocks 2013; Maddocks 2016a). Eight studies reported on breathlessness either as part of a quality of life assessment (Maddocks 2016a; Neder 2002; Sillen 2014a; Vivodtzev 2006), the Medical Research Council breathlessness scale (Sillen 2014a; Tasdemir 2015), or at an equivalent workload during an

exercise test using the Borg, in Bourjeily-Habr 2002, or modified Borg Rating of Perceived Exertion scale (Vivodtzev 2012). Ten studies reported quality of life using different assessment tools: St George's Respiratory Disease Questionnaire (SGRQ) (Greening 2014; Maddocks 2016a; Sillen 2014a; Tasdemir 2015; Vieira 2014) 36-Item Short Form Health Survey (SF-36) (Quittan 2001), Chronic Respiratory Questionnaire (Maddocks 2016a; Neder 2002; Sillen 2014a), Minnesota Living with Heart Failure Questionnaire (Nuhr 2004), Maugeri Foundation Respiratory Failure Questionnaire (Vivodtzev 2006), and European Organisation for the Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30) (Maddocks 2013).

Excluded studies

We excluded a total of 75 studies in this update (71 in the original review, and four in this update). The previous review did not correctly list all 71 excluded studies, which we have now corrected in this update.

In the previous review, studies requiring discussion were excluded, for example on the basis of not including participants with advanced disease (Sumin 2009a), failing to meet the review criteria for the proportion of participants with advanced disease (equal to or greater than 50%) (Banerjee 2009; Deley 2005; Dobsák 2006a; Harris 2003; LeMaitre 2006), randomising at the level of the limb rather than the participant, with NMES applied to one leg and the same participant's other leg being used as a control (Giavedoni 2010), or using magnetic rather than electrical stimulation to elicit muscle contractions (Bustamante 2010). In this update we excluded one study because it was not possible to define advanced disease in multiple sclerosis (Coote 2015), one study because it did not use a randomised design (Tasdemir 2015), one study because it was a substudy examining the acute effects of a single session of NMES (Sillen 2014b), and a final study because it randomised participants to receive one of two different NMES programmes, but did not include a comparator group (Chaplin 2013). For further details on all excluded studies, see the Characteristics of excluded studies table.

Risk of bias in included studies

See Characteristics of included studies, Figure 2, and Figure 3.

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

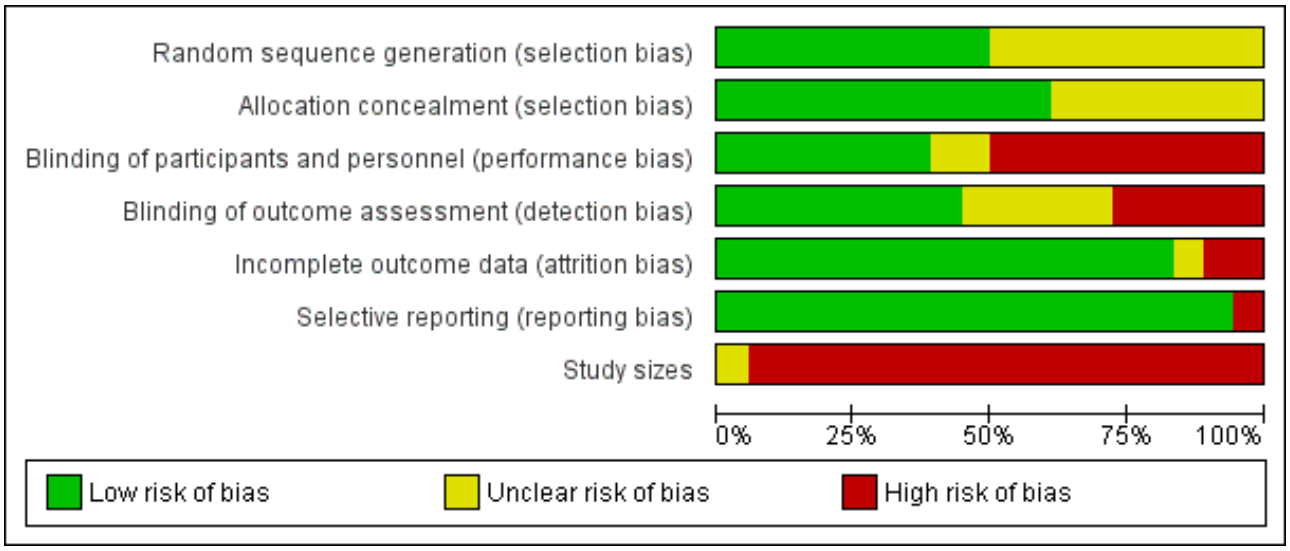
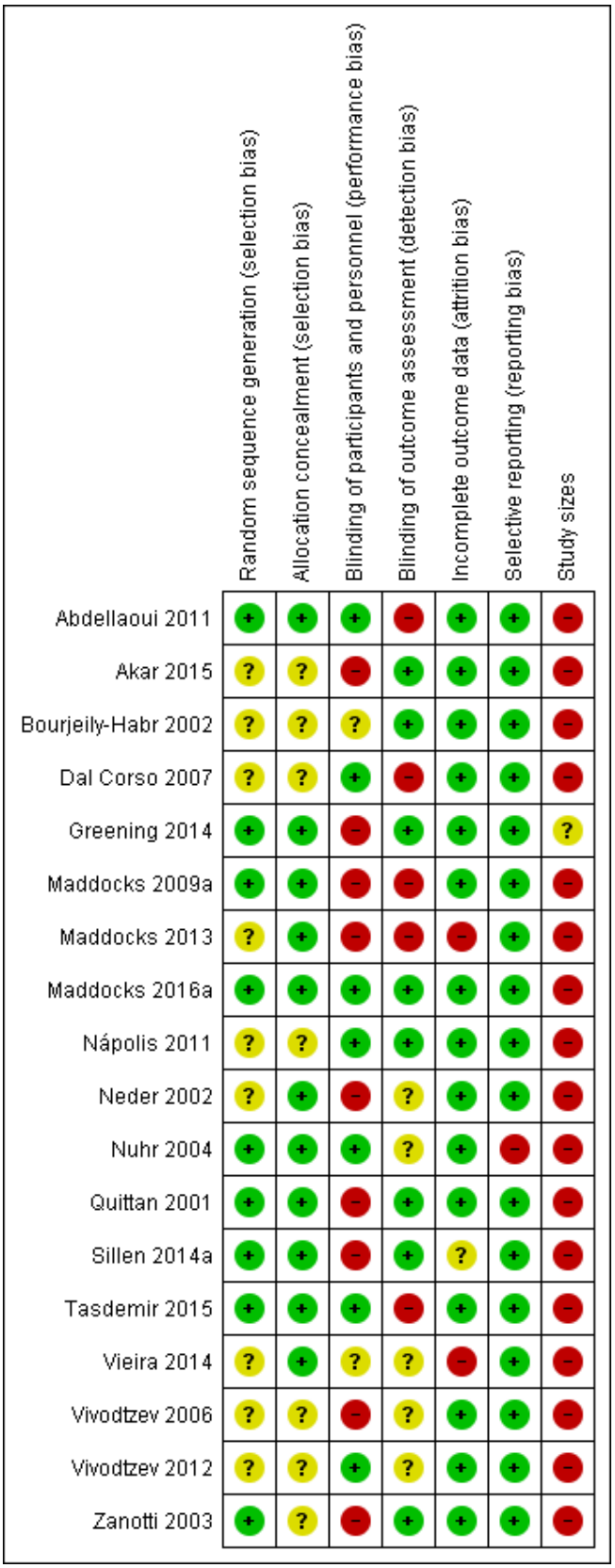


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All 18 studies were randomised to minimise selection bias. In nine studies the description of sequence generation was adequate, for example with studies using block-wise randomisation, in Abdellaoui 2011, Maddocks 2009a, Maddocks 2013, Quittan 2001, or minimisation (Maddocks 2016a), and so we judged them to be at low risk of bias for this domain. An adequate description of sequence generation was not provided for the remaining nine studies, and we judged them to be at unclear risk of bias for this domain.

Eleven studies described the methods used to conceal group allocation, using sealed, opaque envelopes (Abdellaoui 2011; Maddocks 2009a; Nuhr 2004; Tasdemir 2015), web-based system (Greening 2014; Maddocks 2016a), telephone system (Maddocks 2013), or secure locked codes (Neder 2002; Quittan 2001; Sillen 2014a; Vieira 2014). We therefore judged these studies to be at low risk of bias for this domain. In seven studies there was insufficient information to assess allocation concealment (Akar 2015; Bourjeily-Habr 2002; Dal Corso 2007; Nápolis 2011; Vivodtzev 2006; Vivodtzev 2012; Zanotti 2003), and we judged these studies to be at unclear risk of bias. We did not identify any studies at high risk of selection bias.

Blinding

Seven studies used a placebo model of NMES as a control to blind participants, and we judged them to be at low risk of performance bias. Placebo models generally used the same physical setup but restricted the stimulation output, in Abdellaoui 2011, Maddocks 2016a, Nuhr 2004, and/or reduced stimulation parameters, in Dal Corso 2007, Maddocks 2016a, Nápolis 2011, Tasdemir 2015, Vivodtzev 2012, to avoid any visible or palpable muscle contraction. Two studies used a sham model with no stimulator output (Bourjeily-Habr 2002; Vieira 2014), and we judged the risk of bias to be unclear as there would have been a clear difference in the experience of NMES and control interventions. No study reported on the effectiveness of participant blinding. Where no sham model was used, studies recommended that participants continue with their usual activities of daily living whilst keeping a diary (Quittan 2001), undertake other forms of rehabilitation, for example active limb mobilisations, light walking (Akar 2015; Greening 2014; Sillen 2014a; Vivodtzev 2006; Zanotti 2003), or offered no intervention (Maddocks 2009a; Maddocks 2013; Neder 2002). We therefore judged these studies to be at high risk of performance bias.

Blinding of outcome assessors was adequately described in eight studies (Akar 2015; Bourjeily-Habr 2002; Greening 2014; Maddocks 2016a; Nápolis 2011; Quittan 2001; Sillen 2014a; Zanotti 2003), and we juddged these studies to be at low risk of detection bias. Five studies did not blind the outcome assessor (Abdellaoui 2011; Dal Corso 2007; Maddocks 2009a, Maddocks 2013; Tasdemir 2015), and we judged them to be at high risk of bias for this domain. The remaining five studies provided insufficient information to assess blinding, and we judged them to be at unclear risk of detection bias.

Incomplete outcome data

Overall, 93 out of 933 randomised participants (10%) withdrew from a study prior to the postprogramme assessment. In one study, three participants withdrew from the intervention arm due to muscle discomfort (Maddocks 2013), and in another study there was an increased number of exacerbations in the control arm (Vieira 2014). We therefore judged both of these studies to have a high risk of attrition bias. A further study reported participants declining due to severe disability (Sillen 2014a), and we judged the risk of attrition bias to be unclear. In the remaining 15 studies, attrition was similar across NMES and control groups, and missing outcome information was generally due to technical error (e.g. Maddocks 2009a; Nápolis 2011). We judged the risk of attrition bias for these studies to be low.

Selective reporting

We found evidence of selective reporting in one study report in which a lack of strengthening effect of NMES was presented as evidence of safety (Nuhr 2004), and therefore judged the risk of reporting bias to be high. We judged the remaining 17 studies to be at low risk of detection bias.

Other potential sources of bias

Seventeen studies had fewer than 50 participants per study arm, and as such we judged these studies to have a high risk of bias due to small study size. We judged the remaining study to have an unclear risk of bias relating to study size (Greening 2014) (see Characteristics of included studies, Figure 2, and Figure 3).

Effects of interventions

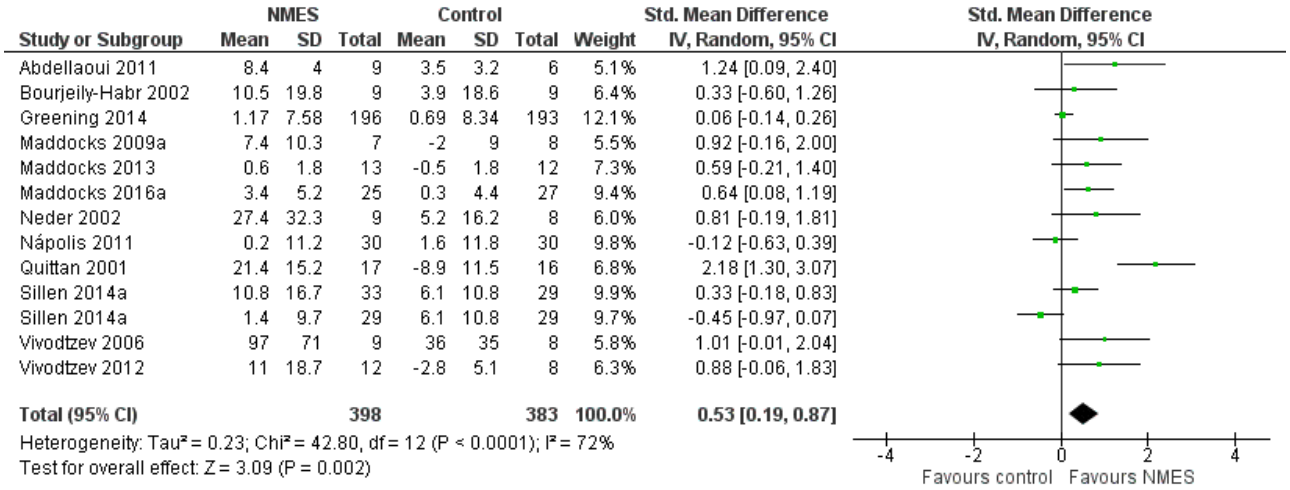
See: **Summary of findings for the main comparison** Neuromuscular electrical stimulation (NMES) versus control for adults with advanced disease for muscle weakness

Primary outcome

Quadriceps muscle strength

Twelve studies (781 participants) assessed quadriceps strength using dynamometry (Abdellaoui 2011; Bourjeily-Habr 2002; Dal Corso 2007; Greening 2014; Maddocks 2009a; Maddocks 2013; Maddocks 2016a; Nápolis 2011; Neder 2002; Quittan 2001; Sillen 2014a; Vivodtzev 2006; Vivodtzev 2012). There was considerable heterogeneity among studies (I^2 = 72%), and we thus used a random-effects model for the pooled analysis (Analysis 1.1; Figure 4). Compared to control groups, NMES significantly improved quadriceps strength by a standardised mean difference (SMD) of 0.53 (95% confidence interval (CI) 0.19 to 0.87), which would be considered a moderate effect size (Cohen 1988). Sensitivity analyses removing studies where participants (SMD 0.54, 95% CI 0.11 to 0.98) or outcome assessors (SMD 0.45, 95% CI 0.07 to 0.84) were not blinded did not affect the overall findings. Removing a study where NMES was compared to a resistance training intervention, Sillen 2014a, increased the point estimate for effectiveness (SMD 0.68, 95% CI 0.28 to 1.09) but did not alter heterogeneity (I^2 = 72%). In subgroup analyses, the overall direction of a strengthening effect was similar between studies involving participants with COPD (SMD 0.39, 95% CI 0.03 to 0.76; I^2 = 57%) and without (SMD 1.23, 95% CI 0.23 to 2.24; I^2 = 72%). Clinical heterogeneity was too high to compare by subgroups according to the muscle group(s) stimulated or the overall programme duration. We judged the quality of the evidence for quadriceps muscle strength to be low. We downgraded the quality of the evidence by one level for inconsistency due to the high degree of heterogeneity between studies, I^2 greater than 0.5. Regarding imprecision, the lower 95% CI for the effect estimate was below what is considered to be a small effect size (SMD 0.2), so we decided to downgrade on this basis (see Summary of findings for the main comparison).

Figure 4. Forest plot of quadriceps muscle strength for NMES versus control.



Secondary outcomes

Adherence to prescribed programmes

Where reported, rates of adherence with the recommended programme were generally high, with mean values of 95% (Bourjeily-Habr 2002), 97% (Abdellaoui 2011; Quittan 2001), 100% (Nuhr 2004; Vivodtzev 2006), and a median of 80% (Maddocks 2009a). One study described participants as "compliant" (Vivodtzev 2012), and another as "excellent" (Neder 2002). In the only "pragmatic" study, 61% of participants reported daily adherence to the home-based component of a programme utilising NMES alongside other interventions (Greening 2014). Four studies noted that participants with COPD were able to commence, in Greening 2014, or continue, in Abdellaoui 2011, Nápolis 2011, Neder 2002, to use NMES during an acute exacerbation of disease. We judged the quality of the evidence for adherence to be low. We downgraded the evidence due to indirect assessment of adherence in most studies, which was by self report, and inconsistency in adherence estimates from each study, given the wide range (61% to 97%).

Occurrence of adverse events

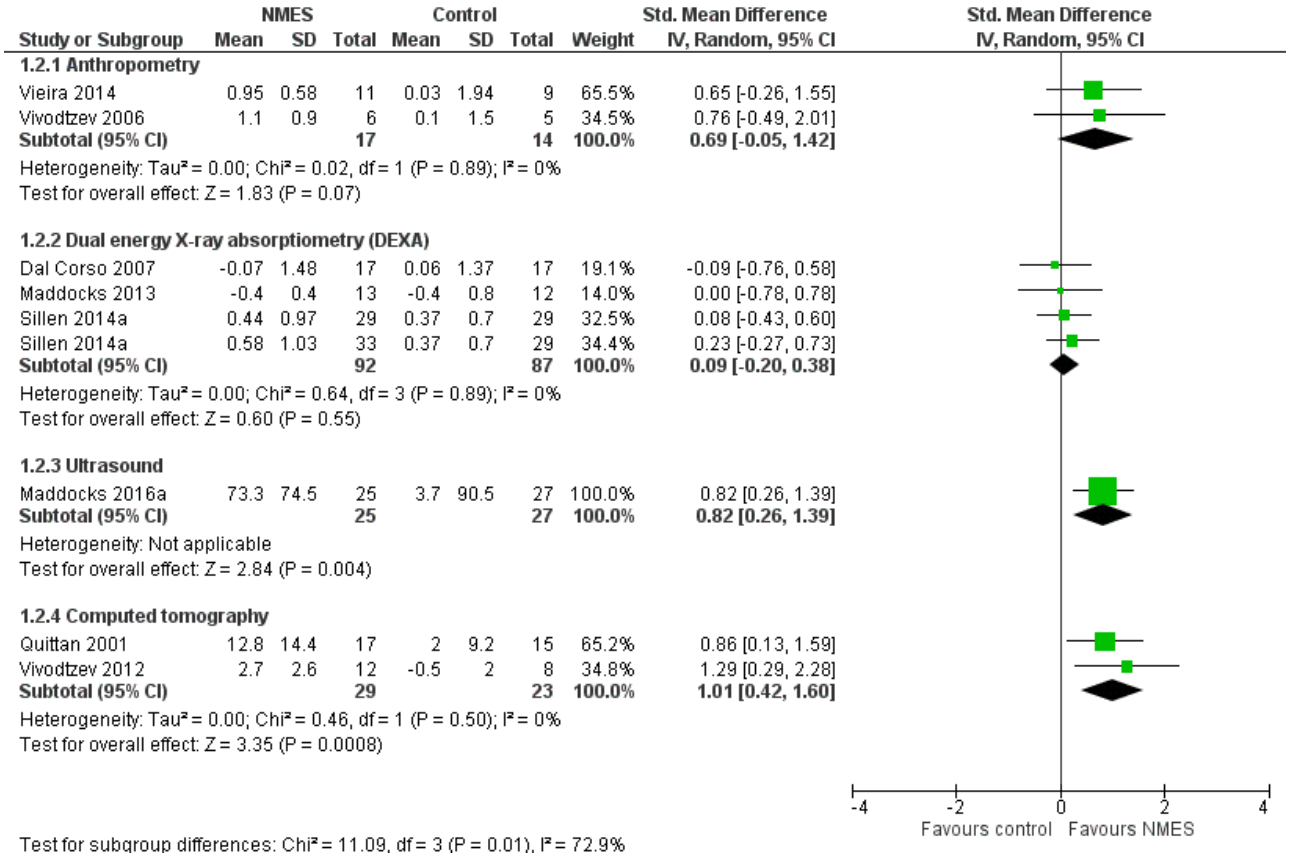
No serious adverse events were reported. Nineteen of the 518 participants (4%) allocated to NMES across four studies reported muscle discomfort following NMES during the initial few days of a programme (Bourjeily-Habr 2002; Maddocks 2009a; Maddocks 2013; Quittan 2001). A further two participants (less than 1%) from one study reported persistent erythema, which was considered possibly related to use of adhesive electrodes (Maddocks 2016a). All other studies stated that no adverse events occurred. For both serious adverse events and adverse events, we judged the quality of the evidence to be moderate. We downgraded the evidence due to the small overall sample size and limitations in reporting of safety data collection.

Muscle strength, endurance, and mass

Hamstring muscle strength increased following NMES in two studies (Bourjeily-Habr 2002; Quittan 2001), with statistically significant differences favouring NMES compared to control groups. Peripheral muscle strength was increased following NMES, as compared to the control condition, in one study (Zanotti 2003), but not in another (Akar 2015). A statistically significant improvement in quadriceps endurance following NMES, as compared to the control condition, was reported in all three studies assessing this outcome (Neder 2002; Quittan 2001; Vivodtzev 2012). We judged the quality of the evidence for these outcomes to be low. We downgraded the quality of the evidence as we deemed studies to have a high risk of performance or detection bias, and point estimates varied widely.

Eight studies (314 participants) assessed quadriceps muscle mass using either anthropometry (Vieira 2014; Vivodtzev 2006), DEXA scan (Dal Corso 2007; Maddocks 2013; Sillen 2014a), ultrasound (Maddocks 2016a), or computed tomography (Quittan 2001; Vivodtzev 2012). Overall, an improvement in muscle mass was observed following a NMES programme. The detected effect appeared dependent on the assessment modality used; there was no evidence of effect in studies using anthropometry or DEXA, though moderate to large effects sizes (SMD) observed in studies using ultrasound 0.82 (95% CI 0.26 to 1.39) or computed tomography 1.01 (95% CI 0.42 to 1.60) (Analysis 1.2; Figure 5). We judged the quality of the evidence for muscle mass to be very low. We deemed studies to have a high risk of bias where participants or outcome assessors, or both were not blinded to group allocation, and there was inconsistency of results according to assessment modality, wide variation of point estimates, and inconsistency regarding the direction of an effect or whether or not an effect was present. Findings derived from computed tomography were from a single study (see Summary of findings for the main comparison).

Figure 5. Forest plot of muscle mass for NMES versus control.

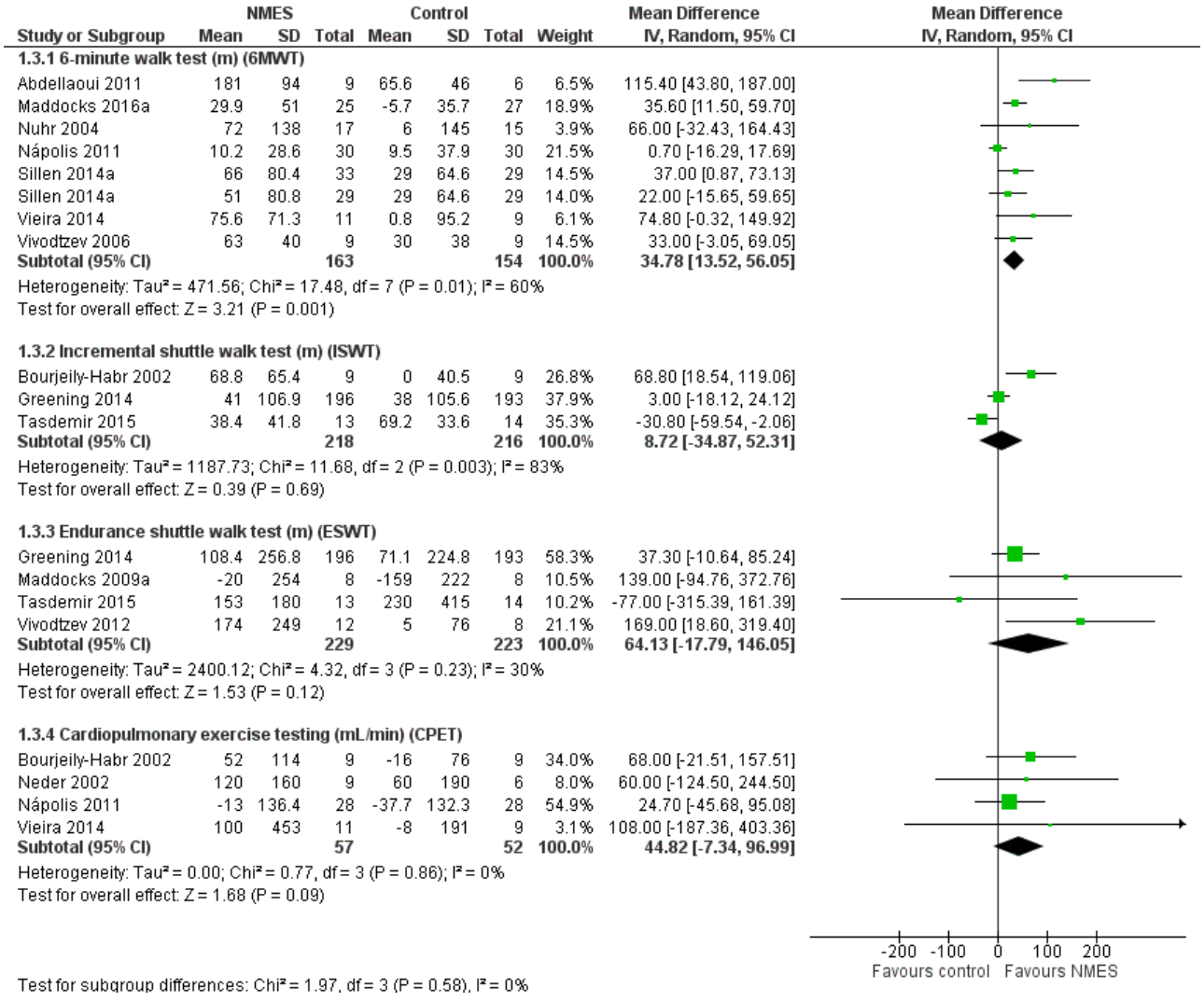


Exercise performance

Seven studies (317 participants) used the 6MWT as an outcome measure (Abdellaoui 2011; Maddocks 2016a; Nápolis 2011; Nuhr 2004; Sillen 2014a; Vieira 2014). The overall mean difference (MD) for NMES compared to control was 35 m (95% CI 14 to 56; P = 0.001). Three studies (434 participants) used the ISWT (Bourjeily-Habr 2002; Greening 2014; Tasdemir 2015), and four studies (452 participants) used the endurance shuttle walk test (ESWT) (Greening 2014; Maddocks 2009a; Tasdemir 2015; Vivodtzev 2012). There was no statistically significant effect of NMES compared to control group in these studies: ISWT 9 m (95% CI -35 to 52; P = 0.69); ESWT 64 m (95% CI -18 to 146; P = 0.12) (Analysis 1.3; Figure 6).

Six studies (141 participants) assessed peak oxygen uptake using progressive cardiopulmonary exercise testing with cycle ergometry (Bourjeily-Habr 2002; Nápolis 2011; Neder 2002; Nuhr 2004; Vieira 2014). There was no significant difference in peak oxygen uptake following use of NMES compared to control conditions (MD 44.82 mL/min, 95% CI -7.3 to 97.0; P = 0.09) (Analysis 1.3; Figure 6). We judged the overall quality of the evidence for exercise performance to be very low to low. We deemed studies to have a high risk of bias where participants or outcome assessors, or both were not blinded to group allocation, and there was a high degree of heterogeneity between studies (I^2 greater than 0.5) and inconsistency regarding whether or not an effect was present (see Summary of findings for the main comparison).

Figure 6. Forest plot of exercise performance for NMES versus control.



Breathlessness

Self reported breathlessness during daily life significantly improved following NMES in two of four studies that used quality of life questionnaires containing "dyspnoea", in Neder 2002, or "dyspnoea in daily tasks", in Vivodtzev 2006, domains. Two studies that assessed disability due to breathlessness using the Medical Research Council breathlessness scale found no differences in scores following NMES versus control (Sillen 2014a; Tasdemir 2015). Breathlessness at an equivalent workload during a walking test was significantly reduced following NMES in one study (Bourjeily-Habr 2002), though it remained unchanged in another study (Vivodtzev 2012). Given the very limited data, we judged the quality of the evidence for breathlessness to be very low.

Health-related quality of life

There was inadequate information to support statistical pooling. Most studies reported no significant differences following NMES as compared to control in either quality of life domains or overall scores, or both using the Chronic Respiratory Questionnaire (Maddocks 2016a; Sillen 2014a), EQ-5D index (Maddocks 2016a), EORTC QLQ-C30 (Maddocks 2013), Minnesota Living with Heart Failure Questionnaire (Nuhr 2004), SGRQ (Greening 2014; Maddocks 2016a; Sillen 2014a; Tasdemir 2015), or SF-36 (Quittan 2001). One study reported a significant between-group difference, favouring NMES, in quality of life as assessed by the Chronic Respiratory Questionnaire, which arose primarily from an effect in the "dyspnoea" domain (Neder 2002). Similarly, another study reported a significant between-group difference in the SGRQ favouring NMES, which arose from the "activity" domain (Vieira 2014). One further study reported a significant between-group difference in the "dyspnoea in daily tasks" domain of the Maugeri Foundation Respiratory Failure Questionnaire in favour of NMES (Vivodtzev 2006), but the total score was not significantly different between groups. Given the very limited data, we judged the quality of the evidence for health-related quality of life to be very low.

Insufficient data were available to compare secondary outcomes by subgroups according to stimulated muscle groups or programme duration.

DISCUSSION

This review is an update of a previously published review in The Cochrane Database of Systematic Reviews Issue 1, 2013 on Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease.

Summary of main results

A programme of neuromuscular electrical stimulation (NMES) offered to people with advanced disease appears to be safe and acceptable to people with advanced disease affected by muscle weakness. Compared to control conditions, NMES led to a statistically significant improvement in quadriceps muscle strength with a moderate effect size (SMD 0.53, 95% CI 0.19 to 0.87) which, based on the mean of standard deviations at baseline, equates to a difference of approximately 1.1 kg. The direction and consistency of effect was similar across subgroups with and without COPD, and did not change when studies with a high risk of performance or detection bias were removed from the pooled analysis. The clinical relevance of this change is uncertain as a minimally important difference for quadriceps strength has yet to be determined. However, in people with a high level of functional impairment, even modest changes in lower limb strength may be important to preserve independence and prevent disability relating to daily tasks, for example sit-to-stand transfers (Canavan 2015). Coupled with this improvement in strength following NMES, this updated review identified increased lower limb muscle mass. The identification of an effect on mass appeared to be moderated by the assessment modality used; it was detected within studies using more precise measures, for example computed tomography, but not observed in studies using skin-fold techniques, where measurement error is relatively high, or whole-body assessments, which can be unresponsive to change. There may be instances where improvements in strength represent neural changes in muscle, for example better synchronisation of motor units during contractions, but changes in muscle strength and mass would be expected to occur in parallel.

Changes in secondary outcomes, including exercise performance, were less consistent across studies. The pooled mean differences for the ISWT and ESWT did not support an overall effect from NMES, and the pooled mean difference of 35 m (95% CI 14 to 56) for the 6MWT only marginally exceeded the minimally important difference of 30 m (Holland 2014). The secondary effect of muscle strengthening on exercise performance likely reflects muscle performance as one of many limiting factors to exercise. There was limited high-quality, randomised controlled evidence to support effects on other outcomes. A small number of programmes led to favourable changes in aspects of quality of life, mostly concerned with exertional breathlessness and physical functioning. We could not determine the most beneficial type of NMES programme due to the diverse range of measurement tools, limited numbers of study participants, and the degree of clinical heterogeneity among studies.

Overall completeness and applicability of evidence

Our findings are based on 18 studies involving 933 participants, most of which were conducted in a single centre in a small group of participants (fewer than 50 per study arm in 16 studies, Figure 3). Small-study bias must be considered when interpreting the data, as the largest study by some margin shows the smallest effect size estimate for NMES (Greening 2014). The level of supervision offered in this study was minimal, and self reported adherence was low, therefore treatment infidelity might explain the discrepancy in findings between this and other studies. The starting of NMES at the onset of an acute exacerbation of disease might also be important, though it is not possible to determine which factor(s) contributed to the difference in findings. Other methodological quality markers varied across the studies we considered in this review. The randomisation and concealment process was generally adequately described. The majority of studies had an apparent risk of bias arising from a lack of participant or assessor blinding (Figure 3). Producing legitimate placebo controls for this type of intervention can be challenging, and the lack of controlling for incidental features of NMES programmes might have led to an overestimation of effect size (Maddocks 2016b). Whilst our sensitivity analyses showed this did not affect quadriceps strength outcomes, it may have contributed to an overestimation of effect size for our secondary outcome measures, which could also be influenced by performance bias and external encouragement or feedback. Reporting bias was not apparent within the included studies, but the degree to which selective reporting of secondary outcomes occurred is uncertain in the absence of published protocols. Studies frequently provided sufficient information on the setting and participants, however additional information on those patients who refused to take part would assist in interpreting the generalisability of findings.

Quality of the evidence

We ranked the quality of the evidence from moderate to very low across the different outcomes. The main limiting factor, which was the reason for downgrading quality in some outcomes, was the inconsistency of results across studies and imprecision regarding estimates of effect, especially on our secondary outcomes. We downgraded the quality of the evidence due to the risk of bias in studies where participants or outcome assessors, or both were not blinded to group allocation. Overall we judged the evidence to be of low quality, which means that 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.

Potential biases in the review process

The search strategy used in this review led to the identification of studies both in languages other than English, Sumin 2009a, and from beyond the electronic search. The possibility remains that additional studies have been conducted but not published. However, we are confident that the large majority of published studies relevant to the review objectives have been identified. We collected and analysed study data according to a predetermined protocol, and most requests for additional information from study authors were fulfilled, allowing for more inclusive meta-analyses. Nonetheless, not all studies could be pooled due to variation in outcome, and an acceptable but important degree of statistical heterogeneity was apparent within many of the meta-analyses, for example quadriceps muscle strength ($P < 0.001$, $I^2 = 72\%$). We deemed the pooling of clinical outcome data across different patient populations to be acceptable given the similarities in the aetiology, consequences, and reversibility of muscle dysfunction. Nonetheless, the classification systems used to determine advanced disease varied across the conditions studied and were based on different constructs, for example symptom, in NYHA 1994, versus disease-based criteria (GOLD 2005).

A performance-based measure that can be applied across diseases would have been preferable, for example muscle weakness, but these were rarely used as study eligibility criteria, and thus could not function as an inclusion criterion for this systematic review.

We decided to pool studies that compared NMES interventions to usual care/no treatment, placebo, and active comparators, including one study that compared NMES to resistance training alongside inpatient rehabilitation (Sillen 2014a). The heterogeneity of comparators is acknowledged, and the effect size estimate for NMES was lower when this study was included in our primary meta-analysis (SMD increased from 0.53 to 0.68), though clinical heterogeneity remained high. We will consider seperate meta-analyses according to the control addition in future review updates. Finally, the wide range of measures limited the analysis of secondary outcomes, and so these findings should be interpreted cautiously.

Agreements and disagreements with other studies or reviews

Our findings are consistent with two of three previous reviews into the use NMES in people with cardiorespiratory disease. Roig 2009 examined five RCTs across people with COPD of any severity and found pooled mean differences (from three studies) in peak quadriceps torque and exercise performance of 9.6 Nm (95% CI 1.2 to 18.1) and 48 m (95% CI 9 to 86), respectively. The authors suggested that the most impaired participants responded more favourably to NMES, which may explain our finding of a greater strengthening effect. Data were insufficient to draw conclusions regarding an effect on muscle mass. Sillen 2009 described a total of 14 studies (9 chronic heart failure; 5 COPD), again not limited by disease severity, and concluded that NMES looked "promising as a means of rehabilitating patients", with most studies reporting positive effects on skeletal muscle function, exercise capacity, and disease-specific health status. In contrast, the authors of a recent meta-analysis in people with COPD concluded that evidence was inadequate to support the use of NMES (Pan 2014). Their pooled analyses did not support an effect from NMES on quadriceps strength (4 studies; SMD 0.38, 95% CI -0.13 to 0.89) or 6MWT distance (2 studies; MD 14 m, 95% CI -17 to 45). However, the meta-analyses excluded studies for which published data were available (e.g. Abdellaoui 2011), which accounts for the discrepancy in the overall finding. This underscores the need for a comprehensive search strategy, which should include contacting corresponding authors for primary data.

NMES has not been directly compared to alternative forms of exercise in people with advanced disease. However, comparing evidence from reviews concerning participants with any severity of disease suggests that compared to NMES, more active forms of exercise have the potential to provide equal or greater improvements in outcome. For example, a Cochrane review of pulmonary rehabilitation following an acute exacerbation of COPD identified mean differences in 6MWT and ISWT distance of 78 m (95% CI 12 to 143) and 64 m (95% CI 41 to 87), respectively (Puhan 2011), and a review of progressive resistance training in people with COPD found weighted mean differences in quadriceps muscle strength of 0.52 (95% CI 0.30 to 0.74) (O'Shea 2009). Unlike NMES, these forms of exercise also have supporting evidence for beneficial effect on quality of life.

AUTHORS' CONCLUSIONS

Implications for practice

The overall conclusions have not changed from the last publication of this review, although we included more data, new analyses, and an assessment of the quality of the evidence using the GRADE approach in this update.

For people with advanced disease

This review suggests that NMES may be an effective treatment for muscle weakness that can occur as a result of diseases such as cancer, COPD, and chronic heart failure. There were no serious safety concerns following use of NMES in a research study, though 1 in every 20 people that used NMES reported muscle soreness following the initial few sessions. We suggest that NMES could be used within rehabilitation programmes, though clinicians providing care may be in a position to advise further. As most studies we considered compared NMES to a group that received no treatment or a sham treatment, it is not possible to judge how NMES compares to other forms of exercise such as weight training. There was also very limited evidence on the effect NMES has on a person's ability to exercise or their quality of life.

For clinicians

There was low-quality evidence supporting NMES as an effective treatment for muscle weakness in adults with progressive diseases such as cancer, COPD, and chronic heart failure. The studies in our review reported no serious adverse events and a low incidence of muscle discomfort. Based on this evidence, NMES could be considered as a component treatment for use within a wider approach to reduce disability. It is difficult to draw conclusions about the clinical significance of the effect on muscle strength, as a minimum clinically important difference for muscle strength is not known, but the magnitude of the treatment effect appears to be small to moderate and approximately a 1.1 kg change. The evidence for an effect from NMES on exercise performance and quality of life was of very low quality. For these outcomes, current evidence would support the use conventional exercise training over NMES. However, when patients are unwilling or unable to undertake other forms of training, the evidence supports NMES as a means to manage muscle weakness.

For policymakers

There was low-quality evidence for a strengthening effect from NMES to manage muscle weakness in adults with advanced disease. Based on current evidence, NMES appears to lead to a short-term, small-to-moderate increase in muscle strength as compared to control, with a mean difference of approximately 1.1 kg. It is difficult to draw conclusions about the clinical significance of this effect, as a minimum clinically important difference for muscle strength is not known. There was very low-quality evidence for an effect from NMES on muscle mass, exercise performance, breathlessness, or health-related quality of life.

For funders

There was low-quality evidence for a strengthening effect from NMES to manage muscle weakness in adults with advanced disease, but very low quality evidence for any additional effect on muscle mass, exercise performance, breathlessness, or health-related quality of life. Based on this evidence, NMES could be

considered as a component treatment for use within a wider approach to reduce disability, however there is very limited research on which to guide this practice. Future studies should move beyond testing whether NMES can produce a strengthening effect, and seek to understand its role in relation to existing rehabilitation approaches. Given the small sample sizes of current studies, larger trials may assist in providing more robust evidence.

Implications for research

General implications

Based on current evidence, future studies should move beyond testing whether NMES can produce a strengthening effect, and seek to understand the role of NMES in relation to existing rehabilitation approaches. Studies might consider using NMES as an adjuvant to exercise programmes to enhance their impact on muscle performance, adding behaviour change components to NMES to use gains in muscle strength to change physical activity and dependence, or using NMES as a bridge to support patients who demonstrate difficulty engaging in comprehensive rehabilitation programmes.

Design

Due to the predominance of small studies, we encourage large and pragmatic randomised controlled trials, focusing on outcomes such as exercise performance and physical independence and/or disability. With examples of successful placebo comparators, future studies can avoid a 'no treatment' arm and seek to include a comparator that accounts for the interaction and expectation effects of a NMES intervention. The lack of longitudinal data should also be addressed through longer follow-up periods and/or use of longitudinal outcomes, for example event rates or incident disability.

ACKNOWLEDGEMENTS

The 2016 update was undertaken with support from Anna Erskine, Managing Editor, Cochrane Pain Palliative and Supportive Care (PaPaS) Review Group. The search strategy was developed with the assistance of Joanne Abbott, Information Specialist, Cochrane PaPaS Group. Dr Hristina Petkova helped with the eligibility assessment for one excluded study published in Russian (Sumin 2009a).

Cochrane Review Group funding acknowledgement: The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane PaPaS Group. Disclaimer: The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, National Health Service (NHS), or the Department of Health.

REFERENCES

References to studies included in this review

Abdellaoui 2011 *{published data only}*

* Abdellaoui A, Préfaut C, Gouzi F, Couillard A, Coisy-Quivy M, Hugon G, et al. Skeletal muscle effects of electrostimulation after COPD exacerbation: a pilot study. *European Respiratory Journal* 2001;**38**:781-8.

Akar 2015 *{published data only}*

Akar O, Gunay E, Ulasli S, Ulasli AM, Kacar E, Sariaydin M, et al. Efficacy of neuromuscular electrical stimulation in patients with COPD followed in intensive care unit. *Clinical Respiratory Journal* 2015;**24 November**:Epub ahead of print. [DOI: 10.1111/crj.12411]

Bourjeily-Habr 2002 *{published data only}*

* Bourjeily-Habr G, Rochester CL, Palermo F, Snyder P, Mohsenin V. Randomised controlled trial of transcutaneous electrical muscle stimulation of the low extremities in patients with chronic obstructive pulmonary disease. *Thorax* 2002;**57**:1045-9.

Dal Corso 2007 *{published data only}*

* Dal Corso S, Nápolis L, Malaguti C, Gimenes AC, Albuquerque A, Nogueira CR, et al. Skeletal muscle structure and function in response to electrical stimulation in moderately impaired COPD patients. *Respiratory Medicine* 2007;**101**:1236-43.

Greening 2014 *{published and unpublished data}*

Greening NJ, Williams JE, Hussain SF, Harvey-Dunstan TC, Bankart MJ, Chaplin EJ, et al. An early rehabilitation intervention to enhance recovery during hospital admission for an exacerbation of chronic respiratory disease: randomised controlled trial. *BMJ* 2014;**349**:g4315.

Maddocks 2009a *{published data only}*

* Maddocks M, Lewis M, Chauhan A, Manderson C, Hocknell J, Wilcock A. Randomised controlled pilot study of neuromuscular electrical stimulation of the quadriceps in patients with non-small cell lung cancer. *Journal of Pain and Symptom Management* 2009;**38**(6):950-6.

Maddocks 2013 *{published data only}*

Maddocks M, Halliday V, Chauhan A, Taylor V, Nelson A, Sampson C, et al. Neuromuscular electrical stimulation of the quadriceps in patients with non-small cell lung cancer receiving palliative chemotherapy: a randomized phase II study. *PLoS One* 2013;**8**(12):e86059.

Maddocks 2016a *{published data only}*

Maddocks M, Nolan CM, Man WD, Polkey MI, Hart N, Gao W, et al. Neuromuscular electrical stimulation to improve exercise capacity in patients with severe COPD: a randomised double-blind, placebo-controlled trial. *Lancet Respiratory Medicine* 2016;**4**:27-36.

Nápolis 2011 *{published data only}*

* Nápolis LM, Dal Corso S, Neder JA, Malaguti C, Gimenes ACO, Nery LE. Neuromuscular electrical stimulation improves exercise tolerance in chronic obstructive pulmonary disease patients with better preserved fat-free mass. *Clinics (São Paulo)* 2011;**66**:401-6.

Neder 2002 *{published data only}*

* Neder JA, Sword D, Ward SA, Mackay E, Cochrane LM, Clark CJ. Home based neuromuscular electrical stimulation as a new rehabilitative strategy for severely disabled patients with chronic obstructive pulmonary disease (COPD). *Thorax* 2002;**57**:333-7.

Nuhr 2004 *{published data only}*

* Nuhr MJ, Pette D, Berger R, Quittan M, Crevanna R, Huelsman M, et al. Beneficial effects of chronic low-frequency stimulation of thigh muscles in patients with advanced chronic heart failure. *European Heart Journal* 2004;**25**:136-43.

Quittan 2001 *{published data only}*

* Quittan M, Wiesinger GF, Sturm B, Puig S, Mayr W, Sochor A, et al. Improvement of thigh muscles by neuromuscular electrical stimulation in patients with refractory heart failure: a single-blind, randomised, controlled trial. *American Journal of Physical Medicine and Rehabilitation* 2001;**80**:206-14.

Sillen 2014a *{published data only}*

Sillen MJ, Franssen FM, Delbressine JM, Vaes AW, Wouters EF, Spruit MA. Efficacy of lower-limb muscle training modalities in severely dyspnoeic individuals with COPD and quadriceps muscle weakness: results from the DICES trial. *Thorax* 2014;**69**(6):525-31.

Tasdemir 2015 *{published data only}*

Tasdemir F, Inal-Ince D, Ergun P, Kaymaz D, Demir N, Demirci E, et al. Neuromuscular electrical stimulation as an adjunct to endurance and resistance training during pulmonary rehabilitation in stable chronic obstructive pulmonary disease. *Expert Review of Respiratory Medicine* 2015;**9**(4):493-502.

Vieira 2014 *{published data only}*

Vieira PJ, Chiappa AM, Cipriano G Jr, Umpierre D, Arena R, Chiappa GR. Neuromuscular electrical stimulation improves clinical and physiological function in COPD patients. *Respiratory Medicine* 2014;**108**(4):609-20.

Vivodtzev 2006 *{published data only}*

* Vivodtzev I, Pépin J-L, Vottero G, Mayer V, Porsin B, Lévy P, et al. Improvement in quadriceps strength and dyspnea in daily tasks after 1 month of electrical stimulation in severely disabled and malnourished COPD. *Chest* 2006;**129**:1540-8.

Vivodtzev 2012 *{published data only}*

* Vivodtzev I, DeBigaré R, Gagnon P, Mainguy V, Saey D, Dubé A, et al. Functional and muscular effects of neuromuscular electrical stimulation in patients with severe COPD: a randomized clinical trial. *Chest* 2012;**141**:716-25.

Zanotti 2003 *{published data only}*

* Zanotti E, Felicetti G, Maini M, Fracchia C. Peripheral muscle strength training in bed-bound patients with COPD receiving mechanical ventilation: effect of electrical stimulation. *Chest* 2003;**124**:292-6.

References to studies excluded from this review

Ambrosino 2004 *{published data only}*

Ambrosino N, Strambi S. New strategies to improve exercise tolerance in chronic obstructive pulmonary disease. *European Respiratory Journal* 2004;**24**(2):313-22.

Ambrosino 2008 *{published data only}*

Ambrosino N, Casaburi R, Ford G, Goldstein R, Morgan MD, Rudolf M, et al. Developing concepts in the pulmonary rehabilitation of COPD. *Journal of Respiratory Medicine* 2008;**102**(Suppl 1):S17-26.

Arena 2010 *{published data only}*

Arena R, Pinkstaff S, Wheeler E, Peberdy MA, Guazzi M, Myers J. Neuromuscular electrical stimulation and inspiratory muscle training as potential adjunctive rehabilitation options for patients with heart failure. *Journal of Cardiopulmonary Rehabilitation and Prevention* 2010;**30**(4):209-23.

Banerjee 2009 *{published data only}*

* Banerjee P, Card D, Caulfield B, Crowe L, Clark AL. Prolonged electrical muscle stimulation exercise improves strength, peak VO_2 and exercise capacity in patients with stable chronic heart failure. *Journal of Cardiac Failure* 2009;**15**:319-26.

Banerjee 2010 *{published data only}*

Banerjee P. Electrical muscle stimulation for chronic heart failure: an alternative tool for exercise training?. *Current Heart Failure Reports* 2010;**7**(2):52-8.

Bausewein 2008 *{published data only}*

Bausewein C, Booth S, Gysels M, Higginson I. Non-pharmacological interventions for breathlessness in advanced stages of malignant and non-malignant diseases. *Cochrane Database of Systematic Reviews* 2008, Issue 2. [DOI: 10.1002/14651858.CD005623.pub3]

Bax 2005 *{published data only}*

Bax L, Staes F, Verhagen A. Does neuromuscular electrical stimulation strengthen the quadriceps femoris? A systematic review of randomised controlled trials. *Sports Medicine* 2005;**35**(3):191-212.

Bertoti 2000 *{published data only}*

Bertoti DB. Electrical stimulation: a reflection on current clinical practices. *Assistive Technology* 2000;**12**(1):21-32.

Bustamante 2010 *{published data only}*

* Bustamante V, Santa María EL, Corostiza A, Jiménez U, Gáldiz JB. Muscle training with repetitive magnetic stimulation of the quadriceps in severe COPD patients. *Respiratory Medicine* 2010;**102**:237-45.

Carvalho 2011 *{published data only}*

Carvalho VO, Roque JM, Bocchi EA, Ciolac EG, Guimarães GV. Hemodynamic response in one session of strength exercise with and without electrostimulation in heart failure patients: a randomized controlled trial. *Cardiology Journal* 2011;**18**(1):39-46.

Chaplin 2013 *{published data only}*

Chaplin EJ, Houchen L, Greening NJ, Harvey-Dunstan T, Morgan MD, Steiner MC, et al. Neuromuscular stimulation of quadriceps in patients hospitalised during an exacerbation of COPD: a comparison of low (35 Hz) and high (50 Hz) frequencies. *Physiotherapy Research International* 2013;**18**(3):148-56.

Claydon 2010 *{published data only}*

Claydon L, Stewart C, Durairaj R, Postans N, Miller K, Koufali M, et al. Strength training with electrical stimulation - Is this a viable method of facilitating independent mobility and improving quality of life after a moderate to severe stroke. Proceedings of SRR. 2010.

Collier 2009 *{published data only}*

Collier R, Burdon J, Revitt O, Morgan M, Steiner M, Singh S. Is NMES effective at maintaining peripheral muscle strength during hospitalization for an acute exacerbation of COPD? A pilot study. ERS Congress Proceedings. 2009.

Coote 2015 *{published data only}*

Coote S, Hughes L, Rainsford G, Minogue C, Donnelly A. Pilot randomized trial of progressive resistance exercise augmented by neuromuscular electrical stimulation for people with multiple sclerosis who use walking aids. *Archives of Physical Medicine and Rehabilitation* 2015;**96**:197-204.

Crevenna 2003 *{published data only}*

Crevenna R, Mayr W, Keilani M, Pleiner J, Nuhr M, Quittan M, et al. Safety of a combined strength and endurance training using neuromuscular electrical stimulation of thigh muscles in patients with heart failure and bipolar sensing cardiac pacemakers. *Wiener Klinische Wochenschrift* 2003;**115**(19-20):710-4.

Crevenna 2004 *{published data only}*

Crevenna R, Wolzt M, Fialka-Moser V, Keilani M, Nuhr M, Paternostro-Sluga T, et al. Long-term transcutaneous neuromuscular electrical stimulation in patients with bipolar sensing implantable cardioverter defibrillators: a pilot safety study. *Artificial Organs* 2004;**28**(1):99-102.

Crevenna 2006 *{published data only}*

Crevenna R, Marosi C, Schmidinger M, Fialka-Moser V. Neuromuscular electrical stimulation for a patient with metastatic lung cancer - a case report. *Supportive Care in Cancer* 2006;**14**(9):970-3.

Dehail 2008 *{published data only}*

Dehail P, Duclos C, Barat M. Electrical stimulation and muscle strengthening. *Annales de Readaptation et de Medecine Physique* 2008;**51**(6):441-51.

Deley 2005 *{published data only}*

* Deley G, Kervio G, Verges B, Hannequin A, Petitdant MF, Salmi-Belmihoub S, et al. Comparison of low-frequency electrical myostimulation and conventional aerobic exercise training in patients with chronic heart failure. *European Journal of Cardiovascular Prevention and Rehabilitation* 2005;**12**:229-33.

Deley 2008 *{published data only}*

Deley G, Kervio G, Verges B, Hannequin A, Petitdant MF, Grassi B, et al. Neuromuscular adaptations to low-frequency stimulation training in a patient with chronic heart failure. *American Journal of Physical Medicine & Rehabilitation* 2008;**87**(6):502-9.

Dobsák 2006a *{published data only}*

* Dobsák P, Nováková M, Fiser B, Siegelová J, Balcárková P, Špinarová L, et al. Electrical stimulation of skeletal muscles: an alternative to aerobic training in patients with chronic heart failure?. *International Heart Journal* 2006;**47**:441-53.

Dobsák 2006b *{published data only}*

Dobsák P, Nováková M, Siegelová J, Fiser B, Vítovec J, Nagasaka M, et al. Low-frequency electrical stimulation increases muscle strength and improves blood supply in patients with chronic heart failure. *Circulation Journal* 2006;**70**(1):75-82.

Dourado 2004 *{published data only}*

Dourado VZ, Godoy I. Muscle reconditioning in COPD: main interventions and new tendencies. *Rev Bras Med Esporte* 2004;**10**(4):335-8.

Duffell 2008 *{published data only}*

Duffell LD, Donaldson Nde N, Perkins TA, Rushton DN, Hunt KJ, Kakebeeke TH, et al. Long-term intensive electrically stimulated cycling by spinal cord-injured people: effect on muscle properties and their relation to power output. *Muscle & Nerve* 2008;**38**(4):1304-11.

Ergun 2010 *{published data only}*

* Ergun P, Kaymaz D, Erturk H, Selcuk NT, Demir N, Sengul F. The efficiency of NMES and endurance exercise training in moderate-severe COPD patients with peripheral muscle loss: the evaluation of cross-sectional area of quadriceps muscle with CT. European Research Society Proceedings. 2010; Vol. 640s:E3541.

Gaines 2004 *{published data only}*

Gaines JM, Metter EJ, Talbot LA. The effect of neuromuscular electrical stimulation on arthritis knee pain in older adults with osteoarthritis of the knee. *Applied Nursing Research* 2004;**17**(3):201-6.

Gerovasili 2009 *{published data only}*

Gerovasili V, Stefanidis K, Vitzilaios K, Karatzanos E, Politis P, Koroneos A, et al. Electrical muscle stimulation preserves the muscle mass of critically ill patients: a randomized study. *Critical Care* 2009;**13**(5):R161.

Giavedoni 2010 *{published data only}*

* Giavedoni S, MacNee W, Rabinovich RA. Neuromuscular electrical stimulation (NMES) in patients with COPD during an exacerbation (AECOPD). American Journal of Respiratory and Critical Care Medicine. 2010; Vol. 181:A2852.

Gremeaux 2008 *{published data only}*

Gremeaux V, Renault J, Pardon L, Deley G, Lepers R, Casillas JM. Low-frequency electric muscle stimulation combined with physical therapy after total hip arthroplasty for hip osteoarthritis in elderly patients: a randomized controlled trial. *Arch Phys Med Rehabil* 2008;**89**(12):2265-73.

Gruther 2010 *{published data only}*

Gruther W, Kainberger F, Fialka-Moser V, Paternostro-Sluga T, Quittan M, Spiss C, et al. Effects of neuromuscular electrical stimulation on muscle layer thickness of knee extensor muscles in intensive care unit patients: a pilot study. *J Rehabil Med* 2010;**42**(6):593-7.

Harris 2003 *{published data only}*

* Harris S, LeMaitre JP, Mackenzie G, Fox KAA, Denvir MA. A randomised study of home-based electrical stimulation of the legs and conventional bicycle exercise training for patients with chronic heart failure. *European Heart Journal* 2003;**24**:871-8.

Hennessy 2010a *{published data only}*

Hennessy EA, Coughlan GF, Cauffield B, Crowe L, Perumal SD, McDonnell TJ. An investigation into the acute effects of electrical muscle stimulation on cardiopulmonary function in a chronic obstructive pulmonary disease patient - a pilot case study. 1st Annual Conference of the International Functional Electrical Stimulation Society. 2010.

Hennessy 2010b *{published data only}*

Hennessy EA, Coughlan GF, Caulfield B, Crowe L, Perumal SD, McDonnell TJ. The effects of electrical muscle stimulation training in a chronic obstructive pulmonary disease population - a pilot study. 1st Annual Conference of the International Functional Electrical Stimulation Society. 2010.

Jancik 2003 *{published data only}*

Jancik J, Dobsak P, Eicher JC, Varnayova L, Kozantova L, Siegelova J, et al. Increase in muscle strength after low-frequency electrical stimulation in chronic heart failure. *Scripta Medica* 2003;**76**(5):285-90.

Karavidas 2010 *{published data only}*

Karavidas A, Parissis JT, Matzaraki V, Arapi S, Varounis C, Ikonomidis I, et al. Functional electrical stimulation is more effective in severe symptomatic heart failure patients and improves their adherence to rehabilitation programs. *Journal of Cardiac Failure* 2010;**16**(3):244-9.

Kaymaz 2015 *{published data only}*

Kaymaz D, Ergun P, Demirci E, Demir N. Comparison of the effects of neuromuscular electrical stimulation and endurance training in patients with severe chronic obstructive pulmonary disease. *Tuberk Toraks* 2015;**63**(1):1-7.

Larsen 2004 *{published data only}*

Larsen AI, Dickstein K. Can sedentary patients with heart failure achieve the beneficial effect of exercise training without moving?. *European Heart Journal* 2004;**25**(2):104-6.

LeMaitre 2006 *{published data only}*

* LeMaitre JP, Harris S, Hannan J, Fox KAA, Denvir MA. Maximum oxygen uptake corrected for skeletal muscle mass accurately predicts functional improvements following exercise training in chronic heart failure. *European Journal of Heart Failure* 2006;**8**:243-8.

Maddocks 2007 *{published data only}*

Maddocks M, Mockett S, Wilcock A. Neuromuscular electrical stimulation (NMES): a reactive palliative therapy, a proactive supportive therapy or both?. *Supportive Care in Cancer* 2007;**15**(1):111; author reply 113.

Mador 2000 *{published data only}*

Mador JM, Kufel TJ, Pineda L. Quadriceps fatigue after cycle exercise in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine* 2000;**161**(2 Pt 1):447-53.

Maffiuletti 2010 *{published data only}*

Maffiuletti NA. Physiological and methodological considerations for the use of neuromuscular electrical stimulation. *Eur J Appl Physiol* 2010;**110**(2):223-34.

Maillefert 1998 *{published data only}*

Maillefert JF, Eicher JC, Walker P, Dulieu V, Rouhier-Marcer I, Branly F, et al. Effects of low-frequency electrical stimulation of quadriceps and calf muscles in patients with chronic heart failure. *Journal of Cardiopulmonary Rehabilitation* 1998;**18**(4):277-82.

Malaguti 2009 *{published data only}*

Malaguti C, Rondelli RR, Paz JR, Reis LC, Dal Corso S. Constant or adjustable intensity of electrical current does not elicit different level of quadriceps femoris fatigue during neuromuscular electrical stimulation. Am J Respir Crit Care Med. 2009; Vol. 179:A3402.

Marsolais 1983 *{published data only}*

Marsolais EB, Kobetic R. Functional walking in paralyzed patients by means of electrical stimulation. *Clinical Orthopaedics & Related Research* 1983;**175**:30-6.

Middlekauff 2010 *{published data only}*

Middlekauff HR. Making the case for skeletal myopathy as the major limitation of exercise capacity in heart failure. [Review]. *Circulation: Heart Failure* 2010;**3**(4):537-46.

Mifkova 2004 *{published data only}*

Mifkova L, Dobsak P, Jancik J, Eicher JC, Svacinova H, Placheta Z, et al. Improvement of muscular performance in patients with chronic heart failure after some weeks of low-frequency electrical stimulation. *Scripta Medica* 2004;**77**(5-6):291-6.

Needham 2009 *{published data only}*

Needham DM, Truong AD, Fan E. Technology to enhance physical rehabilitation of critically ill patients. *Critical Care Medicine* 2009;**37**(10 Suppl):S436-41.

Palmieri-Smith 2010 *{published data only}*

Palmieri-Smith RM, Thomas AC, Karvonen-Gutierrez C, Sowers M. A clinical trial of neuromuscular electrical stimulation in improving quadriceps muscle strength and activation among women with mild and moderate osteoarthritis. *Physical Therapy* 2010;**90**(10):1441-52.

Piepoli 2010 *{published data only}*

Piepoli MF, Guazzi M, Boriani G, Cicoira M, Corra U, Dalla Libera L, et al. Working Group 'Exercise Physiology, Sport Cardiology and Cardiac Rehabilitation' of the Italian Society of Cardiology (Italian Federation of Cardiology). Exercise intolerance in chronic heart failure: mechanisms and therapies. Part II. *European Journal of Preventive Cardiology* 2010;**17**(6):643-8.

Piva 2007 *{published data only}*

Piva SR, Goodnite EA, Azuma K, Woollard JD, Goodpaster BH, Wasko MC, et al. Neuromuscular electrical stimulation and volitional exercise for individuals with rheumatoid arthritis: a multiple-patient case report. *Physical Therapy* 2007;**87**(8):1064-77.

Quittan 1999 *{published data only}*

Quittan M, Sochor A, Wiesinger GF, Kollmitzer J, Sturm B, Pacher R, et al. Strength improvement of knee extensor muscles in patients with chronic heart failure by neuromuscular electrical stimulation. *Artificial Organs* 1999;**23**(5):432-5.

Roig 2009 *{published data only}*

Roig M, Reid WD. Electrical stimulation and peripheral muscle function in COPD: a systematic review. *Respiratory Medicine* 2009;**103**(4):485-95.

Routsi 2010 *{published data only}*

Routsi C, Gerovasili V, Vasileiadis I, Karatzanos E, Pitsolis T, Tripodaki E, et al. Electrical muscle stimulation prevents critical illness polyneuromyopathy: a randomized parallel intervention trial. *Critical Care* 2010;**14**(2):R74.

Sbruzzi 2010 *{published data only}*

Sbruzzi G, Ribeiro RA, Schaan BD, Signori LU, Silva AM, Irigoyen MC, et al. Functional electrical stimulation in the treatment of patients with chronic heart failure: a meta-analysis of randomized controlled trials. *European Journal of Preventive Cardiology* 2010;**17**(3):254-60.

Sbruzzi 2011 *{published data only}*

Sbruzzi G, Schaan BD, Pimentel GL, Signori LU, Da Silva AN, Oshiro MS, et al. Effects of low frequency functional electrical stimulation with 15 and 50 Hz on muscle strength in heart failure patients. *Disability and Rehabilitation* 2011;**33**(6):486-93.

Scott 2007 *{published data only}*

Scott WB, Oursler KK, Katzel LI, Ryan AS, Russ DW. Central activation, muscle performance, and physical function in men infected with human immunodeficiency virus. *Muscle & Nerve* 2007;**36**(3):374-83.

Sheffler 2007 *{published data only}*

Sheffler LR, Chae J. Neuromuscular electrical stimulation in neurorehabilitation. *Muscle & Nerve* 2007;**35**(5):562-90.

Sillen 2008 *{published data only}*

Sillen MJ, Janssen PP, Akkermans MA, Wouters EF, Spruit MA. The metabolic response during resistance training and neuromuscular electrical stimulation (NMES) in patients with COPD, a pilot study. *Respiratory Medicine* 2008;**102**(5):786-9.

Sillen 2009 *{published data only}*

Sillen MJ, Speksnijder CM, Eterman RM, Janssen PP, Wagers SS, Wouters EF, et al. Effects of neuromuscular electrical stimulation of muscles of ambulation in patients with chronic heart failure or COPD: a systematic review of the English-language literature. *Chest* 2009;**136**(1):44-61.

Sillen 2010 *{published data only}*

Sillen MJH, Wouters EFM, Franssen FME, Meijer K, Stakenborg KHP, Spruit MA. Metabolic load and symptom perception during NMES in COPD. ERS Congress Proceedings. 2010.

Sillen 2011 *{published data only}*

Sillen MJ, Wouters EF, Franssen FM, Meijer K, Stakenborg KH, Spruit MA. Oxygen uptake, ventilation, and symptoms during low-frequency versus high-frequency NMES in COPD: a pilot study. *Lung* 2011;**189**(1):21-6.

Sillen 2014b *{published data only}*

Sillen MJ, Franssen FM, Vaes AW, Delbressine JM, Wouters EF, Spruit MA. Metabolic load during strength training or NMES in individuals with COPD: results from the DICES trial. *BMC Pulm Med* 2014;**14**:146.

Stevens-Lapsley 2012 *{published data only}*

Stevens-Lapsley JE. Early neuromuscular electrical stimulation to improve quadriceps muscle strength after total knee arthroplasty: a randomized controlled trial. *Physical Therapy* 2012;**92**(2):210-26.

Strasser 2009 *{published data only}*

Strasser EM, Stattner S, Karner J, Klimpfinger M, Freynhofer M, Zaller V, et al. Neuromuscular electrical stimulation reduces skeletal muscle protein degradation and stimulates insulin-like growth factors in an age- and current-dependent manner: a randomized, controlled clinical trial in major abdominal surgical patients. *Annals of Surgery* 2009;**249**(5):738-43.

Sumin 2008 *{published data only}*

Sumin AN, Snitskaia NA, Arkhipov OG. Electrostimulation of skeletal muscles in combined rehabilitation of patients with chronic pulmonary heart. *Kin Med (Mosk)* 2008;**86**(3):26-32.

Sumin 2009a *{published data only}*

* Sumin AN, Snitskaia NA, Arkhipov OG. Electrostimulation of the skeletal muscles in rehabilitation of patients with chronic cor pulmonale: effects on arrhythmogenesis and vegetative status. *Terapevtichesky Arkhiv* 2009;**81**:45-51.

Sumin 2009b *{published data only}*

Sumin AN, Snitskaia NA, Arkhipov OG. Electrostimulation of the skeletal muscles in rehabilitation of patients with chronic cor pulmonale: effects on arrhythmogenesis and vegetative state. *Ter Arkh* 2009;**81**(9):45-51.

Talbot 2003 *{published data only}*

Talbot LA, Gaines JM, Ling SM, Metter EJ. A home-based protocol of electrical muscle stimulation for quadriceps muscle strength in older adults with osteoarthritis of the knee. *Journal of Rheumatology* 2003;**30**(7):1571-8.

Vaquero 1998 *{published data only}*

Vaquero AF, Chicharro JL, Gil L, Ruiz MP, Sánchez V, Lucía A, et al. Effects of muscle electrical stimulation on peak VO2 in cardiac transplant patients. *Int J Sports Med* 1998;**19**(5):317-22.

Vivodtzev 2008 *{published data only}*

Vivodtzev I, Lacasse Y, Maltais F. Neuromuscular electrical stimulation of the lower limbs in patients with chronic obstructive pulmonary disease. *Journal of Cardiopulmonary Rehabilitation and Prevention* 2008;**28**(2):79-91.

Vivodtzev 2009 *{published data only}*

Vivodtzev I, Lacasse Y. Stimulating advances in chronic heart failure and COPD. *Chest* 2009;**136**(1):5-6.

Vivodtzev 2010 *{published data only}*

Vivodtzev I, Debigare R, Dube A, Pare M, Gagnon P, Mainguy V, et al. Molecular mechanisms of muscle hypertrophy after neuromuscular electrical stimulation in patients with severe COPD. Am J Respir Crit Care Med Proceedings. 2010; Vol. 181:A3762.

Vivodtzev 2014 *{published data only}*

Vivodtzev I, Rivard B, Gagnon P, Mainguy V, Dubé A, Bélanger M, et al. Tolerance and physiological correlates of neuromuscular electrical stimulation in COPD: a pilot study. *PLoS One* 2014;**9**(5):e94850.

Walls 2010 *{published data only}*

Walls RJ, McHugh G, O'Gorman DJ, Moyna NM, O'Byrne JM. Effects of preoperative neuromuscular electrical stimulation on quadriceps strength and functional recovery in total knee arthroplasty. A pilot study. *BMC Musculoskeletal Disorders* 2010;**14**(11):119.

Windholz 2011 *{published data only}*

Windholz T, Swanson T, Brandy L, Vanderbyl BL, Jagoe RT. The feasibility and acceptability of neuromuscular electrical stimulation in patients with advanced cancer. *J Cachexia sarcopenia Muscle* 2011;**2**:260.

Additional references

Baker 2000

Baker LL, Wederich CL, McNeal DR, Newsam C, Waters RL. Neuro Muscular Electrical Stimulation: A Practical Guide. 4th Edition. Los Amigos Research & Education Institute Inc, 2000.

Canavan 2015

Canavan JL, Maddocks M, Nolan CM, Jones SE, Kon SS, Clark AL, et al. Functionally relevant cut point for isometric quadriceps muscle strength in chronic respiratory disease. *Am J Respir Crit Care Med* 2015;**192**(3):395-7.

Cohen 1988

Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd Edition. Hillsdale, NJ: Erlbaum, 1988.

Cramp 2008

Cramp F, Daniel J. Exercise for the management of cancer-related fatigue in adults. *Cochrane Database of Systematic Reviews* 2008, Issue 2. [DOI: 10.1002/14651858.CD006145.pub2]

Dodson 2011

Dodson S, Baracos VE, Jatoi A, Evans WJ, Cella D, Dalton JT, et al. Muscle wasting in cancer cachexia: clinical implications, diagnosis and emerging treatment strategies. *Annual Reviews in Medicine* 2011;**62**:265-79.

Donaldson 2012

Donaldson AV, Maddocks M, Martolini D, Polkey MI, Man WD. Muscle function in COPD: a complex interplay. *International Journal of Chronic Obstructive Pulmonary Disease* 2012;**7**:523-35.

Elbourne 2002

Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington FC, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**:140-9.

Evans 2008

Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. *Clinical Nutrition* 2008;**27**:793-9.

Fischer 2009

Fischer MJ, Scharloo M, Abbink JJ, van't Hul AJ, van Ranst D, Rudolphus A, et al. Drop-out and attendance in pulmonary rehabilitation: the role of clinical and psychosocial variables. *Respiratory Medicine* 2009;**103**:1564-71.

GOLD 2005

Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. www.goldcopd.org/Guidelines/guidelines-global-strategy-for-diagnosis-management-2005.html 2005.

Gondin 2011

Gondin J, Brocca L, Bellinzona E, D'Antona G, Maffiuletti NA, Miotti D, et al. Neuromuscular electrical stimulation training induces atypical adaptations of the human skeletal muscle phenotype: a functional and proteomic analysis. *Journal of Applied Physiology* 2011;**110**(2):433-50.

GRADEpro GDT 2015 [Computer program]

McMaster University (developed by EvidencePrime Inc). GRADEPro GDT 2015: GRADEpro Guideline Development Tool. Available from www.gradepro.org: McMaster University (developed by EvidencePrime Inc), 2015.

Greening 2015

Greening NJ, Harvey-Dunstan TC, Chaplin EJ, Vincent EE, Morgan MD, Singh SJ, et al. Bedside assessment of quadriceps muscle by ultrasound after admission for acute exacerbations of chronic respiratory disease. *Am J Respir Crit Care Med* 2015;**192**(7):810-6.

Gysels 2007

Gysels M, Bausewein C, Higginson IJ. Experiences of breathlessness: a systematic review of the qualitative literature. *Palliative and Supportive Care* 2007;**5**:281–302.

Higgins 2002

Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**:1539-58.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Available from www.cochrane-handbook.org Version 5.1.0 [updated March 2011].

Holland 2014

Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *European Respiratory Journal* 2014;**44**:1428-46.

Hozo 2005

Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology* 2005;**5(Suppl 1)**:13.

Lacasse 2006

Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2006, Issue 4. [DOI: 10.1002/14651858.CD003793.pub2]

Maddocks 2009b

Maddocks M, Mockett S, Wilcock A. Is exercise an acceptable and practical therapy for people with or cured of cancer? A systematic review. *Cancer Treatment Reviews* 2009;**35**:383-90.

Maddocks 2016b

Maddocks M, Kerry R, Turner A, Howick J. Problematic placebos in physical therapy trials. *J Eval Clin Pract* 2016;**22**(4):598–602. [DOI: 10.1111/jep.12582]

Man 2009

Man WD, Kemp P, Moxham J, Polkey MI. Exercise and muscle dysfunction in COPD: implications for pulmonary rehabilitation. *Clinical Sciences* 2009;**117**:281-91.

Muscaritoli 2010

Muscaritoli M, Anker SD, Argilés J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". *Clinical Nutrition* 2010;**29**:154-9.

NYHA 1994

New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Edition. Boston: Little, Brown & Co, 1994:253-6.

O'Shea 2009

O'Shea SD, Taylor NF, Paratz FD. Progressive resistance exercise improves muscle strength and may improve elements of performance of daily activities for people with COPD: a systematic review. *Chest* 2009;**106**(5):1269-83.

Pan 2014

Pan L, Guo Y, Liu X, Yan J. Lack of efficacy of neuromuscular electrical stimulation of the lower limbs in chronic obstructive pulmonary disease patients: a meta-analysis. *Respirology* 2014;**19**(1):22-9.

Puhan 2011

Puhan MA, Gimeno-Santos E, Scharplatz M, Troosters T, Walters EH, Steurer J. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2011, Issue 10. [DOI: 10.1002/14651858.CD005305.pub3]

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Robertson 2006

Robertson V, Ward A, Low J, Reed A. Electrotherapy Explained: Principles and Practice. 4th Edition. London: Butterworth Heinemann Elsevier, 2006.

Skinner 2005

Skinner JS. Exercise Testing and Exercise Prescription for Special Cases: Theoretical Basis and Clinical Application. 3rd Edition. New York: Lippincott Williams & Wilkins, 2005.

Strassburg 2005

Strassburg S, Springer J, Anker SD. Muscle wasting in cardiac cachexia. *International Journal of Biochemistry and Cell Biology* 2005;**37**:1938-47.

Thompson 2010

Thompson WR, Gordon NF, Pescatello LS. ACSM's guidelines for exercise testing and prescription. 8th Edition. London: Lippincott Williams & Wilkins, 2010.

WHO 2007

World Health Organization. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf 2007.

References to other published versions of this review

Maddocks 2013

Maddocks M, Gao W, Higginson IJ, Wilcock A. Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease. *Cochrane Database of Systematic Reviews* 2013, Issue 1. [DOI: 10.1002/14651858.CD009419.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abdellaoui 2011

Methods	2-arm parallel RCT (n = 17)
Participants	Inclusion criteria: acute exacerbation of COPD, age < 75 years, body mass index < 30 kg/m^2 Exclusion criteria: locomotor or neurological condition or disability that could limit ability to exercise, implanted cardiac pacemaker Gender: 13 male, 2 female (2 unknown due to attrition) Age: median (IQR) 59 (57, 69) and 67 (59, 72) years Illness severity: median (IQR) FEV_1 15 (10, 27) and 25 (17, 41) % predicted
Interventions	NMES: bilateral quadriceps and hamstrings stimulation (35 Hz, 400 µs, duty cycle 33%) for 1 hour, 5 times each week for 6 weeks. Amplitude set to elicit visible contraction to maximum tolerated intensity. Control: parameters as per NMES arm, amplitude set to avoid visible or palpable muscle contraction

Abdellaoui 2011 *(Continued)*

Outcomes	Isometric quadriceps strength (hand-held dynamometry), submaximal exercise capacity (6MWT)
Notes	Standard deviations for laboratory outcomes derived from standard errors reported in original report and from authors by request

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes prepared independently
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo/sham model used.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessors not blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All appropriate participants included in analysis, all attrition accounted for, similar across groups (1 participant each), and not related to study intervention (disease-related readmission and family refusal)
Selective reporting (reporting bias)	Low risk	Full results provided in online supplement
Study sizes	High risk	< 50 participants

Akar 2015

Methods	3-arm parallel RCT (n = 30)
Participants	Inclusion criteria: intubated COPD patients, GOLD stage C or D, concious, without deep vein thrombosis (examined with bilateral lower extremity Doppler ultrasonography) Exclusion criteria: patients monitored on mechanical ventilation for less than 24 h and discharged from intensive care unit within 48 h, concurrent comorbidities (e.g. renal failure, congestive heart failure, cerebrovascular diseases, neuromuscular diseases, diabetes mellitus, malignancy), haemodynamically unstable patients Gender: 15 male, 15 female Age: mean (SD) 67 (12) years Illness severity: GOLD stage C or D
Interventions	NMES: bilateral quadriceps and deltoid muscle stimulation (50 Hz, pulse width and duty cycle not reported) for 4 weeks, 5 times per week. NMES intensity was adjusted to individual toleration. NMES plus active mobilisation: bilateral quadriceps and deltoid muscle stimulation as above, plus active mobilisation using joint range of motion exercises for the upper and lower limbs. Passive or active-assisted exercises used in participant unable to perform active exercises.

Akar 2015 *(Continued)*

	Control: active mobilisation using joint range of motion exercises for the upper and lower limbs. Passive or active-assisted exercises used in participant unable to perform active exercises.
Outcomes	Lower and upper extremity muscle strength (manual muscle testing), days to demonstrate abilty to sit up in bed, at the bedside, get into standing, and transfer from bed to chair, and intensive care unit stay in days
Notes	Lower extremity muscle strength outcomes were not clearly limited to quadriceps and were excluded from meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised", but no further details reported.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo/sham model used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors blinded to group allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis.
Selective reporting (reporting bias)	Low risk	Full results provided.
Study sizes	High risk	< 50 participants per study arm

Bourjeily-Habr 2002

Methods	2-arm parallel RCT (n = 18)
Participants	Inclusion criteria: moderate to severe COPD FEV_1< 65% predicted, age < 70 years, limited exercise tolerance Exclusion criteria: cardiovascular or neurological condition, active or debilitating joint disease, pulmonary rehabilitation previous 2 years Gender: 10 male, 8 female Age: mean (SD) 59 (2) and 62 (2) years Illness severity: GOLD stage III/IV
Interventions	NMES: bilateral quadriceps, hamstrings, and calve stimulation (50 Hz, 200 µs, duty cycle 13%) for 1 hour (20 min each muscle), 3 times each week for 6 weeks. Amplitude set to maximum tolerated intensity

Bourjeily-Habr 2002 *(Continued)*

	Control: set up as per NMES arm but no active stimulation
Outcomes	Isokinetic quadriceps and hamstring strength (dynamometry), maximal exercise capacity (incremental shuttle walk test)
Notes	Standard deviation derived from standard errors reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo/sham model used but with no output.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors blinded to group allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis.
Selective reporting (reporting bias)	Low risk	Full results provided.
Study sizes	High risk	< 50 participants per study arm

Dal Corso 2007

Methods	2-arm cross-over RCT (n = 17)
Participants	Inclusion criteria: COPD FEV_1:FVC < 70%, MRC breathlessness score II/III, stable medication previous 3 months Exclusion criteria: locomotor or neurological condition, malignancy, severe endocrine, hepatic, or renal disease, cardiac failure, implanted cardiac pacemaker, distal arteriopathy, recent surgery, use of anticoagulant medication Gender: 16 male, 1 female Age: mean (SD) 66 (9) years Illness severity: GOLD stage III/IV
Interventions	NMES: bilateral quadriceps stimulation (50 Hz, 400 µs, duty cycle 16% to 33%) for 1 hour, 5 times each week for 6 weeks. Amplitude set to elicit visible contraction to maximum tolerated intensity Control: bilateral quadriceps stimulation (10 Hz, 50 µs, duty cycle 16% to 33%) for 1 hour, 5 times each week for 6 weeks. Amplitude limited to 10 mA set to avoid muscle contraction

Dal Corso 2007 *(Continued)*

Outcomes	Isokinetic quadriceps strength (dynamometry), submaximal exercise capacity (6MWT), body composition (DEXA)
Notes	Participants included in Nápolis 2011 clinical outcomes (excluded from meta-analysis to avoid multiplicity). Laboratory outcomes included separately. The wash-out period was deemed sufficient to include both study phases in the meta-analysis. Results from paired analyses were used as recommended by Elbourne 2002.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly allocated
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo/sham model used.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Muscle biopsies only taken in NMES arm.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis.
Selective reporting (reporting bias)	Low risk	Full results provided.
Study sizes	High risk	< 50 participants per study arm

Greening 2014

Methods	2-arm parallel RCT (n = 389)
Participants	Inclusion criteria: admitted to hospital with an exacerbation of chronic respiratory disease, diagnosis of chronic respiratory disease (COPD, asthma, bronchiectasis, or ILD), self reported breathlessness on exertion (MRC grade 3 or worse), and age ≥ 40 years Exclusion criteria: inability to provide consent, concomitant acute cardiac event, musculoskeletal, neurological, or psychiatric comorbidities, more than 4 emergency admissions for any cause in the previous 12 months Gender: 173 male, 216 female Age: mean (SD) 71.1 (9.7) years Illness severity: mean (SD) FEV_1 54.7 (24.5) (82% of participants had COPD)
Interventions	Early rehabilitation: bilateral NMES of the quadriceps (50 Hz, 300 ms, 15 s on and 5 s off) for 30 minutes daily for 6 weeks. The intensity was increased by therapist or participant in accordance with tolerance. NMES used in addition to strength and aerobic training.

Greening 2014 *(Continued)*

	Usual care: no intervention other than usual care from the ward
Outcomes	Isometric quadriceps strength (dynamometer), maximal exercise capacity (ISWT), submaximal exercise capacity (ESWT), health-related quality of life (SGRQ)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised on a 1:1 basis
Allocation concealment (selection bias)	Low risk	Automated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants was not possible. No placebo/sham model used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All investigators performing outcome measures blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Full results provided.
Study sizes	Unclear risk	50 to 200 participants per study arm

Maddocks 2009a

Methods	2-arm parallel RCT (n = 16)
Participants	Inclusion criteria: non-small cell lung cancer, Eastern Cooperative Oncology Group performance status 0 to 1, < 10% weight loss Exclusion criteria: chemotherapy or radiotherapy previous 4 weeks, change in medication previous week, ischaemic heart disease, implanted cardiac pacemaker Gender: 9 male, 7 female Age: mean (SD) 64 (5) and 56 (9) years Illness severity: locally advanced or metastatic, stage III/IV
Interventions	NMES: bilateral quadriceps stimulation (50 Hz, 350 µs, duty cycle 11% to 25%) for 30 minutes daily for 4 weeks. Amplitude set to elicit visible contraction to maximum tolerated intensity Control: no intervention

Maddocks 2009a *(Continued)*

Outcomes	Isokinetic quadriceps strength (dynamometry), submaximal exercise capacity (endurance shuttle walk test), physical activity level (accelerometer)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted block generated independently.
Allocation concealment (selection bias)	Low risk	Using sealed, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo/sham model
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessors not blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis. Data on 1 participant (NMES group) missing for each quadriceps strength and physical activity level due to technical problems
Selective reporting (reporting bias)	Low risk	Full results provided.
Study sizes	High risk	< 50 participants per study arm

Maddocks 2013

Methods	2-arm parallel RCT (n = 49)
Participants	Inclusion criteria: adults with advanced (stage IV) NSCLC confirmed by histology or cytology, Eastern Cooperative Oncology Group performance status 0 to 2 scheduled to receive first-line palliative chemotherapy Exclusion criteria: spinal cord compression, epilepsy, cardiac pacemaker Gender: 28 male, 21 female Age: mean (SD) 69.1 (9.4) years Illness severity: advanced stage IV NSCLC
Interventions	NMES: bilateral quadriceps stimulation (50 Hz, 350 µs, duty cycle 11% to 25%) for 30 minutes daily, at a minimum of 3 times per week, commencing 1 week after chemotherapy started and continued for 8 or 11 weeks. Amplitude was set to elicit visible contraction to maximum tolerated intensity. Control: no intervention

Maddocks 2013 *(Continued)*

Outcomes	Isometric quadriceps strength (dynamometry), body composition (DEXA), physical activity level (accelerometer), fatigue (Multidimensional Fatigue Inventory), quality of life (EORTC QLQ-C30)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly allocated
Allocation concealment (selection bias)	Low risk	Permuted block generated independently.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo/sham model
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were not blinded to the participant group allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	All appropriate participants included in the analysis, all attrition accounted for. Data were missing in 8 participants for body composition due to inability to scan before chemotherapy (n = 5) and participant choice (n = 3). 3 further participants withdrew due to NMES-related muscle discomfort.
Selective reporting (reporting bias)	Low risk	Full results reported.
Study sizes	High risk	< 50 participants per study arm

Maddocks 2016a

Methods	2-arm parallel RCT (n = 52)
Participants	Inclusion criteria: aged 18 years or older, diagnosis of severe COPD consistent with GOLD criteria (FEV_1% predicted ≤ 50) and incapacitating breathlessness (MRC dyspnoea scale 4 or 5) Exclusion criteria: implanted cardiac pacemaker, coexisting neurological condition, had changes to their medication, or had experienced an acute exacerbation requiring hospitalisation or systemic corticosteroids in the preceding 4 weeks, regular exercisers (defined as those enrolled in pulmonary rehabilitation or undertaking structured exercise training ≥ 3 times per week within the past month)
Interventions	NMES: bilateral quadriceps stimulation (50 Hz, 350 µs, duty cycle 13% to 66%) for 30 minutes daily. Amplitude was set to elicit visible contraction to maximum tolerated intensity. Placebo: parameters as per NMES arm, however amplitude was set between 0 mA and 20 mA to provide a sensory stimulus that was detectable by the participant.
Outcomes	Submaximal exercise capacity (6MWT), voluntary and involuntary isometric quadriceps strength (dynamometer), body composition (BIA), health-related quality of life (SGRQ, CRQ, and EQ-5D), physical activity level (accelerometer)

Maddocks 2016a *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned (1:1) at the individual level
Allocation concealment (selection bias)	Low risk	Randomised using an independent, web-based randomisation system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo/sham model used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded to the participant group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All attrition accounted for. Data analysed by intention to treat, and missing data were handled by a multiple imputation approach.
Selective reporting (reporting bias)	Low risk	Full results provided.
Study sizes	High risk	< 50 participants per study arm

Neder 2002

Methods	2-arm parallel RCT (n = 15)
Participants	Inclusion criteria: severe COPD FEV_1 < 50% predicted, MRC breathlessness score IV/V Exclusion criteria: locomotor or neurological condition, change in medication or exacerbation in previous 4 weeks Gender: 9 male, 6 female Age: mean (SD) 67 (8) and 65 (5) years Illness severity: GOLD stage IV
Interventions	NMES: bilateral quadriceps stimulation (50 Hz, 300 µs to 400 µs, duty cycle 11% to 25%) for 30 minutes, 5 times each week for 6 weeks. Amplitude set to elicit visible contraction to maximum tolerated intensity Control: no intervention
Outcomes	Isokinetic and isometric quadriceps strength (dynamometry), quadriceps endurance (constant load), maximal exercise capacity (CPET cycle ergometry), quality of life (CRQ)
Notes	Control participants received NMES after the first study period, and pre-post changes reported. These data were not used in meta-analysis. Change score for the meta-analysis for quadriceps strength and

Neder 2002 *(Continued)*

	exercise capacity were estimated using the difference between pre- and post-intervention groups means the widest standard deviations as per a previous review (Roig 2009).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised
Allocation concealment (selection bias)	Low risk	"Referers" blinded to sequence allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo/sham model used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Selective reporting (reporting bias)	Low risk	Full results provided.
Study sizes	High risk	< 50 participants per study arm

Nuhr 2004

Methods	2-arm parallel RCT (n = 34)
Participants	Inclusion criteria: symptomatic left ventricular fraction < 35%, optimised medication Exclusion criteria: acute heart failure, angina, arrhythmia, implanted cardiac pacemaker Gender: 29 male, 5 female Age: mean (SD) 53 (10) years Illness severity: NYHA stage II to IV
Interventions	NMES: bilateral quadriceps and hamstrings stimulation (15 Hz, 500 µs, duty cycle 33%) for 4 hours, daily for 10 weeks. Amplitude set to elicit visible contraction to maximum tolerated intensity. Control: parameters as per NMES arm, amplitude set to avoid visible or palpable muscle contraction
Outcomes	Maximal exercise capacity (CPET cycle ergometry), submaximal exercise capacity (6MWT), quality of life (Minnesota Living With Heart Failure Questionnaire)
Notes	

Risk of bias

Nuhr 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo/sham model used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All attrition accounted for, small number of participants (n = 2) and not related to study intervention (urgent heart transplantation).
Selective reporting (reporting bias)	High risk	Under adverse events subheading "maximum voluntary strength of the stimulated muscle groups did not differ from baseline data"
Study sizes	High risk	< 50 participants per study arm

Nápolis 2011

Methods	2-arm cross-over RCT (n = 30)
Participants	Inclusion criteria: COPD FEV_1:FVC < 70%, MRC breathlessness score I/III Exclusion criteria: locomotor or neurological condition, malignancy, severe endocrine, hepatic, or renal disease, cardiac failure, implanted cardiac pacemaker, distal arteriopathy, recent surgery, use of anticoagulant medication, change in medication or exacerbation in previous 4 weeks, regular physical activity, previous pulmonary rehabilitation Gender: 26 male, 4 female Age: mean (SD) 64 (7) years Illness severity: GOLD stage II/III
Interventions	NMES: bilateral quadriceps stimulation (50 Hz, 300 µs to 400 µs, duty cycle 16% to 33%) for up to 1 hour, 5 times each week for 6 weeks. Amplitude set to elicit visible contraction to maximum tolerated intensity Control: bilateral quadriceps stimulation (50 Hz, 200 µs, duty cycle 16%) for 15 minutes, 3 times each week for 6 weeks. Amplitude limited to 10 mA set to avoid muscle contraction
Outcomes	Isokinetic quadriceps strength (dynamometry), maximal exercise capacity (CPET cycle ergometry), submaximal exercise capacity (6MWT)
Notes	Participants from Dal Corso 2007 were included in this study (for clinical outcomes Nápolis 2011 data were used in meta-analysis to avoid multiplicity). The wash-out period was deemed sufficient to include both study phases in the meta-analysis. Results from paired analyses were used as recommended by Elbourne 2002.

Nápolis 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	After randomisation
Allocation concealment (selection bias)	Unclear risk	As per Dal Corso 2007
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo/sham model used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors blinded to participant treatment sequence
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis. Data on 2 and 4 participants were missing for maximal and submaximal exercise capacity, respectively due to technical problems (group allocation unknown).
Selective reporting (reporting bias)	Low risk	Full results provided.
Study sizes	High risk	< 50 participants per study arm

Quittan 2001

Methods	2-arm parallel RCT (n = 42)
Participants	Inclusion criteria: severe chronic heart failure, optimised drug therapy Exclusion criteria: unstable disease, peripheral oedema, implanted cardiac pacemaker Gender: 21 male, 12 female Age: mean (SD) 59 (6) and 57 (8) years Illness severity: NYHA stage II to IV
Interventions	NMES: bilateral quadriceps and hamstrings stimulation (50 Hz, 700 µs, duty cycle 25%) for up to 1 hour, 5 times each week for 8 weeks. Amplitude set to elicit visible contraction to maximum tolerated intensity Control: encouraged to continue engagement in usual activities of daily living recorded in diary
Outcomes	Isokinetic and isometric quadriceps and hamstrings strength (dynamometry), quadriceps endurance (interval fixed load), body composition (computed tomography), lower limb functional activities (stair climb, rise from chair, rise from supine), quality of life (SF-36)
Notes	Standard deviations for outcomes of quadriceps and hamstrings strength, quadriceps endurance, and body composition were derived from reported 95% confidence intervals.

Risk of bias

Quittan 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block-wise randomisation using list provided by independent staff
Allocation concealment (selection bias)	Low risk	Randomisation code locked until the end of the study
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo/sham model
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were not aware of the participants' group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All attrition accounted for, similar numbers across groups (NMES n = 2, control n = 5) and not related to study intervention (urgent heart transplantation n = 6, pacemaker implanted n = 1, renal failure n = 1, died (control) n = 1)
Selective reporting (reporting bias)	Low risk	Full results provided.
Study sizes	High risk	< 50 participants per study arm

Sillen 2014a

Methods	3-arm parallel RCT (n = 120)
Participants	Inclusion criteria: primary diagnosis of COPD, baseline MRC dyspnoea grade 3 or 4, quadriceps weakness (peak torque ≤ 80% predicted) Exclusion criteria: neuromuscular diseases, joint disorders in hip/leg and/or knees, metal implants in hip, leg, and/or knee, cardiac pacemaker or internal cardiac defibrillator, and/or outpatient pulmonary rehabilitation programme Gender: 62 male, 58 female Age: mean (SD) 64.8 (8.8) years Illness severity: mean (SD) FEV_1 33 (11) % predicted
Interventions	High-frequency NMES: bilateral quadriceps and calf muscle stimulation (75 Hz, 400 µs, duty cycle was 38%) for 8 weeks, twice per day, 5 times per week. After a 3-minute warm-up at 5 Hz, intensity was adjusted to individual toleration during each 18-minute session. Low-frequency NMES: same as the high-frequency NMES protocol, however the frequency used was 15 Hz Control: strength training consisting of bilateral leg extension and bilateral leg press exercises at 70% 1 RPM, 4 sets of 8 for each exercise with at least 2 minutes of recovery between sets. Training load was set to increase by 5% every 2 weeks.
Outcomes	Isokinetic quadriceps muscle strength (dynamometry), isokinetic quadriceps endurance (constant load), submaximal exercise capacity (6MWT), endurance (constant work rate cycle endurance test),

Sillen 2014a *(Continued)*

	anxiety and depression (HADS), health-related quality of life (SGRQ), problematic activities of daily living (COPM)
Notes	Standard deviations for laboratory outcomes derived from standard errors reported in the original paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation schedule generated by a computer.
Allocation concealment (selection bias)	Low risk	Sequence was concealed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants randomly assigned to one of the NMES groups were blinded for stimulation frequency, however no placebo/sham in the control group (the main comparison for this review).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation schedule was maintained centrally, and the investigator was not involved in the assessment and treatment of participants. Investigators supervising the interventions were blinded for initial results, and were not involved in the initial or outcome assessments.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No imputations. Attrition accounted for but not similar between the groups, highest attrition in the low-frequency group
Selective reporting (reporting bias)	Low risk	Full results provided.
Study sizes	High risk	< 50 participants per study arm

Tasdemir 2015

Methods	2-arm parallel RCT (n = 34)
Participants	Inclusion criteria: aged between 40 and 75 years, eligible to participate in exercise, no acute exacerbations within the past month, and no drug or antibiotic usage within the past 4 weeks Exclusion criteria: suffering from orthopaedic or neuromuscular disorders, metal implants in the lower limb, suffered from advanced heart failure, aortic stenosis, or deep vein thrombosis, required cardiac pacemaker, had a pulmonary artery pressure > 50 mmHg, suffered an acute exacerbation within the past 4 weeks, unable to understand the questionnaires, and were unable to co-operate Gender: 24 male, 3 female Age: mean (SD) 62.1 (7.9) and 62.9 (7.5) years Illness severity: GOLD stages 1 = 0, II = 9, III = 9, IV = 9
Interventions	NMES: bilateral quadriceps stimulation (50 Hz, 300 µs, duty cycle was 50%) for 20 minutes, 2 days per week, for 10 weeks. Intensity was increased to each participant's maximum individual tolerance level. Control: parameters as per NMES arm, with the exception of stimulation frequency of 5 Hz, which caused a visible twitch

Tasdemir 2015 *(Continued)*

	All participants undertook a pulmonary rehabilitation programme consisting of exercise training and additional intervention such as education and nutritional and psychological support. Exercise training consisted of 10 weeks of endurance training, quadriceps resistance training, and low-level resistance training for the upper limbs.
Outcomes	Maximal exercise capacity (ISWT), submaximal exercise capacity (ESWT), body composition (BIA), quadriceps function (1-repetition maximum and 30-second sit-to-stand test), quadriceps endurance (squat test and 2-minute step-in-place test), health-related quality of life (SGRQ)
Notes	Mean and standard deviation values were estimated from reported median and range values using the formulae published by Hozo 2005.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo/sham model used.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessors were not blinded for the final evaluation assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All attrition accounted for, similar across groups (NMES n = 4, control n = 3) and not related to study intervention
Selective reporting (reporting bias)	Low risk	Full results provided.
Study sizes	High risk	< 50 participants per study arm

Vieira 2014

Methods	2-arm parallel RCT (n = 30)
Participants	Inclusion criteria: diagnosis of COPD with FEV_1 < 50% predicted, self reported dyspnoea and/or arm fatigue during at least 1 activity of daily living that required arm exercise Exclusion criteria: musculoskeletal or neurological condition that could affect exercise performance, symptomatic cardiac disease or previous lung surgery, an acute exacerbation of COPD that required a change in pharmacological management within the preceding 2 months, use of oral corticosteroids, a change in medication dosage or exacerbation of symptoms in the preceding 12 weeks, implantable electrical devices Gender: 24 male, 0 female Age: mean (SD) 56.4 (11.8) years

Vieira 2014 *(Continued)*

	Illness severity: GOLD stage III/IV, mean (SD) 38.1 (12.4)% predicted
Interventions	NMES: bilateral quadriceps stimulation (50 Hz, 300 µs to 400 µs, duty cycle 10% to 33%) for 60 minutes per session, 5 times per week, twice per day for 8 weeks. Amplitude was set to elicit visible contraction to maximum tolerated intensity. Control: parameters as per NMES arm, but no active stimulation All participants received respiratory physiotherapy, i.e. breathing and stretching exercises.
Outcomes	Submaximal exercise capacity (6MWT), cardiopulmonary exercise testing (constant work test at 80% peak workload), body composition (BIA), quality of life (SGRQ)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly allocated
Allocation concealment (selection bias)	Low risk	2 investigators were blinded to the order of participant allocation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Active and sham devices were utilised, however the sham device produced no stimulation.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Within group health-related quality of life reporting
Incomplete outcome data (attrition bias) All outcomes	High risk	17% attrition, causing an imbalance between the groups. Increased dropouts due to an exacerbation in the control group compared to the NMES group
Selective reporting (reporting bias)	Low risk	Full results provided.
Study sizes	High risk	< 50 participants per study arm

Vivodtzev 2006

Methods	2-arm parallel RCT (n = 17)
Participants	Inclusion criteria: severe COPD, COPD FEV_1:FVC < 70%, FEV_1 < 50% predicted, body mass index < 22 kg/m^2, quadriceps maximum voluntary strength < 50% predicted Exclusion criteria: cardiovascular, renal, or hepatic disease, acute respiratory failure Gender: 11 male, 6 female Age: mean (SD) 59 (15) and 68 (12) years Illness severity: GOLD stage IV

Vivodtzev 2006 *(Continued)*

Interventions	NMES: bilateral quadriceps stimulation (35 Hz, 400 µs, duty cycle 47%) for 30 minutes, 4 times each week for 4 weeks. Amplitude set to elicit visible contraction to maximum tolerated intensity. Additional usual rehabilitation as described below. Control: usual rehabilitation limb mobilisations, slow treadmill walking, light upper limb resistance training for ˜30 minutes, 4 times each week for 4 weeks
Outcomes	Isometric quadriceps strength (dynamometry), submaximal exercise capacity (6MWT), body composition (anthropometry), quality of life (Maugeri Foundation Respiratory Failure Questionnaire)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised into 2 groups
Allocation concealment (selection bias)	Unclear risk	Inadequately described to judge
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo/sham model used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Body composition assessments optional
Selective reporting (reporting bias)	Low risk	Full results provided, body composition assessments optional, similar numbers across groups (NMES n = 6, control n = 5).
Study sizes	High risk	< 50 participants per study arm

Vivodtzev 2012

Methods	2-arm parallel RCT (n = 22)
Participants	Inclusion criteria: severe COPD FEV_1:FVC < 70%, FEV_1 < 50% predicted, 6-minute walking distance < 400 metres, > 20-year smoking pack-year history, sedentary lifestyle, < 1 hour from hospital Exclusion criteria: acute exacerbation or systemic steroids in previous 4 weeks, condition associated with muscle wasting including active inflammatory illness, heart failure, or diabetes Gender: 13 male, 7 female Age: mean (SD) 68 (9) and 70 (3) years Illness severity: GOLD stage IV

Vivodtzev 2012 *(Continued)*

Interventions	NMES: bilateral quadriceps and calve stimulation (50 Hz, 400 µs, duty cycle 27%) for 1 hour (35 minutes quadriceps and 25 minutes calves), 5 times each week for 6 weeks. Amplitude set to elicit visible contraction to maximum tolerated intensity Control: bilateral quadriceps stimulation (5 Hz, 100 µs, continuous) for 1 hour (35 minutes quadriceps and 25 minutes calves), 5 times each week for 6 weeks
Outcomes	Isometric quadriceps strength (dynamometry), quadriceps endurance (constant load test), body composition (computed tomography), submaximal exercise capacity (endurance shuttle walk test)
Notes	Standard deviations for all outcomes derived from standard errors reported in original report and from authors by request.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned
Allocation concealment (selection bias)	Unclear risk	Inadequately described to judge
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo/sham model used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Inadequately described to judge
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Selective reporting (reporting bias)	Low risk	Full results provided.
Study sizes	High risk	< 50 participants per study arm

Zanotti 2003

Methods	2-arm parallel RCT (n = 24)
Participants	Inclusion criteria: chronic hypercapnic respiratory failure, COPD FEV_1:FVC < 70%, mechanically ventilated, severe peripheral muscle atrophy, bed-bound > 30 days Exclusion criteria: condition or disease other than COPD, change in medication within previous 4 weeks, corticosteroid use > 5 days whilst on intensive care unit Gender: 17 male, 7 female Age: mean (SD) 68 (8) and 65 (4) years Illness severity: respiratory failure due to COPD

Zanotti 2003 *(Continued)*

Interventions	NMES: bilateral quadriceps and glutei stimulation (35 Hz, 350 µs, duty cycle not reported) for 30 minutes, 5 times each week for 4 weeks. Amplitude not reported. Used as adjunct to active limb mobilisation described below Control: active limb mobilisation of upper and lower limbs for up to 30 minutes within participant tolerance, 5 times each week for 4 weeks
Outcomes	Peripheral muscle strength (manual muscle testing), number of days to transfer from bed to chair
Notes	Peripheral muscle strength outcome not clearly limited to quadriceps and excluded from meta-analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned
Allocation concealment (selection bias)	Unclear risk	Inadequately described to judge
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo/sham model used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Selective reporting (reporting bias)	Low risk	Full results provided.
Study sizes	High risk	< 50 participants per study arm

Abbreviations: 6MWT = 6-minute walk test, BIA = bioelectrical impedance analysis, COPD = chronic obstructive pulmonary disease, COPM = Canadian Occupational Performance Measure, CPET = cardiopulmonary exercise testing, CRQ = Chronic Respiratory Questionnaire, DEXA = dual energy X-ray absorptiometry, EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer Quality of Life Core 30, ESWT = endurance shuttle walk test, FEV1 forced expiratory volume in 1 second, FVC = forced vital capacity, HADS = Hospital Anxiety and Depression Scale, ILD = interstitial lung disease, IQR = interquartile range, ISWT = incremental shuttle walk test, mA = maximum amplitude, MRC = Medical Research Council, NMES = neuromuscular electrical stimulation, NSCLC = non-small cell lung cancer, NYHA = New York Heart Association, RCT = randomised controlled trial, RPM = revolutions per minute, SD = standard deviation, SF-36 = 36-Item Short Form Health Survey, SGRQ = St George's Respiratory Disease Questionnaire

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ambrosino 2004	Review, perspective
Ambrosino 2008	Review, perspective

Study	Reason for exclusion
Arena 2010	Review, perspective
Banerjee 2009	The majority of participants (9/10) had early-stage (NYHA II) disease.
Banerjee 2010	Review, perspective
Bausewein 2008	Review, meta-analysis
Bax 2005	Review, perspective
Bertoti 2000	Review, perspective
Bustamante 2010	The intervention studied involved magnetic rather than electrical stimulation to elicit a muscular contraction.
Carvalho 2011	Acute-effects study
Chaplin 2013	The study compared high-frequency and low-frequency NMES, no comparison to an inactive control or an active control such as exercise present.
Claydon 2010	Poststroke
Collier 2009	Observation
Coote 2015	Difficult to define advanced disease in multiple sclerosis
Crevenna 2003	Case series
Crevenna 2004	Case series
Crevenna 2006	Case report
Dehail 2008	Review, perspective
Deley 2005	The majority of participants (18/24) had early-stage (NYHA II) disease.
Deley 2008	Observational
Dobsák 2006a	The majority of participants (22/30) had early-stage (NYHA II) disease.
Dobsák 2006b	Observational
Dourado 2004	Review, perspective
Duffell 2008	Spinal cord injury
Ergun 2010	Group allocation reportedly occurred according to level of illness severity and muscle dysfunction: "due to illness severity and muscle dysfunction 8 patients were included in NMES and 11 patients were included in endurance program".
Gaines 2004	Osteoarthritis
Gerovasili 2009	Critically ill patient including sepsis and trauma

Study	Reason for exclusion
Giavedoni 2010	Randomisation occurred at the level of the limb, with one leg stimulated and the other acting as a control.
Gremeaux 2008	Total hip replacement
Gruther 2010	Critically ill patient including sepsis and trauma
Harris 2003	The majority of participants (35/46) had early-stage (NYHA II) disease.
Hennessy 2010a	Acute-effects study
Hennessy 2010b	Acute-effects study
Jancik 2003	Observational
Karavidas 2010	Frequency-matched case-control
Kaymaz 2015	Observational
Larsen 2004	Review, perspective
LeMaitre 2006	The majority of participants (28/35) had early-stage (NYHA II) disease.
Maddocks 2007	Review, perspective
Mador 2000	Assessment using ES not intervention
Maffiuletti 2010	Review, perspective
Maillefert 1998	Observational
Malaguti 2009	Compared 2 intensity protocols
Marsolais 1983	Spinal cord injury, paralysis
Middlekauff 2010	Review, perspective
Mifkova 2004	Observational
Needham 2009	Review, perspective
Palmieri-Smith 2010	Osteoarthritis
Piepoli 2010	Review, perspective
Piva 2007	Case series
Quittan 1999	Observational
Roig 2009	Review, meta-analysis
Routsi 2010	Critically ill patient including sepsis and trauma
Sbruzzi 2010	Review, meta-analysis

Study	Reason for exclusion
Sbruzzi 2011	Compared 2 NMES frequencies
Scott 2007	Assessment using ES not intervention
Sheffler 2007	Review, perspective
Sillen 2008	Acute-effects study
Sillen 2009	Review, meta-analysis
Sillen 2010	Acute-effects study
Sillen 2011	Acute-effects study
Sillen 2014b	Measurements made following 1 session/acute-effects study.
Stevens-Lapsley 2012	Total knee replacement
Strasser 2009	Abdominal surgery
Sumin 2008	Repeat report
Sumin 2009a	The majority of participants (99/101) had early-stage disease.
Sumin 2009b	Repeat report
Talbot 2003	Osteoarthritis
Vaquero 1998	Post-cardiac transplantation
Vivodtzev 2008	Review, perspective
Vivodtzev 2009	Review, perspective
Vivodtzev 2010	Repeat report
Vivodtzev 2014	Repeat report
Walls 2010	Total knee replacement
Windholz 2011	Observational

NMES = neuromuscular electrical stimulation, NYHA = New York Heart Association

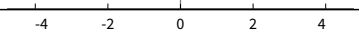
DATA AND ANALYSES

Comparison 1. Neuromuscular electrical stimulation versus control

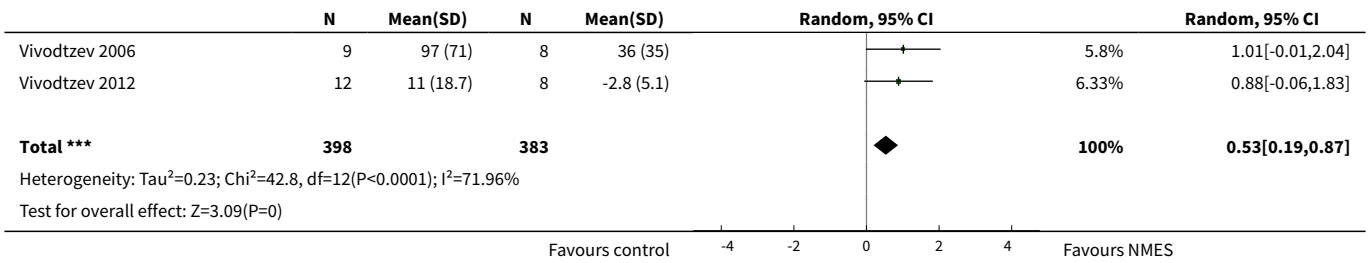
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Quadriceps muscle strength	12	781	Std. Mean Difference (IV, Random, 95% CI)	0.53 [0.19, 0.87]
2 Muscle mass	8		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Anthropometry	2	31	Std. Mean Difference (IV, Random, 95% CI)	0.69 [-0.05, 1.42]
2.2 Dual energy X-ray absorptiometry (DEXA)	3	179	Std. Mean Difference (IV, Random, 95% CI)	0.09 [-0.20, 0.38]
2.3 Ultrasound	1	52	Std. Mean Difference (IV, Random, 95% CI)	0.82 [0.26, 1.39]
2.4 Computed tomography	2	52	Std. Mean Difference (IV, Random, 95% CI)	1.01 [0.42, 1.60]
3 Exercise performance	13		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 6-minute walk test (m) (6MWT)	7	317	Mean Difference (IV, Random, 95% CI)	34.78 [13.52, 56.05]
3.2 Incremental shuttle walk test (m) (ISWT)	3	434	Mean Difference (IV, Random, 95% CI)	8.72 [-34.87, 52.31]
3.3 Endurance shuttle walk test (m) (ESWT)	4	452	Mean Difference (IV, Random, 95% CI)	64.13 [-17.79, 146.05]
3.4 Cardiopulmonary exercise testing (mL/min) (CPET)	4	109	Mean Difference (IV, Random, 95% CI)	44.82 [-7.34, 96.99]

Analysis 1.1. Comparison 1 Neuromuscular electrical stimulation versus control, Outcome 1 Quadriceps muscle strength.

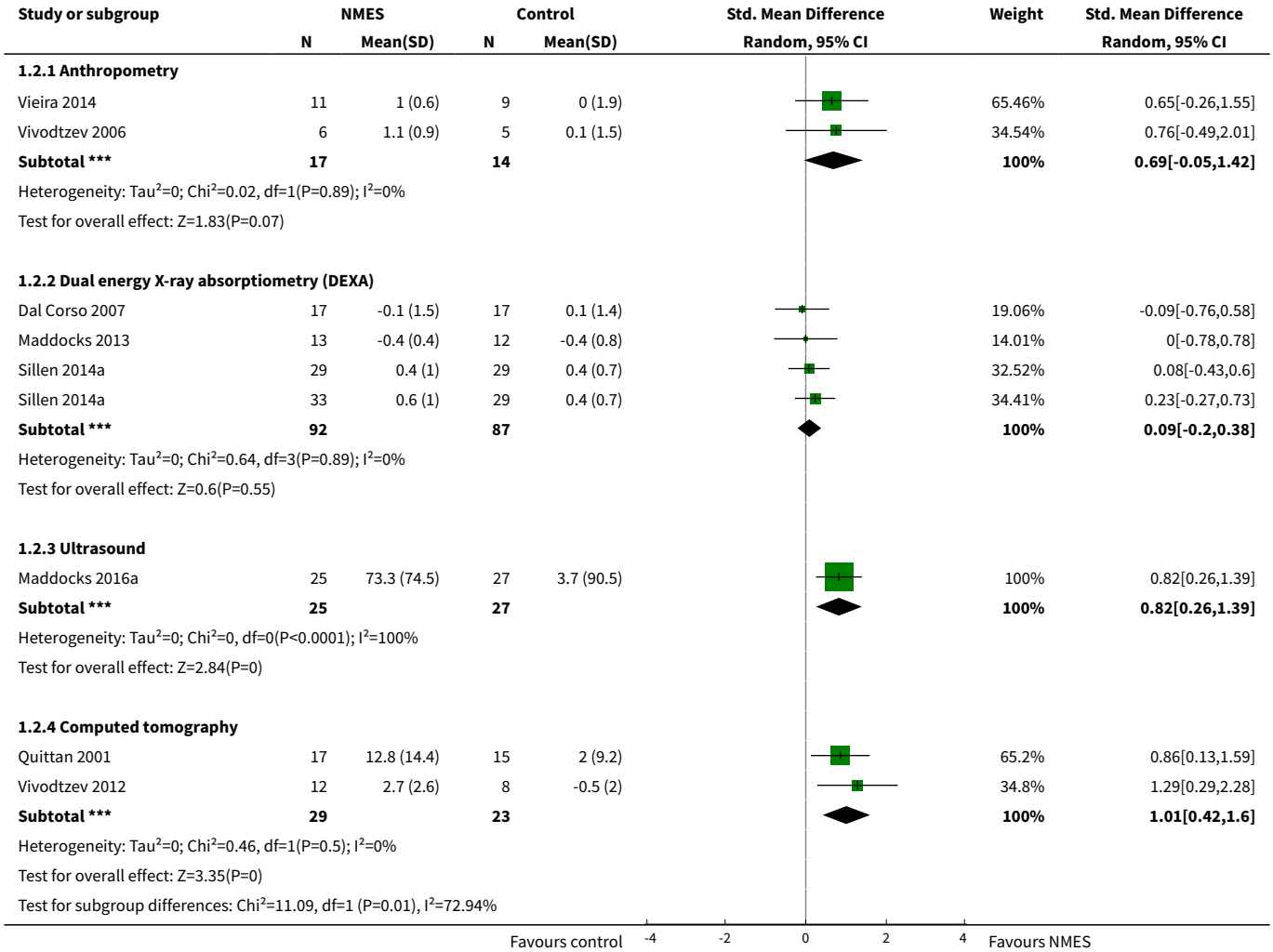
Study or subgroup	NMES		Control		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Abdellaoui 2011	9	8.4 (4)	6	3.5 (3.2)		5.08%	1.24[0.09,2.4]
Bourjeily-Habr 2002	9	10.5 (19.8)	9	3.9 (18.6)		6.42%	0.33[-0.6,1.26]
Greening 2014	196	1.2 (7.6)	193	0.7 (8.3)		12.09%	0.06[-0.14,0.26]
Maddocks 2009a	7	7.4 (10.3)	8	-2 (9)		5.47%	0.92[-0.16,2]
Maddocks 2013	13	0.6 (1.8)	12	-0.5 (1.8)		7.34%	0.59[-0.21,1.4]
Maddocks 2016a	25	3.4 (5.2)	27	0.3 (4.4)		9.37%	0.64[0.08,1.19]
Neder 2002	9	27.4 (32.3)	8	5.2 (16.2)		5.97%	0.81[-0.19,1.81]
Nápolis 2011	30	0.2 (11.2)	30	1.6 (11.8)		9.82%	-0.12[-0.63,0.39]
Quittan 2001	17	21.4 (15.2)	16	-8.9 (11.5)		6.76%	2.18[1.3,3.07]
Sillen 2014a	33	10.8 (16.7)	29	6.1 (10.8)		9.86%	0.33[-0.18,0.83]
Sillen 2014a	29	1.4 (9.7)	29	6.1 (10.8)		9.69%	-0.45[-0.97,0.07]



Favours control — Favours NMES

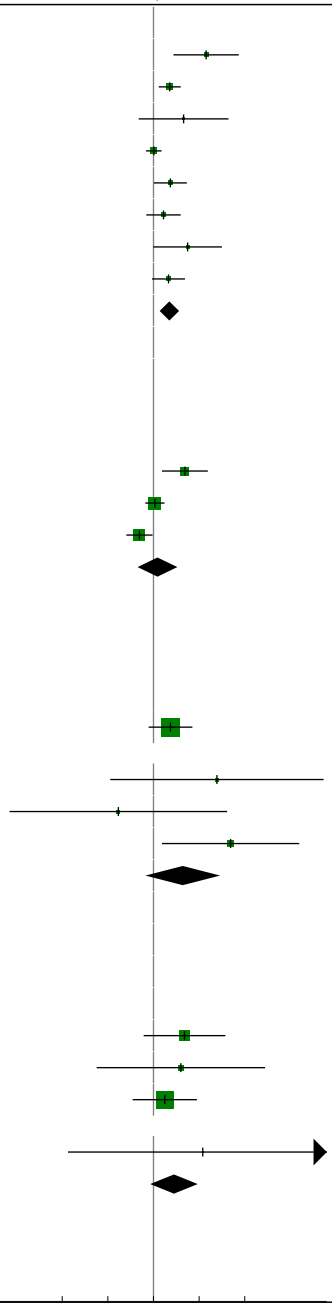


Analysis 1.2. Comparison 1 Neuromuscular electrical stimulation versus control, Outcome 2 Muscle mass.



Analysis 1.3. Comparison 1 Neuromuscular electrical stimulation versus control, Outcome 3 Exercise performance.

Study or subgroup	NMES N	NMES Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.3.1 6-minute walk test (m) (6MWT)							
Abdellaoui 2011	9	181 (94)	6	65.6 (46)		6.52%	115.4[43.8,187]
Maddocks 2016a	25	29.9 (51)	27	-5.7 (35.7)		18.9%	35.6[11.5,59.7]
Nuhr 2004	17	72 (138)	15	6 (145)		3.93%	66[-32.43,164.43]
Nápolis 2011	30	10.2 (28.6)	30	9.5 (37.9)		21.53%	0.7[-16.29,17.69]
Sillen 2014a	33	66 (80.4)	29	29 (64.6)		14.51%	37[0.87,73.13]
Sillen 2014a	29	51 (80.8)	29	29 (64.6)		14%	22[-15.65,59.65]
Vieira 2014	11	75.6 (71.3)	9	0.8 (95.2)		6.07%	74.8[-0.32,149.92]
Vivodtzev 2006	9	63 (40)	9	30 (38)		14.54%	33[-3.05,69.05]
Subtotal ***	**163**		**154**			**100%**	**34.78[13.52,56.05]**
Heterogeneity: Tau^2=471.56; Chi^2=17.48, df=7(P=0.01); I^2=59.96%							
Test for overall effect: Z=3.21(P=0)							
1.3.2 Incremental shuttle walk test (m) (ISWT)							
Bourjeily-Habr 2002	9	68.8 (65.4)	9	0 (40.5)		26.8%	68.8[18.54,119.06]
Greening 2014	196	41 (106.9)	193	38 (105.6)		37.94%	3[-18.12,24.12]
Tasdemir 2015	13	38.4 (41.8)	14	69.2 (33.6)		35.26%	-30.8[-59.54,-2.06]
Subtotal ***	**218**		**216**			**100%**	**8.72[-34.87,52.31]**
Heterogeneity: Tau^2=1187.73; Chi^2=11.68, df=2(P=0); I^2=82.87%							
Test for overall effect: Z=0.39(P=0.69)							
1.3.3 Endurance shuttle walk test (m) (ESWT)							
Greening 2014	196	108.4 (256.8)	193	71.1 (224.8)		58.26%	37.3[-10.64,85.24]
Maddocks 2009a	8	-20 (254)	8	-159 (222)		10.51%	139[-94.76,372.76]
Tasdemir 2015	13	153 (180)	14	230 (415)		10.16%	-77[-315.39,161.39]
Vivodtzev 2012	12	174 (249)	8	5 (76)		21.07%	169[18.6,319.4]
Subtotal ***	**229**		**223**			**100%**	**64.13[-17.79,146.05]**
Heterogeneity: Tau^2=2400.12; Chi^2=4.32, df=3(P=0.23); I^2=30.49%							
Test for overall effect: Z=1.53(P=0.12)							
1.3.4 Cardiopulmonary exercise testing (mL/min) (CPET)							
Bourjeily-Habr 2002	9	52 (114)	9	-16 (76)		33.96%	68[-21.51,157.51]
Neder 2002	9	120 (160)	6	60 (190)		7.99%	60[-124.5,244.5]
Nápolis 2011	28	-13 (136.4)	28	-37.7 (132.3)		54.93%	24.7[-45.68,95.08]
Vieira 2014	11	100 (453)	9	-8 (191)		3.12%	108[-187.36,403.36]
Subtotal ***	**57**		**52**			**100%**	**44.82[-7.34,96.99]**
Heterogeneity: Tau^2=0; Chi^2=0.77, df=3(P=0.86); I^2=0%							
Test for overall effect: Z=1.68(P=0.09)							
Test for subgroup differences: Chi^2=1.97, df=1 (P=0.58), I^2=0%							



APPENDICES

Appendix 1. Search strategies

2016 search strategies

CENTRAL, DARE & CDSR (the Cochrane Library)

#1 MeSH descriptor: [Electric Stimulation Therapy] explode all trees

#2 ((muscle* or muscular or neuromuscular or neuro-muscular) and electric* and stimulat*):ti,ab,kw (Word variations have been searched)

#3 NMES:ti,ab,kw (Word variations have been searched)

#4 #1 or #2 or #3

#5 MeSH descriptor: [Muscle Weakness] this term only

#6 ((muscle* or muscular) and (weak* or fatigue or strength)):ti,ab,kw (Word variations have been searched)

#7 #5 or #6

#8 (advance* near/6 (disease* or illness*)):ti,ab,kw (Word variations have been searched)

#9 MeSH descriptor: [Neoplasms] explode all trees

#10 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour* or metasta* or adenocarcinoma* or lymphoma* or leukemia* or leukaemia*):ti,ab,kw (Word variations have been searched)

#11 MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees

#12 (chronic and obstruct* and (pulmonary or airway* or airflow or lung*)):ti,ab,kw (Word variations have been searched)

#13 COPD:ti,ab,kw (Word variations have been searched)

#14 ((pulmonary or respiratory) near/6 disease*):ti,ab,kw (Word variations have been searched)

#15 MeSH descriptor: [Heart Diseases] explode all trees

#16 (((cardi* or heart) near/6 (disease* or failure)) or CHF):ti,ab,kw (Word variations have been searched)

#17 MeSH descriptor: [HIV] explode all trees

#18 human immunodeficiency virus*:ti,ab,kw (Word variations have been searched)

#19 human immuno-deficiency virus*:ti,ab,kw (Word variations have been searched)

#20 acquired immunodeficiency syndrome*:ti,ab,kw (Word variations have been searched)

#21 acquired immuno-deficiency syndrome*:ti,ab,kw (Word variations have been searched)

#22 (HIV or AIDS):ti,ab,kw (Word variations have been searched)

#23 (#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22)

#24 (#4 and #7 and #23)

MEDLINE (OVID)

1 exp Electric Stimulation Therapy/

2 ((muscle* or muscular or neuromuscular or neuro-muscular) and electric* and stimulat*).mp.

3 NMES.mp.

4 or/1-3

5 Muscle Weakness/

6 ((muscle* or muscular) and (weak* or fatigue or strength)).mp.

7 5 or 6

8 (advance* adj6 (disease* or illness*)).mp.

9 exp neoplasms/

10 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour* or metasta* or adenocarcinoma* or lymphoma* or leukemia* or leukaemia*).mp.

11 exp Pulmonary Disease, Chronic Obstructive/

12 (chronic and obstruct* and (pulmonary or airway* or airflow or lung*)).mp.

13 COPD.mp.

14 ((pulmonary or respiratory) adj6 disease*).mp.

15 exp heart diseases/

16 (((cardi* or heart) adj6 (disease* or failure)) or CHF).mp.

17 exp HIV/

18 human immunodeficiency virus*.mp.

19 human immuno-deficiency virus*.mp.

20 acquired immunodeficiency syndrome*.mp.

21 acquired immuno-deficiency syndrome*.mp.

22 (HIV or AIDS).mp.

23 or/8-22

24 4 and 7 and 23

25 (201207* or 201208* or 201209* or 201210* or 201211* or 201212* or 2013* or 2014* or 2015* or 2016*).ed.

26 24 and 25

Embase (OVID)

1 neuromuscular electrical stimulation/

2 ((muscle* or muscular or neuromuscular or neuro-muscular) and electric* and stimulat*).mp.

3 NMES.mp.

4 or/1-3

5 exp Muscle Weakness/

6 ((muscle* or muscular) and (weak* or fatigue or strength)).mp.

7 5 or 6

8 (advance* adj6 (disease* or illness*)).mp.

9 exp neoplasm/

10 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour* or metasta* or adenocarcinoma* or lymphoma* or leukemia* or leukaemia*).mp.

11 chronic obstructive lung disease/

12 (chronic and obstruct* and (pulmonary or airway* or airflow or lung*)).mp.

13 COPD.mp.

14 ((pulmonary or respiratory) adj6 disease*).mp.

15 exp heart disease/

16 (((cardi* or heart) adj6 (disease* or failure)) or CHF).mp.

17 exp Human immunodeficiency virus/

18 human immunodeficiency virus*.mp.

19 human immuno-deficiency virus*.mp.

20 acquired immunodeficiency syndrome*.mp.

21 acquired immuno-deficiency syndrome*.mp.

22 (HIV or AIDS).mp.

23 or/8-22

24 4 and 7 and 23

25 (201207* or 201208* or 201209* or 201210* or 201211* or 201212* or 2013* or 2014* or 2015* or 2016*).dd.

26 24 and 25

27 random$.tw.

28 factorial$.tw.

29 crossover$.tw.

30 cross over$.tw.

31 cross-over$.tw.

32 placebo$.tw.

33 (doubl$ adj blind$).tw.

34 (singl$ adj blind$).tw.

35 assign$.tw.

36 allocat$.tw.

37 volunteer$.tw.

38 Crossover Procedure/

39 double-blind procedure.tw.

40 Randomized Controlled Trial/

41 Single Blind Procedure/

42 or/27-41

43 (animal/ or nonhuman/) not human/

44 42 not 43

45 26 and 44

PsycINFO (OVID)

1 ((muscle* or muscular or neuromuscular or neuro-muscular) and electric* and stimulat*).mp.

2 NMES.mp.

3 ((muscle* or muscular) and (weak* or fatigue or strength)).mp.

4 (advance* adj6 (disease* or illness*)).mp.

5 exp neoplasm/

6 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour* or metasta* or adenocarcinoma* or lymphoma* or leukemia* or leukaemia*).mp.

7 chronic obstructive pulmonary disease/

8 (chronic and obstruct* and (pulmonary or airway* or airflow or lung*)).mp.

9 COPD.mp.

10 ((pulmonary or respiratory) adj6 disease*).mp.

11 exp heart disorders/

12 (((cardi* or heart) adj6 (disease* or failure)) or CHF).mp.

13 exp Human immunodeficiency virus/

14 human immunodeficiency virus*.mp.

15 human immuno-deficiency virus*.mp.

16 acquired immunodeficiency syndrome*.mp.

17 acquired immuno-deficiency syndrome*.mp.

18 (HIV or AIDS).mp.

19 or/4-18

20 1 or 2

21 3 and 19 and 20

22 limit 21 to yr="2012 -Current"

CINAHL (EBSCO)

S26 S24 AND S25

S25 EM 20120701-20150131

S24 S4 AND S7 AND S23

S23 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22

S22 (HIV or AIDS)

S21 acquired immuno-deficiency syndrome*

S20 acquired immunodeficiency syndrome*

S19 human immuno-deficiency virus*

S18 human immunodeficiency virus*

S17 (MH "Human Immunodeficiency Virus+")

S16 (((cardi* or heart) N6 (disease* or failure)) or CHF)

S15 (MH "Heart Diseases+")

S14 ((pulmonary or respiratory) N6 disease*)

S13 COPD

S12 (chronic and obstruct* and (pulmonary or airway* or airflow or lung*))

S11 (MH "Pulmonary Disease, Chronic Obstructive+")

S10 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour* or metasta* or adenocarcinoma* or lymphoma* or leukemia* or leukaemia*)

S9 (MH "Neoplasms+")

S8 (advance* N6 (disease* or illness*))

S7 S5 OR S6

S6 ((muscle* or muscular) and (weak* or fatigue or strength))

S5 (MH "Muscle Weakness")

S4 S1 OR S2 OR S3

S3 NMES

S2 ((muscle* or muscular or neuromuscular or neuro-muscular) and electric* and stimulat*)

S1 (MH "Electric Stimulation+")

2012 search strategies

MEDLINE, CINAHL, EMBASE, and PsycINFO (Ovid Web)

1. exp Electric Stimulation Therapy/
2. ((muscle* or muscular or neuromuscular or neuro-muscular) and electric* and stimulat*).mp.
3. NMES.mp.
4. 1 or 2 or 3
5. Muscle Weakness/
6. ((muscle* or muscular) and (weak* or fatigue or strength)).mp.
7. 5 or 6
8. (advance* adj6 (disease* or illness*)).mp.
9. exp neoplasms/
10. (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour* or metasta* or adenocarcinoma* or lymphoma* or leukemia* or leukaemia*).mp.
11. exp Pulmonary Disease, Chronic Obstructive/
12. (chronic and obstruct* and (pulmonary or airway* or airflow or lung*)).mp.
13. COPD.mp.
14. ((pulmonary or respiratory) adj6 disease*).mp.
15. exp heart diseases/
16. (((cardi* or heart) adj6 (disease* or failure)) or CHF).mp.
17. exp HIV/
18. human immunodeficiency virus*.mp.

19. human immuno-deficiency virus*.mp.

20. acquired immunodeficiency syndrome*.mp.

21. acquired immuno-deficiency syndrome*.mp.

22. (HIV or AIDS).mp.

23. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22

24. 4 and 7 and 23

British Nursing Index (ProQuest)

1. NMES

2. muscle stimulation

3. neuromuscular electrical stimulation

4. (1 or 2 or 3)

Science Citation Index Expanded (Web of Science)

1. ((muscle* or muscular or neuromuscular or neuro-muscular) and electric* and stimulat*). ti.

2. NMES. ti.

3. 1 or 2

4. (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour* or metasta* or adenocarcinoma* or lymphoma* or leukemia* or leukaemia*). ti.

5. ((chronic and obstruct* and (pulmonary or airway* or airflow or lung*)) or COPD). ti.

6. (((cardi* or heart) adj6 (disease* or failure)) or CHF). ti.

7. (human immunodeficiency virus* or HIV or AIDS). ti.

8. 4 or 5 or 6 or 7

9. 3 and 8

The Cochrane Library (Wiley Online Library)

1. ELECTRIC STIMULATION THERAPY single term (MeSH)

2. RESISTANCE TRAINING single term (MeSH)

3. ((muscle* or muscular or neuromuscular or neuro-muscular) and electric* and stimulat*).ti.

4. (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour* or metasta* or adenocarcinoma* or lymphoma* or leukemia* or leukaemia*)

5. (COPD or chronic and obstruct* and (pulmonary or airway* or airflow or lung*))

6. (((cardi* or heart) adj6 (disease* or failure)) or CHF)

7. HIV or human immunodeficiency virus*

8. 3 and (4 or 5 or 6 or 7)

key: [mp = protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] [ti = title].

WHAT'S NEW

Date	Event	Description
18 October 2016	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 11, 2011
Review first published: Issue 1, 2013

Date	Event	Description
14 March 2016	New citation required but conclusions have not changed	This review is an update of a previously published review in the Cochrane Database of Systematic Reviews Issue 1, 2013. The search for the original review was performed on 1 July 2012. The search period for this update was to 6 January 2016. We identified an additional seven studies involving 715 additional participants (Akar 2015; Greening 2014; Maddocks 2013; Maddocks 2016a; Sillen 2014a; Tasdemir 2015; Vieira 2014). Based on the new findings, we extended our pooled analyses for quadriceps muscle strength (Figure 4) and exercise performance (Figure 6), and completed a further analysis on muscle mass (Figure 5). The updated search has not altered the overall conclusions from the last publication of this review. However, this update includes more data, new analyses, and an assessment of the quality of the evidence using the GRADE approach, and we recommend previous readers of the review should read this update.
14 March 2016	New search has been performed	This review has been updated to include the results of a new search, and 'Risk of bias' tables and a 'Summary of findings' table have been added.

CONTRIBUTIONS OF AUTHORS

All authors were involved in the drafting of the protocol and final review. MM and AW developed the search strategy and searched for and obtained copies of studies for potential inclusion. SJ, WG, AW, and MM selected studies for inclusion, and all authors extracted data from studies and assessed risk of bias. SJ, MM, and WG entered data into Review Manager 5 (RevMan 2014), carried out analyses, and performed the GRADE assessments. All authors interpreted findings and approved the final review manuscript. MM is responsible for conducting any future updates.

DECLARATIONS OF INTEREST

SJ: none known. SJ is a physiotherapist and manages patients with respiratory conditions.

WD-CM is a consultant chest physician and manages patients with respiratory conditions. He has received reimbursement for travel and accommodation costs from Boehringher Ingelheim arising from attendance at the European Respiratory Society Congress meeting in 2013.

WG: none known. WG coauthored one of the studies included in this review (Maddocks 2016a). She was not involved in the data extraction or 'Risk of bias' assessment for this study.

IJH: none known. IJH is a consultant palliative care physician and manages patients with advanced and/or progressive conditions.

AW: none known. AW is a consultant palliative care physician and manages patients with advanced and/or progressive conditions. He coauthored two of the studies included in this review (Maddocks 2009a; Maddocks 2013). He was not involved in the data extraction or 'Risk of bias' assessment for these studies.

MM: none known. MM coauthored three of the studies included in this review (Maddocks 2009a; Maddocks 2013; Maddocks 2016a). He was not involved in the data extraction or 'Risk of bias' assessment for these studies.

SOURCES OF SUPPORT

Internal sources

- Department of Palliative Medicine, Nottingham University Hospitals NHS Trust, UK.

  AW is employed by Nottingham University Hospitals NHS Trust.
- King's College London, Cicely Saunders Institute, Division of Palliative Care, Policy & Rehabilitation, UK.

  MM, WG, and IJH are employed by King's College London.
- Royal Brompton & Harefield NHS Foundation Trust and Imperial College, UK.

  SJ and WD-CM are employed by the Royal Brompton & Harefield NHS Foundation Trust.

External sources

- National Institute of Health Research, UK.

  IJH is a NIHR Senior Investigator. MM is supported by a NIHR post-doctoral fellowship and a NIHR Clinical Trials Fellowship. MM and IJH are supported by the NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) for South London. WD-CM is supported by the NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) for North West London, NIHR Clinician Scientist Award, NIHR Clinical Trials Fellowship, and the NIHR Respiratory Biomedical Research Unit, Royal Brompton & Harefield NHS Foundation Trust and Imperial College, London, UK.
- Cicely Saunders International, UK.

  MM and IJH are supported by Cicely Saunders International.
- Medical Research Council, UK.

  WD-CM is supported by a Medical Research Council (UK) New Investigator Research Grant.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this 2016 updated review we considered study size as a new 'Risk of bias' item to check for possible bias from small study size. We also included GRADE assessments of the quality of the evidence and added a 'Summary of findings' table. We did not include studies examining the acute effects of NMES following a single session.

NOTES

A new search within two years is not likely to identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in five years. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Chronic Disease; Disease Progression; Heart Failure [complications]; Leg; Muscle Strength; Muscle Weakness [etiology] [*therapy]; Muscle, Skeletal [anatomy & histology]; Physical Exertion [physiology]; Pulmonary Disease, Chronic Obstructive [complications]; Quadriceps Muscle [physiology]; Randomized Controlled Trials as Topic; Respiration Disorders [complications]; Thoracic Neoplasms [complications]; Transcutaneous Electric Nerve Stimulation [adverse effects] [*methods]

MeSH check words

Adult; Humans