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Title Page

Effectiveness of combined exercise and nutrition interventions in pre-frail or frail older hospitalised patients: a systematic review and meta-analysis

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Abstract

Objectives: To determine the effectiveness of combined exercise-nutrition interventions in pre-frail/frail hospitalised older adults on frailty, frailty-related indicators, quality of life (QoL), falls and its cost-effectiveness.

Design: Randomised controlled trials (RCTs) of combined exercise-nutrition interventions on hospitalised pre-frail/frail older adults ≥ 65 years were collated from seven databases. Methodological quality was appraised, and data were summarised descriptively or by meta-analyses using a fixed effects model. Standardised mean difference (SMD) or mean difference (MD) with 95% confidence intervals (CIs) was calculated.

Results: Twenty articles (11 RCTs) experimenting exercise-nutrition interventions on hospitalised older adults were included. Nine articles were suitable for meta-analyses. One study had low risk of bias and found improvements in physical performance and frailty-related biomarkers. Exercise interventions were mostly supervised by a physiotherapist, focusing on strength, ranging 2-5 times/week, of 20-90 minutes duration. Most nutrition interventions involved education and supplementation but had dietitian supervision in only three studies. Meta-analyses suggest that participants who received exercise-nutrition intervention had greater reduction in frailty scores (n=3, SMD 0.25; 95% CI 0.03-0.46; P=0.02) and improvement in short physical performance battery (SPPB) scores (n=3, MD 0.48; 95% CI 0.12-0.84; P=0.008) compared to standard care. Only chair-stand test (n=3) out of the three SPPB components was significantly improved (MD 0.26; 95% CI 0.09-0.43; P=0.003). Patients were more independent in activities of daily living in intervention groups, but high heterogeneity was observed (I^2=96%, P<0.001). The pooled effect for handgrip (n=3) +/- knee extension muscle strength (n=4) was not statistically significant. Nutritional status, cognition,

biomarkers, QoL, falls and cost-effectiveness were summarised descriptively due to insufficient data.

Conclusions: There is evidence, albeit weak, showing that exercise-nutrition interventions are effective to improve frailty and frailty-related indicators in hospitalised older adults. Robust research that pays attention to effect of assignment to intervention is needed to increase the confidence in results.

PROSPERO registration number: CRD42020153934

Strengths and limitations of study

- This is the first comprehensive systematic review with meta-analysis on the effectiveness of exercise-nutrition interventions on frailty and outcomes related to frailty in hospitalised and pre-frail/frail older adults.
- Only randomised controlled trials describing existing exercise-nutrition interventions in frail older hospitalised patients were included.
- There was a moderate risk of bias for most included studies such that the findings of this review are inconclusive, making it difficult to draw firm conclusions.

Introduction

Frailty is a major contributor to late-life disability as it leads to loss of independence.[1] It is also associated with poor health outcomes, and, increased health-care costs and service use.[1] Frailty has been defined for clinical research by Fried et al[2] as a combination of unintentional weight loss, weakness, exhaustion, slowness and reduced physical activity. Older adults (aged >65 years) that have been classified as frail and are hospitalised, have a three-fold higher risk of readmission or death, as compared to the younger population.[3] The management of older adults who are frail has an incremental effect on health expenditures with an additional equivalent of

AU$2400 per frail patient per year.[4] With 21% of the population over 65 years estimated to be frail and 48% estimated to be pre-frail, concerns of economic impact are compounded by an ageing population.[5]

Exercise and nutrition are inextricably linked, in particular strength training can address component issues of the frail phenotype.[6] Yet evidence supporting the effectiveness of exercise-nutrition interventions for reversal of frailty is limited to community-dwelling older adults.[7] In a study of community participants, a 3-month combined exercise-nutrition intervention resulted in a significant reversal of frailty (reduction in Fried frailty score) at 6-months, compared to the control group (between-group difference −0.34; 95% confidence interval [CI] -0.52 to −0.16; $P < 0.001$).[8] The combination of exercise therapy and dietary intervention in older adults who are frail, has also been reported to increase muscle strength (knee extension between-group difference 1.84 kg, 95% CI 0.17–3.51, $P = 0.03$)[9] and improve nutritional status (Mini Nutritional Assessment (MNA) Short Form between group difference 1.4, 95% CI 0.9-1.9, $P < 0.01$).[10]

A recent meta-analysis suggested that although effective, exercise combined with nutrition was not more effective in treating frailty than exercise alone.[11] However, the majority of included studies were conducted in a community setting, with only 15% of older adults either hospitalised or recruited from acute care settings. No study has systematically evaluated evidence for interventions that commence during acute hospitalisation or early post discharge (in the high-risk period for post-hospital syndrome).

Hospitalisation is a vulnerable period, especially for older adults who are frail and therefore at higher risk of functional loss,[12] malnutrition[13, 14] and further decline in frailty status. Malnutrition is ubiquitous in older hospitalised patients with a prevalence as high as 50%.[15] Since many domains of frailty are attributed to poor nutrition,[16] the effect of nutrition intervention when combined with exercise, may be more significant in the hospitalised population.[16] Nutritional therapy extends beyond protein or nutrition supplementation as reported in previous studies and may be more effective as part of individualised medical nutrition therapies involving dietitians to improve diet adequacy.[17]

This study aims to determine the effectiveness of combined exercise-nutrition interventions on (1) frailty, (2) frailty-related indicators, falls, quality of life (QoL) and (3) its cost effectiveness on pre-frail or frail hospitalised older adults.

Materials and Methods

Protocol and registration

The protocol for this review was compliant with Cochrane systematic review guidelines,[18] and registered with the International Prospective Register of Systematic Reviews (PROSPERO), CRD42020153934. The study is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] Patients and/or members of the public were not involved in this study.

Search methods

Systematic searches of electronic databases (Medline, Emcare, CINAHL, Ageline, Scopus, Cochrane and PEDro) were conducted by the lead author (CH) from inception until 10th October 2019 using search strategies reviewed by an academic librarian (search queries available in Supplementary file 1). Additionally, related citations to eligible items were identified using the suggested related citation function in Pubmed. Reference lists of eligible items were also screened.

Inclusion and exclusion criteria

The inclusion criteria were: 1) randomised controlled trials; 2) inclusion of pre-frail or frail participants (as defined by study authors); 3) recruitment of older adult inpatients and/or those hospitalised within the past 30 days of recruitment; 4) interventions that started while patients were admitted and continued in the community/post-hospitalisation, or, commenced within 30 days of hospital discharge; 5) interventions that involved both physical exercises and nutritional interventions (dietary modifications/education/training alone or combined with oral nutrition supplementation); 6) measured frailty with an assessment tool or at least one indicator relevant to frailty (nutritional status, physical function, cognitive function and mood, physical activity level or biomarkers, falls and QoL and/or economic analysis of interventions. Studies were excluded if they described protocols with no pilot outcomes, interventions delivered as a part of a palliative care program, or interventions solely designed to facilitate discharge planning (e.g. telephone support services, providing no pre-frailty or frailty intervention element). Studies that recruited participants admitted following a mental health episode were also excluded.

Study selection and data extraction

Covidence[20] was used to manage citations for title and abstract, and full-text screening, in duplicate (CH and YS, supplement 1). The reviewers were unblinded to authors, journals and countries of origin. Any disagreement was resolved through discussion or consensus opinion with the other authors. A data extraction form was developed a priori by the research team, such that two researchers (CH and YS) performed data extraction independently, on eligible full-text articles. Where available, continuous data were extracted as (i) mean change with standard deviation (SD), standard error of mean (SE) or 95% confidence interval (CI), or (ii) mean or median values with SD, SE or interquartile range post intervention. If required data were not reported within a publication (including change in means for outcomes of interest), corresponding authors were emailed to request for it.

Quality of the studies

The risk of bias in the individual studies was assessed by the Revised Cochrane risk-of-bias tool for randomised trials (RoB-2) by two researchers (CH and YS) independently.[21] Any disagreements were resolved by discussion or if required with consensus of a third reviewer. The Cochrane risk-of-bias tool is widely used to assess randomised controlled trials (RCT) for best practice.[22] Studies were given an overall risk-of-bias judgement of low, some concerns or high. Overall risk-of-bias was determined as having "some concerns" if any one of the risks of bias domains was rated as having "some concerns". Likewise, studies were deemed to have an overall high risk of bias if any one domain had a high risk of bias.

Data synthesis and statistical analyses

Where possible, meta-analysis was performed; continuous outcome data were pooled and either mean difference (MD) or standardised mean difference (SMD) with 95% CI reported if there were two or more studies. Studies presenting SE were converted to SD via the conversion formula.[18] Fixed-effect meta-analyses were carried out with Cochrane Review Manager (RevMan) 5.3.[23] A P value of <0.05 was considered statistically significant. The variability between studies (heterogeneity) was assessed by I^2 and its 95% CI.[24] For studies with unobtainable missing, or incomparable data, results were qualitatively synthesised.

Patient and public involvement

No patients were involved in this study

Results

Study selection

The flow of studies through the review process is summarised in Figure 1. Twenty articles reporting on 11 studies were eligible for data synthesis and analysis. Three of 11 studies presented results from their cohort across separate publications. Firstly, Villareal et al[25] reported on physical functioning outcomes with biomarker results in the publication of Armamento-Villareal et al.[26] Secondly, Cameron et al[27] reported on frailty and some physical function outcomes, with other physical function outcomes in a secondary publication[28] fall rates[29] and cost-analysis in another.[30] Thirdly, Luger et al[31] reported on frailty and nutritional status, with physical functioning outcomes across two other publications,[32, 33] fall efficacy[34] and quality of life.[35] For clarity, the primary articles that report frailty or physical function outcomes are cited for descriptive data in Tables 1-3 while individual articles are cited for synthesis of outcome results.

Study and sample characteristics

Details of study characteristics are available in Table 1. Across all studies, a total of 2307 participants were investigated. Most studies reported that patients were recruited from hospital wards (n=7)[27, 36-41] while the other four studies[25, 31, 42, 43] included patients that were recruited from hospital wards and community. Seven studies included only frail participants,[25, 27, 38-41, 43] and the remaining four studies[31, 36, 37, 42] included frail, pre-frail and non-frail participants. The Fried frailty phenotype criteria[2] were used most frequently to classify frailty (n=4).[27, 36, 37, 42] with participants considered non-frail, pre-frail or frail if 0, 1-2, 3-5 criteria were present, respectively. Luger et al used the Frailty Instrument for Primary Care of the Survey of Health, Ageing, and Retirement in Europe (SHARE-FI)[31] which integrates components of exhaustion, appetite, handgrip strength, walking difficulties and physical activity.[44] Five studies did not report any assessment method to define frailty.[38-41, 43] One study used a combination of three tools – modified Physical Performance Test, the measurement of VO_2 peak, and the Functional Status Questionnaire.[25]

Table 1. Characteristics of included studies examining pre-frail or frail hospitalised older adults

Study	Country	n	Mean age	Study participants, characteristics	Recruitment site	Duration of intervention	Follow-up period	Frailty diagnostic tool/criteria used	Reported % of prefrail, frail
Arrieta *et al*, 2019[35]	France	302	76.7 ±5.0	Frail, onco-geriatric, older men & women; BMI: 26.1 ±4.6 kg/m^2 (UCG); 26.2 ±4.4 kg/m^2 (IG)	Acute hospital	1y	1y, 2y	Fried frailty phenotype criteria	Non-frail: 73.6% Frail: 26.4%
Rodriguez-Manas *et al*, 2019[41]	Spain	964	78.0 ±5.44	Frail older men and women with T2DM; BMI: 29.6 ±5.0 kg/m^2	Acute hospitals or primary care sites	4.5m (exercise), 3.5-4w (nutrition)	1y	Fried frailty phenotype criteria	Pre-frail: 62.2% Frail: 37.8%
Niccoli *et al*, 2017[36]	Canada	47	81.3 ±1.0	Frail older men and women hospitalised patients; BMI: 26.4 ±6.6 kg/m^2 (UCG), 24.2 ±5.2 kg/m^2 (IG)	Acute hospital	Average LOS (days): 20.9 (UCG), 26.5 (IG)	Upon discharge	Fried frailty phenotype criteria	Pre-frail: at least 87.8% Frail: NR
Luger *et al*, 2016*[30]	Austria	80	82.8 ±8.0	Frail older men and women; BMI: 27.2 ±4.3 kg/m^2	Acute hospital and community	3m	3m	SHARE-FI (female>0.315; male: >1.212 points)	Non-frail: 1% pre-frail: 35%, frail: 64%
Milte *et al*, 2016[37]	Australia	175	83.0 ±6.2 (UCG), 82.4 ±5.7 (IG)	Frail older men and women post hip fracture, BMI: NR	Acute hospital	6m	6m	NR	Frail: 100% as determined by study authors
Cameron *et al*, 2013†[26]	Australia	241	83.3 ±5.9	Frail older men and women, BMI: 26.4 ±6.0 kg/m^2 (UCG) 26.1 ±5.9 kg/m^2 (IG)	Acute hospital	1y	3m, 1y	Fried frailty phenotype criteria	Frail: 100% as determined by study authors
Singh *et al*, 2012[38]	Australia	124	79.3 ± 9.6	Frail older men and women; BMI: NR	Acute hospital	1y	4m, 1y	NR	Frail: 100% as determined by study authors
Villareal *et al*, 2011‡[24]	United States	107	69.3 ±4.1	Frail obese older men; BMI: 36.8 ±4.6 kg/m^2	Acute hospital and community	1y	6m, 1y	≥2 criteria: Modified PPT score 18–32; VO^2 peak of 11–18 ml ml/kg; difficulty in performing 2 IADL or 1 basic ADL	Mild-moderate frailty: 100%

Azad *et al*, 2008[42]	Canada	91	74.2 and 75.8	Frail CHF older women; BMI: NR	Acute hospital and community	6 weeks	6w, 6m	Screened by a CHF coordinator, frailty assessment undefined	Frail: 100% as determined by study authors
Blanc-Bisson *et al*, 2008[39]	France	76	85.4 ±6.6	Frail older men and women; BMI: 24.0 ±5.1 kg/m²	Acute hospital	Until clinical stability	Clinically stable, 1m	NR	Frail: 100% as determined by study authors
Miller *et al*, 2006[40]	Australia	100	83.5 ±2.8	Frail older men and women with LL fracture; BMI: 22.1 ±4.3 kg/m² (ACG), 23.2 ± kg/m² (IG)	Acute hospital	3m	3m	NR	Frail: 100%

Abbreviations: *BMI, Body Mass Index; w, Weeks; m, Months; y, Years; VO^2 max, maximal oxygen uptake; PPT, physical performance test; IADL, Instrumental Activities of Daily Living; ADL, Activities of Daily Living; SHARE-FI, Survey of Health, Ageing and Retirement in Europe-Frailty Instrument; T2DM, Type 2 Diabetes Mellitus; CHF, Chronic Heart Failure; LL, Lower Limb, LOS, length of stay; IG, Intervention group; UCG, Usual care group; ACG, Attention control group; NR, not reported; BMI presented in Mean ±standard deviation*

Multiple articles reported from same study, study chosen to represent other reports from the same study: *Luger et al[31] – Haider et al 2017[32], Winzer et al 2019[33], Kapan et al 2017[34], Kapan et al 2017[35]; †Cameron et al 2013[27] – Fairhall et al 2012[28], Fairhall et al 2014[29], Fairhall et al 2015[30]; ‡Villareal et al 2011[25] – Armamento-Villareal 2016[26]

Table 2. Assessment of methodology quality of included studies using Cochrane Risk of Rias 2.0 tool

Study	Cochrane Risk of Bias 2.0 tool assessment domains					
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Arrieta *et al*, 2019[35]	+	?	?	?	+	?
Rodriguez-Manas *et al*, 2019[41]	+	?	+	?	+	?
Niccoli *et al*, 2017[36]	?	?	+	?	+	?
Luger *et al*, 2016*[30]	+	+	+	?	+	?
Milte *et al*, 2016[37]	+	?	+	+	+	?
Cameron *et al*, 2013†[26]	+	?	+	+	+	?
Singh *et al*, 2012[38]	+	?	+	—	+	—
Villareal *et al*, 2011‡[24]	+	+	+	+	+	+
Azad *et al*, 2008[42]	+	?	+	?	+	?
Blanc-Bisson *et al*, 2008[39]	+	?	+	?	+	?
Miller *et al*, 2006[40]	+	?	+	+	+	?

Key: + = Low risk of bias; ? = Some concerns of risk of bias; — = High risk of bias
[a]Deviations from intended interventions (effect starting and adhering to intervention)
Multiple articles reported from same study, study chosen to represent other reports from the same study: *Luger et al[31] – Haider et al 2017[32], Winzer et al 2019[33], Kapan et al 2017[34], Kapan et al 2017[35]; †Cameron et al 2013[27] – Fairhall et al 2012[28], Fairhall et al 2014[29], Fairhall et al 2015[30]; ‡Villareal et al 2011[25] – Armamento-Villareal 2016[26]

Risk of bias within individual studies

Table 2 outlines the risk of bias in individual studies. One study[25] had a low risk of bias and one study had a high risk of bias (including unblinded secondary outcome assessment and insufficient detail on standard care in control groups across recruitment sites). The other nine studies[27, 31, 36-38, 40-43] were rated as having some concerns overall, of which five could have been improved in ≥1 domain. The remaining four studies[27, 31, 39, 41] that were rated as having "some concerns" overall, had risk in only one domain with the most common reason being failure to blind intervention/allocated group to participants. Examples of other concerns about risk of bias included: assessors being aware of the group allocation[31] (measurement of outcomes domain); or a lack of information about participants/researcher blinding to group allocation.[25, 27, 42]

Characteristics of exercise intervention component

Characteristics of the exercise interventions used in studies are outlined in Table 3, and included combinations of the following: supervised individual exercises (n=10),[25, 27, 36-43] group exercises (n=3),[25, 39, 43] education including support with resources (digital versatile disc (DVD) or visual aid instruction booklet, n=2),[31, 36] and motivational interviewing using a standardised protocol (n=1).[31] Three studies[37, 40, 42] had inpatient only interventions, five[36, 38, 39, 41, 43] had interventions that extended from inpatient to post-discharge, two[27, 31] studies offered the intervention post-discharge only and one[25] did not report.

In the majority of studies (n=9), the exercise component was delivered by a physiotherapist.[25, 36-43] Two studies used trained fitness instructors,[36, 39] and another engaged lay volunteers who received training for the study.[31] All studies included strength exercises as part of their interventions. Three studies described guidance on training intensity based on repetition maximum's (RM) between 40-80%.[25, 39, 42] Other components of exercise programs included

Table 3. Characteristics of exercise and nutrition intervention and controls of included studies

Study	Exercise intervention	Nutrition intervention	Control intervention
Arrieta *et al*, 2019[35]	**Type:** *Strength* **–** Intensity range from low to high, starting at 10 repetition per exercise **(UL, LL)** with option of progressive loading *Aerobic, Flexibility, Balance* **–** intensity individualised **Frequency:** 2 sessions/week, duration per session NR + home exercises duration NR **Setting:** Inpatient (supervised, individual) + post-discharge (unsupervised, individual) **Additional support reported:** Phone consults (by trainer 2x/month for first 6 months then monthly for 1 year); Education resource	**Self-guided education resource:** Provided with French National Nutrition Health Program education booklet - *Programme National Nutrition Santé* (PNNS)	**Usual care:** NR, variable between study sites **Self-guided education resource:** Provided with French National Nutrition Health Program education booklet - *Programme National Nutrition Santé* (PNNS)
Rodriguez-Manas *et al*, 2019[41]	**Type:** *Strength* – 40-80% of estimated 1RM, 8–10 repetitions **(LL)** **Frequency:** 2-weeks pretraining followed by 16-week program of 2 days/week; 20-30 minutes/sessions **Setting:** Inpatient (supervised, individual)	**Nutrition consultation/education:** 7 educational sessions, each 45 minutes, delivered by a trained researcher or nutritional therapist, twice a week over 3.5-4 weeks. Therapy focused on behavioural change, nutrition optimisation and diabetes.	**Usual care:** usual health care from local health system and/or general practitioner
Niccoli *et al*, 2017[36]	**Type:** *Strength, Aerobic, Flexibility, Balance* – intensity and target muscle group individualised based on patient's baseline assessment **Frequency:** individualised based on patient's baseline assessment **Setting:** Inpatient (supervised, individual)	**Supplements:** Daily ONS with 24g whey protein per day (*9g breakfast, 7.5g at lunch and dinner*) in addition to usual diet	**Usual care:** usual medical care, no whey protein supplementation. **Individual supervised exercise**: Individualised exercises as per intervention.
Luger *et al*, 2016*[30]	**Type:** *Strength* –2 sets of 15 repetitions **(UL, LL)** until muscular exhaustion, **Frequency:** 2x/week, >30 minutes each session **Setting:** Post-discharge (supervised, individual) **Additional support reported:** Physical education (2-3 times/week, 30 minutes each session); Exercise education resource (demonstration DVD); Motivational interviewing.	**Nutrition consultation/education** Trained lay volunteers visit twice/week for dietary discussions aimed at achieving adequate energy, protein and other nutrients. Taught how to enrich food with protein, recipes, healthy for life plate which consists of food-cards and a play board. **Motivational interviewing**: Techniques utilised with nutrition goal setting and tools to reinforce self-efficacy.	**Usual care with attention control:** Trained lay "buddies" visit twice a week but doing a portfolio of possible activities (go out, have a chat, and sharing interest), especially cognitive training
Milte *et al*, 2016[37]	**Type:** *Strength, Balance (Otago exercise program)* – Intensity and repetitions NR, at the discretion of the treating physiotherapist **(LL)**	**Nutrition consultation/education:** Individualised nutrition therapy aimed at	**Usual care:** Usual rehabilitation program recommended during hospitalisation, social visits

	Frequency: 3 times/week, 20-30minutes/session for 12 weeks **Setting:** Inpatient (supervised, individual) + post-discharge (supervised, individual)	improving energy and protein intake to meet requirements by dietitian who visits fortnightly. **Meal program:** ordered as deemed necessary by dietitian. **Supplements:** commercial ONS recommended if needed by dietitian	weekly from trial staff and generic nutrition, exercise and falls prevention information
Cameron *et al*, 2013†[26]	**Type:** *Strength, Balance, Aerobic + WEBB program* – intensity and target muscle groups NR **Frequency:** Exercises prescribed 3-5x/week (with 2 sessions for mobility training) for 1 year, supported by up to 10 home visits **Setting:** Post-discharge (supervised, individual) + (unsupervised, individual)	**Nutrition consultation/education:** Clinical evaluation of nutritional intake at home. A series of diet intervention as needed by dietitian. **Meal program:** ordered as deemed necessary by dietitian. **Supplements:** commercial ONS recommended if needed by dietitian	**Usual care:** usual health care during hospitalisation and from their general practitioner and community services after discharge
Singh *et al*, 2012[38]	**Type:** *Strength* **–** 80% of most recent 1RM or RPE <15, 3 sets of 8 repetitions **(UL, LL)** **Frequency:** 2 sessions/week, session duration NR, over average of 80 sessions in 1 year, start as early as post assessment in hospital or at home. **Setting:** Inpatient (supervised, individual) + (supervised, group-based) **Additional support reported:** Monthly phone consults	**Nutrition consultation/education:** Counselling on increase in diet quality, frequency NR **Supplements:** ONS +/- dietary advice to increase daily energy (400-600 kcal) and protein (20 g/day) intake. For those calcium or vit-D deficient (52%), 12 months of vit-D orally (1000 IU/day) or calcium (1200 mg/d) and vit-D combination supplement **Self-guided nutrition resource:** Food sources of calcium, vitamin D and sun exposure	**Usual care:** standard service offered for hip fracture in the area health service, including orthogeriatric care, rehabilitation service, other medical and allied health consultation as required, and physiotherapy.
Villareal *et al*, 2011‡[24]	**Type:** *Strength* **–** 65% of 1RM; 8-12 repetitions of each exercise **(UL, LL)** with options for progression *Aerobic,* ~65% of peak HR with gradual progression to 70-85% *Flexibility, Balance* **Frequency:** 90 minutes, 3 sessions/week **Setting:** Inpatient (supervised, group-based)	**Nutrition consultation/education:** prescribed a balanced diet with energy deficit of 500-750 kcal/d from daily energy requirement, 1 g of high-quality protein/kgbw/d. Weekly group consultation with dietitian for adjustments of their caloric intake, goals and behavioral therapy. **Supplements:** 1500 mg of calcium/d day and ~1000 IU vitamin D/d	**Usual care:** General healthy lifestyle advice **Supplements:** 1500 mg of calcium/d day and ~1000 IU vitamin D/d
Azad *et al*, 2008[42]	**Type:** 'Comprehensive exercise program'; type, intensity and target muscle groups NR **Frequency:** 11 sessions over 6 weeks + NR home exercises **Setting:** Inpatient (supervised, group-based), post-discharge (unsupervised, individual)	**Nutrition consultation/education:** 3 sessions of individualized counselling about diet and nutrition in the management of CHF by dietitian	**Usual care:** Optimal medical care

Blanc-Bisson *et al*, 2008[39]	**Type:** *Strength* **–** intensity (RM) NR, 10 x repetitions each exercise **(LB)** **Frequency:** 30 minutes, twice/day, five days/week **Setting:** Inpatient **(**supervised, individual)	**Meal program:** Geriatric hospital meals of 1800-2000 kcal/d **Supplements:** 1 daily ONS of 200 kcal and 15g protein	**Usual care:** From day 3 to 6, patients started to walk with human help with or without technical assistance in the physiotherapy room for three sessions per week until discharge. **Individual supervised exercise:** Physiotherapy continued at home for one month.
Miller *et al*, 2006[40]	**Type:** *Strength* – intensity (RM) NR, 2 sets of 8 repetitions (**LL**) with progressive loading, at the discretion of the treating physiotherapist **Frequency:** 3 times/week, 20-30minutes/session for 12 weeks **Setting:** Inpatient (supervised, individual) + Post-discharge (supervised, individual)	**Nutrition consultation/education:** Individualised nutrition therapy by dietitian. **Supplements:** single type of ONS to cover the shortfall between individual estimated energy and protein requirements and actual intake over 42 days.	**Usual care with attention control group** - received tri-weekly visits weeks 1-6, then weekly visits 7-12 to account for the possibility of the attention effect.

Abbreviations: *UL, Upper Limb; LL, Lower Limb; NR, not reported; HR, Heart Rate; CHF, Chronic Heart Failure; ONS, Oral Nutrition Supplements, RM, Repetition Max; DVD, Digital Versatile Disc; WEBB, Weight-Bearing for Better Balance exercise program is designed to improve mobility, increase physical activity and prevent falls; Otago exercise program - series of 17 strength and balance at-home exercises for fall prevention program in frail older adults.*

Multiple articles reported from same study, study chosen to represent other reports from the same study: *Luger et al[31] – Haider et al 2017[32], Winzer et al 2019[33], Kapan et al 2017[34], Kapan et al 2017[35]; †Cameron et al 2013[27] – Fairhall et al 2012[28], Fairhall et al 2014[29], Fairhall et al 2015[30]; ‡Villareal et al 2011[25] – Armamento-Villareal 2016[26]

aerobic fitness,[25, 27, 36, 37] flexibility,[25, 36, 37] and/or balance.[25, 27, 36, 37]. The frequency of interventions ranged from two[31, 36, 39, 42, 43] to five[27, 40] sessions a week, lasting between 20[38, 41, 42] to 90 minutes[25] each. The duration of exercise intervention varied from six weeks[43] to one year.[25, 27, 36, 39]

Characteristics of nutrition intervention component

Characteristics of the nutritional interventions used in studies, are outlined in Table 3, and included combinations of the following: nutrition consultation/education (n=8),[25, 27, 31, 38-41, 43] oral nutrition and/or multivitamin/mineral supplements (n=7), [25, 27, 37-41] meal programs (n=3),[27, 38, 40] self-guided education materials (n=2),[36, 39] and motivational interviewing (n=1).[31] The most common combination of nutrition intervention was consultation/education with oral nutrition and/or multivitamin/mineral supplements (n=5).[25, 38, 41, 43] Five of nine nutrition consultation/education interventions were performed by dietitians.[25, 38, 41, 43] Other studies used trained lay volunteers,[31] a researcher/nutrition therapist or did not specify a skill set for who delivered the consultation/education.[42]

All counselling/education-based interventions aimed to achieve adequate dietary targets for energy, protein and other nutrients. One study on obese frail participants aimed for calorie deficit but ensured that all achieved 1g/kg/day of protein in the intervention group.[25] The reported frequency of consultations ranged from twice a week[31, 42] to fortnightly.[38, 41] Oral nutrition supplements (ONS) were the most common supplements prescribed to intervention group participants (n=7),[25, 37, 38, 40, 41, 43] typically providing 200-300kcal and 12-24g protein per serve with a frequency of consumption up to seven times a week[37, 40] or as prescribed by dietitians[25, 38, 41, 43] to cover any identified deficits between individually estimated energy and protein requirements and actual intake. Calcium and vitamin D were the two most commonly supplemented micronutrients [25, 39] at doses in the range of 1200-1500mg/d and 1000IU/d, respectively. Meal programs were either delivered as inpatient specialised geriatric meals providing 1800-2000kcal/d or home-delivered meal programs.[27, 38, 40]

Frailty outcomes

Data on frailty outcomes were available for quantitative analysis from three studies.[27, 31, 37] The meta-analysis is presented in Figure 2 and suggested that participants who received exercise-nutrition intervention had a greater reduction in frailty score compared to those who received standard care (SMD 0.25; 95% CI 0.03-0.46; P=0.02); no heterogeneity was observed (I^2=0%; P=0.58).

Physical functioning outcomes

Short Physical Performance Battery (SPPB)

Data on the SPPB were available for quantitative analysis from 3 studies, [27, 42, 45] with results from meta-analysis presented in Figure 3. Participants who received exercise-nutrition intervention had a statistically significant improvement in SPPB score, compared to those that received standard care (MD 0.48; 95% CI 0.12-0.84; P=0.008), with moderate heterogeneity[18] observed (I^2 = 52%; P=0.13).[20, 32, 33] The analysis of SPPB components across all studies showed no statistically significant differences in gait speed[27, 37, 42, 45] (MD 0.02; 95% CI -0.02 to 0.06; P = 0.31; I^2 = 37%, P = 0.[19]) or balance [27, 42, 45] (MD 0.13; 95% CI -0.04 to 0.30; P=0.14; I^2=0%, P =0.22) between groups. There were significantly greater improvements in chair stand test results[27, 42, 45] in the intervention group as compared to the control (MD 0.26; 95% CI 0.09-0.43; P=0.003; I^2 = 23%, P=0.23). Two studies that were not suitable for meta-analysis and are instead qualitatively described. Arrieta et al reported no significant differences between groups in the percentage of participants who had a ≥1 point decrease in SPPB score at one and two years (P=0.772, P=0.057, respectively).[36] With use of an alternative measure of physical function (modified physical performance test), Villareal at al[25] reported a significant improvement in their exercise- nutrition interventions group as compared to exercise only (P=0.04), nutrition only (P<0.001), or controls.

Activities of daily living

Data on activities of daily living (ADL) from four studies[28, 33, 39, 42] underwent meta-analysis, from which participants who received exercise-nutrition intervention were determined to have greater ADL independence post-intervention than those who received standard care (SMD 0.92; 95% CI 0.78-1.05 to 0.85; P<0.001, Figure 3). However, high heterogeneity was observed (I^2=96%, P<0.001). Results from two studies[40, 43] were unable to be included meta-analysis (data unavailable).

Muscle strength

Meta-analysis showed no statistically significant differences in muscle strength between participants who received exercise-nutrition intervention and those that received standard care, when handgrip strength was analysed from three studies[27, 37, 45] (MD 0.46; 95% -0.38 to 0.85; P = 0.28; I^2 = 49%, P = 0.14), or, when of handgrip and quadriceps strength was combined (n=4 studies)[27, 37, 42, 45] using a published methodology[46] (SMD 0.10; 95% CI -0.09 to 0.29; P=0.24, I^2=28%, P=0.30) (Figure 3).

Nutrition, Cognition and Biomarkers outcomes

Most studies assessed participants' nutritional status at baseline, while only one study[31] assessed it as an outcome. Luger et al reported a 1.54-point improvement in the MNA long form in participants who received exercise-nutrition intervention compared to those who received standard care (95% CI 0.51-2.56, P=0.004). Combined exercise-nutrition intervention did not affect cognitive status (mini-mental state examination (MMSE)) or mood (geriatric depression scale (GDS)).[43] Armamento-Villareal et al reported a significant decrease in total and free estradiol in their frail obese older men (attributed to weight loss from lifestyle change rather than the intervention), without a clinically meaningful increase in total or free testosterone levels.[26] In one study that reported C-reactive protein (CRP) levels, this inflammatory marker remained stable in the exercise-nutrition intervention group participants, compared to an increase in the social support control group at the end of 12 weeks (P=0.04).[47]

Quality of life and falls

Three studies[30, 35, 38] that evaluated quality of life could not find statistically significant improvement in the intervention as compared to the control group though Milte el al[38] found a trend favouring intervention. Fairhall et al[29] found that risk factors related to falls (physical tests as mentioned above) but not rate of falls were reduced while Kapan et al[34] found that a 10% reduction in fear of falling as ascertained by the falls efficacy scale.

Economic analyses

Only two studies examined the cost-effectiveness of their exercise-nutrition intervention. Fairhall et al[30] reported no additional resource cost in terms of medical (P=0.87) or nursing and health professional appointments (P=0.32). Similarly, Milte et al[38] reported no cost differences between groups (P=0.868).

Discussion

Main findings

The present systematic review and meta-analysis present updated evidence that suggest exercise with nutrition intervention to be effective on frailty and frailty-related physical outcomes in hospitalised older adult patients. When compared to standard care, combined exercise-nutrition interventions improved frailty status as determined by the Fried Frailty criteria [2] and the SHARE-FI.[44] They also improved physical function according to the SPPB and ADLs. One study found significant improvement in nutrition score.[31] The two economic analyses included in this review suggested that combined exercise-nutrition interventions, though more effective, were no more costly than standard care.

Existing reviews of exercise and nutrition interventions have highlighted heterogeneity in study protocols (including intervention descriptions), which limits potential for meta-analysis. They have also focussed on community dwelling participants.[48] This study is novel in reviewing a more vulnerable hospitalised population that has not been previously investigated, and specifically targeting pre-frail or frail older adults. However, only three studies in this review used a validated assessment tool and were included in the meta-analysis of frailty as an outcome. This could be because the frailty phenotype was first described 2001, with a systematic evaluation of frailty tools a decade later.[2, 49] Accordingly, the authors decided to additionally evaluate frailty components such as physical function, nutrition, cognition and biomarkers as baseline and outcome measures. Although not specific to frailty, these measures provide insights to the effectiveness of exercise-nutrition interventions on improving various components of frailty and may inform future studies.

Previous reviews have found mixed results[48] or have concluded that evidence for combined interventions is limited but increasing.[50] Our results concur with RCTs of exercise-nutrition interventions conducted in community dwelling frail older adults. Tarazona-santabalbina and colleagues found significant improvement in SPPB in participants on an exercise-nutrition intervention as compared to controls in a community dwelling frail population – intervention group 9.5±1.8 vs control group 7.1±2.8, P=0.007.[51] Similarly, Kim et al reported a community-based study of frail older adults that found SPPB to remain stable in the intervention group, while it decreased by 12.5% (1 point) in controls (P=0.039).[52] Our meta-analysis of individual components of the SPPB suggest that the significant improvements in functional muscle strength as represented by the chair stand component of the SPPB may be pivotal to the increase in overall SPPB post intervention, and reflect the functional lower limb strength training focus of the exercise interventions. However, the meta-analysis of handgrip +/- quadriceps strength did not produce a similar trend. Diversity in outcome measures for frailty and frailty-related domains like physical function is a challenge for comparative analyses between studies. Future studies should carefully consider measure responsiveness when selecting outcome tools.

Nutrition is another important domain within frailty. Yet the majority of studies included in this review only reported nutrition status at baseline, with only one study reporting follow-up nutrition assessment at the end of the intervention.[31] Luger et al described an improvement in nutrition status in a sample of at risk malnourished pre-frail/frail patients (thus likely to benefit most from nutrition therapy). As hospitalised patients have greater energy deficits due to catabolic stress of acute illness, they are a population that requires careful determination of energy/protein requirements and in whom additive effects of nutrition supplementation to exercise may have greatest impact on outcomes such as muscle strength.[51] As none of the studies in the present review reported on energy deficits, it is not known whether these patients received adequate replacement. Nutrition supplementation should also not be confused with nutrition or diet modifications. The provision of ONS alone is unlikely to augment diet adequacy as completely as diet modification that involves a wider range of nutrients and non-nutrients[53] especially when led by dietitians.[54, 55]

For both exercise and nutrition based interventions, an understanding of patient participation dynamics and compliance is required because of how they can impact on effectiveness.[56] Only five studies in this review reported attendance to program/home visits or phone calls or adherence to prescribed exercise/diet or related advice at rates of 50-90% and 70-93% for nutrition and exercise interventions, respectively. Issues with participants resulting in poorer compliance were not reported in these articles, such that the authors recommend that future studies explore barriers and enablers to adherence in multi-modal interventions.

Cognition is another critical domain in the multidimensional nature of frailty. Exercise[57] and nutrition interventions[58] may have a far reaching, positive effect on cognition in older adults. However, there was no evidence of an impact on cognition from a single study[41] in the present review. This is consistent with a network meta-analysis of 13 RCTs that examined exercise and nutrition interventions in frail older adults.[11] One suggested explanation is that different neuronal mechanisms could result in a misfit between combinatory approaches of nutrition and physical interventions [59] highlighting that more in-depth research is required.[60]

The economic delivery of new interventions and models of care is important to a range of stakeholders[61] but has been infrequently conducted in previous studies.[48] In this review, only two out of 11 studies included an economic analysis, with the majority of costs coming from delivery of exercise and nutrition support. The types of consumables that were considered in analyses included nutrition supplements, ankle/wrist weights, mobility aids and medications. Elements of service provision that were considered included community, rehabilitation, residential and transition care service use, which were often reduced and contributed to the net result. The results of this review support previous findings of beneficial effects on frailty-related outcomes, without increased costs.[48] However, results should be interpreted with caution as omission of other services (such as medication reviews) within a multimodal intervention can impact costings, and there are instances where interventions have not been found to be more-cost effective than usual care.[62] The approach of streamlining and reorganising existing services rather than creating entirely new systems may be preferred.

Strength and weakness

This study was robust and underwent peer review by an academic librarian. We did not have a language restriction on the search, and we did not find nor include studies in other languages.

We chose to use of an updated version of the Cochrane risk of bias tool (RoB 2), which addresses issues of confusion common to its first version.

By focussing on exercise-nutrition interventions only, this study addresses a gap as identified in a recent review of multi-domain interventions in pre-frail or frail elderly adults, in which some interventions may have been be too broad to directly impact frailty, and functional and cognitive status.[50] Multidisciplinary team based approaches remain recommended and are a bedrock of quality standard care; they may also already include goals for exercise and nutrition such that it may be difficult to solely attribute outcomes to a targeted but supplementary exercise-nutrition program. Social relationships affect health behaviour and physical health,[63] such that intervention benefits may in part come from social interactions. Nevertheless, several studies[27, 31, 41] have demonstrated significant improvements even when control participants are provided with the social aspect of an intervention, such that exercise and nutrition are expected to improve outcomes independent of social interactions.

Implications and future research

This review is a useful resource for researchers and multi-disciplinary clinicians who are seeking to generate evidence or evaluate their practices of exercise-nutrition interventions for frail hospitalised older adults. The authors interpretation of the quality of studies in this review is that the evidence base is low, but the inclusion of future studies may change estimates of the intervention effects. While blinding of participants to the intervention is acknowledged to be difficult, future studies should be adequately powered, use allocation concealment with blinding outcome assessors and data analysts at least. Improved reporting of intervention details is also required,[64] which may assist in answering research questions around the optimal duration, dose, modality and timing of intervention(s) across the hospital to community continuum. In the present review, potential beneficial effects of combined interventions could have been negated given the short durations reported by most studies. Thus, future studies may be extended for >6-12 months, or employ principles of chronic condition self-management,[65] to determine delayed improvements and achieve long-lasting sustainability of interventions. There are many ongoing research activities relevant to the scope of this review,[66-69] yet only one has reported plans for economic analysis in the study protocol.[66] Economic evaluations can expand current evidence on the sustainability of incorporating such services within resource-constrained healthcare systems.

Conclusion

Exercise-nutrition interventions that start while patients are admitted to hospital and continue in the community/post-hospital, or, commence early post discharge, appear to be effective in reducing frailty and some frailty-related physical indicators. Though effective, the quality of the evidence in this review is low as most studies included had some concerns for risk of bias. Given the paucity of high-quality studies on the effectiveness of combined exercise-nutrition interventions on hospitalised frail older adult patients, more robust research that pays attention to effect of assignment to intervention is needed to increase the confidence in results.

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Author Contributions

All authors contributed to the conception and design of review. CH and YS read and screened titles and abstract of potentially relevant studies. CH and YS evaluated the selected studies and performed data extraction. CH, MM, AY, CB reviewed the evidence. RW provided statistical expertise on meta-analyses. CH drafted the article and all authors provided critical revisions and final approval of the manuscript. All authors had access to the data in the study and can take responsibility for the integrity of the reported findings. All authors fulfil the ICMJE criteria for authorship.

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Competing interests

None declared.

Patient consent

Not required.

Data sharing statement

Details of the excluded papers are available from the corresponding author upon request.

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Figure captions

Fig.1 Flow diagram illustrating results of the search and study selection process as described in the PRISMA statement

Fig 2. Meta-analysis of reduction in frailty score for exercise and nutrition intervention vs standard care

Fig.3 Meta-analyses of Short physical performance battery, Gait speed, Balance test, Chair stand test, Activities of daily living, handgrip and muscle strength

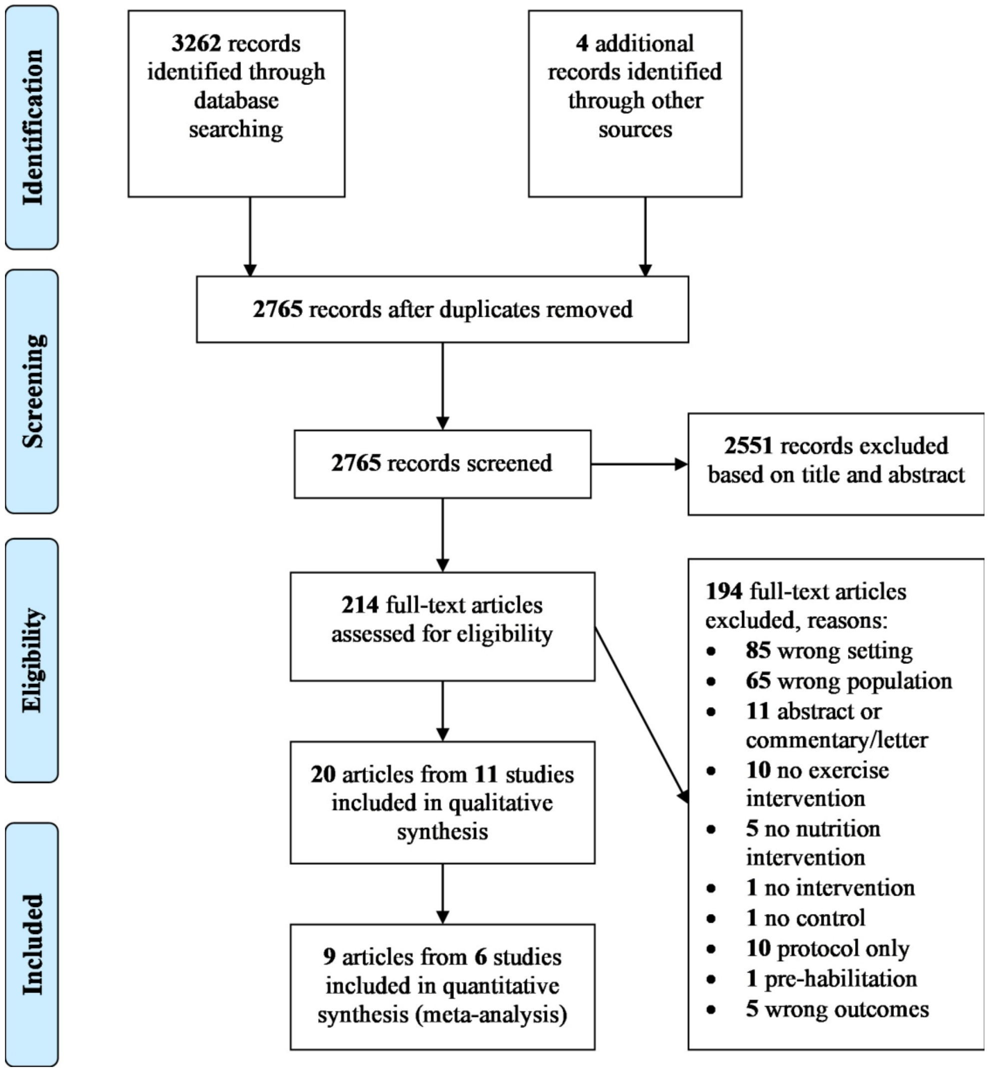
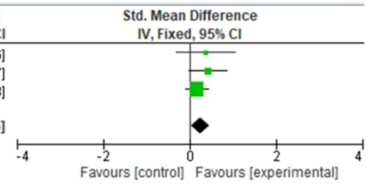


Fig.1 Flow diagram illustrating results of the search and study selection process as described in the PRISMA statement

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Niccoli 2017	0.333	0.724	15	0.105	0.459	19	9.8%	0.38 [-0.31, 1.06]
Luger 2016	0.71	1.11	39	0.35	0.459	41	23.3%	0.42 [-0.02, 0.87]
Cameron 2013	0.56	1.1	108	0.39	0.92	117	66.9%	0.17 [-0.09, 0.43]
Total (95% CI)			**162**			**177**	**100.0%**	**0.25 [0.03, 0.46]**

Heterogeneity: Chi² = 1.10, df = 2 (P = 0.58); I² = 0%
Test for overall effect: Z = 2.27 (P = 0.02)



Abbreviations: *CI confidence interval; IV inverse variance; SD standard deviation*

Fig.2 Meta-analysis of reduction in frailty score for exercise and nutrition intervention vs standard care

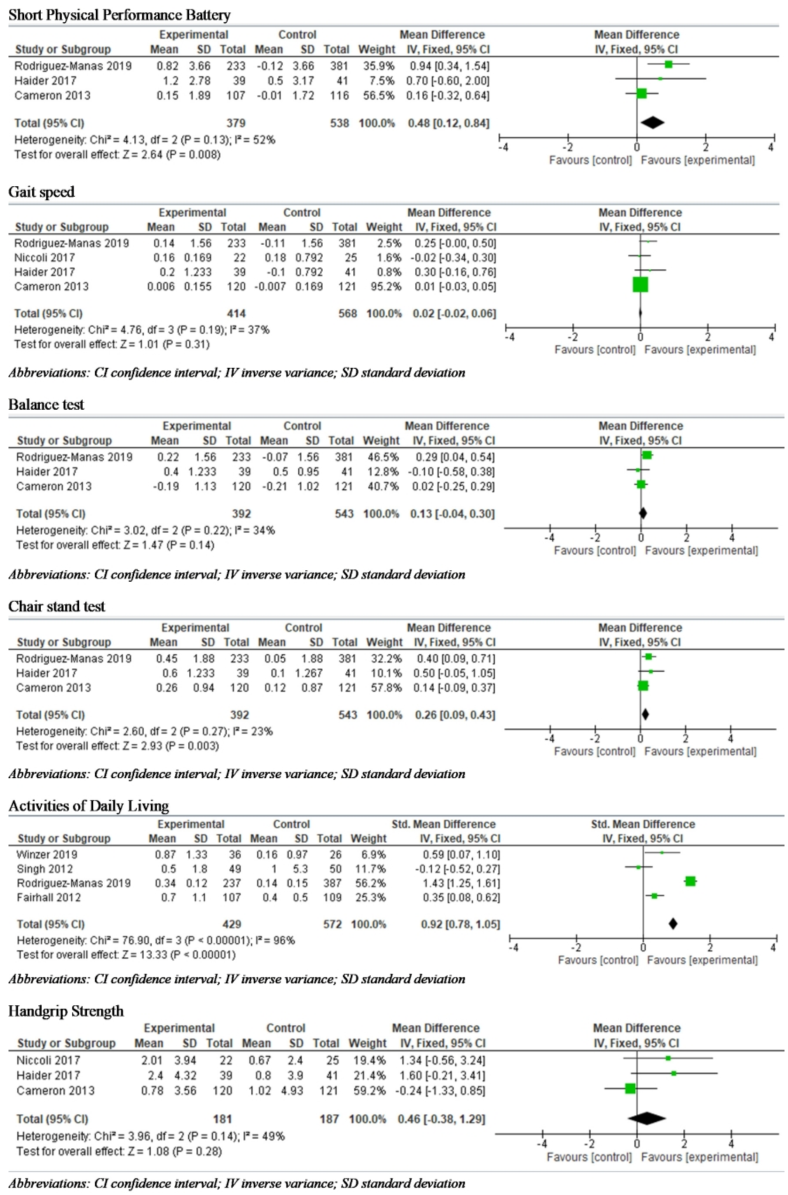


Fig.3 Meta-analyses of Short physical performance battery, Gait speed, Balance test, Chair stand test, Activities of daily living, handgrip and muscle strength

Search Strategy – Medline

#	Searches
1	"diet, food, AND nutrition"/ or food/ or diet/
2	dietary proteins/ or dietary supplements/
3	Nutritional Status/ or Feeding Behavior/
4	Dietitian/
5	Nutrition Assessment/ or Nutrition Therapy/
6	((diet* or nutrition* or food*) adj5 (intervention or program or supplement or educat* or assess* or advic* or counsel* or treat*)).tw,kf.
7	or/1-6
8	motor activity/ or exercise/ or muscle strength/ or physical endurance/ or physical fitness.mp.
9	Exercise/ or resistance training/
10	(exercis* or "resistance training" or "exercis* therapy" or "muscle stretching exercis*" or "physical exercis*" or "strength train*" or "aerobic exercis*" or hydrotherapy or rehabilitat* or walk* or cycl* or conditioning* or "leg press" or flexib*).mp.
11	Physiotherapy/
12	((exercise* or resistan* or strength) adj5 (intervention or program or educat* or advice* or treat* or train* or rehabilit*)).tw,kf.
13	or/8-12
14	frail elderly/ or pre-frail elderly/
15	frail*.mp.
16	(functional* adj2 (declin* or impair*) adj3 (aged or aging or elderly or elder* or old* or senior*)).mp.
17	(frail* and (geriatric* or gerontolog* or (vulnerable and older))).mp.
18	(frail* and (aged or aging or elderly or elder* or older or senior*)).mp.
19	(frail* and (geriatric* or gerontolog* or aging)).mp.
20	("geriatric assess*" or "functionally-impaired elder*").mp.
21	14 or 15 or 16 or 17 or 18 or 19 or 20
22	7 and 13 and 21

Translated above strategy for other databases: **CINAHL, Emcare, Scopus, Cochrane, Ageline and PEDro**

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5-6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	nil
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8, fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10-11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-18
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-18, fig. 2 & 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8, Fig 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	nil
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22-23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	24

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Effectiveness of combined exercise and nutrition interventions in pre-frail or frail older hospitalised patients: a systematic review and meta-analysis

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Title Page

Effectiveness of combined exercise and nutrition interventions in pre-frail or frail older hospitalised patients: a systematic review and meta-analysis

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Keywords: frail; pre-frail; older people; exercise; nutrition

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Abstract

Objectives: To determine the effectiveness of combined exercise-nutrition interventions in pre-frail/frail hospitalised older adults on frailty, frailty-related indicators, quality of life (QoL), falls and its cost-effectiveness.

Design: Randomised controlled trials (RCTs) of combined exercise-nutrition interventions on hospitalised pre-frail/frail older adults ≥65 years were collated from MEDLINE, Emcare, CINAHL, Ageline, Scopus, Cochrane and PEDro on 10th October 2019. The methodological quality was appraised, and data were summarised descriptively or by the meta-analyses using a fixed effects model. The standardised mean difference (SMD) or difference of means (MD) with 95% confidence intervals (CIs) was calculated.

Results: Twenty articles from 11 RCTs experimenting exercise-nutrition interventions on hospitalised older adults were included. Eight articles were suitable for the meta-analyses. One study had low risk of bias and found improvements in physical performance and frailty-related biomarkers. Exercise interventions were mostly supervised by a physiotherapist, focusing on strength, ranging 2-5 times/week, of 20-90 minutes duration. Most nutrition interventions involved education and supplementation but had dietitian supervision in only three studies. The meta-analyses suggest that participants who received exercise-nutrition intervention had greater reduction in frailty scores (n=3, SMD 0.25; 95% CI 0.03-0.46; P=0.02) and improvement in short physical performance battery (SPPB) scores (n=3, MD 0.48; 95% CI 0.12-0.84; P=0.008) compared to standard care. Only the chair-stand test (n=3) out of the three SPPB components was significantly improved (MD 0.26; 95% CI 0.09-0.43; P=0.003). Patients were more independent in activities of daily living in intervention groups, but high heterogeneity was observed (I^2=96%, P<0.001). The pooled effect for handgrip (n=3) +/- knee extension muscle strength (n=4) was not statistically significant. Nutritional status, cognition,

biomarkers, QoL, falls and cost-effectiveness were summarised descriptively due to insufficient data.

Conclusions: There is evidence, albeit weak, showing that exercise-nutrition interventions are effective to improve frailty and frailty-related indicators in hospitalised older adults.

PROSPERO registration number: CRD42020153934

Strengths and limitations of study

- This is the first comprehensive systematic review with meta-analysis on the effectiveness of exercise-nutrition interventions on frailty and outcomes related to frailty in hospitalised and pre-frail/frail older adults.
- Only randomised controlled trials describing existing exercise-nutrition interventions in frail older hospitalised patients were included.
- There was a moderate risk of bias for most included studies such that the findings of this review are inconclusive, making it difficult to draw firm conclusions.

Introduction

Frailty is a major contributor to late-life disability as it leads to loss of independence.[1] It is also associated with poor health outcomes, and, increased health-care costs and service use.[1] Frailty has been defined for clinical research by Fried et al[2] as a combination of unintentional weight loss, weakness, exhaustion, slowness and reduced physical activity. Older adults (aged >65 years) that have been classified as frail and are hospitalised, have a three-fold higher risk of readmission or death, as compared to the younger population.[3] The management of older adults who are frail has an incremental effect on health expenditures with an additional equivalent of AU$2400 per frail patient per year.[4] With 21% of the population over 65 years estimated to be frail and 48% estimated to be pre-frail, concerns of economic impact are compounded by an ageing population.[5]

Exercise and nutrition are inextricably linked, in particular strength training can address component issues of the frail phenotype.[6] Yet evidence supporting the effectiveness of exercise-nutrition interventions for reversal of frailty is limited to community-dwelling older adults.[7] In a study of community participants, a 3-month combined exercise-nutrition intervention resulted in a significant reversal of frailty (reduction in Fried frailty score) at 6-months, compared to the control group (between-group difference −0.34; 95% confidence interval [CI] -0.52 to −0.16; P<0.001).[8] The combination of exercise therapy and dietary intervention in older adults who are frail, has also been reported to increase muscle strength (knee extension between-group difference 1.84 kg, 95% CI 0.17–3.51, P=0.03)[9] and improve nutritional status (Mini Nutritional Assessment (MNA) Short Form between group difference 1.4, 95% CI 0.9-1.9, P<0.01).[10]

A recent meta-analysis suggested that although effective, exercise combined with nutrition was not more effective in treating frailty than exercise alone.[11] However, the majority of included studies were conducted in a community setting, with only 15% of older adults either hospitalised or recruited from acute care settings. No study has systematically evaluated evidence for interventions that commence during acute hospitalisation or early post discharge (in the high-risk period for post-hospital syndrome).

Hospitalisation is a vulnerable period, especially for older adults who are frail and therefore at higher risk of functional loss,[12] malnutrition[13, 14] and further decline in frailty status. Malnutrition is ubiquitous in older hospitalised patients with a prevalence as high as 50%.[15] Since many domains of frailty are attributed to poor nutrition,[16] the effect of nutrition intervention when combined with exercise, may be more significant in the hospitalised population.[16] Also, recent review suggest that nutrition support, provided by a multidisciplinary team, may have a positive impact on mortality and quality of life in hospitalised older adult patients.[17] Nutritional therapy extends beyond protein or nutrition supplementation as reported in previous studies and may be more effective as part of individualised medical nutrition therapies involving dietitians to improve diet adequacy.[18]

This study aims to determine the effectiveness of combined exercise-nutrition interventions on (1) frailty, (2) frailty-related indicators, falls, quality of life (QoL) and (3) its cost effectiveness on pre-frail or frail hospitalised older adults.

Materials and Methods

Protocol and registration

The protocol for this review was compliant with Cochrane systematic review guidelines,[19] and registered with the International Prospective Register of Systematic Reviews (PROSPERO), CRD42020153934. The study is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20] Patients and/or members of the public were not involved in this study.

Search methods

Systematic searches of electronic databases (MEDLINE, Emcare, CINAHL, Ageline, Scopus, Cochrane and PEDro) were conducted by the lead author (CH) from inception until 10th October 2019 using search strategies reviewed by an academic librarian (search queries available in Supplementary file 1). Additionally, related citations to eligible items were identified using the suggested related citation function in Pubmed. Reference lists of eligible items were also screened.

Inclusion and exclusion criteria

The inclusion criteria were: 1) randomised controlled trials; 2) inclusion of pre-frail or frail participants (as defined by study authors); 3) recruitment of older adult inpatients and/or those hospitalised within the past 30 days of recruitment; 4) interventions that started while patients were admitted and continued in the community/post-hospitalisation, or, commenced within 30 days of hospital discharge; 5) interventions that involved both physical exercises and nutritional interventions (dietary modifications/education/training alone or combined with oral nutrition supplementation); 6) measured frailty with an assessment tool or at least one indicator relevant to frailty (nutritional status, physical function, cognitive function and mood, physical activity level or biomarkers, falls and QoL and/or economic analysis of interventions. Studies were excluded if they described protocols with no pilot outcomes, interventions delivered as a part of a palliative care program, or interventions solely designed to facilitate discharge planning (e.g. telephone support services, providing no pre-frailty or frailty intervention element), recruited participants admitted following a mental health episode.

Study selection and data extraction

Covidence[21] was used to manage citations for title and abstract, and full-text screening, in duplicate (CH and YS, supplement 1). The reviewers were unblinded to authors, journals and countries of origin. Any disagreement was resolved through discussion or consensus opinion with the other authors. A data extraction form was developed a priori by the research team, such that two researchers (CH and YS) performed data extraction independently, on eligible full-text articles. Where available, the continuous data were extracted as (i) mean change with standard deviation (SD), standard error of mean (SE) or 95% confidence interval (CI), or (ii) mean or median values with SD, SE or interquartile range post intervention. If the required data were not reported within a publication (including change in means for outcomes of interest), the authors were emailed to request for it.

Quality of the studies

The risk of bias in the individual studies was assessed by the Revised Cochrane risk-of-bias tool for randomised trials (RoB-2) by two researchers (CH and YS) independently.[22] Any disagreements were resolved by discussion or if required with consensus of a third reviewer. The Cochrane risk-of-bias tool is widely used to assess randomised controlled trials (RCT) for best practice.[23] Studies were given an overall risk-of-bias judgement of low, some concerns or high. Overall risk-of-bias was determined as having "some concerns" if any one of the risks of bias domains was rated as having "some concerns". Likewise, studies were deemed to have an overall high risk of bias if any one domain had a high risk of bias.

Data synthesis and statistical analyses

Where possible, a meta-analysis was performed; continuous outcome data were pooled and reported as either the difference of means (MD) if the same outcome assessment tools were used or the standardised mean difference (SMD) if different outcome assessment tools were used, and the 95% CI, if there were two or more studies. The SMD is the mean difference when the outcome for each study is standardised to have mean zero and SD=1. Studies presenting SE were converted to SD via the conversion formula.[19] The fixed-effect meta-analyses were carried out with Cochrane Review Manager (RevMan) 5.3.[24] A P value of <0.05 was considered statistically significant. The variability between studies (heterogeneity) was assessed by I^2 and its 95% CI.[25] For studies with unobtainable missing, or incomparable data, results were qualitatively synthesised.

Patient and public involvement

No patients were involved in this study

Results

Study selection

The flow of studies through the review process is summarised in Figure 1. Twenty articles reporting on 11 studies were eligible for data synthesis and analysis. Three of 11 studies presented results from their cohort across separate publications. Firstly, Villareal et al[26] reported on physical functioning outcomes with biomarker results in the publication of Armamento-Villareal et al.[27] Secondly, Cameron et al[28] reported on frailty and some physical function outcomes, with other physical function outcomes in a secondary publication[29] fall rates[30] and cost-analysis in another.[31] Thirdly, Luger et al[32] reported on frailty and nutritional status, with physical functioning outcomes across two other publications,[33, 34] fall efficacy[35] and quality of life.[36] For clarity, the primary articles that report frailty or physical function outcomes are cited for descriptive data in Tables 1-3 while individual articles are cited for synthesis of outcome results.

Study and sample characteristics

Details of study characteristics are available in Table 1. Across all studies, a total of 2307 participants were investigated. Most studies reported that patients were recruited from hospital wards (n=7)[28, 37-42] while the other four studies[26, 32, 43, 44] included patients that were recruited from hospital wards and community. Seven studies included only frail participants,[26, 28, 39-42, 44] and the remaining four studies[32, 37, 38, 43] included frail, pre-frail and non-frail participants. The Fried frailty phenotype criteria[2] were used most frequently to classify frailty (n=4).[28, 37, 38, 43] with participants considered non-frail, pre-frail or frail if 0, 1-2, 3-5 criteria were present, respectively. Luger et al used the Frailty Instrument for Primary Care of the Survey of Health, Ageing, and Retirement in Europe (SHARE-FI)[32] which integrates components of exhaustion, appetite, handgrip strength, walking difficulties and physical activity.[45] Five studies did not report any assessment method to define frailty.[39-42, 44] One study used a combination of three tools – modified Physical Performance Test, the measurement of VO_2 peak, and the Functional Status Questionnaire.[26]

Risk of bias within individual studies

Table 2 outlines the risk of bias in individual studies. One study[26] had a low risk of bias and one study had a high risk of bias (including unblinded secondary outcome assessment and insufficient detail on standard care in control groups across recruitment sites). The other nine studies[28, 32, 37-39, 41-44] were rated as having some concerns overall, of which five could have been improved in ≥1 domain. The remaining four studies[27, 31, 39, 41] that were rated as having "some concerns" overall, had risk in only one domain with the most common reason being failure to blind intervention/allocated group to participants. Examples of other concerns about risk of bias included: assessors being aware of the group allocation[32] (measurement of outcomes domain); or a lack of information about participants/researcher blinding to group allocation.[26, 28, 43]

Characteristics of exercise intervention component

Characteristics of the exercise interventions used in studies are outlined in Table 3, and included combinations of the following: supervised individual exercises (n=10),[26, 28, 37-44] group exercises (n=3),[26, 40, 44] education including support with resources (digital versatile disc (DVD) or visual aid instruction booklet, n=2),[32, 37] and motivational interviewing using a standardised protocol (n=1).[32] Three studies[38, 41, 43] had inpatient only interventions, five[37, 39, 40, 42, 44] had interventions that extended from inpatient to post-discharge, two[28, 32] studies offered the intervention post-discharge only and one[26] did not report.

In the majority of studies (n=9), the exercise component was delivered by a physiotherapist.[26, 37-44] Two studies used trained fitness instructors,[37, 40] and another engaged lay volunteers who

Table 1. Characteristics of included studies examining pre-frail or frail hospitalised older adults

Study	Country	n	Mean age	Study participants, characteristics	Recruitment site	Duration of intervention	Follow-up period	Frailty diagnostic tool/criteria used	Reported % of prefrail, frail
Arrieta *et al*, 2019[35]	France	302	76.7 ±5.0	Frail, onco-geriatric, older men & women; BMI: 26.1 ±4.6 kg/m^2 (UCG); 26.2 ±4.4 kg/m^2 (IG)	Acute hospital	1y	1y, 2y	Fried frailty phenotype criteria	Non-frail: 73.6% Frail: 26.4%
Rodriguez-Manas *et al*, 2019[41]	Spain	964	78.0 ±5.44	Frail older men and women with T2DM; BMI: 29.6 ±5.0 kg/m^2	Acute hospitals or primary care sites	4.5m (exercise), 3.5-4w (nutrition)	1y	Fried frailty phenotype criteria	Pre-frail: 62.2% Frail: 37.8%
Niccoli *et al*, 2017[36]	Canada	47	81.3 ±1.0	Frail older men and women hospitalised patients; BMI: 26.4 ±6.6 kg/m^2 (UCG), 24.2 ±5.2 kg/m^2 (IG)	Acute hospital	Average LOS (days): 20.9 (UCG), 26.5 (IG)	Upon discharge	Fried frailty phenotype criteria	Pre-frail: at least 87.8% Frail: NR
Luger *et al*, 2016*[30]	Austria	80	82.8 ±8.0	Frail older men and women; BMI: 27.2 ±4.3 kg/m^2	Acute hospital and community	3m	3m	SHARE-FI (female>0.315; male: >1.212 points)	Non-frail: 1% pre-frail: 35%, frail: 64%
Milte *et al*, 2016[37]	Australia	175	83.0 ±6.2 (UCG), 82.4 ±5.7 (IG)	Frail older men and women post hip fracture, BMI: NR	Acute hospital	6m	6m	NR	Frail: 100% as determined by study authors
Cameron *et al*, 2013†[26]	Australia	241	83.3 ±5.9	Frail older men and women, BMI: 26.4 ±6.0 kg/m^2 (UCG) 26.1 ±5.9 kg/m^2 (IG)	Acute hospital	1y	3m, 1y	Fried frailty phenotype criteria	Frail: 100% as determined by study authors
Singh *et al*, 2012[38]	Australia	124	79.3 ± 9.6	Frail older men and women; BMI: NR	Acute hospital	1y	4m, 1y	NR	Frail: 100% as determined by study authors
Villareal *et al*, 2011‡[24]	United States	107	69.3 ±4.1	Frail obese older men; BMI: 36.8 ±4.6 kg/m^2	Acute hospital and community	1y	6m, 1y	≥2 criteria: Modified PPT score 18–32; VO^2 peak of 11–18 ml ml/kg; difficulty in performing 2 IADL or 1 basic ADL	Mild-moderate frailty: 100%

Azad *et al*, 2008[42]	Canada	91	74.2 and 75.8	Frail CHF older women; BMI: NR	Acute hospital and community	6 weeks	6w, 6m	Screened by a CHF coordinator, frailty assessment undefined	Frail: 100% as determined by study authors
Blanc-Bisson *et al*, 2008[39]	France	76	85.4 ±6.6	Frail older men and women; BMI: 24.0 ±5.1 kg/m^2	Acute hospital	Until clinical stability	Clinically stable, 1m	NR	Frail: 100% as determined by study authors
Miller *et al*, 2006[40]	Australia	100	83.5 ±2.8	Frail older men and women with LL fracture; BMI: 22.1 ±4.3 kg/m^2 (ACG), 23.2 ± kg/m^2 (IG)	Acute hospital	3m	3m	NR	Frail: 100%

Abbreviations: *BMI, Body Mass Index; w, Weeks; m, Months; y, Years; VO^2 max, maximal oxygen uptake; PPT, physical performance test; IADL, Instrumental Activities of Daily Living; ADL, Activities of Daily Living; SHARE-FI, Survey of Health, Ageing and Retirement in Europe-Frailty Instrument; T2DM, Type 2 Diabetes Mellitus; CHF, Chronic Heart Failure; LL, Lower Limb, LOS, length of stay; IG, Intervention group; UCG, Usual care group; ACG, Attention control group; NR, not reported; BMI presented in Mean ±standard deviation*

Multiple articles reported from same study, study chosen to represent other reports from the same study: *Luger et al[31] – Haider et al 2017[32], Winzer et al 2019[33], Kapan et al 2017[34], Kapan et al 2017[35]; †Cameron et al 2013[27] – Fairhall et al 2012[28], Fairhall et al 2014[29], Fairhall et al 2015[30]; ‡Villareal et al 2011[25] – Armamento-Villareal 2016[26]

Table 2. Assessment of methodology quality of included studies using Cochrane Risk of Rias 2.0 tool

Study	Cochrane Risk of Bias 2.0 tool assessment domains					
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Arrieta *et al*, 2019[35]	+	?	?	?	+	?
Rodriguez-Manas *et al*, 2019[41]	+	?	+	?	+	?
Niccoli *et al,* 2017[36]	?	?	+	?	+	?
Luger *et al,* 2016*[30]	+	+	+	?	+	?
Milte *et al*, 2016[37]	+	?	+	+	+	?
Cameron *et al*, 2013†[26]	+	?	+	+	+	?
Singh *et al,* 2012[38]	+	?	+	—	+	—
Villareal *et al*, 2011‡[24]	+	+	+	+	+	+
Azad *et al*, 2008[42]	+	?	+	?	+	?
Blanc-Bisson *et al*, 2008[39]	+	?	+	?	+	?
Miller *et al*, 2006[40]	+	?	+	+	+	?

Key: + = Low risk of bias; ? = Some concerns of risk of bias; — = High risk of bias
[a]Deviations from intended interventions (effect starting and adhering to intervention)
Multiple articles reported from same study, study chosen to represent other reports from the same study: *Luger et al[31] – Haider et al 2017[32], Winzer et al 2019[33], Kapan et al 2017[34], Kapan et al 2017[35]; †Cameron et al 2013[27] – Fairhall et al 2012[28], Fairhall et al 2014[29], Fairhall et al 2015[30]; ‡Villareal et al 2011[25] – Armamento-Villareal 2016[26]

221 **Table 3. Characteristics of exercise and nutrition intervention and controls of included studies**

Study	Exercise intervention	Nutrition intervention	Control intervention
Arrieta *et al*, 2019[35]	**Type:** *Strength* **–** Intensity range from low to high, starting at 10 repetition per exercise **(UL, LL)** with option of progressive loading *Aerobic, Flexibility, Balance* **–** intensity individualised **Frequency:** 2 sessions/week, duration per session NR + home exercises duration NR **Setting:** Inpatient (supervised, individual) + post-discharge (unsupervised, individual) **Additional support reported:** Phone consults (by trainer 2x/month for first 6 months then monthly for 1 year); Education resource	**Self-guided education resource:** Provided with French National Nutrition Health Program education booklet - *Programme National Nutrition Santé* (PNNS)	**Usual care:** NR, variable between study sites **Self-guided education resource:** Provided with French National Nutrition Health Program education booklet - *Programme National Nutrition Santé* (PNNS)
Rodriguez-Manas *et al*, 2019[41]	**Type:** *Strength* – 40-80% of estimated 1RM, 8–10 repetitions **(LL)** **Frequency:** 2-weeks pretraining followed by 16-week program of 2 days/week; 20-30 minutes/sessions **Setting:** Inpatient (supervised, individual)	**Nutrition consultation/education:** 7 educational sessions, each 45 minutes, delivered by a trained researcher or nutritional therapist, twice a week over 3.5-4 weeks. Therapy focused on behavioural change, nutrition optimisation and diabetes.	**Usual care:** usual health care from local health system and/or general practitioner
Niccoli *et al,* 2017[36]	**Type:** *Strength, Aerobic, Flexibility, Balance* – intensity and target muscle group individualised based on patient's baseline assessment **Frequency:** individualised based on patient's baseline assessment **Setting:** Inpatient (supervised, individual)	**Supplements:** Daily ONS with 24g whey protein per day (*9g breakfast, 7.5g at lunch and dinner*) in addition to usual diet	**Usual care:** usual medical care, no whey protein supplementation. **Individual supervised exercise**: Individualised exercises as per intervention.
Luger *et al*, 2016*[30]	**Type:** *Strength* –2 sets of 15 repetitions **(UL, LL)** until muscular exhaustion, **Frequency:** 2x/week, >30 minutes each session **Setting:** Post-discharge (supervised, individual) **Additional support reported:** Physical education (2-3 times/week, 30 minutes each session); Exercise education resource (demonstration DVD); Motivational interviewing.	**Nutrition consultation/education** Trained lay volunteers visit twice/week for dietary discussions aimed at achieving adequate energy, protein and other nutrients. Taught how to enrich food with protein, recipes, healthy for life plate which consists of food-cards and a play board. **Motivational interviewing**: Techniques utilised with nutrition goal setting and tools to reinforce self-efficacy.	**Usual care with attention control:** Trained lay "buddies" visit twice a week but doing a portfolio of possible activities (go out, have a chat, and sharing interest), especially cognitive training
Milte *et al*, 2016[37]	**Type:** *Strength, Balance (Otago exercise program)* – Intensity and repetitions NR, at the discretion of the treating physiotherapist **(LL)**	**Nutrition consultation/education:** Individualised nutrition therapy aimed at	**Usual care:** Usual rehabilitation program recommended during hospitalisation, social visits

	Frequency: 3 times/week, 20-30minutes/session for 12 weeks **Setting:** Inpatient (supervised, individual) + post-discharge (supervised, individual)	improving energy and protein intake to meet requirements by dietitian who visits fortnightly. **Meal program:** ordered as deemed necessary by dietitian. **Supplements:** commercial ONS recommended if needed by dietitian	weekly from trial staff and generic nutrition, exercise and falls prevention information
Cameron *et al*, 2013†[26]	**Type:** *Strength, Balance, Aerobic + WEBB program* – intensity and target muscle groups NR **Frequency:** Exercises prescribed 3-5x/week (with 2 sessions for mobility training) for 1 year, supported by up to 10 home visits **Setting:** Post-discharge (supervised, individual) + (unsupervised, individual)	**Nutrition consultation/education:** Clinical evaluation of nutritional intake at home. A series of diet intervention as needed by dietitian. **Meal program:** ordered as deemed necessary by dietitian. **Supplements:** commercial ONS recommended if needed by dietitian	**Usual care:** usual health care during hospitalisation and from their general practitioner and community services after discharge
Singh *et al*, 2012[38]	**Type:** *Strength* **–** 80% of most recent 1RM or RPE <15, 3 sets of 8 repetitions **(UL, LL)** **Frequency:** 2 sessions/week, session duration NR, over average of 80 sessions in 1 year, start as early as post assessment in hospital or at home. **Setting:** Inpatient (supervised, individual) + (supervised, group-based) **Additional support reported:** Monthly phone consults	**Nutrition consultation/education:** Counselling on increase in diet quality, frequency NR **Supplements:** ONS +/- dietary advice to increase daily energy (400-600 kcal) and protein (20 g/day) intake. For those calcium or vit-D deficient (52%), 12 months of vit-D orally (1000 IU/day) or calcium (1200 mg/d) and vit-D combination supplement **Self-guided nutrition resource:** Food sources of calcium, vitamin D and sun exposure	**Usual care:** standard service offered for hip fracture in the area health service, including orthogeriatric care, rehabilitation service, other medical and allied health consultation as required, and physiotherapy.
Villareal *et al*, 2011‡[24]	**Type:** *Strength* **–** 65% of 1RM; 8-12 repetitions of each exercise **(UL, LL)** with options for progression *Aerobic,* ~65% of peak HR with gradual progression to 70-85% *Flexibility, Balance* **Frequency:** 90 minutes, 3 sessions/week **Setting:** Inpatient (supervised, group-based)	**Nutrition consultation/education:** prescribed a balanced diet with energy deficit of 500-750 kcal/d from daily energy requirement, 1 g of high-quality protein/kgbw/d. Weekly group consultation with dietitian for adjustments of their caloric intake, goals and behavioral therapy. **Supplements:** 1500 mg of calcium/d day and ~1000 IU vitamin D/d	**Usual care:** General healthy lifestyle advice **Supplements:** 1500 mg of calcium/d day and ~1000 IU vitamin D/d
Azad *et al,* 2008[42]	**Type:** 'Comprehensive exercise program'; type, intensity and target muscle groups NR **Frequency:** 11 sessions over 6 weeks + NR home exercises **Setting:** Inpatient (supervised, group-based), post-discharge (unsupervised, individual)	**Nutrition consultation/education:** 3 sessions of individualized counselling about diet and nutrition in the management of CHF by dietitian	**Usual care:** Optimal medical care

Blanc-Bisson *et al*, 2008[39]	**Type:** *Strength* **–** intensity (RM) NR, 10 x repetitions each exercise **(LB)** **Frequency:** 30 minutes, twice/day, five days/week **Setting:** Inpatient (supervised, individual)	**Meal program:** Geriatric hospital meals of 1800-2000 kcal/d **Supplements:** 1 daily ONS of 200 kcal and 15g protein	**Usual care:** From day 3 to 6, patients started to walk with human help with or without technical assistance in the physiotherapy room for three sessions per week until discharge. **Individual supervised exercise:** Physiotherapy continued at home for one month.
Miller *et al*, 2006[40]	**Type:** *Strength* – intensity (RM) NR, 2 sets of 8 repetitions (**LL**) with progressive loading, at the discretion of the treating physiotherapist **Frequency:** 3 times/week, 20-30minutes/session for 12 weeks **Setting:** Inpatient (supervised, individual) + Post-discharge (supervised, individual)	**Nutrition consultation/education:** Individualised nutrition therapy by dietitian. **Supplements:** single type of ONS to cover the shortfall between individual estimated energy and protein requirements and actual intake over 42 days.	**Usual care with attention control group** - received tri-weekly visits weeks 1-6, then weekly visits 7-12 to account for the possibility of the attention effect.

222 Abbreviations: *UL, Upper Limb; LL, Lower Limb; NR, not reported; HR, Heart Rate; CHF, Chronic Heart Failure; ONS, Oral Nutrition Supplements, RM, Repetition Max; DVD, Digital Versatile Disc; WEBB,*
223 *Weight-Bearing for Better Balance exercise program is designed to improve mobility, increase physical activity and prevent falls; Otago exercise program - series of 17 strength and balance at-home exercises for fall*
224 *prevention program in frail older adults.*
225 Multiple articles reported from same study, study chosen to represent other reports from the same study: *Luger et al[31] – Haider et al 2017[32], Winzer et al 2019[33], Kapan et al 2017[34], Kapan et al 2017[35]; †Cameron et al
226 2013[27] – Fairhall et al 2012[28], Fairhall et al 2014[29], Fairhall et al 2015[30]; ‡Villareal et al 2011[25] – Armamento-Villareal 2016[26]

received training for the study.[32] All studies included strength exercises as part of their interventions. Three studies described guidance on training intensity based on repetition maximum's (RM) between 40-80%.[26, 40, 43] Other components of exercise programs included aerobic fitness,[26, 28, 37, 38] flexibility,[26, 37, 38] and/or balance.[26, 28, 37, 38]. The frequency of interventions ranged from two[32, 37, 40, 43, 44] to five[28, 41] sessions a week, lasting between 20[39, 42, 43] to 90 minutes[26] each. The duration of exercise intervention varied from six weeks[44] to one year.[26, 28, 37, 40]

Characteristics of nutrition intervention component

Characteristics of the nutritional interventions used in studies, are outlined in Table 3, and included combinations of the following: nutrition consultation/education (n=8),[26, 28, 32, 39-42, 44] oral nutrition and/or multivitamin/mineral supplements (n=7), [26, 28, 38-42] meal programs (n=3),[28, 39, 41] self-guided education materials (n=2),[37, 40] and motivational interviewing (n=1).[32] The most common combination of nutrition intervention was consultation/education with oral nutrition and/or multivitamin/mineral supplements (n=5).[26, 39, 42, 44] Five of nine nutrition consultation/education interventions were performed by dietitians.[26, 39, 42, 44] Other studies used trained lay volunteers,[32] a researcher/nutrition therapist or did not specify a skill set for who delivered the consultation/education.[43]

All counselling/education-based interventions aimed to achieve adequate dietary targets for energy, protein and other nutrients. One study on obese frail participants aimed for calorie deficit but ensured that all achieved 1g/kg/day of protein in the intervention group.[26] The reported frequency of consultations ranged from twice a week[32, 43] to fortnightly.[39, 42] Oral nutrition supplements (ONS) were the most common supplements prescribed to intervention group participants (n=7),[26, 38, 39, 41, 42, 44] typically providing 200-300kcal and 12-24g protein per serve with a frequency of consumption up to seven times a week[38, 41] or as prescribed by dietitians[26, 39, 42, 44] to cover any identified deficits between individually estimated energy and protein requirements and actual intake. Calcium and vitamin D were the two most commonly supplemented micronutrients [26, 40] at doses in the range of 1200-1500mg/d and 1000IU/d, respectively. Meal programs were either delivered as inpatient specialised geriatric meals providing 1800-2000kcal/d or home-delivered meal programs.[28, 39, 41]

Frailty outcomes

Data on frailty outcomes were available for quantitative analysis from three studies.[28, 32, 38] The meta-analysis is presented in Figure 2 and suggested that participants who received exercise-nutrition intervention had a greater reduction in frailty score compared to those who received standard care (SMD 0.25; 95% CI 0.03-0.46; P=0.02); no heterogeneity was observed (I^2=0%; P=0.58).

Physical functioning outcomes

Short Physical Performance Battery (SPPB)

Data on the SPPB were available for quantitative analysis from 3 studies, [28, 43, 46] with results from the meta-analysis presented in Figure 3. Participants who received exercise-nutrition intervention had a statistically significant improvement in SPPB score, compared to those that received standard care (MD 0.48; 95% CI 0.12-0.84; P=0.008), with moderate heterogeneity[19] observed (I^2 = 52%; P=0.13).[20, 32, 33] The analysis of SPPB components across all studies showed no statistically significant differences in gait speed[28, 38, 43, 46] (MD 0.02; 95% CI -0.02 to 0.06; P=0.31; I^2=37%, P=0.19) or balance [28, 43, 46] (MD 0.13; 95% CI -0.04 to 0.30; P=0.14; I^2=0%, P=0.22) between groups. There were significantly greater improvements in chair stand test results[28, 43, 46] in the intervention group as compared to the control (MD 0.26; 95% CI 0.09-0.43; P=0.003; I^2 = 23%, P=0.23). Two studies that were not suitable for meta-analysis (as data could not be provided by authors[37] and a different measurement was used[26]) are instead qualitatively described. Arrieta et al reported no significant differences between groups in the percentage of participants who had a ≥1 point decrease in SPPB score at one and two years (P=0.772, P=0.057, respectively).[37] With use of an alternative measure of physical function (modified physical performance test – includes book lift, put on and take off a coat, pick up a penny, chair rise, turn 360, 50-foot walk, 10-steps of stairs, four flight of stairs and progressive Romberg test), Villareal at al[26] reported a significant improvement in their exercise- nutrition interventions group as compared to exercise only (P=0.04), nutrition only (P<0.001), or controls.

Activities of daily living

Data on activities of daily living (ADL) from three studies[29, 34, 43] underwent meta-analysis, from which participants who received exercise-nutrition intervention were determined to have greater ADL independence post-intervention than those who received standard care (SMD 1.06; 95% CI 0.91-1.20; P<0.001, Figure 3). However, high heterogeneity was observed (I^2=96%, P<0.001). As such, additional random effects model was performed (SMD 0.80; 95% CI 0.00-1.60; P<0.001; supplement 2). Data from two studies[41, 44] were unavailable to be included the meta-analysis. One study[40] was excluded due to high risk of bias in outcome measurements but reported that basic ADL declined lesser (P<0.0001) in the intervention vs control group.

Muscle strength

The meta-analysis showed no statistically significant differences in muscle strength between participants who received exercise-nutrition intervention and those that received standard care, when handgrip strength was analysed from three studies[28, 38, 46] (MD 0.46; 95% -0.38 to 0.85; P=0.28; I^2=49%, P=0.14), or, when of handgrip and quadriceps strength was combined (n=4 studies)[28, 38, 43, 46] using a published methodology[47] (SMD 0.10; 95% CI -0.09 to 0.29; P=0.24, I^2=28%, P=0.30) (Figure 3).

Nutrition, Cognition and Biomarkers outcomes

Most studies assessed participants' nutritional status at baseline, while only one study[32] assessed it as an outcome. Luger et al reported a 1.54-point improvement in the MNA long form in participants who received exercise-nutrition intervention compared to those who received standard care (95% CI 0.51-2.56, P=0.004). Combined exercise-nutrition intervention did not affect cognitive status (mini-mental state examination (MMSE)) or mood (geriatric depression scale (GDS)).[44] Armamento-Villareal et al reported a significant decrease in total and free estradiol in their frail obese older men (attributed to weight loss from lifestyle change rather than the intervention), without a clinically meaningful increase in total or free testosterone levels.[27] In one study that reported C-reactive protein (CRP) levels, this inflammatory marker remained stable in the exercise-nutrition intervention group participants, compared to an increase in the social support control group at the end of 12 weeks (P=0.04).[48]

Quality of life and falls

Three studies[31, 36, 39] that evaluated quality of life could not find statistically significant improvement in the intervention as compared to the control group though Milte el al[39] found a trend favouring intervention. Fairhall et al[30] found that risk factors related to falls (physical tests as mentioned above) but not rate of falls were reduced while Kapan et al[35] found that a 10% reduction in fear of falling as ascertained by the falls efficacy scale.

Economic analyses

Only two studies examined the cost-effectiveness of their exercise-nutrition intervention. Fairhall et al[31] reported no additional resource cost in terms of medical (P=0.87) or nursing and health professional appointments (P=0.32). Similarly, Milte et al[39] reported no cost differences between groups (P=0.868).

Discussion

Main findings

The present systematic review and meta-analysis present updated evidence that suggest exercise with nutrition intervention to be effective on frailty and frailty-related physical outcomes in hospitalised older adult patients. When compared to standard care, combined exercise-nutrition interventions improved frailty status as determined by the Fried Frailty criteria [2] and the SHARE-FI.[45] They also improved physical function according to the SPPB and ADLs. Only one study measured and found significant improvement in nutrition score.[32] The two economic analyses included in this review suggested that combined exercise-nutrition interventions, though more effective, were no more costly than standard care.

Existing reviews of exercise and nutrition interventions have highlighted heterogeneity in study protocols (including intervention descriptions), which limits potential for quantitative analysis. They have also focussed on community dwelling participants.[49] This study is novel in reviewing a more vulnerable hospitalised population that has not been previously investigated, and specifically targeting pre-frail or frail older adults. However, out of five studies in this review that used a validated frailty assessment tool, only three had assessed frailty at outcome, and available for quantitative analysis. This could be because the frailty phenotype was first described 2001, with a systematic evaluation of frailty tools a decade later.[2, 50] Accordingly, the authors decided to additionally evaluate frailty components such as physical function, nutrition, cognition and biomarkers as baseline and outcome measures. Although not specific to frailty, these measures provide insights to the effectiveness of exercise-nutrition interventions on improving various components of frailty and may inform future studies.

Previous reviews have found mixed results[49] or have concluded that evidence for combined interventions is limited but increasing.[51] Our results concur with RCTs of exercise-nutrition interventions conducted in community dwelling frail older adults. Tarazona-santabalbina and colleagues found significant improvement in SPPB in participants on a 24-weeks exercise-nutrition intervention as compared to controls in a community dwelling frail population – intervention group 9.5±1.8 vs control group 7.1±2.8, P=0.007.[52] Similarly, Kim et al reported a 12-weeks, community-based study of frail older adults that found SPPB to remain stable in the intervention group, while it decreased by 12.5% (1 point) in controls (P=0.039).[53] Our meta-analysis of individual components of the SPPB suggest that the significant improvements in functional muscle strength as represented by the chair stand component of the SPPB may be pivotal to the increase in overall SPPB post intervention, and reflect the functional lower limb strength training focus of the exercise interventions. However, the meta-analysis of handgrip +/- quadriceps strength did not produce a similar trend. Diversity in outcome measures for frailty and frailty-related domains like physical function is a challenge for comparative analyses between studies. Future studies should carefully consider measure responsiveness when selecting outcome tools.

Nutrition is another important domain within frailty. Yet the majority of studies included in this review only reported nutrition status at baseline, with only one study reporting follow-up nutrition assessment at the end of the intervention.[32] Luger et al described an improvement in nutrition status in a sample of at risk malnourished pre-frail/frail patients (thus likely to benefit most from nutrition therapy). As hospitalised patients have greater energy deficits due to catabolic stress of acute illness, they are a population that requires careful determination of energy/protein requirements and in whom additive effects of nutrition supplementation to exercise may have greatest impact on outcomes such as muscle strength.[52] As none of the studies in the present review reported on energy deficits, it is not known whether these patients received adequate replacement. Nutrition supplementation should also not be confused with nutrition or diet modifications. The provision of ONS alone is unlikely to augment diet adequacy as completely as diet modification that involves a wider range of nutrients and non-nutrients[54] especially when led by dietitians.[55, 56]

For both exercise and nutrition based interventions, an understanding of patient participation dynamics and compliance is required because of how they can impact on effectiveness.[57] Only five studies in this review reported attendance to program/home visits or phone calls or adherence to prescribed exercise/diet or related advice at rates of 50-90% and 70-93% for nutrition and exercise interventions, respectively. Issues with participants resulting in poorer compliance were not reported in these articles, such that the authors recommend that future studies explore barriers and enablers to adherence in multi-modal interventions.

Cognition is another critical domain in the multidimensional nature of frailty. Exercise[58] and nutrition interventions[59] may have a far reaching, positive effect on cognition in older adults. However, there was no evidence of an impact on cognition from a single study[41] in the present review. This is consistent with a network meta-analysis of 13 RCTs that examined exercise and nutrition interventions in frail older adults.[11] One suggested explanation is that different neuronal mechanisms could result in a misfit between combinatory approaches of nutrition and physical interventions [60] highlighting that more in-depth research is required.[61]

The economic delivery of new interventions and models of care is important to a range of stakeholders[62] but has been infrequently conducted in previous studies.[49] In this review, only two out of 11 studies included an economic analysis, with the majority of costs coming from delivery of exercise and nutrition support. The types of consumables that were considered in analyses included nutrition supplements, ankle/wrist weights, mobility aids and medications. Elements of service provision that were considered included community, rehabilitation, residential and transition care service use, which were often reduced and contributed to the net result. The results of this review support previous findings of beneficial effects on frailty-related outcomes, without increased costs.[49] However, results should be interpreted with caution as omission of other services (such as medication reviews) within a multimodal intervention can impact costings, and there are instances where interventions have not been found to be more-cost effective than usual care.[63] The approach of streamlining and reorganising existing services rather than creating entirely new systems may be preferred.

Strength and weakness

This study was robust and underwent peer review by an academic librarian. We did not have a language restriction on the search, and we did not find nor include studies in other languages. We chose to use of an updated version of the Cochrane risk of bias tool (RoB 2), which addresses issues of confusion common to its first version.

By focussing on exercise-nutrition interventions only, this study addresses a gap as identified in a recent review of multi-domain interventions in pre-frail or frail elderly adults, in which some interventions may have been be too broad to directly impact frailty, and functional and cognitive status.[51] Multidisciplinary team based approaches remain recommended and are a bedrock of quality standard care; they may also already include goals for exercise and nutrition such that it may be difficult to solely attribute outcomes to a targeted but supplementary exercise-nutrition program. Social relationships affect health behaviour and physical health,[64] such that intervention benefits may in part come from social interactions. Nevertheless, several studies[28, 32, 42] have demonstrated significant improvements even when control participants are provided with the social aspect of an intervention, such that exercise and nutrition are expected to improve outcomes independent of social interactions. Among the three studies[28, 32, 38] included in the meta-analysis of reduction in frailty score, one study[32] included patients from community. However, when combined with data from the other two studies,[28, 38] participants recruited from the hospital made up majority (~80%) of the entire cohort in that meta-analysis.

Implications and future research

This review is a useful resource for researchers and multi-disciplinary clinicians who are seeking to generate evidence or evaluate their practices of exercise-nutrition interventions for frail hospitalised older adults. The authors interpretation of the quality of studies in this review is that the evidence base is low, but the inclusion of future studies may change estimates of the intervention effects. While blinding of participants to the intervention is acknowledged to be difficult, future studies should be adequately powered, use allocation concealment with blinding outcome assessors and data analysts at least. Improved reporting of intervention details is also required,[65] which may assist in answering research questions around the optimal duration, dose, modality and timing of intervention(s) across the hospital to community continuum. In the present review, potential beneficial effects of combined interventions could have been negated given the short durations reported by most studies. Thus, future studies may be extended for >6-12 months, or employ principles of chronic condition self-management,[66] to determine delayed improvements and achieve long-lasting sustainability of interventions. The lack of evidence from non-western countries, or low- and middle-income countries indicate the need for research to be conducted in those populations too. There are many ongoing research activities relevant to the scope of this review,[67-70] yet only one has reported plans for economic analysis in the study protocol.[67] Economic evaluations can expand current evidence on the sustainability of incorporating such services within resource-constrained healthcare systems.

Conclusion

Exercise-nutrition interventions that start while patients are admitted to hospital and continue in the community/post-hospital, or, commence early post discharge, appear to be effective in reducing frailty and some frailty-related physical indicators. Though effective, the quality of the evidence in this review is low as most studies included had some concerns for risk of bias. Given the paucity of high-quality studies on the effectiveness of combined exercise-nutrition interventions on hospitalised frail older adult patients, more robust research that pays attention to effect of assignment to intervention is needed to increase the confidence in results.

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Author Contributions

All authors contributed to the conception and design of review. CH and YS read and screened titles and abstract of potentially relevant studies. CH and YS evaluated the selected studies and performed data extraction. CH, MM, AY, CB reviewed the evidence. RW provided statistical expertise on meta-analyses. CH drafted the article and all authors provided critical revisions and final approval of the manuscript. All authors had access to the data in the study and can take responsibility for the integrity of the reported findings. All authors fulfil the ICMJE criteria for authorship.

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Competing interests

None declared.

Patient consent

Not required.

Data sharing statement

Details of the excluded papers are available from the corresponding author upon request.

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Figure captions

Fig.1 Flow diagram illustrating results of the search and study selection process as described in the PRISMA statement

Fig 2. Meta-analysis of reduction in frailty score for exercise and nutrition intervention vs standard care

Fig.3 Meta-analyses of Short physical performance battery, Gait speed, Balance test, Chair stand test, Activities of daily living, handgrip strength

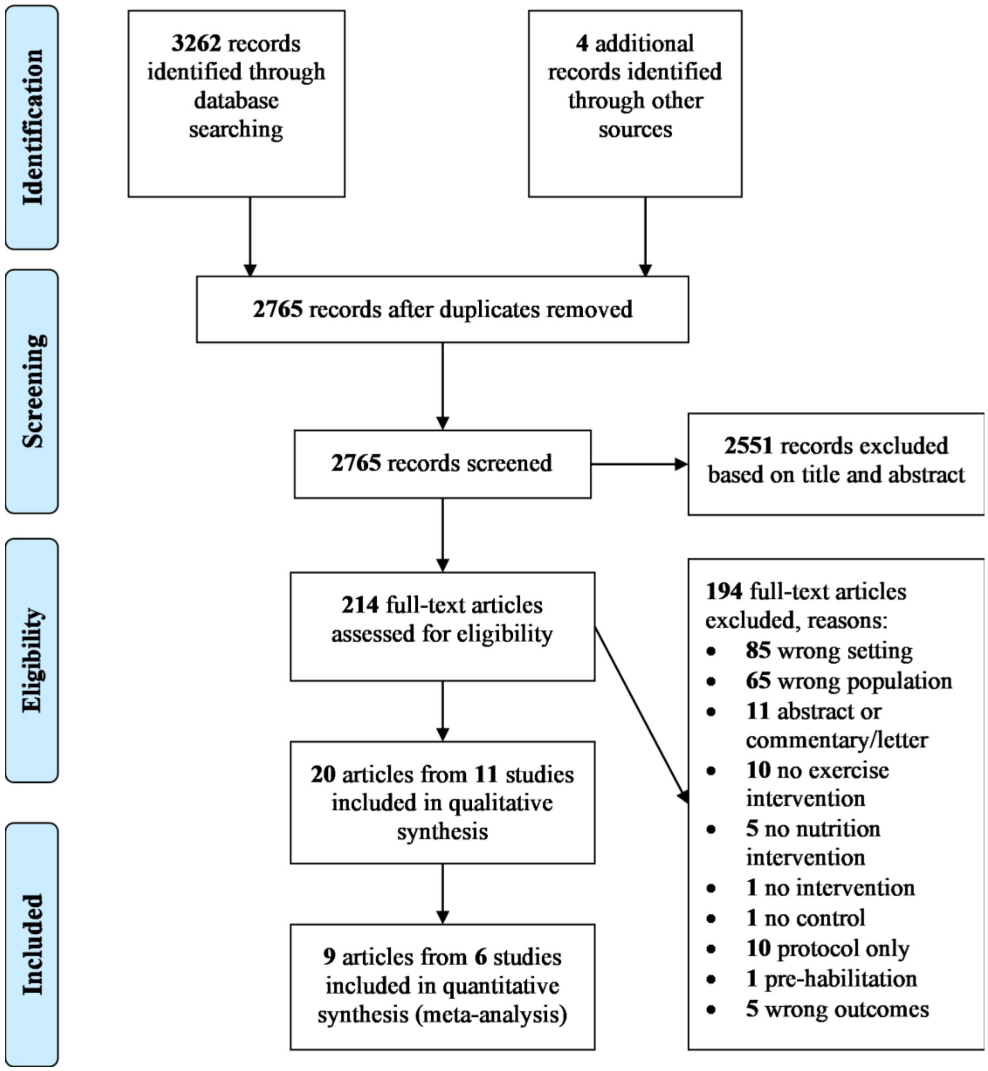


Fig.1 Flow diagram illustrating results of the search and study selection process as described in the PRISMA statement

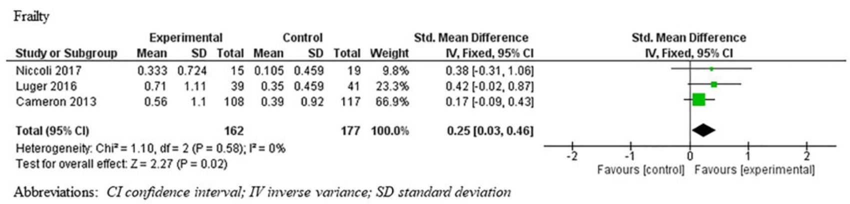


Fig 2. Meta-analysis of reduction in frailty score for exercise and nutrition intervention vs standard care

268x338mm (300 x 300 DPI)

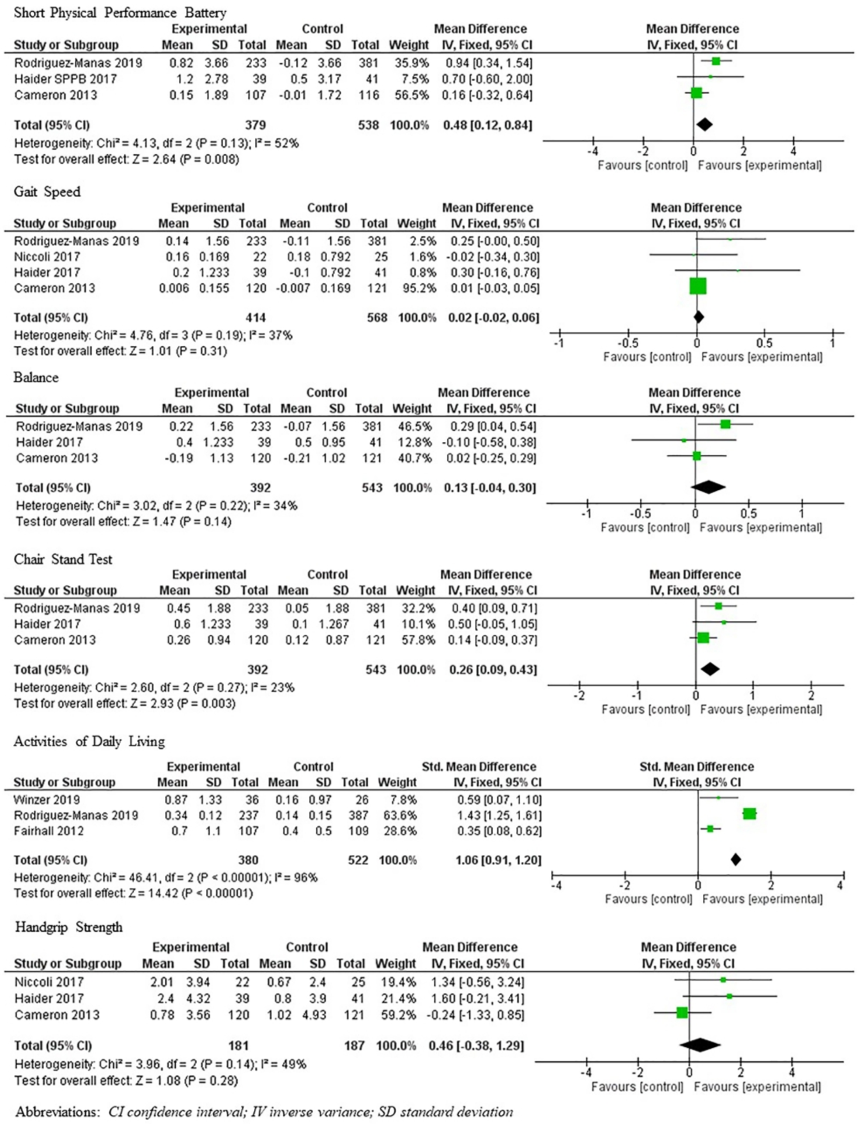


Fig.3 Meta-analyses of Short physical performance battery, Gait speed, Balance test, Chair stand test, Activities of daily living, handgrip strength

268x338mm (300 x 300 DPI)

Search Strategy – Medline

#	Searches
1	"diet, food, AND nutrition"/ or food/ or diet/
2	dietary proteins/ or dietary supplements/
3	Nutritional Status/ or Feeding Behavior/
4	Dietitian/
5	Nutrition Assessment/ or Nutrition Therapy/
6	((diet* or nutrition* or food*) adj5 (intervention or program or supplement or educat* or assess* or advic* or counsel* or treat*)).tw,kf.
7	or/1-6
8	motor activity/ or exercise/ or muscle strength/ or physical endurance/ or physical fitness.mp.
9	Exercise/ or resistance training/
10	(exercis* or "resistance training" or "exercis* therapy" or "muscle stretching exercis*" or "physical exercis*" or "strength train*" or "aerobic exercis*" or hydrotherapy or rehabilitat* or walk* or cycl* or conditioning* or "leg press" or flexib*).mp.
11	Physiotherapy/
12	((exercise* or resistan* or strength) adj5 (intervention or program or educat* or advice* or treat* or train* or rehabilit*)).tw,kf.
13	or/8-12
14	frail elderly/ or pre-frail elderly/
15	frail*.mp.
16	(functional* adj2 (declin* or impair*) adj3 (aged or aging or elderly or elder* or old* or senior*)).mp.
17	(frail* and (geriatric* or gerontolog* or (vulnerable and older))).mp.
18	(frail* and (aged or aging or elderly or elder* or older or senior*)).mp.
19	(frail* and (geriatric* or gerontolog* or aging)).mp.
20	("geriatric assess*" or "functionally-impaired elder*").mp.
21	14 or 15 or 16 or 17 or 18 or 19 or 20
22	7 and 13 and 21

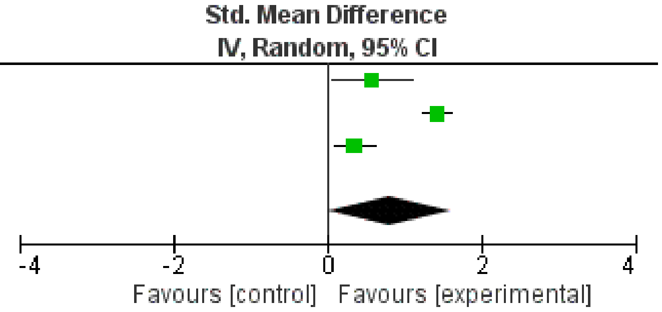
Translated above strategy for other databases: **CINAHL, Emcare, Scopus, Cochrane, Ageline and PEDro**

Activities of Daily Living – Random Effects Model

	Experimental			Control				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Winzer 2019	0.87	1.33	36	0.16	0.97	26	31.0%	0.59 [0.07, 1.10]
Rodriguez-Manas 2019	0.34	0.12	237	0.14	0.15	387	34.9%	1.43 [1.25, 1.61]
Fairhall 2012	0.7	1.1	107	0.4	0.5	109	34.1%	0.35 [0.08, 0.62]
Total (95% CI)			**380**			**522**	**100.0%**	**0.80 [0.00, 1.60]**

Heterogeneity: Tau² = 0.47; Chi² = 46.41, df = 2 (P < 0.00001); I² = 96%

Test for overall effect: Z = 1.96 (P = 0.05)



Abbreviations: *CI confidence interval; IV inverse variance; SD standard deviation*

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5-6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	nil
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8, fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10-11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-18
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-18, fig. 2 & 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8, Fig 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	nil
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22-23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	24

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

Effectiveness of combined exercise and nutrition interventions in pre-frail or frail older hospitalised patients: a systematic review and meta-analysis

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Secondary Subject Heading:	Rehabilitation medicine
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Title Page

Effectiveness of combined exercise and nutrition interventions in pre-frail or frail older hospitalised patients: a systematic review and meta-analysis

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Keywords: frail; pre-frail; older people; exercise; nutrition

Word count: 4677 (excluding abstract, references, tables, figures)

PROSPERO registration: CRD42020153934

Abstract

Objectives: To determine the effectiveness of combined exercise-nutrition interventions in pre-frail/frail hospitalised older adults on frailty, frailty-related indicators, quality of life (QoL), falls and its cost-effectiveness.

Design: Randomised controlled trials (RCTs) of combined exercise-nutrition interventions on hospitalised pre-frail/frail older adults ≥65 years were collated from MEDLINE, Emcare, CINAHL, Ageline, Scopus, Cochrane and PEDro on 10th October 2019. The methodological quality was appraised, and data were summarised descriptively or by meta-analysis using a fixed effects model. The standardised mean difference (SMD) or difference of means (MD) with 95% confidence intervals (CIs) was calculated.

Results: Twenty articles from 11 RCTs experimenting exercise-nutrition interventions on hospitalised older adults were included. Eight articles were suitable for the meta-analyses. One study had low risk of bias and found improvements in physical performance and frailty-related biomarkers. Exercise interventions were mostly supervised by a physiotherapist, focusing on strength, ranging 2-5 times/week, of 20-90 minutes duration. Most nutrition interventions involved counselling and supplementation but had dietitian supervision in only three studies. The meta-analyses suggest that participants who received exercise-nutrition intervention had greater reduction in frailty scores (n=3, SMD 0.25; 95% CI 0.03-0.46; P=0.02) and improvement in short physical performance battery (SPPB) scores (n=3, MD 0.48; 95% CI 0.12-0.84; P=0.008) compared to standard care. Only the chair-stand test (n=3) out of the three SPPB components was significantly improved (MD 0.26; 95% CI 0.09-0.43; P=0.003). Patients were more independent in activities of daily living in intervention groups, but high heterogeneity was observed (I^2=96%, P<0.001). The pooled effect for handgrip (n=3) +/- knee extension muscle strength (n=4) was not statistically significant. Nutritional status, cognition,

biomarkers, QoL, falls and cost-effectiveness were summarised descriptively due to insufficient data.

Conclusions: There is evidence, albeit weak, showing that exercise-nutrition interventions are effective to improve frailty and frailty-related indicators in hospitalised older adults.

PROSPERO registration number: CRD42020153934

Strengths and limitations of study

- This is the first comprehensive systematic review with meta-analysis on the effectiveness of exercise-nutrition interventions on frailty and outcomes related to frailty in hospitalised and pre-frail/frail older adults.
- Only randomised controlled trials describing existing exercise-nutrition interventions in pre-frail/frail older hospitalised patients were included.
- There was a moderate risk of bias for most included studies such that the findings of this review are inconclusive, making it difficult to draw firm conclusions.

Introduction

Frailty is a major contributor to late-life disability as it leads to loss of independence.[1] It is also associated with poor health outcomes, and, increased health-care costs and service use.[1] Frailty has been defined for clinical research by Fried et al[2] as a combination of unintentional weight loss, weakness, exhaustion, slowness and reduced physical activity. Pre-frailty is a stage before frailty, where one or two of the five aforementioned symptoms are present.[2] There are no gold standard in the clinical care setting to define frailty or pre-frailty but is commonly understood as age-related physiological decline, resulting in increased vulnerability to health crises.[3] Older adults (aged >65 years) that have been classified as frail and are hospitalised, have a three-fold higher risk of readmission or death, as compared to the younger population.[4] The management of older adults who are frail has an incremental effect on health expenditures with an additional equivalent of AU$2400 per frail patient per year.[5] With 21% of the population over 65 years estimated to be frail and 48% estimated to be pre-frail, concerns of economic impact are compounded by an ageing population.[6]

Exercise and nutrition are inextricably linked, in particular strength training can address component issues of the frail phenotype.[7] Yet evidence supporting the effectiveness of exercise-nutrition interventions for reversal of frailty is limited to community-dwelling older adults.[8] In a study of community participants, a 3-month combined exercise-nutrition intervention resulted in a significant reversal of frailty (reduction in Fried frailty score) at 6-months, compared to the control group (between-group difference −0.34; 95% confidence interval [CI] -0.52 to −0.16; $P<0.001$).[9] The combination of exercise therapy and dietary intervention in older adults who are frail, has also been reported to increase muscle strength (knee extension between-group difference 1.84 kg, 95% CI 0.17–3.51, P=0.03)[10] and improve nutritional status (Mini Nutritional Assessment (MNA) Short Form between group difference 1.4, 95% CI 0.9-1.9, $P<0.01$).[11]

A recent meta-analysis suggested that although effective, exercise combined with nutrition was not more effective in treating frailty than exercise alone.[12] However, the majority of included studies were conducted in a community setting, with only 15% of older adults either hospitalised or recruited from acute care settings. No study has systematically evaluated evidence for interventions that commence during acute hospitalisation or early post discharge (in the high-risk period for post-hospital syndrome).

Hospitalisation is a vulnerable period, especially for older adults who are frail and therefore at higher risk of functional loss,[13] malnutrition[14, 15] and further decline in frailty status. Malnutrition is ubiquitous in older hospitalised patients with a prevalence as high as 50%.[16]

Since many domains of frailty are attributed to poor nutrition,[17] the effect of nutrition intervention when combined with exercise, may be more significant in the hospitalised population.[17] Also, a recent review suggests that nutrition support, provided by a multidisciplinary team, may have a positive impact on mortality and quality of life in hospitalised older adult patients.[18] Nutritional therapy extends beyond protein or nutrition supplementation as reported in previous studies and may be more effective as part of individualised medical nutrition therapies involving dietitians to improve diet adequacy.[19]

This study aims to determine the effectiveness of combined exercise-nutrition interventions on (1) frailty, (2) frailty-related indicators, falls, quality of life (QoL) and (3) its cost effectiveness on pre-frail or frail hospitalised older adults.

Materials and Methods

Protocol and registration

The protocol for this review was compliant with Cochrane systematic review guidelines,[20] and registered with the International Prospective Register of Systematic Reviews (PROSPERO), CRD42020153934. The study is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[21] Patients and/or members of the public were not involved in this study.

Search methods

Systematic searches of electronic databases (MEDLINE, Emcare, CINAHL, Ageline, Scopus, Cochrane and PEDro) were conducted by the lead author (CH) from inception until 10th October 2019 using search strategies reviewed by an academic librarian (search queries available in Supplementary file 1). Additionally, related citations to eligible items were identified using the suggested related citation function in Pubmed. Reference lists of eligible items were also screened.

Inclusion and exclusion criteria

The inclusion criteria were: 1) randomised controlled trials; 2) inclusion of pre-frail or frail participants (as defined by study authors); 3) recruitment of older adult inpatients and/or those hospitalised within the past 30 days of recruitment; 4) interventions that started while patients were admitted and continued in the community/post-hospitalisation, or, commenced within 30 days of hospital discharge; 5) interventions that involved both physical exercises and nutritional interventions (dietary modifications/education/training alone or combined with oral nutrition supplementation); 6) measured frailty with an assessment tool or at least one indicator relevant to frailty (nutritional status, physical function, cognitive function and mood, physical activity level or biomarkers, falls and QoL and/or economic analysis of interventions. Studies were excluded if they described protocols with no pilot outcomes, interventions delivered as a part of a palliative care program, or interventions solely designed to facilitate discharge planning (e.g. telephone support services, providing no pre-frailty or frailty intervention element), recruited participants admitted following a mental health episode.

Study selection and data extraction

Covidence[22] was used to manage citations for title and abstract, and full-text screening, in duplicate (CH and YS, Supplementary file 1). The reviewers were unblinded to authors, journals and countries of origin. Any disagreement was resolved through discussion or consensus opinion with the other authors. A data extraction form was developed a priori by the research team, such that two researchers (CH and YS) performed data extraction independently, on eligible full-text articles. Where available, the continuous data were extracted as (i) mean change with standard deviation (SD), standard error of mean (SE) or 95%

confidence interval (CI), or (ii) mean or median values with SD, SE or interquartile range post intervention. If the required data were not reported within a publication (including change in means for outcomes of interest), the authors were emailed to request for it.

Quality of the studies

The risk of bias in the individual studies was assessed by the Revised Cochrane risk-of-bias tool for randomised trials (RoB-2) by two researchers (CH and YS) independently.[23] Any disagreements were resolved by discussion or if required with consensus of a third reviewer. The Cochrane risk-of-bias tool is widely used to assess randomised controlled trials (RCT) for best practice.[24] Studies were given an overall risk-of-bias judgement of low, some concerns or high. Overall risk-of-bias was determined as having "some concerns" if any one of the risks of bias domains was rated as having "some concerns". Likewise, studies were deemed to have an overall high risk of bias if any one domain had a high risk of bias.

Data synthesis and statistical analyses

Where possible, a meta-analysis was performed; continuous outcome data were pooled and reported as either the difference of means (MD) if the same outcome assessment tools were used or the standardised mean difference (SMD) if different outcome assessment tools were used, and the 95% CI, if there were two or more studies. The SMD is the mean difference when the outcome for each study is standardised to have mean zero and SD=1. Studies presenting SE were converted to SD via the conversion formula.[20] The fixed-effect meta-analyses were carried out with Cochrane Review Manager (RevMan) 5.3.[25] A P value of <0.05 was considered statistically significant. The variability between studies (heterogeneity) was assessed by I^2 and its 95% CI.[26] For studies with unobtainable missing, or incomparable data, results were qualitatively synthesised.

Patient and public involvement

No patients were involved in this study

Results

Study selection

The flow of studies through the review process is summarised in Figure 1. Twenty articles reporting on 11 studies were eligible for data synthesis and analysis. Three of 11 studies presented results from their cohort across separate publications. Firstly, Villareal et al[27] reported on physical functioning outcomes with biomarker results in the publication of Armamento-Villareal et al.[28] Secondly, Cameron et al[29] reported on frailty and some physical function outcomes, with other physical function outcomes in a secondary publication[30] fall rates[31] and cost-analysis in another.[32] Thirdly, Luger et al[33] reported on frailty and nutritional status, with physical functioning outcomes across two other publications,[34, 35] fall efficacy[36] and quality of life.[37] For clarity, the primary articles that report frailty or physical function outcomes are cited for descriptive data in Tables 1-3 while individual articles are cited for synthesis of outcome results.

Study and sample characteristics

Details of study characteristics are available in Table 1. Across all studies, a total of 2307 participants were investigated. Most studies reported that patients were recruited from hospital wards (n=7)[29, 38-43] while the other four studies[27, 33, 44, 45] included patients that were recruited from hospital wards and community. Seven studies included only frail participants,[27, 29, 40-43, 45] and the remaining four studies[33, 38, 39, 44] included frail, pre-frail and non-frail participants. The Fried frailty phenotype criteria[2] were used most frequently to classify frailty (n=4).[29, 38, 39, 44] with participants considered non-frail, pre-frail or frail if 0, 1-2, 3-5 criteria were present, respectively. Luger et al used the Frailty Instrument for Primary Care of the Survey of Health, Ageing, and Retirement in Europe (SHARE-FI)[33] which integrates components of exhaustion, appetite, handgrip strength, walking difficulties and physical activity.[46] Five studies did not report any assessment method to define frailty.[40-43, 45] One study used a combination of three tools – modified Physical Performance Test, the measurement of VO_2 peak, and the Functional Status Questionnaire.[27]

Risk of bias within individual studies

Table 2 outlines the risk of bias in individual studies. One study[27] had a low risk of bias and one study[41] had a high risk of bias (including unblinded secondary outcome assessment and insufficient detail on standard care in control groups across recruitment sites). The other nine studies[29, 33, 38-40, 42-45] were rated as having some concerns overall, of which five could have been improved in ≥1 domain. The remaining four studies[27, 31, 39, 41] that were rated as having "some concerns" overall, had risk in only one domain with the most common reason being failure to blind intervention/allocated group to participants. Examples of other concerns about risk of bias included: assessors being aware of the group allocation[33] (measurement of outcomes domain); or a lack of information about participants/researcher blinding to group allocation.[27, 29, 44]

Characteristics of exercise intervention component

Characteristics of the exercise interventions used in studies are outlined in Table 3, and included combinations of the following: supervised individual exercises (n=10),[27, 29, 38-45] group exercises (n=3),[27, 41, 45] education including support with resources (digital versatile disc (DVD) or visual aid instruction booklet, n=2),[33, 38] and motivational interviewing using a standardised protocol (n=1).[33] Three studies[39, 42, 44] had inpatient only interventions, five[38, 40, 41, 43, 45] had interventions that extended from inpatient to post-discharge, two[29, 33] studies offered the intervention post-discharge only and one[27] did not report.

In the majority of studies (n=9), the exercise component was delivered by a physiotherapist.[27, 38-45] Two studies used trained fitness instructors,[38, 41] and another engaged lay volunteers who received training for the study.[33] All studies included strength exercises as part of their interventions. Three studies described guidance on training intensity based on repetition maximum's (RM) between 40-80%.[27, 41, 44] Other components of exercise programs included aerobic fitness,[27, 29, 38, 39] flexibility,[27, 38, 39] and/or balance.[27, 29, 38, 39]. The frequency of interventions ranged from two[33, 38, 41, 44, 45] to five[29, 42] sessions a week, lasting between 20[40, 43, 44] to 90 minutes[27] each. The duration of exercise intervention varied from six weeks[45] to one year.[27, 29, 38, 41]

Characteristics of nutrition intervention component

Characteristics of the nutritional interventions used in studies, are outlined in Table 3, and included combinations of the following: nutrition counselling (n=8),[27, 29, 33, 40-43, 45] oral nutrition and/or multivitamin/mineral supplements (n=7), [27, 29, 39-43] meal programs (n=3),[29, 40, 42] self-guided education materials (n=2).[38, 41] The most common combination of nutrition intervention was counselling with oral nutrition and/or multivitamin/mineral supplements (n=5).[27, 40, 43, 45] Five of nine nutrition counselling interventions were performed by dietitians.[27, 40, 43, 45] Other studies used trained lay volunteers,[33] a researcher/nutrition therapist or did not specify a skill set for who delivered the counselling.[44]

All counselling interventions aimed to achieve adequate dietary targets for energy, protein and other nutrients. One study on obese frail participants aimed for calorie deficit but ensured that all achieved 1g/kg/day of protein in the intervention group.[27] The reported frequency of counselling ranged from twice a week[33, 44] to fortnightly.[40, 43] Oral nutrition supplements (ONS) were the most common supplements prescribed to intervention.

Table 1. Characteristics of included studies examining pre-frail or frail hospitalised older adults

Study	Country	n	Mean age	Study participants, characteristics	Recruitment site	Duration of intervention	Follow-up period	Frailty diagnostic tool/criteria used	Reported % of prefrail, frail
Arrieta *et al*, 2019[35]	France	302	76.7 ±5.0	Frail, onco-geriatric, older men & women; BMI: 26.1 ±4.6 kg/m^2 (UCG); 26.2 ±4.4 kg/m^2 (IG)	Acute hospital	1y	1y, 2y	Fried frailty phenotype criteria	Non-frail: 73.6% Frail: 26.4%
Rodriguez-Manas *et al*, 2019[41]	Spain	964	78.0 ±5.44	Frail older men and women with T2DM; BMI: 29.6 ±5.0 kg/m^2	Acute hospitals or primary care sites	4.5m (exercise), 3.5-4w (nutrition)	1y	Fried frailty phenotype criteria	Pre-frail: 62.2% Frail: 37.8%
Niccoli *et al,* 2017[36]	Canada	47	81.3 ±1.0	Frail older men and women hospitalised patients; BMI: 26.4 ±6.6 kg/m^2 (UCG), 24.2 ±5.2 kg/m^2 (IG)	Acute hospital	Average LOS (days): 20.9 (UCG), 26.5 (IG)	Upon discharge	Fried frailty phenotype criteria	Pre-frail: at least 87.8% Frail: NR
Luger *et al*, 2016*[30]	Austria	80	82.8 ±8.0	Frail older men and women; BMI: 27.2 ±4.3 kg/m^2	Acute hospital and community	3m	3m	SHARE-FI (female>0.315; male: >1.212 points)	Non-frail: 1% pre-frail: 35%, frail: 64%
Milte *et al*, 2016[37]	Australia	175	83.0 ±6.2 (UCG), 82.4 ±5.7 (IG)	Frail older men and women post hip fracture, BMI: NR	Acute hospital	6m	6m	NR	Frail: 100% as determined by study authors
Cameron *et al*, 2013†[26]	Australia	241	83.3 ±5.9	Frail older men and women, BMI: 26.4 ±6.0 kg/m^2 (UCG) 26.1 ±5.9 kg/m^2 (IG)	Acute hospital	1y	3m, 1y	Fried frailty phenotype criteria	Frail: 100% as determined by study authors
Singh *et al*, 2012[38]	Australia	124	79.3 ± 9.6	Frail older men and women; BMI: NR	Acute hospital	1y	4m, 1y	NR	Frail: 100% as determined by study authors
Villareal *et al*, 2011‡[24]	United States	107	69.3 ±4.1	Frail obese older men; BMI: 36.8 ±4.6 kg/m^2	Acute hospital and community	1y	6m, 1y	≥2 criteria: Modified PPT score 18–32; VO^2 peak of 11–18 ml ml/kg; difficulty in performing 2 IADL or 1 basic ADL	Mild-moderate frailty: 100%

Azad *et al*, 2008[42]	Canada	91	74.2 and 75.8	Frail CHF older women; BMI: NR	Acute hospital and community	6 weeks	6w, 6m	Screened by a CHF coordinator, frailty assessment undefined	Frail: 100% as determined by study authors
Blanc-Bisson *et al*, 2008[39]	France	76	85.4 ±6.6	Frail older men and women; BMI: 24.0 ±5.1 kg/m^2	Acute hospital	Until clinical stability	Clinically stable, 1m	NR	Frail: 100% as determined by study authors
Miller *et al*, 2006[40]	Australia	100	83.5 ±2.8	Frail older men and women with LL fracture; BMI: 22.1 ±4.3 kg/m^2 (ACG), 23.2 ± kg/m^2 (IG)	Acute hospital	3m	3m	NR	Frail: 100%

Abbreviations: *BMI, Body Mass Index; w, Weeks; m, Months; y, Years; VO^2 max, maximal oxygen uptake; PPT, physical performance test; IADL, Instrumental Activities of Daily Living; ADL, Activities of Daily Living; SHARE-FI, Survey of Health, Ageing and Retirement in Europe-Frailty Instrument; T2DM, Type 2 Diabetes Mellitus; CHF, Chronic Heart Failure; LL, Lower Limb, LOS, length of stay; IG, Intervention group; UCG, Usual care group; ACG, Attention control group; NR, not reported; BMI presented in Mean ±standard deviation*

Multiple articles reported from same study, study chosen to represent other reports from the same study: *Luger et al[31] – Haider et al 2017[32], Winzer et al 2019[33], Kapan et al 2017[34], Kapan et al 2017[35]; †Cameron et al 2013[27] – Fairhall et al 2012[28], Fairhall et al 2014[29], Fairhall et al 2015[30]; ‡Villareal et al 2011[25] – Armamento-Villareal 2016[26]

Table 2. Assessment of methodology quality of included studies using Cochrane Risk of Bias 2.0 tool

Study	Cochrane Risk of Bias 2.0 tool assessment domains					
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Arrieta *et al*, 2019[35]	+	?	?	?	+	?
Rodriguez-Manas *et al*, 2019[41]	+	?	+	?	+	?
Niccoli *et al*, 2017[36]	?	?	+	?	+	?
Luger *et al*, 2016*[30]	+	+	+	?	+	?
Milte *et al*, 2016[37]	+	?	+	+	+	?
Cameron *et al*, 2013†[26]	+	?	+	+	+	?
Singh *et al*, 2012[38]	+	?	+	—	+	—
Villareal *et al*, 2011‡[24]	+	+	+	+	+	+
Azad *et al*, 2008[42]	+	?	+	?	+	?
Blanc-Bisson *et al*, 2008[39]	+	?	+	?	+	?
Miller *et al*, 2006[40]	+	?	+	+	+	?

Key: + = Low risk of bias; ? = Some concerns of risk of bias; — = High risk of bias
[a]Deviations from intended interventions (effect starting and adhering to intervention)
Multiple articles reported from same study, study chosen to represent other reports from the same study: *Luger et al[31] – Haider et al 2017[32], Winzer et al 2019[33], Kapan et al 2017[34], Kapan et al 2017[35]; †Cameron et al 2013[27] – Fairhall et al 2012[28], Fairhall et al 2014[29], Fairhall et al 2015[30]; ‡Villareal et al 2011[25] – Armamento-Villareal 2016[26]

Table 3. Characteristics of exercise and nutrition intervention and controls of included studies

Study	Exercise intervention	Nutrition intervention	Control intervention
Arrieta *et al*, 2019[35]	**Type:** *Strength* **–** Intensity range from low to high, starting at 10 repetition per exercise **(UL, LL)** with option of progressive loading *Aerobic, Flexibility, Balance* **–** intensity individualised **Frequency:** 2 sessions/week, duration per session NR + home exercises duration NR **Setting:** Inpatient (supervised, individual) + post-discharge (unsupervised, individual) **Additional support reported:** Phone consults (by trainer 2x/month for first 6 months then monthly for 1 year); Education resource	**Self-guided education resource:** Provided with French National Nutrition Health Program education booklet - *Programme National Nutrition Santé* (PNNS)	**Usual care:** NR, variable between study sites **Self-guided education resource:** Provided with French National Nutrition Health Program education booklet - *Programme National Nutrition Santé* (PNNS)
Rodriguez-Manas *et al*, 2019[41]	**Type:** *Strength* – 40-80% of estimated 1RM, 8–10 repetitions **(LL)** **Frequency:** 2-weeks pretraining followed by 16-week program of 2 days/week; 20-30 minutes/sessions **Setting:** Inpatient (supervised, individual)	**Nutrition counselling:** 7 educational sessions, each 45 minutes, delivered by a trained researcher or nutritional therapist, twice a week over 3.5-4 weeks. Therapy focused on behavioural change, nutrition optimisation and diabetes.	**Usual care:** usual health care from local health system and/or general practitioner
Niccoli *et al,* 2017[36]	**Type:** *Strength, Aerobic, Flexibility, Balance* – intensity and target muscle group individualised based on patient's baseline assessment **Frequency:** individualised based on patient's baseline assessment **Setting:** Inpatient (supervised, individual)	**Supplements:** Daily ONS with 24g whey protein per day (*9g breakfast, 7.5g at lunch and dinner*) in addition to usual diet	**Usual care:** usual medical care, no whey protein supplementation. **Individual supervised exercise**: Individualised exercises as per intervention.
Luger *et al*, 2016*[30]	**Type:** *Strength* –2 sets of 15 repetitions **(UL, LL)** until muscular exhaustion, **Frequency:** 2x/week, >30 minutes each session **Setting:** Post-discharge (supervised, individual) **Additional support reported:** Physical education (2-3 times/week, 30 minutes each session); Exercise education resource (demonstration DVD); Motivational interviewing.	**Nutrition counselling:** Trained, supervised lay volunteers visit twice/week for dietary discussions aimed at achieving adequate energy, protein and other nutrients. Taught how to enrich food with protein, recipes, healthy for life plate which consists of food-cards and a play board.	**Usual care with attention control:** Trained lay "buddies" visit twice a week but doing a portfolio of possible activities (go out, have a chat, and sharing interest), especially cognitive training
Milte *et al*, 2016[37]	**Type:** *Strength, Balance (Otago exercise program)* – Intensity and repetitions NR, at the discretion of the treating physiotherapist **(LL)**	**Nutrition counselling: I**ndividualised nutrition therapy aimed at improving energy and protein	**Usual care:** Usual rehabilitation program recommended during hospitalisation, social visits

	Frequency: 3 times/week, 20-30minutes/session for 12 weeks **Setting:** Inpatient (supervised, individual) + post-discharge (supervised, individual)	intake to meet requirements by dietitian who visits fortnightly. **Meal program:** ordered as deemed necessary by dietitian. **Supplements:** commercial ONS recommended if needed by dietitian	weekly from trial staff and generic nutrition, exercise and falls prevention information
Cameron *et al*, 2013†[26]	**Type:** *Strength, Balance, Aerobic* + *WEBB program* – intensity and target muscle groups NR **Frequency:** Exercises prescribed 3-5x/week (with 2 sessions for mobility training) for 1 year, supported by up to 10 home visits **Setting:** Post-discharge (supervised, individual) + (unsupervised, individual)	**Nutrition counselling:** Clinical evaluation of nutritional intake at home. A series of diet intervention as needed by dietitian. **Meal program:** ordered as deemed necessary by dietitian. **Supplements:** commercial ONS recommended if needed by dietitian	**Usual care:** usual health care during hospitalisation and from their general practitioner and community services after discharge
Singh *et al*, 2012[38]	**Type:** *Strength* **–** 80% of most recent 1RM or RPE <15, 3 sets of 8 repetitions **(UL, LL)** **Frequency:** 2 sessions/week, session duration NR, over average of 80 sessions in 1 year, start as early as post assessment in hospital or at home. **Setting:** Inpatient (supervised, individual) + (supervised, group-based) **Additional support reported:** Monthly phone consults	**Nutrition counselling:** Counselling on increase in diet quality, frequency NR **Supplements:** ONS +/- dietary advice to increase daily energy (400-600 kcal) and protein (20 g/day) intake. For those calcium or vit-D deficient (52%), 12 months of vit-D orally (1000 IU/day) or calcium (1200 mg/d) and vit-D combination supplement **Self-guided nutrition resource:** Food sources of calcium, vitamin D and sun exposure	**Usual care:** standard service offered for hip fracture in the area health service, including orthogeriatric care, rehabilitation service, other medical and allied health consultation as required, and physiotherapy.
Villareal *et al*, 2011‡[24]	**Type:** *Strength* **–** 65% of 1RM; 8-12 repetitions of each exercise **(UL, LL)** with options for progression *Aerobic,* ~65% of peak HR with gradual progression to 70-85% *Flexibility, Balance* **Frequency:** 90 minutes, 3 sessions/week **Setting:** Inpatient (supervised, group-based)	**Nutrition counselling:** prescribed a balanced diet with energy deficit of 500-750 kcal/d from daily energy requirement, 1 g of high-quality protein/kgbw/d. Weekly group consultation with dietitian for adjustments of their caloric intake, goals and behavioral therapy. **Supplements:** 1500 mg of calcium/d day and ~1000 IU vitamin D/d	**Usual care:** General healthy lifestyle advice **Supplements:** 1500 mg of calcium/d day and ~1000 IU vitamin D/d
Azad *et al,* 2008[42]	**Type:** 'Comprehensive exercise program'; type, intensity and target muscle groups NR **Frequency:** 11 sessions over 6 weeks + NR home exercises **Setting:** Inpatient (supervised, group-based), post-discharge (unsupervised, individual)	**Nutrition counselling:** 3 sessions of individualized counselling about diet and nutrition in the management of CHF by dietitian	**Usual care:** Optimal medical care

Blanc-Bisson *et al*, 2008[39]	**Type:** *Strength* **–** intensity (RM) NR, 10 x repetitions each exercise **(LB)** **Frequency:** 30 minutes, twice/day, five days/week **Setting:** Inpatient **(**supervised, individual)	**Meal program:** Geriatric hospital meals of 1800-2000 kcal/d **Supplements:** 1 daily ONS of 200 kcal and 15g protein	**Usual care:** From day 3 to 6, patients started to walk with human help with or without technical assistance in the physiotherapy room for three sessions per week until discharge. **Individual supervised exercise:** Physiotherapy continued at home for one month.
Miller *et al*, 2006[40]	**Type:** *Strength* – intensity (RM) NR, 2 sets of 8 repetitions (**LL**) with progressive loading, at the discretion of the treating physiotherapist **Frequency:** 3 times/week, 20-30minutes/session for 12 weeks **Setting:** Inpatient (supervised, individual) + Post-discharge (supervised, individual)	**Nutrition counselling:** Individualised nutrition therapy by dietitian. **Supplements:** single type of ONS to cover the shortfall between individual estimated energy and protein requirements and actual intake over 42 days.	**Usual care with attention control group** - received tri-weekly visits weeks 1-6, then weekly visits 7-12 to account for the possibility of the attention effect.

Abbreviations: *UL, Upper Limb; LL, Lower Limb; NR, not reported; HR, Heart Rate; CHF, Chronic Heart Failure; ONS, Oral Nutrition Supplements, RM, Repetition Max; DVD, Digital Versatile Disc; WEBB, Weight-Bearing for Better Balance exercise program is designed to improve mobility, increase physical activity and prevent falls; Otago exercise program - series of 17 strength and balance at-home exercises for fall prevention program in frail older adults.*

Multiple articles reported from same study, study chosen to represent other reports from the same study: *Luger et al[31] – Haider et al 2017[32], Winzer et al 2019[33], Kapan et al 2017[34], Kapan et al 2017[35]; †Cameron et al 2013[27] – Fairhall et al 2012[28], Fairhall et al 2014[29], Fairhall et al 2015[30]; ‡Villareal et al 2011[25] – Armamento-Villareal 2016[26]

group participants (n=7),[27, 39, 40, 42, 43, 45] typically providing 200-300kcal and 12-24g protein per serve with a frequency of consumption up to seven times a week[39, 42] or as prescribed by dietitians[27, 40, 43, 45] to cover any identified deficits between individually estimated energy and protein requirements and actual intake. Calcium and vitamin D were the two most commonly supplemented micronutrients [27, 41] at doses in the range of 1200-1500mg/d and 1000IU/d, respectively. Meal programs were either delivered as inpatient specialised geriatric meals providing 1800-2000kcal/d or home-delivered meal programs.[29, 40, 42]

Frailty outcomes

Data on frailty outcomes were available for quantitative analysis from three studies.[29, 33, 39] The meta-analysis is presented in Figure 2 and suggested that participants who received exercise-nutrition intervention had a greater reduction in frailty score compared to those who received standard care (SMD 0.25; 95% CI 0.03-0.46; P=0.02); no heterogeneity was observed (I^2=0%; P=0.58).

Physical functioning outcomes

<u>Short Physical Performance Battery (SPPB)</u>

Data on the SPPB were available for quantitative analysis from three studies, [29, 44, 47] with results from the meta-analysis presented in Figure 3. Participants who received exercise-nutrition intervention had a statistically significant improvement in SPPB score, compared to those that received standard care (MD 0.48; 95% CI 0.12-0.84; P=0.008), with moderate heterogeneity[20] observed (I^2 = 52%; P=0.13).[20, 32, 33] The analysis of SPPB components across all studies showed no statistically significant differences in gait speed[29, 39, 44, 47] (MD 0.02; 95% CI -0.02 to 0.06; P=0.31; I^2=37%, P=0.19) or balance [29, 44, 47] (MD 0.13; 95% CI -0.04 to 0.30; P=0.14; I^2=0%, P=0.22) between groups. There were significantly greater improvements in chair stand test results[29, 44, 47] in the intervention group as compared to the control (MD 0.26;

95% CI 0.09-0.43; P=0.003; I^2 = 23%, P=0.23). Two studies that were not suitable for meta-analysis (as data could not be provided by authors[38] and a different measurement was used[27]) are instead qualitatively described. Arrieta et al reported no significant differences between groups in the percentage of participants who had a ≥1 point decrease in SPPB score at one and two years (P=0.772, P=0.057, respectively).[38] With use of an alternative measure of physical function (modified physical performance test – includes book lift, put on and take off a coat, pick up a penny, chair rise, turn 360, 50-foot walk, 10-steps of stairs, four flight of stairs and progressive Romberg test), Villareal at al[27] reported a significant improvement in their exercise- nutrition interventions group as compared to exercise only (P=0.04), nutrition only (P<0.001), or controls.

Activities of daily living

Data on activities of daily living (ADL) from three studies[30, 35, 44] underwent meta-analysis, from which participants who received exercise-nutrition intervention were determined to have greater ADL independence post-intervention than those who received standard care (SMD 1.06; 95% CI 0.91-1.20; P<0.001, Figure 3). However, high heterogeneity was observed (I^2=96%, P<0.001). As such, additional random effects model was performed (SMD 0.80; 95% CI 0.00-1.60; P<0.001; Supplementary file 2). Data from two studies[42, 45] were unavailable to be included the meta-analysis. One study[41] was excluded due to high risk of bias in outcome measurements but reported that basic ADL declined lesser (P<0.0001) in the intervention vs control group.

Muscle strength

The meta-analysis showed no statistically significant differences in muscle strength between participants who received exercise-nutrition intervention and those that received standard care, when handgrip strength was analysed from three studies[29, 39, 47] (MD 0.46; 95% -0.38 to 0.85;

299 P=0.28; I^2=49%, P=0.14), or, when of handgrip and quadriceps strength was combined (n=4 studies)[29, 39, 44, 47] using a published methodology[48] (SMD 0.10; 95% CI -0.09 to 0.29; P=0.24, I^2=28%, P=0.30) (Figure 3).

302 *Nutrition, Cognition and Biomarkers outcomes*

303 Most studies assessed participants' nutritional status at baseline, while only one study[33] assessed it as an outcome. Luger et al reported a 1.54-point improvement in the MNA long form in participants who received exercise-nutrition intervention compared to those who received standard care (95% CI 0.51-2.56, P=0.004). Combined exercise-nutrition intervention did not affect cognitive status (mini-mental state examination (MMSE)) or mood (geriatric depression scale (GDS)).[45] Armamento-Villareal et al reported a significant decrease in total and free estradiol in their frail obese older men (attributed to weight loss from lifestyle change rather than the intervention), without a clinically meaningful increase in total or free testosterone levels.[28] In one study that reported C-reactive protein (CRP) levels, this inflammatory marker remained stable in the exercise-nutrition intervention group participants, compared to an increase in the social support control group at the end of 12 weeks (P=0.04).[49]

314 *Quality of life and falls*

315 Three studies[32, 37, 40] that evaluated quality of life did not find a statistically significant improvement in the intervention as compared to the control group though Milte el al[40] found a trend favouring intervention. Fairhall et al[31] found that risk factors related to falls (physical tests as mentioned above) but not rate of falls were reduced while Kapan et al[36] found that a 10% reduction in fear of falling as ascertained by the falls efficacy scale.

320 *Economic analyses*

321 Only two studies examined the cost-effectiveness of their exercise-nutrition intervention. Fairhall et al[32] reported no additional resource cost in terms of medical (P=0.87) or nursing and

health professional appointments (P=0.32). Similarly, Milte et al[40] reported no cost differences between groups (P=0.868).

Discussion

Main findings

The present systematic review and meta-analysis present updated evidence that suggests exercise with nutrition intervention to be effective on frailty and frailty-related physical outcomes in hospitalised older adult patients. When compared to standard care, combined exercise-nutrition interventions improved frailty status as determined by the Fried Frailty criteria [2] and the SHARE-FI.[46] They also improved physical function according to the SPPB and ADLs. Only one study measured and found significant improvement in nutrition score.[33] The two economic analyses included in this review suggested that combined exercise-nutrition interventions, though more effective, were no more costly than standard care.

Existing reviews of exercise and nutrition interventions have highlighted heterogeneity in study protocols (including intervention descriptions), which limits potential for quantitative analysis. They have also focussed on community dwelling participants.[50] This study is novel in reviewing a more vulnerable hospitalised population that has not been previously investigated, and specifically targeting pre-frail or frail older adults. However, out of five studies in this review that used a validated frailty assessment tool, only three had assessed frailty at outcome, and available for quantitative analysis. This could be because the frailty phenotype was first described 2001, with a systematic evaluation of frailty tools a decade later.[2, 51] Accordingly, the authors decided to additionally evaluate frailty components such as physical function, nutrition, cognition and biomarkers as baseline and outcome measures. Although not specific to frailty, these measures provide insights to the effectiveness of exercise-nutrition interventions on improving various components of frailty and may inform future studies.

Previous reviews have found mixed results[50] or have concluded that evidence for combined interventions is limited but increasing.[52] Our results concur with RCTs of exercise-nutrition interventions conducted in community dwelling frail older adults. Tarazona-Santabalbina and colleagues found significant improvement in SPPB in participants on a 24-weeks exercise-nutrition intervention as compared to controls in a community dwelling frail population – intervention group 9.5±1.8 vs control group 7.1±2.8, P=0.007.[53] Similarly, Kim et al reported a 12-weeks, community-based study of frail older adults that found SPPB to remain stable in the intervention group, while it decreased by 12.5% (1 point) in controls (P=0.039).[54] Our meta-analysis of individual components of the SPPB suggests that the significant improvements in functional muscle strength as represented by the chair stand component of the SPPB may be pivotal to the increase in overall SPPB post intervention, and reflect the functional lower limb strength training focus of the exercise interventions. However, the meta-analysis of handgrip +/- quadriceps strength did not produce a similar trend. Diversity in outcome measures for frailty and frailty-related domains like physical function is a challenge for comparative analyses between studies. Future studies should carefully consider measure responsiveness when selecting outcome tools.

Nutrition is another important domain within frailty. Yet the majority of studies included in this review only reported nutrition status at baseline, with only one study reporting follow-up nutrition assessment at the end of the intervention.[33] Luger et al described an improvement in nutrition status in a sample of at risk malnourished pre-frail/frail patients (thus likely to benefit most from nutrition therapy). As hospitalised patients have greater energy deficits due to catabolic stress of acute illness, they are a population that requires careful determination of energy/protein requirements and in whom additive effects of nutrition supplementation to exercise may have greatest impact on outcomes such as muscle strength.[53] As none of the studies in the present review reported on energy deficits, it is not known whether these patients received adequate replacement. Nutrition supplementation should also not be confused with nutrition or diet modifications. The provision of ONS alone is unlikely to augment diet adequacy as completely as diet modification that involves a wider range of nutrients and non-nutrients[55] especially when led by dietitians.[56, 57]

For both exercise and nutrition based interventions, an understanding of patient participation dynamics and compliance is required because of how they can impact on effectiveness.[58] Only five studies in this review reported attendance to program/home visits or phone calls or adherence to prescribed exercise/diet or related advice at rates of 50-90% and 70-93% for nutrition and exercise interventions, respectively. Issues with participants resulting in poorer compliance were not reported in these articles, such that the authors recommend that future studies explore barriers and enablers to adherence in multi-modal interventions.

Cognition is another critical domain in the multidimensional nature of frailty. Exercise[59] and nutrition interventions[60] may have a far reaching, positive effect on cognition in older adults. However, there was no evidence of an impact on cognition from a single study[41] in the present review. This is consistent with a network meta-analysis of 13 RCTs that examined exercise and nutrition interventions in frail older adults.[11] One suggested explanation is that different neuronal mechanisms could result in a misfit between combinatory approaches of nutrition and physical interventions [61] highlighting that more in-depth research is required.[62]

The economic delivery of new interventions and models of care is important to a range of stakeholders[63] but has been infrequently conducted in previous studies.[50] In this review, only two out of 11 studies included an economic analysis, with the majority of costs coming from delivery of exercise and nutrition support. The types of consumables that were considered in analyses included nutrition supplements, ankle/wrist weights, mobility aids and medications. Elements of service provision that were considered included community, rehabilitation, residential and transition care service use, which were often reduced and contributed to the net result. The results of this review support previous findings of beneficial effects on frailty-related outcomes, without increased costs.[50] However, results should be interpreted with caution as omission of other services (such as medication reviews) within a multimodal intervention can impact costings, and there are instances where interventions have not been found to be more-cost effective than usual care.[64] The approach of streamlining and reorganising existing services rather than creating entirely new systems may be preferred.

Strength and weakness

This study was robust and underwent peer review by an academic librarian. We did not have a language restriction on the search, and we did not find nor include studies in other languages. We chose to use of an updated version of the Cochrane risk of bias tool (RoB 2), which addresses issues of confusion common to its first version.

By focussing on exercise-nutrition interventions only, this study addresses a gap as identified in a recent review of multi-domain interventions in pre-frail or frail elderly adults, in which some interventions may have been be too broad to directly impact frailty, and functional and cognitive status.[52] Multidisciplinary team based approaches remain recommended and are a bedrock of quality standard care; they may also already include goals for exercise and nutrition such that it may be difficult to solely attribute outcomes to a targeted but supplementary exercise-nutrition program. Social relationships affect health behaviour and physical health,[65] such that intervention benefits may in part come from social interactions. Nevertheless, several studies[29, 33, 43] have demonstrated significant improvements even when control participants are provided with the social aspect of an intervention, such that exercise and nutrition are expected to improve outcomes independent of social interactions. Among the three studies[29, 33, 39] included in the meta-analysis of reduction in frailty score, one study[33] included patients from community. However, when combined with data from the other two studies,[29, 39] participants recruited from the hospital made up majority (~80%) of the entire cohort in that meta-analysis.

Implications and future research

This review is a useful resource for researchers and multi-disciplinary clinicians who are seeking to generate evidence or evaluate their practices of exercise-nutrition interventions for frail hospitalised older adults. The authors interpretation of the quality of studies in this review is that the evidence base is low, but the inclusion of future studies may change estimates of the intervention effects. While blinding of participants to the intervention is acknowledged to be difficult, future studies should be adequately powered, use allocation concealment with blinding outcome assessors and data analysts at least. Improved reporting of intervention details is also required,[66] which may assist in answering research questions around the optimal duration, dose, modality and timing of intervention(s) across the hospital to community continuum. In the present review, potential beneficial effects of combined interventions could have been negated given the short durations reported by most studies. Thus, future studies may be extended for >6-12 months, or employ principles of chronic condition self-management,[67] to determine delayed improvements and achieve long-lasting sustainability of interventions. The lack of evidence from non-western countries, or low- and middle-income countries indicate the need for research to be conducted in those populations too. There are many ongoing research activities relevant to the scope of this review,[68-71] yet only one has reported plans for economic analysis in the study protocol.[68] Economic evaluations can expand current evidence on the sustainability of incorporating such services within resource-constrained healthcare systems.

Conclusion

Exercise-nutrition interventions that start while patients are admitted to hospital and continue in the community/post-hospital, or, commence early post discharge, appear to be effective in reducing frailty and some frailty-related physical indicators. Though effective, the quality of the evidence in this review is low as most studies included had some concerns for risk of bias. Given the paucity of high-quality studies on the effectiveness of combined exercise-nutrition interventions on hospitalised frail older adult patients, more robust research that pays attention to effect of assignment to intervention is needed to increase the confidence in results.

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Author Contributions

All authors contributed to the conception and design of review. CH and YS read and screened titles and abstract of potentially relevant studies. CH and YS evaluated the selected studies and performed data extraction. CH, MM, AY, CB reviewed the evidence. RW provided statistical expertise on meta-analyses. CH drafted the article and all authors provided critical revisions and final approval of the manuscript. All authors had access to the data in the study and can take responsibility for the integrity of the reported findings. All authors fulfil the ICMJE criteria for authorship.

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Competing interests

None declared.

Patient consent

Not required.

Data sharing statement

Details of the excluded papers are available from the corresponding author upon request.

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Figure captions

Fig.1 Flow diagram illustrating results of the search and study selection process as described in the PRISMA statement

Fig 2. Meta-analysis of reduction in frailty score for exercise and nutrition intervention vs standard care

Fig.3 Meta-analyses of Short physical performance battery, Gait speed, Balance test, Chair stand test, Activities of daily living, handgrip strength

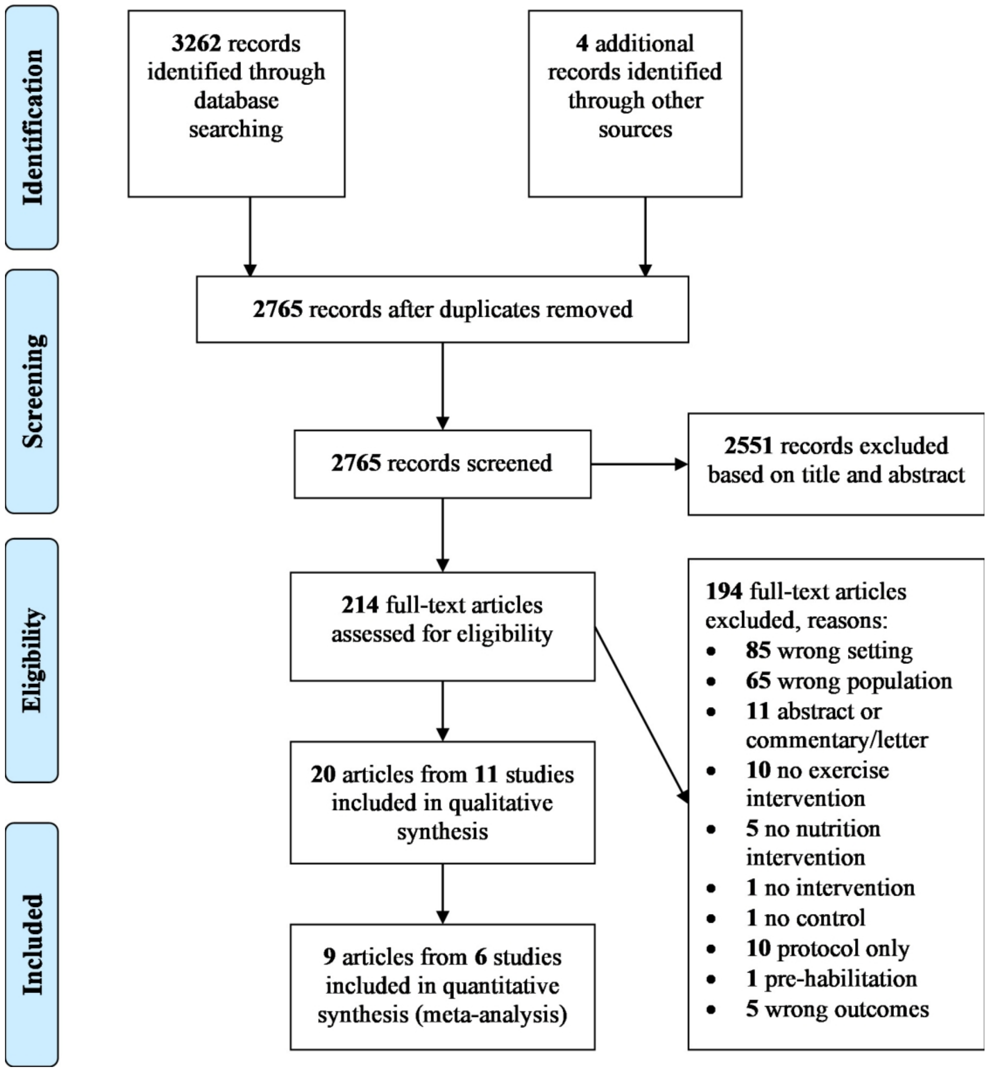
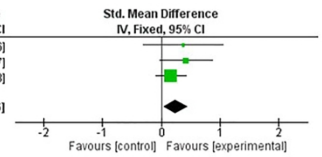


Fig.1 Flow diagram illustrating results of the search and study selection process as described in the PRISMA statement

Frailty

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Niccoli 2017	0.333	0.724	15	0.105	0.459	19	9.8%	0.38 [-0.31, 1.06]
Luger 2016	0.71	1.11	39	0.35	0.459	41	23.3%	0.42 [-0.02, 0.87]
Cameron 2013	0.56	1.1	108	0.39	0.92	117	66.9%	0.17 [-0.09, 0.43]
Total (95% CI)			**162**			**177**	**100.0%**	**0.25 [0.03, 0.46]**

Heterogeneity: Chi² = 1.10, df = 2 (P = 0.58); I² = 0%
Test for overall effect: Z = 2.27 (P = 0.02)



Abbreviations: *CI confidence interval; IV inverse variance; SD standard deviation*

Fig 2. Meta-analysis of reduction in frailty score for exercise and nutrition intervention vs standard care

268x338mm (300 x 300 DPI)

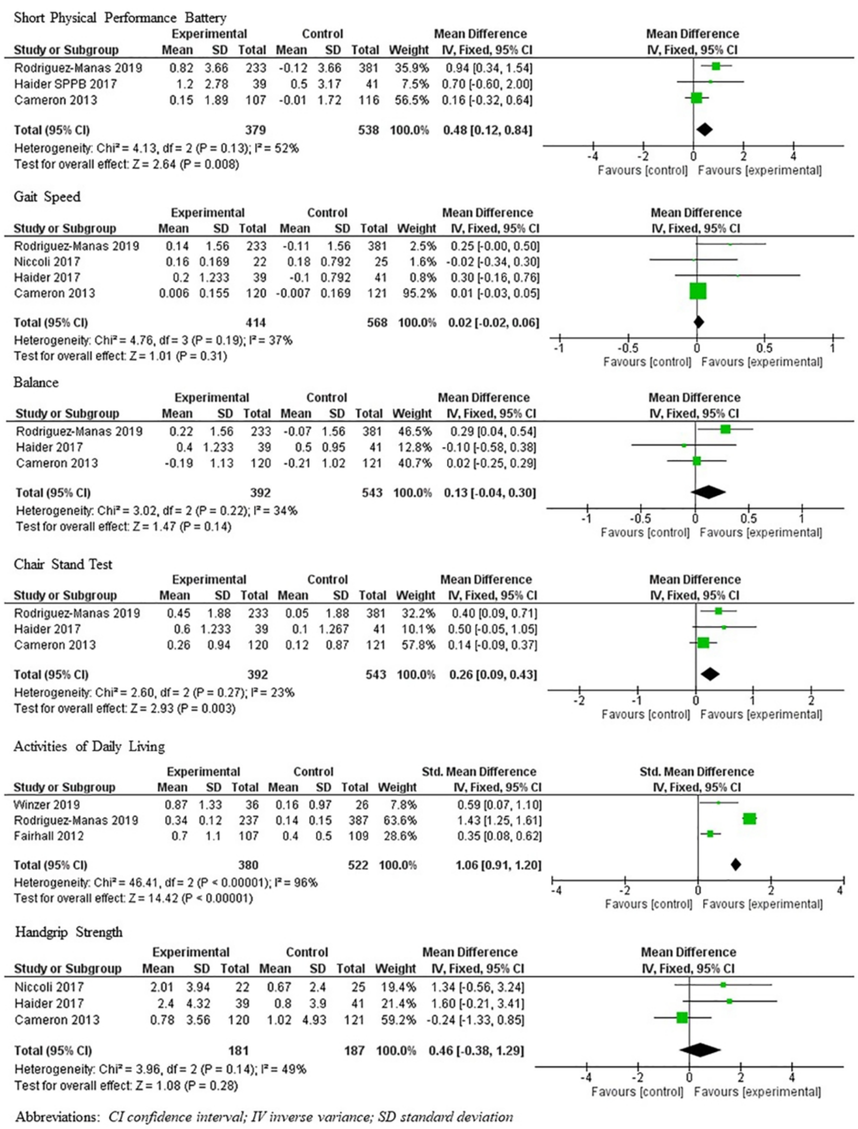


Fig.3 Meta-analyses of Short physical performance battery, Gait speed, Balance test, Chair stand test, Activities of daily living, handgrip strength

268x338mm (300 x 300 DPI)

Search Strategy – Medline

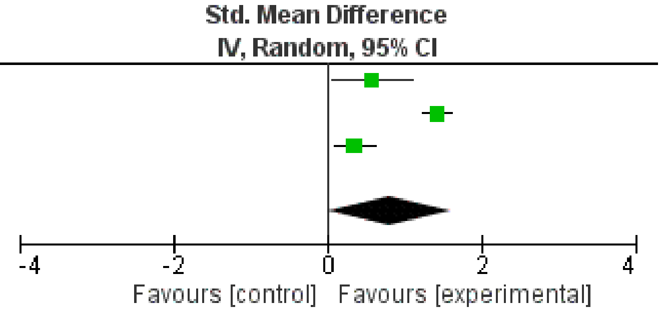
#	Searches
1	"diet, food, AND nutrition"/ or food/ or diet/
2	dietary proteins/ or dietary supplements/
3	Nutritional Status/ or Feeding Behavior/
4	Dietitian/
5	Nutrition Assessment/ or Nutrition Therapy/
6	((diet* or nutrition* or food*) adj5 (intervention or program or supplement or educat* or assess* or advic* or counsel* or treat*)).tw,kf.
7	or/1-6
8	motor activity/ or exercise/ or muscle strength/ or physical endurance/ or physical fitness.mp.
9	Exercise/ or resistance training/
10	(exercis* or "resistance training" or "exercis* therapy" or "muscle stretching exercis*" or "physical exercis*" or "strength train*" or "aerobic exercis*" or hydrotherapy or rehabilitat* or walk* or cycl* or conditioning* or "leg press" or flexib*).mp.
11	Physiotherapy/
12	((exercise* or resistan* or strength) adj5 (intervention or program or educat* or advice* or treat* or train* or rehabilit*)).tw,kf.
13	or/8-12
14	frail elderly/ or pre-frail elderly/
15	frail*.mp.
16	(functional* adj2 (declin* or impair*) adj3 (aged or aging or elderly or elder* or old* or senior*)).mp.
17	(frail* and (geriatric* or gerontolog* or (vulnerable and older))).mp.
18	(frail* and (aged or aging or elderly or elder* or older or senior*)).mp.
19	(frail* and (geriatric* or gerontolog* or aging)).mp.
20	("geriatric assess*" or "functionally-impaired elder*").mp.
21	14 or 15 or 16 or 17 or 18 or 19 or 20
22	7 and 13 and 21

Translated above strategy for other databases: **CINAHL, Emcare, Scopus, Cochrane, Ageline and PEDro**

Activities of Daily Living – Random Effects Model

	Experimental			Control				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Winzer 2019	0.87	1.33	36	0.16	0.97	26	31.0%	0.59 [0.07, 1.10]
Rodriguez-Manas 2019	0.34	0.12	237	0.14	0.15	387	34.9%	1.43 [1.25, 1.61]
Fairhall 2012	0.7	1.1	107	0.4	0.5	109	34.1%	0.35 [0.08, 0.62]
Total (95% CI)			**380**			**522**	**100.0%**	**0.80 [0.00, 1.60]**

Heterogeneity: Tau² = 0.47; Chi² = 46.41, df = 2 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.96 (P = 0.05)



Abbreviations: *CI confidence interval; IV inverse variance; SD standard deviation*

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5-6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	nil
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8, fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10-11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-18
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-18, fig. 2 & 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8, Fig 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	nil
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22-23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	24

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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