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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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2
3 **Title Page**
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7
8 3 hospitalised patients: a systematic review and meta-analysis
9

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1
2
3 22 **Abstract**
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5

6 23 Objectives: To determine the effectiveness of combined exercise-nutrition interventions in pre-
7
8 24 frail/frail hospitalised older adults on frailty, frailty-related indicators, quality of life (QoL),
9
10 25 falls and its cost-effectiveness.

11
12
13 26 Design: Randomised controlled trials (RCTs) of combined exercise-nutrition interventions on
14
15 27 hospitalised pre-frail/frail older adults ≥ 65 years were collated from seven databases.
16
17 28 Methodological quality was appraised, and data were summarised descriptively or by meta-
18
19 29 analyses using a fixed effects model. Standardised mean difference (SMD) or mean difference
20
21 30 (MD) with 95% confidence intervals (CIs) was calculated.

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25
26 31 Results: Twenty articles (11 RCTs) experimenting exercise-nutrition interventions on
27
28 32 hospitalised older adults were included. Nine articles were suitable for meta-analyses. One
29
30 33 study had low risk of bias and found improvements in physical performance and frailty-related
31
32 34 biomarkers. Exercise interventions were mostly supervised by a physiotherapist, focusing on
33
34 35 strength, ranging 2-5 times/week, of 20-90 minutes duration. Most nutrition interventions
35
36 36 involved education and supplementation but had dietitian supervision in only three studies.
37
38 37 Meta-analyses suggest that participants who received exercise-nutrition intervention had
39
40 38 greater reduction in frailty scores (n=3, SMD 0.25; 95% CI 0.03-0.46; P=0.02) and
41
42 39 improvement in short physical performance battery (SPPB) scores (n=3, MD 0.48; 95% CI
43
44 40 0.12-0.84; P=0.008) compared to standard care. Only chair-stand test (n=3) out of the three
45
46 41 SPPB components was significantly improved (MD 0.26; 95% CI 0.09-0.43; P=0.003).
47
48 42 Patients were more independent in activities of daily living in intervention groups, but high
49
50 43 heterogeneity was observed ($I^2=96\%$, $P<0.001$). The pooled effect for handgrip (n=3) +/- knee
51
52 44 extension muscle strength (n=4) was not statistically significant. Nutritional status, cognition,
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3 45 biomarkers, QoL, falls and cost-effectiveness were summarised descriptively due to
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5 46 insufficient data.
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8 47 Conclusions: There is evidence, albeit weak, showing that exercise-nutrition interventions are
9
10 48 effective to improve frailty and frailty-related indicators in hospitalised older adults. Robust
11
12 49 research that pays attention to effect of assignment to intervention is needed to increase the
13
14 50 confidence in results.
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18 51 **PROSPERO registration number: CRD42020153934**
19

20 21 52 **Strengths and limitations of study**

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23
24 53 • This is the first comprehensive systematic review with meta-analysis on the
25
26 54 effectiveness of exercise-nutrition interventions on frailty and outcomes related to
27
28 55 frailty in hospitalised and pre-frail/frail older adults.
- 29
30 56 • Only randomised controlled trials describing existing exercise-nutrition interventions
31
32 57 in frail older hospitalised patients were included.
- 33
34 58 • There was a moderate risk of bias for most included studies such that the findings of
35
36 59 this review are inconclusive, making it difficult to draw firm conclusions.
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40 41 60 **Introduction**

42
43
44 61 Frailty is a major contributor to late-life disability as it leads to loss of independence.¹ It is also
45
46 62 associated with poor health outcomes, and, increased health-care costs and service use.¹ Frailty
47
48 63 has been defined for clinical research by Fried et al² as a combination of unintentional weight
49
50 64 loss, weakness, exhaustion, slowness and reduced physical activity. Older adults (aged >65
51
52 65 years) that have been classified as frail and are hospitalised, have a three-fold higher risk of
53
54 66 readmission or death, as compared to the younger population.³ The management of older adults
55
56 67 who are frail has an incremental effect on health expenditures with an additional equivalent of
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3 68 AU\$2400 per frail patient per year.⁴ With 21% of the population over 65 years estimated to be
4
5 69 frail and 48% estimated to be pre-frail, concerns of economic impact are compounded by an
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7
8 70 ageing population.⁵
9

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11 71 Exercise and nutrition are inextricably linked, in particular strength training can address
12
13 72 component issues of the frail phenotype.⁶ Yet evidence supporting the effectiveness of
14
15 73 exercise-nutrition interventions for reversal of frailty is limited to community-dwelling older
16
17 74 adults.⁷ In a study of community participants, a 3-month combined exercise-nutrition
18
19 75 intervention resulted in a significant reversal of frailty (reduction in Fried frailty score) at 6-
20
21 76 months, compared to the control group (between-group difference -0.34 ; 95% confidence
22
23 77 interval [CI] -0.52 to -0.16 ; $P < 0.001$).⁸ The combination of exercise therapy and dietary
24
25 78 intervention in older adults who are frail, has also been reported to increase muscle strength
26
27 79 (knee extension between-group difference 1.84 kg, 95% CI $0.17-3.51$, $P = 0.03$)⁹ and improve
28
29 80 nutritional status (Mini Nutritional Assessment (MNA) Short Form between group difference
30
31 81 1.4 , 95% CI $0.9-1.9$, $P < 0.01$).¹⁰
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36
37 82 A recent meta-analysis suggested that although effective, exercise combined with nutrition was
38
39 83 not more effective in treating frailty than exercise alone.¹¹ However, the majority of included
40
41 84 studies were conducted in a community setting, with only 15% of older adults either
42
43 85 hospitalised or recruited from acute care settings. No study has systematically evaluated
44
45 86 evidence for interventions that commence during acute hospitalisation or early post discharge
46
47 87 (in the high-risk period for post-hospital syndrome).
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50
51 88 Hospitalisation is a vulnerable period, especially for older adults who are frail and therefore at
52
53 89 higher risk of functional loss,¹² malnutrition^{13, 14} and further decline in frailty status.
54
55 90 Malnutrition is ubiquitous in older hospitalised patients with a prevalence as high as 50%.¹⁵
56
57 91 Since many domains of frailty are attributed to poor nutrition,¹⁶ the effect of nutrition
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3 92 intervention when combined with exercise, may be more significant in the hospitalised
4
5 93 population.¹⁶ Nutritional therapy extends beyond protein or nutrition supplementation as
6
7 94 reported in previous studies and may be more effective as part of individualised medical
8
9 95 nutrition therapies involving dietitians to improve diet adequacy.¹⁷
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12

13 96 This study aims to determine the effectiveness of combined exercise-nutrition interventions on
14
15 97 (1) frailty, (2) frailty-related indicators, falls, quality of life (QoL) and (3) its cost effectiveness
16
17 98 on pre-frail or frail hospitalised older adults.
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21 99 22 23 100 **Materials and Methods**

24 25 26 101 *Protocol and registration*

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28
29 102 The protocol for this review was compliant with Cochrane systematic review guidelines,¹⁸ and
30
31 103 registered with the International Prospective Register of Systematic Reviews (PROSPERO),
32
33 104 CRD42020153934. The study is reported according to Preferred Reporting Items for
34
35 105 Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁹ Patients and/or members of
36
37 106 the public were not involved in this study.
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41 107 *Search methods*

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43
44 108 Systematic searches of electronic databases (Medline, Emcare, CINAHL, Ageline, Scopus,
45
46 109 Cochrane and PEDro) were conducted by the lead author (CH) from inception until 10th
47
48 110 October 2019 using search strategies reviewed by an academic librarian (search queries
49
50 111 available in Supplementary file 1). Additionally, related citations to eligible items were
51
52 112 identified using the suggested related citation function in Pubmed. Reference lists of eligible
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54 113 items were also screened.
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59 114 *Inclusion and exclusion criteria*

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3 115 The inclusion criteria were: 1) randomised controlled trials; 2) inclusion of pre-frail or frail
4
5 116 participants (as defined by study authors); 3) recruitment of older adult inpatients and/or those
6
7 117 hospitalised within the past 30 days of recruitment; 4) interventions that started while patients
8
9 118 were admitted and continued in the community/post-hospitalisation, or, commenced within 30
10
11 119 days of hospital discharge; 5) interventions that involved both physical exercises and
12
13 120 nutritional interventions (dietary modifications/education/training alone or combined with oral
14
15 121 nutrition supplementation); 6) measured frailty with an assessment tool or at least one indicator
16
17 122 relevant to frailty (nutritional status, physical function, cognitive function and mood, physical
18
19 123 activity level or biomarkers, falls and QoL and/or economic analysis of interventions. Studies
20
21 124 were excluded if they described protocols with no pilot outcomes, interventions delivered as a
22
23 125 part of a palliative care program, or interventions solely designed to facilitate discharge
24
25 126 planning (e.g. telephone support services, providing no pre-frailty or frailty intervention
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27 127 element). Studies that recruited participants admitted following a mental health episode were
28
29 128 also excluded.
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36 129 *Study selection and data extraction*

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39 130 Covidence²⁰ was used to manage citations for title and abstract, and full-text screening, in
40
41 131 duplicate (CH and YS, supplement 1). The reviewers were unblinded to authors, journals and
42
43 132 countries of origin. Any disagreement was resolved through discussion or consensus opinion
44
45 133 with the other authors. A data extraction form was developed a priori by the research team,
46
47 134 such that two researchers (CH and YS) performed data extraction independently, on eligible
48
49 135 full-text articles. Where available, continuous data were extracted as (i) mean change with
50
51 136 standard deviation (SD), standard error of mean (SE) or 95% confidence interval (CI), or (ii)
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53 137 mean or median values with SD, SE or interquartile range post intervention. If required data
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55 138 were not reported within a publication (including change in means for outcomes of interest),
56
57 139 corresponding authors were emailed to request for it.
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140 *Quality of the studies*

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

149 *Data synthesis and statistical analyses*

150 Where possible, meta-analysis was performed; continuous outcome data were pooled and
151 either mean difference (MD) or standardised mean difference (SMD) with 95% CI reported if
152 there were two or more studies. Studies presenting SE were converted to SD via the conversion
153 formula.¹⁸ Fixed-effect meta-analyses were carried out with Cochrane Review Manager
154 (RevMan) 5.3.²³ A P value of <0.05 was considered statistically significant. The variability
155 between studies (heterogeneity) was assessed by I² and its 95% CI.²⁴ For studies with
156 unobtainable missing, or incomparable data, results were qualitatively synthesised.

157 *Patient and public involvement*

158 No patients were involved in this study

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160 **Results**

161 *Study selection*

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3 162 The flow of studies through the review process is summarised in Figure 1. Twenty articles
4
5 163 reporting on 11 studies were eligible for data synthesis and analysis. Three of 11 studies
6
7 164 presented results from their cohort across separate publications. Firstly, Villareal et al²⁵
8
9 165 reported on physical functioning outcomes with biomarker results in the publication of
10
11 166 Armamento-Villareal et al.²⁶ Secondly, Cameron et al²⁷ reported on frailty and some physical
12
13 167 function outcomes, with other physical function outcomes in a secondary publication²⁸ fall
14
15 168 rates²⁹ and cost-analysis in another.³⁰ Thirdly, Luger et al³¹ reported on frailty and nutritional
16
17 169 status, with physical functioning outcomes across two other publications,^{32, 33} fall efficacy³⁴
18
19 170 and quality of life.³⁵ For clarity, the primary articles that report frailty or physical function
20
21 171 outcomes are cited for descriptive data in Tables 1-3 while individual articles are cited for
22
23 172 synthesis of outcome results.

24 173 *Study and sample characteristics*

25
26 174 Details of study characteristics are available in Table 1. Across all studies, a total of 2307
27
28 175 participants were investigated. Most studies reported that patients were recruited from hospital
29
30 176 wards (n=7)^{27, 36-41} while the other four studies^{25, 31, 42, 43} included patients that were recruited
31
32 177 from hospital wards and community. Seven studies included only frail participants,^{25, 27, 38-41, 43}
33
34 178 and the remaining four studies^{31, 36, 37, 42} included frail, pre-frail and non-frail participants. The
35
36 179 Fried frailty phenotype criteria² were used most frequently to classify frailty (n=4).^{27, 36, 37, 42}
37
38 180 with participants considered non-frail, pre-frail or frail if 0, 1-2, 3-5 criteria were present,
39
40 181 respectively. Luger et al used the Frailty Instrument for Primary Care of the Survey of Health,
41
42 182 Ageing, and Retirement in Europe (SHARE-FI)³¹ which integrates components of exhaustion,
43
44 183 appetite, handgrip strength, walking difficulties and physical activity.⁴⁴ Five studies did not
45
46 184 report any assessment method to define frailty.^{38-41, 43} One study used a combination of three
47
48 185 tools – modified Physical Performance Test, the measurement of VO₂ peak, and the Functional
49
50 186 Status Questionnaire.²⁵

187 **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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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/kg; difficulty in performing 2 IADL or 1 basic ADL	Mild-moderate frailty: 100%

Azad <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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; VO² 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* 2017³², Winzer *et al* 2019³³, Kapan *et al* 2017³⁴, Kapan *et al* 2017³⁵; †Cameron *et al* 2013²⁷ – Fairhall *et al* 2012²⁸, Fairhall *et al* 2014²⁹, Fairhall *et al* 2015³⁰; ‡Villareal *et al* 2011²⁵ – Armamento-Villareal 2016²⁶

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 <i>et al</i> , 2019 ³⁵	+	?	?	?	+	?
Rodriguez-Manas <i>et al</i> , 2019 ⁴¹	+	?	+	?	+	?
Niccoli <i>et al</i> , 2017 ³⁶	?	?	+	?	+	?
Luger <i>et al</i> , 2016 ^{*30}	+	+	+	?	+	?
Milte <i>et al</i> , 2016 ³⁷	+	?	+	+	+	?
Cameron <i>et al</i> , 2013 ^{†26}	+	?	+	+	+	?
Singh <i>et al</i> , 2012 ³⁸	+	?	+	—	+	—
Villareal <i>et al</i> , 2011 ^{‡24}	+	+	+	+	+	+
Azad <i>et al</i> , 2008 ⁴²	+	?	+	?	+	?
Blanc-Bisson <i>et al</i> , 2008 ³⁹	+	?	+	?	+	?
Miller <i>et al</i> , 2006 ⁴⁰	+	?	+	+	+	?

Key: + = Low risk of bias; ? = Some concerns of risk of bias; — = High risk of bias
 *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* 2017³², Winzer *et al* 2019³³, Kapan *et al* 2017³⁴, Kapan *et al* 2017³⁵; †Cameron *et al* 2013²⁷ – Fairhall *et al* 2012²⁸, Fairhall *et al* 2014²⁹, Fairhall *et al* 2015³⁰; ‡Villareal *et al* 2011²⁵ – Armamento-Villareal 2016²⁶

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3 198 *Risk of bias within individual studies*
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6 199 Table 2 outlines the risk of bias in individual studies. One study²⁵ had a low risk of bias and
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8 200 one study had a high risk of bias (including unblinded secondary outcome assessment and
9
10 201 insufficient detail on standard care in control groups across recruitment sites). The other nine
11
12 202 studies^{27, 31, 36-38, 40-43} were rated as having some concerns overall, of which five could have
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14
15 203 been improved in ≥ 1 domain. The remaining four studies^{27, 31, 39, 41} that were rated as having
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17 204 “some concerns” overall, had risk in only one domain with the most common reason being
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19 205 failure to blind intervention/allocated group to participants. Examples of other concerns about
20
21 206 risk of bias included: assessors being aware of the group allocation³¹ (measurement of
22
23 207 outcomes domain); or a lack of information about participants/researcher blinding to group
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25 208 allocation.^{25, 27, 42}
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30 209 *Characteristics of exercise intervention component*
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32
33 210 Characteristics of the exercise interventions used in studies are outlined in Table 3, and
34
35 211 included combinations of the following: supervised individual exercises (n=10),^{25, 27, 36-43} group
36
37 212 exercises (n=3),^{25, 39, 43} education including support with resources (digital versatile disc (DVD)
38
39 213 or visual aid instruction booklet, n=2),^{31, 36} and motivational interviewing using a standardised
40
41 214 protocol (n=1).³¹ Three studies^{37, 40, 42} had inpatient only interventions, five^{36, 38, 39, 41, 43} had
42
43 215 interventions that extended from inpatient to post-discharge, two^{27, 31} studies offered the
44
45 216 intervention post-discharge only and one²⁵ did not report.
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49 217 In the majority of studies (n=9), the exercise component was delivered by a physiotherapist.^{25,}
50
51 218 ³⁶⁻⁴³ Two studies used trained fitness instructors,^{36, 39} and another engaged lay volunteers who
52
53 219 received training for the study.³¹ All studies included strength exercises as part of their
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55 220 interventions. Three studies described guidance on training intensity based on repetition
56
57 221 maximum's (RM) between 40-80%.^{25, 39, 42} Other components of exercise programs included
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59
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Table 3. Characteristics of exercise and nutrition intervention and controls of included studies

Study	Exercise intervention	Nutrition intervention	Control intervention
Arrieta <i>et al</i> , 2019 ³⁵	<p>Type: <i>Strength</i> – Intensity range from low to high, starting at 10 repetition per exercise (UL, LL) with option of progressive loading</p> <p><i>Aerobic, Flexibility, Balance</i> – intensity individualised</p> <p>Frequency: 2 sessions/week, duration per session NR + home exercises duration NR</p> <p>Setting: Inpatient (supervised, individual) + post-discharge (unsupervised, individual)</p> <p>Additional support reported: Phone consults (by trainer 2x/month for first 6 months then monthly for 1 year); Education resource</p>	<p>Self-guided education resource: Provided with French National Nutrition Health Program education booklet - <i>Programme National Nutrition Santé</i> (PNNS)</p>	<p>Usual care: NR, variable between study sites</p> <p>Self-guided education resource: Provided with French National Nutrition Health Program education booklet - <i>Programme National Nutrition Santé</i> (PNNS)</p>
Rodriguez-Manas <i>et al</i> , 2019 ⁴¹	<p>Type: <i>Strength</i> – 40-80% of estimated 1RM, 8–10 repetitions (LL)</p> <p>Frequency: 2-weeks pretraining followed by 16-week program of 2 days/week; 20-30 minutes/sessions</p> <p>Setting: Inpatient (supervised, individual)</p>	<p>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.</p>	<p>Usual care: usual health care from local health system and/or general practitioner</p>
Niccoli <i>et al</i> , 2017 ³⁶	<p>Type: <i>Strength, Aerobic, Flexibility, Balance</i> – intensity and target muscle group individualised based on patient’s baseline assessment</p> <p>Frequency: individualised based on patient’s baseline assessment</p> <p>Setting: Inpatient (supervised, individual)</p>	<p>Supplements: Daily ONS with 24g whey protein per day (<i>9g breakfast, 7.5g at lunch and dinner</i>) in addition to usual diet</p>	<p>Usual care: usual medical care, no whey protein supplementation.</p> <p>Individual supervised exercise: Individualised exercises as per intervention.</p>
Luger <i>et al</i> , 2016 ^{*30}	<p>Type: <i>Strength</i> –2 sets of 15 repetitions (UL, LL) until muscular exhaustion,</p> <p>Frequency: 2x/week, >30 minutes each session</p> <p>Setting: Post-discharge (supervised, individual)</p> <p>Additional support reported: Physical education (2-3 times/week, 30 minutes each session); Exercise education resource (demonstration DVD); Motivational interviewing.</p>	<p>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.</p> <p>Motivational interviewing: Techniques utilised with nutrition goal setting and tools to reinforce self-efficacy.</p>	<p>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</p>
Milte <i>et al</i> , 2016 ³⁷	<p>Type: <i>Strength, Balance (Otago exercise program)</i> – Intensity and repetitions NR, at the discretion of the treating physiotherapist (LL)</p>	<p>Nutrition consultation/education: Individualised nutrition therapy aimed at</p>	<p>Usual care: Usual rehabilitation program recommended during hospitalisation, social visits</p>

	<p>Frequency: 3 times/week, 20-30minutes/session for 12 weeks</p> <p>Setting: Inpatient (supervised, individual) + post-discharge (supervised, individual)</p>	<p>improving energy and protein intake to meet requirements by dietitian who visits fortnightly.</p> <p>Meal program: ordered as deemed necessary by dietitian.</p> <p>Supplements: commercial ONS recommended if needed by dietitian</p>	<p>weekly from trial staff and generic nutrition, exercise and falls prevention information</p>
Cameron <i>et al</i> , 2013 ^{†26}	<p>Type: <i>Strength, Balance, Aerobic + WEBB program</i> – intensity and target muscle groups NR</p> <p>Frequency: Exercises prescribed 3-5x/week (with 2 sessions for mobility training) for 1 year, supported by up to 10 home visits</p> <p>Setting: Post-discharge (supervised, individual) + (unsupervised, individual)</p>	<p>Nutrition consultation/education: Clinical evaluation of nutritional intake at home. A series of diet intervention as needed by dietitian.</p> <p>Meal program: ordered as deemed necessary by dietitian.</p> <p>Supplements: commercial ONS recommended if needed by dietitian</p>	<p>Usual care: usual health care during hospitalisation and from their general practitioner and community services after discharge</p>
Singh <i>et al</i> , 2012 ³⁸	<p>Type: <i>Strength</i> – 80% of most recent 1RM or RPE <15, 3 sets of 8 repetitions (UL, LL)</p> <p>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.</p> <p>Setting: Inpatient (supervised, individual) + (supervised, group-based)</p> <p>Additional support reported: Monthly phone consults</p>	<p>Nutrition consultation/education: Counselling on increase in diet quality, frequency NR</p> <p>Supplements: ONS +/- dietary advice to increase daily energy (400-600 kcal) and protein (20 g/day) intake.</p> <p>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</p> <p>Self-guided nutrition resource: Food sources of calcium, vitamin D and sun exposure</p>	<p>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.</p>
Villareal <i>et al</i> , 2011 ^{‡24}	<p>Type: <i>Strength</i> – 65% of 1RM; 8-12 repetitions of each exercise (UL, LL) with options for progression</p> <p><i>Aerobic</i>, ~65% of peak HR with gradual progression to 70-85%</p> <p><i>Flexibility, Balance</i></p> <p>Frequency: 90 minutes, 3 sessions/week</p> <p>Setting: Inpatient (supervised, group-based)</p>	<p>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.</p> <p>Supplements: 1500 mg of calcium/d day and ~1000 IU vitamin D/d</p>	<p>Usual care: General healthy lifestyle advice</p> <p>Supplements: 1500 mg of calcium/d day and ~1000 IU vitamin D/d</p>
Azad <i>et al</i> , 2008 ⁴²	<p>Type: ‘Comprehensive exercise program’; type, intensity and target muscle groups NR</p> <p>Frequency: 11 sessions over 6 weeks + NR home exercises</p> <p>Setting: Inpatient (supervised, group-based), post-discharge (unsupervised, individual)</p>	<p>Nutrition consultation/education: 3 sessions of individualized counselling about diet and nutrition in the management of CHF by dietitian</p>	<p>Usual care: Optimal medical care</p>

Blanc-Bisson <i>et al</i> , 2008 ³⁹	<p>Type: <i>Strength</i> – intensity (RM) NR, 10 x repetitions each exercise (LB)</p> <p>Frequency: 30 minutes, twice/day, five days/week</p> <p>Setting: Inpatient (supervised, individual)</p>	<p>Meal program: Geriatric hospital meals of 1800-2000 kcal/d</p> <p>Supplements: 1 daily ONS of 200 kcal and 15g protein</p>	<p>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.</p> <p>Individual supervised exercise: Physiotherapy continued at home for one month.</p>
Miller <i>et al</i> , 2006 ⁴⁰	<p>Type: <i>Strength</i> – intensity (RM) NR, 2 sets of 8 repetitions (LL) with progressive loading, at the discretion of the treating physiotherapist</p> <p>Frequency: 3 times/week, 20-30minutes/session for 12 weeks</p> <p>Setting: Inpatient (supervised, individual) + Post-discharge (supervised, individual)</p>	<p>Nutrition consultation/education: Individualised nutrition therapy by dietitian.</p> <p>Supplements: single type of ONS to cover the shortfall between individual estimated energy and protein requirements and actual intake over 42 days.</p>	<p>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.</p>

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* 2017³², Winzer *et al* 2019³³, Kapan *et al* 2017³⁴, Kapan *et al* 2017³⁵; †Cameron *et al* 2013²⁷ – Fairhall *et al* 2012²⁸, Fairhall *et al* 2014²⁹, Fairhall *et al* 2015³⁰; *Villareal *et al* 2011²⁵ – Armamento-Villareal 2016²⁶

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3 222 aerobic fitness,^{25, 27, 36, 37} flexibility,^{25, 36, 37} and/or balance.^{25, 27, 36, 37} The frequency of
4
5 223 interventions ranged from two^{31, 36, 39, 42, 43} to five^{27, 40} sessions a week, lasting between 20^{38, 41,}
6
7 224 ⁴² to 90 minutes²⁵ each. The duration of exercise intervention varied from six weeks⁴³ to one
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9 225 year.^{25, 27, 36, 39}

226 *Characteristics of nutrition intervention component*

16 227 Characteristics of the nutritional interventions used in studies, are outlined in Table 3, and
17
18 228 included combinations of the following: nutrition consultation/education (n=8),^{25, 27, 31, 38-41, 43}
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20 229 oral nutrition and/or multivitamin/mineral supplements (n=7),^{25, 27, 37-41} meal programs
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22 230 (n=3),^{27, 38, 40} self-guided education materials (n=2),^{36, 39} and motivational interviewing (n=1).³¹
23
24 231 The most common combination of nutrition intervention was consultation/education with oral
25
26 232 nutrition and/or multivitamin/mineral supplements (n=5).^{25, 38, 41, 43} Five of nine nutrition
27
28 233 consultation/education interventions were performed by dietitians.^{25, 38, 41, 43} Other studies used
29
30 234 trained lay volunteers,³¹ a researcher/nutrition therapist or did not specify a skill set for who
31
32 235 delivered the consultation/education.⁴²

37 236 All counselling/education-based interventions aimed to achieve adequate dietary targets for
38
39 237 energy, protein and other nutrients. One study on obese frail participants aimed for calorie
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41 238 deficit but ensured that all achieved 1g/kg/day of protein in the intervention group.²⁵ The
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43 239 reported frequency of consultations ranged from twice a week^{31, 42} to fortnightly.^{38, 41} Oral
44
45 240 nutrition supplements (ONS) were the most common supplements prescribed to intervention
46
47 241 group participants (n=7),^{25, 37, 38, 40, 41, 43} typically providing 200-300kcal and 12-24g protein
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49 242 per serve with a frequency of consumption up to seven times a week^{37, 40} or as prescribed by
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51 243 dietitians^{25, 38, 41, 43} to cover any identified deficits between individually estimated energy and
52
53 244 protein requirements and actual intake. Calcium and vitamin D were the two most commonly
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55 245 supplemented micronutrients^{25, 39} at doses in the range of 1200-1500mg/d and 1000IU/d,
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246 respectively. Meal programs were either delivered as inpatient specialised geriatric meals
247 providing 1800-2000kcal/d or home-delivered meal programs.^{27, 38, 40}

248 *Frailty outcomes*

249 Data on frailty outcomes were available for quantitative analysis from three studies.^{27, 31, 37} The
250 meta-analysis is presented in Figure 2 and suggested that participants who received exercise-
251 nutrition intervention had a greater reduction in frailty score compared to those who received
252 standard care (SMD 0.25; 95% CI 0.03-0.46; P=0.02); no heterogeneity was observed (I²=0%;
253 P=0.58).

254 *Physical functioning outcomes*

255 *Short Physical Performance Battery (SPPB)*

256 Data on the SPPB were available for quantitative analysis from 3 studies,^{27, 42, 45} with results
257 from meta-analysis presented in Figure 3. Participants who received exercise-nutrition
258 intervention had a statistically significant improvement in SPPB score, compared to those that
259 received standard care (MD 0.48; 95% CI 0.12-0.84; P=0.008), with moderate heterogeneity¹⁸
260 observed (I² = 52%; P=0.13).^{20, 32, 33} The analysis of SPPB components across all studies
261 showed no statistically significant differences in gait speed^{27, 37, 42, 45} (MD 0.02; 95% CI -0.02
262 to 0.06; P = 0.31; I² = 37%, P = 0.19) or balance^{27, 42, 45} (MD 0.13; 95% CI -0.04 to 0.30; P=0.14;
263 I²=0%, P =0.22) between groups. There were significantly greater improvements in chair stand
264 test results^{27, 42, 45} in the intervention group as compared to the control (MD 0.26; 95% CI 0.09-
265 0.43; P=0.003; I² = 23%, P=0.23). Two studies that were not suitable for meta-analysis and are
266 instead qualitatively described. Arrieta et al reported no significant differences between groups
267 in the percentage of participants who had a ≥ 1 point decrease in SPPB score at one and two
268 years (P=0.772, P=0.057, respectively).³⁶ With use of an alternative measure of physical
269 function (modified physical performance test), Villareal et al²⁵ reported a significant

270 improvement in their exercise- nutrition interventions group as compared to exercise only
271 (P=0.04), nutrition only (P<0.001), or controls.

272 Activities of daily living

273 Data on activities of daily living (ADL) from four studies^{28, 33, 39, 42} underwent meta-analysis,
274 from which participants who received exercise-nutrition intervention were determined to have
275 greater ADL independence post-intervention than those who received standard care (SMD
276 0.92; 95% CI 0.78-1.05 to 0.85; P<0.001, Figure 3). However, high heterogeneity was observed
277 (I²=96%, P<0.001). Results from two studies^{40, 43} were unable to be included meta-analysis
278 (data unavailable).

279 Muscle strength

280 Meta-analysis showed no statistically significant differences in muscle strength between
281 participants who received exercise-nutrition intervention and those that received standard care,
282 when handgrip strength was analysed from three studies^{27, 37, 45} (MD 0.46; 95% -0.38 to 0.85;
283 P = 0.28; I² = 49%, P = 0.14), or, when of handgrip and quadriceps strength was combined
284 (n=4 studies)^{27, 37, 42, 45} using a published methodology⁴⁶ (SMD 0.10; 95% CI -0.09 to 0.29;
285 P=0.24, I²=28%, P=0.30) (Figure 3).

286 Nutrition, Cognition and Biomarkers outcomes

287 Most studies assessed participants' nutritional status at baseline, while only one study³¹
288 assessed it as an outcome. Luger et al reported a 1.54-point improvement in the MNA long
289 form in participants who received exercise-nutrition intervention compared to those who
290 received standard care (95% CI 0.51-2.56, P=0.004). Combined exercise-nutrition intervention
291 did not affect cognitive status (mini-mental state examination (MMSE)) or mood (geriatric
292 depression scale (GDS)).⁴³ Armamento-Villareal et al reported a significant decrease in total
293 and free estradiol in their frail obese older men (attributed to weight loss from lifestyle change

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3 294 rather than the intervention), without a clinically meaningful increase in total or free
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5 295 testosterone levels.²⁶ In one study that reported C-reactive protein (CRP) levels, this
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8 296 inflammatory marker remained stable in the exercise-nutrition intervention group participants,
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10 297 compared to an increase in the social support control group at the end of 12 weeks (P=0.04).⁴⁷
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13 298 Quality of life and falls

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16 299 Three studies^{30, 35, 38} that evaluated quality of life could not find statistically significant
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18 300 improvement in the intervention as compared to the control group though Milte et al³⁸ found a
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20 301 trend favouring intervention. Fairhall et al²⁹ found that risk factors related to falls (physical
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22 302 tests as mentioned above) but not rate of falls were reduced while Kapan et al³⁴ found that a
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24 303 10% reduction in fear of falling as ascertained by the falls efficacy scale.
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29 305 Economic analyses

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33 306 Only two studies examined the cost-effectiveness of their exercise-nutrition intervention.
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35 307 Fairhall et al³⁰ reported no additional resource cost in terms of medical (P=0.87) or nursing and
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37 308 health professional appointments (P=0.32). Similarly, Milte et al³⁸ reported no cost differences
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39 309 between groups (P=0.868).
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44 311 **Discussion**

45 312 *Main findings*

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48 313 The present systematic review and meta-analysis present updated evidence that suggest
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50 314 exercise with nutrition intervention to be effective on frailty and frailty-related physical
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52 315 outcomes in hospitalised older adult patients. When compared to standard care, combined
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54 316 exercise-nutrition interventions improved frailty status as determined by the Fried Frailty
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56 317 criteria² and the SHARE-FI.⁴⁴ They also improved physical function according to the SPPB
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3 318 and ADLs. One study found significant improvement in nutrition score.³¹ The two economic
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5 319 analyses included in this review suggested that combined exercise-nutrition interventions,
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7 320 though more effective, were no more costly than standard care.

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10 321 Existing reviews of exercise and nutrition interventions have highlighted heterogeneity in study
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12 322 protocols (including intervention descriptions), which limits potential for meta-analysis. They
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14 323 have also focussed on community dwelling participants.⁴⁸ This study is novel in reviewing a
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16 324 more vulnerable hospitalised population that has not been previously investigated, and
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18 325 specifically targeting pre-frail or frail older adults. However, only three studies in this review
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20 326 used a validated assessment tool and were included in the meta-analysis of frailty as an
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22 327 outcome. This could be because the frailty phenotype was first described 2001, with a
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24 328 systematic evaluation of frailty tools a decade later.^{2, 49} Accordingly, the authors decided to
25
26 329 additionally evaluate frailty components such as physical function, nutrition, cognition and
27
28 330 biomarkers as baseline and outcome measures. Although not specific to frailty, these measures
29
30 331 provide insights to the effectiveness of exercise-nutrition interventions on improving various
31
32 332 components of frailty and may inform future studies.

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34 333 Previous reviews have found mixed results⁴⁸ or have concluded that evidence for combined
35
36 334 interventions is limited but increasing.⁵⁰ Our results concur with RCTs of exercise-nutrition
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38 335 interventions conducted in community dwelling frail older adults. Tarazona-santabalbina and
39
40 336 colleagues found significant improvement in SPPB in participants on an exercise-nutrition
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42 337 intervention as compared to controls in a community dwelling frail population – intervention
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44 338 group 9.5 ± 1.8 vs control group 7.1 ± 2.8 , $P=0.007$.⁵¹ Similarly, Kim et al reported a community-
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46 339 based study of frail older adults that found SPPB to remain stable in the intervention group,
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48 340 while it decreased by 12.5% (1 point) in controls ($P=0.039$).⁵² Our meta-analysis of individual
49
50 341 components of the SPPB suggest that the significant improvements in functional muscle
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52 342 strength as represented by the chair stand component of the SPPB may be pivotal to the increase

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3 343 in overall SPPB post intervention, and reflect the functional lower limb strength training focus
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5 344 of the exercise interventions. However, the meta-analysis of handgrip +/- quadriceps strength
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7 345 did not produce a similar trend. Diversity in outcome measures for frailty and frailty-related
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9 346 domains like physical function is a challenge for comparative analyses between studies. Future
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11 347 studies should carefully consider measure responsiveness when selecting outcome tools.
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15 348 Nutrition is another important domain within frailty. Yet the majority of studies included in
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17 349 this review only reported nutrition status at baseline, with only one study reporting follow-up
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19 350 nutrition assessment at the end of the intervention.³¹ Luger et al described an improvement in
20
21 351 nutrition status in a sample of at risk malnourished pre-frail/frail patients (thus likely to benefit
22
23 352 most from nutrition therapy). As hospitalised patients have greater energy deficits due to
24
25 353 catabolic stress of acute illness, they are a population that requires careful determination of
26
27 354 energy/protein requirements and in whom additive effects of nutrition supplementation to
28
29 355 exercise may have greatest impact on outcomes such as muscle strength.⁵¹ As none of the
30
31 356 studies in the present review reported on energy deficits, it is not known whether these patients
32
33 357 received adequate replacement. Nutrition supplementation should also not be confused with
34
35 358 nutrition or diet modifications. The provision of ONS alone is unlikely to augment diet
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37 359 adequacy as completely as diet modification that involves a wider range of nutrients and non-
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39 360 nutrients⁵³ especially when led by dietitians.^{54, 55}
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46 361 For both exercise and nutrition based interventions, an understanding of patient participation
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48 362 dynamics and compliance is required because of how they can impact on effectiveness.⁵⁶ Only
49
50 363 five studies in this review reported attendance to program/home visits or phone calls or
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52 364 adherence to prescribed exercise/diet or related advice at rates of 50-90% and 70-93% for
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54 365 nutrition and exercise interventions, respectively. Issues with participants resulting in poorer
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56 366 compliance were not reported in these articles, such that the authors recommend that future
57
58 367 studies explore barriers and enablers to adherence in multi-modal interventions.
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3 368 Cognition is another critical domain in the multidimensional nature of frailty. Exercise⁵⁷ and
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5 369 nutrition interventions⁵⁸ may have a far reaching, positive effect on cognition in older adults.
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8 370 However, there was no evidence of an impact on cognition from a single study⁴¹ in the present
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10 371 review. This is consistent with a network meta-analysis of 13 RCTs that examined exercise and
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12 372 nutrition interventions in frail older adults.¹¹ One suggested explanation is that different
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14 373 neuronal mechanisms could result in a misfit between combinatory approaches of nutrition and
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16 374 physical interventions⁵⁹ highlighting that more in-depth research is required.⁶⁰
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20 375 The economic delivery of new interventions and models of care is important to a range of
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22 376 stakeholders⁶¹ but has been infrequently conducted in previous studies.⁴⁸ In this review, only
23
24 377 two out of 11 studies included an economic analysis, with the majority of costs coming from
25
26 378 delivery of exercise and nutrition support. The types of consumables that were considered in
27
28 379 analyses included nutrition supplements, ankle/wrist weights, mobility aids and medications.
29
30 380 Elements of service provision that were considered included community, rehabilitation,
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32 381 residential and transition care service use, which were often reduced and contributed to the net
33
34 382 result. The results of this review support previous findings of beneficial effects on frailty-
35
36 383 related outcomes, without increased costs.⁴⁸ However, results should be interpreted with
37
38 384 caution as omission of other services (such as medication reviews) within a multimodal
39
40 385 intervention can impact costings, and there are instances where interventions have not been
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42 386 found to be more-cost effective than usual care.⁶² The approach of streamlining and
43
44 387 reorganising existing services rather than creating entirely new systems may be preferred.

388 *Strength and weakness*

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

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3 391 We chose to use of an updated version of the Cochrane risk of bias tool (RoB 2), which
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5 392 addresses issues of confusion common to its first version.
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8 393 By focussing on exercise-nutrition interventions only, this study addresses a gap as identified
9
10 394 in a recent review of multi-domain interventions in pre-frail or frail elderly adults, in which
11
12 395 some interventions may have been be too broad to directly impact frailty, and functional and
13
14 396 cognitive status.⁵⁰ Multidisciplinary team based approaches remain recommended and are a
15
16 397 bedrock of quality standard care; they may also already include goals for exercise and nutrition
17
18 398 such that it may be difficult to solely attribute outcomes to a targeted but supplementary
19
20 399 exercise-nutrition program. Social relationships affect health behaviour and physical health,⁶³
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22 400 such that intervention benefits may in part come from social interactions. Nevertheless, several
23
24 401 studies^{27, 31, 41} have demonstrated significant improvements even when control participants are
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26 402 provided with the social aspect of an intervention, such that exercise and nutrition are expected
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28 403 to improve outcomes independent of social interactions.
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34 404 *Implications and future research*

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37 405 This review is a useful resource for researchers and multi-disciplinary clinicians who are
38
39 406 seeking to generate evidence or evaluate their practices of exercise-nutrition interventions for
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41 407 frail hospitalised older adults. The authors interpretation of the quality of studies in this review
42
43 408 is that the evidence base is low, but the inclusion of future studies may change estimates of the
44
45 409 intervention effects. While blinding of participants to the intervention is acknowledged to be
46
47 410 difficult, future studies should be adequately powered, use allocation concealment with
48
49 411 blinding outcome assessors and data analysts at least. Improved reporting of intervention
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51 412 details is also required,⁶⁴ which may assist in answering research questions around the optimal
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53 413 duration, dose, modality and timing of intervention(s) across the hospital to community
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55 414 continuum. In the present review, potential beneficial effects of combined interventions could
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3 415 have been negated given the short durations reported by most studies. Thus, future studies may
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5 416 be extended for >6-12 months, or employ principles of chronic condition self-management,⁶⁵
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7 417 to determine delayed improvements and achieve long-lasting sustainability of interventions.
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9 418 There are many ongoing research activities relevant to the scope of this review,⁶⁶⁻⁶⁹ yet only
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11 419 one has reported plans for economic analysis in the study protocol.⁶⁶ Economic evaluations can
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13 420 expand current evidence on the sustainability of incorporating such services within resource-
14
15 421 constrained healthcare systems.

422 *Conclusion*

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

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433 **Author Contributions**

434 All authors contributed to the conception and design of review. CH and YS read and screened
435 titles and abstract of potentially relevant studies. CH and YS evaluated the selected studies and
436 performed data extraction. CH, MM, AY, CB reviewed the evidence. RW provided statistical
437 expertise on meta-analyses. CH drafted the article and all authors provided critical revisions
438 and final approval of the manuscript. All authors had access to the data in the study and can

1
2
3 439 take responsibility for the integrity of the reported findings. All authors fulfil the ICMJE criteria
4
5 440 for authorship.
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7

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17

18 19 445 **Competing interests**

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22 446 None declared.
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25 447 **Patient consent**

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28 448 Not required.
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31 449 **Data sharing statement**

32
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34 450 Details of the excluded papers are available from the corresponding author upon request.
35
36

37 451 **References**

- 38
39
40 452 1. Le Cossec C, Perrine AL, Beltzer N, Fuhrman C, Carcaillon-Bentata L. Pre-Frailty,
41 453 Frailty, and Multimorbidity: Prevalences and Associated Characteristics from Two French
42 454 National Surveys. *J Nutr Health Aging*. 2016;20(8):860-9.
43 455 2. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in
44 456 older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146-56.
45 457 3. Considine J, Fox K, Plunkett D, Mecner M, M OR, Darzins P. Factors associated with
46 458 unplanned readmissions in a major Australian health service. *Aust Health Rev*. 2019;43(1):1-
47 459 9.
48
49 460 4. Sirven N, Rapp T. The cost of frailty in France. *Eur J Health Econ*. 2017;18(2):243-53.
50 461 5. Thompson MQ, Theou O, Karnon J, Adams RJ, Visvanathan R. Frailty prevalence in
51 462 Australia: Findings from four pooled Australian cohort studies. *Australas J Ageing*.
52 463 2018;37(2):155-8.
53 464 6. Giné-Garriga M, Roqué-Fíguls M, Coll-Planas L, Sitja-Rabert M, Salvà A. Physical
54 465 exercise interventions for improving performance-based measures of physical function in
55 466 community-dwelling, frail older adults: a systematic review and meta-analysis. *Archives of*
56 467 *physical medicine and rehabilitation*. 2014;95(4):753-69. e3.
57
58
59
60

- 1
2
3 468 7. Ng TP, Feng L, Nyunt MS, Feng L, Niti M, Tan BY, et al. Nutritional, Physical,
4 469 Cognitive, and Combination Interventions and Frailty Reversal Among Older Adults: A
5 470 Randomized Controlled Trial. *American Journal of Medicine*. 2015;128(11):1225-36.e1.
- 6 471 8. Hsieh TJ, Su SC, Chen CW, Kang YW, Hu MH, Hsu LL, et al. Individualized home-
7 472 based exercise and nutrition interventions improve frailty in older adults: a randomized
8 473 controlled trial. *Int J Behav Nutr Phys Act*. 2019;16(1):119.
- 9 474 9. Lozano-Montoya I, Correa-Perez A, Abraha I, Soiza RL, Cherubini A, O'Mahony D, et
10 475 al. Nonpharmacological interventions to treat physical frailty and sarcopenia in older patients:
11 476 a systematic overview - the SENATOR Project ONTOP Series. *Clinical Interventions In*
12 477 *Aging*. 2017;12:721-40.
- 13 478 10. Abizanda P, López MD, García VP, Estrella JdD, da Silva González Á, Vilardell NB,
14 479 et al. Effects of an Oral Nutritional Supplementation Plus Physical Exercise Intervention on
15 480 the Physical Function, Nutritional Status, and Quality of Life in Frail Institutionalized Older
16 481 Adults: The ACTIVNES Study. *Journal of the American Medical Directors Association*.
17 482 2015;16(5):439.e9-.e16.
- 18 483 11. Negm AM, Kennedy CC, Thabane L, Veroniki AA, Adachi JD, Richardson J, et al.
19 484 Management of Frailty: A Systematic Review and Network Meta-analysis of Randomized
20 485 Controlled Trials. *J Am Med Dir Assoc*. 2019;20(10):1190-8.
- 21 486 12. Rozzini R, Sabatini T, Cassinadri A, Boffelli S, Ferri M, Barbisoni P, et al. Relationship
22 487 between functional loss before hospital admission and mortality in elderly persons with
23 488 medical illness. *J Gerontol A Biol Sci Med Sci*. 2005;60(9):1180-3.
- 24 489 13. Covinsky KE, Martin GE, Beyth RJ, Justice AC, Sehgal AR, Landefeld CS. The
25 490 relationship between clinical assessments of nutritional status and adverse outcomes in older
26 491 hospitalized medical patients. *J Am Geriatr Soc*. 1999;47(5):532-8.
- 27 492 14. Sharma Y, Thompson C, Shari R, Hakendorf P, Miller M. Malnutrition in Acutely
28 493 Unwell Hospitalized Elderly - "The Skeletons Are Still Rattling in the Hospital Closet". *J Nutr*
29 494 *Health Aging*. 2017;21(10):1210-5.
- 30 495 15. Sharma Y, Miller M, Shahi R, Hakendorf P, Horwood C, Thompson C. Malnutrition
31 496 screening in acutely unwell elderly inpatients. *Br J Nurs*. 2016;25(18):1006-14.
- 32 497 16. Laur CV, McNicholl T, Valaitis R, Keller HH. Malnutrition or frailty? Overlap and
33 498 evidence gaps in the diagnosis and treatment of frailty and malnutrition. *Applied Physiology,*
34 499 *Nutrition & Metabolism*. 2017;42(5):449-58.
- 35 500 17. Wilkinson R, Arensberg ME, Hickson M, Dwyer JT. Frailty Prevention and Treatment:
36 501 Why Registered Dietitian Nutritionists Need to Take Charge. *J Acad Nutr Diet*.
37 502 2017;117(7):1001-9.
- 38 503 18. Higgins JP, Green S. *Cochrane handbook for systematic reviews of interventions:*
39 504 *Cochrane book series*. 2008.
- 40 505 19. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic
41 506 reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62(10):1006-12.
- 42 507 20. Innovation VH. Covidence systematic review software. Veritas Health Innovation
43 508 Melbourne, VIC; 2017.
- 44 509 21. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a
45 510 revised tool for assessing risk of bias in randomised trials. *Bmj*. 2019;366:l4898.
- 46 511 22. Farrah K, Young K, Tunis MC, Zhao L. Risk of bias tools in systematic reviews of
47 512 health interventions: an analysis of PROSPERO-registered protocols. *Systematic reviews*.
48 513 2019;8(1):280.
- 49 514 23. RevMan. Review manager (revman)[computer program]. version 5.3. The Nordic
50 515 Cochrane Centre, The Cochrane Collaboration Copenhagen, Denmark; 2014.
- 51 516 24. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-
52 517 analyses. *Bmj*. 2003;327(7414):557-60.

- 1
2
3 518 25. Villareal DT, Chode S, Parimi N, Sinacore DR, Hilton T, Armamento-Villareal R, et
4 519 al. Weight loss, exercise, or both and physical function in obese older adults. *New England*
5 520 *Journal of Medicine*. 2011;364(13):1218-29.
- 6 521 26. Armamento-Villareal R, Aguirre LE, Qualls C, Villareal DT. Effect of lifestyle
7 522 intervention on the hormonal profile of frail, obese older men. *Journal of Nutrition, Health and*
8 523 *Aging*. 2016;20(3):334-40.
- 9 524 27. Cameron ID, Fairhall N, Langron C, Lockwood K, Monaghan N, Aggar C, et al. A
10 525 multifactorial interdisciplinary intervention reduces frailty in older people: randomized trial.
11 526 *BMC Med*. 2013;11:65.
- 12 527 28. Fairhall N, Sherrington C, Kurrle SE, Lord SR, Lockwood K, Cameron ID. Effect of a
13 528 multifactorial interdisciplinary intervention on mobility-related disability in frail older people:
14 529 randomised controlled trial. *BMC Med*. 2012;10:120.
- 15 530 29. Fairhall N, Sherrington C, Lord SR, Kurrle SE, Langron C, Lockwood K, et al. Effect
16 531 of a multifactorial, interdisciplinary intervention on risk factors for falls and fall rate in frail
17 532 older people: a randomised controlled trial. *Age & Ageing*. 2014;43(5):616-22.
- 18 533 30. Fairhall N, Sherrington C, Kurrle SE, Lord SR, Lockwood K, Howard K, et al.
19 534 Economic evaluation of a multifactorial, interdisciplinary intervention versus usual care to
20 535 reduce frailty in frail older people. *Journal of the American Medical Directors Association*.
21 536 2015;16(1):41-8.
- 22 537 31. Luger E, Dorner TE, Haider S, Kapan A, Lackinger C, Schindler K. Effects of a Home-
23 538 Based and Volunteer-Administered Physical Training, Nutritional, and Social Support
24 539 Program on Malnutrition and Frailty in Older Persons: A Randomized Controlled Trial. *Journal*
25 540 *of the American Medical Directors Association*. 2016;17(7):671.e9-.e16.
- 26 541 32. Haider S, Dorner TE, Luger E, Kapan A, Titze S, Lackinger C, et al. Impact of a Home-
27 542 Based Physical and Nutritional Intervention Program Conducted by Lay-Volunteers on
28 543 Handgrip Strength in Prefrail and Frail Older Adults: A Randomized Control Trial. *PLoS ONE*
29 544 [Electronic Resource]. 2017;12(1):e0169613.
- 30 545 33. Winzer E, Dorner TE, Grabovac I, Haider S, Kapan A, Lackinger C, et al. Behavior
31 546 changes by a buddy-style intervention including physical training, and nutritional and social
32 547 support. *Geriatrics & Gerontology International*. 2019;19(4):323-9.
- 33 548 34. Kapan A, Luger E, Haider S, Titze S, Schindler K, Lackinger C, et al. Fear of falling
34 549 reduced by a lay led home-based program in frail community-dwelling older adults: A
35 550 randomised controlled trial. *Archives of Gerontology & Geriatrics*. 2017;68:25-32.
- 36 551 35. Kapan A, Winzer E, Haider S, Titze S, Schindler K, Lackinger C, et al. Impact of a lay-
37 552 led home-based intervention programme on quality of life in community-dwelling pre-frail and
38 553 frail older adults: a randomized controlled trial. *BMC Geriatrics*. 2017;17:1-11.
- 39 554 36. Arrieta H, Astrugue C, Regueme S, Durrieu J, Maillard A, Rieger A, et al. Effects of a
40 555 physical activity programme to prevent physical performance decline in onco-geriatric
41 556 patients: a randomized multicentre trial. *Journal of Cachexia, Sarcopenia and Muscle*.
42 557 2019;10(2):287-97.
- 43 558 37. Niccoli S, Kolobov A, Bon T, Rafilovich S, Munro H, Tanner K, et al. Whey Protein
44 559 Supplementation Improves Rehabilitation Outcomes in Hospitalized Geriatric Patients: A
45 560 Double Blinded, Randomized Controlled Trial. *Journal of Nutrition in Gerontology and*
46 561 *Geriatrics*. 2017;36(4):149-65.
- 47 562 38. Milte R, Miller MD, Crotty M, Mackintosh S, Thomas S, Cameron ID, et al. Cost-
48 563 effectiveness of individualized nutrition and exercise therapy for rehabilitation following hip
49 564 fracture. *Journal of Rehabilitation Medicine (Stiftelsen Rehabiliteringsinformation)*.
50 565 2016;48(4):378-85.
- 51 566 39. Singh NA, Quine S, Clemson LM, Williams EJ, Williamson DA, Stavrinou TM, et al.
52 567 Effects of high-intensity progressive resistance training and targeted multidisciplinary

- 1
2
3 568 treatment of frailty on mortality and nursing home admissions after hip fracture: a randomized
4 569 controlled trial. *Journal of the American Medical Directors Association*. 2012;13(1):24-30.
- 5 570 40. Blanc-Bisson C, Dechamps A, Gouspillou G, Dehail P, Bourdel-Marchasson I. A
6 571 randomized controlled trial on early physiotherapy intervention versus usual care in acute car
7 572 unit for elderly: Potential benefits in light of dietary intakes. *Journal of Nutrition, Health and*
8 573 *Aging*. 2008;12(6):395-9.
- 9 574 41. Miller MD, Crotty M, Whitehead C, Bannerman E, Daniels LA. Nutritional
10 575 supplementation and resistance training in nutritionally at risk older adults following lower
11 576 limb fracture: a randomized controlled trial. *Clinical Rehabilitation*. 2006;20(4):311-23.
- 12 577 42. Rodriguez-Manas L, Laosa O, Vellas B, Paolisso G, Topinkova E, Oliva-Moreno J, et
13 578 al. Effectiveness of a multimodal intervention in functionally impaired older people with type
14 579 2 diabetes mellitus. *J Cachexia Sarcopenia Muscle*. 2019;10(4):721-33.
- 15 580 43. Azad N, Molnar F, Byszewski A. Lessons learned from a multidisciplinary heart failure
16 581 clinic for older women: a randomised controlled trial. *Age Ageing*. 2008;37(3):282-7.
- 17 582 44. Romero-Ortuno R, Walsh CD, Lawlor BA, Kenny RA. A frailty instrument for primary
18 583 care: findings from the Survey of Health, Ageing and Retirement in Europe (SHARE). *BMC*
19 584 *geriatrics*. 2010;10(1):57.
- 20 585 45. Haider S, Dorner TE, Luger E, Kapan A, Titze S, Lackinger C, et al. Impact of a home-
21 586 based physical and nutritional intervention program conducted by lay-volunteers on handgrip
22 587 strength in prefrail and frail older adults: A randomized control trial. *PLoS ONE*. 2017;12(1).
23 588 46. Wright J, Baldwin C. Oral nutritional support with or without exercise in the
24 589 management of malnutrition in nutritionally vulnerable older people: A systematic review and
25 590 meta-analysis. *Clin Nutr*. 2018;37(6 Pt A):1879-91.
- 26 591 47. Haider S, Grabovac I, Winzer E, Kapan A, Schindler KE, Lackinger C, et al. Change
27 592 in inflammatory parameters in prefrail and frail persons obtaining physical training and
28 593 nutritional support provided by lay volunteers: A randomized controlled trial. *PLoS ONE*.
29 594 2017;12(10).
- 30 595 48. Apóstolo J, Cooke R, Bobrowicz-Campos E, Santana S, Marcucci M, Cano A, et al.
31 596 Effectiveness of interventions to prevent pre-frailty and frailty progression in older adults: a
32 597 systematic review. *JBIC database of systematic reviews and implementation reports*.
33 598 2018;16(1):140.
- 34 599 49. De Vries N, Staal J, Van Ravensberg C, Hobbelen J, Rikkert MO, Nijhuis-Van der
35 600 Sanden M. Outcome instruments to measure frailty: a systematic review. *Ageing research*
36 601 *reviews*. 2011;10(1):104-14.
- 37 602 50. Dedebye L, Deschodt M, Verschueren S, Tournoy J, Gielen E. Effects of multi-domain
38 603 interventions in (pre)frail elderly on frailty, functional, and cognitive status: a systematic
39 604 review. *Clin Interv Aging*. 2017;12:873-96.
- 40 605 51. Tarazona-Santabalbina FJ, Gomez-Cabrera MC, Perez-Ros P, Martinez-Arnau FM,
41 606 Cabo H, Tsaparas K, et al. A Multicomponent Exercise Intervention that Reverses Frailty and
42 607 Improves Cognition, Emotion, and Social Networking in the Community-Dwelling Frail
43 608 Elderly: A Randomized Clinical Trial. *J Am Med Dir Assoc*. 2016;17(5):426-33.
- 44 609 52. Kim CO, Lee KR. Preventive effect of protein-energy supplementation on the
45 610 functional decline of frail older adults with low socioeconomic status: a community-based
46 611 randomized controlled study. *Journals of Gerontology Series A: Biological Sciences &*
47 612 *Medical Sciences*. 2013;68(3):309-16.
- 48 613 53. Denison HJ, Cooper C, Sayer AA, Robinson SM. Prevention and optimal management
49 614 of sarcopenia: a review of combined exercise and nutrition interventions to improve muscle
50 615 outcomes in older people. *Clinical interventions in aging*. 2015;10:859.
- 51 616 54. Munk T, Tolstrup U, Beck AM, Holst M, Rasmussen HH, Hovhannisyanyan K, et al.
52 617 Individualised dietary counselling for nutritionally at-risk older patients following discharge

- 1
2
3 618 from acute hospital to home: a systematic review and meta-analysis. *Journal of Human*
4 619 *Nutrition & Dietetics*. 2016;29(2):196-208.
- 5 620 55. Beck AM, Kjær S, Hansen BS, Storm RL, Thal-Jantzen K, Bitz C. Follow-up home
6 621 visits with registered dietitians have a positive effect on the functional and nutritional status of
7 622 geriatric medical patients after discharge: a randomized controlled trial. *Clinical Rehabilitation*.
8 623 2013;27(6):483-93.
- 9 624 56. Fairhall N, Sherrington C, Cameron ID, Kurrle SE, Lord SR, Lockwood K, et al. A
10 625 multifactorial intervention for frail older people is more than twice as effective among those
11 626 who are compliant: complier average causal effect analysis of a randomised trial. *Journal of*
12 627 *physiotherapy*. 2017;63(1):40-4.
- 13 628 57. Brisswalter J, Collardeau M, René A. Effects of acute physical exercise characteristics
14 629 on cognitive performance. *Sports medicine*. 2002;32(9):555-66.
- 15 630 58. Klímová B, Vališ M. Nutritional interventions as beneficial strategies to delay cognitive
16 631 decline in healthy older individuals. *nutrients*. 2018;10(7):905.
- 17 632 59. Schättin A, Baur K, Stutz J, Wolf P, de Bruin ED. Effects of physical exercise combined
18 633 with nutritional supplements on aging brain related structures and functions: a systematic
19 634 review. *Frontiers in aging neuroscience*. 2016;8:161.
- 20 635 60. Hardman RJ, Kennedy G, Macpherson H, Scholey AB, Pipingas A. A randomised
21 636 controlled trial investigating the effects of Mediterranean diet and aerobic exercise on cognition
22 637 in cognitively healthy older people living independently within aged care facilities: the
23 638 *Lifestyle Intervention in Independent Living Aged Care (LILAC)* study protocol
24 639 [ACTRN12614001133628]. *Nutrition journal*. 2015;14(1):53.
- 25 640 61. Drummond MF, Stoddart GL. Economic analysis and clinical trials. *Controlled clinical*
26 641 *trials*. 1984;5(2):115-28.
- 27 642 62. Ruikes FG, Adang EM, Assendelft WJ, Schers HJ, Koopmans RT, Zuidema SU. Cost-
28 643 effectiveness of a multicomponent primary care program targeting frail elderly people. *BMC*
29 644 *family practice*. 2018;19(1):62.
- 30 645 63. Umberson D, Karas Montez J. Social relationships and health: A flashpoint for health
31 646 policy. *Journal of health and social behavior*. 2010;51(1_suppl):S54-S66.
- 32 647 64. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better
33 648 reporting of interventions: template for intervention description and replication (TIDieR)
34 649 checklist and guide. *Bmj*. 2014;348:g1687.
- 35 650 65. Battersby M, Harris M, Smith D, Reed R, Woodman R. A pragmatic randomized
36 651 controlled trial of the Flinders Program of chronic condition management in community health
37 652 care services. *Patient Education and Counseling*. 2015;98(11):1367-75.
- 38 653 66. Fairhall N, Kurrle SE, Sherrington C, Lord SR, Lockwood K, John B, et al.
39 654 Effectiveness of a multifactorial intervention on preventing development of frailty in pre-frail
40 655 older people: Study protocol for a randomised controlled trial. *BMJ Open*. 2015;5(2).
- 41 656 67. Gonzalez-Sanchez M, Cuesta-Vargas AI, Del Mar Rodriguez Gonzalez M, Caro ED,
42 657 Nunez GO, Galan-Mercant A, et al. Effectiveness of a muticomponent workout program
43 658 integrated in an evidence based multimodal program in hyperfrail elderly patients:
44 659 POWERAGING randomized clinical trial protocol. *BMC Geriatrics*. 2019;19(1).
- 45 660 68. Jadcak AD, Luscombe-Marsh N, Taylor P, Barnard R, Makwana N, Visvanathan R.
46 661 The EXPRESS Study: Exercise and Protein Effectiveness Supplementation Study supporting
47 662 autonomy in community dwelling frail older people-study protocol for a randomized controlled
48 663 pilot and feasibility study. *Pilot & Feasibility Studies*. 2018;4:8.
- 49 664 69. Landi F, Cesari M, Calvani R, Cherubini A, Di Bari M, Bejuit R, et al. The 'Sarcopenia
50 665 and Physical fRailty IN older people: multi-componenT Treatment strategies' (SPRINTT)
51 666 randomized controlled trial: design and methods. *Aging Clinical & Experimental Research*.
52 667 2017;29(1):89-100.

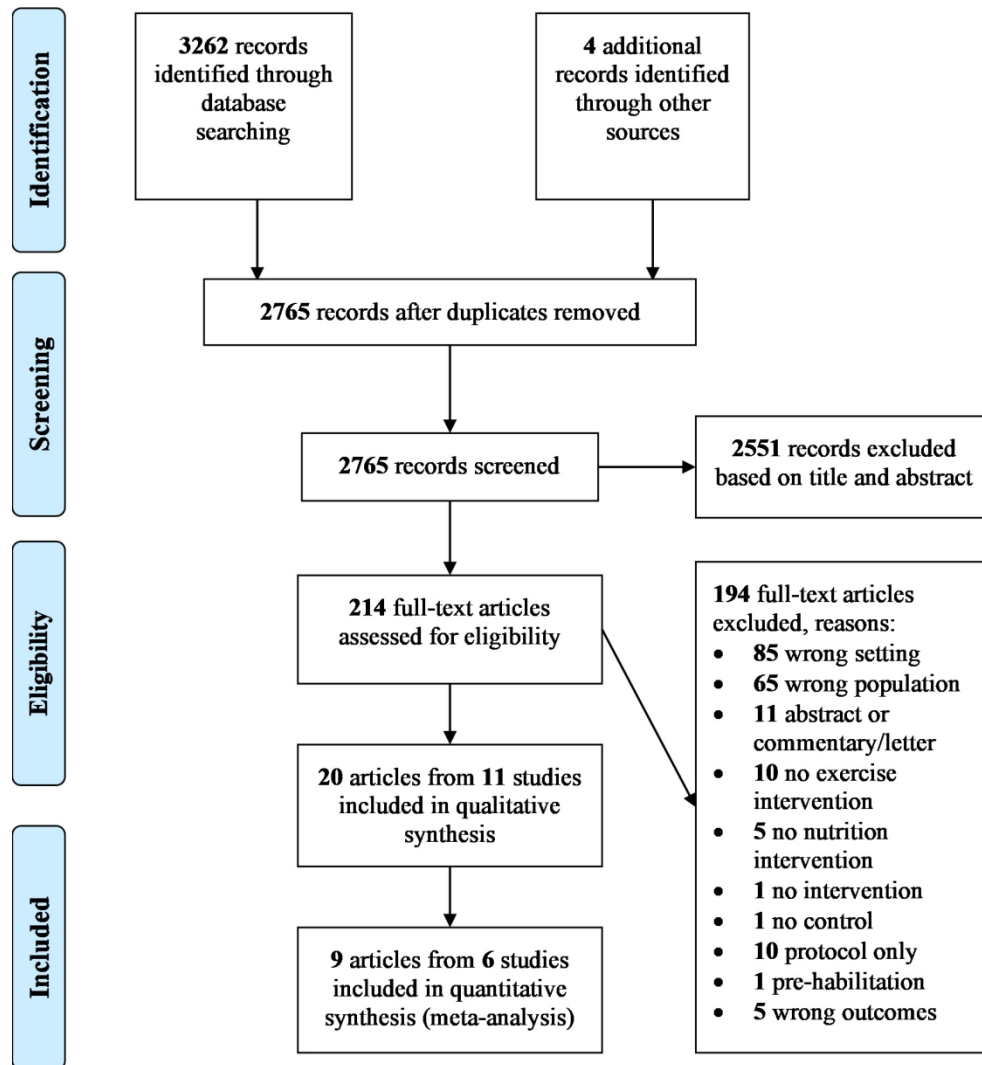
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6 669 **Figure captions**
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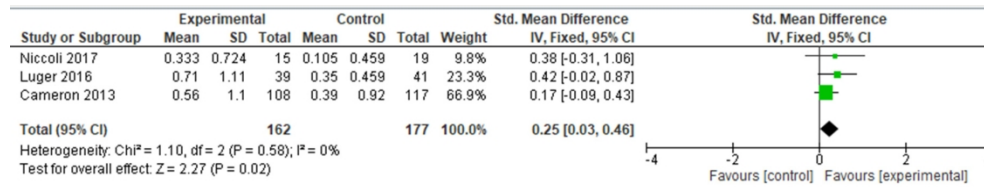
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9 670 Fig.1 Flow diagram illustrating results of the search and study selection process as described
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14 672 Fig 2. Meta-analysis of reduction in frailty score for exercise and nutrition intervention vs
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19 674 Fig.3 Meta-analyses of Short physical performance battery, Gait speed, Balance test, Chair
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45 Fig.1 Flow diagram illustrating results of the search and study selection process as described in the PRISMA
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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

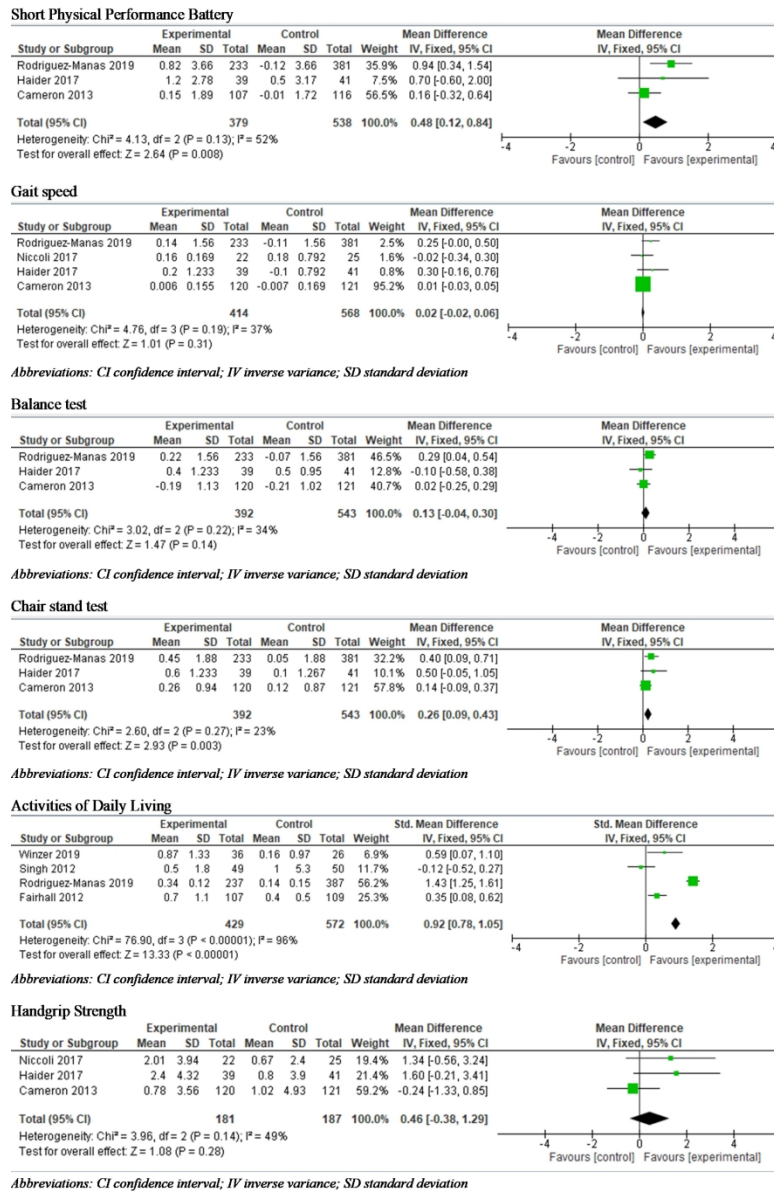


Fig.3 Meta-analyses of Short physical performance battery, Gait speed, Balance test, Chair stand test, Activities of daily living, handgrip and muscle strength

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

For peer review only



PRISMA 2009 Checklist

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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

Page 1 of 2

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

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2
3 **Title Page**
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8 3 hospitalised patients: a systematic review and meta-analysis
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1
2
3 22 **Abstract**
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5

6 23 Objectives: To determine the effectiveness of combined exercise-nutrition interventions in pre-
7
8 24 frail/frail hospitalised older adults on frailty, frailty-related indicators, quality of life (QoL),
9
10 25 falls and its cost-effectiveness.
11
12

13
14 26 Design: Randomised controlled trials (RCTs) of combined exercise-nutrition interventions on
15
16 27 hospitalised pre-frail/frail older adults ≥ 65 years were collated from MEDLINE, Emtree,
17
18 28 CINAHL, Ageline, Scopus, Cochrane and PEDro on 10th October 2019. The methodological
19
20 29 quality was appraised, and data were summarised descriptively or by the meta-analyses using
21
22 30 a fixed effects model. The standardised mean difference (SMD) or difference of means (MD)
23
24 31 with 95% confidence intervals (CIs) was calculated.
25
26
27

28 32 Results: Twenty articles from 11 RCTs experimenting exercise-nutrition interventions on
29
30 33 hospitalised older adults were included. Eight articles were suitable for the meta-analyses. One
31
32 34 study had low risk of bias and found improvements in physical performance and frailty-related
33
34 35 biomarkers. Exercise interventions were mostly supervised by a physiotherapist, focusing on
35
36 36 strength, ranging 2-5 times/week, of 20-90 minutes duration. Most nutrition interventions
37
38 37 involved education and supplementation but had dietitian supervision in only three studies. The
39
40 38 meta-analyses suggest that participants who received exercise-nutrition intervention had
41
42 39 greater reduction in frailty scores (n=3, SMD 0.25; 95% CI 0.03-0.46; P=0.02) and
43
44 40 improvement in short physical performance battery (SPPB) scores (n=3, MD 0.48; 95% CI
45
46 41 0.12-0.84; P=0.008) compared to standard care. Only the chair-stand test (n=3) out of the three
47
48 42 SPPB components was significantly improved (MD 0.26; 95% CI 0.09-0.43; P=0.003).
49
50 43 Patients were more independent in activities of daily living in intervention groups, but high
51
52 44 heterogeneity was observed ($I^2=96\%$, $P<0.001$). The pooled effect for handgrip (n=3) +/- knee
53
54 45 extension muscle strength (n=4) was not statistically significant. Nutritional status, cognition,
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3 46 biomarkers, QoL, falls and cost-effectiveness were summarised descriptively due to
4
5 47 insufficient data.
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7

8 48 Conclusions: There is evidence, albeit weak, showing that exercise-nutrition interventions are
9
10 49 effective to improve frailty and frailty-related indicators in hospitalised older adults.
11
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14 50 **PROSPERO registration number: CRD42020153934**
15

16 17 51 **Strengths and limitations of study** 18

- 19
20 52 • This is the first comprehensive systematic review with meta-analysis on the
21
22 53 effectiveness of exercise-nutrition interventions on frailty and outcomes related to
23
24 54 frailty in hospitalised and pre-frail/frail older adults.
25
26 55 • Only randomised controlled trials describing existing exercise-nutrition interventions
27
28 56 in frail older hospitalised patients were included.
29
30 57 • There was a moderate risk of bias for most included studies such that the findings of
31
32 58 this review are inconclusive, making it difficult to draw firm conclusions.
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35

36 37 59 **Introduction** 38

39
40 60 Frailty is a major contributor to late-life disability as it leads to loss of independence.¹ It is also
41
42 61 associated with poor health outcomes, and, increased health-care costs and service use.¹ Frailty
43
44 62 has been defined for clinical research by Fried et al² as a combination of unintentional weight
45
46 63 loss, weakness, exhaustion, slowness and reduced physical activity. Older adults (aged >65
47
48 64 years) that have been classified as frail and are hospitalised, have a three-fold higher risk of
49
50 65 readmission or death, as compared to the younger population.³ The management of older adults
51
52 66 who are frail has an incremental effect on health expenditures with an additional equivalent of
53
54 67 AU\$2400 per frail patient per year.⁴ With 21% of the population over 65 years estimated to be
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3 68 frail and 48% estimated to be pre-frail, concerns of economic impact are compounded by an
4
5 69 ageing population.⁵
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8 70 Exercise and nutrition are inextricably linked, in particular strength training can address
9
10 71 component issues of the frail phenotype.⁶ Yet evidence supporting the effectiveness of
11
12 72 exercise-nutrition interventions for reversal of frailty is limited to community-dwelling older
13
14 73 adults.⁷ In a study of community participants, a 3-month combined exercise-nutrition
15
16 74 intervention resulted in a significant reversal of frailty (reduction in Fried frailty score) at 6-
17
18 75 months, compared to the control group (between-group difference -0.34 ; 95% confidence
19
20 76 interval [CI] -0.52 to -0.16 ; $P < 0.001$).⁸ The combination of exercise therapy and dietary
21
22 77 intervention in older adults who are frail, has also been reported to increase muscle strength
23
24 78 (knee extension between-group difference 1.84 kg, 95% CI 0.17 – 3.51 , $P = 0.03$)⁹ and improve
25
26 79 nutritional status (Mini Nutritional Assessment (MNA) Short Form between group difference
27
28 80 1.4 , 95% CI 0.9 - 1.9 , $P < 0.01$).¹⁰
29
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33

34 81 A recent meta-analysis suggested that although effective, exercise combined with nutrition was
35
36 82 not more effective in treating frailty than exercise alone.¹¹ However, the majority of included
37
38 83 studies were conducted in a community setting, with only 15% of older adults either
39
40 84 hospitalised or recruited from acute care settings. No study has systematically evaluated
41
42 85 evidence for interventions that commence during acute hospitalisation or early post discharge
43
44 86 (in the high-risk period for post-hospital syndrome).
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49 87 Hospitalisation is a vulnerable period, especially for older adults who are frail and therefore at
50
51 88 higher risk of functional loss,¹² malnutrition^{13, 14} and further decline in frailty status.
52
53 89 Malnutrition is ubiquitous in older hospitalised patients with a prevalence as high as 50%.¹⁵
54
55 90 Since many domains of frailty are attributed to poor nutrition,¹⁶ the effect of nutrition
56
57 91 intervention when combined with exercise, may be more significant in the hospitalised
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2
3 92 population.¹⁶ Also, recent review suggest that nutrition support, provided by a multidisciplinary
4
5 93 team, may have a positive impact on mortality and quality of life in hospitalised older adult
6
7 94 patients.¹⁷ Nutritional therapy extends beyond protein or nutrition supplementation as reported
8
9 95 in previous studies and may be more effective as part of individualised medical nutrition
10
11 96 therapies involving dietitians to improve diet adequacy.¹⁸
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14

15 97 This study aims to determine the effectiveness of combined exercise-nutrition interventions on
16
17 98 (1) frailty, (2) frailty-related indicators, falls, quality of life (QoL) and (3) its cost effectiveness
18
19 99 on pre-frail or frail hospitalised older adults.
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23 100

26 101 **Materials and Methods**

29 102 *Protocol and registration*

31
32 103 The protocol for this review was compliant with Cochrane systematic review guidelines,¹⁹ and
33
34 104 registered with the International Prospective Register of Systematic Reviews (PROSPERO),
35
36 105 CRD42020153934. The study is reported according to Preferred Reporting Items for
37
38 106 Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²⁰ Patients and/or members of
39
40 107 the public were not involved in this study.
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44 108 *Search methods*

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46
47 109 Systematic searches of electronic databases (MEDLINE, Emcare, CINAHL, Ageline, Scopus,
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49 110 Cochrane and PEDro) were conducted by the lead author (CH) from inception until 10th
50
51 111 October 2019 using search strategies reviewed by an academic librarian (search queries
52
53 112 available in Supplementary file 1). Additionally, related citations to eligible items were
54
55 113 identified using the suggested related citation function in Pubmed. Reference lists of eligible
56
57 114 items were also screened.
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3 115 *Inclusion and exclusion criteria*
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6 116 The inclusion criteria were: 1) randomised controlled trials; 2) inclusion of pre-frail or frail
7
8 117 participants (as defined by study authors); 3) recruitment of older adult inpatients and/or those
9
10 118 hospitalised within the past 30 days of recruitment; 4) interventions that started while patients
11
12 119 were admitted and continued in the community/post-hospitalisation, or, commenced within 30
13
14 120 days of hospital discharge; 5) interventions that involved both physical exercises and
15
16 121 nutritional interventions (dietary modifications/education/training alone or combined with oral
17
18 122 nutrition supplementation); 6) measured frailty with an assessment tool or at least one indicator
19
20 123 relevant to frailty (nutritional status, physical function, cognitive function and mood, physical
21
22 124 activity level or biomarkers, falls and QoL and/or economic analysis of interventions. Studies
23
24 125 were excluded if they described protocols with no pilot outcomes, interventions delivered as a
25
26 126 part of a palliative care program, or interventions solely designed to facilitate discharge
27
28 127 planning (e.g. telephone support services, providing no pre-frailty or frailty intervention
29
30 128 element), recruited participants admitted following a mental health episode.
31
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36 129 *Study selection and data extraction*
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39 130 Covidence²¹ was used to manage citations for title and abstract, and full-text screening, in
40
41 131 duplicate (CH and YS, supplement 1). The reviewers were unblinded to authors, journals and
42
43 132 countries of origin. Any disagreement was resolved through discussion or consensus opinion
44
45 133 with the other authors. A data extraction form was developed a priori by the research team,
46
47 134 such that two researchers (CH and YS) performed data extraction independently, on eligible
48
49 135 full-text articles. Where available, the continuous data were extracted as (i) mean change with
50
51 136 standard deviation (SD), standard error of mean (SE) or 95% confidence interval (CI), or (ii)
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55 137 mean or median values with SD, SE or interquartile range post intervention. If the required
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3 138 data were not reported within a publication (including change in means for outcomes of
4
5 139 interest), the authors were emailed to request for it.
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8 140 *Quality of the studies* 9

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11 141 The risk of bias in the individual studies was assessed by the Revised Cochrane risk-of-bias
12
13 142 tool for randomised trials (RoB-2) by two researchers (CH and YS) independently.²² Any
14
15 143 disagreements were resolved by discussion or if required with consensus of a third reviewer.
16
17 144 The Cochrane risk-of-bias tool is widely used to assess randomised controlled trials (RCT) for
18
19 145 best practice.²³ Studies were given an overall risk-of-bias judgement of low, some concerns or
20
21 146 high. Overall risk-of-bias was determined as having “some concerns” if any one of the risks of
22
23 147 bias domains was rated as having “some concerns”. Likewise, studies were deemed to have an
24
25 148 overall high risk of bias if any one domain had a high risk of bias.
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29 149 *Data synthesis and statistical analyses* 30

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33 150 Where possible, a meta-analysis was performed; continuous outcome data were pooled and
34
35 151 reported as either the difference of means (MD) if the same outcome assessment tools were
36
37 152 used or the standardised mean difference (SMD) if different outcome assessment tools were
38
39 153 used, and the 95% CI, if there were two or more studies. The SMD is the mean difference when
40
41 154 the outcome for each study is standardised to have mean zero and SD=1. Studies presenting
42
43 155 SE were converted to SD via the conversion formula.¹⁹ The fixed-effect meta-analyses were
44
45 156 carried out with Cochrane Review Manager (RevMan) 5.3.²⁴ A P value of <0.05 was
46
47 157 considered statistically significant. The variability between studies (heterogeneity) was
48
49 158 assessed by I² and its 95% CI.²⁵ For studies with unobtainable missing, or incomparable data,
50
51 159 results were qualitatively synthesised.
52
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55 160 *Patient and public involvement* 56

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58
59 161 No patients were involved in this study
60

162 **Results**

163 *Study selection*

164 The flow of studies through the review process is summarised in Figure 1. Twenty articles
165 reporting on 11 studies were eligible for data synthesis and analysis. Three of 11 studies
166 presented results from their cohort across separate publications. Firstly, Villareal et al²⁶
167 reported on physical functioning outcomes with biomarker results in the publication of
168 Armamento-Villareal et al.²⁷ Secondly, Cameron et al²⁸ reported on frailty and some physical
169 function outcomes, with other physical function outcomes in a secondary publication²⁹ fall
170 rates³⁰ and cost-analysis in another.³¹ Thirdly, Luger et al³² reported on frailty and nutritional
171 status, with physical functioning outcomes across two other publications,^{33, 34} fall efficacy³⁵
172 and quality of life.³⁶ For clarity, the primary articles that report frailty or physical function
173 outcomes are cited for descriptive data in Tables 1-3 while individual articles are cited for
174 synthesis of outcome results.

175 *Study and sample characteristics*

176 Details of study characteristics are available in Table 1. Across all studies, a total of 2307
177 participants were investigated. Most studies reported that patients were recruited from hospital
178 wards (n=7)^{28, 37-42} while the other four studies^{26, 32, 43, 44} included patients that were recruited
179 from hospital wards and community. Seven studies included only frail participants,^{26, 28, 39-42, 44}
180 and the remaining four studies^{32, 37, 38, 43} included frail, pre-frail and non-frail participants. The
181 Fried frailty phenotype criteria² were used most frequently to classify frailty (n=4).^{28, 37, 38, 43}
182 with participants considered non-frail, pre-frail or frail if 0, 1-2, 3-5 criteria were present,
183 respectively. Luger et al used the Frailty Instrument for Primary Care of the Survey of Health,
184 Ageing, and Retirement in Europe (SHARE-FI)³² which integrates components of exhaustion,
185 appetite, handgrip strength, walking difficulties and physical activity.⁴⁵ Five studies did not

1
2
3 186 report any assessment method to define frailty.^{39-42, 44} One study used a combination of three
4
5 187 tools – modified Physical Performance Test, the measurement of VO₂ peak, and the Functional
6
7 188 Status Questionnaire.²⁶
8
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10 189 *Risk of bias within individual studies*

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13
14 190 Table 2 outlines the risk of bias in individual studies. One study²⁶ had a low risk of bias and
15
16 191 one study had a high risk of bias (including unblinded secondary outcome assessment and
17
18 192 insufficient detail on standard care in control groups across recruitment sites). The other nine
19
20 193 studies^{28, 32, 37-39, 41-44} were rated as having some concerns overall, of which five could have
21
22
23 194 been improved in ≥ 1 domain. The remaining four studies^{27, 31, 39, 41} that were rated as having
24
25 195 “some concerns” overall, had risk in only one domain with the most common reason being
26
27 196 failure to blind intervention/allocated group to participants. Examples of other concerns about
28
29
30 197 risk of bias included: assessors being aware of the group allocation³² (measurement of
31
32 198 outcomes domain); or a lack of information about participants/researcher blinding to group
33
34 199 allocation.^{26, 28, 43}
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36

37 200 *Characteristics of exercise intervention component*

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39
40 201 Characteristics of the exercise interventions used in studies are outlined in Table 3, and
41
42 202 included combinations of the following: supervised individual exercises (n=10),^{26, 28, 37-44} group
43
44 203 exercises (n=3),^{26, 40, 44} education including support with resources (digital versatile disc (DVD)
45
46 204 or visual aid instruction booklet, n=2),^{32, 37} and motivational interviewing using a standardised
47
48 205 protocol (n=1).³² Three studies^{38, 41, 43} had inpatient only interventions, five^{37, 39, 40, 42, 44} had
49
50 206 interventions that extended from inpatient to post-discharge, two^{28, 32} studies offered the
51
52 207 intervention post-discharge only and one²⁶ did not report.
53
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56
57 208 In the majority of studies (n=9), the exercise component was delivered by a physiotherapist.^{26,}
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59 209 ³⁷⁻⁴⁴ Two studies used trained fitness instructors,^{37, 40} and another engaged lay volunteers who
60

210 **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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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/kg; difficulty in performing 2 IADL or 1 basic ADL	Mild-moderate frailty: 100%

Azad <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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%

211 Abbreviations: BMI, Body Mass Index; w, Weeks; m, Months; y, Years; VO² max, maximal oxygen uptake; PPT, physical performance test; IADL, Instrumental Activities of Daily Living; ADL, Activities of Daily
 212 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
 213 group; UCG, Usual care group; ACG, Attention control group; NR, not reported; BMI presented in Mean ±standard deviation
 214 Multiple articles reported from same study, study chosen to represent other reports from the same study: *Luger *et al*³¹ – Haider *et al* 2017³², Winzer *et al* 2019³³, Kapan *et al* 2017³⁴, Kapan *et al* 2017³⁵; †Cameron *et al*
 215 2013²⁷ – Fairhall *et al* 2012²⁸, Fairhall *et al* 2014²⁹, Fairhall *et al* 2015³⁰; ‡Villareal *et al* 2011²⁵ – Armamento-Villareal 2016²⁶

216 **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 <i>et al</i> , 2019 ³⁵	+	?	?	?	+	?
Rodriguez-Manas <i>et al</i> , 2019 ⁴¹	+	?	+	?	+	?
Niccoli <i>et al</i> , 2017 ³⁶	?	?	+	?	+	?
Luger <i>et al</i> , 2016 ^{*30}	+	+	+	?	+	?
Milte <i>et al</i> , 2016 ³⁷	+	?	+	+	+	?
Cameron <i>et al</i> , 2013 ^{†26}	+	?	+	+	+	?
Singh <i>et al</i> , 2012 ³⁸	+	?	+	—	+	—
Villareal <i>et al</i> , 2011 ^{‡24}	+	+	+	+	+	+
Azad <i>et al</i> , 2008 ⁴²	+	?	+	?	+	?
Blanc-Bisson <i>et al</i> , 2008 ³⁹	+	?	+	?	+	?
Miller <i>et al</i> , 2006 ⁴⁰	+	?	+	+	+	?

217 Key: + = Low risk of bias; ? = Some concerns of risk of bias; — = High risk of bias

218 ^aDeviations from intended interventions (effect starting and adhering to intervention)

219 Multiple articles reported from same study, study chosen to represent other reports from the same study: *Luger *et al*³¹ – Haider *et al* 2017³², Winzer *et al* 2019³³, Kapan *et al* 2017³⁴, Kapan *et al* 2017³⁵; †Cameron *et al*
 220 2013²⁷ – Fairhall *et al* 2012²⁸, Fairhall *et al* 2014²⁹, Fairhall *et al* 2015³⁰; ‡Villareal *et al* 2011²⁵ – Armamento-Villareal 2016²⁶

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

Study	Exercise intervention	Nutrition intervention	Control intervention
Arrieta <i>et al</i> , 2019 ³⁵	<p>Type: <i>Strength</i> – Intensity range from low to high, starting at 10 repetition per exercise (UL, LL) with option of progressive loading</p> <p><i>Aerobic, Flexibility, Balance</i> – intensity individualised</p> <p>Frequency: 2 sessions/week, duration per session NR + home exercises duration NR</p> <p>Setting: Inpatient (supervised, individual) + post-discharge (unsupervised, individual)</p> <p>Additional support reported: Phone consults (by trainer 2x/month for first 6 months then monthly for 1 year); Education resource</p>	<p>Self-guided education resource: Provided with French National Nutrition Health Program education booklet - <i>Programme National Nutrition Santé</i> (PNNS)</p>	<p>Usual care: NR, variable between study sites</p> <p>Self-guided education resource: Provided with French National Nutrition Health Program education booklet - <i>Programme National Nutrition Santé</i> (PNNS)</p>
Rodriguez-Manas <i>et al</i> , 2019 ⁴¹	<p>Type: <i>Strength</i> – 40-80% of estimated 1RM, 8–10 repetitions (LL)</p> <p>Frequency: 2-weeks pretraining followed by 16-week program of 2 days/week; 20-30 minutes/sessions</p> <p>Setting: Inpatient (supervised, individual)</p>	<p>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.</p>	<p>Usual care: usual health care from local health system and/or general practitioner</p>
Niccoli <i>et al</i> , 2017 ³⁶	<p>Type: <i>Strength, Aerobic, Flexibility, Balance</i> – intensity and target muscle group individualised based on patient's baseline assessment</p> <p>Frequency: individualised based on patient's baseline assessment</p> <p>Setting: Inpatient (supervised, individual)</p>	<p>Supplements: Daily ONS with 24g whey protein per day (<i>9g breakfast, 7.5g at lunch and dinner</i>) in addition to usual diet</p>	<p>Usual care: usual medical care, no whey protein supplementation.</p> <p>Individual supervised exercise: Individualised exercises as per intervention.</p>
Luger <i>et al</i> , 2016 ^{*30}	<p>Type: <i>Strength</i> – 2 sets of 15 repetitions (UL, LL) until muscular exhaustion,</p> <p>Frequency: 2x/week, >30 minutes each session</p> <p>Setting: Post-discharge (supervised, individual)</p> <p>Additional support reported: Physical education (2-3 times/week, 30 minutes each session); Exercise education resource (demonstration DVD); Motivational interviewing.</p>	<p>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.</p> <p>Motivational interviewing: Techniques utilised with nutrition goal setting and tools to reinforce self-efficacy.</p>	<p>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</p>
Milte <i>et al</i> , 2016 ³⁷	<p>Type: <i>Strength, Balance (Otago exercise program)</i> – Intensity and repetitions NR, at the discretion of the treating physiotherapist (LL)</p>	<p>Nutrition consultation/education: Individualised nutrition therapy aimed at</p>	<p>Usual care: Usual rehabilitation program recommended during hospitalisation, social visits</p>

	<p>Frequency: 3 times/week, 20-30minutes/session for 12 weeks</p> <p>Setting: Inpatient (supervised, individual) + post-discharge (supervised, individual)</p>	<p>improving energy and protein intake to meet requirements by dietitian who visits fortnightly.</p> <p>Meal program: ordered as deemed necessary by dietitian.</p> <p>Supplements: commercial ONS recommended if needed by dietitian</p>	<p>weekly from trial staff and generic nutrition, exercise and falls prevention information</p>
Cameron <i>et al</i> , 2013 ^{†26}	<p>Type: <i>Strength, Balance, Aerobic + WEBB program</i> – intensity and target muscle groups NR</p> <p>Frequency: Exercises prescribed 3-5x/week (with 2 sessions for mobility training) for 1 year, supported by up to 10 home visits</p> <p>Setting: Post-discharge (supervised, individual) + (unsupervised, individual)</p>	<p>Nutrition consultation/education: Clinical evaluation of nutritional intake at home. A series of diet intervention as needed by dietitian.</p> <p>Meal program: ordered as deemed necessary by dietitian.</p> <p>Supplements: commercial ONS recommended if needed by dietitian</p>	<p>Usual care: usual health care during hospitalisation and from their general practitioner and community services after discharge</p>
Singh <i>et al</i> , 2012 ³⁸	<p>Type: <i>Strength</i> – 80% of most recent 1RM or RPE <15, 3 sets of 8 repetitions (UL, LL)</p> <p>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.</p> <p>Setting: Inpatient (supervised, individual) + (supervised, group-based)</p> <p>Additional support reported: Monthly phone consults</p>	<p>Nutrition consultation/education: Counselling on increase in diet quality, frequency NR</p> <p>Supplements: ONS +/- dietary advice to increase daily energy (400-600 kcal) and protein (20 g/day) intake.</p> <p>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</p> <p>Self-guided nutrition resource: Food sources of calcium, vitamin D and sun exposure</p>	<p>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.</p>
Villareal <i>et al</i> , 2011 ^{‡24}	<p>Type: <i>Strength</i> – 65% of 1RM; 8-12 repetitions of each exercise (UL, LL) with options for progression</p> <p><i>Aerobic</i>, ~65% of peak HR with gradual progression to 70-85%</p> <p><i>Flexibility, Balance</i></p> <p>Frequency: 90 minutes, 3 sessions/week</p> <p>Setting: Inpatient (supervised, group-based)</p>	<p>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.</p> <p>Supplements: 1500 mg of calcium/d day and ~1000 IU vitamin D/d</p>	<p>Usual care: General healthy lifestyle advice</p> <p>Supplements: 1500 mg of calcium/d day and ~1000 IU vitamin D/d</p>
Azad <i>et al</i> , 2008 ⁴²	<p>Type: ‘Comprehensive exercise program’; type, intensity and target muscle groups NR</p> <p>Frequency: 11 sessions over 6 weeks + NR home exercises</p> <p>Setting: Inpatient (supervised, group-based), post-discharge (unsupervised, individual)</p>	<p>Nutrition consultation/education: 3 sessions of individualized counselling about diet and nutrition in the management of CHF by dietitian</p>	<p>Usual care: Optimal medical care</p>

Blanc-Bisson <i>et al</i> , 2008 ³⁹	<p>Type: <i>Strength</i> – intensity (RM) NR, 10 x repetitions each exercise (LB)</p> <p>Frequency: 30 minutes, twice/day, five days/week</p> <p>Setting: Inpatient (supervised, individual)</p>	<p>Meal program: Geriatric hospital meals of 1800-2000 kcal/d</p> <p>Supplements: 1 daily ONS of 200 kcal and 15g protein</p>	<p>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.</p> <p>Individual supervised exercise: Physiotherapy continued at home for one month.</p>
Miller <i>et al</i> , 2006 ⁴⁰	<p>Type: <i>Strength</i> – intensity (RM) NR, 2 sets of 8 repetitions (LL) with progressive loading, at the discretion of the treating physiotherapist</p> <p>Frequency: 3 times/week, 20-30minutes/session for 12 weeks</p> <p>Setting: Inpatient (supervised, individual) + Post-discharge (supervised, individual)</p>	<p>Nutrition consultation/education: Individualised nutrition therapy by dietitian.</p> <p>Supplements: single type of ONS to cover the shortfall between individual estimated energy and protein requirements and actual intake over 42 days.</p>	<p>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.</p>

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* 2017³², Winzer *et al* 2019³³, Kapan *et al* 2017³⁴, Kapan *et al* 2017³⁵; †Cameron *et al* 2013²⁷ – Fairhall *et al* 2012²⁸, Fairhall *et al* 2014²⁹, Fairhall *et al* 2015³⁰; *Villareal *et al* 2011²⁵ – Armamento-Villareal 2016²⁶

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3 227 received training for the study.³² All studies included strength exercises as part of their
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5 228 interventions. Three studies described guidance on training intensity based on repetition
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7 229 maximum's (RM) between 40-80%.^{26, 40, 43} Other components of exercise programs included
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9 230 aerobic fitness,^{26, 28, 37, 38} flexibility,^{26, 37, 38} and/or balance.^{26, 28, 37, 38} The frequency of
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11 231 interventions ranged from two^{32, 37, 40, 43, 44} to five^{28, 41} sessions a week, lasting between 20^{39, 42,}
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13 232 ⁴³ to 90 minutes²⁶ each. The duration of exercise intervention varied from six weeks⁴⁴ to one
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15 233 year.^{26, 28, 37, 40}

20 234 *Characteristics of nutrition intervention component*

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23 235 Characteristics of the nutritional interventions used in studies, are outlined in Table 3, and
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25 236 included combinations of the following: nutrition consultation/education (n=8),^{26, 28, 32, 39-42, 44}
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27 237 oral nutrition and/or multivitamin/mineral supplements (n=7),^{26, 28, 38-42} meal programs
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29 238 (n=3),^{28, 39, 41} self-guided education materials (n=2),^{37, 40} and motivational interviewing (n=1).³²
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31 239 The most common combination of nutrition intervention was consultation/education with oral
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33 240 nutrition and/or multivitamin/mineral supplements (n=5).^{26, 39, 42, 44} Five of nine nutrition
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35 241 consultation/education interventions were performed by dietitians.^{26, 39, 42, 44} Other studies used
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37 242 trained lay volunteers,³² a researcher/nutrition therapist or did not specify a skill set for who
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39 243 delivered the consultation/education.⁴³

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44 244 All counselling/education-based interventions aimed to achieve adequate dietary targets for
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46 245 energy, protein and other nutrients. One study on obese frail participants aimed for calorie
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48 246 deficit but ensured that all achieved 1g/kg/day of protein in the intervention group.²⁶ The
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50 247 reported frequency of consultations ranged from twice a week^{32, 43} to fortnightly.^{39, 42} Oral
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52 248 nutrition supplements (ONS) were the most common supplements prescribed to intervention
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54 249 group participants (n=7),^{26, 38, 39, 41, 42, 44} typically providing 200-300kcal and 12-24g protein
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56 250 per serve with a frequency of consumption up to seven times a week^{38, 41} or as prescribed by
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3 251 dietitians^{26, 39, 42, 44} to cover any identified deficits between individually estimated energy and
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5 252 protein requirements and actual intake. Calcium and vitamin D were the two most commonly
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7 253 supplemented micronutrients ^{26, 40} at doses in the range of 1200-1500mg/d and 1000IU/d,
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10 254 respectively. Meal programs were either delivered as inpatient specialised geriatric meals
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12 255 providing 1800-2000kcal/d or home-delivered meal programs.^{28, 39, 41}

15 256 *Frailty outcomes*

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18 257 Data on frailty outcomes were available for quantitative analysis from three studies.^{28, 32, 38} The
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20 258 meta-analysis is presented in Figure 2 and suggested that participants who received exercise-
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22 259 nutrition intervention had a greater reduction in frailty score compared to those who received
23
24 260 standard care (SMD 0.25; 95% CI 0.03-0.46; P=0.02); no heterogeneity was observed (I²=0%;
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26 261 P=0.58).

30 262 *Physical functioning outcomes*

33 263 *Short Physical Performance Battery (SPPB)*

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36 264 Data on the SPPB were available for quantitative analysis from 3 studies, ^{28, 43, 46} with results
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38 265 from the meta-analysis presented in Figure 3. Participants who received exercise-nutrition
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40 266 intervention had a statistically significant improvement in SPPB score, compared to those that
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42 267 received standard care (MD 0.48; 95% CI 0.12-0.84; P=0.008), with moderate heterogeneity¹⁹
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44 268 observed (I² = 52%; P=0.13).^{20, 32, 33} The analysis of SPPB components across all studies
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46 269 showed no statistically significant differences in gait speed^{28, 38, 43, 46} (MD 0.02; 95% CI -0.02
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48 270 to 0.06; P=0.31; I²=37%, P=0.19) or balance ^{28, 43, 46} (MD 0.13; 95% CI -0.04 to 0.30; P=0.14;
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50 271 I²=0%, P=0.22) between groups. There were significantly greater improvements in chair stand
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52 272 test results^{28, 43, 46} in the intervention group as compared to the control (MD 0.26; 95% CI 0.09-
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54 273 0.43; P=0.003; I² = 23%, P=0.23). Two studies that were not suitable for meta-analysis (as data
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56 274 could not be provided by authors³⁷ and a different measurement was used²⁶) are instead

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3 275 qualitatively described. Arrieta et al reported no significant differences between groups in the
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5 276 percentage of participants who had a ≥ 1 point decrease in SPPB score at one and two years
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7 277 ($P=0.772$, $P=0.057$, respectively).³⁷ With use of an alternative measure of physical function
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9 278 (modified physical performance test – includes book lift, put on and take off a coat, pick up a
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11 279 penny, chair rise, turn 360, 50-foot walk, 10-steps of stairs, four flight of stairs and progressive
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13 280 Romberg test), Villareal et al²⁶ reported a significant improvement in their exercise- nutrition
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15 281 interventions group as compared to exercise only ($P=0.04$), nutrition only ($P<0.001$), or
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17 282 controls.

22 283 Activities of daily living

25 284 Data on activities of daily living (ADL) from three studies^{29, 34, 43} underwent meta-analysis,
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27 285 from which participants who received exercise-nutrition intervention were determined to have
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29 286 greater ADL independence post-intervention than those who received standard care (SMD
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31 287 1.06; 95% CI 0.91-1.20; $P<0.001$, Figure 3). However, high heterogeneity was observed
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33 288 ($I^2=96\%$, $P<0.001$). As such, additional random effects model was performed (SMD 0.80; 95%
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35 289 CI 0.00-1.60; $P<0.001$; supplement 2). Data from two studies^{41, 44} were unavailable to be
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37 290 included the meta-analysis. One study⁴⁰ was excluded due to high risk of bias in outcome
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39 291 measurements but reported that basic ADL declined lesser ($P<0.0001$) in the intervention vs
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41 292 control group.

46 293 Muscle strength

49 294 The meta-analysis showed no statistically significant differences in muscle strength between
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51 295 participants who received exercise-nutrition intervention and those that received standard care,
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53 296 when handgrip strength was analysed from three studies^{28, 38, 46} (MD 0.46; 95% -0.38 to 0.85;
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55 297 $P=0.28$; $I^2=49\%$, $P=0.14$), or, when of handgrip and quadriceps strength was combined ($n=4$
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3 298 studies)^{28, 38, 43, 46} using a published methodology⁴⁷ (SMD 0.10; 95% CI -0.09 to 0.29; P=0.24,
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5 299 I²=28%, P=0.30) (Figure 3).
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8 300 Nutrition, Cognition and Biomarkers outcomes

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11 301 Most studies assessed participants' nutritional status at baseline, while only one study³²
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13 302 assessed it as an outcome. Luger et al reported a 1.54-point improvement in the MNA long
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15 303 form in participants who received exercise-nutrition intervention compared to those who
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17 304 received standard care (95% CI 0.51-2.56, P=0.004). Combined exercise-nutrition intervention
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19 305 did not affect cognitive status (mini-mental state examination (MMSE)) or mood (geriatric
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21 306 depression scale (GDS)).⁴⁴ Armamento-Villareal et al reported a significant decrease in total
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23 307 and free estradiol in their frail obese older men (attributed to weight loss from lifestyle change
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25 308 rather than the intervention), without a clinically meaningful increase in total or free
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27 309 testosterone levels.²⁷ In one study that reported C-reactive protein (CRP) levels, this
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29 310 inflammatory marker remained stable in the exercise-nutrition intervention group participants,
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31 311 compared to an increase in the social support control group at the end of 12 weeks (P=0.04).⁴⁸
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36 312 Quality of life and falls

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40 313 Three studies^{31, 36, 39} that evaluated quality of life could not find statistically significant
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42 314 improvement in the intervention as compared to the control group though Milte et al³⁹ found a
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44 315 trend favouring intervention. Fairhall et al³⁰ found that risk factors related to falls (physical
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46 316 tests as mentioned above) but not rate of falls were reduced while Kapan et al³⁵ found that a
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48 317 10% reduction in fear of falling as ascertained by the falls efficacy scale.
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51 318 Economic analyses

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55 319 Only two studies examined the cost-effectiveness of their exercise-nutrition intervention.
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57 320 Fairhall et al³¹ reported no additional resource cost in terms of medical (P=0.87) or nursing and
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3 321 health professional appointments (P=0.32). Similarly, Milte et al³⁹ reported no cost differences
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5 322 between groups (P=0.868).
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10 324 **Discussion**

13 325 *Main findings*

16 326 The present systematic review and meta-analysis present updated evidence that suggest
17 327 exercise with nutrition intervention to be effective on frailty and frailty-related physical
18 328 outcomes in hospitalised older adult patients. When compared to standard care, combined
19 329 exercise-nutrition interventions improved frailty status as determined by the Fried Frailty
20 330 criteria² and the SHARE-FI.⁴⁵ They also improved physical function according to the SPPB
21 331 and ADLs. Only one study measured and found significant improvement in nutrition score.³²
22 332 The two economic analyses included in this review suggested that combined exercise-nutrition
23 333 interventions, though more effective, were no more costly than standard care.

24 334 Existing reviews of exercise and nutrition interventions have highlighted heterogeneity in study
25 335 protocols (including intervention descriptions), which limits potential for quantitative analysis.
26 336 They have also focussed on community dwelling participants.⁴⁹ This study is novel in
27 337 reviewing a more vulnerable hospitalised population that has not been previously investigated,
28 338 and specifically targeting pre-frail or frail older adults. However, out of five studies in this
29 339 review that used a validated frailty assessment tool, only three had assessed frailty at outcome,
30 340 and available for quantitative analysis. This could be because the frailty phenotype was first
31 341 described 2001, with a systematic evaluation of frailty tools a decade later.^{2, 50} Accordingly,
32 342 the authors decided to additionally evaluate frailty components such as physical function,
33 343 nutrition, cognition and biomarkers as baseline and outcome measures. Although not specific

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3 344 to frailty, these measures provide insights to the effectiveness of exercise-nutrition
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5 345 interventions on improving various components of frailty and may inform future studies.
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8 346 Previous reviews have found mixed results⁴⁹ or have concluded that evidence for combined
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10 347 interventions is limited but increasing.⁵¹ Our results concur with RCTs of exercise-nutrition
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12 348 interventions conducted in community dwelling frail older adults. Tarazona-santabalbina and
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14 349 colleagues found significant improvement in SPPB in participants on a 24-weeks exercise-
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16 350 nutrition intervention as compared to controls in a community dwelling frail population –
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18 351 intervention group 9.5 ± 1.8 vs control group 7.1 ± 2.8 , $P=0.007$.⁵² Similarly, Kim et al reported
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20 352 a 12-weeks, community-based study of frail older adults that found SPPB to remain stable in
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22 353 the intervention group, while it decreased by 12.5% (1 point) in controls ($P=0.039$).⁵³ Our meta-
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24 354 analysis of individual components of the SPPB suggest that the significant improvements in
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26 355 functional muscle strength as represented by the chair stand component of the SPPB may be
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28 356 pivotal to the increase in overall SPPB post intervention, and reflect the functional lower limb
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30 357 strength training focus of the exercise interventions. However, the meta-analysis of handgrip
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32 358 +/- quadriceps strength did not produce a similar trend. Diversity in outcome measures for
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34 359 frailty and frailty-related domains like physical function is a challenge for comparative
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36 360 analyses between studies. Future studies should carefully consider measure responsiveness
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38 361 when selecting outcome tools.
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46 362 Nutrition is another important domain within frailty. Yet the majority of studies included in
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48 363 this review only reported nutrition status at baseline, with only one study reporting follow-up
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50 364 nutrition assessment at the end of the intervention.³² Luger et al described an improvement in
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52 365 nutrition status in a sample of at risk malnourished pre-frail/frail patients (thus likely to benefit
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54 366 most from nutrition therapy). As hospitalised patients have greater energy deficits due to
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56 367 catabolic stress of acute illness, they are a population that requires careful determination of
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58 368 energy/protein requirements and in whom additive effects of nutrition supplementation to
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3 369 exercise may have greatest impact on outcomes such as muscle strength.⁵² As none of the
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5 370 studies in the present review reported on energy deficits, it is not known whether these patients
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8 371 received adequate replacement. Nutrition supplementation should also not be confused with
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10 372 nutrition or diet modifications. The provision of ONS alone is unlikely to augment diet
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12 373 adequacy as completely as diet modification that involves a wider range of nutrients and non-
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14 374 nutrients⁵⁴ especially when led by dietitians.^{55, 56}

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17 375 For both exercise and nutrition based interventions, an understanding of patient participation
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19 376 dynamics and compliance is required because of how they can impact on effectiveness.⁵⁷ Only
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21 377 five studies in this review reported attendance to program/home visits or phone calls or
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23 378 adherence to prescribed exercise/diet or related advice at rates of 50-90% and 70-93% for
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25 379 nutrition and exercise interventions, respectively. Issues with participants resulting in poorer
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27 380 compliance were not reported in these articles, such that the authors recommend that future
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29 381 studies explore barriers and enablers to adherence in multi-modal interventions.

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34 382 Cognition is another critical domain in the multidimensional nature of frailty. Exercise⁵⁸ and
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36 383 nutrition interventions⁵⁹ may have a far reaching, positive effect on cognition in older adults.
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38 384 However, there was no evidence of an impact on cognition from a single study⁴¹ in the present
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40 385 review. This is consistent with a network meta-analysis of 13 RCTs that examined exercise and
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42 386 nutrition interventions in frail older adults.¹¹ One suggested explanation is that different
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44 387 neuronal mechanisms could result in a misfit between combinatory approaches of nutrition and
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46 388 physical interventions⁶⁰ highlighting that more in-depth research is required.⁶¹

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51 389 The economic delivery of new interventions and models of care is important to a range of
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53 390 stakeholders⁶² but has been infrequently conducted in previous studies.⁴⁹ In this review, only
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55 391 two out of 11 studies included an economic analysis, with the majority of costs coming from
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57 392 delivery of exercise and nutrition support. The types of consumables that were considered in
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3 393 analyses included nutrition supplements, ankle/wrist weights, mobility aids and medications.
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5 394 Elements of service provision that were considered included community, rehabilitation,
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7 395 residential and transition care service use, which were often reduced and contributed to the net
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9 396 result. The results of this review support previous findings of beneficial effects on frailty-
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11 397 related outcomes, without increased costs.⁴⁹ However, results should be interpreted with
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13 398 caution as omission of other services (such as medication reviews) within a multimodal
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15 399 intervention can impact costings, and there are instances where interventions have not been
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17 400 found to be more-cost effective than usual care.⁶³ The approach of streamlining and
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19 401 reorganising existing services rather than creating entirely new systems may be preferred.
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24 402 *Strength and weakness*

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27 403 This study was robust and underwent peer review by an academic librarian. We did not have a
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29 404 language restriction on the search, and we did not find nor include studies in other languages.
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31 405 We chose to use of an updated version of the Cochrane risk of bias tool (RoB 2), which
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33 406 addresses issues of confusion common to its first version.
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37 407 By focussing on exercise-nutrition interventions only, this study addresses a gap as identified
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39 408 in a recent review of multi-domain interventions in pre-frail or frail elderly adults, in which
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41 409 some interventions may have been too broad to directly impact frailty, and functional and
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43 410 cognitive status.⁵¹ Multidisciplinary team based approaches remain recommended and are a
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45 411 bedrock of quality standard care; they may also already include goals for exercise and nutrition
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47 412 such that it may be difficult to solely attribute outcomes to a targeted but supplementary
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49 413 exercise-nutrition program. Social relationships affect health behaviour and physical health,⁶⁴
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51 414 such that intervention benefits may in part come from social interactions. Nevertheless, several
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53 415 studies^{28, 32, 42} have demonstrated significant improvements even when control participants are
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55 416 provided with the social aspect of an intervention, such that exercise and nutrition are expected
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3 417 to improve outcomes independent of social interactions. Among the three studies^{28, 32, 38}
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5 418 included in the meta-analysis of reduction in frailty score, one study³² included patients from
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7 419 community. However, when combined with data from the other two studies,^{28, 38} participants
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9 420 recruited from the hospital made up majority (~80%) of the entire cohort in that meta-analysis.
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13 421 *Implications and future research*

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16 422 This review is a useful resource for researchers and multi-disciplinary clinicians who are
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18 423 seeking to generate evidence or evaluate their practices of exercise-nutrition interventions for
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20 424 frail hospitalised older adults. The authors interpretation of the quality of studies in this review
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22 425 is that the evidence base is low, but the inclusion of future studies may change estimates of the
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24 426 intervention effects. While blinding of participants to the intervention is acknowledged to be
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26 427 difficult, future studies should be adequately powered, use allocation concealment with
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28 428 blinding outcome assessors and data analysts at least. Improved reporting of intervention
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30 429 details is also required,⁶⁵ which may assist in answering research questions around the optimal
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32 430 duration, dose, modality and timing of intervention(s) across the hospital to community
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34 431 continuum. In the present review, potential beneficial effects of combined interventions could
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36 432 have been negated given the short durations reported by most studies. Thus, future studies may
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38 433 be extended for >6-12 months, or employ principles of chronic condition self-management,⁶⁶
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40 434 to determine delayed improvements and achieve long-lasting sustainability of interventions.
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42 435 The lack of evidence from non-western countries, or low- and middle-income countries
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44 436 indicate the need for research to be conducted in those populations too. There are many ongoing
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46 437 research activities relevant to the scope of this review,⁶⁷⁻⁷⁰ yet only one has reported plans for
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48 438 economic analysis in the study protocol.⁶⁷ Economic evaluations can expand current evidence
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50 439 on the sustainability of incorporating such services within resource-constrained healthcare
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3 441 *Conclusion*
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6 442 Exercise-nutrition interventions that start while patients are admitted to hospital and continue
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8 443 in the community/post-hospital, or, commence early post discharge, appear to be effective in
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10 444 reducing frailty and some frailty-related physical indicators. Though effective, the quality of
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12 445 the evidence in this review is low as most studies included had some concerns for risk of bias.
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14 446 Given the paucity of high-quality studies on the effectiveness of combined exercise-nutrition
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16 447 interventions on hospitalised frail older adult patients, more robust research that pays attention
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18 448 to effect of assignment to intervention is needed to increase the confidence in results.
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30

31 452 **Author Contributions**
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34 453 All authors contributed to the conception and design of review. CH and YS read and screened
35
36 454 titles and abstract of potentially relevant studies. CH and YS evaluated the selected studies and
37
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39
40 456 expertise on meta-analyses. CH drafted the article and all authors provided critical revisions
41
42 457 and final approval of the manuscript. All authors had access to the data in the study and can
43
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45
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3 464 **Competing interests**
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9 466 **Patient consent**
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12 467 Not required.
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15 468 **Data sharing statement**
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18 469 Details of the excluded papers are available from the corresponding author upon request.
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21 470 **References**
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- 24 471 1. Le Cossec C, Perrine AL, Beltzer N, Fuhrman C, Carcaillon-Bentata L. Pre-Frailty,
25 472 Frailty, and Multimorbidity: Prevalences and Associated Characteristics from Two French
26 473 National Surveys. *J Nutr Health Aging*. 2016;20(8):860-9.
27 474 2. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in
28 475 older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146-56.
29 476 3. Considine J, Fox K, Plunkett D, Mecner M, M OR, Darzins P. Factors associated with
30 477 unplanned readmissions in a major Australian health service. *Aust Health Rev*. 2019;43(1):1-
31 478 9.
32 479 4. Sirven N, Rapp T. The cost of frailty in France. *Eur J Health Econ*. 2017;18(2):243-53.
33 480 5. Thompson MQ, Theou O, Karnon J, Adams RJ, Visvanathan R. Frailty prevalence in
34 481 Australia: Findings from four pooled Australian cohort studies. *Australas J Ageing*.
35 482 2018;37(2):155-8.
36 483 6. Giné-Garriga M, Roqué-Fíguls M, Coll-Planas L, Sitja-Rabert M, Salvà A. Physical
37 484 exercise interventions for improving performance-based measures of physical function in
38 485 community-dwelling, frail older adults: a systematic review and meta-analysis. *Arch Phys Med*
39 486 *Rehabil*. 2014;95(4):753-69. e3.
40 487 7. Ng TP, Feng L, Nyunt MS, Feng L, Niti M, Tan BY, et al. Nutritional, Physical,
41 488 Cognitive, and Combination Interventions and Frailty Reversal Among Older Adults: A
42 489 Randomized Controlled Trial. *Am J Med*. 2015;128(11):1225-36.e1.
43 490 8. Hsieh TJ, Su SC, Chen CW, Kang YW, Hu MH, Hsu LL, et al. Individualized home-
44 491 based exercise and nutrition interventions improve frailty in older adults: a randomized
45 492 controlled trial. *Int J Behav Nutr Phys Act*. 2019;16(1):119.
46 493 9. Lozano-Montoya I, Correa-Perez A, Abraha I, Soiza RL, Cherubini A, O'Mahony D, et
47 494 al. Nonpharmacological interventions to treat physical frailty and sarcopenia in older patients:
48 495 a systematic overview - the SENATOR Project ONTOP Series. *Clin Interv Aging*.
49 496 2017;12:721-40.
50 497 10. Abizanda P, López MD, García VP, Estrella JdD, da Silva González Á, Vilardell NB,
51 498 et al. Effects of an Oral Nutritional Supplementation Plus Physical Exercise Intervention on
52 499 the Physical Function, Nutritional Status, and Quality of Life in Frail Institutionalized Older
53 500 Adults: The ACTIVNES Study. *J Am Med Dir Assoc*. 2015;16(5):439.e9-.e16.
54
55
56
57
58
59
60

11. Negm AM, Kennedy CC, Thabane L, Veroniki AA, Adachi JD, Richardson J, et al. Management of Frailty: A Systematic Review and Network Meta-analysis of Randomized Controlled Trials. *J Am Med Dir Assoc*. 2019;20(10):1190-8.
12. Rozzini R, Sabatini T, Cassinadri A, Boffelli S, Ferri M, Barbisoni P, et al. Relationship between functional loss before hospital admission and mortality in elderly persons with medical illness. *J Gerontol A Biol Sci Med Sci*. 2005;60(9):1180-3.
13. Covinsky KE, Martin GE, Beyth RJ, Justice AC, Sehgal AR, Landefeld CS. The relationship between clinical assessments of nutritional status and adverse outcomes in older hospitalized medical patients. *J Am Geriatr Soc*. 1999;47(5):532-8.
14. Sharma Y, Thompson C, Shari R, Hakendorf P, Miller M. Malnutrition in Acutely Unwell Hospitalized Elderly - "The Skeletons Are Still Rattling in the Hospital Closet". *J Nutr Health Aging*. 2017;21(10):1210-5.
15. Sharma Y, Miller M, Shahi R, Hakendorf P, Horwood C, Thompson C. Malnutrition screening in acutely unwell elderly inpatients. *Br J Nurs*. 2016;25(18):1006-14.
16. Laur CV, McNicholl T, Valaitis R, Keller HH. Malnutrition or frailty? Overlap and evidence gaps in the diagnosis and treatment of frailty and malnutrition. *Applied Physiology, Nutrition & Metabolism*. 2017;42(5):449-58.
17. Rasmussen NM, Belqaid K, Lugnet K, Nielsen AL, Rasmussen HH, Beck AM. Effectiveness of multidisciplinary nutritional support in older hospitalised patients: A systematic review and meta-analyses. *Clinical nutrition ESPEN*. 2018;27:44-52.
18. Wilkinson R, Arensberg ME, Hickson M, Dwyer JT. Frailty Prevention and Treatment: Why Registered Dietitian Nutritionists Need to Take Charge. *J Acad Nutr Diet*. 2017;117(7):1001-9.
19. Higgins JP, Green S. *Cochrane handbook for systematic reviews of interventions: Cochrane book series*. 2008.
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62(10):1006-12.
21. Innovation VH. *Covidence systematic review software*. Veritas Health Innovation Melbourne, VIC; 2017.
22. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
23. Farrah K, Young K, Tunis MC, Zhao L. Risk of bias tools in systematic reviews of health interventions: an analysis of PROSPERO-registered protocols. *Systematic reviews*. 2019;8(1):280.
24. RevMan. Review manager (revman)[computer program]. version 5.3. The Nordic Cochrane Centre, The Cochrane Collaboration Copenhagen, Denmark; 2014.
25. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-60.
26. Villareal DT, Chode S, Parimi N, Sinacore DR, Hilton T, Armamento-Villareal R, et al. Weight loss, exercise, or both and physical function in obese older adults. *N Engl J Med*. 2011;364(13):1218-29.
27. Armamento-Villareal R, Aguirre LE, Qualls C, Villareal DT. Effect of lifestyle intervention on the hormonal profile of frail, obese older men. *Journal of Nutrition, Health and Aging*. 2016;20(3):334-40.
28. Cameron ID, Fairhall N, Langron C, Lockwood K, Monaghan N, Aggar C, et al. A multifactorial interdisciplinary intervention reduces frailty in older people: randomized trial. *BMC Med*. 2013;11:65.
29. Fairhall N, Sherrington C, Kurrle SE, Lord SR, Lockwood K, Cameron ID. Effect of a multifactorial interdisciplinary intervention on mobility-related disability in frail older people: randomised controlled trial. *BMC Med*. 2012;10:120.

- 1
2
3 551 30. Fairhall N, Sherrington C, Lord SR, Kurrle SE, Langron C, Lockwood K, et al. Effect
4 552 of a multifactorial, interdisciplinary intervention on risk factors for falls and fall rate in frail
5 553 older people: a randomised controlled trial. *Age Ageing*. 2014;43(5):616-22.
- 6 554 31. Fairhall N, Sherrington C, Kurrle SE, Lord SR, Lockwood K, Howard K, et al.
7 555 Economic evaluation of a multifactorial, interdisciplinary intervention versus usual care to
8 556 reduce frailty in frail older people. *J Am Med Dir Assoc*. 2015;16(1):41-8.
- 9 557 32. Luger E, Dorner TE, Haider S, Kapan A, Lackinger C, Schindler K. Effects of a Home-
10 558 Based and Volunteer-Administered Physical Training, Nutritional, and Social Support
11 559 Program on Malnutrition and Frailty in Older Persons: A Randomized Controlled Trial. *J Am*
12 560 *Med Dir Assoc*. 2016;17(7):671.e9-.e16.
- 13 561 33. Haider S, Dorner TE, Luger E, Kapan A, Titze S, Lackinger C, et al. Impact of a Home-
14 562 Based Physical and Nutritional Intervention Program Conducted by Lay-Volunteers on
15 563 Handgrip Strength in Prefrail and Frail Older Adults: A Randomized Control Trial. *PLoS ONE*
16 564 [Electronic Resource]. 2017;12(1):e0169613.
- 17 565 34. Winzer E, Dorner TE, Grabovac I, Haider S, Kapan A, Lackinger C, et al. Behavior
18 566 changes by a buddy-style intervention including physical training, and nutritional and social
19 567 support. *Geriatrics & Gerontology International*. 2019;19(4):323-9.
- 20 568 35. Kapan A, Luger E, Haider S, Titze S, Schindler K, Lackinger C, et al. Fear of falling
21 569 reduced by a lay led home-based program in frail community-dwelling older adults: A
22 570 randomised controlled trial. *Arch Gerontol Geriatr*. 2017;68:25-32.
- 23 571 36. Kapan A, Winzer E, Haider S, Titze S, Schindler K, Lackinger C, et al. Impact of a lay-
24 572 led home-based intervention programme on quality of life in community-dwelling pre-frail and
25 573 frail older adults: a randomized controlled trial. *BMC Geriatr*. 2017;17:1-11.
- 26 574 37. Arrieta H, Astrugue C, Regueme S, Durrieu J, Maillard A, Rieger A, et al. Effects of a
27 575 physical activity programme to prevent physical performance decline in onco-geriatric
28 576 patients: a randomized multicentre trial. *Journal of Cachexia, Sarcopenia and Muscle*.
29 577 2019;10(2):287-97.
- 30 578 38. Niccoli S, Kolobov A, Bon T, Rafilovich S, Munro H, Tanner K, et al. Whey Protein
31 579 Supplementation Improves Rehabilitation Outcomes in Hospitalized Geriatric Patients: A
32 580 Double Blinded, Randomized Controlled Trial. *J Nutr Gerontol Geriatr*. 2017;36(4):149-65.
- 33 581 39. Milte R, Miller MD, Crotty M, Mackintosh S, Thomas S, Cameron ID, et al. COST-
34 582 EFFECTIVENESS OF INDIVIDUALIZED NUTRITION AND EXERCISE THERAPY FOR
35 583 REHABILITATION FOLLOWING HIP FRACTURE. *Journal of Rehabilitation Medicine*
36 584 (Stiftelsen Rehabiliteringsinformation). 2016;48(4):378-85.
- 37 585 40. Singh NA, Quine S, Clemson LM, Williams EJ, Williamson DA, Stavrinou TM, et al.
38 586 Effects of high-intensity progressive resistance training and targeted multidisciplinary
39 587 treatment of frailty on mortality and nursing home admissions after hip fracture: a randomized
40 588 controlled trial. *J Am Med Dir Assoc*. 2012;13(1):24-30.
- 41 589 41. Blanc-Bisson C, Dechamps A, Gouspillou G, Dehail P, Bourdel-Marchasson I. A
42 590 randomized controlled trial on early physiotherapy intervention versus usual care in acute car
43 591 unit for elderly: Potential benefits in light of dietary intakes. *Journal of Nutrition, Health and*
44 592 *Aging*. 2008;12(6):395-9.
- 45 593 42. Miller MD, Crotty M, Whitehead C, Bannerman E, Daniels LA. Nutritional
46 594 supplementation and resistance training in nutritionally at risk older adults following lower
47 595 limb fracture: a randomized controlled trial. *Clin Rehabil*. 2006;20(4):311-23.
- 48 596 43. Rodriguez-Manas L, Laosa O, Vellas B, Paolisso G, Topinkova E, Oliva-Moreno J, et
49 597 al. Effectiveness of a multimodal intervention in functionally impaired older people with type
50 598 2 diabetes mellitus. *J Cachexia Sarcopenia Muscle*. 2019;10(4):721-33.
- 51 599 44. Azad N, Molnar F, Byszewski A. Lessons learned from a multidisciplinary heart failure
52 600 clinic for older women: a randomised controlled trial. *Age Ageing*. 2008;37(3):282-7.

- 1
2
3 601 45. Romero-Ortuno R, Walsh CD, Lawlor BA, Kenny RA. A frailty instrument for primary
4 602 care: findings from the Survey of Health, Ageing and Retirement in Europe (SHARE). *BMC*
5 603 *Geriatr.* 2010;10(1):57.
- 6 604 46. Haider S, Dorner TE, Luger E, Kapan A, Titze S, Lackinger C, et al. Impact of a home-
7 605 based physical and nutritional intervention program conducted by lay-volunteers on handgrip
8 606 strength in prefrail and frail older adults: A randomized control trial. *PLoS ONE.* 2017;12(1).
- 9 607 47. Wright J, Baldwin C. Oral nutritional support with or without exercise in the
10 608 management of malnutrition in nutritionally vulnerable older people: A systematic review and
11 609 meta-analysis. *Clin Nutr.* 2018;37(6 Pt A):1879-91.
- 12 610 48. Haider S, Grabovac I, Winzer E, Kapan A, Schindler KE, Lackinger C, et al. Change
13 611 in inflammatory parameters in prefrail and frail persons obtaining physical training and
14 612 nutritional support provided by lay volunteers: A randomized controlled trial. *PLoS One.*
15 613 2017;12(10).
- 16 614 49. Apóstolo J, Cooke R, Bobrowicz-Campos E, Santana S, Marcucci M, Cano A, et al.
17 615 Effectiveness of interventions to prevent pre-frailty and frailty progression in older adults: a
18 616 systematic review. *JB I database of systematic reviews and implementation reports.*
19 617 2018;16(1):140.
- 20 618 50. De Vries N, Staal J, Van Ravensberg C, Hobbelen J, Rikkert MO, Nijhuis-Van der
21 619 Sanden M. Outcome instruments to measure frailty: a systematic review. *Ageing research*
22 620 *reviews.* 2011;10(1):104-14.
- 23 621 51. Dedeysne L, Deschodt M, Verschueren S, Tournoy J, Gielen E. Effects of multi-domain
24 622 interventions in (pre)frail elderly on frailty, functional, and cognitive status: a systematic
25 623 review. *Clin Interv Aging.* 2017;12:873-96.
- 26 624 52. Tarazona-Santabalbina FJ, Gomez-Cabrera MC, Perez-Ros P, Martinez-Arnau FM,
27 625 Cabo H, Tsaparas K, et al. A Multicomponent Exercise Intervention that Reverses Frailty and
28 626 Improves Cognition, Emotion, and Social Networking in the Community-Dwelling Frail
29 627 Elderly: A Randomized Clinical Trial. *J Am Med Dir Assoc.* 2016;17(5):426-33.
- 30 628 53. Kim CO, Lee KR. Preventive effect of protein-energy supplementation on the
31 629 functional decline of frail older adults with low socioeconomic status: a community-based
32 630 randomized controlled study. *Journals of Gerontology Series A: Biological Sciences &*
33 631 *Medical Sciences.* 2013;68(3):309-16.
- 34 632 54. Denison HJ, Cooper C, Sayer AA, Robinson SM. Prevention and optimal management
35 633 of sarcopenia: a review of combined exercise and nutrition interventions to improve muscle
36 634 outcomes in older people. *Clin Interv Aging.* 2015;10:859.
- 37 635 55. Munk T, Tolstrup U, Beck AM, Holst M, Rasmussen HH, Hovhannisyan K, et al.
38 636 Individualised dietary counselling for nutritionally at-risk older patients following discharge
39 637 from acute hospital to home: a systematic review and meta-analysis. *J Hum Nutr Diet.*
40 638 2016;29(2):196-208.
- 41 639 56. Beck AM, Kjær S, Hansen BS, Storm RL, Thal-Jantzen K, Bitz C. Follow-up home
42 640 visits with registered dietitians have a positive effect on the functional and nutritional status of
43 641 geriatric medical patients after discharge: a randomized controlled trial. *Clin Rehabil.*
44 642 2013;27(6):483-93.
- 45 643 57. Fairhall N, Sherrington C, Cameron ID, Kurrle SE, Lord SR, Lockwood K, et al. A
46 644 multifactorial intervention for frail older people is more than twice as effective among those
47 645 who are compliant: complier average causal effect analysis of a randomised trial. *J Physiother.*
48 646 2017;63(1):40-4.
- 49 647 58. Brisswalter J, Collardeau M, René A. Effects of acute physical exercise characteristics
50 648 on cognitive performance. *Sports Med.* 2002;32(9):555-66.
- 51 649 59. Klímová B, Vališ M. Nutritional interventions as beneficial strategies to delay cognitive
52 650 decline in healthy older individuals. *nutrients.* 2018;10(7):905.

- 1
2
3 651 60. Schättin A, Baur K, Stutz J, Wolf P, de Bruin ED. Effects of physical exercise combined
4 652 with nutritional supplements on aging brain related structures and functions: a systematic
5 653 review. *Front Aging Neurosci.* 2016;8:161.
- 6 654 61. Hardman RJ, Kennedy G, Macpherson H, Scholey AB, Pipingas A. A randomised
7 655 controlled trial investigating the effects of Mediterranean diet and aerobic exercise on cognition
8 656 in cognitively healthy older people living independently within aged care facilities: the
9 657 Lifestyle Intervention in Independent Living Aged Care (LIILAC) study protocol
10 658 [ACTRN12614001133628]. *Nutr J.* 2015;14(1):53.
- 11 659 62. Drummond MF, Stoddart GL. Economic analysis and clinical trials. *Control Clin*
12 660 *Trials.* 1984;5(2):115-28.
- 13 661 63. Ruiques FG, Adang EM, Assendelft WJ, Schers HJ, Koopmans RT, Zuidema SU. Cost-
14 662 effectiveness of a multicomponent primary care program targeting frail elderly people. *BMC*
15 663 *Fam Pract.* 2018;19(1):62.
- 16 664 64. Umberson D, Karas Montez J. Social relationships and health: A flashpoint for health
17 665 policy. *J Health Soc Behav.* 2010;51(1_suppl):S54-S66.
- 18 666 65. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better
19 667 reporting of interventions: template for intervention description and replication (TIDieR)
20 668 checklist and guide. *BMJ.* 2014;348:g1687.
- 21 669 66. Battersby M, Harris M, Smith D, Reed R, Woodman R. A pragmatic randomized
22 670 controlled trial of the Flinders Program of chronic condition management in community health
23 671 care services. *Patient Educ Couns.* 2015;98(11):1367-75.
- 24 672 67. Fairhall N, Kurrle SE, Sherrington C, Lord SR, Lockwood K, John B, et al.
25 673 Effectiveness of a multifactorial intervention on preventing development of frailty in pre-frail
26 674 older people: Study protocol for a randomised controlled trial. *BMJ Open.* 2015;5(2).
- 27 675 68. Gonzalez-Sanchez M, Cuesta-Vargas AI, Del Mar Rodriguez Gonzalez M, Caro ED,
28 676 Nunez GO, Galan-Mercant A, et al. Effectiveness of a muticomponent workout program
29 677 integrated in an evidence based multimodal program in hyperfrail elderly patients:
30 678 POWERAGING randomized clinical trial protocol. *BMC Geriatr.* 2019;19(1).
- 31 679 69. Jadczyk AD, Luscombe-Marsh N, Taylor P, Barnard R, Makwana N, Visvanathan R.
32 680 The EXPRESS Study: Exercise and Protein Effectiveness Supplementation Study supporting
33 681 autonomy in community dwelling frail older people-study protocol for a randomized controlled
34 682 pilot and feasibility study. *Pilot & Feasibility Studies.* 2018;4:8.
- 35 683 70. Landi F, Cesari M, Calvani R, Cherubini A, Di Bari M, Bejuit R, et al. The 'Sarcopenia
36 684 and Physical fRailty IN older people: multi-componenT Treatment strategies' (SPRINTT)
37 685 randomized controlled trial: design and methods. *Aging Clin Exp Res.* 2017;29(1):89-100.

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3 692 **Figure captions**
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6 693 Fig.1 Flow diagram illustrating results of the search and study selection process as described
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8 694 in the PRISMA statement
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11 695 Fig 2. Meta-analysis of reduction in frailty score for exercise and nutrition intervention vs
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16 697 Fig.3 Meta-analyses of Short physical performance battery, Gait speed, Balance test, Chair
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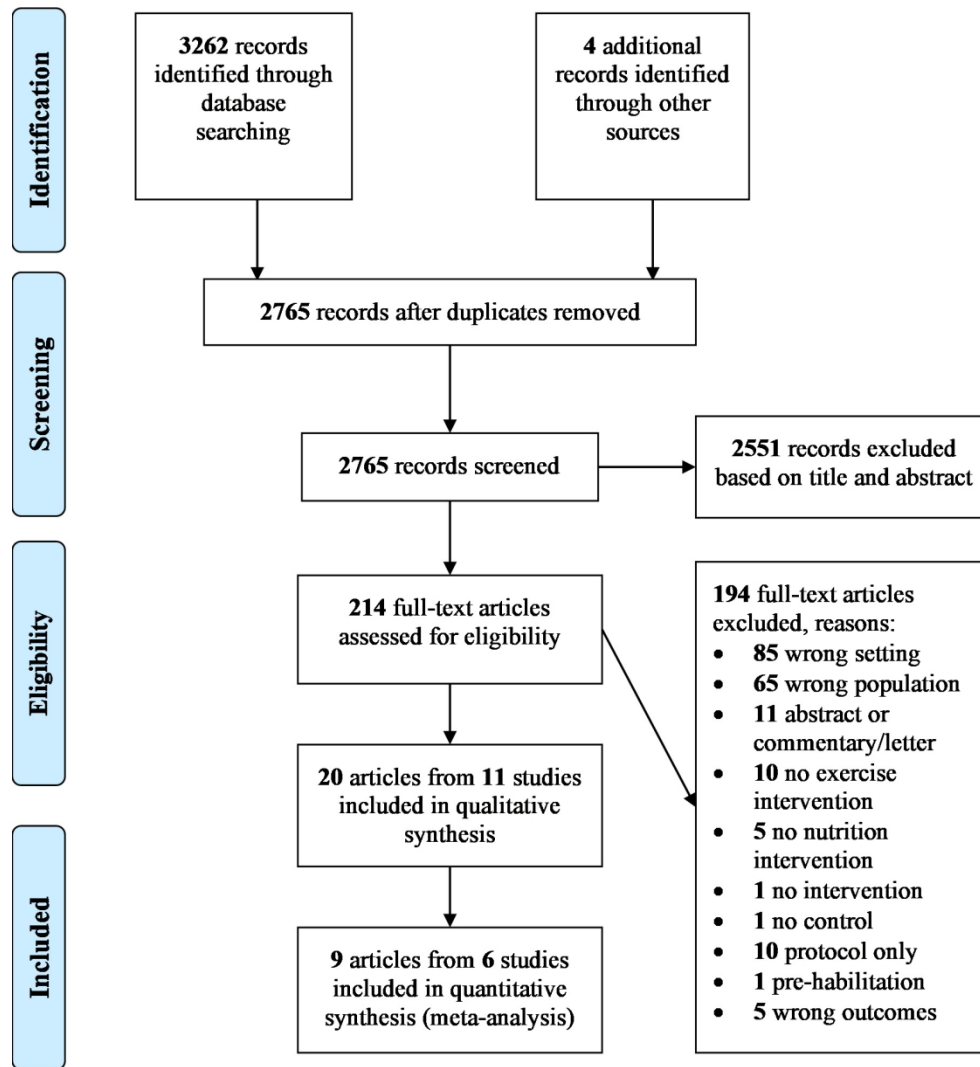


Fig.1 Flow diagram illustrating results of the search and study selection process as described in the PRISMA statement

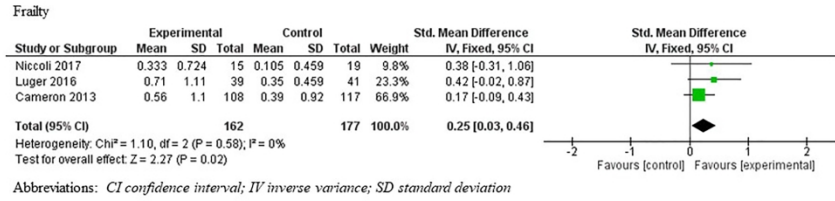


Fig 2. Meta-analysis of reduction in frailty score for exercise and nutrition intervention vs standard care

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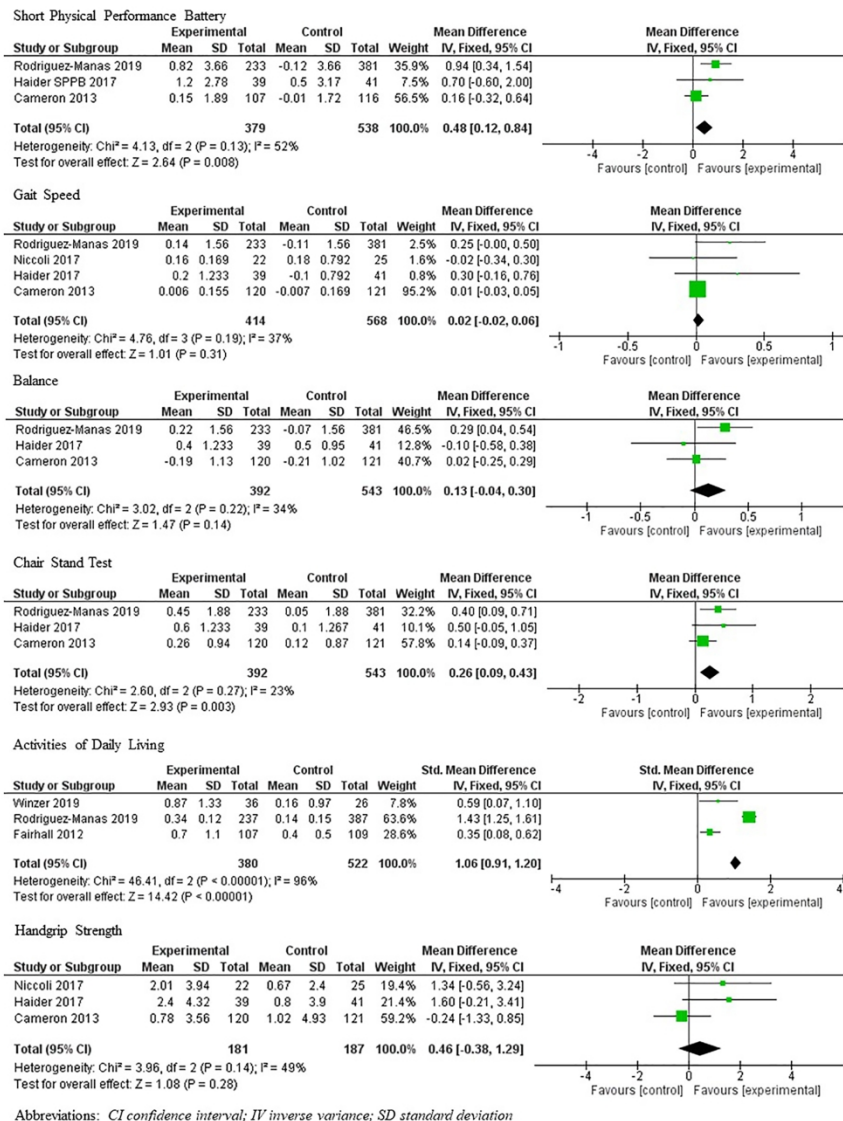


Fig.3 Meta-analyses of Short physical performance battery, Gait speed, Balance test, Chair stand test, Activities of daily living, handgrip strength

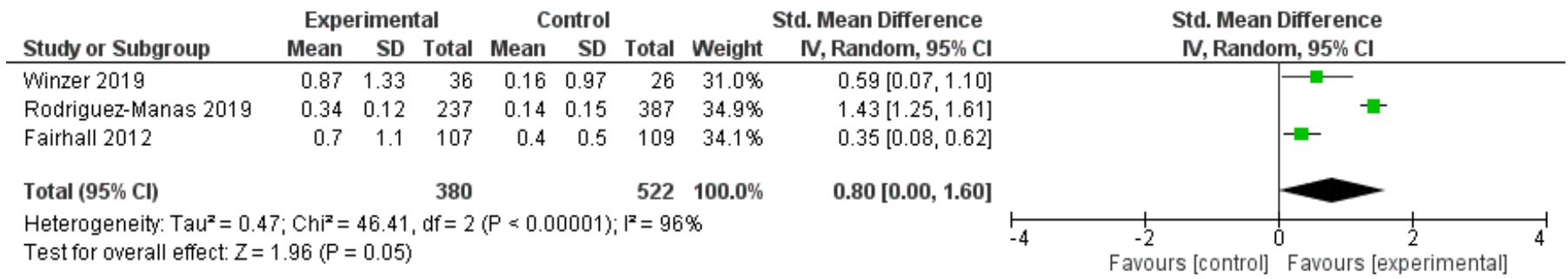
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Search Strategy – Medline

#	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 resistanc* 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



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



PRISMA 2009 Checklist

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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

Page 1 of 2

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

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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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1
2
3 **Title Page**
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6 2 Effectiveness of combined exercise and nutrition interventions in pre-frail or frail older
7
8 3 hospitalised patients: a systematic review and meta-analysis
9

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51

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56 **PROSPERO registration:** CRD42020153934
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22 **Abstract**

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

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

32 Results: Twenty articles from 11 RCTs experimenting exercise-nutrition interventions on
33 hospitalised older adults were included. Eight articles were suitable for the meta-analyses. One
34 study had low risk of bias and found improvements in physical performance and frailty-related
35 biomarkers. Exercise interventions were mostly supervised by a physiotherapist, focusing on
36 strength, ranging 2-5 times/week, of 20-90 minutes duration. Most nutrition interventions
37 involved counselling and supplementation but had dietitian supervision in only three studies.
38 The meta-analyses suggest that participants who received exercise-nutrition intervention had
39 greater reduction in frailty scores (n=3, SMD 0.25; 95% CI 0.03-0.46; P=0.02) and
40 improvement in short physical performance battery (SPPB) scores (n=3, MD 0.48; 95% CI
41 0.12-0.84; P=0.008) compared to standard care. Only the chair-stand test (n=3) out of the three
42 SPPB components was significantly improved (MD 0.26; 95% CI 0.09-0.43; P=0.003).
43 Patients were more independent in activities of daily living in intervention groups, but high
44 heterogeneity was observed ($I^2=96\%$, $P<0.001$). The pooled effect for handgrip (n=3) +/- knee
45 extension muscle strength (n=4) was not statistically significant. Nutritional status, cognition,

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3 46 biomarkers, QoL, falls and cost-effectiveness were summarised descriptively due to
4
5 47 insufficient data.
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8 48 Conclusions: There is evidence, albeit weak, showing that exercise-nutrition interventions are
9
10 49 effective to improve frailty and frailty-related indicators in hospitalised older adults.
11
12

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14 50 **PROSPERO registration number:** CRD42020153934
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16 17 51 **Strengths and limitations of study**

- 18
19 52 • This is the first comprehensive systematic review with meta-analysis on the
20
21 53 effectiveness of exercise-nutrition interventions on frailty and outcomes related to
22
23 54 frailty in hospitalised and pre-frail/frail older adults.
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25
26 55 • Only randomised controlled trials describing existing exercise-nutrition interventions
27
28 56 in pre-frail/frail older hospitalised patients were included.
29
30
31 57 • There was a moderate risk of bias for most included studies such that the findings of
32
33 58 this review are inconclusive, making it difficult to draw firm conclusions.
34
35

36 37 59 **Introduction**

38
39 60 Frailty is a major contributor to late-life disability as it leads to loss of independence.¹ It is also
40
41 61 associated with poor health outcomes, and, increased health-care costs and service use.¹ Frailty
42
43 62 has been defined for clinical research by Fried et al² as a combination of unintentional weight
44
45 63 loss, weakness, exhaustion, slowness and reduced physical activity. Pre-frailty is a stage before
46
47 64 frailty, where one or two of the five aforementioned symptoms are present.² There are no gold
48
49 65 standard in the clinical care setting to define frailty or pre-frailty but is commonly understood
50
51 66 as age-related physiological decline, resulting in increased vulnerability to health crises.³ Older
52
53 67 adults (aged >65 years) that have been classified as frail and are hospitalised, have a three-fold
54
55 68 higher risk of readmission or death, as compared to the younger population.⁴ The management
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3 69 of older adults who are frail has an incremental effect on health expenditures with an additional
4
5 70 equivalent of AU\$2400 per frail patient per year.⁵ With 21% of the population over 65 years
6
7 71 estimated to be frail and 48% estimated to be pre-frail, concerns of economic impact are
8
9
10 72 compounded by an ageing population.⁶

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12
13 73 Exercise and nutrition are inextricably linked, in particular strength training can address
14
15 74 component issues of the frail phenotype.⁷ Yet evidence supporting the effectiveness of
16
17 75 exercise-nutrition interventions for reversal of frailty is limited to community-dwelling older
18
19 76 adults.⁸ In a study of community participants, a 3-month combined exercise-nutrition
20
21 77 intervention resulted in a significant reversal of frailty (reduction in Fried frailty score) at 6-
22
23 78 months, compared to the control group (between-group difference -0.34 ; 95% confidence
24
25 79 interval [CI] -0.52 to -0.16 ; $P < 0.001$).⁹ The combination of exercise therapy and dietary
26
27 80 intervention in older adults who are frail, has also been reported to increase muscle strength
28
29 81 (knee extension between-group difference 1.84 kg, 95% CI 0.17–3.51, $P = 0.03$)¹⁰ and improve
30
31 82 nutritional status (Mini Nutritional Assessment (MNA) Short Form between group difference
32
33 83 1.4, 95% CI 0.9-1.9, $P < 0.01$).¹¹

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39 84 A recent meta-analysis suggested that although effective, exercise combined with nutrition was
40
41 85 not more effective in treating frailty than exercise alone.¹² However, the majority of included
42
43 86 studies were conducted in a community setting, with only 15% of older adults either
44
45 87 hospitalised or recruited from acute care settings. No study has systematically evaluated
46
47 88 evidence for interventions that commence during acute hospitalisation or early post discharge
48
49 89 (in the high-risk period for post-hospital syndrome).

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53 90 Hospitalisation is a vulnerable period, especially for older adults who are frail and therefore at
54
55 91 higher risk of functional loss,¹³ malnutrition^{14, 15} and further decline in frailty status.
56
57 92 Malnutrition is ubiquitous in older hospitalised patients with a prevalence as high as 50%.¹⁶
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3 93 Since many domains of frailty are attributed to poor nutrition,¹⁷ the effect of nutrition
4
5 94 intervention when combined with exercise, may be more significant in the hospitalised
6
7
8 95 population.¹⁷ Also, a recent review suggests that nutrition support, provided by a
9
10 96 multidisciplinary team, may have a positive impact on mortality and quality of life in
11
12 97 hospitalised older adult patients.¹⁸ Nutritional therapy extends beyond protein or nutrition
13
14 98 supplementation as reported in previous studies and may be more effective as part of
15
16 99 individualised medical nutrition therapies involving dietitians to improve diet adequacy.¹⁹
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19
20 100 This study aims to determine the effectiveness of combined exercise-nutrition interventions on
21
22 101 (1) frailty, (2) frailty-related indicators, falls, quality of life (QoL) and (3) its cost effectiveness
23
24 102 on pre-frail or frail hospitalised older adults.
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29

30 104 **Materials and Methods**

31 32 33 105 *Protocol and registration*

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35
36 106 The protocol for this review was compliant with Cochrane systematic review guidelines,²⁰ and
37
38 107 registered with the International Prospective Register of Systematic Reviews (PROSPERO),
39
40 108 CRD42020153934. The study is reported according to Preferred Reporting Items for
41
42 109 Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²¹ Patients and/or members of
43
44 110 the public were not involved in this study.
45
46
47

48 111 *Search methods*

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50
51 112 Systematic searches of electronic databases (MEDLINE, Emcare, CINAHL, Ageline, Scopus,
52
53 113 Cochrane and PEDro) were conducted by the lead author (CH) from inception until 10th
54
55 114 October 2019 using search strategies reviewed by an academic librarian (search queries
56
57 115 available in Supplementary file 1). Additionally, related citations to eligible items were
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3 116 identified using the suggested related citation function in Pubmed. Reference lists of eligible
4
5 117 items were also screened.
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8 118 *Inclusion and exclusion criteria*
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10
11 119 The inclusion criteria were: 1) randomised controlled trials; 2) inclusion of pre-frail or frail
12
13 120 participants (as defined by study authors); 3) recruitment of older adult inpatients and/or those
14
15 121 hospitalised within the past 30 days of recruitment; 4) interventions that started while patients
16
17 122 were admitted and continued in the community/post-hospitalisation, or, commenced within 30
18
19 123 days of hospital discharge; 5) interventions that involved both physical exercises and
20
21 124 nutritional interventions (dietary modifications/education/training alone or combined with oral
22
23 125 nutrition supplementation); 6) measured frailty with an assessment tool or at least one indicator
24
25 126 relevant to frailty (nutritional status, physical function, cognitive function and mood, physical
26
27 127 activity level or biomarkers, falls and QoL and/or economic analysis of interventions. Studies
28
29 128 were excluded if they described protocols with no pilot outcomes, interventions delivered as a
30
31 129 part of a palliative care program, or interventions solely designed to facilitate discharge
32
33 130 planning (e.g. telephone support services, providing no pre-frailty or frailty intervention
34
35 131 element), recruited participants admitted following a mental health episode.
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42 132 *Study selection and data extraction*
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45 133 Covidence²² was used to manage citations for title and abstract, and full-text screening, in
46
47 134 duplicate (CH and YS, Supplementary file 1). The reviewers were unblinded to authors,
48
49 135 journals and countries of origin. Any disagreement was resolved through discussion or
50
51 136 consensus opinion with the other authors. A data extraction form was developed a priori by the
52
53 137 research team, such that two researchers (CH and YS) performed data extraction
54
55 138 independently, on eligible full-text articles. Where available, the continuous data were
56
57 139 extracted as (i) mean change with standard deviation (SD), standard error of mean (SE) or 95%
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3 140 confidence interval (CI), or (ii) mean or median values with SD, SE or interquartile range post
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5 141 intervention. If the required data were not reported within a publication (including change in
6
7 142 means for outcomes of interest), the authors were emailed to request for it.
8
9

10 143 *Quality of the studies*

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12
13 144 The risk of bias in the individual studies was assessed by the Revised Cochrane risk-of-bias
14
15 145 tool for randomised trials (RoB-2) by two researchers (CH and YS) independently.²³ Any
16
17 146 disagreements were resolved by discussion or if required with consensus of a third reviewer.
18
19 147 The Cochrane risk-of-bias tool is widely used to assess randomised controlled trials (RCT) for
20
21 148 best practice.²⁴ Studies were given an overall risk-of-bias judgement of low, some concerns or
22
23 149 high. Overall risk-of-bias was determined as having “some concerns” if any one of the risks of
24
25 150 bias domains was rated as having “some concerns”. Likewise, studies were deemed to have an
26
27 151 overall high risk of bias if any one domain had a high risk of bias.
28
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32 152 *Data synthesis and statistical analyses*

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35 153 Where possible, a meta-analysis was performed; continuous outcome data were pooled and
36
37 154 reported as either the difference of means (MD) if the same outcome assessment tools were
38
39 155 used or the standardised mean difference (SMD) if different outcome assessment tools were
40
41 156 used, and the 95% CI, if there were two or more studies. The SMD is the mean difference when
42
43 157 the outcome for each study is standardised to have mean zero and SD=1. Studies presenting
44
45 158 SE were converted to SD via the conversion formula.²⁰ The fixed-effect meta-analyses were
46
47 159 carried out with Cochrane Review Manager (RevMan) 5.3.²⁵ A P value of <0.05 was
48
49 160 considered statistically significant. The variability between studies (heterogeneity) was
50
51 161 assessed by I² and its 95% CI.²⁶ For studies with unobtainable missing, or incomparable data,
52
53 162 results were qualitatively synthesised.
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59 163 *Patient and public involvement*

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2
3 164 No patients were involved in this study
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5

6 165 **Results**
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8

9 166 *Study selection*
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11

12 167 The flow of studies through the review process is summarised in Figure 1. Twenty articles
13
14 168 reporting on 11 studies were eligible for data synthesis and analysis. Three of 11 studies
15
16 169 presented results from their cohort across separate publications. Firstly, Villareal et al²⁷
17
18 170 reported on physical functioning outcomes with biomarker results in the publication of
19
20 171 Armamento-Villareal et al.²⁸ Secondly, Cameron et al²⁹ reported on frailty and some physical
21
22 172 function outcomes, with other physical function outcomes in a secondary publication³⁰ fall
23
24 173 rates³¹ and cost-analysis in another.³² Thirdly, Luger et al³³ reported on frailty and nutritional
25
26 174 status, with physical functioning outcomes across two other publications,^{34, 35} fall efficacy³⁶
27
28 175 and quality of life.³⁷ For clarity, the primary articles that report frailty or physical function
29
30 176 outcomes are cited for descriptive data in Tables 1-3 while individual articles are cited for
31
32 177 synthesis of outcome results.
33
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37

38 178 *Study and sample characteristics*
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40

41 179 Details of study characteristics are available in Table 1. Across all studies, a total of 2307
42
43 180 participants were investigated. Most studies reported that patients were recruited from hospital
44
45 181 wards (n=7)^{29, 38-43} while the other four studies^{27, 33, 44, 45} included patients that were recruited
46
47 182 from hospital wards and community. Seven studies included only frail participants,^{27, 29, 40-43, 45}
48
49 183 and the remaining four studies^{33, 38, 39, 44} included frail, pre-frail and non-frail participants. The
50
51 184 Fried frailty phenotype criteria² were used most frequently to classify frailty (n=4).^{29, 38, 39, 44}
52
53 185 with participants considered non-frail, pre-frail or frail if 0, 1-2, 3-5 criteria were present,
54
55 186 respectively. Luger et al used the Frailty Instrument for Primary Care of the Survey of Health,
56
57 187 Ageing, and Retirement in Europe (SHARE-FI)³³ which integrates components of exhaustion,
58
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3 188 appetite, handgrip strength, walking difficulties and physical activity.⁴⁶ Five studies did not
4
5 189 report any assessment method to define frailty.^{40-43, 45} One study used a combination of three
6
7 190 tools – modified Physical Performance Test, the measurement of VO₂ peak, and the Functional
8
9 191 Status Questionnaire.²⁷

12 192 *Risk of bias within individual studies*

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14
15
16 193 Table 2 outlines the risk of bias in individual studies. One study²⁷ had a low risk of bias and
17
18 194 one study⁴¹ had a high risk of bias (including unblinded secondary outcome assessment and
19
20 195 insufficient detail on standard care in control groups across recruitment sites). The other nine
21
22 196 studies^{29, 33, 38-40, 42-45} were rated as having some concerns overall, of which five could have
23
24 197 been improved in ≥ 1 domain. The remaining four studies^{27, 31, 39, 41} that were rated as having
25
26 198 “some concerns” overall, had risk in only one domain with the most common reason being
27
28 199 failure to blind intervention/allocated group to participants. Examples of other concerns about
29
30 200 risk of bias included: assessors being aware of the group allocation³³ (measurement of
31
32 201 outcomes domain); or a lack of information about participants/researcher blinding to group
33
34 202 allocation.^{27, 29, 44}

38 203 *Characteristics of exercise intervention component*

39
40 204 Characteristics of the exercise interventions used in studies are outlined in Table 3, and
41
42 205 included combinations of the following: supervised individual exercises (n=10),^{27, 29, 38-45} group
43
44 206 exercises (n=3),^{27, 41, 45} education including support with resources (digital versatile disc (DVD)
45
46 207 or visual aid instruction booklet, n=2),^{33, 38} and motivational interviewing using a standardised
47
48 208 protocol (n=1).³³ Three studies^{39, 42, 44} had inpatient only interventions, five^{38, 40, 41, 43, 45} had
49
50 209 interventions that extended from inpatient to post-discharge, two^{29, 33} studies offered the
51
52 210 intervention post-discharge only and one²⁷ did not report.

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2
3 211 In the majority of studies (n=9), the exercise component was delivered by a physiotherapist.^{27,}
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5 212 ³⁸⁻⁴⁵ Two studies used trained fitness instructors,^{38, 41} and another engaged lay volunteers who
6
7
8 213 received training for the study.³³ All studies included strength exercises as part of their
9
10 214 interventions. Three studies described guidance on training intensity based on repetition
11
12 215 maximum's (RM) between 40-80%.^{27, 41, 44} Other components of exercise programs included
13
14 216 aerobic fitness,^{27, 29, 38, 39} flexibility,^{27, 38, 39} and/or balance.^{27, 29, 38, 39} The frequency of
15
16 217 interventions ranged from two^{33, 38, 41, 44, 45} to five^{29, 42} sessions a week, lasting between 20^{40, 43,}
17
18 218 ⁴⁴ to 90 minutes²⁷ each. The duration of exercise intervention varied from six weeks⁴⁵ to one
19
20 219 year.^{27, 29, 38, 41}

220 *Characteristics of nutrition intervention component*

221 Characteristics of the nutritional interventions used in studies, are outlined in Table 3, and
222 included combinations of the following: nutrition counselling (n=8),^{27, 29, 33, 40-43, 45} oral
223 nutrition and/or multivitamin/mineral supplements (n=7),^{27, 29, 39-43} meal programs (n=3),^{29, 40,}
224 ⁴² self-guided education materials (n=2).^{38, 41} The most common combination of nutrition
225 intervention was counselling with oral nutrition and/or multivitamin/mineral supplements
226 (n=5).^{27, 40, 43, 45} Five of nine nutrition counselling interventions were performed by dietitians.^{27,}
227 ^{40, 43, 45} Other studies used trained lay volunteers,³³ a researcher/nutrition therapist or did not
228 specify a skill set for who delivered the counselling.⁴⁴

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

234 **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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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/kg; difficulty in performing 2 IADL or 1 basic ADL	Mild-moderate frailty: 100%

Azad <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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%

235 Abbreviations: BMI, Body Mass Index; w, Weeks; m, Months; y, Years; VO² max, maximal oxygen uptake; PPT, physical performance test; IADL, Instrumental Activities of Daily Living; ADL, Activities of Daily
 236 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
 237 group; UCG, Usual care group; ACG, Attention control group; NR, not reported; BMI presented in Mean ±standard deviation
 238 Multiple articles reported from same study, study chosen to represent other reports from the same study: *Luger *et al*³¹ – Haider *et al* 2017³², Winzer *et al* 2019³³, Kapan *et al* 2017³⁴, Kapan *et al* 2017³⁵; †Cameron *et al*
 239 2013²⁷ – Fairhall *et al* 2012²⁸, Fairhall *et al* 2014²⁹, Fairhall *et al* 2015³⁰; ‡Villareal *et al* 2011²⁵ – Armamento-Villareal 2016²⁶

240 **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 <i>et al</i> , 2019 ³⁵	+	?	?	?	+	?
Rodriguez-Manas <i>et al</i> , 2019 ⁴¹	+	?	+	?	+	?
Niccoli <i>et al</i> , 2017 ³⁶	?	?	+	?	+	?
Luger <i>et al</i> , 2016 ^{*30}	+	+	+	?	+	?
Milte <i>et al</i> , 2016 ³⁷	+	?	+	+	+	?
Cameron <i>et al</i> , 2013 ^{†26}	+	?	+	+	+	?
Singh <i>et al</i> , 2012 ³⁸	+	?	+	—	+	—
Villareal <i>et al</i> , 2011 ^{‡24}	+	+	+	+	+	+
Azad <i>et al</i> , 2008 ⁴²	+	?	+	?	+	?
Blanc-Bisson <i>et al</i> , 2008 ³⁹	+	?	+	?	+	?
Miller <i>et al</i> , 2006 ⁴⁰	+	?	+	+	+	?

241 Key: + = Low risk of bias; ? = Some concerns of risk of bias; — = High risk of bias
 242 ^aDeviations from intended interventions (effect starting and adhering to intervention)
 243 Multiple articles reported from same study, study chosen to represent other reports from the same study: *Luger *et al*³¹ – Haider *et al* 2017³², Winzer *et al* 2019³³, Kapan *et al* 2017³⁴, Kapan *et al* 2017³⁵; †Cameron *et al*
 244 2013²⁷ – Fairhall *et al* 2012²⁸, Fairhall *et al* 2014²⁹, Fairhall *et al* 2015³⁰; ‡Villareal *et al* 2011²⁵ – Armamento-Villareal 2016²⁶

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

Study	Exercise intervention	Nutrition intervention	Control intervention
Arrieta <i>et al</i> , 2019 ³⁵	<p>Type: <i>Strength</i> – Intensity range from low to high, starting at 10 repetition per exercise (UL, LL) with option of progressive loading</p> <p><i>Aerobic, Flexibility, Balance</i> – intensity individualised</p> <p>Frequency: 2 sessions/week, duration per session NR + home exercises duration NR</p> <p>Setting: Inpatient (supervised, individual) + post-discharge (unsupervised, individual)</p> <p>Additional support reported: Phone consults (by trainer 2x/month for first 6 months then monthly for 1 year); Education resource</p>	<p>Self-guided education resource: Provided with French National Nutrition Health Program education booklet - <i>Programme National Nutrition Santé</i> (PNNS)</p>	<p>Usual care: NR, variable between study sites</p> <p>Self-guided education resource: Provided with French National Nutrition Health Program education booklet - <i>Programme National Nutrition Santé</i> (PNNS)</p>
Rodriguez-Manas <i>et al</i> , 2019 ⁴¹	<p>Type: <i>Strength</i> – 40-80% of estimated 1RM, 8–10 repetitions (LL)</p> <p>Frequency: 2-weeks pretraining followed by 16-week program of 2 days/week; 20-30 minutes/sessions</p> <p>Setting: Inpatient (supervised, individual)</p>	<p>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.</p>	<p>Usual care: usual health care from local health system and/or general practitioner</p>
Niccoli <i>et al</i> , 2017 ³⁶	<p>Type: <i>Strength, Aerobic, Flexibility, Balance</i> – intensity and target muscle group individualised based on patient's baseline assessment</p> <p>Frequency: individualised based on patient's baseline assessment</p> <p>Setting: Inpatient (supervised, individual)</p>	<p>Supplements: Daily ONS with 24g whey protein per day (<i>9g breakfast, 7.5g at lunch and dinner</i>) in addition to usual diet</p>	<p>Usual care: usual medical care, no whey protein supplementation.</p> <p>Individual supervised exercise: Individualised exercises as per intervention.</p>
Luger <i>et al</i> , 2016 ^{*30}	<p>Type: <i>Strength</i> – 2 sets of 15 repetitions (UL, LL) until muscular exhaustion,</p> <p>Frequency: 2x/week, >30 minutes each session</p> <p>Setting: Post-discharge (supervised, individual)</p> <p>Additional support reported: Physical education (2-3 times/week, 30 minutes each session); Exercise education resource (demonstration DVD); Motivational interviewing.</p>	<p>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.</p>	<p>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</p>
Milte <i>et al</i> , 2016 ³⁷	<p>Type: <i>Strength, Balance (Otago exercise program)</i> – Intensity and repetitions NR, at the discretion of the treating physiotherapist (LL)</p>	<p>Nutrition counselling: Individualised nutrition therapy aimed at improving energy and protein</p>	<p>Usual care: Usual rehabilitation program recommended during hospitalisation, social visits</p>

	<p>Frequency: 3 times/week, 20-30minutes/session for 12 weeks</p> <p>Setting: Inpatient (supervised, individual) + post-discharge (supervised, individual)</p>	<p>intake to meet requirements by dietitian who visits fortnightly.</p> <p>Meal program: ordered as deemed necessary by dietitian.</p> <p>Supplements: commercial ONS recommended if needed by dietitian</p>	<p>weekly from trial staff and generic nutrition, exercise and falls prevention information</p>
Cameron <i>et al</i> , 2013 ^{†26}	<p>Type: <i>Strength, Balance, Aerobic + WEBB program</i> – intensity and target muscle groups NR</p> <p>Frequency: Exercises prescribed 3-5x/week (with 2 sessions for mobility training) for 1 year, supported by up to 10 home visits</p> <p>Setting: Post-discharge (supervised, individual) + (unsupervised, individual)</p>	<p>Nutrition counselling: Clinical evaluation of nutritional intake at home. A series of diet intervention as needed by dietitian.</p> <p>Meal program: ordered as deemed necessary by dietitian.</p> <p>Supplements: commercial ONS recommended if needed by dietitian</p>	<p>Usual care: usual health care during hospitalisation and from their general practitioner and community services after discharge</p>
Singh <i>et al</i> , 2012 ³⁸	<p>Type: <i>Strength</i> – 80% of most recent 1RM or RPE <15, 3 sets of 8 repetitions (UL, LL)</p> <p>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.</p> <p>Setting: Inpatient (supervised, individual) + (supervised, group-based)</p> <p>Additional support reported: Monthly phone consults</p>	<p>Nutrition counselling: Counselling on increase in diet quality, frequency NR</p> <p>Supplements: ONS +/- dietary advice to increase daily energy (400-600 kcal) and protein (20 g/day) intake.</p> <p>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</p> <p>Self-guided nutrition resource: Food sources of calcium, vitamin D and sun exposure</p>	<p>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.</p>
Villareal <i>et al</i> , 2011 ^{‡24}	<p>Type: <i>Strength</i> – 65% of 1RM; 8-12 repetitions of each exercise (UL, LL) with options for progression</p> <p><i>Aerobic</i>, ~65% of peak HR with gradual progression to 70-85%</p> <p><i>Flexibility, Balance</i></p> <p>Frequency: 90 minutes, 3 sessions/week</p> <p>Setting: Inpatient (supervised, group-based)</p>	<p>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.</p> <p>Supplements: 1500 mg of calcium/d day and ~1000 IU vitamin D/d</p>	<p>Usual care: General healthy lifestyle advice</p> <p>Supplements: 1500 mg of calcium/d day and ~1000 IU vitamin D/d</p>
Azad <i>et al</i> , 2008 ⁴²	<p>Type: ‘Comprehensive exercise program’; type, intensity and target muscle groups NR</p> <p>Frequency: 11 sessions over 6 weeks + NR home exercises</p> <p>Setting: Inpatient (supervised, group-based), post-discharge (unsupervised, individual)</p>	<p>Nutrition counselling: 3 sessions of individualized counselling about diet and nutrition in the management of CHF by dietitian</p>	<p>Usual care: Optimal medical care</p>

Blanc-Bisson <i>et al</i> , 2008 ³⁹	<p>Type: <i>Strength</i> – intensity (RM) NR, 10 x repetitions each exercise (LB)</p> <p>Frequency: 30 minutes, twice/day, five days/week</p> <p>Setting: Inpatient (supervised, individual)</p>	<p>Meal program: Geriatric hospital meals of 1800-2000 kcal/d</p> <p>Supplements: 1 daily ONS of 200 kcal and 15g protein</p>	<p>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.</p> <p>Individual supervised exercise: Physiotherapy continued at home for one month.</p>
Miller <i>et al</i> , 2006 ⁴⁰	<p>Type: <i>Strength</i> – intensity (RM) NR, 2 sets of 8 repetitions (LL) with progressive loading, at the discretion of the treating physiotherapist</p> <p>Frequency: 3 times/week, 20-30minutes/session for 12 weeks</p> <p>Setting: Inpatient (supervised, individual) + Post-discharge (supervised, individual)</p>	<p>Nutrition counselling: Individualised nutrition therapy by dietitian.</p> <p>Supplements: single type of ONS to cover the shortfall between individual estimated energy and protein requirements and actual intake over 42 days.</p>	<p>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.</p>

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* 2017³², Winzer *et al* 2019³³, Kapan *et al* 2017³⁴, Kapan *et al* 2017³⁵; †Cameron *et al* 2013²⁷ – Fairhall *et al* 2012²⁸, Fairhall *et al* 2014²⁹, Fairhall *et al* 2015³⁰; *Villareal *et al* 2011²⁵ – Armamento-Villareal 2016²⁶

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3 251 group participants (n=7),^{27, 39, 40, 42, 43, 45} typically providing 200-300kcal and 12-24g protein
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5 252 per serve with a frequency of consumption up to seven times a week^{39, 42} or as prescribed by
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7 253 dietitians^{27, 40, 43, 45} to cover any identified deficits between individually estimated energy and
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9 254 protein requirements and actual intake. Calcium and vitamin D were the two most commonly
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11 255 supplemented micronutrients ^{27, 41} at doses in the range of 1200-1500mg/d and 1000IU/d,
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13 256 respectively. Meal programs were either delivered as inpatient specialised geriatric meals
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15 257 providing 1800-2000kcal/d or home-delivered meal programs.^{29, 40, 42}

20 258 *Frailty outcomes*

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23 259 Data on frailty outcomes were available for quantitative analysis from three studies.^{29, 33, 39} The
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25 260 meta-analysis is presented in Figure 2 and suggested that participants who received exercise-
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27 261 nutrition intervention had a greater reduction in frailty score compared to those who received
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29 262 standard care (SMD 0.25; 95% CI 0.03-0.46; P=0.02); no heterogeneity was observed (I²=0%;
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31 263 P=0.58).

35 264 *Physical functioning outcomes*

38 265 *Short Physical Performance Battery (SPPB)*

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41 266 Data on the SPPB were available for quantitative analysis from three studies, ^{29, 44, 47} with
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43 267 results from the meta-analysis presented in Figure 3. Participants who received exercise-
44
45 268 nutrition intervention had a statistically significant improvement in SPPB score, compared to
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47 269 those that received standard care (MD 0.48; 95% CI 0.12-0.84; P=0.008), with moderate
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49 270 heterogeneity²⁰ observed (I² = 52%; P=0.13).^{20, 32, 33} The analysis of SPPB components across
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51 271 all studies showed no statistically significant differences in gait speed^{29, 39, 44, 47} (MD 0.02; 95%
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53 272 CI -0.02 to 0.06; P=0.31; I²=37%, P=0.19) or balance ^{29, 44, 47} (MD 0.13; 95% CI -0.04 to 0.30;
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55 273 P=0.14; I²=0%, P=0.22) between groups. There were significantly greater improvements in
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57 274 chair stand test results^{29, 44, 47} in the intervention group as compared to the control (MD 0.26;

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3 275 95% CI 0.09-0.43; $P=0.003$; $I^2 = 23\%$, $P=0.23$). Two studies that were not suitable for meta-
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5 276 analysis (as data could not be provided by authors³⁸ and a different measurement was used²⁷)
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7 277 are instead qualitatively described. Arrieta et al reported no significant differences between
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9 278 groups in the percentage of participants who had a ≥ 1 point decrease in SPPB score at one and
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11 279 two years ($P=0.772$, $P=0.057$, respectively).³⁸ With use of an alternative measure of physical
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13 280 function (modified physical performance test – includes book lift, put on and take off a coat,
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15 281 pick up a penny, chair rise, turn 360, 50-foot walk, 10-steps of stairs, four flight of stairs and
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17 282 progressive Romberg test), Villareal et al²⁷ reported a significant improvement in their
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19 283 exercise- nutrition interventions group as compared to exercise only ($P=0.04$), nutrition only
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21 284 ($P<0.001$), or controls.

27 Activities of daily living

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29 286 Data on activities of daily living (ADL) from three studies^{30, 35, 44} underwent meta-analysis,
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31 287 from which participants who received exercise-nutrition intervention were determined to have
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33 288 greater ADL independence post-intervention than those who received standard care (SMD
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35 289 1.06; 95% CI 0.91-1.20; $P<0.001$, Figure 3). However, high heterogeneity was observed
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37 290 ($I^2=96\%$, $P<0.001$). As such, additional random effects model was performed (SMD 0.80; 95%
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39 291 CI 0.00-1.60; $P<0.001$; Supplementary file 2). Data from two studies^{42, 45} were unavailable to
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41 292 be included the meta-analysis. One study⁴¹ was excluded due to high risk of bias in outcome
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43 293 measurements but reported that basic ADL declined lesser ($P<0.0001$) in the intervention vs
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45 294 control group.

51 Muscle strength

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53 296 The meta-analysis showed no statistically significant differences in muscle strength between
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55 297 participants who received exercise-nutrition intervention and those that received standard care,
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57 298 when handgrip strength was analysed from three studies^{29, 39, 47} (MD 0.46; 95% -0.38 to 0.85;
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3 299 $P=0.28$; $I^2=49\%$, $P=0.14$), or, when of handgrip and quadriceps strength was combined ($n=4$
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5 300 studies)^{29, 39, 44, 47} using a published methodology⁴⁸ (SMD 0.10; 95% CI -0.09 to 0.29; $P=0.24$,
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7 301 $I^2=28\%$, $P=0.30$) (Figure 3).
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10 302 Nutrition, Cognition and Biomarkers outcomes

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13 303 Most studies assessed participants' nutritional status at baseline, while only one study³³
14 304 assessed it as an outcome. Luger et al reported a 1.54-point improvement in the MNA long
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16 304 assessed it as an outcome. Luger et al reported a 1.54-point improvement in the MNA long
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18 305 form in participants who received exercise-nutrition intervention compared to those who
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20 306 received standard care (95% CI 0.51-2.56, $P=0.004$). Combined exercise-nutrition intervention
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22 307 did not affect cognitive status (mini-mental state examination (MMSE)) or mood (geriatric
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24 308 depression scale (GDS)).⁴⁵ Armamento-Villareal et al reported a significant decrease in total
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26 309 and free estradiol in their frail obese older men (attributed to weight loss from lifestyle change
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28 310 rather than the intervention), without a clinically meaningful increase in total or free
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30 311 testosterone levels.²⁸ In one study that reported C-reactive protein (CRP) levels, this
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32 312 inflammatory marker remained stable in the exercise-nutrition intervention group participants,
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34 313 compared to an increase in the social support control group at the end of 12 weeks ($P=0.04$).⁴⁹
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40 314 Quality of life and falls

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42 315 Three studies^{32, 37, 40} that evaluated quality of life did not find a statistically significant
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44 316 improvement in the intervention as compared to the control group though Milte el al⁴⁰ found a
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46 317 trend favouring intervention. Fairhall et al³¹ found that risk factors related to falls (physical
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48 318 tests as mentioned above) but not rate of falls were reduced while Kapan et al³⁶ found that a
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50 319 10% reduction in fear of falling as ascertained by the falls efficacy scale.
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54 320 Economic analyses

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57 321 Only two studies examined the cost-effectiveness of their exercise-nutrition intervention.
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59 322 Fairhall et al³² reported no additional resource cost in terms of medical ($P=0.87$) or nursing and
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3 323 health professional appointments (P=0.32). Similarly, Milte et al⁴⁰ reported no cost differences
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5 324 between groups (P=0.868).
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10 326 **Discussion**

11 12 13 327 *Main findings*

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16 328 The present systematic review and meta-analysis present updated evidence that suggests
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18 329 exercise with nutrition intervention to be effective on frailty and frailty-related physical
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20 330 outcomes in hospitalised older adult patients. When compared to standard care, combined
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22 331 exercise-nutrition interventions improved frailty status as determined by the Fried Frailty
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24 332 criteria ² and the SHARE-FI.⁴⁶ They also improved physical function according to the SPPB
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26 333 and ADLs. Only one study measured and found significant improvement in nutrition score.³³
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28 334 The two economic analyses included in this review suggested that combined exercise-nutrition
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30 335 interventions, though more effective, were no more costly than standard care.
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35 336 Existing reviews of exercise and nutrition interventions have highlighted heterogeneity in study
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37 337 protocols (including intervention descriptions), which limits potential for quantitative analysis.
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39 338 They have also focussed on community dwelling participants.⁵⁰ This study is novel in
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41 339 reviewing a more vulnerable hospitalised population that has not been previously investigated,
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43 340 and specifically targeting pre-frail or frail older adults. However, out of five studies in this
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45 341 review that used a validated frailty assessment tool, only three had assessed frailty at outcome,
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47 342 and available for quantitative analysis. This could be because the frailty phenotype was first
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49 343 described 2001, with a systematic evaluation of frailty tools a decade later.^{2, 51} Accordingly,
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51 344 the authors decided to additionally evaluate frailty components such as physical function,
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53 345 nutrition, cognition and biomarkers as baseline and outcome measures. Although not specific
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3 346 to frailty, these measures provide insights to the effectiveness of exercise-nutrition
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5 347 interventions on improving various components of frailty and may inform future studies.
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8 348 Previous reviews have found mixed results⁵⁰ or have concluded that evidence for combined
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10 349 interventions is limited but increasing.⁵² Our results concur with RCTs of exercise-nutrition
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12 350 interventions conducted in community dwelling frail older adults. Tarazona-Santabalbina and
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14 351 colleagues found significant improvement in SPPB in participants on a 24-weeks exercise-
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16 352 nutrition intervention as compared to controls in a community dwelling frail population –
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18 353 intervention group 9.5 ± 1.8 vs control group 7.1 ± 2.8 , $P=0.007$.⁵³ Similarly, Kim et al reported
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20 354 a 12-weeks, community-based study of frail older adults that found SPPB to remain stable in
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22 355 the intervention group, while it decreased by 12.5% (1 point) in controls ($P=0.039$).⁵⁴ Our meta-
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24 356 analysis of individual components of the SPPB suggests that the significant improvements in
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26 357 functional muscle strength as represented by the chair stand component of the SPPB may be
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28 358 pivotal to the increase in overall SPPB post intervention, and reflect the functional lower limb
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30 359 strength training focus of the exercise interventions. However, the meta-analysis of handgrip
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32 360 +/- quadriceps strength did not produce a similar trend. Diversity in outcome measures for
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34 361 frailty and frailty-related domains like physical function is a challenge for comparative
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36 362 analyses between studies. Future studies should carefully consider measure responsiveness
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38 363 when selecting outcome tools.
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46 364 Nutrition is another important domain within frailty. Yet the majority of studies included in
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48 365 this review only reported nutrition status at baseline, with only one study reporting follow-up
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50 366 nutrition assessment at the end of the intervention.³³ Luger et al described an improvement in
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52 367 nutrition status in a sample of at risk malnourished pre-frail/frail patients (thus likely to benefit
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54 368 most from nutrition therapy). As hospitalised patients have greater energy deficits due to
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56 369 catabolic stress of acute illness, they are a population that requires careful determination of
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58 370 energy/protein requirements and in whom additive effects of nutrition supplementation to
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3 371 exercise may have greatest impact on outcomes such as muscle strength.⁵³ As none of the
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5 372 studies in the present review reported on energy deficits, it is not known whether these patients
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8 373 received adequate replacement. Nutrition supplementation should also not be confused with
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10 374 nutrition or diet modifications. The provision of ONS alone is unlikely to augment diet
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12 375 adequacy as completely as diet modification that involves a wider range of nutrients and non-
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14 376 nutrients⁵⁵ especially when led by dietitians.^{56, 57}

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18 377 For both exercise and nutrition based interventions, an understanding of patient participation
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20 378 dynamics and compliance is required because of how they can impact on effectiveness.⁵⁸ Only
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22 379 five studies in this review reported attendance to program/home visits or phone calls or
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24 380 adherence to prescribed exercise/diet or related advice at rates of 50-90% and 70-93% for
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26 381 nutrition and exercise interventions, respectively. Issues with participants resulting in poorer
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28 382 compliance were not reported in these articles, such that the authors recommend that future
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30 383 studies explore barriers and enablers to adherence in multi-modal interventions.

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34 384 Cognition is another critical domain in the multidimensional nature of frailty. Exercise⁵⁹ and
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36 385 nutrition interventions⁶⁰ may have a far reaching, positive effect on cognition in older adults.
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38 386 However, there was no evidence of an impact on cognition from a single study⁴¹ in the present
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40 387 review. This is consistent with a network meta-analysis of 13 RCTs that examined exercise and
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42 388 nutrition interventions in frail older adults.¹¹ One suggested explanation is that different
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44 389 neuronal mechanisms could result in a misfit between combinatory approaches of nutrition and
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46 390 physical interventions ⁶¹ highlighting that more in-depth research is required.⁶²

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51 391 The economic delivery of new interventions and models of care is important to a range of
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53 392 stakeholders⁶³ but has been infrequently conducted in previous studies.⁵⁰ In this review, only
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55 393 two out of 11 studies included an economic analysis, with the majority of costs coming from
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57 394 delivery of exercise and nutrition support. The types of consumables that were considered in
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3 395 analyses included nutrition supplements, ankle/wrist weights, mobility aids and medications.
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5 396 Elements of service provision that were considered included community, rehabilitation,
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7 397 residential and transition care service use, which were often reduced and contributed to the net
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9
10 398 result. The results of this review support previous findings of beneficial effects on frailty-
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12 399 related outcomes, without increased costs.⁵⁰ However, results should be interpreted with
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14 400 caution as omission of other services (such as medication reviews) within a multimodal
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16 401 intervention can impact costings, and there are instances where interventions have not been
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18 402 found to be more-cost effective than usual care.⁶⁴ The approach of streamlining and
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20 403 reorganising existing services rather than creating entirely new systems may be preferred.
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25 404 *Strength and weakness*

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27 405 This study was robust and underwent peer review by an academic librarian. We did not have a
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29 406 language restriction on the search, and we did not find nor include studies in other languages.
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31 407 We chose to use of an updated version of the Cochrane risk of bias tool (RoB 2), which
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33 408 addresses issues of confusion common to its first version.
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37 409 By focussing on exercise-nutrition interventions only, this study addresses a gap as identified
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39 410 in a recent review of multi-domain interventions in pre-frail or frail elderly adults, in which
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41 411 some interventions may have been too broad to directly impact frailty, and functional and
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43 412 cognitive status.⁵² Multidisciplinary team based approaches remain recommended and are a
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45 413 bedrock of quality standard care; they may also already include goals for exercise and nutrition
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47 414 such that it may be difficult to solely attribute outcomes to a targeted but supplementary
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49 415 exercise-nutrition program. Social relationships affect health behaviour and physical health,⁶⁵
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51 416 such that intervention benefits may in part come from social interactions. Nevertheless, several
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53 417 studies^{29, 33, 43} have demonstrated significant improvements even when control participants are
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55 418 provided with the social aspect of an intervention, such that exercise and nutrition are expected
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3 419 to improve outcomes independent of social interactions. Among the three studies^{29, 33, 39}
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5 420 included in the meta-analysis of reduction in frailty score, one study³³ included patients from
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7 421 community. However, when combined with data from the other two studies,^{29, 39} participants
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9 422 recruited from the hospital made up majority (~80%) of the entire cohort in that meta-analysis.
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13 423 *Implications and future research*

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16 424 This review is a useful resource for researchers and multi-disciplinary clinicians who are
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18 425 seeking to generate evidence or evaluate their practices of exercise-nutrition interventions for
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20 426 frail hospitalised older adults. The authors interpretation of the quality of studies in this review
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22 427 is that the evidence base is low, but the inclusion of future studies may change estimates of the
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24 428 intervention effects. While blinding of participants to the intervention is acknowledged to be
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26 429 difficult, future studies should be adequately powered, use allocation concealment with
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28 430 blinding outcome assessors and data analysts at least. Improved reporting of intervention
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30 431 details is also required,⁶⁶ which may assist in answering research questions around the optimal
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32 432 duration, dose, modality and timing of intervention(s) across the hospital to community
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34 433 continuum. In the present review, potential beneficial effects of combined interventions could
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36 434 have been negated given the short durations reported by most studies. Thus, future studies may
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38 435 be extended for >6-12 months, or employ principles of chronic condition self-management,⁶⁷
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40 436 to determine delayed improvements and achieve long-lasting sustainability of interventions.
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42 437 The lack of evidence from non-western countries, or low- and middle-income countries
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44 438 indicate the need for research to be conducted in those populations too. There are many ongoing
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46 439 research activities relevant to the scope of this review,⁶⁸⁻⁷¹ yet only one has reported plans for
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48 440 economic analysis in the study protocol.⁶⁸ Economic evaluations can expand current evidence
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50 441 on the sustainability of incorporating such services within resource-constrained healthcare
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52 442 systems.
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3 443 *Conclusion*
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6 444 Exercise-nutrition interventions that start while patients are admitted to hospital and continue
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8 445 in the community/post-hospital, or, commence early post discharge, appear to be effective in
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10 446 reducing frailty and some frailty-related physical indicators. Though effective, the quality of
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12 447 the evidence in this review is low as most studies included had some concerns for risk of bias.
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14 448 Given the paucity of high-quality studies on the effectiveness of combined exercise-nutrition
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16 449 interventions on hospitalised frail older adult patients, more robust research that pays attention
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18 450 to effect of assignment to intervention is needed to increase the confidence in results.
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25

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30

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33

34 455 All authors contributed to the conception and design of review. CH and YS read and screened
35
36 456 titles and abstract of potentially relevant studies. CH and YS evaluated the selected studies and
37
38 457 performed data extraction. CH, MM, AY, CB reviewed the evidence. RW provided statistical
39
40 458 expertise on meta-analyses. CH drafted the article and all authors provided critical revisions
41
42 459 and final approval of the manuscript. All authors had access to the data in the study and can
43
44 460 take responsibility for the integrity of the reported findings. All authors fulfil the ICMJE criteria
45
46 461 for authorship.
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3 466 **Competing interests**

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6 467 None declared.

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9 468 **Patient consent**

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12 469 Not required.

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15 470 **Data sharing statement**

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18 471 Details of the excluded papers are available from the corresponding author upon request.

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21 472 **References**

- 22
23
24 473 1. Le Cossec C, Perrine AL, Beltzer N, Fuhrman C, Carcaillon-Bentata L. Pre-Frailty,
25 474 Frailty, and Multimorbidity: Prevalences and Associated Characteristics from Two French
26 475 National Surveys. *J Nutr Health Aging*. 2016;20(8):860-9.
27 476 2. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in
28 477 older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146-56.
29 478 3. Theou O, Squires E, Mallery K, Lee JS, Fay S, Goldstein J, et al. What do we know
30 479 about frailty in the acute care setting? A scoping review. *BMC Geriatr*. 2018;18(1):139.
31 480 4. Considine J, Fox K, Plunkett D, Mecner M, M OR, Darzins P. Factors associated with
32 481 unplanned readmissions in a major Australian health service. *Aust Health Rev*. 2019;43(1):1-
33 482 9.
34 483 5. Sirven N, Rapp T. The cost of frailty in France. *Eur J Health Econ*. 2017;18(2):243-53.
35 484 6. Thompson MQ, Theou O, Karnon J, Adams RJ, Visvanathan R. Frailty prevalence in
36 485 Australia: Findings from four pooled Australian cohort studies. *Australas J Ageing*.
37 486 2018;37(2):155-8.
38 487 7. Giné-Garriga M, Roqué-Fíguls M, Coll-Planas L, Sitja-Rabert M, Salvà A. Physical
39 488 exercise interventions for improving performance-based measures of physical function in
40 489 community-dwelling, frail older adults: a systematic review and meta-analysis. *Arch Phys Med*
41 490 *Rehabil*. 2014;95(4):753-69. e3.
42 491 8. Ng TP, Feng L, Nyunt MS, Feng L, Niti M, Tan BY, et al. Nutritional, Physical,
43 492 Cognitive, and Combination Interventions and Frailty Reversal Among Older Adults: A
44 493 Randomized Controlled Trial. *Am J Med*. 2015;128(11):1225-36.e1.
45 494 9. Hsieh TJ, Su SC, Chen CW, Kang YW, Hu MH, Hsu LL, et al. Individualized home-
46 495 based exercise and nutrition interventions improve frailty in older adults: a randomized
47 496 controlled trial. *Int J Behav Nutr Phys Act*. 2019;16(1):119.
48 497 10. Lozano-Montoya I, Correa-Perez A, Abraha I, Soiza RL, Cherubini A, O'Mahony D, et
49 498 al. Nonpharmacological interventions to treat physical frailty and sarcopenia in older patients:
50 499 a systematic overview - the SENATOR Project ONTOP Series. *Clin Interv Aging*.
51 500 2017;12:721-40.
52 501 11. Abizanda P, López MD, García VP, Estrella JdD, da Silva González Á, Vilardell NB,
53 502 et al. Effects of an Oral Nutritional Supplementation Plus Physical Exercise Intervention on
54 503 the Physical Function, Nutritional Status, and Quality of Life in Frail Institutionalized Older
55 504 Adults: The ACTIVNES Study. *J Am Med Dir Assoc*. 2015;16(5):439.e9-.e16.

12. Negm AM, Kennedy CC, Thabane L, Veroniki AA, Adachi JD, Richardson J, et al. Management of Frailty: A Systematic Review and Network Meta-analysis of Randomized Controlled Trials. *J Am Med Dir Assoc*. 2019;20(10):1190-8.
13. Rozzini R, Sabatini T, Cassinadri A, Boffelli S, Ferri M, Barbisoni P, et al. Relationship between functional loss before hospital admission and mortality in elderly persons with medical illness. *J Gerontol A Biol Sci Med Sci*. 2005;60(9):1180-3.
14. Covinsky KE, Martin GE, Beyth RJ, Justice AC, Sehgal AR, Landefeld CS. The relationship between clinical assessments of nutritional status and adverse outcomes in older hospitalized medical patients. *J Am Geriatr Soc*. 1999;47(5):532-8.
15. Sharma Y, Thompson C, Shari R, Hakendorf P, Miller M. Malnutrition in Acutely Unwell Hospitalized Elderly - "The Skeletons Are Still Rattling in the Hospital Closet". *J Nutr Health Aging*. 2017;21(10):1210-5.
16. Sharma Y, Miller M, Shahi R, Hakendorf P, Horwood C, Thompson C. Malnutrition screening in acutely unwell elderly inpatients. *Br J Nurs*. 2016;25(18):1006-14.
17. Laur CV, McNicholl T, Valaitis R, Keller HH. Malnutrition or frailty? Overlap and evidence gaps in the diagnosis and treatment of frailty and malnutrition. *Applied Physiology, Nutrition & Metabolism*. 2017;42(5):449-58.
18. Rasmussen NM, Belqaid K, Lugnet K, Nielsen AL, Rasmussen HH, Beck AM. Effectiveness of multidisciplinary nutritional support in older hospitalised patients: A systematic review and meta-analyses. *Clinical nutrition ESPEN*. 2018;27:44-52.
19. Wilkinson R, Arensberg ME, Hickson M, Dwyer JT. Frailty Prevention and Treatment: Why Registered Dietitian Nutritionists Need to Take Charge. *J Acad Nutr Diet*. 2017;117(7):1001-9.
20. Higgins JP, Green S. *Cochrane handbook for systematic reviews of interventions: Cochrane book series*. 2008.
21. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62(10):1006-12.
22. Innovation VH. *Covidence systematic review software*. Veritas Health Innovation Melbourne, VIC; 2017.
23. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
24. Farrah K, Young K, Tunis MC, Zhao L. Risk of bias tools in systematic reviews of health interventions: an analysis of PROSPERO-registered protocols. *Systematic reviews*. 2019;8(1):280.
25. RevMan. Review manager (revman)[computer program]. version 5.3. The Nordic Cochrane Centre, The Cochrane Collaboration Copenhagen, Denmark; 2014.
26. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-60.
27. Villareal DT, Chode S, Parimi N, Sinacore DR, Hilton T, Armamento-Villareal R, et al. Weight loss, exercise, or both and physical function in obese older adults. *N Engl J Med*. 2011;364(13):1218-29.
28. Armamento-Villareal R, Aguirre LE, Qualls C, Villareal DT. Effect of lifestyle intervention on the hormonal profile of frail, obese older men. *Journal of Nutrition, Health and Aging*. 2016;20(3):334-40.
29. Cameron ID, Fairhall N, Langron C, Lockwood K, Monaghan N, Aggar C, et al. A multifactorial interdisciplinary intervention reduces frailty in older people: randomized trial. *BMC Med*. 2013;11:65.
30. Fairhall N, Sherrington C, Kurrle SE, Lord SR, Lockwood K, Cameron ID. Effect of a multifactorial interdisciplinary intervention on mobility-related disability in frail older people: randomised controlled trial. *BMC Med*. 2012;10:120.

- 1
2
3 555 31. Fairhall N, Sherrington C, Lord SR, Kurrle SE, Langron C, Lockwood K, et al. Effect
4 556 of a multifactorial, interdisciplinary intervention on risk factors for falls and fall rate in frail
5 557 older people: a randomised controlled trial. *Age Ageing*. 2014;43(5):616-22.
- 6 558 32. Fairhall N, Sherrington C, Kurrle SE, Lord SR, Lockwood K, Howard K, et al.
7 559 Economic evaluation of a multifactorial, interdisciplinary intervention versus usual care to
8 560 reduce frailty in frail older people. *J Am Med Dir Assoc*. 2015;16(1):41-8.
- 9 561 33. Luger E, Dorner TE, Haider S, Kapan A, Lackinger C, Schindler K. Effects of a Home-
10 562 Based and Volunteer-Administered Physical Training, Nutritional, and Social Support
11 563 Program on Malnutrition and Frailty in Older Persons: A Randomized Controlled Trial. *J Am*
12 564 *Med Dir Assoc*. 2016;17(7):671.e9-.e16.
- 13 565 34. Haider S, Dorner TE, Luger E, Kapan A, Titze S, Lackinger C, et al. Impact of a Home-
14 566 Based Physical and Nutritional Intervention Program Conducted by Lay-Volunteers on
15 567 Handgrip Strength in Prefrail and Frail Older Adults: A Randomized Control Trial. *PLoS ONE*
16 568 [Electronic Resource]. 2017;12(1):e0169613.
- 17 569 35. Winzer E, Dorner TE, Grabovac I, Haider S, Kapan A, Lackinger C, et al. Behavior
18 570 changes by a buddy-style intervention including physical training, and nutritional and social
19 571 support. *Geriatrics & Gerontology International*. 2019;19(4):323-9.
- 20 572 36. Kapan A, Luger E, Haider S, Titze S, Schindler K, Lackinger C, et al. Fear of falling
21 573 reduced by a lay led home-based program in frail community-dwelling older adults: A
22 574 randomised controlled trial. *Arch Gerontol Geriatr*. 2017;68:25-32.
- 23 575 37. Kapan A, Winzer E, Haider S, Titze S, Schindler K, Lackinger C, et al. Impact of a lay-
24 576 led home-based intervention programme on quality of life in community-dwelling pre-frail and
25 577 frail older adults: a randomized controlled trial. *BMC Geriatr*. 2017;17:1-11.
- 26 578 38. Arrieta H, Astrugue C, Regueme S, Durrieu J, Maillard A, Rieger A, et al. Effects of a
27 579 physical activity programme to prevent physical performance decline in onco-geriatric
28 580 patients: a randomized multicentre trial. *Journal of Cachexia, Sarcopenia and Muscle*.
29 581 2019;10(2):287-97.
- 30 582 39. Niccoli S, Kolobov A, Bon T, Rafilovich S, Munro H, Tanner K, et al. Whey Protein
31 583 Supplementation Improves Rehabilitation Outcomes in Hospitalized Geriatric Patients: A
32 584 Double Blinded, Randomized Controlled Trial. *J Nutr Gerontol Geriatr*. 2017;36(4):149-65.
- 33 585 40. Milte R, Miller MD, Crotty M, Mackintosh S, Thomas S, Cameron ID, et al. COST-
34 586 EFFECTIVENESS OF INDIVIDUALIZED NUTRITION AND EXERCISE THERAPY FOR
35 587 REHABILITATION FOLLOWING HIP FRACTURE. *Journal of Rehabilitation Medicine*
36 588 (Stiftelsen Rehabiliteringsinformation). 2016;48(4):378-85.
- 37 589 41. Singh NA, Quine S, Clemson LM, Williams EJ, Williamson DA, Stavrinou TM, et al.
38 590 Effects of high-intensity progressive resistance training and targeted multidisciplinary
39 591 treatment of frailty on mortality and nursing home admissions after hip fracture: a randomized
40 592 controlled trial. *J Am Med Dir Assoc*. 2012;13(1):24-30.
- 41 593 42. Blanc-Bisson C, Dechamps A, Gouspillou G, Dehail P, Bourdel-Marchasson I. A
42 594 randomized controlled trial on early physiotherapy intervention versus usual care in acute car
43 595 unit for elderly: Potential benefits in light of dietary intakes. *Journal of Nutrition, Health and*
44 596 *Aging*. 2008;12(6):395-9.
- 45 597 43. Miller MD, Crotty M, Whitehead C, Bannerman E, Daniels LA. Nutritional
46 598 supplementation and resistance training in nutritionally at risk older adults following lower
47 599 limb fracture: a randomized controlled trial. *Clin Rehabil*. 2006;20(4):311-23.
- 48 600 44. Rodriguez-Manas L, Laosa O, Vellas B, Paolisso G, Topinkova E, Oliva-Moreno J, et
49 601 al. Effectiveness of a multimodal intervention in functionally impaired older people with type
50 602 2 diabetes mellitus. *J Cachexia Sarcopenia Muscle*. 2019;10(4):721-33.
- 51 603 45. Azad N, Molnar F, Byszewski A. Lessons learned from a multidisciplinary heart failure
52 604 clinic for older women: a randomised controlled trial. *Age Ageing*. 2008;37(3):282-7.

- 1
2
3 605 46. Romero-Ortuno R, Walsh CD, Lawlor BA, Kenny RA. A frailty instrument for primary
4 606 care: findings from the Survey of Health, Ageing and Retirement in Europe (SHARE). *BMC*
5 607 *Geriatr.* 2010;10(1):57.
- 6 608 47. Haider S, Dorner TE, Luger E, Kapan A, Titze S, Lackinger C, et al. Impact of a home-
8 609 based physical and nutritional intervention program conducted by lay-volunteers on handgrip
9 610 strength in prefrail and frail older adults: A randomized control trial. *PLoS ONE.* 2017;12(1).
- 10 611 48. Wright J, Baldwin C. Oral nutritional support with or without exercise in the
11 612 management of malnutrition in nutritionally vulnerable older people: A systematic review and
12 613 meta-analysis. *Clin Nutr.* 2018;37(6 Pt A):1879-91.
- 13 614 49. Haider S, Grabovac I, Winzer E, Kapan A, Schindler KE, Lackinger C, et al. Change
15 615 in inflammatory parameters in prefrail and frail persons obtaining physical training and
16 616 nutritional support provided by lay volunteers: A randomized controlled trial. *PLoS One.*
17 617 2017;12(10).
- 18 618 50. Apóstolo J, Cooke R, Bobrowicz-Campos E, Santana S, Marcucci M, Cano A, et al.
19 619 Effectiveness of interventions to prevent pre-frailty and frailty progression in older adults: a
20 620 systematic review. *JB I database of systematic reviews and implementation reports.*
21 621 2018;16(1):140.
- 22 622 51. De Vries N, Staal J, Van Ravensberg C, Hobbelen J, Rikkert MO, Nijhuis-Van der
24 623 Sanden M. Outcome instruments to measure frailty: a systematic review. *Ageing research*
25 624 *reviews.* 2011;10(1):104-14.
- 26 625 52. Dedeyne L, Deschodt M, Verschueren S, Tournoy J, Gielen E. Effects of multi-domain
27 626 interventions in (pre)frail elderly on frailty, functional, and cognitive status: a systematic
28 627 review. *Clin Interv Aging.* 2017;12:873-96.
- 29 628 53. Tarazona-Santabalbina FJ, Gomez-Cabrera MC, Perez-Ros P, Martinez-Arnau FM,
31 629 Cabo H, Tsaparas K, et al. A Multicomponent Exercise Intervention that Reverses Frailty and
32 630 Improves Cognition, Emotion, and Social Networking in the Community-Dwelling Frail
33 631 Elderly: A Randomized Clinical Trial. *J Am Med Dir Assoc.* 2016;17(5):426-33.
- 34 632 54. Kim CO, Lee KR. Preventive effect of protein-energy supplementation on the
35 633 functional decline of frail older adults with low socioeconomic status: a community-based
36 634 randomized controlled study. *Journals of Gerontology Series A: Biological Sciences &*
37 635 *Medical Sciences.* 2013;68(3):309-16.
- 38 636 55. Denison HJ, Cooper C, Sayer AA, Robinson SM. Prevention and optimal management
40 637 of sarcopenia: a review of combined exercise and nutrition interventions to improve muscle
41 638 outcomes in older people. *Clin Interv Aging.* 2015;10:859.
- 42 639 56. Munk T, Tolstrup U, Beck AM, Holst M, Rasmussen HH, Hovhannisyanyan K, et al.
43 640 Individualised dietary counselling for nutritionally at-risk older patients following discharge
44 641 from acute hospital to home: a systematic review and meta-analysis. *J Hum Nutr Diet.*
45 642 2016;29(2):196-208.
- 46 643 57. Beck AM, Kjær S, Hansen BS, Storm RL, Thal-Jantzen K, Bitz C. Follow-up home
48 644 visits with registered dietitians have a positive effect on the functional and nutritional status of
49 645 geriatric medical patients after discharge: a randomized controlled trial. *Clin Rehabil.*
50 646 2013;27(6):483-93.
- 51 647 58. Fairhall N, Sherrington C, Cameron ID, Kurrle SE, Lord SR, Lockwood K, et al. A
52 648 multifactorial intervention for frail older people is more than twice as effective among those
53 649 who are compliant: complier average causal effect analysis of a randomised trial. *J Physiother.*
54 650 2017;63(1):40-4.
- 55 651 59. Brisswalter J, Collardeau M, René A. Effects of acute physical exercise characteristics
56 652 on cognitive performance. *Sports Med.* 2002;32(9):555-66.
- 57 653 60. Klímová B, Vališ M. Nutritional interventions as beneficial strategies to delay cognitive
58 654 decline in healthy older individuals. *nutrients.* 2018;10(7):905.

- 1
2
3 655 61. Schättin A, Baur K, Stutz J, Wolf P, de Bruin ED. Effects of physical exercise combined
4 656 with nutritional supplements on aging brain related structures and functions: a systematic
5 657 review. *Front Aging Neurosci.* 2016;8:161.
- 6 658 62. Hardman RJ, Kennedy G, Macpherson H, Scholey AB, Pipingas A. A randomised
7 659 controlled trial investigating the effects of Mediterranean diet and aerobic exercise on cognition
8 660 in cognitively healthy older people living independently within aged care facilities: the
9 661 Lifestyle Intervention in Independent Living Aged Care (LIILAC) study protocol
10 662 [ACTRN12614001133628]. *Nutr J.* 2015;14(1):53.
- 11 663 63. Drummond MF, Stoddart GL. Economic analysis and clinical trials. *Control Clin*
12 664 *Trials.* 1984;5(2):115-28.
- 13 665 64. Ruiques FG, Adang EM, Assendelft WJ, Schers HJ, Koopmans RT, Zuidema SU. Cost-
14 666 effectiveness of a multicomponent primary care program targeting frail elderly people. *BMC*
15 667 *Fam Pract.* 2018;19(1):62.
- 16 668 65. Umberson D, Karas Montez J. Social relationships and health: A flashpoint for health
17 669 policy. *J Health Soc Behav.* 2010;51(1_suppl):S54-S66.
- 18 670 66. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better
19 671 reporting of interventions: template for intervention description and replication (TIDieR)
20 672 checklist and guide. *BMJ.* 2014;348:g1687.
- 21 673 67. Battersby M, Harris M, Smith D, Reed R, Woodman R. A pragmatic randomized
22 674 controlled trial of the Flinders Program of chronic condition management in community health
23 675 care services. *Patient Educ Couns.* 2015;98(11):1367-75.
- 24 676 68. Fairhall N, Kurrle SE, Sherrington C, Lord SR, Lockwood K, John B, et al.
25 677 Effectiveness of a multifactorial intervention on preventing development of frailty in pre-frail
26 678 older people: Study protocol for a randomised controlled trial. *BMJ Open.* 2015;5(2).
- 27 679 69. Gonzalez-Sanchez M, Cuesta-Vargas AI, Del Mar Rodriguez Gonzalez M, Caro ED,
28 680 Nunez GO, Galan-Mercant A, et al. Effectiveness of a muticomponent workout program
29 681 integrated in an evidence based multimodal program in hyperfrail elderly patients:
30 682 POWERAGING randomized clinical trial protocol. *BMC Geriatr.* 2019;19(1).
- 31 683 70. Jadczyk AD, Luscombe-Marsh N, Taylor P, Barnard R, Makwana N, Visvanathan R.
32 684 The EXPRESS Study: Exercise and Protein Effectiveness Supplementation Study supporting
33 685 autonomy in community dwelling frail older people-study protocol for a randomized controlled
34 686 pilot and feasibility study. *Pilot & Feasibility Studies.* 2018;4:8.
- 35 687 71. Landi F, Cesari M, Calvani R, Cherubini A, Di Bari M, Bejuit R, et al. The 'Sarcopenia
36 688 and Physical fRailty IN older people: multi-componenT Treatment strategies' (SPRINTT)
37 689 randomized controlled trial: design and methods. *Aging Clin Exp Res.* 2017;29(1):89-100.

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3 696 **Figure captions**
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6 697 Fig.1 Flow diagram illustrating results of the search and study selection process as described
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11 699 Fig 2. Meta-analysis of reduction in frailty score for exercise and nutrition intervention vs
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16 701 Fig.3 Meta-analyses of Short physical performance battery, Gait speed, Balance test, Chair
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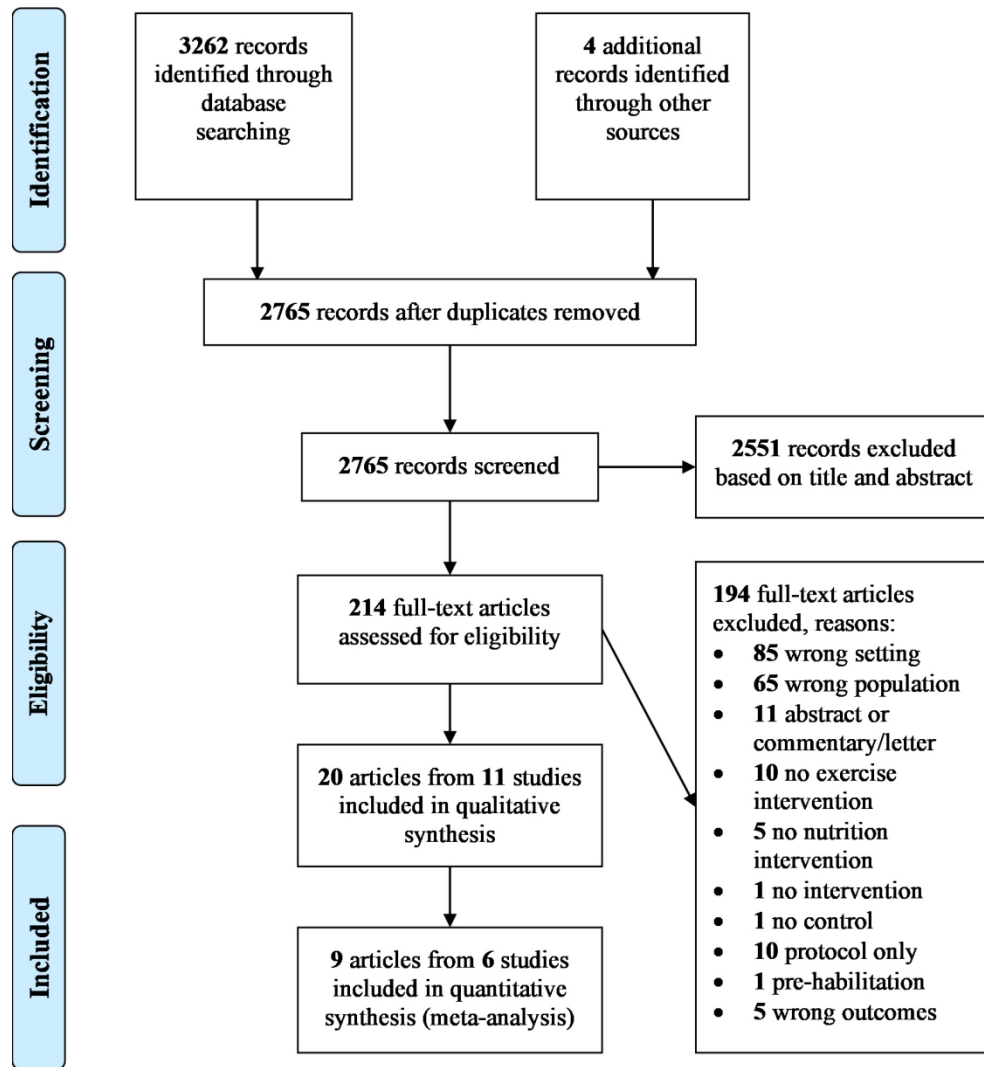


Fig.1 Flow diagram illustrating results of the search and study selection process as described in the PRISMA statement

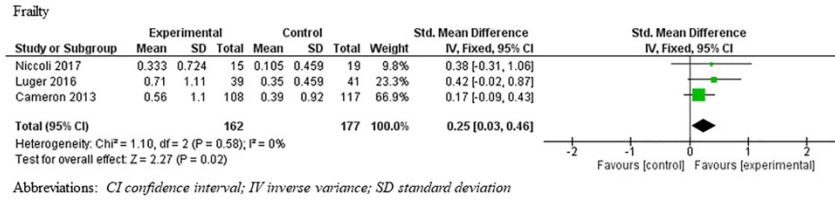


Fig 2. Meta-analysis of reduction in frailty score for exercise and nutrition intervention vs standard care

268x338mm (300 x 300 DPI)

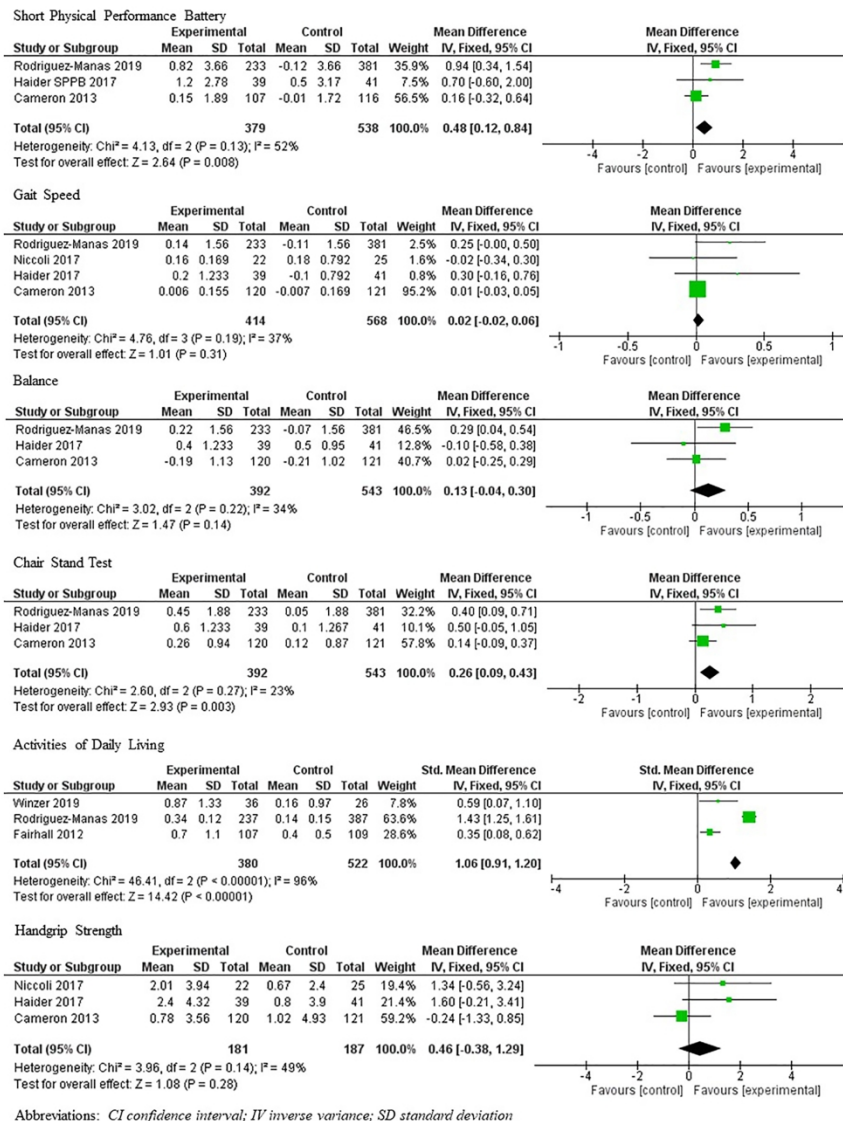


Fig.3 Meta-analyses of Short physical performance battery, Gait speed, Balance test, Chair stand test, Activities of daily living, handgrip strength

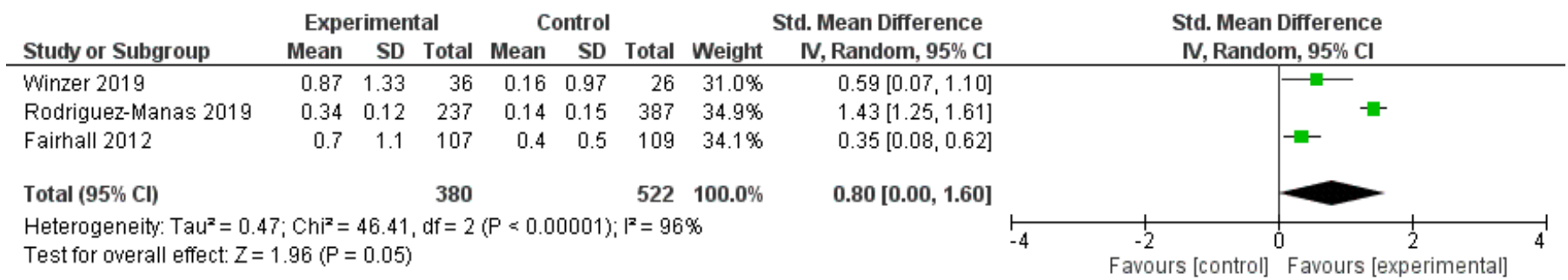
268x338mm (300 x 300 DPI)

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



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

Page 1 of 2

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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