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Research

Effectiveness of nutrition interventions and combined nutrition and physical activity interventions in older adults with frailty or prefrailty: a systematic review and meta-analysis

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Abstract

Background: Although nutrition interventions may reverse frailty, it is unclear which interventions are optimal. We conducted a systematic review and meta-analysis to identify effective nutrition interventions that improve outcomes related to frailty.

Methods: We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials and CINAHL (inception to July 2019) for English-language trials of nutrition and combined-approach (nutrition and exercise) interventions (with a control group) involving prefrail or frail adults aged 65 years or more. Outcomes of interest were frailty, mobility, health (body weight, body mass index), physical function (e.g., activities of daily living, muscle strength, appendicular lean mass), use of health care services (e.g., hospital admissions), quality of life, diet quality, mortality, and caregiver and social support. After data extraction, we assessed the risk of bias using the Cochrane Collaboration risk of bias tool for randomized controlled trials, rated the certainty of evidence with the Grading of Recommendation, Assessment, Development and Evaluations (GRADE) approach, and assessed statistical and methodologic heterogeneity. In addition, we conducted subgroup analyses of studies based on the primary intervention of protein supplementation.

Results: We identified 15 studies involving 1825 prefrail or frail older participants: 7 were nutrition trials, 7 were combined-approach trials, and 1 trial had both a nutrition arm and a combined-approach arm. Seven studies had low risk of bias, 2 studies had high risk of bias, and for 6 studies the risk of bias was unclear. Nutrition interventions had small but significant effects on measures of physical function (standardized mean difference [SMD] 0.16, 95% confidence interval [CI] 0.02 to 0.29), mobility (SMD 0.15, 95% CI 0.00 to 0.30) and frailty (SMD –0.22, 95% CI –0.44 to –0.01) outcomes. Nutrition interventions combined with physical activity also had small but significant effects on physical function (SMD 0.19, 95% CI 0.06 to 0.32), mobility (SMD 0.25, 95% CI 0.02 to 0.48) and frailty (SMD –0.41, 95% CI –0.68 to –0.14; risk ratio 0.72, 95% CI 0.52 to 1.00) measures. Protein supplementation (5 studies) had small but significant effects on physical function measures (SMD 0.16, 95% CI 0.01 to 0.31) and mobility measures (SMD 0.20, 95% CI 0.02 to 0.39), with moderate certainty of evidence.

Interpretation: There is moderate evidence that nutrition (including protein supplementation) and combined interventions are beneficial for prefrail or frail older adults. Trials with clear definitions of frailty and outcomes that reflect frailty identification and diagnosis are needed. **PROSPERO registration:** CRD42020144819

Frailty is a leading contributor to functional decline and early death in older adults.[1] More than 1.5 million Canadians are estimated to be diagnosed as medically frail, and this number is expected to rise to more than 2 million in the next 10 years.[2] Frailty is a syndrome resulting from multiple factors and impairments that can reduce a person's functional ability. It is characterized by reductions in physiologic reserve and a reduced ability to respond to stress.[3,4] Older adults with frailty are at increased risk for

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adverse outcomes such as falls, decline in mobility, hospital admission and death.[5,6] Proper identification and measurement of frailty is necessary to optimize care and treatment.[2]

Frailty is not a natural outcome of aging. Many adults reach advanced ages without developing frailty,[7] and progression can be slowed or reversed through nutrition interventions.[1,8] Since frailty is a multicomponent condition that includes physical factors such as reduced handgrip strength and gait speed, it is important to consider the enhanced impact that adequate nutrition could have on the benefits of physical activity in a frail population. Based on the mixed results from previous reviews looking at both nutrition interventions alone and physical activity interventions with nutrition supplementation,[9–11] it is still unclear what the best interventions are to support older adults with frailty, especially across a range of outcomes and in a population that has been clearly identified as frail.

We conducted a systematic review and meta-analysis focused on nutrition interventions and nutrition interventions combined with physical activity (combined approach) in an identified prefrail or frail population to assess the effectiveness of the interventions in improving outcomes including frailty, mobility, health (body weight, body mass index), physical function (e.g., activities of daily living, muscle strength, appendicular lean mass), use of health care services (e.g., hospital admissions), quality of life, diet quality, mortality, and caregiver and social support. The results of this review, along with the results of a methodologically similar review focused on physical activity interventions,[12] will provide the scientific evidence for the clinical practice guidelines of the Canadian Frailty Network.

Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[13] The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO-CRD42020144556). There were minor variations from the published protocol. These included application of the English-only language restriction on screening rather than as part of the search, and reporting on only the outcomes listed in the protocol that were ranked critical based on the voting of a guideline panel committee. Our methods followed the Cochrane Handbook for Systematic Reviews of Interventions.[14]

Key question

What is the effectiveness of nutrition interventions in older adults (aged ≥ 65 yr) with frailty or prefrailty on clinical outcomes, outcomes that are important to the patient and outcomes related to use of health care services?

Search strategy

We developed the search terms, databases and strategy in consultation with a research librarian; they were informed by previous systematic reviews[9–11] (Appendix 1, available at www.cmajopen.ca/content/9/3/E744/suppl/DC1). We searched MEDLINE (1948 to July 2019), Embase (1974 to July 2019), the Cochrane Central Register of Controlled Trials (2019, Issue 6) and CINAHL (1937 to July 2019), and manually searched reference lists of relevant reviews and included studies for citations not captured in our search. Results from the search were deduplicated, and citations were uploaded to a secure Internet-based platform for screening (DistillerSR, Evidence Partners).

Eligibility criteria

The PICO (population, intervention, comparator, outcomes) inclusion and exclusion criteria are provided in Box 1.

Box 1: Population, intervention, comparator, outcomes (PICO) eligibility criteria

Population

- Adults aged ≥ 65 yr who were selected for and clearly identified as prefrail or frail with any frailty assessment tool, assessment of frailty or other explicit author-established criteria (including studies with subanalyses involving a portion of prefrail or frail participants)
- To make this review relevant to the general frail population, studies that targeted clinical populations, such as patients with obesity or cancer, were excluded

Intervention

- Nutrition interventions involved a nutrition component such as food supplementation, meal programs and education
- Combined-approach interventions must have included both nutrition and physical activity components in the same intervention; physical activity was defined as any bodily movement by skeletal muscles that results in energy expenditure above resting levels, and included various patterns, frequencies, durations, intensities and types
- Studies that included other intervention components, such as memory tasks, were excluded

Comparator

- True control group defined as usual care, routine care or minimal contact that did not include any intervention or intervention group components
- Any head-to-head interventions were excluded

Outcomes

- Frailty (measured with a valid tool)
- Mobility (e.g., gait speed, Timed Up and Go test, Sit-to-Stand test, balance test, Short Physical Performance Battery)
- Health (body weight, body mass index)
- Physical function (e.g., activities of daily living, muscle strength [handgrip and nonhandgrip], appendicular lean mass)
- Use of health care services (e.g., hospital admission, emergency department visits)
- Quality of life (measured with a standardized tool)
- Diet quality (energy in kilocalories)
- Mortality
- Caregiver and social support (measured with the Zarit Burden Interview, Caregiver Burden Scale, Revised Scale for Caregiving Self-Efficacy and Caregiver Reaction Assessment)

We included peer-reviewed studies of interventions with a control group (randomization was not required) available in English. There was no exclusion based on intervention or participant setting.

Outcomes of interest were selected by an interdisciplinary steering committee (L.G., H.K., J.H.-L., A.G., A.T., D.B., J.M.) through a voting process that involved gathering a comprehensive list of outcomes from clinical and research expertise as well as existing relevant systematic reviews. The committee identified any missing outcomes and then anonymously ranked the outcomes on a scale from 1–9 (1–3: not important; 4–6: important; 7–9: critical). Authors not involved in the ranking process (D.S., D.F-L., M.R.) averaged the scores for each outcome and provided the list of outcomes to the committee for final discussion and agreement.

Study selection, data extraction and quality assessment

A series of team members were involved in the screening process (title and abstract, and full text), which resulted in different combinations of reviewers and team members. At all levels of screening, all articles required a minimum of 2 reviews. Multiple publications for the same primary intervention were merged; all data from all publications were extracted for relevant outcomes, but we only describe the study and its characteristics once in our review.

We developed, piloted and deployed standardized forms for data extraction. Two team members independently completed full data extraction (intention-to-treat data) and assessment of study risk of bias using the Cochrane Collaboration risk of bias tool[15] for randomized controlled trials (RCTs). If interventions had multiple treatment arms, only the interventions that met our inclusion criteria were extracted. All extraction was verified independently by a statistician (M.U.A.). Conflicts were resolved by the lead researcher of this review (M.R.).

Data on harms or adverse events were extracted narratively.

Certainty of evidence

We independently evaluated the certainty of the body of evidence using the Grading of Recommendation, Assessment, Development and Evaluations (GRADE) approach[16] with GRADEpro software. With this method, the certainty of a body of evidence is rated as high, moderate, low or very low based on assessment of 5 conditions: methodologic quality; consistency across effect estimates and statistical heterogeneity; directness of the body of evidence to the populations, interventions, comparators or outcomes of interest; precision of results; and indications of reporting bias.

Statistical analysis

All data analysis were planned a priori (Appendix 2, available at www.cmajopen.ca/content/9/3/E744/suppl/DC1). We used a meta-analysis to combine the results across studies by intervention category and outcome using the published data from included studies (full methods in Appendix 3, available at www.cmajopen.ca/content/9/3/E744/suppl/DC1). For continuous outcomes, we used the change from baseline to immediately after the intervention (mean change score, standard deviation [SD] of mean change score) for both intervention and control groups to generate the summary measures of effect in the form of standardized mean difference (SMD).[17] We used the SMD as a summary statistic because many studies in this systematic review assessed the same outcome measured in a variety of ways (e.g., mobility measured as Stair Climb Test, balance test, gait speed, chair rise repetition, Sit-to-Stand test, Short Physical Performance Battery, Timed Up and Go test). In this situation, it was necessary to standardize the results of the studies before they could be compared across studies or combined in a quantitative synthesis. The SMD-based effect sizes represent the magnitude of intervention effect relative to the variability observed within a particular study. Therefore, the studies for which the difference in mean change score was the same as the proportion of SD of mean change score will have the same SMD, regardless of the actual scale or unit of measurement used to access the outcome measures.[18,19] The SMD is interpreted based on its magnitude according to recommended Cohen *d* thresholds (~0.2 = small effect, ~0.5 = medium effect, ~0.8 = large effect).[20] For studies in which measure of variance was reported as confidence intervals (CIs), standard error or *p* values, we used Cochrane-recommended methods to convert these data to SD.[18]

We used a multilevel meta-analytical approach (where applicable) to account for statistical dependence, that is, dependency in effect sizes introduced by comparison of multiple intervention arms within a study to a common control group, or by multiple outcome measures or suboutcome measures of a primary outcome of interest within a study (such as the Short Physical Performance Battery reported as gait speed, balance test and Chair Stand Test separately). In such cases, we nested the correlated measures or effect sizes within studies first, by introducing a random effect to our grouping variables such as studies, outcome measures and intervention arms. This grouping variable, also known as random intercept, told our model to assume different values (intercepts) for each grouping level. Specifically, we used 2 grouping variables: that on level 2, and that on level 3. We assumed that these grouping variables are nested, in the sense that several effect sizes on level 2 together make up a larger cluster on level 3. For pooling of performance measures, we adjusted the direction of effect to ensure consistency of desirable outcome responses.

For dichotomous outcomes, we used the number of events after the intervention to generate the summary measures of effect in the form of risk ratio (RR) using DerSimonian and Laird random-effects models with the Mantel–Haenszel method. We used the Cochran Q ($\alpha = 0.05$) to detect statistical heterogeneity and the I^2 statistic to quantify the magnitude of statistical heterogeneity between studies, where an I^2 value of 30%–60% represents moderate heterogeneity and a value of 60%–90% represents substantial heterogeneity across studies.

We estimated the statistical heterogeneity I^2 statistic in the context of the multilevel meta-analytical approach.[19,21] We

estimated I^2–level 2 to account for the amount of within-cluster heterogeneity (i.e., across effect sizes or multiple arms of same study), I^2–level 3 to account for between-cluster heterogeneity (i.e., effect sizes across studies or subgroups of interest) and I^2–total to represent the heterogeneity not attributable to sample error (sum of values at levels 2 and 3). We added I^2–total to all forest plots for overall pooled effect estimates and summary effect size within subgroups.

We assessed publication bias using funnel plots when there were at least 10 studies in the meta-analysis.[22]

In addition, we conducted subgroup analyses of studies based on the primary intervention of protein supplementation.

All analyses were performed with R software (metaphor and dmetar packages) (R Foundation for Statistical Computing).

Ethics approval

As this study was solely literature based, it was not eligible for institutional ethics approval, and none was sought.

Results

From 3162 citations, we assessed 123 full-text articles for eligibility, and included 15 studies described in 26 publications (Figure 1). One of the included studies consisted of both a nutrition-only treatment arm and a combined-approach treatment arm[23] and was therefore considered in the meta-analysis and qualitative description of both intervention categories. Of the remaining citations, 7 were nutrition RCTS[8,22,24–28] and 7 were combined-approach RCTs or clinical controlled trials.[29–35] We meta-analyzed all 15 studies and their outcomes based on their intervention category. The studies were published from 2000 to 2019. A total of 1825 frail participants aged 65 years or more (mean 70.0–83.1 yr) were included in this review; the proportion of women ranged from 51% to 100%. All included studies had fewer than 250 participants (median 89, quartiles 71, 89, 166, 246).

Characteristics of the included studies are presented in Table 1, and further demographic data from studies can be found in Appendix 4 (available at www.cmajopen.ca/content/9/3/E744/suppl/DC1). Most interventions were conducted in Europe and Asia with community-dwelling participants and lasted between 3 and 6 months. The most common tool to measure frailty status was Fried's frailty phenotype (also known as the Cardiovascular Health Study criteria[47]) (n = 10).

In the nutrition studies, interventions included any or all of the following: nutrition supplementation (n = 4), fortified or enhanced foods (n = 7), and nutrition or dietitian counselling (n = 1). Combined-approach studies also used these 3 nutrition interventions, with 5 studies adding a resistance or strength training component. The physical activity occurred 1–2 times per week and lasted 30 minutes to more than 1 hour.

Adverse effects or harms related to the intervention were reported in 5 studies and included nausea, diarrhea, dyspepsia and acute illness with nutrition interventions, and back pain or other pain related to exercise and heavy study burden with combined-approach interventions.

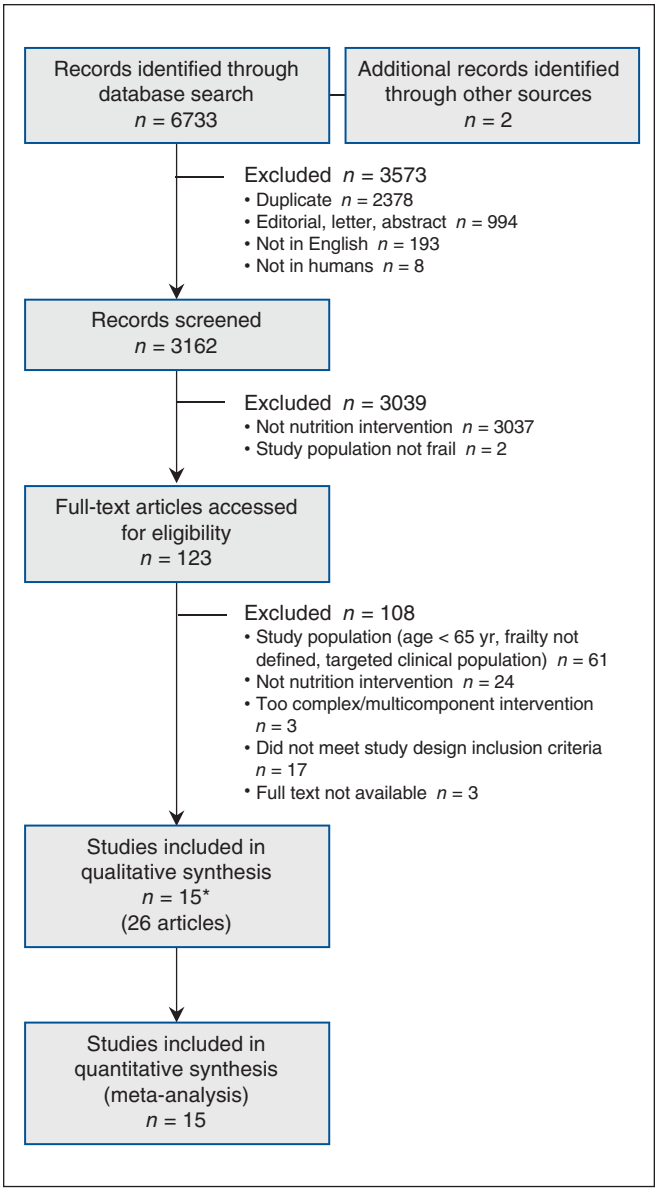


Figure 1: Flow diagram showing study selection. *One citation with 3 articles had both a nutrition-only treatment arm and a combined-approach treatment arm.

Risk of bias and quality

The Cochrane Collaboration risk of bias tool showed that 7 studies had low risk of bias,[8,22,26–28,30,33] 2 studies had high risk of bias,[29,35] and for 6 studies the risk of bias was unclear, mostly owing to unclear allocation and blinding procedures[23–25,31,32,34] (Appendix 5, available at www.cmajopen.ca/content/9/3/E744/suppl/DC1).

The certainty of evidence ranged from very low to moderate but was moderate for most outcomes owing to downgrading for risk of bias or imprecision (Appendix 6, available at www.cmajopen.ca/content/9/3/E744/suppl/DC1).

We did not observe any significant asymmetry across funnel plots for publication bias (Appendix 7, available at www.cmajopen.ca/content/9/3/E744/suppl/DC1).

Table 1 (part 1 of 2): Characteristics of the included studies

Study, year; country	No. of participants (F/M, %)	Age, mean ± SD,* yr	Assessment tool or measure	Design; duration†	Intervention	Control	Outcomes
Nutrition interventions							
Wu et al.,[24] 2018; Taiwan	40 (56/44‡)	O: 74.0 I: 73.5 ± 2.4, 75.0 ± 2.4, 72.8 ± 1.6 C: 75.9 ± 1.7	Fried's frailty phenotype§	RCT; 3 mo	Oral nutrition supplements, fortified/enhanced foods, nutrition/ dietitian counselling	General nutrition information	Health (and death), physical function (and quality of life), mobility, diet quality
Niccoli et al.,[25] 2017; Canada	53 (68/32‡)	O: 81.3 ± 1.0 I: 81.77 ± 1.68 C: 80.33 ± 1.57	Fried's frailty phenotype§	RCT; ~ 3–4 wk	Fortified/enhanced foods	Control food without supplements	Physical function (and quality of life), frailty, mobility
Park et al.,[26] 2018; Korea	120 (65/35)	I: 77.30 ± 3.67, 76.80 ± 3.70 C: 76.83 ± 3.86	Cardiovascular Health Study criteria§	RCT; 12 wk	Fortified/enhanced foods	Placebo powder	Physical function (and quality of life), frailty, mobility, diet quality
Ng et al.,[8,36,37] 2015; Singapore	246 (61/39)	O: 70.0 ± 4.7 I: 69.7 ± 4.23 C: 70.1 ± 5.02	Cardiovascular Health Study criteria§	RCT; 6 mo	Oral nutrition supplements, fortified/enhanced foods	Placebo supplement	Health (and death), physical function (and quality of life), use of health care services, frailty, mobility
Kim et al.,[27] 2013; South Korea	87 (79/21)	I: 78.9 ± 5.5 C: 78.4 ± 6.0	Slow gait speed, MNA	RCT; 12 wk	Oral nutrition supplements, fortified/enhanced foods	No contact or care	Health (and death), physical function (and quality of life), frailty, mobility, diet quality
Tieland et al.,[28,38] 2012; the Netherlands	65 (55/45)	O: 83.1 ± 5.1 I: 78.0 ± 1 C: 81.0 ± 1	Fried's frailty phenotype	RCT; 24 wk	Fortified/enhanced foods	Placebo supplement	Health (and death), physical function (and quality of life), mobility, diet quality
Latham et al.,[22] 2003; New Zealand	243 (53/47)	O: 79.1 ± 6.9 I: 79.0 (95% CI 77 to 80) C: 80.0 (95% CI 78 to 81)	Clinical measures of frailty§	RCT; 3 mo	Oral nutrition supplements	Placebo supplement	Physical function (and quality of life), mobility
de Jong et al.,[23,39,40] 2000;¶ the Netherlands	217 (70/30)	O: 79.0 I: 79.6 ± 4.8 C: 79.3 ± 6.6	Required health care service (e.g., home care, meal delivery)	RCT 17 wk	Fortified/enhanced foods	Control food without supplements	Physical function (and quality of life), mobility, diet quality
Combined-approach interventions							
Kang et al.,[29] 2019; China	115 (62/38)	O: 77.3 I: 76.79 ± 7.11, 78.04 ± 6.82	Fried's frailty phenotype§	CCT; 12 wk	Fortified/enhanced foods, muscle strengthening	Information about diet to maintain current weight, usual daily exercise program	Health (and death), physical function (and quality of life), mobility
Serra-Prat et al.,[30] 2017; Spain	172 (56/44)	O: 78.3 I: 77.9 ± 5.0 C: 78.8 ± 4.9	Fried's frailty phenotype	RCT; 12 mo	Nutrition/dietitian counselling, mixed physical activity (muscle strengthening/ aerobic/exercises)	Usual care	Frailty, health (and death), physical function (and quality of life), mobility
Luger et al.,[31,41–44] 2016; Austria	80 (84/16)	O: 82.8 ± 8.0 I: 83.0 ± 8.1 C: 82.5 ± 8.0	SHARE-FI§	RCT; 12 wk	Nutrition/dietitian counselling, muscle strengthening	Visited 2×/wk by "buddies"	Frailty, physical function (and quality of life), mobility

Table 1 (part 2 of 2): Characteristics of the included studies

Study, year; country	No. of participants (F/M, %)	Age, mean ± SD,* yr	Assessment tool or measure	Design; duration†	Intervention	Control	Outcomes
Kwon et al.,[32] 2015; Japan	89 (100/0)	O: 76.8 I: 76.5 ± 3.8, 77.0 ± 4.2 C: 76.9 ± 3.9	Fried's frailty phenotype§	RCT; 3 mo	Nutrition/dietitian counselling, muscle strengthening	General health education session 1×/mo	Frailty, physical function (and quality of life), mobility
Tieland et al.,[33,45,46] 2012; the Netherlands	62 (66/34)	I: 78 ± 9 C: 79 ± 6	Fried's frailty phenotype	RCT; 24 wk	Fortified/enhanced foods, muscle strengthening	Exercise training 2×/wk, placebo supplement 2×/d	Health (and death), physical function (and quality of life), mobility, diet quality
Yamada et al.,[35] 2012; Japan	77 (51/49‡)	I: 74.4 ± 7.3 C: 75.6 ± 6.0	Frailty status as certified by long-term care insurance service	CCT; 3 mo	Oral nutrition supplements, fortified/enhanced foods, muscle strengthening	Both groups received exercise training	Physical outcomes (and quality of life), mobility
de Jong et al.,[23,39,40] 2000;** the Netherlands	217 (70/30)	O: 79.0 I: 79.2 ± 6.1 C: 79.3 ± 6.6	Required health care service (e.g., home care, meal delivery)	RCT; 17 wk	Fortified/enhanced foods, mixed physical activity (muscle strengthening/aerobic/exercises)	Control food, social program once every 2 wk for 90 min	Physical function (and quality of life), mobility, diet quality
Nykänen et al.,[34] 2012; Finland	159 (79/21)	O: 83.1 ± 5.1 I: 83.2 ± 5.2 C: 82.9 ± 5.0	Cardiovascular Health Study criteria§	CCT; 1 yr	Nutrition/dietitian counselling, mixed physical activity (muscle strengthening/aerobic/exercises)	Usual care	Frailty, diet quality

Note: C = control, CCT = clinical controlled trial, CI = confidence interval, F = female, I = intervention, M = male, MNA = Mini Nutritional Assessment, O = overall, RCT = randomized controlled trial, SD = standard deviation, SHARE-FI = Frailty Instrument of the Survey of Health, Ageing and Retirement in Europe.
*Except where noted otherwise.
†Not including follow-up, if applicable.
‡Values based on reported baseline, which may not equal the number randomly allocated but, rather, the number who completed the intervention.
§Authors indicated that the assessment tool was modified from standard protocol.
¶Describes nutrition-only intervention arm compared to control, as this study was also included in the combined-approach analysis.
**Describes combined-approach intervention arm compared to control, as this study was also included in the nutrition analysis.

Benefits of treatment

The meta-analysis for all outcomes included an examination of the impact of all nutrition interventions together, all combined-approach interventions together and a subgroup of protein supplementation interventions (Table 2).

Nutrition interventions

Nutrition interventions supplemented protein,[24–26,28] other multinutrients and multivitamins,[8,24,27] vitamin D,[22] and fruit and dairy products[23] (Appendix 4, Supplemental Table S1). Overall, nutrition RCTs had small but significant effects on physical, mobility and frailty measures, with moderate certainty of evidence (Table 2; Appendix 6, Supplemental Table S4). There were no significant effects on measures of health, diet quality or quality of life (Table 2; Appendix 8, Supplemental Figures S7–S9, available at www.cmajopen.ca/content/9/3/E744/suppl/DC1).

The 7 RCTs[8,22,24–28] (373 intervention and 321 control participants) had a small but significant pooled effect estimate for physical measures (SMD 0.16, 95% CI 0.02 to 0.29) (Figure 2A). A similar effect was observed for mobility measures (SMD 0.15, 95% CI 0.00 to 0.30) (Figure 2B).

Frailty outcomes were reported in 3 RCTs[8,24,26] from 155 intervention and 100 control participants. These studies had a small but significant pooled effect estimate for frailty (SMD –0.22, 95% CI –0.44 to -0.01) (Figure 2C).

Protein supplementation interventions

We identified 5 studies for subgroup analysis based on the primary intervention of protein supplementation.[24–28] These RCTs had 195 intervention and 149 control participants and ranged in duration from 4 to 24 weeks. There were small but significant effects on physical measures (SMD 0.16, 95% CI 0.01 to 0.31) (Figure 3A) and mobility measures (SMD 0.20, 95% CI 0.02 to 0.39) (Figure 3B), with moderate certainty of evidence (Table 2; Appendix 6, Supplemental Table S5). There were no significant effects on measures of health, frailty or diet quality (Appendix 8, Supplemental Figures S10–S12).

Table 2: Effect estimates for outcomes and certainty of evidence, for all interventions combined and by intervention category

Category; outcome*†	No. of studies	No. of participants	SMD‡ (95% CI)§	GRADE rating
Nutrition interventions				
Physical function	7	694	0.16 (0.02 to 0.29)	Moderate; downgraded for risk of bias
Mobility	7	694	0.15 (0.001 to 0.30)	Moderate; downgraded for risk of bias
Health	4	284	–0.18 (–0.51 to 0.16)	Low; downgraded for risk of bias and imprecision
Frailty	3	255	–0.22 (–0.44 to –0.01)	Moderate; downgraded for risk of bias
Diet quality	5	383	0.10 (–0.47 to 0.67)	Very low; downgraded for risk of bias, inconsistency and imprecision
Quality of life	1	243	–0.12 (–1.39 to 1.15)	Moderate; downgraded for imprecision
Protein supplementation interventions				
Physical function	5	344	0.16 (0.01 to 0.31)	Moderate; downgraded for risk of bias
Mobility	5	344	0.20 (0.02 to 0.39)	Moderate; downgraded for risk of bias
Health	3	177	–0.12 (–0.58 to 0.34)	Low; downgraded for risk of bias and imprecision
Frailty	2	148	–0.18 (–0.45 to 0.09)	Low; downgraded for risk of bias and imprecision
Diet quality	4	297	–0.01 (–0.69 to 0.67)	Very low; downgraded for risk of bias, inconsistency and imprecision
Combined-approach (nutrition and physical activity) interventions				
Physical function	6	514	0.19 (0.06 to 0.32)	Moderate; downgraded for risk of bias
Mobility	6	514	0.25 (0.02 to 0.48)	Moderate; downgraded for risk of bias
Health	3	310	–0.05 (–0.42 to 0.33)	Low; downgraded for risk of bias and imprecision
Frailty	2	213	–0.41 (–0.68 to –0.14)	Moderate; downgraded for risk of bias
	3	359	RR 0.72 (0.52 to 1.00)¶	Moderate; downgraded for risk of bias
Diet quality	2	141	0.53 (–0.98 to 2.04)	Very low; downgraded for risk of bias, inconsistency and imprecision
Quality of life	3	267	0.31 (–0.05 to 0.67)	Low; downgraded for risk of bias and imprecision

Note: CI = confidence interval, RR = risk ratio, SMD = standardized mean difference.
*Physical function: activities of daily living, muscle strength (handgrip and nonhandgrip) and appendicular lean mass; mobility: gait speed, Timed Up and Go test, Sit-to-Stand test, balance test and Short Physical Performance Battery; health: body weight and body mass index; diet quality: energy intake in calories.
†For all interventions, there were no data for death, use of health care services, or caregiver and social support. For protein supplementation interventions, there were no data for quality of life.
‡Except where noted otherwise.
§Large: ~0.8; medium: ~0.5; small: ~0.2.
¶Dichotomous outcome.

Combined-approach interventions

The nutrition component of combined-approach interventions[29–33,35] consisted of protein supplementation, provision of food, vitamin D supplementation, dietary counselling, education or cooking classes. The physical activity component was mostly muscle-strengthening exercises through resistance and strength training, but 3 interventions[23,30,34] also included aerobic exercises (Appendix 4, Supplemental Table S2). Together, the combined-approach interventions had small but significant effects on physical, mobility and frailty measures, with moderate certainty of evidence (Table 2; Appendix 6, Supplemental Table S6). There were no significant effects on measures of health, diet quality or quality of life (Table 2; Appendix 8, Supplemental Figures S13–S15).

The same 6 interventions had data for both physical and mobility meaures.[29–33,35] These interventions involved 258 intervention and 256 control participants and ranged in duration from 12 to 52 weeks. They had small but significant pooled effect estimates for physical measures (SMD 0.19, 95% CI 0.06 to 0.32) (Figure 4A) and mobility measures (SMD 0.25, 95% CI 0.02 to 0.48) (Figure 4B).

Frailty outcomes were reported in 2 RCTs (100 intervention and 113 control participants).[30,31] There was a small but significant pooled effect estimate for frailty (SMD –0.41, 95% CI –0.68 to –0.14) (Figure 4C). Frailty was also measured as

A

Study, year; outcome measure	No. of participants: Intervention	Control	Weight, %	SMD (95% CI)
Activities of daily living				
Latham et al.,[22] 2003	121	122	12.38	0.00 (–0.28 to 0.28)
Kim et al.,[27] 2013	41	43	5.62	0.30 (–0.14 to 0.74)
RE multilevel model for subgroup (Q = 1.29, df = 1, p = 0.3, I^2 = 22.22%)				**0.10 (–1.70 to 1.90)**
Handgrip strength				
Kim et al.,[27] 2013	41	43	5.62	–0.08 (–0.52 to 0.36)
Tieland et al.,[28,39] 2012	34	31	4.88	0.00 (–0.48 to 0.48)
Niccoli et al.,[25] 2017	22	25	3.29	0.40 (–0.19 to 0.99)
Park et al.,[26] 2018 (protein intake; 1.2 g/kg per day)	40	40	5.78	–0.14 (–0.58 to 0.30)
Park et al.,[26] 2018 (protein intake; 1.5 g/kg per day)	40	40	5.78	–0.08 (–0.52 to 0.36)
Wu et al.,[24] 2018 (left – multinutrients only)	8	10	1.20	1.00 (0.00 to 2.00)
Wu et al.,[24] 2018 (left – multinutrients + soy protein)	9	10	1.42	0.37 (–0.55 to 1.29)
Wu et al.,[24] 2018 (left – milk powder + nuts + education)	9	10	1.42	0.61 (–0.31 to 1.53)
Wu et al.,[24] 2018 (right – multinutrients only)	8	10	1.30	0.75 (–0.21 to 1.71)
Wu et al.,[24] 2018 (right – multinutrients + soy protein)	9	10	1.42	0.60 (–0.32 to 1.52)
Wu et al.,[24] 2018 (right – milk powder + nuts + education)	9	10	1.42	0.51 (–0.41 to 1.43)
RE multilevel model for subgroup (Q = 11.80, df = 10, p = 0.3, I^2 = 42.13%)				**0.15 (–0.19 to 0.50)**
Muscle strength (nonhandgrip)				
Latham et al.,[22] 2003; quadriceps strength	121	122	12.38	0.00 (–0.28 to 0.28)
Tieland et al.,[28,39] 2012; leg extension strength	34	31	4.88	0.24 (–0.24 to 0.72)
Tieland et al.,[28,39] 2012; leg press strength	34	31	4.88	0.09 (–0.39 to 0.57)
Ng et al.,[8,36,37] 2015; knee extension strength	49	50	6.63	0.23 (–0.16 to 0.62)
Niccoli et al.,[25] 2017; knee extensor force	22	25	3.29	0.19 (–0.40 to 0.78)
RE multilevel model for subgroup (Q = 1.32, df = 4, p = 0.9, I^2 = 0.00%)				**0.11 (–0.14 to 0.37)**
Appendicular lean mass				
Tieland et al.,[28,39] 2012	34	31	4.88	0.00 (–0.48 to 0.48)
Park et al.,[26] 2018 (protein intake; 1.2 g/kg per day)	40	40	5.78	0.06 (–0.38 to 0.50)
Park et al.,[26] 2018 (protein intake; 1.5 g/kg per day)	40	40	5.78	0.66 (0.22 to 1.10)
RE multilevel model for subgroup (Q = 5.12, df = 2, p = 0.08, I^2 = 60.78%)				**0.25 (–0.67 to 1.16)**
RE multilevel model (Q = 20.57, df = 20, p = 0.4, overall I^2 = 12.46%)			100.00	0.16 (0.02 to 0.29)

B

Study, year; outcome measure	No. of participants: Intervention	Control	Weight, %	SMD (95% CI)
Latham et al.,[22] 2003; balance test	121	122	6.73	0.00 (–0.28 to 0.28)
Latham et al.,[22] 2003; gait speed	121	122	6.73	0.00 (–0.28 to 0.28)
Latham et al.,[22] 2003; Timed Up and Go test	121	122	6.73	0.00 (–0.28 to 0.28)
Kim et al.,[27] 2013; balance test	41	43	4.39	–0.13 (–0.57 to 0.31)
Kim et al.,[27] 2013; gait speed	41	43	4.39	0.63 (0.19 to 1.07)
Kim et al.,[27] 2013; Short Physical Performance Battery	41	43	4.39	0.45 (0.01 to 0.89)
Kim et al.,[27] 2013; Timed Up and Go test	41	43	4.39	0.40 (–0.04 to 0.84)
Tieland et al.,[28,39] 2012; Sit-to-Stand test	34	31	3.54	0.94 (0.42 to 1.46)
Tieland et al.,[28,39] 2012; gait speed	34	31	3.90	0.04 (–0.44 to 0.52)
Tieland et al.,[28,39] 2012; Short Physical Performance Battery	34	31	3.90	0.40 (–0.08 to 0.88)
Ng et al.,[8,36,37] 2015; gait speed	49	50	4.85	0.06 (–0.33 to 0.45)
Niccoli et al.,[25] 2017; gait speed	22	25	2.97	–0.12 (–0.71 to 0.47)
Niccoli et al.,[25] 2017; Timed Up and Go test	22	25	2.97	0.05 (–0.54 to 0.64)
Park et al.,[26] 2018; Sit-to-Stand test (protein intake; 1.2 g/kg per day)	40	40	4.46	0.12 (–0.32 to 0.56)
Park et al.,[26] 2018; Sit-to-Stand test (protein intake; 1.5 g/kg per day)	40	40	4.46	0.24 (–0.20 to 0.68)
Park et al.,[26] 2018; gait speed (protein intake; 1.2 g/kg per day)	40	40	4.46	–0.25 (–0.69 to 0.19)
Park et al.,[26] 2018; gait speed (protein intake; 1.5 g/kg per day)	40	40	4.46	0.70 (0.26 to 1.14)
Park et al.,[26] 2018; Short Physical Performance Battery (protein intake; 1.2 g/kg per day)	40	40	4.46	–0.27 (–0.71 to 0.17)
Park et al.,[26] 2018; Short Physical Performance Battery (protein intake; 1.5 g/kg per day)	40	40	4.46	0.06 (–0.38 to 0.50)
Park et al.,[26] 2018; Timed Up and Go test (protein intake; 1.2 g/kg per day)	40	40	4.46	–0.11 (–0.55 to 0.33)
Park et al.,[26] 2018; Timed Up and Go test (protein intake; 1.5 g/kg per day)	40	40	4.46	0.27 (–0.17 to 0.71)
Wu et al.,[24] 2018; gait speed (multinutrients only)	8	10	1.42	–0.09 (–1.03 to 0.85)
Wu et al.,[24] 2018; gait speed (multinutrients + soy protein)	9	10	1.53	–0.17 (–1.07 to 0.73)
Wu et al.,[24] 2018; gait speed (milk powder + nuts + education)	9	10	1.53	0.27 (–0.63 to 1.17)
RE multilevel model (Q = 39.21, df = 23, p = 0.02, overall I^2 = 43.83%)			100.00	0.15 (0.00 to 0.30)

C

Study, year; outcome measure	No. of participants: Intervention	Control	Weight, %	SMD (95% CI)
Ng et al.,[8,36,37] 2015; Cardiovascular Health Study criteria	49	50	21.07	–0.36 (–0.75 to 0.03)
Park et al.,[26] 2018; Cardiovascular Health Study criteria (protein intake; 1.2 g/kg per day)	40	40	16.86	–0.22 (–0.66 to 0.22)
Park et al.,[26] 2018; Cardiovascular Health Study criteria (protein intake; 1.5 g/kg per day)	40	40	16.86	–0.44 (–0.88 to 0.00)
Park et al.,[26] 2018; KLoSA criteria (protein intake; 1.2 g/kg per day)	40	40	16.86	0.00 (–0.44 to 0.44)
Park et al.,[26] 2018; KLoSA criteria (protein intake; 1.5 g/kg per day)	40	40	16.86	0.00 (–0.44 to 0.44)
Wu et al.,[24] 2018; Fried's criteria (multinutrients only)	8	10	3.66	–0.30 (–1.24 to 0.64)
Wu et al.,[24] 2018; Fried's criteria (multinutrients + soy protein)	9	10	4.01	–0.05 (–0.95 to 0.85)
Wu et al.,[24] 2018; Fried's criteria (milk powder + nuts + education)	9	10	3.83	–0.63 (–1.55 to 0.29)
RE multilevel model (Q = 4.32, df = 7, p = 0.7, overall I^2 = 0.00%)			100.00	–0.22 (–0.44 to –0.01)

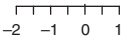


Figure 2: Effects of nutrition interventions on measures of physical outcomes (A), mobility (B) and frailty (C). Weights are from random-effects (RE) multilevel model analysis. Note: CI = confidence interval, df = degrees of freedom, KLoSA = Korean Longitudinal Study of Aging, SMD = standardized mean difference.

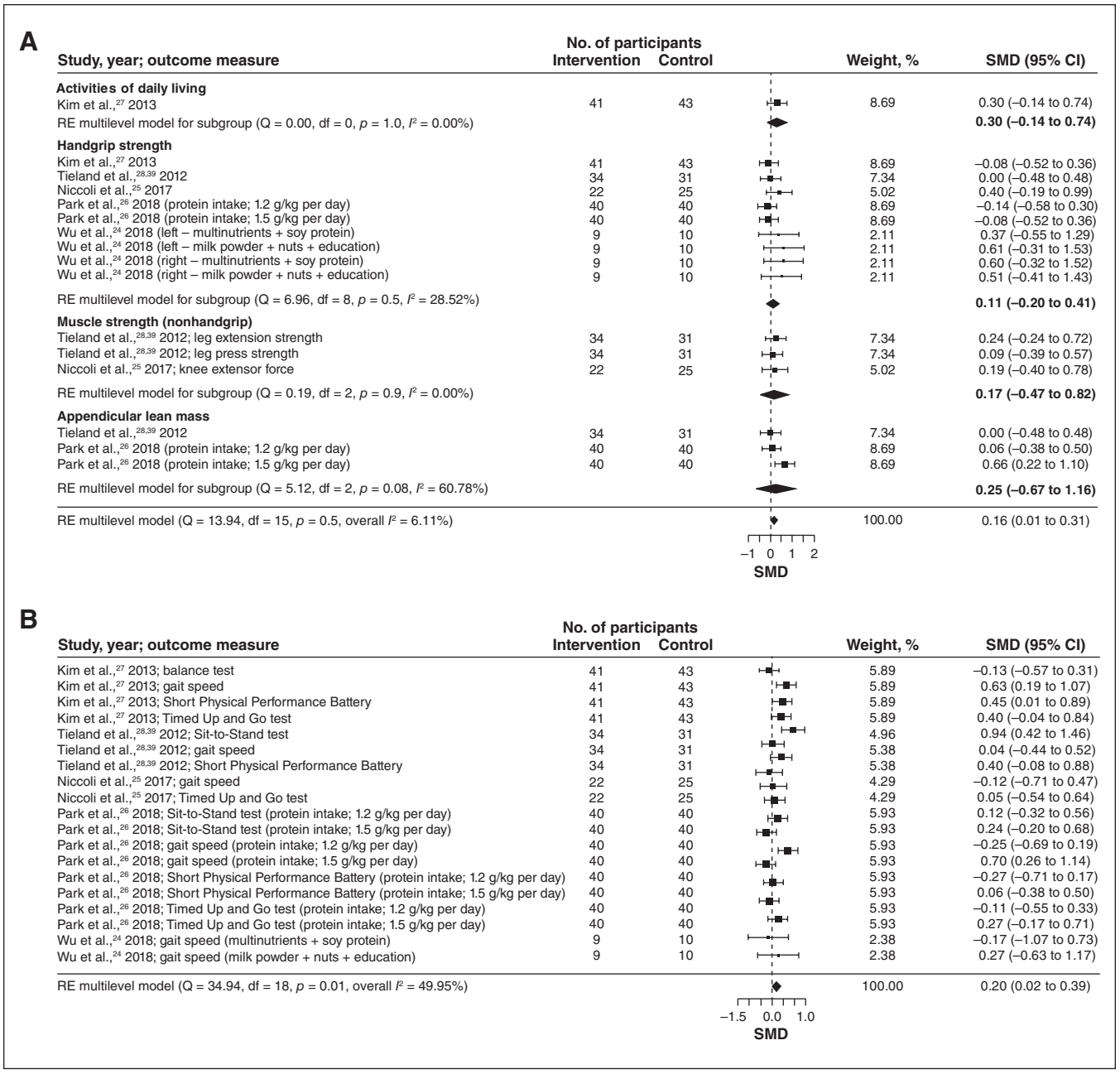


Figure 3: Effects of protein supplementation interventions on measures of physical outcomes (A) and mobility (B). Weights are from random-effects (RE) multilevel model analysis. Note: CI = confidence interval, SMD = standardized mean difference.

prevalence of frailty after the intervention in 3 RCTs[30,31,34] with 174 intervention and 185 control participants; they ranged in duration from 12 to 52 weeks. The pooled effect estimate showed a significant reduction in this outcome (RR 0.72, 95% CI 0.52 to 1.00) (Figure 4D).

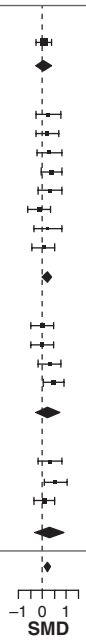
Interpretation

Our review showed a small but significant benefit of nutrition (including protein supplementation) and combined-approach interventions compared to control groups for physical and mobility outcomes, based on moderate certainty of evidence. Our analysis for nutrition and combined-approach interventions showed a small but significant benefit on frailty outcomes, based on moderate certainty of evidence.

Previous systematic reviews and meta-analyses evaluating the benefit of various interventions and their components in frailty prevention and reversal focused on specific settings[10,48] or specific interventions, primarily physical activity interventions.[9,49] Others included a broader mix of interventions,[5,6,50] which made their assessment more heterogeneous than our review. Some reviews lacked meta-analyses[11,51,52] or focused on only a few specific outcomes, such as physical performance,[11] body composition, leg strength and walking speed.[53] Some

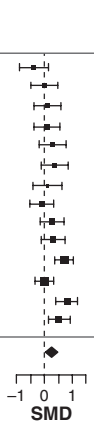
A

Study, year; outcome measure	No. of participants: Intervention	Control	Weight, %	SMD (95% CI)
Activities of daily living				
Serra-Prat et al.,[30] 2017	61	72	11.98	0.04 (–0.30 to 0.38)
RE multilevel model for subgroup (Q = 0.00, df = 0, p = 1.0, I^2 = 0.00%)				**0.04 (–0.30 to 0.38)**
Handgrip strength				
Tieland et al.,[28,39] 2012	31	31	5.13	0.24 (–0.28 to 0.76)
Yamada et al.,[35] 2012	35	35	5.99	0.19 (–0.29 to 0.67)
Kwon et al.,[32] 2015	26	28	5.13	0.27 (–0.25 to 0.79)
Luger et al.,[31,41–44] 2016	39	41	7.19	0.37 (–0.07 to 0.81)
Serra-Prat et al.,[30] 2017 (men)	30	28	5.13	0.31 (–0.21 to 0.83)
Serra-Prat et al.,[30] 2017 (women)	31	44	5.99	–0.15 (–0.63 to 0.33)
Kang et al.,[29] 2019 (men)	25	19	3.99	0.21 (–0.38 to 0.80)
Kang et al.,[29] 2019 (women)	41	30	5.99	0.04 (–0.44 to 0.52)
RE multilevel model for subgroup (Q = 3.28, df = 7, p = 0.9, I^2 = 0.00%)				**0.18 (–0.03 to 0.40)**
Muscle strength (nonhandgrip)				
Tieland et al.,[28,39] 2012; leg extension strength	31	31	5.99	–0.01 (–0.49 to 0.47)
Tieland et al.,[28,39] 2012; leg press strength	31	31	5.99	–0.03 (–0.51 to 0.45)
Yamada et al.,[35] 2012; knee extension torque	35	35	5.99	0.30 (–0.18 to 0.78)
Luger et al.,[31,41–44] 2016; lower limb strength	39	41	7.19	0.46 (0.02 to 0.90)
RE multilevel model for subgroup (Q = 3.13, df = 3, p = 0.4, I^2 = 33.01%)				**0.22 (–0.28 to 0.71)**
Appendicular lean mass				
Tieland et al.,[28,39] 2012	31	31	5.13	0.31 (–0.21 to 0.83)
Yamada et al.,[35] 2012	35	35	5.99	0.53 (0.05 to 1.01)
Luger et al.,[31,41–44] 2016	39	41	7.19	0.08 (–0.36 to 0.52)
RE multilevel model for subgroup (Q = 1.85, df = 2, p = 0.4, I^2 = 0.31%)				**0.29 (–0.31 to 0.90)**
RE multilevel model (Q = 9.54, df = 15, p = 0.8, overall I^2 = 0.00%)			100.00	0.19 (0.06 to 0.32)



B

Study, year; outcome measure	No. of participants: Intervention	Control	Weight, %	SMD (95% CI)
Tieland et al.,[28,39] 2012; Sit-to-Stand test	31	31	6.09	–0.37 (–0.89 to 0.15)
Tieland et al.,[28,39] 2012; gait speed	31	31	6.61	0.00 (–0.48 to 0.48)
Tieland et al.,[28,39] 2012; Short Physical Performance Battery	31	31	6.61	0.11 (–0.37 to 0.59)
Yamada et al.,[35] 2012; Sit-to-Stand test	35	35	6.63	0.09 (–0.39 to 0.57)
Yamada et al.,[35] 2012; gait speed	35	35	6.63	0.28 (–0.20 to 0.76)
Yamada et al.,[35] 2012; Timed Up and Go test	35	35	6.63	0.37 (–0.11 to 0.85)
Kwon et al.,[32] 2015; gait speed	26	28	5.57	0.11 (–0.41 to 0.63)
Luger et al.,[31,41–44] 2016; balance test	39	41	7.33	–0.09 (–0.53 to 0.35)
Luger et al.,[31,41–44] 2016; gait speed	39	41	7.33	0.27 (–0.17 to 0.71)
Luger et al.,[31,41–44] 2016; Short Physical Performance Battery	39	41	7.33	0.31 (–0.13 to 0.75)
Serra-Prat et al.,[30] 2017; gait speed	61	72	8.81	0.70 (0.36 to 1.04)
Serra-Prat et al.,[30] 2017; Timed Up and Go test	61	72	8.81	0.00 (–0.34 to 0.34)
Kang et al.,[29] 2019; Sit-to-Stand test	66	49	7.81	0.81 (0.42 to 1.20)
Kang et al.,[29] 2019; gait speed	66	49	7.81	0.53 (0.14 to 0.92)
RE multilevel model (Q = 28.76, df = 13, p = 0.007, overall I^2 = 56.89%)			100.00	0.25 (0.02 to 0.48)



C

Study, year; outcome measure	No. of participants: Intervention	Control	Weight, %	SMD (95% CI)
Luger et al.,[31,41–44] 2016; Fried's criteria (SHARE-FI)	39	41	37.50	–0.31 (–0.75 to 0.13)
Serra-Prat et al.,[30] 2017; modified Fried's criteria	61	72	62.50	–0.47 (–0.81 to –0.13)
DL RE model (Q = 0.32, df = 1, p = 0.6, overall I^2 = 0.00%)			100.00	–0.41 (–0.68 to –0.14)

D

Study, year; outcome measure	Intervention, no. of participants: Frail	Total	Control, no. of participants: Frail	Total	Weight, %	RR (95% CI)
Nykänen et al.,[34] 2012; Cardiovascular Health Study criteria	19	74	27	72	44.21	0.68 (0.42 to 1.12)
Luger et al.,[31,41–44] 2016; Fried's criteria	17	39	21	41	48.80	0.85 (0.53 to 1.36)
Serra-Prat et al.,[30] 2017; Fried's criteria	3	61	11	72	6.99	0.32 (0.09 to 1.10)
DL RE model (Q = 2.18, df = 2, p = 0.3, overall I^2 = 0.00%)					100.00	0.72 (0.52 to 1.00)

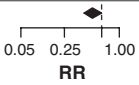


Figure 4: Effects of combined nutrition and physical activity interventions on measures of physical outcomes (A), mobility (B) and frailty (C [continuous] and D [dichotomous]). Weights are from random-effects (RE) multilevel model analysis. Note: CI = confidence interval, DL = DerSimonian and Laird, RR = risk ratio, SHARE-FI = Frailty Instrument of the Survey of Health, Ageing and Retirement in Europe, SMD = standardized mean difference.

reviews of nutrition interventions included participants who were malnourished or sarcopenic and not necessarily frail.[54–56] To address these gaps in the literature, we focused on nutrition and combined-approach studies with participants clearly identified as prefrail or frail, and looked at the benefit of these interventions for a more robust collection of outcomes.

We found mixed effects depending on intervention type and outcomes. Protein supplementation in older adults is a priority, given that many consume less than the recommended daily amounts.[25] Like other investigators,[1,50] we found that protein supplementation RCTs had significant effects on physical and mobility measures, but not frailty. It has been suggested that, for nutrition interventions to be beneficial on their own, without the addition of physical activity, the population may need to be at deficiency or malnourished[1,57] and at similar levels of baseline frailty;[1] however, there is a lack of evidence for this second hypothesis.

The importance of protein supplementation in combination with resistance exercise in healthy older adults has also been established by evidence and reviews. Our review is in agreement with those showing that nutrition interventions combined with physical activity are effective at decreasing frailty and improving gait speed, grip strength and physical performance.[48,50] Although our effect estimates for these interventions were slightly higher than those for nutrition alone, we did not see any additional outcomes of significance with these intervention types, and, overall, the effect estimates were small. Therefore, our analysis does not show that exercise adds significantly to nutrition interventions.

Although our review was selective in defining the population of interest, research is still lacking in the explicit identification of prefrail and frail older adults, and consistency in how these tools are applied. Very few researchers in our review measured frailty as a postintervention outcome. Likewise, the wide range of outcome measures that were used across studies may reflect the lack of clarity in frailty identification and diagnosis. Owing to this lack of clarity, we could not evaluate the effectiveness of interventions by level of frailty, which affected our interpretation of the clinical effectiveness of the studies. However, our use of SMDs provides a magnitude of the effect, which has implications for clinical practice. Well-designed clinical trials that have clear definitions of frailty and use outcomes reflecting frailty identification and diagnosis are needed to inform interventions that prevent or delay frailty progression in older adults.

Limitations

Although our search was comprehensive, we did not explicitly search the literature for combined interventions that included nutrition with physical activity components, so we may have missed potentially relevant studies. We used the strict criterion of frailty in an attempt to identify a more homogeneous population, but it led to a large number of exclusions, which may have included potentially frail populations or those with overlapping conditions. We extracted outcomes immediately after interventions, which leaves the long-lasting effects of these interventions unknown. The protocol of our review has limitations, including restriction to English-language citations, our search end date of July 2019 and the fact that we did not search the grey literature. Last, although we did not observe any significant asymmetry across funnel plots for publication bias, studies were small (< 250 participants) and had risk of bias concerns. The small samples also meant that prefrail and frail participants were grouped together, which did not allow for subanalysis on frailty level.

Although there may be concerns about the reuse of the same participants from the same study to contribute data for multiple measures of a given outcome, our group agreed that this approach is preferred over selective reporting of effect sizes for a given outcome or averaging outcome measures from the same study to conduct a conventional 2-level meta-analysis. Both selective reporting (i.e., choosing 1 outcome measure for a given outcome) and averaging all outcome measures result in the potential loss and dilution of relevant information, and may produce misleading, inaccurate and biased results. These ad hoc approaches may also lead to missed opportunities to use all available data to address the relevant research questions.[58]

Conclusion

This review adds to the body of evidence identifying interventions that benefit components of frailty, such as physical and mobility outcomes, and frailty itself. However, our use of a strict inclusion criterion that identified a prefrail or frail population shows that future studies need to better define frailty, to ensure improved identification of older adults who would benefit from such interventions. This would facilitate the adoption and implementation of effective interventions into clinical practice.

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