Special Article

Nutritional Interventions for the Management of Frailty in Older Adults: Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Abstract

Context: Although nutrition is considered an important intervention for the management of frailty, the actual effectiveness of interventions addressing nutrition in frail older people remains unclear. **Objective:** This systematic review aimed to appraise the evidence regarding the effectiveness of nutritional interventions for the management of frailty in older adults. **Data sources:** The MEDLINE, Embase, CINAHL, CENTRAL, Web of Science and LILACS were searched from January 2001 to November 2019. **Data extraction:** We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Two independent reviewers extracted relevant data. From 2,370 initial records, 19 publications presenting data from 17 studies (1,564 individuals, follow-up: 7 to 96 weeks) were included. **Data analysis:** None of the Bayesian random-effects meta-analyses comparing nutritional supplements with placebo regarding mortality, body mass index, weight, frailty status, muscle strength, gait speed, body composition, and cognitive function showed statistically significant differences. The same applies to a single meta-analysis comparing nutritional education with general health advice regarding muscle strength. **Conclusion:** Our results suggest, mostly with low to very low degrees of certainty, that nutritional supplements or nutritional education delivered in isolation may not be effective for the management of frailty in older people. **Review registration number:** CRD42018111510 (PROSPERO). **Funding:** CAPES (Coordination for the Improvement of Higher Education Personnel – Ministry of Education, Brazil). The sponsor did not play any role concerning study design, data collection and analysis, manuscript preparation, revision and publication decision.

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1. Introduction

Frailty is a clinical syndrome of multicausal origin characterized by a reduction of physiological reserves that increases the vulnerability of an individual to adverse outcomes[1] such as falls,[2] hospital admission,[3] disability[4]and death.[5,6].Frailty has been argued as a clinical marker of biological aging[7] and is considered one of the most important geriatric syndromes.[8].Indeed, the prevention and management of frailty represent important goals of gerontology and geriatrics.

Weight loss, along with the reduction of strength, mobility, and immune dysfunction, represents a typical characteristic of frailty.[9]Nutrition provides energy and essential nutrients and helps the human body to function properly and maintain homeostasis.[10] Despite a limited understanding of the underlying mechanisms linking individual nutrients with frailty, poor nutritional status has been associated with a greater risk of frailty.[11]Besides, there is an overlap between frailty and malnutrition, although they are considered distinct clinical entities.[11]Furthermore, malnutrition is associated with sarcopenia,[12]defined by low muscle strength, low muscle quantity and quality, and low physical performance, leading to poor clinical outcomes.[13]

It has been suggested that frailty can be reversed with appropriate nutritional interventions.[14]The Mediterranean diet, the consumption of fruits, vegetables and protein have all been associated with a lower risk of frailty in observational studies.[15–17]The role of nutrition as a potentially modifiable risk factor is therefore of great interest in designing interventions to halt the progression of frailty.

Although several systematic reviews of randomized clinical trials (RCTs) on the management of frailty have been published,[18–27]those reviews emphasized interventions associated with physical activity and exercise whilst nutritional interventions were assessed briefly and in a secondary manner, if at all. Hence, although nutrition is considered an important intervention

for the management of frailty, the actual effectiveness of interventions addressing nutrition in frail older people remains unclear. Therefore, the aim of the present systematic review of randomized clinical trials, which was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, was to appraise the evidence regarding the effectiveness of nutritional interventions for the management of frailty in older adults.

2. Methods

2.1 Data Source and Search Strategy

We searched the following 6 databases for RCTs of nutritional interventions for the management of frailty in older people: Embase, MEDLINE, Lilacs, CENTRAL (Cochrane Central Register of Controlled Trials), CINAHL (Cumulative Index to Nursing and Allied Health Literature) and Web of Science. We searched for studies published from January 2001 onwards because the most commonly used frailty criteria were first published in 2001.[28,29] The full search strategy is presented in the published protocol[30]. We reviewed reference lists of included studies and searched the following databases for gray literature: System for information on Gray Literature in Europe, Virginia Henderson Global Nursing e-Repository, National Library of Medicine Bookshelf. We also searched ClinicalTrials.gov and the World Health International Clinical Trials Registry Platform for protocols of RCTs. Searches were updated on November 21, 2019. The protocol of this review was registered at PROSPERO (CRD42018111510) and published elsewhere.[30]

2.2 Study Selection

Two reviewers (MB, EIOV) independently screened titles, abstracts, and full texts to ascertain the eligibility of the studies identified in the literature search. The same reviewers independently extracted data from included studies and evaluated risk of bias. Disagreements were resolved by discussion with a third reviewer (CA). Studies were included if they

involved people living at home or in long-term care facilities aged 60 years and older and a diagnosis of frailty or pre-frailty according to any criteria used in the original studies to diagnose that syndrome. Only RCTs were included that implemented at least one of the following nutritional interventions: nutritional education / dietary prescription (e.g. workshops), the use of energy and/or protein dietary oral supplements and the delivery of specific diets. For the purposes of this review we defined protein and energy nutritional supplements as dietary supplements intended to provide nutrient-dense solutions in terms of protein or calorie content, respectively, which are provided as ready to drink liquids, powder or creams, that can be consumed directly or added to foods and drinks. Additionally, we included studies that adopted any of the above interventions concomitantly with another single or multifactorial intervention, as long as the comparator was the same set of interventions without the nutritional intervention component (e.g. physical activity + nutritional intervention compared with physical activity alone). We accepted as comparators the standard of care, placebo, other nutritional interventions, and multifactorial interventions without a nutritional component. We did not impose language restrictions on the selection of studies for this review.

We excluded studies that only included older adults without a diagnosis of frailty or whose nutritional interventions consisted of supplementation of micronutrients alone or other compounds that were not part of protein and/or energy supplements. Further information about the PICOS (Population, Intervention, Comparison, Outcomes, and Study design) criteria is available in Table 1.

2.3 Risk of bias and Methodological Quality Assessment

We used the new Cochrane Risk of Bias tool for RCT (RoB 2)[31] to assess the risk of bias in the included studies. That tool categorizes risk of bias in one of three categories ("low", "some concerns", or "high") for each of the following domains: randomization process,

deviations from intended interventions, missing outcome data, outcome measurement, and the selection of reported results. The combined assessment of those five domains generates an overall risk of bias assessments. For the assessment of deviations from intended interventions domain of risk of bias we adopted the assignment to intervention / intention-to-treat perspective. Additionally, we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to rate the overall certainty (or quality) of the evidence for each outcome.[32,33]The GRADE system evaluates the following dimensions regarding the certainty of evidence: study limitations/risk of bias, inconsistency, indirect effects, inaccuracy, publication bias, and factors that may increase the quality of evidence. According to that system, the certainty of the evidence regarding each outcome is classified into one of four levels: high, moderate, low and very low. Further details regarding the methods of this review are available from our protocol.[30]

2.4 Statistical Analysis

Because the original studies reflected different populations and methods and few studies were eligible to be included in meta-analyses, we decided to perform Bayesian random-effects meta-analyses instead of the more common frequentist fixed-effect or DerSimonian & Laird random-effects methods.[34–36]Bayesian statistics is a different approach to statistics from that of usual frequentist methods. Its most fundamental aspect involves the updating of evidence. In Bayesian statistics the initial uncertainty about a given quantity of interest (e.g. the effect size of an intervention or the amount of heterogeneity across studies) is expressed by a prior distribution, which is updated by the information derived by the empirical data under the form of a likelihood function, so that the combination of the prior distribution and the likelihood function yield a posterior distribution, which reflects the updated degree of uncertainty about that quantity.[37]Frequentist random-effects meta-analyses using the DerSimonian and Laird estimator for between-studies variance (τ^2) are known to underestimate the degree of

statistical uncertainty in the context of meta-analyses with few studies.[36] Bayesian methods are particularly advantageous in such a context because they are able to increase the precision of the between-study variance in a meta-analysis by benefiting from the existing knowledge summarized in libraries of data-based prior distributions of between-studies variance derived from re-analyses of several thousands of meta-analyses from the Cochrane Collaboration.[38,39]Another important advantage of Bayesian methods is that the degree of uncertainty of its estimates are expressed under the form of Credible Intervals (CrI), whose interpretation is much more intuitive than that of Confidence Intervals (CI). For example, a 95% CrI of a risk ratio of 1.13 to 1.50 means that there is a 95% probability that the true risk ratio lies in that interval. On the other hand, the interpretation of a 95% CI is that if we repeated the same experiment an infinitely large number of times with different samples from the same population, we would expect the true effect to fall within the interval estimates 95% of the time.[40]

We performed Bayesian random-effects meta-analysis via the Divergence Restricting Conditional Tesselation algorithm.[41,42] That approach to Bayesian meta-analysis does not entail the use of Markov Chain Monte Carlo computation and has been shown to have advantages over frequentist approaches in meta-analytical settings of few studies.[43–45]We used a uniform noninformative prior for the pooled estimate and informative priors for the between-study heterogeneity parameter τ described by Rhodes et al[39] for continuous outcomes and by Turner et al for dichotomous outcomes[38] based on the assessment of several thousands of meta-analyses from the Cochrane Collaboration. More specifically, for frailty scores, strength, walking speed, Short Physical Performance Battery (SPPB) and physical activity outcomes we used the τ prior associated with "general physical health and adverse event and pain and quality of life/functioning" and non-pharmacological interventions described in table 3 of Rhodes.[39] For the outcomes related to body composition, we used the τ

prior associated with the "biological marker" outcome and non-pharmacological interventions described in the same table of that study. For the cognitive outcomes, we used the τ prior for a general setting without taking into account other meta-analysis characteristics reported in section 3.3 of that same article. In regard to the meta-analyses with dichotomous outcomes, for the mortality and frailty status outcomes we used the informative priors for τ^2 associated with all-cause mortality and general physical health indicators in the context of non-pharmacological interventions vs placebo/control described in table 4 of Turner et al.[38].We used Standardized Mean Differences (SMD) whenever studies included in a meta-analysis reported results using different scales. We interpreted SMD as follows: 0 to 0.20: little to no difference; 0.21 to 0.79: moderate difference; and 0.80 or higher as major differences.[46]

We calculated both pooled estimates with 95% CrI for pooled mean differences (MD) or SMD or odds ratio (OR) and prediction intervals as recommended by Higgins[35] and Guddat.[47] Prediction intervals refer to the predicted effect estimates of new studies that are considered sufficiently similar to be eligible for inclusion in future meta-analyses of the same outcome. We considered the following values as the minimally clinically significant differences for Barthel index, 36-Item Short Form Survey (SF-36), gait speed, strength, SPPB and frailty score (from the Cardiovascular Health Study [CHS] frailty phenotype), respectively: 1.85 point, 4.9 point, 0.20m/s, 5.0kg, 0.3 point, and 0.3 point.[48–53] Meta-analyses were performed using the R software version 3.6.2 employing the metafor[54] and bayesmeta packages.[41] Whenever possible we performed pre-specified subgroup analyses regarding the criteria used to diagnose frailty, types of nutritional supplements and risk of bias of studies included in meta-analyses. The subgroup analyses were performed through the beanz R package[55] using Bayesian models with full stratification with weakly informative priors (mean: 0, Variance: 1000)[56] using 4 chains, 4000 iterations, a warm-up interval of 2000 and a thinning parameter

of 2. Trace plots and the Gelman-Rubin statistic were examined to assess the estimates for convergence.

Because one[57] of the included studies was a cluster randomized clinical trial, when the results of that trial were included in meta-analyses, in order to avoid the occurrence of unit-of-analysis error, we corrected its sample size using the design effect formula recommended by the Cochrane Collaboration[33]. Because that study did not report any Intracluster Correlation Coefficient (ICC), for the calculation of the design effect correction factor we imputed ICC values observed in another cluster randomized clinical trial of a nutritional intervention in long-term care facilities.[58]

We performed funnel plots and the Egger test to investigate small-study effects when 10 or more studies were included in a meta-analysis.

2.5 Changes to the review protocol

We implemented some changes to our review protocol. We decided not to exclude studies based on its language of publication. We added falls, hospitalizations, Body Mass Index (BMI) and body weight as secondary outcomes. Whenever feasible, we performed the following subgroup analyses that had not been pre-specified in our protocol according to type of funding, whether the study population included individuals with pre-frailty or not. We also performed sensitivity analyses that had not been pre-specified in our protocol. The addition of the body weight and BMI outcomes, and the new subgroup and sensitivity analyses were done at the request of the thoughtful peer reviewers who assessed our manuscripts. All changes implemented to our protocol were performed with the intent of improving the quality of our review and did not take into account the presence of statistical significance in any new analyses.

3. Results

3.1 Selection Process and Study Characteristics

Figure 1 presents the flow diagram of the study selection process. We included 19 publications from 17 studies (1,564 older people with a mean follow-up ranging from seven to 96 weeks). A list of the 57 studies excluded after appraisal of their full texts, with reasons for exclusion, is available in Supplementary Table S1. With the exception of one study[57] that was a cluster randomized clinical trial, all remaining studies were individually randomized controlled trials. The main characteristics of the 19 included publications are summarized in Table 2[57,59–75] and details concerning their results can be found in Supplementary Table S2. Most studies[57,59–68] included only frail individuals, two studies[69,70] included only pre-frail individuals and six studies[14,71–75] included participants with both frailty and pre-frailty. The criteria used by each study to diagnose frailty and pre-frailty are described in detail in Suplementary Table S3. None of the included studies were focused on populations with specific comorbidities and several of them excluded patients with cancer (nine studies),[14,59–61,63,64,66,71–74] chronic renal failure (seven studies),[65–67,71–74] diabetes (six studies)[62,67,71–74] and neurologic impairment (seven studies).[62,67,69,71–74] Only one study[66] explicitly allowed the inclusion of patients with cancer or kidney failure, although it is not clear from its report how many participants had those conditions. We present details regarding the comorbidities included/allowed and excluded in each original study in Supplementary Table S4. Eight studies[14,68,69,71–75] used the CHS frailty criteria to define physical frailty based on the following five criteria: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, low physical activity.[28] One study[59,60,63] defined frailty based on the Chin A Paw criteria.[76] One study[70] used a modification of the CHS frailty criteria. Seven studies[57,61,62,64–67] did not use specific instruments to diagnose frailty. In those studies, frailty was defined in general according to the presence of a variety of characteristics such as undernutrition, weight loss, slow gait speed and/or impaired function. Only one of the included studies was restricted to older people with frailty and obesity (BMI $\geq$ 30 kg/m^2).[65]

Regarding the setting of the included studies, 14 studies recruited participants living in the community,[14,59,60,63–66,69–75] three,[57,61,67]studies recruited participants from long-term care facilities, one study included both participants living in long-term care facilities and the community,[62] and another study[68] did not provide a clear description about whether its participants were living in the community or in long-term care facilities (Table 2[57,59–75]). The proportion of women in the included studies ranged from 36% to 100%, and the mean age of participants ranged from 68 to 84 years. With the exception of one study whose participants were restricted to older adults with obesity,[65] the mean BMI of participants in the included studies ranged from 20.1 to 28.7 kg/m². Further details regarding the baseline characteristics of participants of the studies included in our review are shown in Supplementary Table S5.

In 15 of 17 studies the nutritional intervention consisted of nutritional supplements[14,57,61,62,64–69,71–75]and in the two remaining studies[59,60,63,70]the intervention was nutritional education. Five[14,62,68,69,71]of the 15 studies that used nutritional supplements and the two studies[59,60,63,70] that used nutritional education did so in the context of multifactorial interventions where those nutritional interventions were combined with exercise and compared with control interventions without nutritional components (Table S6). Six[68,71–75] studies used only protein supplements, seven other studies[57,57,62,64–67,69] used both energy and protein supplements, and two[14,61] study used only energy supplements. The median protein and energy content of supplements were 15g (interquartile range [IQR]: 11 to 15g) and 275 kcal (IQR: 225 to 300 kcal), respectively. Of the 14 studies that involved protein supplementation, eight studies[57,64–67,71,74,75] offered supplements at least twice daily, three studies[62,72,73] offered them only once daily, and two studies[68,69] did not provide information about the daily frequency at which supplements were dispensed or expected to be consumed. Only 5 studies[57,65,66,69,75] provided information on the total amount of protein consumed by study participants per day (i.e. from both supplements and other dietary sources) at the end of the intervention period (range: 1.2

to 1.5 g/kg/day) in the nutritional supplementation treatment groups. Only one study[75] provided information on the total amount of protein consumed per day by the control group at the end of the intervention period (0.8 g/kg/day). In regard to the comparators used in the 17 included studies, ten studies[14,61,62,65,67,71–75] used a placebo supplement, three studies[59,60,63,69,70] used general health advice, one study[68] used dietary counselling, in two studies[64,66] the control group did not receive any treatment, and in one final study[57] the comparator group received the same standard diet based on the German reference values that the intervention group received but without protein supplementation. Further details concerning the nutritional interventions (e.g. protein and energy content of supplements) and comparators are shown in Table 2[57,59–75].

Regarding the compliance rate of study participants to the nutritional interventions, six studies[59–61,63,65,66]reported compliance rates > 50% at end of the follow-up, 9 studies[14,62,64,67,69,71,73–75] reported compliance rates > 90% at end of the follow-up, and two studies[68,70] did not provide information on that matter.

Of the 15 studies that used nutritional supplements eleven studies[14,57,64–67,71–75]used commercial formulas as their nutritional intervention and eight[57,61,62,64,65,67,71,72]of them were funded by industry. Details about which commercial formulas were used and funding sources of individual studies are shown in Supplementary Table S7.

Baseline differences between intervention and control groups were observed in only one study,[59] where there were more subjects with high school and/or university degrees in the control group compared with the nutritional intervention group.

3.2 Risk of bias and Quality of Evidence

Figure 2[57,59–75] describes the assessment of risk of bias of individual studies. The overall classification of risk of bias for nine studies (11 publications) was considered high,[57,59,60,63–70] as posing some concerns for three,[14,61,62] studies and as low for five studies.[71–755] Main

reasons for classifying studies as having a high risk of bias were issues related to the deviations from intended interventions and the randomization process domains of the risk of bias assessment . We present Summary of Findings tables with the classification of the overall certainty of evidence in accordance with the GRADE32 approach for each outcome across studies in Supplementary Table S8 and Table S9. The certainty of evidence for all but two outcomes was classified as very low or low. Only the language and executive function component of the cognitive outcome and the fat mass component of the body composition outcome were classified as reflecting evidence of moderate certainty. The main reasons for downgrading the quality of evidence were imprecision of findings related to small sample sizes, confidence intervals encompassing both significant benefits and harms and risk of bias in individual studies.

3.3 Outcomes

3.3.1 Mortality

Although none of the included studies specified mortality as an outcome, we were able to extract data on the number of patients who died in the treatment and control arms of seven[14,64,66,69,72,74,75]of the 15 studies that compared nutritional supplements with placebo or no treatment. Considering all seven studies together, there were two deaths among 217 participants in the nutritional supplements arms and two deaths among 2016 individuals in the control groups. The meta-analysis of those studies did not show any significant difference between intervention and control groups (517 subjects; OR = 1.01, 95% CrI: 0.27 to 3.80; τ = 0.125, I^2 = 0.4%, GRADE: Low) (Figure 3[14,64,66,69,72,74,75], Supplementary Table S9).

We were able to perform two pre-planned subgroup analyses for the mortality outcome, one regarding risk of bias (Supplementary Figure S1A) and another concerning the type of nutritional supplement used (Supplementary eFi

gure 1B). In addition, at the request of peer reviewers of the present report we performed two other non-previously planned subgroup analyses regarding the type of funding of studies (Supplementary Figure S1C) and whether studies had included individuals with pre-frailty or not (Supplementary Figure S1D). supplement. None of those four subgroup analyses disclosed any significant difference between subgroups.

3.3.2 Quality of life

One study[64] evaluated the effect of a nutritional supplement on the quality of life of older people with frailty or pre-frailty in comparison with no treatment and did not find any statistically significant difference on quality of life measured by the SF-36 instrument (89 subjects; Mean Difference [MD]: 8.7; 95% CrI: -6.01 to 23.41; GRADE: low) (Supplementary Table S9). Another study[70] compared a nutritional education intervention in association with once-weekly supervised exercise against the same exercise program without the nutritional education component and did not disclose any statistically significant difference between those groups at 3 months for any of the domains of the SF-36 (GRADE: very low) (Supplementary Table S8).

3.3.3 Functioning

3.3.3.1 Nutritional Supplements and Functioning

Activities of Daily Living

We found studies reporting on the following measures of functioning: Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL), gait speed, strength, and the SPPB. Two studies assessed the effectiveness of nutritional supplements on ADL and IADL.[14,69] One study[69] compared a nutritional supplement in association with a supervised exercise program against the same exercise program combined with nutritional counselling and identified a clinically minor but statistically significant difference favoring the use of the nutritional supplement only on the Barthel ADL index after 12 weeks of follow-up (median

scores of 3.0 and 1.5 in the treatment and control groups, respectively, p<0.001). The other study[14] compared a nutritional supplement with placebo and did not find any significant difference regarding the composite outcome measure of ADL and IADL dependence after 12 months of follow-up (99 subjects; Risk Ratio [RR]: 1.02; 95% CI: 0.22 to 4.81). The overall certainty of evidence for nutritional supplements regarding the ADL / IADL outcome was rated as very low (Supplementary Table S9).

Gait Speed

The meta-analysis of seven RCTs[14,66,67,69,73–75] comparing nutritional supplements with placebo or no treatment regarding gait speed did not show any statistically significant difference between those groups (473 subjects; MD = 0.04; 95% CrI: -0.01 to 0.10; τ = 0.027, I^2 = 14.6%; GRADE: low) (Figure 4A[14,66,67,69,73-75]; Table S9).

We were able to perform two pre-planned subgroup analyses for the gait speed outcome regarding risk of bias (Supplementary Figure S2A) and type of nutritional supplement (Supplementary Figure S2B). At the request of peer reviewers of our article, we were also able to perform a non-previously planned subgroup regarding whether individual studies had included only patients with frailty or also with pre-frailty diagnoses (Supplementary Figure S2C). None of the effect sizes of the subgroups examined were significantly different from each other.

Muscle Strength

The meta-analysis of ten studies that compared nutritional supplements with placebo or no treatment in terms of muscle strength with a follow-up of 12 weeks[14,57,64,66–69,73–75] did not find any statistically significant difference between those two groups (674 subjects; SMD: -0.03; 95% CrI: -0.22 to 0.16; τ = 0.113, I^2 = 17,5%; GRADE: low) (Figure 4B[14,66,67,69,73-75]; Supplementary Table S9).

We performed four pre-planned subgroup analyses for the strength outcome regarding the following study characteristics: criteria used to diagnose frailty (Supplementary Figure S3A), type of nutritional supplements used (Supplementary Figure S3B), risk of bias (Supplementary Figure S3C), and whether studies were conducted in the community or in a long-term care facility (Supplementary Figure S3D). Additionally, at the request of peer-reviewers of this article, we were able to perform two subgroup analyses that had not been pre-specified concerning the type of funding (Supplementary Figure S4A) and whether studies had included individuals with pre-frailty or not (Supplementary Figure S4B). None of the six subgroup analyses that we performed disclosed any significant differences between subgroups.

The funnel plot of the meta-analysis comparing nutritional supplements with placebo regarding muscle strength at 12 weeks of follow-up revealed an important asymmetry (Supplementary Figure 5). The Egger's test for small-studies effect was also statistically significant ($P < 0.001$). While examining possible causes for the asymmetry in the funnel plot, we identified that the studies that were mostly responsible for the asymmetry had high risk of bias. Besides, we found that publication bias was an unlikely cause for the asymmetry observed in the funnel plot because the symmetric counterpart of the most extreme study[67] of that plot would have been statistically significant. Hence, we considered that the high risk of bias in the smallest studies was the most likely reason for the asymmetry observed in that plot. Accordingly, we performed a sensitivity analysis by repeating the meta-analysis using a fixed effect model (Supplementary Figure S6), which did not change the overall interpretation of our results. We did not perform another sensitivity analysis restricted to studies with low risk of bias because a subgroup analysis reported in a previous paragraph had already examined that perspective and did not find any significant differences between subgroups (Supplementary Figure S3C).

Four studies[14,67,73,74] also reported on muscle strength with a follow-up of 24 weeks or longer and the meta-analysis of those studies also did not show any statistically significant difference between the intervention and control groups (260 subjects; SMD: 0.09; 95% CrI: -0.21 to 0.39; τ = 0.102, I^2 = 14.1%) (Supplementary Figure S7A).

Short Physical Performance Battery

The meta-analysis of four studies[66,73–75]comparing nutritional supplements with placebo or no treatment regarding physical performance using the SPPB instrument to assess functioning also did not find any statistically significant difference between the two groups (287 subjects; SMD = 0.30; 95% CrI: -0.32 to 1.02; τ = 0.225, I^2 = 17.1%; GRADE: very low) (Figure 4C[66,73-75]; Supplementary Table S9).

3.3.3.2 Nutritional Education and Functioning

Activities of Daily Living

A single study[60] compared nutritional education with general health advice and did not find any differences in ADL (34 subjects; median Functional Impairment Measure [FIM] value for the nutritional education and control groups were 87 with an IQR of 83 to 89, and 88 with an IQR of 84 to 89, respectively), and IADL (34 subjects; median Instrumental Activity Measure [IAM] value of 37 with an IQR of 31 to 41 for the treatment group and 40 with an IQR of 34 to 47 for the control group). The quality of evidence for that dyad of outcomes and intervention was graded as low (Supplementary Table S8).

Muscle Strength

The meta-analysis of two studies[59,70] comparing nutritional education with general health advice in terms of muscle strength with a follow-up of 24 weeks did not find any statistically significant difference between those groups (92 subjects; SMD = -0.30; 95% CrI: -0.95 to 0.35; τ = 0.16, I^2 = 22.3%; GRADE: very low) (Figure 4D[59,70]; Supplementary Table S8).

3.3.4 Physical activity

3.3.4.1 Nutritional Supplements and Physical Activity

The meta-analysis of two studies[14,75] comparing nutritional supplements with placebo did not show any statistically significant difference on physical activity scores with a follow-up period of 12 weeks (175 subjects; SMD: -0.05; 95% CrI: -0.69 to 0.58; τ = 0.182, I^2 = 41.8%; GRADE: low) (Figure 5A[14,75]; Supplementary Table S9).

3.3.4.2 Nutritional Education and Physical Activity

A single study[60] of 31 participants compared nutritional education with general health advice regarding the level of physical activity with a follow-up period of nine months and did not find any statistically significant difference between the two groups (the median physical activity level value for the treatment and control groups were 3, IQR: 2 to 3 in a 6-graded scale). The frequency of walking habits (the median value for the treatment and control groups were 6 [IQR: 4 to 6] and 6 [IQR 5 to 6] in a 7-point ordinal scale, respectively) and its duration (the median value for the treatment and control groups were 2 [IQR: 2 to 2] and 2 [IQR: 2 to 3] in a 5-point ordinal scale, respectively) also were not statistically significant. We graded the quality of evidence of nutritional education for those outcomes as very low (Supplementary Table S8).

3.3.5 Frailty

The meta-analysis of three studies[14,69,75] comparing nutritional supplements with placebo regarding frailty status (number of individuals with frailty) as defined by the CHS criteria did not find statistically significant differences between those groups (215 subjects; Odds Ratio = 2.30; 95% CrI: 0.72 to 7.01; τ = 0.269, I^2 = 5.8%, GRADE: very low) (Figure 5B[14,69,75]; Supplementary Table S9). The meta-analysis of two studies[14,75]comparing nutritional supplements with placebo regarding frailty score as defined by the CHS criteria also did not find statistically significant differences between those groups (175 subjects; MD = 0.09; 95% CrI: -0.45 to 0.62; τ = 0.146, I^2 = 33.2%) (Figure 5C[14,75]).

3.3.6 Cognitive function

Three studies[61,71,72] compared nutritional supplements with placebo regarding cognitive function using a variety of cognitive tests. We were able to pool the results of those studies for two tests assessing declarative memory (Word Learning Test [WLT] delayed and immediate recall) (225 subjects; SMD: 0.03; 95% CrI: -0.31 to 0.36; τ = 0.108, I^2 = 14.1%; and 238 subjects; SMD: 0.26; 95% CrI: -0.14 to 0.65; τ = 0.174, I2 = 30.6%; respectively, GRADE: low) (figure 5D[61,71,72] and Supplementary Figure S7B and ; Supplementary Table S9), and for two other tests evaluating language and executive function (Verbal Fluency test for the following categories: professionals and animals) (238 subjects; MD: 0.87; 95% CrI: -0.28 to 1.94; τ = 0.2, I^2 = 3.8%; and 238 subjects; MD: 0.45; 95% CrI: -0.58 to 1.49; τ = 0.148, I^2 = 2%; GRADE: moderate) (Supplementary Figure S7C and 7D; Supplementary Table S9). None of the meta-analyses of the results of the cognitive tests described above showed any statistically significant differences between the intervention and control groups. As for the assessment of other cognitive domains for which we were not able to pool results across studies, none of them showed statistically significant differences between the nutritional supplementation and the placebo groups in any of the individual studies.

3.3.7 Body Composition

3.3.7.1 Nutritional Supplements and Body Composition

Five studies[57,67,73–75] compared nutritional supplements with placebo regarding body composition outcomes. We were able to pool results regarding appendicular lean mass, which did not show any significant difference between intervention and control groups (198 subjects; MD = 0.60 kg, 95% CrI: -0.82 to 2.01; τ = 0.156, I^2 = 1.7%; GRADE: low) (Figure 6A[73-75]; Supplementary Table S9). The meta-analysis of the results of two studies[73,74] concerning total fat mass also did not show any statistically significant difference between intervention and control groups (118 subjects; MD = 1.67 kg, 95% CrI: -0.63 to 3.96; τ =

0.176, I^2 = 0.8%; GRADE: moderate) (Figure 6B[73,74]; Supplementary Table S9). The meta-analysis of the results of two studies[57,67] concerning fat-free-mass also did not show any statistically significant difference between the two groups (94 subjects; MD = 1.41 kg, 95% CrI: -0.00 to 2.76; τ = 0.173, I^2 = 1.3%; GRADE: very low) (Figure 6C[57,67]; Supplementary Table S9).

3.3.7.2 Nutritional Education and Body Composition

A single study[63] compared nutritional education with general health advice regarding the total fat-free mass of patients and did not find a statistically significant difference between groups (48 subjects; MD: 0.6 kg; 95% CrI: -1 to 2.2; GRADE: very low) (Supplementary Table S8).

3.3.8 Falls

A single study study[14] comparing nutritional supplement with placebo assessed the occurrence of falls at 3, 6 and 12 months of follow-up and did not find any significant difference between the two groups at any of those time points. At 12 months of follow-up there were 4 (8.3%) and 5 (10.4%) participants reporting the occurrence of falls in the intervention and control groups, respectively (RR: 0.82, 95% CI: 0.23 to 2.87, P: 0.75) (GRADE: low) (Supplementary Table S9).

3.3.9 Hospitalization

A single study[14] comparing nutritional supplement with placebo assessed the occurrence of hospitalization at 3, 6 and 12 months of follow-up and did not find any significant difference between the two groups at any of those time points. At 12 months of follow-up there were 1 (2.1%) and 2 (4.2%) participants who had experienced a hospitalization episode in the intervention and control groups, respectively (RR: 0.51, 95% CI: 0.05 to 5.45, P: 0.57) (GRADE: low) (Supplementary Table S9).

3.3.10 Weight

Five studies[57,64,66,73,74]compared nutritional supplements with placebo or no treatment. The meta-analysis of those studies did not show any significant difference between the intervention and control groups (346 subjects; MD = 2.09 kg, 95% CrI: -0.20 to 4.39; τ = 0.158, I^2 = 0.4%, GRADE: low) (Figure 6D[57,64,66,73,74]; Supplementary Table S9).

We performed three pre-planned subgroup analyses for the strength outcome regarding the following study characteristics: criteria used to diagnose frailty (Supplementary Figure S8A), risk of bias (Supplementary Figure S8B), and type of nutritional supplements used (Supplementary Figure S8C), Additionally, at the request of peer-reviewers of this article, we were able to perform two subgroup analyses that had not been pre-specified concerning the type of funding (Supplementary Figure S8D) and whether studies had included individuals with pre-frailty or not (Supplementary Figure S9A). None of the five subgroup analyses that we performed disclosed any significant differences between subgroups.

3.3.11 Body Mass Index

Two studies[14,57]compared nutritional supplements with placebo or no treatment. The meta-analysis of those studies did not show any significant difference between intervention and control groups (143 subjects; MD = 0.03 kg/m², 95% CrI: -1.41 to 1.46; τ = 0.154, I^2 = 2.8%, GRADE: Low) (Figure S9B; Supplementary Table S9).

3.4 Sensitivity analyzes

We performed several sensitivity analyses which involved restricting some meta-analyses to studies whose mean age of participants was above 75 years (Sluplementary Figures S10, S11, S12 and S13); excluding one study whose inclusion criteria had allowed the participation of patients with cancer (Supplementary Figures S14, S15, S16, S17 and S18); excluding studies with high risk of bias or some concerns on that domain (Supplementary Figures S19, S20, S21, S22 and S23); excluding studies that included individuals with pre-frailty (Supplementary Figures S24 and S25); excluding studies that allowed the inclusion of

participants with pre-frailty (Supplementary Figures S26, S27, S28 and S29); restricting analyses to studies that used protein supplements (Supplementary Figures S30, S31, S32, S33 and S34); excluding studies where nutritional interventions were implemented in the presence of co-interventions (Supplementary Figures S35, S36, S37, S38, S39, S40, S41 and S42); studies that used CHS criteria to ascertain the presence of frailty (Supplementary Figures S43, S44, S45, S46, S47 and S48); excluding studies funded by industry (Supplementary Figure S49); and excluding studies performed in long-term care facilities (Supplementary Figures S50, S51, S52, S53, S54 and S55).

With only one exception, none of our sensitivity analyses were associated with a change in the interpretation of our original results. The exception was the sensitivity analysis where the meta-analysis comparing nutritional supplements with placebo or not treatment regarding the weight outcome was restricted to studies whose participants lived in the community (210 subjects; MD: 2.70 kg, 95% CrI: 0.14 to 5.25, τ = 0.158, I2 = 0.3%).

4. Discussion

This systematic review identified 19 references reporting on 17 randomized trials that included a total of 1,564 older people with a mean follow-up between 7 and 96 weeks and found no statistically significant effect of nutritional supplementation or nutritional education regarding any of the outcomes that were assessed in our meta-analyses. The level of certainty associated with these findings was low to very low regarding all outcomes with only two exceptions, fat mass and the verbal fluency test, for which the level of certainty was classified as moderate.

Our results are consistent with those of three recent systematic reviews.[26,77,78] Dedeyne et al[73] compared multi-domain interventions with single-domain interventions for the management of frailty. Although the authors of that review were not able to perform meta-analyses, they argued for a tendency for more beneficial effects related to multi-domain interventions in

comparison with single-domain interventions. Yoshimura et al[78] evaluated the effectiveness of interventions to treat sarcopenia and also found that nutritional supplements in isolation were not effective in improving body composition, grip strength and walking speed. Although the authors of that review suggested that nutritional interventions were effective in improving knee extension strength, such conclusion was not supported by a careful reassessment of the results of the four studies that examined that outcome through a single meta-analysis using SMD.[78] Finally, Negm et al[26] performed a systematic review with network meta-analysis comparing a variety of interventions for the management of frailty regarding the following outcomes: frailty, cognition, depression, quality of life, mental and physical domains of quality of life, adverse events, and serious adverse events. Although that review considered any nutritional intervention (i.e. from parenteral nutrition to supplementation of vitamin D and other individual micronutrients), in any setting (i.e. ranging from hospital to the community), and included only one of the studies included in our review, none of the six network meta-analyses comparing nutritional interventions alone with placebo or standard treatment disclosed any statistically significant difference.

A recent systematic review by Apóstolo et al[27]on a wide range of interventions to prevent the progression of pre-frailty and frailty in any setting (i.e. ranging from hospital to the community) concluded that nutritional supplementation is an effective intervention for increasing physical activity and for reducing long-term exhaustion. However, that review did not perform a single meta-analysis and that conclusion was based on the results of only three RCTs of nutritional interventions in isolation compared with placebo or no treatment. Our review included two of those studies[14,66] and excluded the third[79]because the nutritional supplement used in that study was neither a protein nor an energy supplement.

4.1 Strengths and limitations of this review

Our review has some potential limitations. Frailty is not always well defined or labeled within databases, which may mean that some relevant studies may not have been identified. Additionally, our search strategy and inclusion criteria were centered around the concept of frailty, which means that studies including older adults that were not labeled as frail by their authors were not included in our review even though those studies might have recruited older people with frailty. This is likely a methodological limitation of all systematic reviews on the subject of frailty and several other health conditions.[24,26,27,77] To counterbalance that limitation we accepted very broad definitions of frailty as was adopted in several other reviews on that subject.[18,21,24,26,77] The decision to accept a wide range of definitions of frailty reflects the reality that across the world multiple approaches are used to diagnose frailty and that even at the consensus conference that defined physical frailty no single instrument was recommended for that purpose.[1] In addition, our meta-analyses pooled the results from studies with a range of different characteristics beyond the criteria used to diagnose frailty. For example, in our quantitative syntheses we included studies conducted in the community and in long-term care facilities; and studies whose populations involved only individuals diagnosed with frailty and whose participants had frailty and/or pre-frailty. On the other hand, several arguments indicate that our methodological decision to pool the results of those studies was appropriate. First, all our meta-analyses had low levels of statistical heterogeneity (I^2 statistics for 15 of 18 meta-analyses were below 30% and all of them were below 50%). Second, none of our subgroup analyses identified significant differences between subgroups and only one of 47 sensibility analyses lead to a change in the interpretation of our primary results. Third, there was a large overlap between the baseline characteristics of the participants (e.g. age and functional status) of several studies included in our meta-analyses. Fourth, other systematic reviews about frailty also included older people living in the community and in long-term care facilities, and individuals with pre-frailty as well.[24,80,81]

Another potential limitation of our review involves the fact that most included studies had relatively short follow-up times since clinically important changes might demand longer study durations. Additionally, because of the small number of studies included we were able to perform a limited number of subgroup analyses for few outcomes. For the same reason we were unable to assess small-study effects using funnel plots or statistical tests for most of our meta-analyses. Nevertheless, our subgroup analyses revealed some interesting results, such as the finding that results from industry-funded studies did not differ significantly in their results from studies not funded by industry. Finally, few studies assessed changes in total nutritional intake of patients in the different treatment groups; however, such analyses are often biased because they reflect post-randomization evaluations.

On the other hand, our review has some strengths which include an extensive search strategy, the absence of a language-related exclusion criterion and the performance of Bayesian random-effects meta-analyses. Bayesian meta-analysis with informative heterogeneity priors derived from extensive reviews of Cochrane reviews represents a strength of our study because of the small number of studies that were pooled in the quantitative syntheses.[34-36] In addition, most studies included in our review reported some measure of compliance to the study intervention and more than half of the included studies reported high adherence rates above 90%.

4.2 Implications for practice and research

Our results lend support to the clinical recommendations available in the new guideline on the identification and management of physical frailty by the task force of the International Conference of Frailty and Sarcopenia Research (ICFSR).[82] That guideline does not make any recommendation regarding the use of nutritional supplements in isolation for the management of frailty in general and only recommends the use of protein/caloric supplementation for older patients with frailty when weight loss or undernutrition has been diagnosed. Importantly the

ICFSR recognized that their recommendations regarding the use of nutritional supplements for the management of frailty were of low to very low certainty of evidence.

Future studies should address important clinical outcomes such as mortality, falls and hospital admission, which are known to be adverse events related to frailty but which were not measured in most of the included studies in this review. More robust research studies including larger number of subjects, and longer follow-up periods are needed to establish the role of nutrition in the treatment of frailty.

5. Conclusions

Our results suggest, mostly with low to very low degrees of certainty, that nutritional education or nutritional supplements in isolation may not be effective for the management of frailty in older people.

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7. Supporting Information

Appendix S1

Supplementary Table S1: List of excluded references with reasons.
Supplementary Table S2: detailed information regarding studies' outcomes, how they were measured and the effect sizes of their main findings.
Supplementary Table S3. Diagnostic criteria for frailty and pre-frailty used by each study.
Supplementary Table S4. Comorbidities included/allowed or excluded in each study
Supplementary Table S5. Baseline characteristics of older adults included in each study.
Supplementary Table S6. Details regarding the number of arms in the included studies, which arms were included in meta-analyses, and further details concerning non-nutritional interventions adopted.
Supplementary Table S7. Commercial formulas used in studies of nutritional supplementation and their sources of funding.
Supplementary Table S8. Summary of findings (SOF) table for nutritional education compared with general health advice or no treatment for the management of frailty or pre-frailty in older adults.
Supplementary Table S9. Summary of findings (SOF) table for nutritional supplements compared with placebo or no treatment for the management of frailty or pre-frailty in older adults.
Supplementary figure S1. Subgroup analyses comparing nutritional supplements with placebo or no treatment for the mortality outcome according to risk of bias, type of supplement used, type of funding and type of population.
Supplementary figure S2. Subgroup analyses comparing nutritional supplements with placebo or no treatment regarding gait speed according to type of nutritional supplement used, risk of bias and type of population.
Supplementary figure S3. Subgroup analyses comparing nutritional supplements with placebo or no treatment regarding muscle strength in 12 weeks according to the criteria used to diagnose frailty, type of nutritional supplement used, risk of bias and research setting.
Supplementary figure S4. Subgroup analyses comparing nutritional supplements with placebo or no treatment regarding muscle strength in 12 weeks according to type of funding and type of population.
Supplementary figure S5. Funnel plot for the meta-analysis comparing nutritional supplements with placebo regarding muscle strength at 12 weeks of follow-up.
Supplementary figure S6. Sensitivity analysis: fixed effect meta-analysis comparing nutritional supplements with placebo regarding muscle strength at 12 weeks of follow-up.
Supplementary figure S7. Forest plot of meta-analyses comparing nutritional supplements with placebo or no treatment regarding the following outcomes: muscle strength (follow-up: 24 to 48 weeks) and cognitive function (follow-up: 24 weeks).
Supplementary figure S8. Subgroup analyses comparing nutritional supplements with placebo or no treatment regarding body weight according to criteria used to diagnose frailty, risk of bias, type of nutritional supplement, and type of funding.
Supplementary figure S9. Subgroup analysis comparing nutritional supplements with placebo or no treatment regarding body weight according to type of population and forest plot

of meta-analysis comparing nutritional supplements with placebo or not treatment for the body mass index (BMI) outcome.
Supplementary figure S10. Sensitivity analysis excluding studies with mean age < 75 years for the comparison between nutritional supplements and placebo or no treatment for the frailty status outcome.
Supplementary figure S11. Sensitivity analysis excluding studies with mean age < 75 years for the comparison between nutritional supplements and placebo or no treatment for the gait speed outcome.
Supplementary figure S12. Sensitivity analysis excluding studies with mean age < 75 years for the comparison between nutritional supplements and placebo or no treatment for the mortality outcome.
Supplementary figure S13. Sensitivity analysis excluding studies with mean age < 75 years for the comparison between nutritional supplements and placebo or no treatment for the muscle strength outcome at 12 weeks of follow-up.
Supplementary figure S14. Sensitivity analysis excluding the study whose inclusion criteria allowed the participation of patients with cancer for the comparison between nutritional supplements and placebo or no treatment for the gait speed outcome.
Supplementary figure S15. Sensitivity analysis excluding the study whose inclusion criteria allowed the participation of patients with cancer for the comparison between nutritional supplements and placebo or no treatment for the mortality outcome.
Supplementary figure S16. Sensitivity analysis excluding the study whose inclusion criteria allowed the participation of patients with cancer for the comparison between nutritional supplements and placebo or no treatment for the short physical performance battery (SPPB) outcome.
Supplementary figure S17. Sensitivity analysis excluding the study whose inclusion criteria allowed the participation of patients with cancer for the comparison between nutritional supplements and placebo or no treatment for the muscle strength outcome at 12 weeks of follow-up.
Supplementary figure S18. Sensitivity analysis excluding the study whose inclusion criteria allowed the participation of patients with cancer for the comparison between nutritional supplements and placebo or no treatment for the body weight outcome.
Supplementary figure S19. Sensitivity analysis restricted to studies with low risk of bias for the comparison between nutritional supplements and placebo or no treatment for the short physical performance battery (SPPB) outcome.
Supplementary figure S20. Sensitivity analysis restricted to studies with low risk of bias for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Word learning test - immediate recall).
Supplementary figure S21. Sensitivity analysis restricted to studies with low risk of bias for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Word learning test - delayed recall).
Supplementary figure S22. Sensitivity analysis restricted to studies with low risk of bias for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Verbal fluency test for animals).
Supplementary figure S23. Sensitivity analysis restricted to studies with low risk of bias for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Verbal fluency test for professions).
Supplementary figure S24. Sensitivity analysis excluding studies that included patients with pre-frailty for the comparison between nutritional supplements and placebo or no treatment for the short physical performance battery (SPPB) outcome.

Supplementary figure S25. Sensitivity analysis excluding studies that included patients with pre-frailty for the comparison between nutritional supplements and placebo or no treatment for the frailty status outcome.
Supplementary figure S26. Sensitivity analysis excluding studies that included patients with pre-frailty for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Word learning test - immediate recall).
Supplementary figure S27. Sensitivity analysis excluding studies that included patients with pre-frailty for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Word learning test – delayed recall).
Supplementary figure S28. Sensitivity analysis excluding studies that included patients with pre-frailty for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Verbal fluency test for animals).
Supplementary figure S29. Sensitivity analysis excluding studies that included patients with pre-frailty for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Verbal fluency test for professions).
Supplementary figure S30. Sensitivity analysis restricted to studies that used protein supplements for the comparison between nutritional supplements and placebo or no treatment for the short physical performance battery (SPPB) outcome.
Supplementary figure S31. Sensitivity analysis restricted to studies that used protein supplements for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Word learning test - immediate recall).
Supplementary figure S32. Sensitivity analysis restricted to studies that used protein supplements for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Word learning test - delayed recall).
Supplementary figure S33. Sensitivity analysis restricted to studies that used protein supplements for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Verbal fluency test for animals).
Supplementary figure S34. Sensitivity analysis restricted to studies that used protein supplements for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Verbal fluency test for professions).
Supplementary figure S35. Sensitivity analysis excluding studies where nutritional interventions were implemented in the presence of co-interventions for the comparison between nutritional supplements and placebo or no treatment for the frailty status outcome.
Supplementary figure S36. Sensitivity analysis excluding studies where nutritional interventions were implemented in the presence of co-interventions for the comparison between nutritional supplements and placebo or no treatment for the gait speed outcome.
Supplementary figure S37. Sensitivity analysis excluding studies where nutritional interventions were implemented in the presence of co-interventions for the comparison between nutritional supplements and placebo or no treatment for the mortality outcome.
Supplementary figure S38. Sensitivity analysis excluding studies where nutritional interventions were implemented in the presence of co-interventions for the comparison between nutritional supplements and placebo or no treatment for the muscle strength outcome at 12 weeks of follow-up.
Supplementary figure S39. Sensitivity analysis excluding studies where nutritional interventions were implemented in the presence of co-interventions for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Verbal fluency test for animals).
Supplementary figure S40. Sensitivity analysis excluding studies where nutritional interventions were implemented in the presence of co-interventions for the comparison

between nutritional supplements and placebo or no treatment for the cognitive function outcome (Word learning test immediate recall).
Supplementary figure S41. Sensitivity analysis excluding studies where nutritional interventions were implemented in the presence of co-interventions for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Word learning test delayed recall).
Supplementary figure S43. Sensitivity analysis restricted to studies that used the cardiovascular health study (CHS) criteria to diagnose frailty for the comparison between nutritional supplements and placebo or no treatment for the gait speed outcome.
Supplementary figure S44. Sensitivity analysis restricted to studies that used the cardiovascular health study (CHS) criteria to diagnose frailty for the comparison between nutritional supplements and placebo or no treatment for the mortality outcome.
Supplementary figure S45. Sensitivity analysis restricted to studies that used the cardiovascular health study (CHS) criteria to diagnose frailty for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Word learning test immediate recall).
Supplementary figure S46. Sensitivity analysis restricted to studies that used the cardiovascular health study (CHS) criteria to diagnose frailty for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Word learning test delayed recall).
Supplementary figure S47. Sensitivity analysis restricted to studies that used the cardiovascular health study (CHS) criteria to diagnose frailty for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Verbal fluency test for animals).
Supplementary figure S48. Sensitivity analysis restricted to studies that used the cardiovascular health study (CHS) criteria to diagnose frailty for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Verbal fluency test for professions).
Supplementary figure S49. Sensitivity analysis excluding studies funded by industry for the comparison between nutritional supplements and placebo or no treatment for the gait speed outcome.
Supplementary figure S50. Sensitivity analysis excluding studies performed in long-term care facilities for the comparison between nutritional supplements and placebo or no treatment for the gait speed outcome.
Supplementary figure S51. Sensitivity analysis excluding studies performed in long-term care facilities for the comparison between nutritional supplements and placebo or no treatment for the body weight outcome.
Supplementary figure S52. Sensitivity analysis excluding studies performed in long-term care facilities for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Word learning test immediate recall).
Supplementary figure S53. Sensitivity analysis excluding studies performed in long-term care facilities for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Word learning test delayed recall).
Supplementary figure S54. Sensitivity analysis excluding studies performed in long-term care facilities for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Verbal fluency test for animals).
Supplementary figure S55. Sensitivity analysis excluding studies performed in long-term care facilities for the comparison between nutritional supplements and placebo or no treatment for the cognitive function outcome (Verbal fluency test for professions).

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Table Legends

Table 1. PICOS criteria for inclusion and exclusion of studies.

Table 2. Main Characteristics of studies included.

Figure Legends

Figure 1. Flow diagram of the inclusion of studies in the review.

Figure 2. Assessment of risk of bias of individual studies.

Figure 3. Forest plot of meta-analysis comparing nutritional supplements with placebo or nutritional counselling or no treatment regarding mortality (follow-up: 12 to 48 weeks).

Figure 4. Forest plots of meta-analyses comparing nutritional interventions with placebo, no treatment or standard treatment for functioning outcomes.

Figure 5. Forest plots of meta-analyses comparing nutritional interventions with placebo regarding physical activity, frailty status, frailty score and cognitive function outcomes.

Legend for Figure 5: WLT-d: Word Learning Test delayed recall (Declarative Memory).

Figure 6. Forest plots of meta-analyses comparing nutritional interventions with placebo regarding body composition outcomes and body weight.

Table1. PICOS criteria for inclusion and exclusion of studies.

Criteria	Description
Population	People living at home or in long-term care facilities, who are aged 60 years and older and were diagnosed with frailty or pre-frailty according to any criteria used in the original studies to diagnose that syndrome.
Intervention	Nutritional interventions: nutritional education / dietary prescription (e.g. workshops); the use of protein and / or energy dietary oral supplements; the delivery of specific diets and any of those interventions concomitantly with another single or multifactorial intervention, as long as the comparator was the same set of interventions without the nutritional intervention component.
Comparison	Standard of care, placebo, other nutritional interventions, and multifactorial interventions without a nutritional component.
Outcome	Mortality; quality of life; measures of functioning: activities of daily living, gait speed, muscle strength, Short Physical Performance Battery; physical activity; frailty status; frailty score; cognitive function; body composition; weight, body mass index, falls and hospitalization. All outcomes measured by any instrument.
Study design	Randomized controlled trials.

Table 2. Main Characteristics of studies included

Author, Year, Country (ref)	Population	Sample Size, n	Setting	Nutritional Interventions	Comparators	Duration of the intervention and of follow-up	Outcomes
Lammes et al. (2012)[63], Sweden	Inclusion criteria: ≥ 75 years and frail; Exclusion criteria: cardiac problem; recent hip fracture or surgery during the last six months; present cancer treatment; stroke within the last two years and less than 7	96	Community-dwelling	1 individual dietary counselling session based on the results of the participant's food record; and 5 educational group sessions lasting about 1 hour and covering topics such as the nutritional needs of	General health advice	Duration of intervention: 3 months; Follow-up: 9 months	Nutritional intake; Resting metabolic rate; Body composition (body density, fat mass and fat-free mass)

	points on the short form of MMSE			older adults, optimal meal frequency and cooking methods			
Van de Rest et al. (2014)[71], Netherlands	Inclusion criteria: ≥ 65 years of age, and pre-frail or frail; Exclusion criteria: cancer, chronic obstructive pulmonary disease, muscle disease, type 2 diabetes, renal failure	127	Community-dwelling	Protein-supplemented beverage containing 15g protein (MPC80), 7.1g lactose, 0.5g fat, and 0.4 g calcium (twice daily 250mL)	Placebo supplement	Duration of intervention: 24 weeks; Follow-up: 24 weeks	Cognitive function (standard battery of neuropsychological tests)
Rydwik et al. (2010)[60], Sweden	Inclusion criteria: ≥ 75 years and frail; Exclusion criteria: cardiac problem; recent hip fracture or surgery during	96	Community-dwelling	1 individual dietary counselling session based on the results of the participant's food record; and 5	General health advice	Duration of intervention: 3 months; Follow-up: 24 months	Habitual physical activity level and activities of daily living (ADL and IADL)

	the last six months; present cancer treatment; stroke within the last two years and less than 7 points on the short form of MMSE			educational group sessions lasting about 1 hour and covering topics such as the nutritional needs of older adults, optimal meal frequency and cooking methods			
Wouters-Wesselin g et al. (2005)[61], Netherla nds	Inclusion criteria: ≥ 65 years of age, BMI < 25kg/m², frail; Exclusion criteria: cancer, gastrointestinal disease, need for a therapeutic diet incompatible with	101	Home for elderly persons or sheltered housing residence	Nutritional supplement with 250 kcal energy (Twice daily 125-mL)	Placebo supplement	Duration of intervention: 6 months; Follow-up: 6 months	Cognitive function (word learning test, category fluency test and recognition memory test for words)

	supplementation, or mental incapacity						
Zak et al. (2009)[62], Poland	Inclusion criteria: 60-95 years; being overweight within a 20% range; BMI > 19; Berg Balance Scale > 21; MMSE > 20; Exclusion criteria: cancer, prior surgical treatment of the abdominal area, acute gastric tract disorders, acute pancreatitis or diabetes, any recently sustained fractures, any past cerebral incidents with lasting impairment	91	Long-term care facility and community-dwellers	Liquid formulation supplying 300 kcal in the form of carbohydrate (49%), lipids (35%) and protein (16%) (Once daily 200 ml)	Placebo supplement	Duration of intervention: 7 weeks; Follow-up: 7 weeks	Physical Function and Strength Assessment (leg press and leg extension)

Tieland and Van de Rest et al. (2012)[73], Netherlands	Inclusion criteria: ≥ 65 years of age, frail or pre-frail; Exclusion criteria: cancer, chronic obstructive pulmonary disease (COPD), muscle disease, type 2 diabetes, renal failure	65	Community-dwelling	Protein supplemented beverage containing 15g protein (MPC80), 7.1g lactose, 0.5g fat, and 0.4g calcium (250-mL beverage)	Placebo supplement	Duration of intervention: 24 weeks; Follow-up: 24 weeks	Body composition (lean mass); Muscle fiber cross sectional area; Strength (leg press, leg extension and handgrip); Physical performance (SPPB)
Van der Zwaluw et al. (2014)[72], Netherlands	Inclusion criteria: ≥ 65 years, pre-frail or frail; Exclusion criteria: diabetes mellitus type I or II, cancer, COPD, renal failure	65	Community-dwelling	Protein-supplemented beverage containing 15g protein (MPC80), 7.1g lactose, 0.5g fat, and 0.4g calcium (250-mL beverage)	Placebo supplement	Duration of intervention: 24 weeks; Follow-up: 24 weeks	Cognitive Performance (standard battery of neuropsychological tests)

Tieland and Dirks et al. (2012)[74], Netherlands	Inclusion criteria: > 65 years old) with pre-frailty or frailty; Exclusion criteria: cancer, chronic obstructive pulmonary disease (COPD), muscle disease, type 2 diabetes, renal insufficiency	62	Community-dwelling	Protein supplemented beverage containing 15g protein (MPC80), 7.1g lactose, 0.5g fat, and 0.4 g calcium (Twice daily 250-mL)	Placebo supplement	Duration of intervention: 24 weeks; Follow-up: 24 weeks	Body composition (lean mass); Strength (leg press and leg extension); Physical performance (SPPB)
Park et al. (2018)[75], Republic of Korea	Inclusion criteria: Aged 70–85, pre-frail or frail and at risk of malnutrition; Exclusion criteria: had comorbidities such as kidney or liver failure	120	Community-dwelling	10g-powder protein supplement packs containing 0.5g fat, 0.2g cocoa powder, and 9.3g whey protein (5 × 10-g packs)	Placebo supplement	Duration of intervention:12 weeks; Follow-up: 12 weeks	Body composition (muscle mass); Status frailty; SPPB; Physical activity (IPAQ).

Rydwik et al. (2008)[59], Sweden	Inclusion criteria: ≥ 75 years and frail; Exclusion criteria: cardiac problem; recent hip fracture or surgery during the last six months; present cancer treatment; stroke within the last two years and less than 7 points on the short form of MMSE	96	Community-dwelling	1 individual dietary counselling session based on the results of the participant's food record; and 5 educational group sessions lasting about 1 hour and covering topics such as the nutritional needs of older adults, optimal meal frequency and cooking methods	General health advice	Duration of intervention:3 months; Follow-up: 9 months	Physical performance (leg press strength); Nutritional measures (body composition [fat-free mass] and energy intake); Health belief model
Ng et al. (2015)[14], Malaysia	Inclusion criteria: ≥ 65 years, able to ambulate	246	Community-dwelling	Liquid formula, supplying 300 kcal in the form of	Placebo supplement	Duration of intervention:6 months;	Frailty score; Measures of frailty components; Physical

	without personal assistance; <u>Exclusion criteria:</u> impairment (Mini Mental State Examination score), major depression, severe audiovisual impairment, any progressive, degenerative neurologic disease, terminal illness with life expectancy <12 months			carbohydrate (49%), fat (35%), protein (35%), and dietary fiber (4.6 g per 200 mL) (200-mL)		Follow-up: 12 months	activity (31-item Longitudinal Ageing Physical Activity Questionnaire); Self-reported hospitalizations; Self-reported falls; ADL-IADL dependency; Handgrip strength;
Starr et al.	<u>Inclusion criteria:</u> Obese (BMI ≥ 30 kg/m²); SPPB	67	Community-dwelling	Diet 500 kcal deficit but with a macronutrient	500kcal deficit and prescription	Duration of intervention:6 months;	Function; Body composition (lean mass); Physical

(2016)[65], USA	score of 4–10 out of 12; ≥60 years of age; Exclusion criteria: GFR <45 mL/min/1.73 m², dementia, neurological conditions causing functional limitations, and unstable or terminal medical conditions			distribution of 30% protein, 30% fat, 40% carbohydrate; prescribed protein intake was 1.2 g/kg (30+ grams of lean, high-quality protein three times a day)	of 0.8g/kg/d of protein	Follow-up: 6 months	activity (CHAMPS), and hand grip strength
Payette et al. (2002)[64], Canada	Inclusion criteria: ≥ 65 years and at high nutritional risk; Exclusion criteria: palliative care, alcoholic, cancer	89	Receiving long-term home help services offered by 7 local	Ensure or Ensure plus (Twice daily 235mL)	Did not receive any treatment	Duration of intervention:16 weeks; Follow-up: 16 weeks	Handgrip strength; Isometric elbow flexion and leg extension strengths; Perceived health; Functional status;

			community services centers				Item short form survey (SF-36)
Kim and Lee et al. (2013)[66], South Korea	Inclusion criteria: ≥ 65 years with frailty and low socioeconomic status; could not walk 3-m course within 5 seconds at their usual pace; Exclusion criteria: subjects participating in any kind of exercise program or clinical nutrition program, who were ordered to avoid a high-protein diet by an	87	Community-dwelling	Commercial liquid formula with 400 kcal of energy, 25 g of protein, 9.4 g of essential amino acids (60.2% leucine), 56 g of carbohydrate, 9 g of lipid, 400 mL of water, and micronutrients (Twice daily 200-mL)	Did not receive any treatment	Duration of intervention:12 weeks; Follow-up: 12 weeks	Physical Functioning; SPPB; timed-up-and-go test; one-legged stance; gait speed, hand grip strength; anthropometric data and dietary intake

	internist; who are unable to walk or are too functionally deteriorated						
Bonnefoy et al. (2003)[67], France	Inclusion criteria: frail older adults with multiple medical diagnoses, using several medications, with a length of stay of more than 3 years in retirement homes; Exclusion criteria: uncontrolled or rapidly evolving diseases; Dementia; type 1 diabetes; severe renal insufficiency; functional	57	Retirement homes	Nutritional energy drinks with 200 kcal each, with 15g of proteins (30% of energy), 25g of carbohydrate (50% of energy), and 4·4 g of lipids (20% of energy) (Twice daily 200-mL)	Placebo supplement	Duration of intervention:3 months; Follow-up: 9 months	Body composition (fat-free mass); Resting energy expenditure; Muscle power; BMI; Gait speed; Stair walking; Chair rise

	handicap preventing exercise; long-term corticosteroid therapy; receiving vitamin supplements before the study						
Kwon et al. (2015)[70], Japan	Inclusion criteria: pre-frail elderly women aged ≥70 years; Exclusion criteria: serum albumin ≥4.5 mg/dL, serious musculoskeletal conditions, and taking calcium or vitamin D supplements	89	Community-dwelling	Two once-weekly cooking classes lasting 2-3h, where groups of 15 participants received instructions and practiced preparation of ingredients, nutrition guidance, cooking, eating	General health advice	Duration of intervention: 3 months; Follow-up: 6 months	Physical performance: muscle strength (handgrip strength), balance, and walking; SF-36

				together, washing dishes, and tidying up. Nutritional education within those classes included a 10- to 15-minute lecture on food eating habits that help to strengthen muscles			
Smoliner et al. (2008)[57], Germany	Inclusion criteria: older adults with MNA ≤ 23.5 points; Exclusion criteria: implanted defibrillators; hemiplegia or severe arthritis	65	Nursing home	Diet according to German reference values (approximately 2000kcal of energy, 80g of protein, 60g of fat, and 260g of carbohydrates) plus protein powder	Diet according to German reference values (approximately 2000kcal of	Duration of intervention: 12 weeks; Follow-up: 12 weeks	BMI; Body composition (fat-free mass); Handgrip strength; Respiratory muscle strength; Barthel index (ADL); SF-36

	derived from hydrolyzed milk to enrich soups and sauces, adding energy-enriched soups and sauces and two additional snacks on a milk basis high in protein and energy (300 kcal, 20 g of protein, 20 g of fat, and 20 g of carbohydrates) (5 g of protein powder per 100 mL of soups and sauces; 5 g of	energy, 80 g of protein, 60 g of fat, and 260 g of carbohydrates)

				rapeseed oil per 100 mL of sauce and 10 mL of heavy cream per 100 mL of soup; 150-ml cups of snacks)			
Chatterjee et al. (2018)[69], India	Inclusion criteria: aged ≥60 years and frail; Exclusion criteria: resistive training exercise or nutritional supplementation in the previous 6 months; acute illness; severe obstructive airway disease; severe systolic dysfunction;	66	Community-dwelling	Nutritional supplementation powder with carbohydrates were supplemented at the rate of ≈50% of total daily calorie requirement and protein was supplemented at a rate	Nutritional counselled at baseline about their deficiency	Duration of intervention: 12 weeks; Follow-up: 12 weeks	Gai Speed; Grip strength; IADL; MNA; Frailty assessment; Serum albumin; Modified Physical Performance Test; Berg Balance Scale; Barthel Index (ADL); geriatric depression

	severe depression; severe, painful lower limb muscle condition; and severe cognitive impairment			sufficient to achieve the target of 1.2 g/kg body weight per day			scale (GDS); Cognitive function (Hindi Mental Status Examination)
Otten et al. (2016)[68], Germany	Inclusion criteria: frail malnourished older adult Exclusion criteria: no information	77	No information	Nutritional supplement	Dietary counselling	Duration of intervention: 12 weeks; Follow-up: 12 weeks	Nutritional status; Grip strength; Timed-up-and-go; functional limitations; Quality of life scale

ADL: Acitivities of Daily Living; BMI: Body Mass Index; CHAMPS: Community Health Activity Model Program for Seniors; COPD: Chronic Obstructive Pulmonary Disease; GDS: Geriatric Depression Scale; IADL: Instrumental Activities of Daily Living; IPAC: International Physical Activity Questionnaire; MNA: Mini Nutritional Assessment; MMSE: Mini Mental State Examination; MPC80: Milk Protein Concentrate 80%; SF-36: Short Form 36 quality of life instrument; SPPB: Short Physical Performance Battery;