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The effect of dietary supplements on frailty in older persons: a meta-analysis and systematic review of randomized controlled trials

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Abstract

Frailty is a geriatric syndrome that predicts the onset of disability, morbidity and mortality in elderly people; it is a state of pre-disability and is reversible. This review aimed to assess the impact of dietary supplementation interventions in frail older adults. A systematic search of PubMed, Web of Science, Embase, and the Cochrane Library databases was performed to collect randomized controlled trials of dietary supplements for the treatment of frailty in the elderly published before March 2022. The frailty score, muscle mass, muscle strength and physical performance of the frail elderly were extracted for analysis. Meta-analysis was performed using Review Manager Version 5.4 and Stata version 15.0. Totally, 18 studies met the inclusion criteria, with 1204 participants (603 experiment group vs. 601 control group). Compared to control group, multi-nutrient nutrition intervention can significantly improve the frailty score of the elderly (MD = -0.19, 95% CI: -0.38 to -0.01, P = 0.04, I2 = 0). Protein supplementation intervention significantly improved body weight (MD = 4.86, 95% CI: 1.21 to 8.52, P = 0.009), muscle mass [lean mass (MD = 2.73, 95% CI:1.26 to 4.20, P = 0.0003)], muscle strength (MD = 1.90, 95% CI: 0.68 to 3.12, P = 0.002), and physical performance [chair stand test (MD = -2.15, 95% CI: -3.21 to -1.10, P < 0.0001)] in frail older adults compared to control. This meta-analysis and systematic review suggests that dietary supplements interventions positively influence in older people with frailty.

Keywords: dietary supplements; frailty; muscle mass; muscle strength; physical performance; meta-analysis.

Practical Application: What is already known on this topic: Malnutrition can increase the risk of frailty in the elderly. More and more scholars are paying attention to the relationship between dietary pattern and frailty. But what's still missing is a meta-analysis of how dietary patterns affect frailty in older adults. **What this study adds:** Nutritional supplementations seem to be useful in improving frailty, some muscle mass, muscle strength and physical performance, particularly if they are proteins. **How this study might affect research, practice or policy:** Appropriate nutritional interventions may reduce the risk of frailty, delay or even reverse frailty.

1 Introduction

Frailty has been defined as a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function and increases an individual's vulnerability for developing disability, dependency, or death (Ekram et al., 2021). Frailty is considered one of the important geriatric syndromes, and its prevention and management represent an important goal of geriatrics (Moraes et al., 2018). Studies have shown that the overall prevalence of frailty among community-dwelling older adults in the United States ranges from 7-12%. And the prevalence of frailty increased with age from 3.9% in the 65-74 group to 25% in the 85+ group (Xue, 2011). In addition, the prevalence of frailty among older adults in the community ranged from 4% to 59%, a systematic review found (Collard et al., 2012).

Frailty increases the risk of various negative outcomes, especially in the elderly. Frail older adults have increased hospitalizations, falls, fractures, long-term care and mortality, when compared to those who are nonfrail (Kojima et al., 2019). It is also related to a broad range of other outcomes, such as loneliness, lower quality of life, depression, cognitive decline and dementia (Hoogendijk et al., 2019). Once frailty has developed, it often leads to a downward spiral in overall health. However, frailty is not necessarily an irreversible process but a dynamic continuum state that can both worsen and improve over time.

Currently, it is believed that the risk factors of debility include heredity, comorbidity, multiple drug use, malnutrition and so on. Nutrition, as a modifiable factor, has attracted more and more attention. A meta-analysis of 5447 elderly people in

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the community showed that there was a significant correlation between frailty and the prevalence of malnutrition, and about 90% of the elderly with malnutrition were accompanied by frailty (Verlaan et al., 2017).

A common approach to treat malnutrition is the use of dietary supplementations, i.e. foods defined as either intended to provide nutrients in order to increase the quantity of their consumption or to provide non-nutrient chemicals which are claimed to have a biologically beneficial effect (Traub et al., 2021). More recently another systematic review concluded that dietary supplementation interventions may have beneficial effects on muscle mass, muscle strength (grip strength), and physical performance (gait speed and dynamic balance) in older adults (Wu et al., 2021). But another systematic review reported that the interactive effect of dietary supplementation on muscle function appears limited (Beaudart et al., 2017).

Given this background, we aimed to summarize the effect of dietary supplementation on physical performance and muscle strength outcomes in frailty older people compared to placebo in RCTs involving only frailty older people, stratifying our results by the type of dietary supplementation.

2 Methods

The meta-analysis was conducted and reported in accordance with the PRISMA guidelines to ensure comprehensive and transparent reporting of our methods and results. We have registered our protocol in the PROSPERO database (CRD42022334747).

2.1 Search strategy and selection criteria

PubMed, Web of Science, Embase and the Cochrane Library were electronically searched for papers that were published until March 2022. The search strategy included various combinations of the terms "Frailty", "Frailties", "Frailness", "Frailty Syndrome", "Debility" and "Debilities", with Dietary Supplements terms such as "Food Supplementations" or "Nutraceuticals" or "Herbal Supplements". Randomized controlled trials were specifically targeted using the following search terms: "Randomized controlled trial", "Controlled clinical trial", or "Randomized" or "Randomly" or "Trial" or "Group". The search was limited to human studies.

Studies meeting the following criteria were included: (1) Participants were defined as frailty; (2) Age ≥ 65-year-old; (3) the intervention group underwent nutritional intervention and the control group undergo placebo or daily diet; (4) the randomized control trials investigated the effects of any types of nutrition on muscle mass, muscle strength, and physical performance; and (5) papers published in English. Studies including old people with a specific health conditions such as cancer, diabetes, stroke, human immunodeficiency virus, chronic obstructive pulmonary disease, chronic kidney disease, liver cirrhosis, other critical illness, and recent transplants were excluded. Studies were also excluded if they were published as a pilot study, conference abstract, case report, commentary, editorial, protocol, review article, letter to editor, or duplicate.

2.2 Study selection

The study selection process is outlined in Figure 1. The eligibility assessment was performed by two independent reviewers in a standardized manner. All papers identified using the search strategy were assessed for eligibility, as indicated based on the previously defined inclusion criteria, by reviewing their titles and/or abstracts. If insufficient information was available to evaluate the inclusion or exclusion of an article, then a full-text version was obtained. Full-text versions of all the relevant studies were obtained and reviewed by two independent reviewers to ensure that the studies met the inclusion criteria. Disagreements were resolved by discussion with a third reviewer. When insufficient information or data were available in the included articles, the authors were contacted to obtain additional information if possible.

2.3 Quality assessment

Two reviewers independently assessed the quality of all included studies, using the Downs and Black Quality Index. The scales are designed to assess the methodological quality of randomized studies of health care interventions (Downs & Black, 1998) and include reporting, external validity, bias, confounding, and power, and their maximum scores are 11, 3, 7, 6, and 5, respectively. The maximum possible total score is 32. Quality was then rated on a four-category scale: poor (< 18), moderate (18-23), good (24-29), and excellent (≥ 30).

2.4 Data extraction

Data were extracted from the included articles using a data extraction form (Table 1). Data characteristics were extracted, including: (1) name of first author and year of publication, (2) study nation or area, (3) study source, (4) frailty diagnosis, (5) sample characteristics (intervention and control group sizes, male and female sample size and age), (6) intervention and control protocols (intervention category and duration), and (7) effects of the interventions, including frailty score, muscle mass, muscle strength and physical performance. One investigator performed the data extraction, which was checked by a second investigator.

Since the aim of our study was to explore the effect of dietary supplementations on physical performance and/or muscle

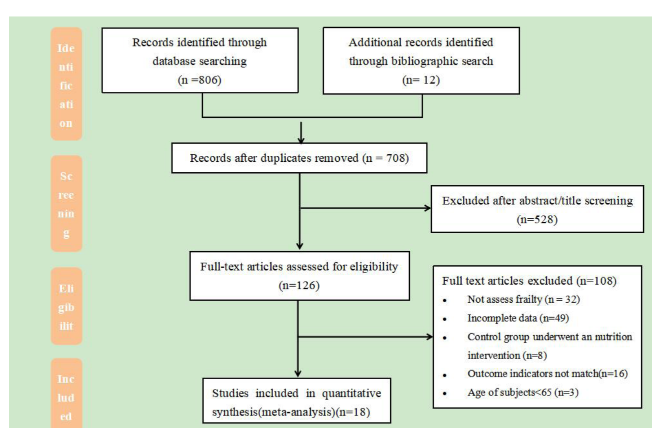

Figure 1. PRISMA flow-chart.

Table 1. Characteristics of included studies.

Study and Year	Nation	Setting	Frailty definition	I Sample Size	C Sample Size	I M/F	C M/F	I Age (years)	C Age (years)	Intervention	Duration	Control	Frailty Outcomes	Risk of Bias
Na 2021	Korea	Community	Prefrailty or frailty	28	25	5/23	4/21	79.5 ± 7.0	82.1 ± 6.9	Multi-nutrient	90 days	Placebo	Frailty score; Muscle mass; Muscle strength	moderate
Peng 2021	China	Community	Prefrailty	29	33	10/19	9/24	70.66 ± 4.16	71.48 ± 3.46	HP-HMB	12 weeks	Daily diet	Muscle mass; Muscle strength; Physical performance	moderate
Hsieh 2019	China	Hospital	Prefrailty or frailty	82	80	45/38	51/29	70.4 ± 5.3	72.5 ± 5.5	Multi-nutrient	6 months	Daily diet	Frailty score; Muscle mass; Muscle strength	good
Kang 2019	China	Hospital	Prefrailty or frailty	66	49	25/41	19/30	76.79 ± 7.11	78.04 ± 6.82	Protein	12 weeks	Daily diet	Muscle strength; Physical performance	good
Park 2018	Korea	Welfare centers	Prefrailty or frailty	40	40	12/28	16/24	76.80 ± 3.70	76.83 ± 3.86	protein	12 weeks	placebo	Physical performance	good
Wu 2018	China	Hospital	Prefrailty or frailty	8	10	2/6	6/4	73.5 ± 2.4/	75.9 ± 1.7	Multi-nutrient	3 months	Daily diet	Muscle mass; Muscle strength	moderate
Dirks 2017	Netherlands	Community	Prefrailty or frailty	17	17	6/11	6/11	76 ± 2	77 ± 2	Protein	24 weeks	Placebo	Muscle mass; Muscle strength; Physical performance	good
Badrasawi 2016	Malaysia	Community	Prefrailty or frailty	26	24	14/12	9/15	68.2 ± 6.3	68.8 ± 6.5	L-carnitine	10 weeks	Placebo	Frailty score; Muscle strength; Physical performance	moderate
Buigues 2016	Spain	Nursing home	Prefrailty or frailty	22	28	6/16	9/19	75.9 ± 7.8	74.9 ± 6.9	Prebiotic	13 weeks	Pacebo	Muscle strength	moderate
Kim 2015	Japan	Community	Frailty	32	32	0/32	0/32	81 ± 2.8	80.3 ± 3.3	Protein	3 months	Placebo	Muscle strength; Physical performance	moderate
Tze 2015	Singapore	Community	Prefrailty or frailty	49	50	17/32	22/28	69.7 ± 4.23	70.1 ± 5.02	Multi-nutrient	24 weeks	Placebo	Frailty score; Muscle strength;	moderate

Table 1. Continued...

Study and Year	Nation	Setting	Frailty definition	I Sample Size	C Sample Size	I M/F	C M/F	I Age (years)	C Age (years)	Intervention	Duration	Control	Frailty Outcomes	Risk of Bias
Kim 2013	Korea	Community	Frailty	43	44	9/34	9/35	78.9 ± 5.5	78.4 ± 6.0	Multi-nutrient	12 weeks	Placebo	Muscle mass; Physical performance	moderate
Tieland 2012	Netherlands	Community	Prefrailty or frailty	34	31	14/20	15/16	78 ± 1	81 ± 1	Protein	24 weeks	Placebo	Muscle mass; Muscle strength; Physical performance	moderate
Smoliner 2008	Germany	Nursing home	Frailty	22	30	5/17	9/21	82.2 ± 9.5	84 ± 9.5	Multi-nutrient	12 weeks	Daily diet	Muscle mass; Muscle strength;	moderate
Bonnefoy 2003	France	Nursing home	Frailty	30	27	6/24	1/26	83 ± 0.91	83 ± 1.24	Multi-nutrient	9 months	placebo	Physical performance	moderate
Jong 2000	Netherlands	Community	Frailty	35	33	11/24	11/22	79.6 ± 5	78.8 ± 6.7	Multi-nutrient	17 weeks	Daily diet	Muscle mass	moderate
Gray-Donald 1995	Canada	Community	Frailty	24	22	——	——	76 ± 7	79 ± 8	Multi-nutrient	12 weeks	Daily diet	Muscle mass; Muscle strength;	moderate
Fiatarone 1994	America	Nursing home	Frailty	24	26	7/17	12/14	85.7 ± 1.2	89.2 ± 0.8	Multi-nutrient	10 weeks	Placebo	Muscle mass; Muscle strength;	moderate

strength, when more than two groups were present, only the data regarding dietary supplementations (without any physical regimen intervention) and placebo (without any physical regimen intervention) were extracted.

2.5 Statistical analysis

The meta-analysis was performed using Review Manager version 5.4 and Stata version 15.0. The I^2 statistic tests were used to evaluate the heterogeneity among the included studies. The random-effects model was utilized to combine the results when heterogeneity was present among the studies ($I^2 > 50\%$ or $P < 0.05$). Otherwise, the fixed-effects model would be used. The intervention effect sizes for continuous variables were measured by determining the MDs between the intervention and control groups with regard to the change observed between the baseline and follow-up scores and their corresponding 95% *CI*. The results were considered statistically significant when $P < 0.05$. Sensitivity analyses were conducted through sequential omission of individual studies and then comparison of the *p*-value. The results were identified as credible when the corresponding *p*-value was not substantially different. Publication bias was assessed using Begg and Egger's test and funnel plot (Weng et al., 2019; Gao et al., 2020). Results were considered statistically significant when $P < 0.05$.

3 Results

3.1 Search results

A total of 806 publications were identified by searching the databases and 12 were identified by other sources; 110 articles were excluded because of duplicate records. After excluding 528 articles based on title/abstract review, 126 articles were retrieved for full-text review and 108 studies were excluded. These studies were excluded because they did not assess frailty, reported incomplete data, their control group underwent an nutrition intervention, or they did not report muscle mass or muscle strength or physical performance as an outcome measurement. Consequently, 18 articles were included in the qualitative and quantitative synthesis (Figure 1).

3.2 Study and patient characteristics

The 18 RCTs (Na et al., 2021; Peng et al., 2021; Hsieh et al., 2019; Kang et al., 2019; Park et al., 2018; Wu et al., 2018; Dirks et al., 2017; Badrasawi et al., 2016; Buigues et al., 2016; Kim et al., 2015; Ng et al., 2015; Kim & Lee, 2013; Tieland et al., 2012; Smoliner et al., 2008; Bonnefoy et al., 2003; Jong et al., 2000; Gray-Donald et al., 1995; Fiatarone et al., 1994) included a total of 1204 older participants (603 experiment group vs. 601 control group). The majority of studies were conducted in Asia and Europe, with ten studies (Na et al., 2021; Peng et al., 2021; Hsieh et al., 2019; Kang et al., 2019; Park et al., 2018; Wu et al., 2018; Badrasawi et al., 2016; Buigues et al., 2016; Kim et al., 2015; Ng et al., 2015; Kim & Lee, 2013) in Asia and six studies (Dirks et al., 2017; Buigues et al., 2016; Tieland et al., 2012; Smoliner et al., 2008; Bonnefoy et al., 2003; Jong et al., 2000) in Europe. The mean age ranged from 68.2 years to 89.2 years and the majority were females (67%). Ten RCTs (Na et al., 2021; Peng et al., 2021; Dirks et al., 2017; Badrasawi et al., 2016; Kim et al., 2015; Ng et al., 2015; Kim & Lee, 2013; Tieland et al., 2012; Jong et al., 2000; Gray-Donald et al., 1995) were made among community-dwelling older adults, among the conditions considered, 7 RCTs (Kim et al., 2015; Kim & Lee, 2013; Smoliner et al., 2008; Bonnefoy et al., 2003; Jong et al., 2000; Gray-Donald et al., 1995; Fiatarone et al., 1994) included only frailty people, whilst 11 RCTs included frailty and prefrailty people.

Multi-nutrient products were the most common nutritional supplementations used (n = 10 studies) including vitamin D/E associated with proteins, hypercaloric products, or amino acids associated with minerals.

The quality of the majority of the studies was moderate, with a mean score of 22.94. Four studies (Kang et al., 2019; Park et al., 2018; Wu et al., 2018; Badrasawi et al., 2016) were rated as of good quality, and 14 studies were deemed to be of moderate quality.

3.3 Effect of dietary supplementation on frailty

Four studies reported the effect of dietary supplementation interventions on frailty scores in older adults. Three of these studies were multi-nutrient nutritional interventions (Na et al., 2021; Hsieh et al., 2019; Ng et al., 2015) and one study (Badrasawi et al., 2016) used prebiotic interventions. There was no significant heterogeneity among these studies ($P = 0.70$, $I^2 = 0$), so the fixed effect model was used for meta-analysis. The results showed that multi-nutrient nutrition intervention can significantly improve the frailty score of the elderly (MD = -0.19, 95% *CI:* -0.38 to -0.01, $P = 0.04$) (Table 2).

None of these outcomes suffered on publication bias as revealed by the visual inspection of the funnel plots and/or using the Egger's test ($P > 0.05$).

3.4 Effect of dietary supplementation on weight and muscle mass

As reported in Table 3, among the single nutritional component examined, proteins supplementation were able to significantly improve weight in 2 RCTs (Dirks et al., 2017; Tieland et al., 2012), (MD = 4.86, 95% *CI:* 1.21 to 8.52, $P = 0.009$), even if this outcome was characterized by a high heterogeneity ($I^2 = 60\%$). A study of HP-HMB reported weight gain in people randomized to this intervention (Peng et al., 2021). On the contrary, we did not observe improvement for the multi-nutrient supplementation in 4 RCTs (Na et al., 2021; Wu et al., 2018; Kim & Lee, 2013; Smoliner et al., 2008) (MD = 0.86, 95% *CI:* -4.00 to 5.73, $P = 0.73$).

Two studies (Dirks et al., 2017; Tieland et al., 2012) effect of protein supplementation on lean mass meta-analysis showed that the intervention increases lean mass (MD = 2.73, 95% *CI*:1.26 to 4.20, $P = 0.0003$). Na et al. (2021) and Jong et al. (2000) studies showed that multi-nutrient supplementation did not increase lean mass.

Two studies (Dirks et al., 2017; Kim et al., 2015) results of the meta-analysis showed that after the protein supplementation intervention, the appendicular lean mass did not change in the

Table 2. Meta-analysis of randomized controlled trials by type of nutritional intervention on frailty.

Analysis	Number of studies	Meta-analysis					Heterogeneity	Model of meta-analysis
		Participants	SD	95% CI		P value	I^2	
Frailty								
Total	4	366						
Multi-nutrient	3	314	-0.19	-0.38	-0.01	0.04	0	Fixed
Prebiotic	1	52						

Table 3. Meta-analysis of randomized controlled trials by type of nutritional intervention on weight and muscle mass.

Analysis	Number of studies	Meta-analysis					Heterogeneity	Model of meta-analysis
		Participants	SD	95% CI		P value	I^2 (%)	
Weight								
Total	7	364						
Multi-nutrient	4	207	0.86	-4.00	5.73	0.73	84	random
Proteins	2	99	4.86	1.21	8.52	0.009	60	random
HP-HMB	1	58						
Lean mass								
Total	3	155						
Multi-nutrient	1	56						
Proteins	2	99	2.73	1.26	4.20	0.0003	0	Fixed
Appendicular lean mass (ALM)								
Total	3	154						
Multi-nutrient	1	56						
Proteins	2	98	0.80	-1.36	2.95	0.47	93	random

frail elderly (MD = 0.80, 95% *CI:* -1.36 to 2.95, $P = 0.470$). Na et al. (2021) study showed that multi-nutrient supplementation did not increase appendicular lean mass.

None of these outcomes suffered on publication bias as revealed by the visual inspection of the funnel plots and/or using the Egger's test ($P > 0.05$).

3.5 Effect of dietary supplementation on muscle strength tests

As reported in Table 4, among the single nutritional component examined, proteins supplementatios were able to significantly improve handgrip strength in 3 RCTs (Kang et al., 2019; Dirks et al., 2017; Tieland et al., 2012), (MD = 1.90, 95% *CI*: 0.68 to 3.12, $P = 0.002$). A study of prebiotic supplementation (Buigues et al., 2016) reported handgrip strength improved in people randomized to this intervention. On the contrary, we did not observe improvement for the multi-nutrient supplementation in 6 RCTs (Na et al., 2021; Hsieh et al., 2019; Wu et al., 2018; Kim & Lee, 2013; Smoliner et al., 2008; Gray-Donald et al., 1995) (MD = 0.29, 95% *CI:* -0.83 to 1.41, $P = 0.45$). Moreover Peng et al. (2021) and Badrasawi et al. (2016) came to similar conclusions.

None of these outcomes suffered on publication bias as revealed by the visual inspection of the funnel plots and/or using the Egger's test ($P > 0.05$).

3.6 Effect of dietary supplementation on physical performance tests

The results of the chair stand test of 3 RCTs (Kang et al., 2019; Kim et al., 2015; Tieland et al., 2012) for protein interventions on the frail elderly showed that the heterogeneity was high. After excluding the study of Kim et al. (2015), the heterogeneity was reduced and the model was stable ($P = 0.45$, $I^2 = 0$). Protein supplementation intervention can improve its chair stand test results (MD = -2.15, 95% *CI*: -3.21 to -1.10, $P < 0.0001$). And a study of multi-nutrient supplementation (Kim & Lee, 2013) reported improved chair stand test in people randomized to this intervention. Conversely, Badrasawi et al. (2016) and Peng et al. (2021) study showed that L-carnitine and HP-HMB intervention did not change the chair stand test (Table 5).

Five studies showed no significant effect of dietary supplementation interventions on physical performance in frail older adults, two (Peng et al., 2021; Kim & Lee, 2013) of which were multi-nutrient interventions(MD = 0.34, 95% *CI*: -0.18 to 0.87, $P = 0.20$) and three (Kang et al., 2019; Park et al., 2018; Dirks et al., 2017) were proteins interventions(MD = 0.02, 95% *CI*: -1.05 to 1.09, $P = 0.97$) (Table 5).

None of these outcomes suffered on publication bias as revealed by the visual inspection of the funnel plots and/or using the Egger's test ($P > 0.05$).

Table 4. Meta-analysis of randomized controlled trials by type of nutritional intervention on muscle strength.

Analysis	Number of studies	Meta-analysis					Heterogeneity	Model of meta-analysis
		Participants	SD	95% CI		P value	I^2 (%)	
Handgrip strength								
Total	12	786						
Multi-nutrient	6	416	0.29	-0.83	1.41	0.45	0	Fixed
Proteins	3	204	1.90	0.68	3.12	0.002	0	Fixed
HP-HMB	1	58						
L-carnitine	1	52						
Prebiotic	1	56						

Table 5. Meta-analysis of randomized controlled trials by type of nutritional intervention on physical performance.

Analysis	Number of studies	Meta-analysis					Heterogeneity	Model of meta-analysis
		Participants	SD	95% CI		P value	I^2 (%)	
Short physical performance battery								
Total	5	378						
Multi-nutrient	2	149	0.34	-0.18	0.87	0.20	0	Fixed
Proteins	3	229	0.02	-1.05	1.09	0.97	91	random
Chair stand test								
Total	6							
Multi-nutrient	1	288						
Proteins	3	180	-2.15	-3.21	-1.10	< 0.0001	0	Fixed
L-carnitine	1	50						
HP-HMB	1	58						

4 Discussion

In this systematic review and meta-analysis including 18 RCTs placebo-controlled and 1204 older pre-frail or frail participants, we found that proteins and multi-nutrient supplementations (i.e. nutritional supplements made of several nutritional components) appeared to have a positive effect on improving frailty, muscle mass, certain physical functions, and muscle strength tests in older people.

The pathological loss of muscle mass is an important topic in geriatric medicine and poor nutritional status seems to play an important role in the development of frailty. It is widely known that there is a significant decline in food and energy intake with increasing age, estimated in an average fall of around 25% between the ages of 40 and 70 years (Nieuwenhuizen et al., 2010). Therefore, the European Society of Parenteral and Enteral Nutrition (ESPEN) recommends, with an evidence level A, the use of nutritional supplements to improve or maintain the health status of frail elderly people (Cederholm et al., 2017).

Focusing more on the topics of physical performance and muscle strength, several systematic reviews have reported findings on these outcomes with nutritional supplementation, but no definitive findings, mainly because the randomized controlled trials included in these meta-analyses only involved very good, Nutrient-rich individuals, small sample size, heterogeneous age, and different physical activity regimens (Beaudart et al., 2017; Denison et al., 2015). We tried to overcome these limitations with our work, using very strict criteria (i.e. only randomised controlled trials, including only pre-frail or frail older adults), if possible, without the use of physical exercise in the available arm, but our results are essentially the same as those that have been published. We can be sure that the effect of nutritional supplements is limited to some physical performance tests, and to further improve muscle strength, resistance exercise should be performed (Beaudart et al., 2017). Unfortunately, several RCTs included in our meta-analysis did not report sufficient information on the characteristics of the applied physical activity regimen, and we decided to focus as much as possible on the role of nutritional supplements and therefore did not consider the arm randomized to the physical activity program. (If there is). In addition, multiple nutrients appear to improve frailty conditions in old age. As frailty in the elderly is multifactorial (Cereda et al., 2018), multicomponent nutritional supplementations can work better than supplementations with single components, but other studies are needed in this sense since only a few outcomes were improved by this kind of supplementation.

Another interesting finding of our study is that protein supplementation appears to be superior to multi-nutrient supplements and other single-nutrient supplements (HP-HMB, prebiotic, L-carnitine) on muscle mass, muscle strength, and physical performance tests of frail older adults. The likely reason is that frailty exacerbates the effects of age on protein metabolism through a range of factors, such as loss of muscle mass and increased muscle catabolism, implying that supplementation is insufficient to counteract this effect if its use is limited over time (Morais et al., 2000). Studies have observed that a higher intake of amino acids and proteins is associated with a lower prevalence of frailty in women (Verlaan et al., 2017). And an assessment of 2066 elderly people study demonstrated the association between protein intake and changes in lean mass, elderly people in the highest quintile in terms of protein intake lost 40% less lean mass and appendicular lean mass over three years than those in the lowest intake quintile (Houston et al., 2008). Another possible reason is that the sample size included in this study is limited, and more large-sample randomized controlled studies are needed to verify the results in the future.

In order to avoid, postpone, or reverse the severity of frailty and lessen the negative health effects of frailty upon persons, effective dietary treatments for frailty syndrome must be used (Davinelli et al., 2021). It has been shown in the past that a number of dietary supplements may prevent or lessen severe symptoms. A diet rich in protein benefits health, aids in the recovery of sick people, and maintains functional status in elderly people (Prokopidis et al., 2022a). An efficient method for improving muscle growth and strength as well as overall physical performance in older persons is the combination of resistance training and post-exercise protein supplementation (Khor et al., 2022; Velasco et al., 2022). Vitamin D intake is critical for older adults because of its widely recognized links to bone health, muscle strength and function (Li et al., 2022; Prokopidis et al., 2022b; Wang et al., 2022). The predominant form of vitamin D found in circulation is 25-hydroxyvitamin D (25(OH)D) (Bollen et al., 2022). Falls, fractures, discomfort, and low levels of 25(OH)D are all related to alterations in balance (Kupisz-Urbańska et al., 2021). All of these factors might result in a life of inactivity and weakness because of frailty.

The findings of our meta-analysis should be interpreted within its limitations. First, the number of studies included for each outcome was not sufficient. Second, it is possible that the different period of exposure to an oral supplementation can lead to different results in terms of efficacy. Finally, the median follow-up period was only 12 weeks. Despite these limitations, our study has some important strengths. For example, no low-quality literature was included and frail or pre-frail older adults were included (with frailty diagnostic assessments). These differ from previously published meta-analyses/systematic reviews.

In conclusion, nutritional supplementations seem to be useful in improving frailty, some muscle mass, muscle strength and physical performance, particularly if they are proteins. Other high-quality RCTs are needed to confirm our findings.

Ethical approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of The General Hospital of Ningxia Medical University. All participants signed an informed consent form for inclusion in the study.

Conflict of interest

All of the authors had no any personal, financial, commercial or academic conflicts of interest separately.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

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Author contributions

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References

Badrasawi, M., Shahar, S., Zahara, A. M., Fadilah, R. N., & Singh, D. K. A. (2016). Efficacy of L-carnitine supplementation on frailty status and its biomarkers, nutritional status, and physical and cognitive function among prefrail older adults: a double-blind, randomized, placebo-controlled clinical trial. *Clinical Interventions in Aging*, 11, 1675-1686. http://dx.doi.org/10.2147/CIA.S113287. PMid:27895474.

Beaudart, C., Dawson, A., Shaw, S. C., Harvey, N. C., Kanis, J. A., Binkley, N., Reginster, J. Y., Chapurlat, R., Chan, D. C., Bruyère, O., Rizzoli, R., Cooper, C., & Dennison, E. M. (2017). Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review. *Osteoporosis International*, 28(6), 1817-1833. http://dx.doi.org/10.1007/s00198-017-3980-9. PMid:28251287.

Bollen, S. E., Bass, J. J., Fujita, S., Wilkinson, D., Hewison, M., & Atherton, P. J. (2022). The vitamin D/vitamin D receptor (VDR) axis in muscle atrophy and sarcopenia. *Cellular Signalling*, 96, 110355. http://dx.doi.org/10.1016/j.cellsig.2022.110355. PMid:35595176.

Bonnefoy, M., Cornu, C., Normand, S., Boutitie, F., Bugnard, F., Rahmani, A., Lacour, J. R., & Laville, M. (2003). The effects of exercise and protein-energy supplements on body composition and muscle function in frail elderly individuals: a long-term controlled randomised study. *British Journal of Nutrition*, 89(5), 731-738. http://dx.doi.org/10.1079/BJN2003836. PMid:12720593.

Buigues, C., Fernández-Garrido, J., Pruimboom, L., Hoogland, A. J., Navarro-Martínez, R., Martínez-Martínez, M., Verdejo, Y., Mascarós, M. C., Peris, C., & Cauli, O. (2016). Effect of a prebiotic formulation on frailty syndrome: a randomized, double-blind clinical trial. *International Journal of Molecular Sciences*, 17(6), 932. http://dx.doi.org/10.3390/ijms17060932. PMid:27314331.

Cederholm, T., Barazzoni, R., Austin, P., Ballmer, P., Biolo, G., Bischoff, S. C., Compher, C., Correia, I., Higashiguchi, T., Holst, M., Jensen, G. L., Malone, A., Muscaritoli, M., Nyulasi, I., Pirlich, M., Rothenberg, E., Schindler, K., Schneider, S. M., van der Schueren, M. A., Sieber, C., Valentini, L., Yu, J. C., Van Gossum, A., & Singer, P. (2017). ESPEN guidelines on definitions and terminology of clinical nutrition. *Clinical Nutrition*, 36(1), 49-64. http://dx.doi.org/10.1016/j.clnu.2016.09.004. PMid:27642056.

Cereda, E., Veronese, N., & Caccialanza, R. (2018). The final word on nutritional screening and assessment in older persons. *Current Opinion in Clinical Nutrition and Metabolic Care*, 21(1), 24-29. http://dx.doi.org/10.1097/MCO.0000000000000431. PMid:29035968.

Collard, R. M., Boter, H., Schoevers, R. A., & Voshaar, R. C. O. (2012). Prevalence of frailty in community-dwelling older persons: a systematic review. *Journal of the American Geriatrics Society*, 60(8), 1487-1492. http://dx.doi.org/10.1111/j.1532-5415.2012.04054.x. PMid:22881367.

Davinelli, S., Corbi, G., & Scapagnini, G. (2021). Frailty syndrome: a target for functional nutrients? *Mechanisms of Ageing and Development*, 195, 111441. http://dx.doi.org/10.1016/j.mad.2021.111441. PMid:33539905.

Denison, H. J., Cooper, C., Sayer, A. A., & Robinson, S. M. (2015). Prevention and optimal management of sarcopenia: a review of combined exercise and nutrition interventions to improve muscle outcomes in older people. *Clinical Interventions in Aging*, 10, 859-869. PMid:25999704.

Dirks, M. L., Tieland, M., Verdijk, L. B., Losen, M., Nilwik, R., Mensink, M., Groot, L. C. P. G. M., & van Loon, L. J. C. (2017). Protein supplementation augments muscle fiber hypertrophy but does not modulate satellite cell content during prolonged resistance-type exercise training in frail elderly. *Journal of the American Medical Directors Association*, 18(7), 608-615. http://dx.doi.org/10.1016/j.jamda.2017.02.006. PMid:28377156.

Downs, S. H., & Black, N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of Epidemiology and Community Health*, 52(6), 377-384. http://dx.doi.org/10.1136/jech.52.6.377. PMid:9764259.

Ekram, A. R. M. S., Woods, R. L., Britt, C., Espinoza, S., Ernst, M. E., & Ryan, J. (2021). The association between frailty and all-cause mortality in community-dwelling older individuals: an umbrella review. *The Journal of Frailty & Aging*, 10(4), 320-326. PMid:34549245.

Fiatarone, M. A., O'Neill, E. F., Ryan, N. D., Clements, K. M., Solares, G. R., Nelson, M. E., Roberts, S. B., Kehayias, J. J., Lipsitz, L. A., & Evans, W. J. (1994). Exercise training and nutritional supplementation for physical frailty in very elderly people. *The New England Journal of Medicine*, 330(25), 1769-1775. http://dx.doi.org/10.1056/NEJM199406233302501. PMid:8190152.

Gao, H., Ma, H. J., Li, Y. J., Yin, C., & Li, Z. (2020). Prevalence and risk factors of postoperative delirium after spinal surgery: a meta-analysis. *Journal of Orthopaedic Surgery and Research*, 15(1), 138. http://dx.doi.org/10.1186/s13018-020-01651-4. PMid:32272939.

Gray-Donald, K., Payette, H., & Boutier, V. (1995). Randomized clinical trial of nutritional supplementation shows little effect on functional status among free-living frail elderly. *The Journal of Nutrition*, 125(12), 2965-2971. PMid:7500174.

Hoogendijk, E. O., Afilalo, J., Ensrud, K. E., Kowal, P., Onder, G., & Fried, L. P. (2019). Frailty: implications for clinical practice and public health. *Lancet*, 394(10206), 1365-1375. http://dx.doi.org/10.1016/S0140-6736(19)31786-6. PMid:31609228.

Houston, D. K., Nicklas, B. J., Ding, J., Harris, T. B., Tylavsky, F. A., Newman, A. B., Lee, J. S., Sahyoun, N. R., Visser, M., & Kritchevsky, S. B. (2008). Dietary protein intake is associated with lean mass change in older, community-dwelling adults: the Health, Aging, and Body Composition (Health ABC) study. *The American Journal of Clinical Nutrition*, 87, 150-155. http://dx.doi.org/10.1093/ajcn/87.1.150. PMid:18175749.

Hsieh, T. J., Su, S. C., Chen, C. W., Kang, Y. W., Hu, M. H., Hsu, L. L., Wu, S. Y., Chen, L., Chang, H. Y., Chuang, S. Y., Pan, W. H., & Hsu, C. C. (2019). Individualized home-based exercise and nutrition interventions improve frailty in older adults: a randomized controlled trial. *The International Journal of Behavioral Nutrition and Physical Activity*, 16(1), 119. http://dx.doi.org/10.1186/s12966-019-0855-9. PMid:31791364.

Jong, N., Paw, M. J. C. A., Groot, L. C., Hiddink, G. J., & van Staveren, W. A. (2000). Dietary supplements and physical exercise affecting bone and body composition in frail elderly persons. *American Journal of Public Health*, 90(6), 947-954. http://dx.doi.org/10.2105/AJPH.90.6.947. PMid:10846514.

Kang, L., Gao, Y., Liu, X. H., Liang, Y. H., Chen, Y. W., Liang, Y. H., Zhang, L., Chen, W., Pang, H. Y., & Peng, L. N. (2019). Effects of whey protein nutritional supplement on muscle function among community-dwelling frail older people: a multicenter study in China. *Archives of Gerontology and Geriatrics*, 83, 7-12. http://dx.doi.org/10.1016/j.archger.2019.03.012. PMid:30921603.

Khor, P. Y., Vearing, R. M., & Charlton, K. E. (2022). The effectiveness of nutrition interventions in improving frailty and its associated constructs related to malnutrition and functional decline among community-dwelling older adults: a systematic review. *Journal of Human Nutrition and Dietetics*, 35(3), 566-582. http://dx.doi.org/10.1111/jhn.12943. PMid:34494314.

Kim, C. O., & Lee, K. R. (2013). Preventive effect of protein-energy supplementation on the functional decline of frail older adults with low socioeconomic status: a community-based randomized controlled study. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 68(3), 309-316. http://dx.doi.org/10.1093/gerona/gls167. PMid:22879453.

Kim, H., Suzuki, T., Kim, M., Kojima, N., Ota, N., Shimotoyodome, A., Hase, T., Hosoi, E., & Yoshida, H. (2015). Effects of exercise and milk fat globule membrane (MFGM) supplementation on body composition, physical function, and hematological parameters in community-dwelling frail Japanese women: a randomized double blind, placebo-controlled, follow-up trial. *PLoS One*, 10(2), e0116256. http://dx.doi.org/10.1371/journal.pone.0116256. PMid:25659147.

Kojima, G., Taniguchi, Y., Iliffe, S., Urano, T., & Walters, K. (2019). Factors associated with improvement in frailty status defined using the frailty phenotype: a systematic review and meta-analysis. *Journal of the American Medical Directors Association*, 20(12), 1647-1649. E2. http://dx.doi.org/10.1016/j.jamda.2019.05.018. PMid:31301987.

Kupisz-Urbańska, M., Płudowski, P., & Marcinowska-Suchowierska, E. (2021). Vitamin D deficiency in older patients-problems of sarcopenia, drug interactions, management in deficiency. *Nutrients*, 13(4), 1247. http://dx.doi.org/10.3390/nu13041247. PMid:33920130.

Li, A., Shen, P., Liu, S., Wang, J., Zeng, J., & Du, C. (2022). Vitamin D alleviates skeletal muscle loss and insulin resistance by inducing vitamin D receptor expression and regulating the AMPK/SIRT1 signaling pathway in mice. *Food Science and Technology*, 42, e47921. http://dx.doi.org/10.1590/fst.47921.

Moraes, M. B., Araujo, C. F. M., Avgerinou, C., & Vidal, E. I. O. (2018). Nutritional interventions for the treatment of frailty in older adults: a systematic review protocol. *Medicine*, 97(52), e13773. http://dx.doi.org/10.1097/MD.0000000000013773. PMid:30593155.

Morais, J. A., Ross, R., Gougeon, R., Pencharz, P. B., Jones, P. J., & Marliss, E. B. (2000). Distribution of protein turnover changes with age in humans as assessed by whole-body magnetic resonance image analysis to quantify tissue volumes. *The Journal of Nutrition*, 130(4), 784-791. http://dx.doi.org/10.1093/jn/130.4.784. PMid:10736330.

Na, W., Kim, J., Kim, H., Lee, Y., Jeong, B., Lee, S. P., & Sohn, C. (2021). Evaluation of oral nutritional supplementation in the management of frailty among the elderly at facilities of community care for the elderly. *Clinical Nutrition Research*, 10(1), 24-35. http://dx.doi.org/10.7762/cnr.2021.10.1.24. PMid:33564650.

Ng, T. P., Feng, L., Nyunt, M. S., Feng, L., Niti, M., Tan, B. Y., Chan, G., Khoo, S. A., Chan, S. M., Yap, P., & Yap, K. B. (2015). Nutritional, physical, cognitive, and combination interventions and frailty reversal among older adults: a randomized controlled trial. *The American Journal of Medicine*, 128(11), 1225-1236.E1. http://dx.doi.org/10.1016/j.amjmed.2015.06.017. PMid:26159634.

Nieuwenhuizen, W. F., Weenen, H., Rigby, P., & Hetherington, M. M. (2010). Older adults and patients in need of nutritional support: review of current treatment options and factors influencing nutritional intake. *Clinical Nutrition*, 29(2), 160-169. http://dx.doi.org/10.1016/j.clnu.2009.09.003. PMid:19828215.

Park, Y., Choi, J.-E., & Hwang, H.-S. (2018). Protein supplementation improves muscle mass and physical performance in undernourished prefrail and frail elderly subjects: a randomized, double-blind, placebo-controlled trial. *The American Journal of Clinical Nutrition*, 108(5), 1026-1033. http://dx.doi.org/10.1093/ajcn/nqy214. PMid:30475969.

Peng, L. N., Cheng, Y. C., Yu, P. C., Lee, W. J., Lin, M. H., & Chen, L. K. (2021). Oral nutritional supplement with β-hydroxy-β-methylbutyrate (HMB) improves nutrition, physical performance and ameliorates intramuscular adiposity in pre-frail older adults: a randomized controlled trial. *The Journal of Nutrition, Health & Aging*, 25(6), 767-773. http://dx.doi.org/10.1007/s12603-021-1621-7. PMid:34179932.

Prokopidis, K., Giannos, P., Triantafyllidis, K. K., Kechagias, K. S., Mesinovic, J., Witard, O. C., & Scott, D. (2022a). Effect of vitamin D monotherapy on indices of sarcopenia in community-dwelling older adults: a systematic review and meta-analysis. *Journal of Cachexia, Sarcopenia and Muscle*, 13(3), 1642-1652. http://dx.doi.org/10.1002/jcsm.12976. PMid:35261183.

Prokopidis, K., Mazidi, M., Sankaranarayanan, R., Tajik, B., McArdle, A., & Isanejad, M. (2022b). Effects of whey and soy protein supplementation on inflammatory cytokines in older adults: a systematic review and meta-analysis. *British Journal of Nutrition*, 1-12. Ahead of print. http://dx.doi.org/10.1017/S0007114522001787. PMid:35706399.

Smoliner, C., Norman, K., Scheufele, R., Hartig, W., Pirlich, M., & Lochs, H. (2008). Effects of food fortification on nutritional and functional status in frail elderly nursing home residents at risk of malnutrition. *Nutrition*, 24(11-12), 1139-1144. http://dx.doi.org/10.1016/j.nut.2008.06.024. PMid:18789649.

Tieland, M., Dirks, M. L., van der Zwaluw, N., Verdijk, L. B., van de Rest, O., Groot, L. C., & van Loon, L. J. (2012). Protein supplementation increases muscle mass gain during prolonged resistance-type exercise training in frail elderly people: a randomized, double-blind, placebo-controlled trial. *Journal of the American Medical Directors Association*, 13(8), 713-719. http://dx.doi.org/10.1016/j.jamda.2012.05.020. PMid:22770932.

Traub, J., Reiss, L., Aliwa, B., & Stadlbauer, V. (2021). Malnutrition in patients with liver cirrhosis. *Nutrients*, 13(2), 540. http://dx.doi.org/10.3390/nu13020540. PMid:33562292.

Velasco, G. S., Ribeiro, C. B., Ramos, G. L. P. A., Silva, G. V. L. C., Silva, M. C., Silva, M. A. P., & Cappato, L. P. (2022). Supplement consumption profile by strength training practitioners in Brazil: a literature review. *Food Science and Technology*, 42, e113021. http://dx.doi.org/10.1590/fst.113021.

Verlaan, S., Ligthart-Melis, G. C., Wijers, S. L. J., Cederholm, T., Maier, A. B., & van der Schueren, M. A. E. (2017). High prevalence of physical frailty among community-dwelling malnourished older adults-a systematic review and meta-analysis. *Journal of the American Medical Directors Association*, 18(5), 374-382. http://dx.doi.org/10.1016/j.jamda.2016.12.074. PMid:28238676.

Wang, G., Zhang, J., Zhang, K., Zhao, Q., Zhou, F., Xu, J., Xue, W., Zhang, C., & Fu, C. (2022). Possible action mechanisms of vitamin D supplementation in combating obesity and obesity-related issues of bone health: a mini review. *Food Science and Technology*, 42, e114621. http://dx.doi.org/10.1590/fst.114621.

Weng, S., Wang, W., Wei, Q., Lan, H., Su, J., & Xu, Y. (2019). Effect of tranexamic acid in patients with traumatic brain injury: a systematic review and meta-analysis. *World Neurosurgery*, 123, 128-135. http://dx.doi.org/10.1016/j.wneu.2018.11.214. PMid:30529516.

Wu, P. Y., Huang, K. S., Chen, K. M., Chou, C. P., & Tu, Y. K. (2021). Exercise, nutrition, and combined exercise and nutrition in older adults with sarcopenia: a systematic review and network meta-analysis. *Maturitas*, 145, 38-48. http://dx.doi.org/10.1016/j.maturitas.2020.12.009. PMid:33541561.

Wu, S. Y., Hsu, L. L., Hsu, C. C., Hsieh, T. J., Su, S. C., Peng, Y. W., Guo, T. M., Kang, Y. W., & Pan, W. H. (2018). Dietary education with customised dishware and food supplements can reduce frailty and improve mental well-being in elderly people: a single-blind randomized controlled study. *Asia Pacific Journal of Clinical Nutrition*, 27(5), 1018-1030. PMid:30272850.

Xue, Q. L. (2011). The frailty syndrome: definition and natural history. *Clinics in Geriatric Medicine*, 27(1), 1-15. http://dx.doi.org/10.1016/j.cger.2010.08.009. PMid:21093718.