UNIVERSIDADE ESTADUAL PAULISTA "JÚLIO DE MESQUITA FILHO" FACULDADE DE MEDICINA

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Intervenções nutricionais para o tratamento da síndrome de fragilidade em idosos: revisão sistemática e metanálise

Dissertação apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Campus de Botucatu, para obtenção do título de Mestre em Saúde Coletiva.

Orientador: Prof. Dr. Edison Iglesias de Oliveira Vidal
Coorientadora: Profa. Dra. Christina Avgerinou

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DEDICATÓRIA

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RESUMO

A síndrome de fragilidade é definida como uma síndrome clínica de origem multicausal caracterizada por redução de reservas fisiológicas que aumentam a vulnerabilidade de um indivíduo a desfechos adversos como quedas, hospitalização, desenvolvimento de dependência funcional e morte. Acredita-se que a síndrome da fragilidade pode ser potencialmente modificável ou reversível mediante intervenções apropriadas. Esta é a primeira revisão sistemática com metanálise de ensaios clínicos randomizados para avaliar a eficácia de intervenções nutricionais para o tratamento da síndrome da fragilidade em idosos. Foram incluídos 11 ensaios clínicos randomizados com idosos de 60 anos ou mais com diagnóstico de síndrome da fragilidade ou pré-fragilidade. Metanálises bayesianas de efeitos randômicos não revelaram diferenças estatisticamente significativas ao comparar a suplementação nutricional isolada com grupos controle que receberam placebo ou nenhum tratamento em relação ao escore de síndrome da fragilidade (MD: 0,09 pontos, IC 95%: -0,45 a 0,62), Bateria de Desempenho Físico Breve (SMD: 0,29, IC 95%: -0,55 a 1,40), força muscular (SMD: -0,14, IC 95%: -0,38 a 0,09), velocidade da marcha (SMD: 0,06, IC 95%: -0,04 a 0,17), massa magra apendicular (MD: 0,60kg, IC 95%: -0,82 a 2,01), massa gorda (MD: 1,67kg, IC 95%: -0,63 a 3,96), memória declarativa (SMD: 0,11, IC 95%: -0,31 a 0,53), linguagem e função executiva (MD: 0,21 pontos, IC 95%: -0,99 a 1,42) e outros resultados. Estudo único de intervenção de educação nutricional também não demostrou melhorias significativas em comparação com aconselhamento genérico de saúde. A qualidade geral das evidências avaliadas usando o sistema GRADE foi classificada como muito baixa a moderada devido a imprecisão das estimativas de efeito. Conclui-se que os presentes resultados sugerem com grau de certeza muito baixo a moderado que o uso de suplementos nutricionais ou de educação nutricional isoladamente não são efetivos para o tratamento da síndrome de fragilidade em idosos. Mais e maiores ensaios clínicos randomizados se fazem necessários para determinar o papel de intervenções nutricionais no tratamento da síndrome de fragilidade. (PROSPERO: CRD42018111510).

ABSTRACT

Frailty is a clinical syndrome of multicausal origin characterized by a reduction of physiological reserves that increase the vulnerability of an individual to adverse outcomes such as falls, hospital admission, disability and death. It has been suggested that frailty can be potentially modifiable or even reversible with appropriate interventions. This is the first systematic review with meta-analysis or Randomized Clinical Trials (RCTs) to appraise the effectiveness of nutritional interventions for the treatment of frailty in older adults. We included 11 RCTs of people aged 60 years and older with a diagnosis of frailty or pre-frailty. Bayesian random effects meta-analyses found no statistically significant differences when comparing nutritional supplementation alone with control groups receiving placebo or no treatment regarding frailty score (MD: 0.09 points, 95%CI: -0.45 to 0.62), Short Physical Performance Battery (SMD: 0.29, 95%CI: -0.55 to 1.40), muscle strength (SMD: -0.14, 95%CI: -0.38 to 0.09), gait speed (SMD: 0.06, 95%CI: -0.04 to 0.17), appendicular lean mass (MD: 0.60kg, 95%CI: -0.82 to 2.01), fat mass (MD: 1.67kg, 95%CI: -0.63 to 3.96), declarative memory (SMD: 0.11, 95%CI: -0.31 to 0.53), language & executive function (MD: 0.21 points, 95%CI: -0.99 to 1.42) and other outcomes. Single study of nutritional education interventions also did not show any significant improvements in comparison with general health advice. The overall quality of evidence assessed using the GRADE system was classified as very low to moderate because of imprecision of findings. Our results suggest with very low to moderate certainty that neither nutritional education nor nutritional supplements in isolation are effective for the management of frailty in older people. More and larger RCTs are warranted to establish the role of nutritional interventions for the treatment of frailty. (PROSPERO: CRD42018111510)

Sumário

1. INTRODUÇÃO

A síndrome de fragilidade é definida como uma síndrome clínica de origem multicausal caracterizada por redução de reservas fisiológicas que aumentam a vulnerabilidade de um indivíduo a desfechos adversos como quedas, hospitalização, desenvolvimento de dependência funcional e morte(1–6).

A síndrome de fragilidade é considerada hoje como uma das mais importantes síndromes geriátricas, constituindo um importante campo de pesquisa dentro da gerontologia(7,8). O conceito de síndrome de fragilidade contribuiu de forma importante para o desenvolvimento desse campo ao chamar atenção para uma multiplicidade de fatores subclínicos que contribuem para a redução da capacidade dos idosos em manterem sua homeostase frente a eventos estressores(9). De fato, estudos utilizando inclusive diferentes definições operacionais de síndrome de fragilidade demonstraram que a mesma representa um importante fator de risco para uma variedade de desfechos negativos. Por exemplo, a síndrome de fragilidade mostrou-se associada a uma chance de quedas 84% superior quando comparada a idosos não frágeis(10). Essa síndrome também associou-se a uma chance 70% maior de fraturas(11), aumento de 30% na chance de demência(12) e um aumento de 90% no risco de hospitalização(3). Observa-se também uma associação inversa entre síndrome de fragilidade e qualidade de vida de idosos residentes na comunidade(13).

Esses dados são especialmente relevantes quando se leva em consideração os resultados dos estudos de prevalência dessa síndrome entre os idosos e as perspectivas de envelhecimento populacional em todo o mundo(14). Revisão sistemática sobre a prevalência da síndrome de fragilidade entre idosos residentes na comunidade identificou que essa prevalência variou de 4 a 59%, com uma média ponderada de 11%(15). Nota-se ainda importante aumento da prevalência dessa síndrome entre indivíduos de idade mais avançada, chegando a alcançar valores médios de cerca de 27% entre idosos com mais de 85 anos de idade. Já entre idosos institucionalizados a sua prevalência variou de 19 a 76%, com média ponderada de 52%(16).

Um importante painel de especialistas responsáveis pela primeira reunião de consenso internacional bem sucedida sobre a definição da síndrome de fragilidade considerou que havia alguma evidência apontando para possíveis

benefícios de quatro intervenções para o manejo dessa condição: exercício físico, suporte calórico e proteico, suplementação de vitamina D e redução de polifarmácia(1).

A perda de massa muscular é uma das consequências da perda de peso em idosos, assim como a redução de força, de mobilidade e a disfunção imunológica, os quais também representam características típicas dos estados de fragilidade(17). Apesar de uma compreensão limitada dos mecanismos subjacentes que associam os nutrientes individuais à síndrome da fragilidade, a desnutrição tem sido associada a um maior risco desta síndrome(18). Adicionalmente, as alterações relacionadas à idade no metabolismo das proteínas são exacerbadas pela fragilidade, o que leva a um estado catabólico adicional e à perda de massa muscular(19). A menor ingestão alimentar também está ligada ao risco de um estado nutricional abaixo do ideal combinado à deficiência de micronutrientes(20).

A síndrome da fragilidade pode ser potencialmente modificável ou reversível, se houver intervenções apropriadas(21). Existem padrões alimentares, como a dieta do mediterrâneo, que foram associados a um menor risco de síndrome da fragilidade(22). Há também evidências de que o consumo de frutas e vegetais pode estar associado a um menor risco dessa síndrome(23). Além disso, maior ingestão de proteínas na dieta pode estar intimamente ligado a um menor risco de fragilidade(24). O papel da nutrição como um fator potencialmente modificável é, portanto, de grande interesse no manejo para interromper a progressão da fragilidade.

Embora várias revisões sistemáticas de ensaios clínicos randomizados (ECRs) sobre o manejo da síndrome da fragilidade tenham sido feitas(14,25–31), essas revisões enfatizaram intervenções associadas à atividade física, enquanto as intervenções nutricionais foram avaliadas brevemente e de forma secundária.

Em função do fenômeno global do envelhecimento populacional(14), do aumento da prevalência da síndrome de fragilidade em idades mais avançadas e das consequências negativas dessa síndrome em termos de risco de deterioração funcional, desenvolvimento de dependência, morte e outras complicações, adquire especial relevância a produção de sínteses do

conhecimento existente sobre a eficácia e efetividade de intervenções para o manejo dessa síndrome visando à prevenção de tais eventos adversos. Tendo em vista a relevância do tema e os argumentos apresentados acima propomos a presente revisão sistemática com o objetivo de avaliar a efetividade de intervenções nutricionais no tratamento da síndrome da fragilidade em idosos.

Após a elaboração e inscrição do protocolo desta revisão sistemática junto a *International Prospective Register of Systematic Reviews* – PROSPERO (Anexo 1), publicamos o protocolo no periódico *Medicine*(32) (Anexo 2). Optamos por apresentar também os resultados, discussão e conclusões desta revisão sistemática e metanálise no formato artigo, na língua inglesa, com vistas a pronta submissão deste.

2. PROTOCOLO PUBLICADO NO PERIÓDICO *MEDICINE*

Nutritional interventions for the treatment of frailty in older adults: a systematic review protocol

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Abstract

Background: Frailty has been defined as a clinical syndrome of multicausal origin characterized by a reduction of physiologic reserves that increase the vulnerability of an individual to adverse outcomes such as the development of functional dependence and death. Considered one of the most important geriatric syndromes, frailty's prevention and management represent

important goals for gerontology and geriatrics. Although nutrition plays an important role within the multifactorial susceptibility for this syndrome, up to the present no systematic review specifically addressed the effectiveness of nutritional interventions for the treatment of frailty. Therefore, we propose the present systematic review with the aim to assess the effectiveness of nutritional interventions for the treatment of frailty in older adults living in the community or in long-term care facilities.

Methods: We will search Medline (via Pubmed), Embase, Cinahl, Central, Lilacs, Web of Science, and sources of gray literature. We will accept trials whereby the unit of randomization consisted of individuals or clusters of individuals. Our primary outcome is all-cause mortality. Secondary outcomes are quality of life, functional status, cognitive function, frailty status, body composition, and physical activity. Risk of bias will be assessed using the Cochrane Collaboration tool. We will analyze the overall strength of the evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool. Two independent researchers will conduct all evaluations and any disagreements will be resolved through the participation of a 3rd author. If possible, we will perform random-effects meta-analyses and subgroup analyses concerning specific details of nutritional interventions (e.g., components and duration), research scenario, risk of bias, and criteria used to diagnose frailty.

Conclusion: In this systematic review protocol we outline the details of the aims and methods of a systematic review on the effectiveness of nutritional interventions for the management of frailty in older adults living in the community or in long-term care facilities.

Abbreviations: GRADE = Grading of Recommendations Assessment, Development, and Evaluation, GRADEPRO = Grading of Recommendations Assessment, Development, and Evaluation Profiler Software, ICTRP = World Health International Clinical Trials Registry Platform, OPEN GRAY = Gray Literature in Europe, PROSPERO = International Prospective Register of Systematic Reviews.

Keywords: aged, diet, dietary supplements, feeding, frailty, nutrition, systematic review

Introduction

Frailty has been defined as a clinical syndrome of multicausal origin characterized by a reduction of physiological reserves that increase the vulnerability of an individual to adverse outcomes such as the development of functional dependence and death [1].

Considered one of the most important geriatric syndromes, frailty's prevention and management represent important goals for gerontology and geriatrics [2]. The concept of frailty has greatly contributed to the development of this field by highlighting a multiplicity of subclinical factors (i.e. going beyond the presence of functional dependence and comorbidities) and contributing to the reduction of the capacity of older adults to maintain their homeostasis when exposed to stressor events [3]. In fact, studies using different operational definitions of frailty have shown that it represents an important risk factor for a variety of negative outcomes. For example, frail older adults were found to be at an increased risk of falling by 84%, when compared to those who are non-frail [4]. The frailty syndrome has also been associated with 70% greater chance of fractures [5], 30% increase in the risk of developing dementia [6], and 90% increase in the risk of hospitalization [7]. An inverse association between frailty and quality of life of older adults living in the community has also been observed [8].

These data are especially relevant when one considers the results of studies reporting the prevalence of this syndrome among older adults and the perspectives of population aging worldwide[9]. A systematic review on the prevalence of frailty among community-dwelling elderly identified that prevalence ranged from four to 59%, with a weighted average of 11%[10]. A significant increase in the prevalence of this syndrome is also noted among individuals of a more advanced age, reaching an average of about 27% among adults older than 85 years of age[11]. Amidst institutionalized older adults, the prevalence of frailty ranged from 19 to 76%, with a weighted average of 52%[11].

An important meeting of experts, leading to the first successful international consensus on the definition of frailty, considered that there was some evidence suggesting possible benefits of four types of interventions for managing this condition: physical exercise, caloric and protein support, vitamin D supplementation and reduction of polypharmacy[1].

Loss of muscle mass is one of the consequences of weight loss in older adults, along with reduction of strength, mobility and immune dysfunction, which represent typical characteristics of frailty. In addition, malnutrition in older adults increases the risk of hospitalization, functional dependence and death in this population[12]. The association between nutritional factors and the occurrence of frailty was also observed in the systematic review of Lorenzo-López L et al.,that analyzed data from 19 observational studies[13]. The nutritional factors examined by this review were micronutrients, macronutrients, diet quality, antioxidants and score in the Mini Nutritional Assessment[13].

Due to the global phenomenon of population ageing[2], the increased prevalence of frailty at more advanced ages and the negative consequences of this syndrome, studies about efficacy and effectiveness of interventions to manage this syndrome have great importance, particularly aiming at the prevention of such adverse events. In view of the relevance of the topic and the arguments presented above, we propose the present systematic review with the aim to assess the effectiveness of nutritional interventions for the treatment of frailty in older adults living in the community or in long-term care facilities.

Methods

Study registration

This systematic review protocol has been registered on PROSPERO under the number of CRD42018111510, and was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocol[14]. This is a literature-based study, so ethical approval is unnecessary.

Selection criteria

Types of studies

We will include only parallel-group randomized clinical trials published since 2001 in English, Portuguese or Spanish. We will accept trials whereby the unit of randomization consisted of individuals or clusters of individuals.

Types of participants

We will include studies that recruited older adults (aged 60 years or older) with a diagnosis of frailty or pre-frailty and living in the community or in long-term care facilities. We will accept any criteria used by original studies to diagnose that syndrome. Studies that have been performed during hospitalization episodes will

not be included.

Types of interventions

We will include studies that have implemented at least one of the following nutritional interventions: nutritional education / dietary prescription, the use of hypercaloric or hyperproteic dietary oral supplements and the delivery of specific diets. Additionally, we will also include studies that adopted any of the above interventions concomitantly with another single or multifactorial intervention provided that the comparator was the same set of interventions without the nutritional intervention component. We will accept as comparators standard treatment, placebo, other nutritional interventions, and multifactorial interventions without a nutritional component.

Types of outcomes

We will include studies if they report at least one of the following outcome measures.

Primary outcomes

(1) Mortality

Secondary outcomes

(1) Quality of life, measured by any instrument.

(2) Functional capacity, measured by any instrument.

(3) Cognitive function, measured by any instrument.

(4) State of frailty, measured by any instrument.

(5) Body composition, measured by any instrument.

(6) Physical activity, measured by any instrument.

Search methods for study identification

Two independent researchers will examine the lists of references identified through electronic search. We will also hand-search reference lists of relevant publications including review articles on frailty and of original studies considered eligible for the review. Additionally, we will contact experts in the field of nutrition and frailty to ask for references to published and unpublished data. We also intend to contact researchers to request relevant unpublished data whenever possible.

Electronic searches

We will search the following databases for relevant studies, using the

search terms detailed in Appendix 1: Medline (via Pubmed), Embase, Cinahl, Central, Lilacs e Web of Science.

Other resources

We will search the following databases for gray literature: System for information on Gray Literature in Europe (Open Gray), Virginia Henderson Global Nursing e-Repository, National Library of Medicine Bookshelf, ClinicalTrials.gov, and World Health International Clinical Trials Registry Platform (ICTRP).

Data collection and analysis

Selection of studies

For all studies identified, two authors will independently screen and review the titles and abstracts. Full versions of potentially relevant studies will be obtained. Where applicable, we will contact the authors of selected studies to ask for additional data. Disputes regarding the inclusion of a study will be resolved through discussion with a third reviewer.

Data extraction and management

Two reviewers will extract data independently using a standardized pre-piloted form including the following data: complete reference; time period when the study was conducted; geographical location; presence of divergences between the study protocol and published results; study design; types of interventions and comparators; duration of the intervention and of follow-up; inclusion/exclusion criteria; sample size; characteristics of the population; balance between groups at the baseline; funding source; method of randomization; presence of simultaneous interventions; diagnostic criteria of frailty; nutritional interventions; details of the intervention, including type, dose, frequency, and duration; control treatment; outcome measures; blinding (patients, field professionals and outcome assessors); duration of follow-up; loss of follow-up; results; intention-to-treat analysis; conclusions reported by the study authors; and research limitations. In addition, there will be a field for the registration of other information deemed relevant by the reviewers.

Disagreements about extracted data will be resolved by consensus, and an independent reviewer will be consulted if disagreement persists.

Assessment of bias risk

To assess the risk of bias in the included studies, two review authors will

independently use The Cochrane Collaboration's Risk of Bias tool for randomized clinical trials[15]. Accordingly, the following domains will be assessed: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other bias. Each of these criteria will be assigned one of the following categories: low risk of bias; high risk of bias; or unclear risk of bias, where unclear relates to the lack of precise information or uncertainty over the potential for bias.

Where applicable, the investigators of selected trials will be contacted to provide additional relevant information. Disagreements between the authors regarding the assessment of risk of bias will be resolved by consensus, and a third reviewer will be consulted when needed.

Rating quality of evidence

We will analyze the overall strength of the evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool. This system represents a method that evaluates the quality of evidence in systematic reviews explicitly, comprehensively, transparently and pragmatically[16]. The GRADE system evaluates the following dimensions regarding the quality of evidence: study limitations / risk of bias, inconsistency, indirect effects, inaccuracy, publication bias, and factors that may increase the quality of evidence. According to GRADE, the quality of the evidence regarding each outcome analyzed is classified into one of four levels: high, moderate, low and very low[16].

We will use the GRADE profiler software (GRADEPRO) to create 'summary of findings' tables with outcome specific information concerning the overall quality of evidence and the magnitude of effect of the interventions examined by the examined body of evidence.

Measures of treatment effects

Dichotomous data: the results will be presented as the risk ratios with 95% confidence intervals. Continuous data: the results will be presented as the mean difference, if outcomes are measured using similar scales between trials. We will use the standardized mean difference to combine trials that measure the same outcome using different scales or instruments.

Unit of analysis issues

The appropriate unit of analysis will be the individual patient, rather than hospitals or health centers. In studies with multiple intervention groups, we will include only the comparisons between groups that meet our eligibility criteria. If more than one pair of intervention comparisons are eligible for a given meta-analysis and those pairs of comparisons have at least one intervention group in common, we will proceed using one of the methods recommended by the Cochrane Collaboration in the following order of preference according to the feasibility of each approach: 1) we will attempt to merge the intervention groups in order to yield a single pairwise comparison; 2) we will attempt to account for the correlation between correlated comparisons by calculating a weighted average of the different pairwise comparisons; 3) we will perform a network meta-analysis.

Missing data

Where applicable, we will contact the chief investigators of clinical trials with missing data or unclear information (e.g. unclear risk of bias). Whenever possible will include in meta-analyses data from intention-to-treat (ITT) analyses. We will not perform imputation procedures for missing data.

Assessment of reporting biases

If there are sufficient numbers of trials (at least ten), we will construct a funnel plot and we will apply the Egger tests and the Trim and Fill method in the evaluation of publication bias.

Data synthesis

We will organize the synthesis of data according to the types of nutritional interventions studied, the types of comparators, and populations studied (i.e. older adults living in the community or in long-term care facilities).

If the included studies are sufficiently similar in terms of population, inclusion criteria, interventions and results, we will perform quantitative synthesis using the random effects models.

Assessment of heterogeneity

If the available data allows the performance of meta-analyses, we will assess statistical heterogeneity by means of I^2 statistics, which will be interpreted according to the current Cochrane Collaboration guidance as follows: 0–40% might not be important; 30–60% may represent moderate heterogeneity; 50–90%

may represent substantial heterogeneity; 75–100% considerable heterogeneity[15]. If we find substantial heterogeneity we will attempt to perform subgroup analyses as described below.

Subgroup analyses

If sufficient data are available, we will perform the following subgroup analyses: concerning specific details of nutritional interventions (e.g. components and duration), research scenario (i.e. community or long-term care facilities), risk of bias and criteria used to diagnose frailty.

Sensitivity analysis

We have not planned any sensitivity analyses.

Discussion

Nutrition plays an important role within the multifactorial susceptibility of this syndrome; however, up to the present no systematic review specifically addressed the effectiveness of nutritional interventions for the treatment of frailty. The systematic reviews identified in the literature on this topic emphasize interventions related to physical activity without any particular focus to nutritional interventions, which were generally analyzed briefly and in a secondary manner [9,13,17–22].

Conflict of interest

The authors have no conflict of interest to disclose

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3. ARTIGO CONTENDO OS RESULTADOS DA REVISÃO SISTEMÁTICA COM METANÁLISE

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

Although nutrition is considered an important component of interventions used in the management of frailty, the actual effectiveness of interventions addressing nutrition in frail older people remains unclear. We aimed to appraise the evidence regarding the effectiveness of nutritional interventions for the management of frailty in older adults. We searched MEDLINE, Embase, CINAHL, CENTRAL, Web of Science and LILACS from 2000 to November 2019 to identify randomized controlled trials. A Bayesian random-effects model was used for pooled data analysis. Continuous variables were expressed as mean differences or standardized mean differences and 95%CrI (credible interval). Eighteen (18) publications presenting data from 16 studies (1,493 older people with a mean follow-up of three – 24 months) were included. Meta-analyses showed that no outcome changed significantly (Standard Mean Difference: 0.01; 95% CrI: -0.21 to 0.20; Tau = 0.13, I^2 = 21%). Our results suggest with a degree of certainty ranging from very low to moderate that neither nutritional education nor nutritional supplements delivered in isolation are significantly effective for the management of frailty in older people. (PROSPERO: CRD42018111510).

Keywords: Aged, Frailty, Nutrition, Systematic Review, Meta-analysis

1. Introduction

Frailty is a clinical syndrome of multicausal origin characterized by a reduction of physiological reserves that increase 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 reduction of strength, mobility and immune dysfunction, represent typical characteristics 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). In addition, 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 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. Furthermore, to our knowledge, no meta-analysis focusing on RCTs of

nutritional interventions for the management of frailty has been published. Hence, the present systematic review aims 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 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 hypercaloric or hyperproteic dietary oral supplements and the delivery of specific diets. 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 for 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 hyperproteic and/or hypercaloric supplements.

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, assignment to intervention, adhering to intervention, missing outcome data, measurement of the outcome, reported result and overall risk of bias. 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 strengthof 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 only 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). We performed Bayesian random-effects meta-analysis via the Divergence Restricting Conditional Tesselation algorithm(37,38). 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(39–41). We used a uniform noninformative prior for the mean values of the pooled estimate and informative priors for the between-study heterogeneity parameter tau described by Rhodes et al(42) based on the assessment of 6,672 continuous-outcome meta-analyses from the Cochrane Collaboration. More specifically, for frailty status, strength, walking speed, Short Physical Performance Battery (SPPB) and physical activity outcomes we used the tau 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(42). For the outcomes related to body composition we used the tau 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 tau prior for a general setting without taking into account other meta-analysis characteristics reported in section 3.3 of that same article.

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(43).

We calculated both pooled estimates with 95% credible intervals (CrI) for pooled mean differences (MD) or SMD and prediction intervals as recommended by Higgins(35) and Gudat(44). 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(45–50). All analyses were performed using the R software version 3.6.0 by means of the metafor(51) and bayesmeta packages(37).

2.5 Changes to the review protocol

We implemented the following changes to our review protocol: 1) we decided not to exclude studies based on its language of publication; 2) we added

falls and hospitalizations as secondary outcomes. Those changes were performed with the intent of improving the quality of our review.

3. Results

3.1 Selection Process and Study Characteristics

Figure 1 presents the flow diagram of the study selection process. We included 18 publications from 16 studies (1,493 older people with a mean follow-up of three – 24 months). The main characteristics of the 18 included publications are summarized in Table 1. All studies(52–69) recruited subjects with frailty or pre-frailty. Most studies excluded patients with cancer (eight studies), chronic renal failure (seven studies), diabetes (six studies) and neurologic impairment. Seven studies(52,57–59,61,62,69) 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(53,54,60) defined frailty based on the Chin A Paw criteria(70). One study(66) used a modification of the CHS frailty criteria. Seven studies(55,56,63–65,67,68) 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 ≥ 30 kg/m²)(64).

Regarding the setting of the included studies, 11 studies recruited participants living in the community(54,59–63,65,66,69), four studies recruited participants from a home for elderly persons or sheltered housing(55,63,67,68), and another study included both participants living in nursing homes and in the community(64) (Table 1).

In 14 studies the nutritional intervention consisted of nutritional supplements(52,55–59,61–65,67–69) and in two studies the intervention was individual dietary counselling(53,54,60,66). Nutritional supplements in all but one study(62) involved protein supplementation (median: 15g, interquartile range [IQR]: 11 to 15g). In eight studies(55,56,62,63,65,67–69) nutritional supplements were hypercaloric and contained a median value of 275 kcal (IQR: 225 to 300 kcal). Regarding the use of comparators, ten studies(52,55–59,61,62,64,68) used a placebo supplement, three studies(53,54,60,66,69) used general health advice, in two studies(63,65) the control group did not receive any treatment and one study(67) used dietary recommendations based on the German reference values (Table 1).

Baseline differences between intervention and control groups were observed in one study(54) 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

Table 2 describes the assessment of risk of bias of individual studies. The overall classification of risk of bias for eight studies was considered high (53,54,60,63–69), as posing some concerns for three studies(55,56,62), and as low for five studies(52,57–59,61). Main reasons for classifying studies as having high risk of bias were issues related to the assignment to intervention and randomization process domains. We present Summary of Findings tables with the classification of the overall certainty of evidence following the GRADE approach for each outcome across studies in the appendix (Supplementary tables 1 and 2) (32). The certainty of evidence for all outcomes was classified as

very low, low or moderate and the main reasons for downgrading the quality of evidence was imprecision of findings related to small sample sizes, confidence intervals encompassing both significant benefits and harms and high risk of bias in individual studies.

3.3 Outcomes

3.3.1 Mortality

We did not find any RCTs that assessed our primary outcome, mortality, in the context of this review.

3.3.2 Quality of life

One study evaluated the effect of a nutritional supplement on the quality of life of older people with frailty or pre-frailty compared with no treatment and did not find any statistically significant difference on quality of life measured by the SF-36 instrument(63) (89 subjects; Mean Difference [MD]: 8.7; 95% CrI: -6.01 to 23.41; GRADE: low) (Appendix - Supplementary Table 2). Another study(66) compared a nutritional education plus 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) (Appendix - Supplementary Table 1).

3.3.3 Functioning

3.3.3.1 Nutritional Supplements and Functioning

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(62,69). One study(69) compared

nutritional supplement plus exercise against exercise plus 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, respectively, p<0.001). The other study(62) compared nutritional supplement with placebo and did not find any significant differences 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 (Appendix - Supplementary Table 2).

The meta-analysis of seven RCTs(57,58,61,62,65,68,69) comparing nutritional supplements with placebo or no treatment regarding gait speed did not show any statistically significant difference between those groups (473 subjects; SMD = 0.04; 95% CrI: -0.01 to 0.10; Tau = 0.03, I^2 = 14%; GRADE: low) (Figure 2I; Appendix - Supplementary Table 2).

The meta-analysis of nine studies that compared nutritional supplements with placebo or no treatment in terms of muscle strength with a follow-up of 12 weeks (57,58,61–63,65,67–69) did not find any statistically significant difference between the two groups (603 subjects; SMD: -0.01; 95% CrI: -0.21 to 0.20; Tau = 0.13, I^2 = 21%; GRADE: low) (Figure 2H; Appendix - Supplementary Table 2). Four studies(57,58,62,68) also reported on muscle strength with a follow-up period of 24 weeks or longer and also did not show any statistically significant difference between the two groups (260 subjects; SMD: 0.09; 95% CrI: -0.21 to 0.39; Tau = 0.11, I^2 = 14%) (Figure 2D; Appendix – Supplementary Table 2).

The meta-analysis of four studies(57,58,61,65) 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; Tau = 0.3, I^2 = 17%; GRADE: very low) (Figure 2G; Appendix - Supplementary Table 2).

3.3.3.2 Nutritional Education and Functioning

A single study(53) 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 and IQR of 34 to 47 for the control group). The quality of evidence for that dyad of outcome and intervention was graded as low (Appendix - Supplementary Table 1).

The meta-analysis of two studies(54,66) 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; Tau = 0.16, I^2 = 22%; GRADE: Very Low) (Figure 3A; Appendix - Supplementary Table 1).

3.3.4 Physical activity

3.3.4.1 Nutritional Supplements and Physical Activity

The meta-analysis of two studies(61,62) 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; Tau = 0.18, I^2 = 42%; GRADE: low) (Figure 2A;

Appendix - Supplementary Table 2).

3.3.4.2 Nutritional Education and Physical Activity

A single study(53) 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 with and 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) with 31 subjects. We graded the quality of evidence for nutritional education for those outcomes as very low (Appendix - Supplementary Table 1).

3.3.5 Frailty status

The metanalysis of three studies(61,62,69) comparing nutritional supplements with placebo regarding frailty status 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; Tau = 0.27, I^2 = 6%, GRADE: very low) (Figure 2F; Appendix - Supplementary Table 2).

3.3.6 Cognitive function

Three studies(52,55,59) 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] immediate and delayed recall) (180 subjects; SMD: 0.30; 95% CrI: -0.28 to 0.86; Tau = 0.22, I^2 = 42%; and 167 subjects; SMD: 0.11;

95% CrI: -0.31 to 0.53; Tau = 0.12, I^2 = 16%; GRADE: low) (Figure 2B and 2L; Appendix - Supplementary Table 2), and for two other tests evaluating language and executive function (Verbal Fluency test for the following categories: professionals and animals) (180 subjects; MD: 1.10; 95% CrI: -0.18 to 2.29; Tau = 0.19, I^2 = 3.5%;; and 180 subjects; MD: 0.21; 95% CrI: -0.99 to 1.42; Tau = 0.15, I^2 = 1.8%; GRADE: moderate) (Figure 2C and 2M; Appendix - Supplementary Table 2). None of the meta-analyses of the results of the cognitive tests described above showed any statistically significant differences between the treatment 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(57,58,61,67,68) 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; Tau = 0.18, I^2 = 0%; GRADE: low) (Figure 2J; Appendix - Supplementary Table 2). The meta-analysis of the results of two studies(57,58) concerning total fat mass also did not show any statistically significant differences between intervention and control groups (118 subjects; MD = 1.67 kg, 95% CrI: -0.63 to 3.96; Tau = 0.18, I^2 = 0%; GRADE: moderate) (Figure 2K; Appendix - Supplementary Table 2). The meta-analysis of the results of two studies(67,68) concerning fat-free-mass also did not show any statistically significant differences

between the two groups (94 subjects; MD = 1.41 kg, 95% CrI: -0.00 to 2.76; Tau = 1.74, I^2 = 1.2%; GRADE: very low) (Figure 2E; Appendix - Supplementary Table 2).

3.3.7.2 Nutritional Education and Body Composition

A single study(60) 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) (Appendix - Supplementary Table 1).

3.3.8 Falls

We did not find any RCTs that assessed the falls outcome in the context of this review.

3.3.9 Hospitalization

We did not find any RCTs that assessed hospitalization as an outcome in the context of this review.

4. Discussion

This systematic review identified 18 studies reporting on 16 randomized trials that included a total of 2,253 older people with a mean follow-up between 3 and 24 months 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(26,71,72). Dedeyne et al(71) 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(72) 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(72). 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. from hospital to the community), and included only one of the studies included in our review, none of the 6 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 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 alone compared with placebo or no treatment. Our review included two of those studies(14,65) and excluded the third(73) because the nutritional supplement used in that study was neither hypercaloric nor hyperproteic.

4.2 Strengths and limitations of this review

Our review has a number of potential limitations. Frailty is not always well defined or labeled within databases, which may mean that some relevant studies may not have been included. 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 of several other health conditions(24,26,27,71). To counterbalance that limitation we accepted very broad definitions of frailty as was adopted in several other reviews on that subject (18,21,24,26,71). 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). Additionally, because of the small number of studies included we were not able to perform subgroup analyses for most outcomes. Finally, we did not assess the change in total nutritional intake for 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 a number of 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 an extensive review 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).

4.4 Implications for practice and research

Our results are consistent with 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)(74). 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 include important clinical outcomes such as mortality and hospital admission, which are known to be adverse events related to frailty but were not measured in any of the included studies in this review. More robust research studies including larger number of subjects are needed to establish the role of nutrition in the treatment of frailty.

5. Conclusions

Our results suggest mostly with low to very low degree of certainty that neither nutritional education nor nutritional supplements in isolation are effective for the management of frailty in older people.

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Figure 1. Flow chart diagram

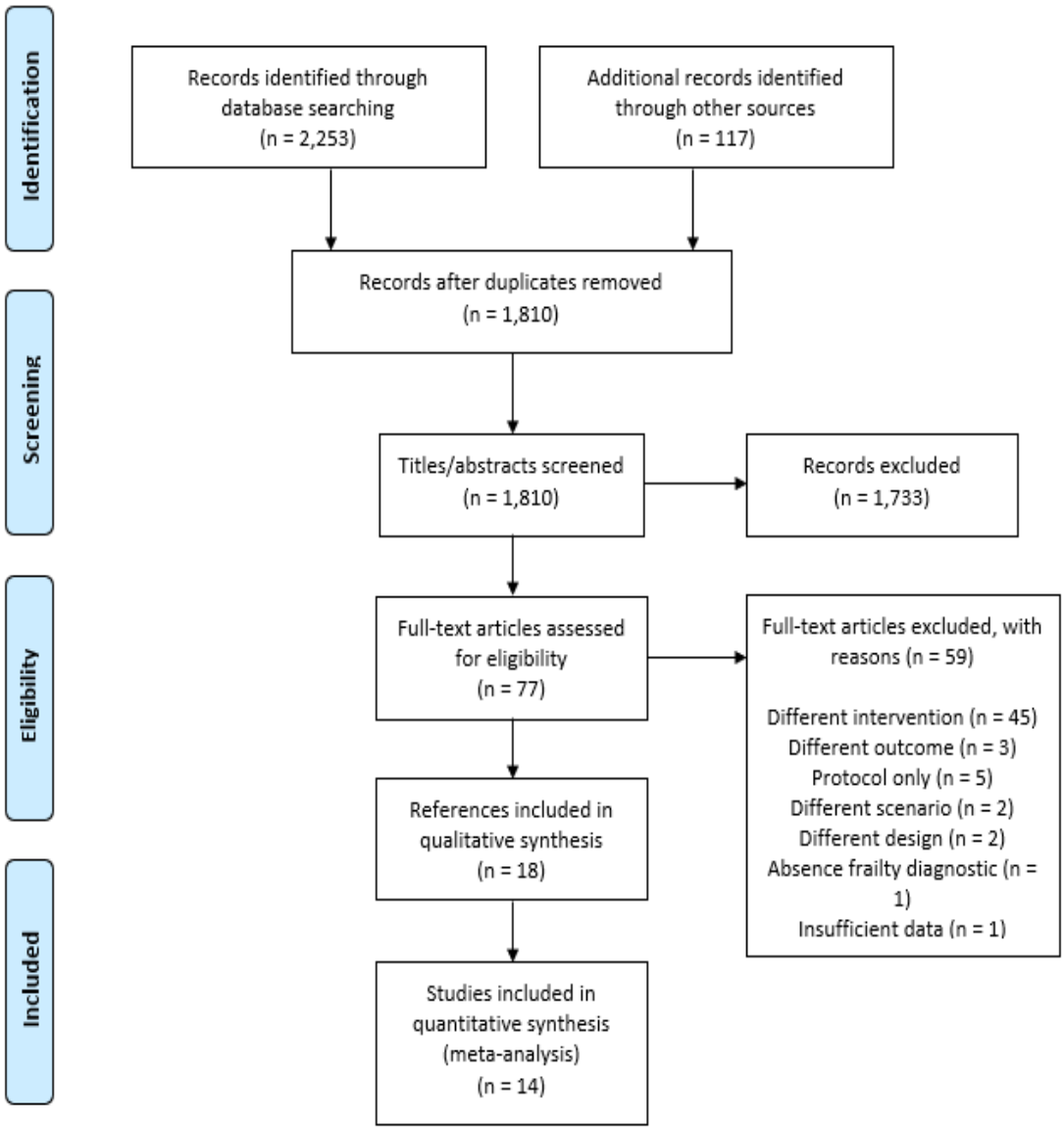


Table 1. Main Characteristics of studies included

Author, Year, Country (ref)	Population	Sample Size, n	Setting	Diagnostic criteria for frailty	Nutritional Interventions	Comparators	Duration of the intervention and of follow-up	Outcomes
Lammes, 2012, Sweden(60)	Inclusion: ≥ 75 years of age, defined as frail; Exclusion: 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 the Mini Mental State Examination (MMSE)	96	Community-dwelling	Chin A Paw	Individual dietary counselling	General advice	3 months and 9 months	Nutritional intake; Resting metabolic rate; Body composition (body density, fat mass and fat-free mass)
Van de Rest, 2014, Netherlands(52)	Inclusion: ≥ 65 years of age, defined for pre-frailty and frailty;	127	Community-dwelling	mCHS	250-mL protein supplement	Placebo supplement	24 weeks and 24 weeks	Cognitive function (standard battery of neuropsychological tests)

	Exclusion: cancer, chronic obstructive pulmonary disease, muscle disease, type 2 diabetes, renal insufficiency							
Rydwik, 2010, Sweden(53)	Inclusion: ≥ 75 years defined as frail Exclusion: 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 the MMSE	96	Community-dwelling	Chin A Paw	Individual dietary counselling	General advice	3 months and 24 months	Habitual physical activity level and activities of daily living (ADL and IADL)
Wouters-Wesseling, 2005, Netherlands(55)	Inclusion: ≥ 65 years of age, who had a	101	Home for elderly persons	General according to the presence	125-mL nutritional supplement	Placebo supplement	6 months and 6 months	Cognitive function (word learning test, category fluency

		body mass index (BMI) less than 25kg/m², defined as frail; Exclusion: cancer, gastrointestinal disease, need for a therapeutic diet incompatible with supplementation, or mental inability		or sheltered housing residence	of BMI less than 25 kg/m²				test and recognition memory test for words)
Zak, Poland(56)	2009,	Inclusion: 60-95 years; overweight within a 20% range; BMI > 19; Berg Balance Scale > 21; MMSE > 20; Exclusion: cancer, prior surgical treatment of the abdominal area, acute gastric tract disorders,	91	Nursing home and community-dwellers	General according to the presence of BMI > 19kg/m², individual balance > 21 score and score of >20 MMSE	200-mL nutritional supplement	Placebo supplement	7 weeks and 7 weeks	Physical Function and Strength Assessment (leg press and leg extension)

	acute pancreatitis or diabetes, Any recently sustained fractures, any past cerebral incidents whose lasting functional							
Tieland and Van de Rest, 2012, Netherlands(58)	Inclusion: ≥ 65 years of age, defined as pre-frailty and frailty; Exclusion: cancer, chronic obstructive pulmonary disease (COPD), muscle disease, type 2 diabetes, renal insufficiency	65	Community-dwelling	mCHS	500-mL protein supplement	Placebo supplement	24 weeks and 24 weeks	Body composition (lean mass); Muscle fiber cross sectional area; Strength Physical performance (leg press, leg extension and handgrip); Physical performance (short physical performance battery [SPPB])
Van der Zwaluw, 2014, Netherlands(75)	Inclusion: ≥ 65 years of age. Defined pre-frail or frailty; Exclusion: diabetes mellitus type I or II, cancer, COPD, renal	65	Community-dwelling	mCHS	250-mL protein supplement	Placebo supplement	24 weeks and 24 weeks	Cognitive Performance (standard battery of neuropsychological tests)

	failure							
Tieland and Dirks, 2012, Netherlands(57)	Inclusion: > 65 years old) with pre-frailty or frailty; Exclusion: cancer, chronic obstructive pulmonary disease (COPD), muscle disease, type 2 diabetes, renal insufficiency	62	Community-dwelling	mCHS	250-mL protein supplement	Placebo supplement	24 weeks and 24 weeks	Body composition (lean mass); Strength (leg press and leg extension); Physical performance (SPPB)
Park, 2018, Republic of Korea(61)	Inclusion: Aged 70–85 who were pre-frail or frail and at risk of malnutrition; Exclusion: had comorbidities such as kidney or liver failure	120	Community-dwelling	mCHS	Protein supplement (5 × 10-g packs)	Placebo supplement	12 weeks and 12 weeks	Body composition (muscle mass); Status frailty; SPPB; Physical activity (IPAQ).
Rydwik, 2008, Sweden(54)	Inclusion: ≥ 75 in the city of Solna, with frailty or pre-frailty Exclusion:	96	Community-dwelling	Chin A Paw	Individual dietary counselling	General advice	3 months and 9 months	Physical performance (leg press strength); Nutritional measures (body composition [fat-free

	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 the MMSE							mass] and energy intake); Health belief model
Ng, 2015, Malaysia(14)	Inclusion: ≥ 65 years, able to ambulate without personal assistance; Exclusion: impairment (Mini Mental State Examination score), major depression, severe audiovisual impairment, any progressive, degenerative	246	Community-dwelling	mCHS	Nutritional supplement	Placebo supplement	6 months and 12 months	Frailty score; Measures of frailty components; Physical activity (31-item Longitudinal Ageing Physical Activity Questionnaire); Self-reported hospitalizations; Self-reported falls; Instrumental activities of daily living and activities of daily living; Handgrip strength; dependency

		neurologic disease, terminal illness with life expectancy <12 months							
Starr, USA(64)	2016,	Inclusion: Obese (BMI ≥ 30 kg/m²); SPPB score of 4–10 out of 12; ≥60 years of age; Exclusion: GFR <45 mL/min/1.73 m², dementia, neurological conditions causing functional limitations, and unstable or terminal medical conditions	67	Community-dwelling	General according to the presence of functionally impaired (SPPB score of 4–10 out of 12)	500kcal deficit and protein supplement (60 g)	500kcal deficit and intake protein normal	6 months and 6 months	Function; Body composition (lean mass); Physical activity (CHAMPS), and hand grip strength
Payette, Canada(63)	2002,	Inclusion: ≥ 65 years who were at high nutritional risk; Exclusion: palliative care, alcoholic, cancer	89	Receiving long-term home help services offered by 7 local communit	General according to the presence of high nutritional risk	470-mL nutritional supplement	Did not receive any treatment	16 weeks and 16 weeks	Handgrip strength; Isometric elbow flexion and leg extension strengths; Perceived health; Functional status; Item short form survey (SF-36)

				y services centers					
Kim and Lee, 2013, South Korea(65)	Inclusion: ≥ 65 years with frailty and low socioeconomic status; could not walk 3-m course within 5 seconds at their usual pace; Exclusion: subjects participating in any kind of exercise program or clinical nutrition program, who were ordered to restrict a high-protein diet by an internist; who are unable to walk or are too functionally deteriorated	87	Community-dwelling	Interventions on Frailty Working Group	400-mL Protein Energy Supplementation	Did not receive any treatment	12 weeks and 12 weeks	Physical Functioning; SPPB; time-up-and-go test; one-legged stance; gait speed, hand grip strength; anthropometric data and dietary intake
Bonnefoy, 2003, France(68)	Inclusion: mean age 83 years; multiple diagnoses; several medications,	57	Retirement homes	Characteristics agreement with frailty	400-ml Protein Energy Supplementation	Placebo supplement	3 months and 9 months	Body composition (fat-free mass); Resting energy expenditure; Muscle power; BMI; Gait velocity; Stair

		length of stay of more than 3 years in retirement homes for elderly; Exclusion: uncontrolled or rapidly evolving diseases; Dementia; type 1 diabetes; severe renal insufficiency Functional; handicap preventing Exercising; long-term corticosteroid therapy with receipt of vitamin supplements before the study; age under 72							walking; Chair rise
Kwon, Japan(66)	2015,	Inclusion: pre-frail elderly women aged ≥70 years; Exclusion: serum albumin ≥4.5 mg/dL,	89	Community-dwelling	Modification of the criteria for frailty by Fried	Nutrition education	General health education	3 months and 6 months	Physical performance: muscle strength (handgrip strength), balance, and walking; SF-36

	serious musculoskeletal conditions, and taking calcium or vitamin D supplements							
Smoliner, 2008, Germany(67)	Inclusion: elderly with Mini Nutritional Assessment (MNA) ≤ 23.5 points; Exclusion: implanted defibrillators; hemiplegia or severe arthritis	65	Nursing home	(MNA) ≤ 23.5 points	Diet according to German reference values with protein and energy-enriched soups, sauces and snacks	Diet according to German reference values	12 weeks and 12 weeks	BMI; Body composition (fat-free mass); Handgrip strength; Respiratory muscle strength; Barthel index; SF-36
Chatterjee, 2018, India(69)	Inclusion: aged ≥60 years with frailty Exclusion: resistive training exercise or nutritional supplementation in the previous 6 months; acute illness; severe obstructive airway disease;	66	Community-dwelling	mCHS	Supplemented with the deficit quantity of Nutrients (carbohydrates and proteins), as per individual need	Nutritional counselled at baseline about their deficiency	12 weeks and 12 weeks	Gai Speed; Grip strength; IADL; MNA; Frailty assessment; Serum albumin; Modified Physical Performance Test; Berg Balance Scale; Barthel activity of daily living; geriatric depression scale (GDS); Cognitive function (Hindi Mental Status Examination)

	severe systolic dysfunction; severe depression; severe, painful lower limb muscle condition; and severe cognitive impairment	

Table 2. Classification of risk of bias of included studies based on the Cochrane Risk of Bias tool for randomized clinical trials (RoB 2)

Authors, year	Randomization process	Assignment to intervention	Adhering to intervention	Missing outcome data	Measurement of the outcome	Reported result	OVERALL RISK OF BIAS
Lammes, 2012	High	High	Some concerns	Low	Low	Some concerns	High
Ng, 2015	Low	Some concerns	Low	Low	Low	Low	Some concerns
Park, 2018	Low	Low	Low	Low	Low	Low	Low
Payette, 2002	Some concerns	High	Low	Low	Low	Some concerns	High
Rydwik, 2008	High	High	Some concerns	Low	Low	Some concerns	High
Rydwik, 2010	High	High	Some concerns	Low	Low	Some concerns	High
Starr, 2016	Some concerns	High	Low	High	Low	Low	High
Tieland and Dirks, 2012	Low	Low	Low	Low	Low	Low	Low
Tieland and Van de Rest, 2012	Low	Low	Low	Low	Low	Low	Low

Van de Rest, 2014	Low	Low	Low	Low	Low	Low	Low
Van der Zwaluw, 2014	Low	Low	Low	Low	Low	Low	Low
Wouters-Wesseling, 2005	Low	Low	Low	Low	Low	Some concerns	Some concerns
Zak, 2009	Some concerns	Low	Low	Low	Low	Low	Some concerns
Kim and Lee, 2013	Low	High	Low	Low	Low	Low	High
Kwon, 2015	Low	High	High	Low	Low	Some concerns	High
Smoliner, 2008	High	High	High	Low	Low	Some concerns	High
Bonnefoy, 2003	Some concerns	High	Low	Low	Low	Some concerns	High
Chatterjee, 2018	Low	High	Low	Low	High	Low	High

Appendix: Supplementary

Table 1. Grade System for Nutritional education compared to general health or no treatments for management of frailty in older adults.

Nutritional education compared to General health advice for management of frailty in older adults

Patient or population: management of frailty in older adults
Setting: Older adults in the community
Intervention: Nutritional education
Comparison: General health advice

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with General health advice	**Risk with Nutritional education**				
Quality of life assessed with: SF-36 follow up: mean 3 months [a]	They did not disclose any statistically significant difference between those groups			89 (1 RCT)	⨁◯◯◯ VERY LOW [b,c]	The evidence regarding the effects of nutritional education on quality of life is too uncertain.
Functioning: ADL and IADL assessed with: FIM and IAM follow up: 24 months [d,e]	The median FIM value for the treatment and control groups at 24 months were 87 (IQR: 83 to 89) and 88 (IQR: 84 to 89), respectively; the median IAM value for the treatment and control groups at 24 months were 37 (IQR: 31 to 41) and 40 (IQR: 34 to 47), respectively. [e]			34 (1 RCT)	⨁⨁◯◯ LOW [c,f]	Nutritional education likely does not increase/reduce functioning: ADL and IADL . [d]
Body Composition: Fat-Free Mass (Fat-		MD **0.6 kg higher** (1 lower to 2.2 higher)	-	48 (1 RCT)	⨁◯◯◯ VERY LOW [f,g]	The evidence regarding the effects of nutritional education on body composition (fat-free mass) is too uncertain.

Free Mass) assessed with: DXA follow up: 9 months					
Physical Activity assessed with: Classification of Physical Activity follow up: 9 months	The median physical activity level value for the treatment and control group at 9 months were 3 (IQR: 2 to 3), for both; for the walking habits frequency value for the treatment and control group 6 (IQR: 4 to 6) and 6 (5 and 6), respectively; for walking habits duration value for the treatment and control group 2 (IQR: 2 to 2) and 2 (2 and 3), respectively.			31 (1 RCT)	⨁◯◯◯ VERY LOW [f,g]	The evidence regarding the effects of nutritional education on physical activity is too uncertain.
Muscle strength assessed with: Handgrip and Leg Pres (kg) follow up: 24 weeks	-	SMD **0.3 SD lower** (0.95 lower to 0.35 higher)	-	92 (2 RCTs)	⨁◯◯◯ VERY LOW [b,c]	The evidence regarding the effects of nutritional education on muscle strength is too uncertain.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **SMD:** Standardised mean difference

Explanations

a. The Short Form Health Survey is a 36-item
b. Classification of Risk of Bias was considered high because of problems related to allocation concealment, lack of blinding and absence of information regarding adherence to the assigned intervention regimen
c. Small simple size (less than 400)
d. ADL: activities of daily living; IADL: instrumental activities of daily living
e. FIM: Functional Independence Measure; IAM: Instrumental Activity Measures
f. Classification of Risk of Bias was considered high because of problems related to allocation concealment, lack of blinding, absence of information regarding adherence to the assigned intervention regimen and absence of registered protocol
g. Sample size too small and confidence intervals included both significant harm and benefits

Appendix: Supplementary

Table 2. Grade System for Nutritional supplements compared to Placebo or no treatments for management of frailty in older adults.

Nutritional supplements compared to Placebo or no treatments for management of frailty in older adults

Patient or population: management of frailty in older adults
Setting: Older adults in the community or long-term care facilities
Intervention: Nutritional supplements
Comparison: Placebo or no treatments

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo or no treatments	Risk with Nutritional supplements				
Quality of life assessed with: SF-36 follow up: 16 weeks [a,b]		MD **8.7 higher** (6.01 lower to 23.41 higher)	-	81 (1 RCT)	⨁⨁◯◯ LOW [c]	Nutritional supplements may not increase quality of life. Other subscales of SF-36 that were assessed; vitality (MD: -5.9; 95% CI: -14.82 to -3.02); Physical role functioning (MD: -6.4; 95% CI: -22,28 to 9.48). [b]
Functioning assessed with: Prevalence of ADL and IADL dependence follow up: mean 12 months [d]	One study the Barthel ADL index after 12 weeks of follow-up (Median scores of 3.0 and 1.5, respectively, p<0.001). And other study showed after 12 months of follow-up (99 subjects; Risk Ratio [RR]: 1.02; 95% CI: 0.22 to 4.81)			135 (2 RCTs)	⨁◯◯◯ VERY LOW [c,e]	Evidence does not suggest benefits of nutritional supplements in terms of functioning
Functioning: Gait Speed (Gait Speed) assessed with: m/s		MD **0.04 higher** (0.01 lower to 0.1 higher)	-	473 (7 RCTs)	⨁⨁◯◯ LOW [e]	Nutritional supplements likely results in little to no difference in physical performance: Gait Speed .

follow up: 12 to 24 weeks						
Functioning: Strength (Strength) follow up: 12 weeks	-	SMD **0.01 SD lower** (0.21 lower to 0.2 higher)	-	603 (9 RCTs)	⨁⨁◯◯ LOW [e]	Nutritional supplements probably result in little to no difference in strength.
Functioning: SPPB (SPPB) assessed with: 0 to 12 scale were higher numbers mean better performance follow up: 12 to 24 weeks [f]		MD **0.3 higher** (0.32 lower to 1.02 higher)	-	287 (4 RCTs)	⨁◯◯◯ VERY LOW [c,g,h]	Nutritional supplements may not increase functioning: SPPB. [f]
Cognitive function: Declarative memory (Memory) assessed with: Word Learning test delayed recall follow up: 24 weeks	-	SMD **0.11 SD higher** (0.31 lower to 0.53 higher)	-	167 (3 RCTs)	⨁⨁◯◯ LOW [c]	Nutritional supplements probably do not increase cognitive function: Declarative memory. For the immediate recall part of the word learning test there was also no evidence that nutrition supplementation improved cognitive performance (SMD: 0.30; 95% CI: -0.28 to 0.86, 3 studies).
Cognitive function: language and executive function (Language and executive		MD **0.21 SD higher** (0.99 lower to 1.42 higher)	-	180 (3 RCTs)	⨁⨁⨁◯ MODERATE [i]	Nutritional supplements likely result in little to no difference in cognitive function: language and executive function. For the verbal fluency test using professions and p word as the prompting semantic category there was also no evidence that nutrition supplementation improved cognitive performance (MD: 1.10; 95% CI: -0.18 to 2.29, 3 studies).

function) assessed with: Verbal fluency test (animals) follow up: 24 weeks						
Body composition: Appendicular lean mass (Appendicular lean mass) assessed with: DXA (kg) follow up: 12 weeks [j]		MD **0.6 higher** (0.82 lower to 2.01 higher)	-	198 (5 RCTs)	⨁⨁◯◯ LOW [e,i]	Nutritional supplements likely result in little to no difference in body composition: Appendicular lean mass.
Physical activity assessed with: Various scales follow up: 12 weeks	-	SMD **0.5 SD lower** (0.69 lower to 0.58 higher)	-	175 (2 RCTs)	⨁⨁◯◯ LOW [c]	The effect of nutritional supplement on physical activity is too uncertain.
Frail assessed with: number of individuals with frailty follow up: 12 weeks	83 per 1.000	**173 per 1.000** (61 to 389)	**OR 2.30** (0.72 to 7.01)	215 (3 RCTs)	⨁◯◯◯ VERY LOW [c,g,j]	Nutritional supplements may not decrease number of individuals with frailty.
Body composition: Fat mass assessed with: DXA		MD **1.67 higher** (0.63 lower to 3.96 higher)	-	118 (2 RCTs)	⨁⨁⨁◯ MODERATE [i]	Nutritional supplements likely result in little to no difference in body composition (fat-free mass).

(kg) follow up: 12 weeks [j]						
Body composition: Fat-free mass assessed with: DXA (kg) follow up: 12 weeks [j]		MD **1.41 higher** (0 to 2.76 higher)	-	94 (2 RCTs)	⨁◯◯◯ VERY LOW [e,i]	Evidence does not suggest benefits of nutritional supplements in terms of body composition (fat mass).

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **SMD:** Standardised mean difference; **OR:** Odds ratio

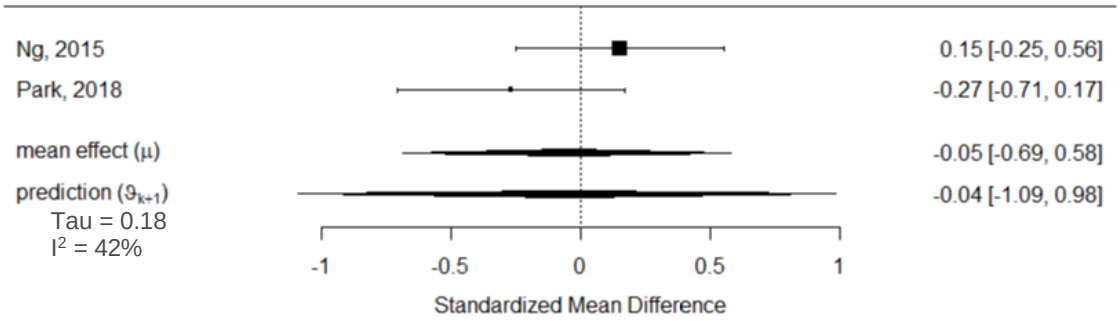
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

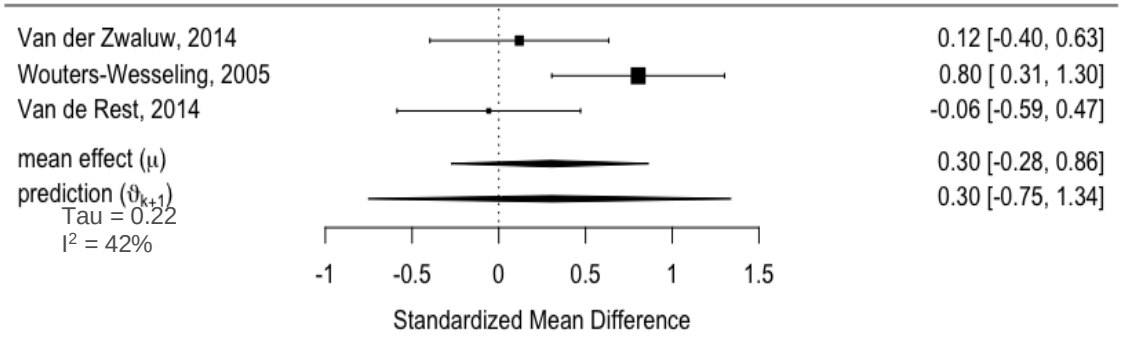
a. Emotional Role Functioning Subscale of SF-36
b. SF-36: 36-Item Short Form Health Survey
c. Sample size too small and confidence intervals included both significant harm and benefits
d. ADL: activities of daily living; IADL: instrumental activities of daily living
e. Risk of bias high mainly assignment to intervention and adhering to intervention
f. SPPB: Short Physical Performance Battery
g. Risk of bias high mainly assignment to intervention
h. For the SPPB outcome we considered a change of 0.3 to be the minimally clinically significant difference according KWON 2019.
i. Small sample size (less than 400)
j. DEXA: Dual-energy X-ray absorptiometry

Figure 2. Forest plots of meta-analyses comparing nutritional supplements with placebo

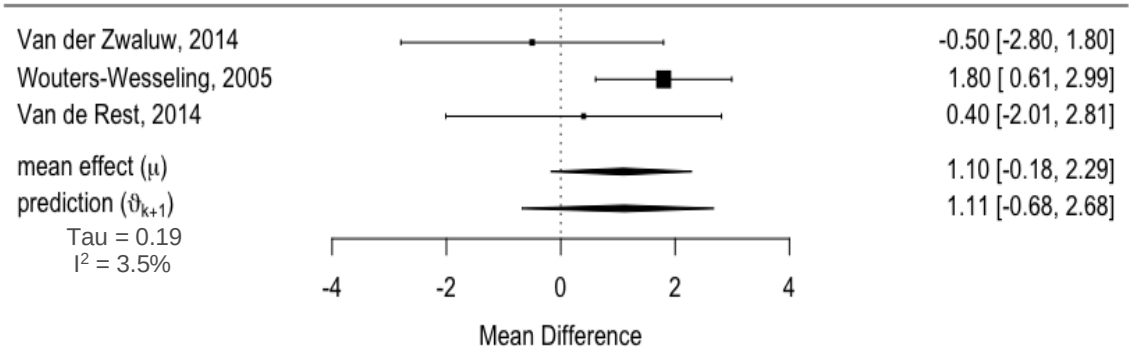
A) Physical Activity follow-up 12 weeks.



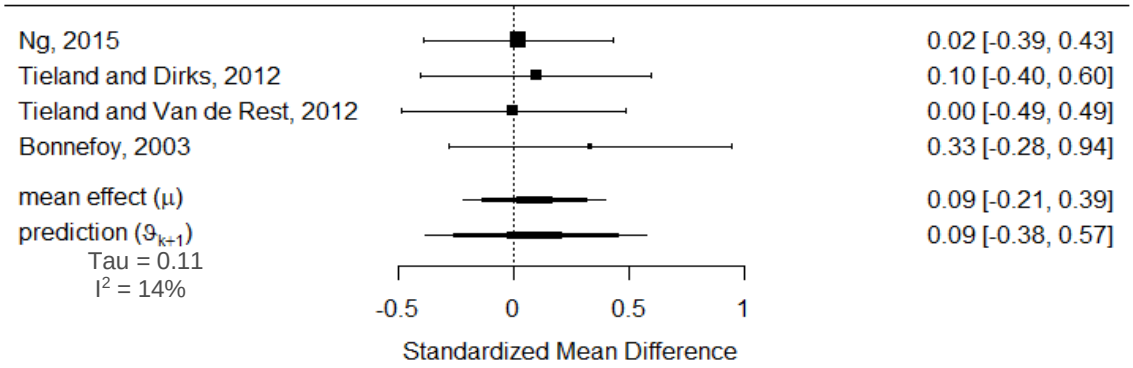
B) Cognitive function: Declarative memory assessed with: Word Learning test follow-up 24 weeks.



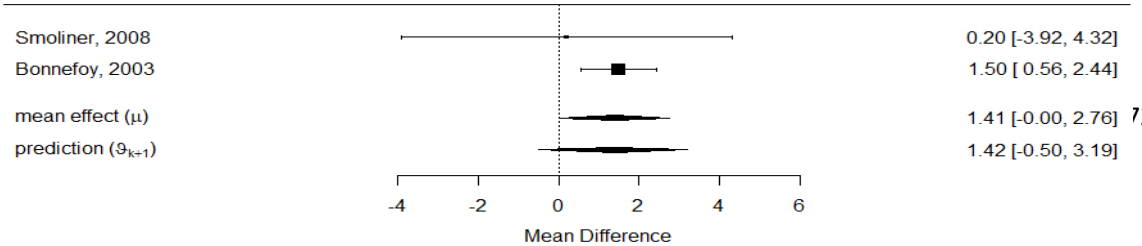
C) Cognitive function: Language and executive function Word Fluency “P” and Professionals follow-up 24 weeks.



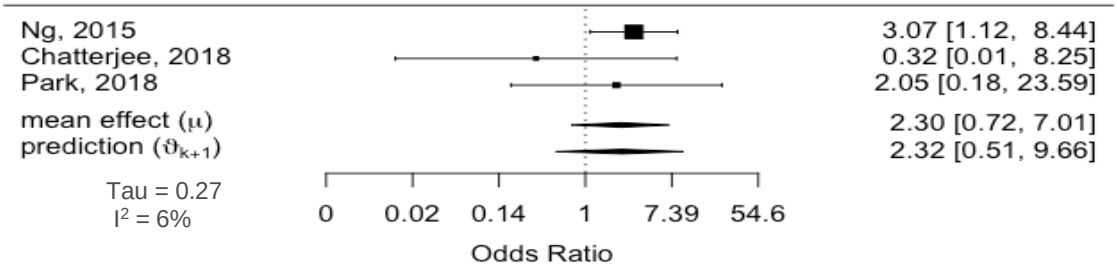
D) Functioning: Muscle strength



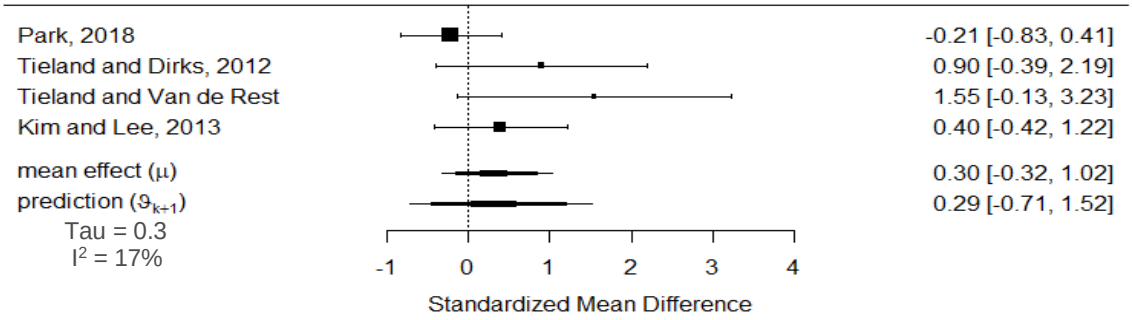
E) Body composition: Fat-free mass follow-up 12 weeks



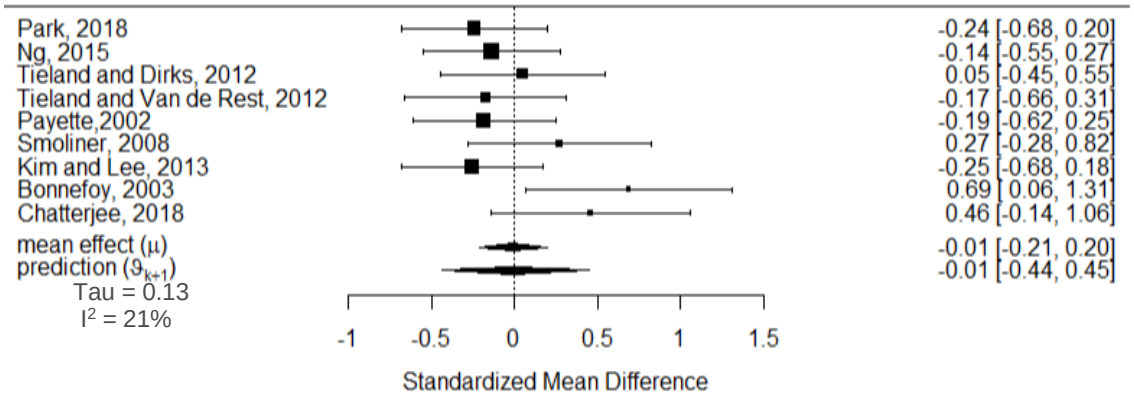
F) Frail



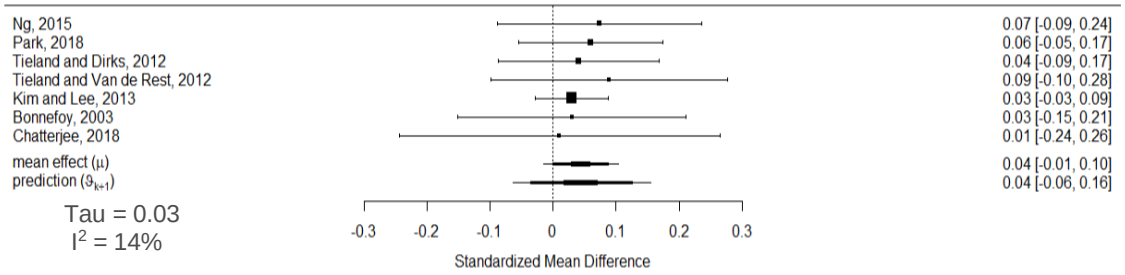
G) Functioning: Short Physical Performance Battery follow-up 12 weeks.



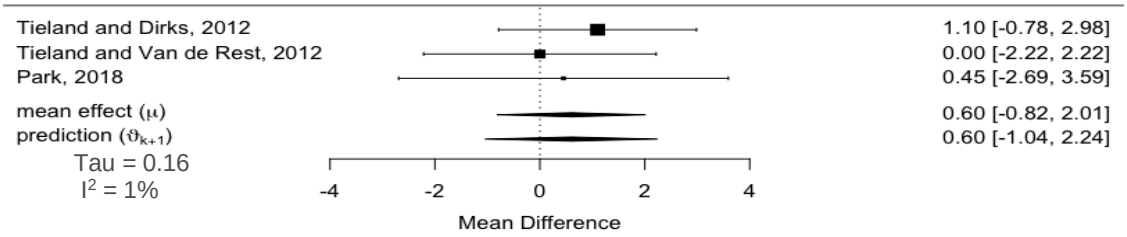
H) Functioning: Muscle Strength follow-up 12 weeks.



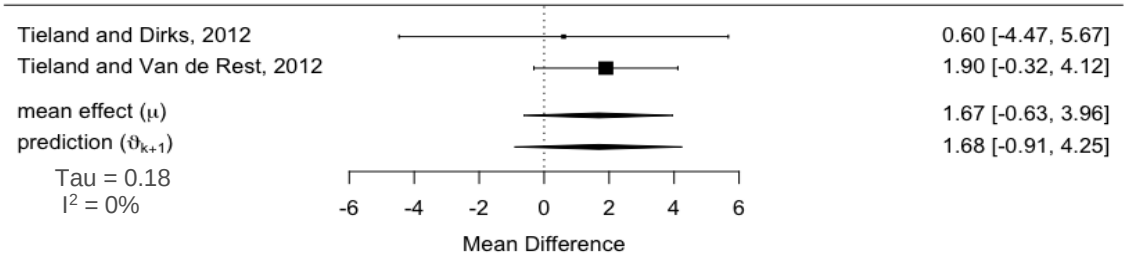
I) Functioning: Gait Speed



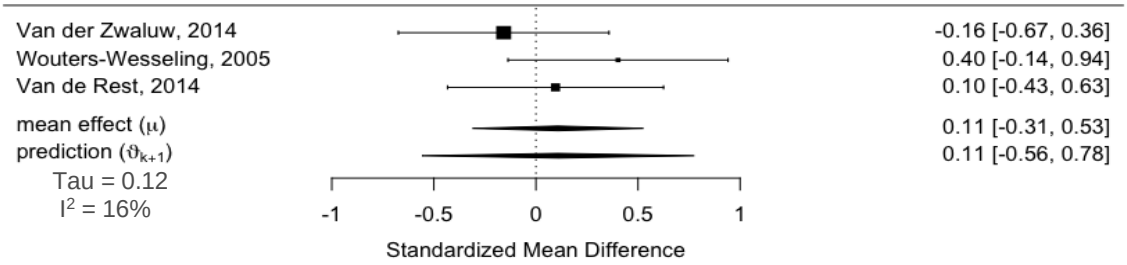
J) Body composition: Appendicular lean mass follow-up 12 weeks.



K) Body composition: Fat mass follow-up 12 weeks.



L) Cognitive function: Declarative memory assessed with: Word Learning Test Delayed follow-up 24 weeks.



M) Cognitive function: Language and executive function Word Fluency Animals follow-up 24 weeks.

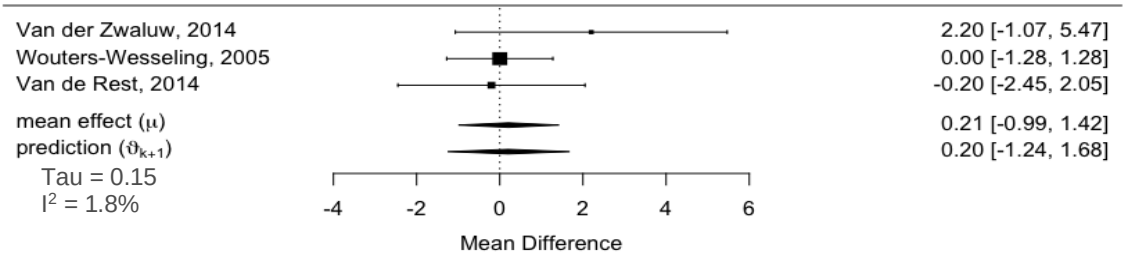
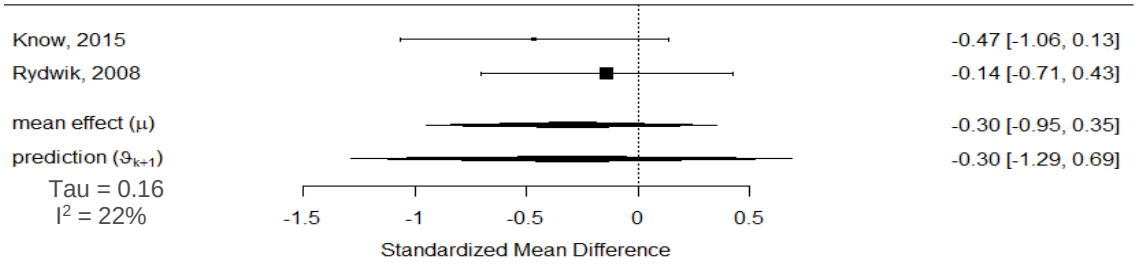


Figure 3. Forest plots of meta-analyses comparing nutritional education with general health

A) Muscle strength



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APÊNDICE 1: Protocolo registrado na base PROSPERO

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Nutritional interventions for the treatment of frailty in older adults: systematic review

Mariana Moraes, Carolina Araujo, Christina Avgerinou, Edison Vidal

Citation

Mariana Moraes, Carolina Araujo, Christina Avgerinou, Edison Vidal. Nutritional interventions for the treatment of frailty in older adults: systematic review. PROSPERO 2018 CRD42018111510 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018111510

Review question

Can nutritional interventions help treatment of frailty in older adults living in the community or in long-term care facilities?

Searches

Two independent researchers will examine the lists of references identified through electronic search. We will also hand-search reference lists of relevant publications including review articles on frailty and of original studies considered eligible for the review. Additionally, we will contact experts in the field of nutrition and frailty to ask for references to published and unpublished data. We also intend to contact researchers to request relevant unpublished data whenever possible.

We will search the following databases for relevant studies: MEDLINE (via PubMed), Embase, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), LILACS and Web of Science.

We will search the following databases for gray literature: System for information on Gray Literature in Europe (Open Gray), Virginia Henderson Global Nursing e-Repository, National Library of Medicine Bookshelf, ClinicalTrials.gov, and World Health International Clinical Trials Registry Platform (ICTRP).

We will include only parallel-group randomized clinical trials published since 2001 in English, Portuguese or Spanish. We will accept trials whereby the unit of randomization consisted of individuals or clusters of individuals.

Search strategy

https://www.crd.york.ac.uk/PROSPEROFILES/111510_STRATEGY_20181003.pdf

Types of study to be included

Randomized clinical trials. We will accept trials whose unit of randomization were individuals or clusters of individuals.

Condition or domain being studied

Frailty has been defined as a clinical syndrome of multicausal origin characterized by a reduction of physiological reserves that increase the vulnerability of an individual to adverse outcomes such as the development of functional dependence and death. Considered one of the most important geriatric syndromes, frailty's prevention and management represent important goals for gerontology and geriatrics. Although nutrition plays an important role within the multifactorial susceptibility for this syndrome, up to present no systematic review addressed the effectiveness of nutritional interventions for the treatment of frailty.

Participants/population

We will include studies that recruited older adults (aged 60 years or older) with a diagnosis of frailty or pre-frailty and living in the community or in long-term care facilities. We will accept any criteria used by original studies to diagnose that syndrome. Studies that have been performed during hospitalization episodes will not be included.

Intervention(s), exposure(s)

We will include studies that have implemented at least one of the following nutritional interventions: nutritional education / dietary prescription, the use of hypercaloric or hyperproteic dietary oral supplements

and the delivery of specific diets. Additionally, we will also include studies that adopted any of the above interventions concomitantly with another single or multifactorial intervention provided that the comparator was the same set of interventions without the nutritional intervention component.

Comparator(s)/control

We will accept as comparators standard treatment, placebo, other nutritional interventions, and multifactorial interventions without a nutritional component.

Context

Main outcome(s)

Mortality.

Additional outcome(s)

1. Quality of life, measured by any instrument.

2. Functional capacity, measured by any instrument.

3. Cognitive function, measured by any instrument.

4. State of frailty, measured by any instrument.

5. Body composition, measured by any instrument.

6. Physical activity, measured by any instrument.

Data extraction (selection and coding)

Two reviewers will extract data independently using a standardized pre-piloted form including the following data: complete reference; time period when the study was conducted; geographical location; presence of divergences between the study protocol and published results; study design; types of interventions and comparators; duration of the intervention and of follow-up; inclusion/exclusion criteria; sample size; characteristics of the population; balance between groups at the baseline; funding source; method of randomization; presence of simultaneous interventions; diagnostic criteria of frailty; nutritional interventions; details of the intervention, including type, dose, frequency, and duration; control treatment; outcome measures; blinding (patients, field professionals and outcome assessors); duration of follow-up; loss of follow-up; results; intention-to-treat analysis; conclusions reported by the study authors; and research limitations. In addition, there will be a field for the registration of other information deemed relevant by the reviewers.

Disagreements about extracted data will be resolved by consensus, and an independent reviewer will be consulted if disagreement persists.

Risk of bias (quality) assessment

To assess the risk of bias in the included studies, two review authors will independently use The Cochrane Collaboration's Risk of Bias tool for randomized clinical trials. Accordingly, the following domains will be assessed: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other bias. Each of these criteria will be assigned one of the following categories: low risk of bias; high risk of bias; or unclear risk of bias, where unclear relates to the lack of precise information or uncertainty over the potential for bias.

Where applicable, the investigators of selected trials will be contacted to provide additional relevant information. Disagreements between the authors regarding the assessment of risk of bias will be resolved by consensus, and a third reviewer will be consulted when needed.

Strategy for data synthesis

We will organize the synthesis of data according to the types of nutritional interventions studied, the types of comparators, and populations studied (i.e. older adults living in the community or in long-term care facilities).

If the included studies are sufficiently similar in terms of population, inclusion criteria, interventions and

results, we will perform quantitative synthesis using the random effects models.

Dichotomous data: the results will be presented as the risk ratios with 95% confidence intervals. Continuous data: the results will be presented as the mean difference, if outcomes are measured using similar scales between trials. We will use the standardized mean difference to combine trials that measure the same outcome using different scales or instruments.

Analysis of subgroups or subsets

If sufficient data is available, we will perform the following subgroup analyses: concerning specific details of nutritional interventions (e.g. components and duration), research scenario (i.e. community or long-term care facilities), risk of bias and criteria used to diagnose frailty.

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Type and method of review

Intervention, Meta-analysis, Narrative synthesis, Systematic review

Anticipated or actual start date

01 March 2018

Anticipated completion date

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Conflicts of interest

None known

Language

English, Portuguese-Brazil

Country

Brazil, England

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Adult; Aged; Frail Elderly; Frailty; Humans

Date of registration in PROSPERO

29 October 2018

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29 October 2018

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions
29 October 2018

APÊNDICE 2: Protocolo publicado no periódico Medicine

Study Protocol Systematic Review

Medicine®

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Nutritional interventions for the treatment of frailty in older adults: a systematic review protocol

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Abstract

Background: Frailty has been defined as a clinical syndrome of multicausal origin characterized by a reduction of physiologic reserves that increase the vulnerability of an individual to adverse outcomes such as the development of functional dependence and death. Considered one of the most important geriatric syndromes, frailty's prevention and management represent important goals for gerontology and geriatrics. Although nutrition plays an important role within the multifactorial susceptibility for this syndrome, up to the present no systematic review specifically addressed the effectiveness of nutritional interventions for the treatment of frailty. Therefore, we propose the present systematic review with the aim to assess the effectiveness of nutritional interventions for the treatment of frailty in older adults living in the community or in long-term care facilities.

Methods: We will search Medline (via Pubmed), Embase, Cinahl, Central, Lilacs, Web of Science, and sources of gray literature. We will accept trials whereby the unit of randomization consisted of individuals or clusters of individuals. Our primary outcome is all-cause mortality. Secondary outcomes are quality of life, functional status, cognitive function, frailty status, body composition, and physical activity. Risk of bias will be assessed using the Cochrane Collaboration tool. We will analyze the overall strength of the evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool. Two independent researchers will conduct all evaluations and any disagreements will be resolved through the participation of a 3rd author. If possible, we will perform random-effects meta-analyses and subgroup analyses concerning specific details of nutritional interventions (e.g., components and duration), research scenario, risk of bias, and criteria used to diagnose frailty.

Conclusion: In this systematic review protocol we outline the details of the aims and methods of a systematic review on the effectiveness of nutritional interventions for the management of frailty in older adults living in the community or in long-term care facilities". We believe this wording to be more objective and balanced than the previous one. We understand that it is not ideal to propose changes to the text after manuscripts have been accepted. However, we feel that the new wording of the conclusion section of the abstract is more consistent with the overall content of the main text of the review than its previous version. Hence, we hope you may accept our request.

Abbreviations: GRADE = Grading of Recommendations Assessment, Development, and Evaluation, GRADEPRO = Grading of Recommendations Assessment, Development, and Evaluation Profiler Software, ICTRP = World Health International Clinical Trials Registry Platform, OPEN GRAY = Gray Literature in Europe, PROSPERO = International Prospective Register of Systematic Reviews.

Keywords: aged, diet, dietary supplements, feeding, frailty, nutrition, systematic review

1. Introduction

Frailty has been defined as a clinical syndrome of multicausal origin characterized by a reduction of physiologic reserves that increase the vulnerability of an individual to adverse outcomes such as the development of functional dependence and death.[1]

Considered one of the most important geriatric syndromes, frailty's prevention and management represent important goals for gerontology and geriatrics.[2] The concept of frailty has greatly contributed to the development of this field by highlighting a multiplicity of subclinical factors (i.e., going beyond the presence of functional dependence and comorbidities) and contributing to the reduction of the capacity of older adults to maintain their homeostasis when exposed to stressor events.[3] In fact, studies using different operational definitions of frailty have shown that it represents an important risk factor for a variety of negative outcomes. For example, frail older adults were found to be at an increased risk of falling by 84%, when

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The authors have no conflicts of interest to disclose.

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compared to those who are nonfrail.[4] The frailty syndrome has also been associated with 70% greater chance of fractures,[5] 30% increase in the risk of developing dementia,[6] and 90% increase in the risk of hospitalization.[7] An inverse association between frailty and quality of life of older adults living in the community has also been observed.[8]

These data are especially relevant when one considers the results of studies reporting the prevalence of this syndrome among older adults and the perspectives of population aging worldwide.[9] A systematic review on the prevalence of frailty among community-dwelling elderly identified that prevalence ranged from 4% to 59%, with a weighted average of 11%.[10] A significant increase in the prevalence of this syndrome is also noted among individuals of a more advanced age, reaching an average of about 27% among adults older than 85 years of age.[11] Amid institutionalized older adults, the prevalence of frailty ranged from 19% to 76%, with a weighted average of 52%.[11]

An important meeting of experts, leading to the 1st successful international consensus on the definition of frailty, considered that there was some evidence suggesting possible benefits of 4 types of interventions for managing this condition: physical exercise, caloric and protein support, vitamin D supplementation, and reduction of polypharmacy.[1]

Loss of muscle mass is one of the consequences of weight loss in older adults, along with reduction of strength, mobility, and immune dysfunction, which represent typical characteristics of frailty. In addition, malnutrition in older adults increases the risk of hospitalization, functional dependence, and death in this population.[12] The association between nutritional factors and the occurrence of frailty was also observed in the systematic review of Lorenzo-López et al that analyzed data from 19 observational studies.[13] The nutritional factors examined by this review were micronutrients, macronutrients, diet quality, antioxidants, and score in the Mini Nutritional Assessment.[13]

Due to the global phenomenon of population ageing,[2] the increased prevalence of frailty at more advanced ages and the negative consequences of this syndrome, studies about efficacy and effectiveness of interventions to manage this syndrome have great importance, particularly aiming at the prevention of such adverse events. In view of the relevance of the topic and the arguments presented above, we propose the present systematic review with the aim to assess the effectiveness of nutritional interventions for the treatment of frailty in older adults living in the community or in long-term care facilities.

2. Methods

2.1. Study registration

This systematic review protocol has been registered on PROSPERO under the number of CRD42018111510, and was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocol.[14] This is a literature-based study, so ethical approval is unnecessary.

2.2. Selection criteria

2.2.1. Types of studies. We will include only parallel-group randomized clinical trials published since 2001 in English, Portuguese, or Spanish. We will accept trials whereby the unit of randomization consisted of individuals or clusters of individuals.

2.2.2. Types of participants. We will include studies that recruited older adults (aged 60 years or older) with a diagnosis of frailty or prefrailty and living in the community or in long-term care facilities. We will accept any criteria used by original studies to diagnose that syndrome. Studies that have been performed during hospitalization episodes will not be included.

2.2.3. Types of interventions. We will include studies that have implemented at least one of the following nutritional interventions: nutritional education/dietary prescription, the use of hypercaloric or hyperproteic dietary oral supplements and the delivery of specific diets. Additionally, we will also include studies that adopted any of the above interventions concomitantly with another single or multifactorial intervention provided that the comparator was the same set of interventions without the nutritional intervention component. We will accept as comparators standard treatment, placebo, other nutritional interventions, and multifactorial interventions without a nutritional component.

2.2.4. Types of outcomes. We will include studies if they report at least one of the following outcome measures.

2.2.4.1. Primary outcomes.

1. Mortality.

2.2.4.2. Secondary outcomes.

1. Quality of life, measured by any instrument
2. Functional capacity, measured by any instrument.
3. Cognitive function, measured by any instrument.
4. State of frailty, measured by any instrument.
5. Body composition, measured by any instrument.
6. Physical activity, measured by any instrument.

2.3. Search methods for study identification

Two independent researchers will examine the lists of references identified through electronic search. We will also hand-search reference lists of relevant publications including review articles on frailty and of original studies considered eligible for the review. Additionally, we will contact experts in the field of nutrition and frailty to ask for references to published and unpublished data. We also intend to contact researchers to request relevant unpublished data whenever possible.

2.3.1. Electronic searches. We will search the following databases for relevant studies, using the search terms detailed in Appendix 1: http://links.lww.com/MD/C725 Medline (via Pubmed), Embase, Cinahl, Central, Lilacs e Web of Science.

2.3.2. Other resources. We will search the following databases for gray literature: System for information on Gray Literature in Europe (Open Gray), Virginia Henderson Global Nursing e-Repository, National Library of Medicine Bookshelf, ClinicalTrials.gov, and World Health International Clinical Trials Registry Platform (ICTRP).

2.4. Data collection and analysis

2.4.1. Selection of studies. For all studies identified, 2 authors will independently screen and review the titles and abstracts. Full versions of potentially relevant studies will be obtained. Where applicable, we will contact the authors of selected studies to ask for additional data. Disputes regarding the inclusion of a study will be resolved through discussion with a 3rd reviewer.

2.5. Data extraction and management

Two reviewers will extract data independently using a standardized prepiloted form including the following data: complete reference; time period when the study was conducted; geographical location; presence of divergences between the study protocol and published results; study design; types of interventions and comparators; duration of the intervention and of follow-up; inclusion/exclusion criteria; sample size; characteristics of the population; balance between groups at the baseline; funding source; method of randomization; presence of simultaneous interventions; diagnostic criteria of frailty; nutritional interventions; details of the intervention, including type, dose, frequency, and duration; control treatment; outcome measures; blinding (patients, field professionals and outcome assessors); duration of follow-up; loss of follow-up; results; intention-to-treat analysis; conclusions reported by the study authors; and research limitations. In addition, there will be a field for the registration of other information deemed relevant by the reviewers.

Disagreements about extracted data will be resolved by consensus, and an independent reviewer will be consulted if disagreement persists.

2.5.1. Assessment of bias risk. To assess the risk of bias in the included studies, 2 review authors will independently use The Cochrane Collaboration's Risk of Bias tool for randomized clinical trials.[15] Accordingly, the following domains will be assessed: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias. Each of these criteria will be assigned one of the following categories: low risk of bias; high risk of bias; or unclear risk of bias, where unclear relates to the lack of precise information or uncertainty over the potential for bias.

Where applicable, the investigators of selected trials will be contacted to provide additional relevant information. Disagreements between the authors regarding the assessment of risk of bias will be resolved by consensus, and a 3rd reviewer will be consulted when needed.

2.5.2. Rating quality of evidence. We will analyze the overall strength of the evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool. This system represents a method that evaluates the quality of evidence in systematic reviews explicitly, comprehensively, transparently, and pragmatically.[16] The GRADE system evaluates the following dimensions regarding the quality of evidence: study limitations/risk of bias, inconsistency, indirect effects, inaccuracy, publication bias, and factors that may increase the quality of evidence. According to GRADE, the quality of the evidence regarding each outcome analyzed is classified into 1/4 levels: high, moderate, low, and very low.[16]

We will use the GRADE profiler software (GRADEPRO) to create "summary of findings" tables with outcome specific information concerning the overall quality of evidence and the magnitude of effect of the interventions examined by the examined body of evidence.

2.5.3. Measures of treatment effects. Dichotomous data: the results will be presented as the risk ratios with 95% confidence intervals. Continuous data: the results will be presented as the mean difference, if outcomes are measured using similar scales between trials. We will use the standardized mean difference to combine trials that measure the same outcome using different scales or instruments.

2.5.4. Unit of analysis issues. The appropriate unit of analysis will be the individual patient, rather than hospitals or health centers. In studies with multiple intervention groups, we will include only the comparisons between groups that meet our eligibility criteria. If more than 1 pair of intervention comparisons are eligible for a given meta-analysis and those pairs of comparisons have at least 1 intervention group in common, we will proceed using one of the methods recommended by the Cochrane Collaboration in the following order of preference according to the feasibility of each approach: we will attempt to merge the intervention groups to yield a single pairwise comparison; we will attempt to account for the correlation between correlated comparisons by calculating a weighted average of the different pairwise comparisons; and we will perform a network meta-analysis.

2.5.5. Missing data. Where applicable, we will contact the chief investigators of clinical trials with missing data or unclear information (e.g., unclear risk of bias). Whenever possible we will include in meta-analyses data from intention-to-treat analyses. We will not perform imputation procedures for missing data.

2.5.6. Assessment of reporting biases. If there are sufficient numbers of trials (at least 10), we will construct a funnel plot and we will apply the Egger tests and the Trim and Fill method in the evaluation of publication bias.

2.5.7. Data synthesis. We will organize the synthesis of data according to the types of nutritional interventions studied, the types of comparators, and populations studied (i.e., older adults living in the community or in long-term care facilities).

If the included studies are sufficiently similar in terms of population, inclusion criteria, interventions, and results, we will perform quantitative synthesis using the random effects models.

2.5.8. Assessment of heterogeneity. If the available data allow the performance of meta-analyses, we will assess statistical heterogeneity by means of I^2 statistics, which will be interpreted according to the current Cochrane Collaboration guidance as follows: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; 75% to 100% considerable heterogeneity.[15] If we find substantial heterogeneity, we will attempt to perform subgroup analyses as described in the following sections.

2.5.9. Subgroup analyses. If sufficient data are available, we will perform the following subgroup analyses: concerning specific details of nutritional interventions (e.g., components and duration), research scenario (i.e., community or long-term care facilities), risk of bias, and criteria used to diagnose frailty.

2.5.10. Sensitivity analysis. We have not planned any sensitivity analyses.

3. Discussion

Nutrition plays an important role within the multifactorial susceptibility of this syndrome; however, up to the present no systematic review addressed the effectiveness of nutritional interventions for the treatment of frailty. The systematic specifically reviews identified in the literature on this topic emphasize interventions related to physical activity without any particular focus to nutritional interventions, which were generally analyzed briefly and in a secondary manner.[9,13,17–22]

Author contributions

Conceptualization: Mariana Bordinhon de Moraes, Edison Iglesias de Oliveira Vidal.
Data curation: Mariana Bordinhon de Moraes, Edison Iglesias de Oliveira Vidal.
Formal analysis: Mariana Bordinhon de Moraes, Christina Avgerinou, Edison Iglesias de Oliveira Vidal.
Investigation: Mariana Bordinhon de Moraes, Carolina Fumico Massuda Araujo, Edison Iglesias de Oliveira Vidal.
Methodology: Mariana Bordinhon de Moraes, Carolina Fumico Massuda Araujo, Edison Iglesias de Oliveira Vidal.
Project administration: Mariana Bordinhon de Moraes, Christina Avgerinou, Edison Iglesias de Oliveira Vidal.
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Visualization: Mariana Bordinhon de Moraes, Carolina Fumico Massuda Araujo.
Writing – original draft: Mariana Bordinhon de Moraes, Carolina Fumico Massuda Araujo.
Writing – review & editing: Mariana Bordinhon de Moraes, Christina Avgerinou, Edison Iglesias de Oliveira Vidal.

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Erratum

Medicine

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Nutritional interventions for the treatment of frailty in older adults: a systematic review protocol: Erratum

In the article, "Nutritional interventions for the treatment of frailty in the older adults a systematic review protocol",[1] which appeared in Volume 97 Issue 52 of *Medicine*, there was a publisher error in which additional comments were added to the paper's abstract conclusion section.

The abstract's conclusion should read: "In this systematic review protocol we outline the details of the aims and methods of a systematic review on the effectiveness of nutritional interventions for the management of frailty in older adults living in the community or in long-term care facilities."

In addition, the word "specifically"' was misplaced in the discussion section. The discussion section should read: "Nutrition plays an important role within the multifactorial susceptibility of this syndrome; however, up to the present no systematic review specifically addressed the effectiveness of nutritional interventions for the treatment of frailty. The systematic reviews identified in the literature on this topic emphasize interventions related to physical activity without any particular focus to nutritional interventions, which were generally analyzed briefly and in a secondary manner.[9,13,17–22]„

Finally, the full affiliation of Mariana Bordinhon de Moraes and Carolina Fumico Massuda Araujo should read: Department of Public Health, São Paulo State University (UNESP), Botucatu Medical School, SP, Brazil.

Reference

[1] Moraes MBd, Araujo CFM, Avgerinou C. Nutritional interventions for the treatment of frailty in older adults: a systematic review protocol. *Medicine*. 97;52: e13773.