Ageing Research Reviews 51 (2019) 48–54

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Effect of nutritional supplementations on physical performance and muscle strength parameters in older people: A systematic review and meta-analysis

Nicola Veronese[a,*], Brendon Stubbs[b,c,d], Leonardo Punzi[e], Pinar Soysal[f], Raffaele Antonelli Incalzi[g], Alois Saller[h], Stefania Maggi[a]

[a] National Research Council, Neuroscience Institute, Aging Branch, Padova, Italy
[b] Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London, United Kingdom
[c] Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom
[d] Faculty of Health, Social Care and Education, Anglia Ruskin University, Chelmsford, United Kingdom
[e] Rheumatology Center, SS Giovanni e Paolo Hospital, Venice, Italy
[f] Department of Geriatric Medicine, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Turkey
[g] Unit of Geriatrics, Campus Bio-Medico University, Rome, Italy
[h] Internal Medicine, Department of Medicine DIMED, University-Hospital of Padova, Padova, Italy

ARTICLE INFO

Keywords:
Nutrition
Sarcopenia
Physical performance
Muscle strength
Meta-analysis

ABSTRACT

Malnutrition plays a role in the development of poor physical performance, frailty and sarcopenia. The use of nutritional supplementations for improving physical performance and muscle strength parameters in older people is unclear. We therefore aimed to summarize the effect of nutritional supplementations compared to placebo on physical performance (i.e. tests more investigating physical function, utilising aerobic capacity & muscle power) and muscle strength (i.e. tests depending on muscle power) outcomes in older people in randomized controlled trials (RCTs). A literature search in major databases was undertaken until the 01st September 2018. Eligible studies were RCTs investigating the effect of nutritional supplementations vs. placebo in older people (people having an age > 60 years). Standardized mean differences (SMD) and 95% confidence intervals (CIs) were used through a random effect model. Over 4007 potentially eligible articles, 32 RCTs for a total of 4137 older participants (2097 treated and 2040 placebo) (mean age: 76.3 years; 65% females) were included. Compared to placebo, multi-nutrient supplementations significantly improved chair rise time (n = 3; SMD = -0.90; 95%CI: -1.46 to -0.33; I^2 = 87%). Multi-nutrients significantly improved handgrip strength when compared to placebo (n = 6; 780 participants; SMD = 0.41; 95%CI: 0.06 to 0.76; I^2 = 79%), as did nutritional supplementations including protein (n = 7; 535 participants; SMD = 0.24; 95%CI: 0.07 to 0.41; I^2 = 16%).Nutritional supplementations also led to a significant improvement in chair rise time and in handgrip strength in participants affected by frailty/sarcopenia and in those affected by medical conditions. In conclusion, nutritional supplementation can improve a number of physical performance outcomes in older people, particularly when they include multi-nutrients and in people already affected by specific medical conditions, or by frailty/sarcopenia.

1. Introduction

Malnutrition (i.e. deficiency, excess or imbalance in a person's intake of energy and/or nutrients) is a common condition in older people (Cereda et al., 2016). Its prevalence differs significantly across the healthcare settings and populations, but approximately one in ten older person experiences malnutrition (Cereda et al., 2016). The consequences of malnutrition are multiple, but an increasing amount of research is reporting that malnutrition may play a role in the development of poor physical performance (i.e. tests typically measuring function, depending on aerobic capacity and muscle power, such as gait speed, chair rise time or timed up and go) (Singh et al., 2014), frailty (Boulos et al., 2016) and sarcopenia (Sánchez-Rodríguez et al., 2017). It exists a vicious circle starting from poor physical performance leading to sarcopenia and finally to frailty that increases the risk of several negative conditions in older people, including disability and mortality (Cesari et al., 2014). Thus, the treatment of malnutrition in older adults may have important and beneficial consequences in

* Corresponding author at: National Research Council, Neuroscience Institute, Aging Branch, Via Giustiniani, 2 35128 Padova, Italy.
E-mail address: nicola.veronese1@aulss3.veneto.it (N. Veronese).

https://doi.org/10.1016/j.arr.2019.02.005
Received 22 December 2018; Received in revised form 18 February 2019; Accepted 26 February 2019
Available online 28 February 2019

preventing the pathological loss of muscle mass and its function that precede the onset of disability.

A common approach to treat malnutrition is the use of nutritional supplementations, i.e. foods defined as either intended to provide nutrients in order to increase the quantity of their consumption or to provide non-nutrient chemicals which are claimed to have a biologically beneficial effect (Gall et al., 2001). Regarding this topic (i.e. the use of nutritional supplementations for improving muscle mass and muscle performance), a number of earlier systematic reviews and meta-analyses have been published. In 2014, Cruz-Jentoft et al. concluded that in older people affected by sarcopenia, the use of nutritional supplementations in 12 randomised control trials (RCTs) was limited, mainly due to the low number of studies and heterogeneous study design (Cruz-Jentoft et al., 2014). More recently another systematic review concluded that nutritional supplementations can be useful for treating poor physical performance if combined with exercise training, but that existing evidence is still not univocal due to the different participants included in the RCTs, supplementations strategies and type of exercise used (Denison et al., 2015). Finally, another more recent systematic review reported that the interactive effect of dietary supplementation on muscle function appears limited, mostly because these supplementations were used in well-nourished people (Beaudart et al., 2017a).

Whilst the previous reviews have advanced our knowledge regarding the possible effect of nutritional supplementations on physical performance and muscle strength, a number of limitations persist, such as that the control groups were heterogenous (placebo, no intervention, other active interventions) and that some included middle-aged individuals, who clearly have a different prevalence of low physical performance, sarcopenia and frailty, when compared to older populations.

Given this background, we aimed to summarize the effect of nutritional supplementations on physical performance (i.e. functional tests more depending more on aerobic capacity than muscle power) and muscle strength (i.e. tests more depending on muscle power than aerobic capacity) outcomes in older people compared to placebo in RCTs involving only older people, stratifying our results by the type of nutritional supplementation and by condition.

2. Methods

This systematic review adhered to the PRISMA (Liberati et al., 2009) and MOOSE (Stroup et al., 2000) statements and followed a structured, but unpublished protocol.

2.1. Data sources and literature search strategy

Two investigators (NV and BS) independently conducted a literature search using PubMed, EMBASE, SCOPUS, Cochrane Central Register of Controlled Trials and Clinicaltrials.gov without language restriction, from database inception until 01st September 2018 for RCTs investigating the effect of any nutritional supplements compared to placebo for improving physical performance and/or muscle strength parameters. Any inconsistencies were resolved by consensus with a third author (SM).

In PubMed, the following search strategy was used: "(supplement* OR nutrition OR nutrient* OR neutraceutical* OR vitamin OR mineral OR fish oil OR omega OR DHA OR docosaesaenoic acid OR EPA OR eicosapentaenoic acid OR NAC OR N-Acetyl Cysteine OR SAM OR S-adenosil methionine OR omega 3 OR omega 6) AND (physical performance OR gait speed OR walking speed OR handgrip strength OR strength OR sarcopenia OR frailty) AND (older* OR elderly OR older adult) AND (random* OR placebo)". Conference abstracts and reference lists of included articles were hand-searched to identify and potential additional relevant articles.

2.2. Study selection

Inclusion criteria for this meta-analysis were: i) RCTs with at least one arm using placebo; ii) use of nutritional supplementations, defined as any dietary supplement that is intended to provide nutrients that may otherwise not be consumed in sufficient quantities and given orally. Nutritional supplementations were categorized as vitamin D metabolites, proteins/amino acids, multi-nutrients (i.e. nutritional supplementations including more than one nutrient), fish oil or vitamin K metabolites; iii) included data regarding physical performance (i.e. tests more depending on aerobic capacity than muscle power) (Veronese et al., 2017) or muscle strength (i.e. tests more depending on muscle power than aerobic capacity) (Veronese et al., 2017) outcomes; iv) included only older subjects. For reaching this specific aim each RCT should declare that all subjects were > 60 years or that the mean age of the sample included was at least 70 years, independently from the standard deviation.

Studies were excluded if: i) did not include humans; ii) did not include at least one control group taking placebo; iii) included less than 15 subjects for treated or placebo group; iv) had a mean follow-up less than 4 week.

2.3. Data extraction

Two independent investigators (NV and PS) extracted key data from the included articles in a standardized Excel sheet. A third independent investigator (SM) checked the extracted data. For each article, we extracted data about authors, year of publication, country, setting, condition, number of participants, demographics (mean age, % of females), type of supplementation and follow-up (in weeks).

Since the aim of our study was to explore the effect of nutritional supplementations on physical performance and/or muscle strength, when more than two groups were present, only the data regarding nutritional supplementations (without any physical regimen intervention) and placebo (without any physical regimen intervention) were extracted.

2.4. Outcomes

The primary outcomes were considered the changes (between follow-up and baseline) in physical performance tests having at least 4 studies for all the kinds of nutritional supplementations considered together. The included tests were timed up and go, short physical performance battery (SPPB), gait speed, chair rise time. The tests of muscle strength (i.e. leg extension, leg flexion, leg press, maximal isometric strength and handgrip strength) were considered as co-primary outcomes.

2.5. Assessment of study quality

Two independent authors (NV, BS) completed scoring using the Jadad's scale (Jadad et al., 1996) for assessing the quality and the risk of bias of the RCTs included. This quantifies the trial quality based on the description and appropriateness of randomization (2 points), blinding procedures (2 points), and description of withdrawals (1 point). A value less than 3 (over a maximum of 5) usually indicates a low-quality study at high risk of bias (Jadad, 2009).

2.6. Data synthesis and statistical analysis

All analyses were performed using Comprehensive Meta-Analysis (CMA) 3. When multiple assessments were made, the longest follow-up time was included in our analyses. Intention to treat was preferred to per protocol analysis, where available.

The primary analysis compared the values of physical performance tests between participants treated with nutritional supplementations vs.

placebo by the type of nutritional supplementation used. We calculated the difference between the means of the treatment and control groups using the changes (calculated as follow-up less baseline data) through standardized mean differences (SMD) with their 95% confidence intervals (CIs), applying a random-effect model (Higgins and Green, 2008).

Heterogeneity across studies was assessed by the I^2 metric. Given significant heterogeneity ($I^2 > 50\%$ and/or $p < 0.05$) (Higgins et al., 2011) and having at least 10 studies for each outcome, we planned to run some meta-regression analyses, taking as moderators the following factors: mean age of the whole population, percentage of females and the follow-up period. However, no outcome included 10 studies and so these analyses were not possible.

Publication bias was assessed by a visual inspection of funnel plots and calculating the Egger bias test (Egger et al., 1997).

For all analyses, a p-value less than 0.05 was considered statistically significant.

3. Results

3.1. Search results

As shown in Fig. 1, altogether, the searches yielded 4007 non-duplicated articles. After excluding 3864 articles based on title/abstract review, 143 articles were retrieved for full text review. Among these, 111 articles were excluded, most commonly because they did not include only older people (n = 46). Consequently, 32 articles were included in the qualitative and quantitative synthesis (Bauer et al., 2015; Bjornsen et al., 2016; Bo et al., 2018; Da Boit et al., 2017; Dal Negro et al., 2012; Dhesi et al., 2004; Englund et al., 2017; Fiatarone et al., 1994; Flakoll et al., 2004; Fulton et al., 2016; Glendenning et al., 2012; Grieger et al., 2009; Hutchins-Wiese et al., 2013; Kenny et al., 2003; Kim et al., 2015; Latham et al., 2003; Levis and Gomez-Marin, 2017; Lips et al., 2010; Rondanelli et al., 2016; Rondanelli et al., 2011; Songpatanasilp et al., 2009; Stout et al., 2013; Strike et al., 2016; Tarnopolsky et al., 2007; Tieland et al., 2012a; Tieland et al., 2012b; Uusi-Rasi et al., 2015; Wouters-Wesseling, 2003; Zak et al., 2009; Zdzieblik et al., 2015; Zhu et al., 2010; Zhu et al., 2015).

3.2. Study and patient characteristics

The 32 RCTs included a total of 4137 older participants (2097 treated vs. 2040 placebo). Approximately half of the studies were conducted in Europe. The mean age of the participants was 76.3 ± 5.6 years and the majority were females (65%). Twenty-one RCTs were made among community-dwelling older adults and, among the conditions considered, 13 RCTs included only healthy people, whilst 14 RCTs included only participants affected by frailty/sarcopenia/vulnerability/previous falls. In only eight RCTs (Bjornsen et al., 2016; Da Boit et al., 2017; Englund et al., 2017; Rondanelli et al., 2016; Tarnopolsky et al., 2007; Tieland et al., 2012a; Zak et al., 2009; Zdzieblik et al., 2015), data regarding physical exercise regimen were reported.

Multi-nutrient products were the most common nutritional supplementations used (n = 12 studies) including vitamin D/E associated with proteins, hypercaloric products, or amino acids associated with minerals.

The median follow-up period was 24 (range: 7–108) weeks, whilst the quality of the studies was generally good as shown by the median Jadad's score (= 5/5) (range: 3–5), without any RCT at high risk of bias (Jadad et al., 1996).

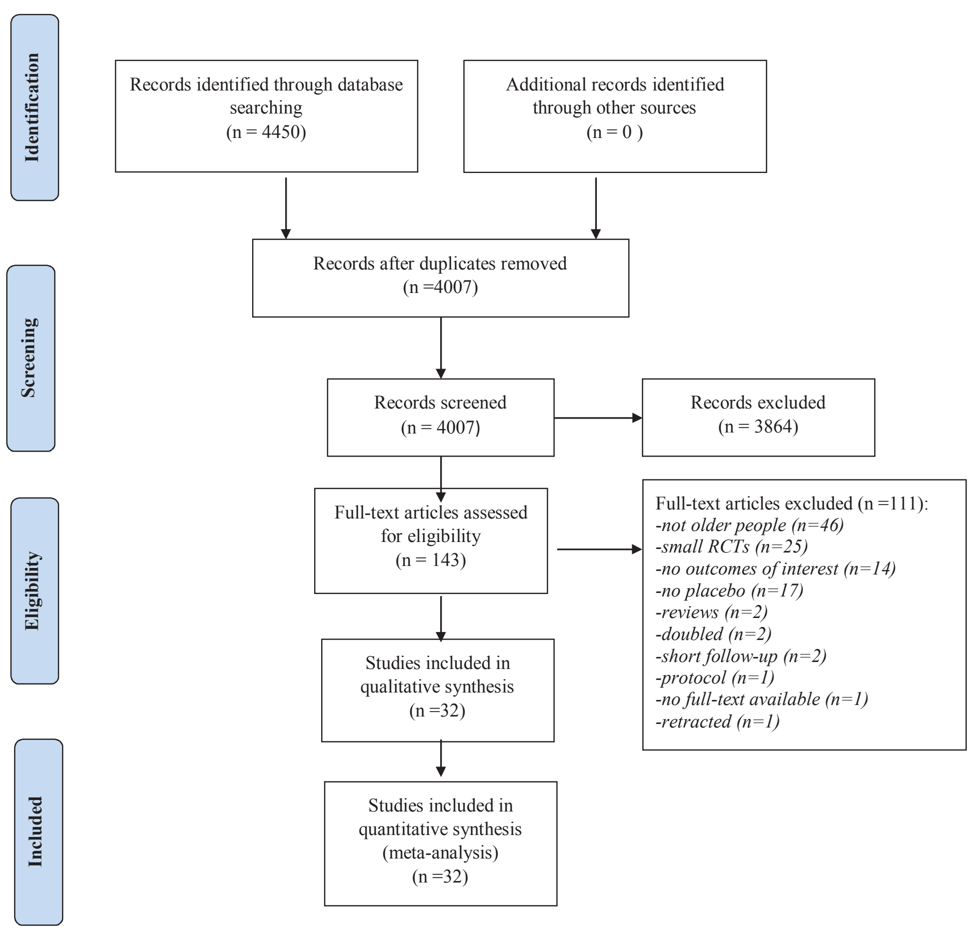

Fig. 1. PRISMA flow-chart.

Table 1
Meta-analysis of randomized controlled trials by type of nutritional intervention on physical performance outcomes.

Analysis	Number of studies	Meta-analysis					Heterogeneity
		Participants	SMD	95% CI		P value	I^2
Timed up and go							
Total	11	2000					–
Multi-nutrient	*3*	*297*	*−0.33*	*−1.05*	*0.38*	*0.36*	*89*
Proteins	*3*	*286*	*0.10*	*−0.13*	*0.33*	*0.40*	*0*
Vitamin D	*5*	*1417*	*0.03*	*−0.08*	*0.14*	*0.57*	*6*
Short physical performance battery							
Total	6	975					–
Multi-nutrient	*2*	*517*	*−0.46*	*−1.50*	*0.58*	*0.58*	*0*
Proteins	*1*	*55*	*0.07*	*−0.46*	*0.60*	*0.81*	–
Vitamin D	*2*	*326*	*−0.22*	*−0.43*	*0.00*	*0.05*	*45*
Vitamin K	***1***	***77***	***−0.82***	***−1.29***	***−0.36***	***0.001***	–
Gait speed							
Total	15						–
Fish oil	*2*	*176*	*0.26*	*−0.14*	*0.66*	*0.20*	*33*
Multi-nutrient	*5*	*654*	*−0.09*	*−0.85*	*0.66*	*0.81*	*94*
Proteins	*3*	*182*	*0.00*	*−0.29*	*0.30*	*0.97*	*0*
Vitamin D	*5*	*796*	*−0.06*	*−0.20*	*0.08*	*0.37*	*0*
Chair rise time							
Total	10						–
Fish oil	*2*	*176*	*0.17*	*−0.26*	*0.60*	*0.43*	*42*
Multi-nutrient	***3***	***577***	***−0.90***	***−1.46***	***−0.33***	***0.002***	***87***
Proteins	*2*	*120*	*−0.12*	*−0.76*	*0.51*	*0.71*	*68*
Vitamin D	*3*	*361*	*0.07*	*−0.27*	*0.41*	*0.68*	*59*

Abbreviations: SMD: standardized mean difference; CI; confidence interval.
In bold significant values, as p-values < 0.05.

3.3. Effect of nutritional supplementation on physical performance tests

As reported in Table 1, among the single nutritional component examined, multi-nutrient supplementations were able to significantly improve chair rise time in 3 RCTs (Bauer et al., 2015; Bo et al., 2018; Englund et al., 2017) (577 participants; SMD = −0.90; 95%CI: −1.46 to −0.33), even if this outcome was characterized by a high heterogeneity (I^2 = 87%). On the contrary, we did not observe any improvement in timed up and go, SPPB, or gait speed for the nutritional supplementations used, such as proteins, vitamin D, or multi-nutrient supplementations. For vitamin K, one study (Fulton et al., 2016) reported that people randomized to use this intervention had a significant decrease in this test (77 participants; SMD = −0.82; 95%CI: −1.29 to −0.36; p = 0.001) (Table 1).

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

3.4. Effect of nutritional supplementation on muscle strength tests

As shown in Table 2, nutritional supplementations did not significantly improve leg extension, leg flexion, leg pression or maximal isometric strength. Conversely, multi-nutrients significantly improved handgrip strength when compared to placebo (n = 6; 780 participants; SMD = 0.41; 95%CI: 0.06 to 0.76; I^2 = 79%) (Bauer et al., 2015; Bo et al., 2018; Flakoll et al., 2004; Grieger et al., 2009; Rondanelli et al., 2016; Wouters-Wesseling, 2003), similarly to nutritional supplementations including proteins (n = 7; 535 participants; SMD = 0.24; 95%CI: 0.07 to 0.41; I^2 = 16%) (Dal Negro et al., 2012; Kim et al., 2015; Rondanelli et al., 2011; Stout et al., 2013; Tieland et al., 2012a, b; Zhu et al., 2015) (Table 2).

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

3.5. Effect of nutritional supplementation on physical performance and muscle strength by condition

Table 3 shows the analyses stratified by the type of condition of inclusion in the RCTs. We observed that two outcomes (i.e. chair rise time with a p-value = 0.01 and handgrip strength with a p-value = 0.001) reported a significant interaction between nutritional supplementation by condition. In particular, nutritional supplementations improved chair rise time in frail/sarcopenic subjects (SMD = −0.60; 95%CI: −1.10 to −0.10; p = 0.02; I^2 = 88%) (Bauer et al., 2015; Bo et al., 2018; Englund et al., 2017; Tieland et al., 2012a, b) and handgrip strength in people affected by frailty/sarcopenia (SMD = 0.35; 95%CI: 0.03 to 0.67; p = 0.03; I^2 = 76%) (Bauer et al., 2015; Bo et al., 2018; Flakoll et al., 2004; Kim et al., 2015; Rondanelli et al., 2016; Tieland et al., 2012a,b) and in other conditions than sarcopenia/frailty (SMD = 0.59; 95%CI: 0.09–1.09; p = 0.03; I^2 = 67%) (Dal Negro et al., 2012; Fulton et al., 2016; Rondanelli et al., 2011) (Table 3).

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

4. Discussion

In this systematic review and meta-analysis including 32 RCTs placebo-controlled and 4137 older participants, we found that multi-nutrient supplementations (i.e. nutritional supplementations made of several nutritional components) appear to have a positive impact for improving some physical performance and muscle strength tests in older people. Our review also reported that nutritional supplementations led to a significant improvement in chair rise time and in handgrip strength in not healthy participants, even if several outcomes of both physical performance and muscle strength were not significant.

The pathological loss of muscle mass is an important topic in geriatric medicine and poor nutritional status seems to play an important role in the development of sarcopenia. It is widely known that there is a significant decline in food and energy intake with increasing age,

Table 2
Meta-analysis of randomized controlled trials by type of nutritional intervention on muscle strength outcomes.

Analysis	Number of studies	Meta-analysis					Heterogeneity
		Participants	SMD	95% CI		P value	I^2
Leg extension							
Total	11	1001					
Multi-nutrient	*5*	*311*	*−0.01*	*−0.32*	*0.29*	*0.94*	*40*
Proteins	*4*	*344*	*0.14*	*−0.07*	*0.36*	*0.18*	*0*
Vitamin D	*2*	*346*	*1.41*	*−1.33*	*4.15*	*0.31*	*99*
Leg flexion							
Total	6	712					
Multi-nutrient	*3*	*227*	*−0.10*	*−1.04*	*0.84*	*0.84*	*90*
Proteins	*2*	*224*	*−0.27*	*−0.67*	*0.13*	*0.19*	*40*
Vitamin D	*1*	*261*	*0.00*	*−0.24*	*0.24*	*1.00*	–
Leg pression							
Total	5						
Multi-nutrient	*2*	*84*	*0.21*	*−0.22*	*0.64*	*0.34*	*0*
Proteins	*3*	*159*	*0.09*	*−0.22*	*0.40*	*0.58*	*0*
Maximal isometric strength							
Total	7						
Fish oil	*1*	*50*	*0.01*	*−0.54*	*0.57*	*0.97*	–
Proteins	*2*	*101*	*−0.13*	*−0.52*	*0.27*	*0.53*	*0*
Vitamin D	*4*	*498*	*0.15*	*−0.05*	*0.36*	*0.15*	*52*
Handgrip strength							
Total	17						
Fish oil	1	*126*	*−0.26*	*−0.63*	*0.12*	*0.18*	*0*
Multi-nutrient	**6**	***780***	***0.41***	***0.06***	***0.76***	***0.02***	*79*
Proteins	**7**	***535***	***0.24***	***0.07***	***0.41***	***0.006***	*16*
Vitamin D	2	*799*	*−0.06*	*−0.20*	*0.08*	*0.42*	*4*
Vitamin K	1	*77*	*0.21*	*−0.24*	*0.66*	*0.37*	–

Abbreviations: SMD: standardized mean difference; CI: confidence interval.
In bold significant values, as pas p-values < 0.05.

estimated in an average fall of around 25% between the ages of 40 and 70 years (Nieuwenhuizen et al., 2010). Therefore, the use of nutritional supplementations is usually recommended among older people, even if these recommendations are more based on clinical practice than on solid scientific knowledge (Buhr and Bales, 2009). In this line, a large Cochrane review reported that the use of antioxidant is not able to decrease mortality in healthy and non-healthy people and, paradoxically, high doses of vitamin A, beta-carotene and vitamin E seem to increase mortality (Bjelakovic et al., 2012).

More focusing on the topic of physical performance and muscle strength, some systematic reviews already reported findings regarding the use of nutritional supplementations on these outcomes, with not univocal findings, mainly due to the fact that the RCTs included in these meta-analyses involved only well-nourished people, small sample sizes, heterogenous ages and different physical exercise regimens (Beaudart et al., 2017a; Cruz-Jentoft et al., 2014; Denison et al., 2015). We tried to overcome these limitations with our work using very restrictive criteria (i.e. only large RCTs including only older people) and where available arms not using physical exercise, if possible, but our results are substantially like those already published. We can affirm that the effect of nutritional supplementations is limited to only some physical performance tests and that for further improving muscle strength, resistance exercise should be undertaken (Beaudart et al., 2017b). Unfortunately several RCTs included in our meta-analysis did not report sufficient information regarding the characteristics of the physical exercise regimen applied and we decided to focus on the role of nutritional supplementations where possible, thus not considering arms randomized to physical exercise programs, where available. Moreover, multi-nutrients seem to be better for improving physical performance tests than single nutrients. We can hypothesize that, being malnutrition in older people multifactorial (Cereda et al., 2018), multicomponent nutritional supplementations can work better than supplementations with single components, but other studies are needed in this sense since only a few outcomes were improved by this kind of supplementations.

Another point of importance is that the RCTs included mainly healthy participants. This is a limitation of the current literature regarding the role of nutritional interventions in older people as acknowledged by other authors. (Cruz-Jentoft et al., 2014) However, in this sense, our work supported the idea that nutritional supplementations are useful for improving two important outcomes, i.e. chair rise time and handgrip strength in people affected by sarcopenia/frailty and other medical conditions, whilst the effect in healthy participants was not significant. Since the effect of nutritional supplementations in improving other outcomes of physical activity (e.g. gait speed and SPPB) was not significant, other high quality RCTs are needed, particularly in order to take into consideration the role of other specific conditions. Indeed, while the chair rise time and handgrip strength are mainly affected by the muscle strength, gait speed and SPPB are probably more affected by pulmonary, cardiovascular and bone conditions. In this sense, our data are in agreement with a recent systematic review and meta-analysis showing that the use of nutritional supplementations in improving physical function in people affected by osteoarthritis is very limited and that the most widely used supplements do not provide any clinically important effect on osteoarthritis (Liu et al., 2017), suggesting, again, that more research is needed regarding the possible use of nutritional supplementations in osteoarticular conditions.

As final recommendation, our research suggests that nutritional supplementations are probably most useful when they are utilised as multi-nutrients, i.e. include more than one component and when people are vulnerable. This is probably due to the higher presence of malnutrition in vulnerable than healthy older people that justify the use of nutritional supplementations in the treatment (more than in the prevention) of poor physical performance/muscle strength in older people.

The findings of our meta-analysis should be interpreted within its limitations. First, the results were heterogenous. Even if we planned to run a meta-regression analysis for explain this point, the number of

Table 3
Meta-analysis of randomized controlled trials by type of condition.

Analysis	Number of studies	Meta-analysis					Heterogeneity
		Participants	SMD	95% CI		P value	I^2
Timed up and go							
Healthy	*4*	*974*	*0.11*	*−0.02*	*0.23*	*0.10*	*0*
Other conditions	*2*	*246*	*0.05*	*−0.21*	*0.30*	*0.76*	*0*
Frailty/sarcopenia	*5*	*780*	*−0.23*	*−0.59*	*0.14*	*0.23*	*84*
Short physical performance battery							
Healthy	*1*	*113*	*−0.27*	*−0.64*	*0.10*	*0.16*	*0*
Other conditions	*2*	*290*	*−0.48*	*−1.10*	*0.14*	*0.13*	*82*
Frailty/sarcopenia	*3*	*572*	*−0.29*	*−1.02*	*0.43*	*0.43*	*93*
Gait speed							
Healthy	*6*	*431*	*0.10*	*−0.18*	*0.38*	*0.47*	*48*
Other conditions	*2*	*396*	*−0.04*	*−0.24*	*0.16*	*0.68*	*0*
Frailty/sarcopenia	*7*	*981*	*−0.15*	*−0.60*	*0.29*	*0.51*	*90*
Chair rise time*							
Healthy	*4*	*354*	*0.18*	*−0.11*	*0.47*	*0.21*	*42*
Other conditions	*1*	*183*	*−0.11*	*−0.40*	*0.18*	*0.47*	*0*
Frailty/sarcopenia	***5***	***697***	***−0.60***	***−1.10***	***−0.10***	***0.02***	*88*
Leg extension							
Healthy	*4*	*308*	*0.14*	*−0.09*	*0.36*	*0.24*	*0*
Other conditions	*1*	*261*	*0.02*	*−0.22*	*0.27*	*0.85*	*0*
Frailty/sarcopenia	*6*	*432*	*0.51*	*−0.33*	*1.36*	*0.24*	*94*
Leg flexion							
Healthy	*2*	*224*	*−0.27*	*−0.67*	*0.13*	*0.19*	*40*
Other conditions	*1*	*261*	*0.00*	*−0.24*	*0.24*	*1.00*	*0*
Frailty/sarcopenia	*3*	*227*	*−0.10*	*−1.04*	*0.84*	*0.84*	*90*
Leg press							
Healthy	*3*	*123*	*0.25*	*−0.11*	*0.60*	*0.18*	*0*
Frailty/sarcopenia	*2*	*120*	*0.01*	*−0.35*	*0.37*	*0.95*	*0*
Maximal isometric strength							
Healthy	*4*	*242*	*0.22*	*−0.02*	*0.48*	*0.08*	*0*
Frailty/sarcopenia	*3*	*407*	*0.001*	*−0.19*	*0.20*	*0.99*	*0*
Handgrip strength*							
Healthy	*7*	*1309*	*−0.008*	*−0.14*	*0.12*	*0.90*	*16*
Other conditions	***3***	***206***	***0.59***	***0.09***	***1.09***	***0.02***	***67***
Frailty/sarcopenia	***7***	***802***	***0.35***	***0.03***	***0.67***	***0.03***	***76***

Abbreviations: SMD: standardized mean difference; CI: confidence interval.

* The asterisk indicates a p for interaction across strata < 0.05.

studies included for each outcome was not sufficient. For example, it is possible that the different period of exposure to an oral supplementation can lead to different results in terms of efficacy. Second, the data regarding physical exercise regimen were reported for only eight RCTs and thus it was not possible to explore the impact of exercise on the outcomes of our meta-analysis. Finally, the median follow-up period was only 24 weeks. Despite these limitations, our study has some important strengths such as the inclusion of sufficient quality RCTs, the inclusion of only older people (differently from meta-analyses/systematic reviews published before), the inclusion of people having different rates of multimorbidity and malnutrition, and the large number of people involved.

In conclusion, nutritional supplementations seem to be useful in improving only some physical performance outcomes in older people, particularly if they are multi-nutrients and when not including healthy participants. No evidence was found for several physical performance (e.g. timed up and go or gait speed) and muscle strength (e.g. lower limbs strength) tests. Other high quality RCTs are needed to confirm our findings.

Funding source

This work is supported with an unconditioned grant of Fidia.

Conflict of interest

The authors have not conflict of interest to declare for this work.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2019.02.005.

References

Bauer, J.M., Verlaan, S., Bautmans, I., Brandt, K., Donini, L.M., Maggio, M., McMurdo, M.E., Mets, T., Seal, C., Wijers, S.L., Ceda, G.P., De Vito, G., Donders, G., Drey, M., Greig, C., Holmback, U., Narici, M., McPhee, J., Poggiogalle, E., Power, D., Scafoglieri, A., Schultz, R., Sieber, C.C., Cederholm, T., 2015. Effects of a vitamin D and leucine-enriched whey protein nutritional supplement on measures of sarcopenia in older adults, the PROVIDE study: a randomized, double-blind, placebo-controlled trial. J. Am. Med. Dir. Assoc. 16, 740–747.
Beaudart, C., Dawson, A., Shaw, S.C., Harvey, N.C., Kanis, J.A., Binkley, N., Reginster, J.Y., Chapurlat, R., Chan, D.C., Bruyere, O., Rizzoli, R., Cooper, C., Dennison, E.M., 2017a. Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review. Osteoporos. Int. 28, 1817–1833.
Beaudart, C., Dawson, A., Shaw, S.C., Harvey, N.C., Kanis, J.A., Binkley, N., Reginster, J.Y., Chapurlat, R., Chan, D.C., Bruyere, O., Rizzoli, R., Cooper, C., Dennison, E.M., 2017b. Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review. Osteoporos. Int.
Bjelakovic, G., Nikolova, D., Gluud, L.L., Simonetti, R.G., Gluud, C., 2012. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Cochrane Database Syst. Rev., CD007176.
Bjornsen, T., Salvesen, S., Berntsen, S., Hetlelid, K.J., Stea, T.H., Lohne-Seiler, H., Rohde,

G., Haraldstad, K., Raastad, T., Kopp, U., Haugeberg, G., Mansoor, M.A., Bastani, N.E., Blomhoff, R., Stolevik, S.B., Seynnes, O.R., Paulsen, G., 2016. Vitamin C and E supplementation blunts increases in total lean body mass in elderly men after strength training. Scand. J. Med. Sci. Sports 26, 755–763.
Bo, Y., Liu, C., Ji, Z., Yang, R., An, Q., Zhang, X., You, J., Duan, D., Sun, Y., Zhu, Y., 2018. A high whey protein, vitamin D and E supplement preserves muscle mass, strength, and quality of life in sarcopenic older adults: a double-blind randomized controlled trial. Clin. Nutr.
Boulos, C., Salameh, P., Barberger-Gateau, P., 2016. Malnutrition and frailty in community dwelling older adults living in a rural setting. Clin. Nutr. 35, 138–143.
Buhr, G., Bales, C.W., 2009. Nutritional supplements for older adults: review and recommendations-part I. J. Nutr. Elder. 28, 5–29.
Cereda, E., Pedrolli, C., Klersy, C., Bonardi, C., Quarleri, L., Cappello, S., Turri, A., Rondanelli, M., Caccialanza, R., 2016. Nutritional status in older persons according to healthcare setting: a systematic review and meta-analysis of prevalence data using MNA(R). Clin. Nutr. 35, 1282–1290.
Cereda, E., Veronese, N., Caccialanza, R., 2018. The final word on nutritional screening and assessment in older persons. Curr. Opin. Clin. Nutr. Metab. Care 21, 24–29.
Cesari, M., Landi, F., Vellas, B., Bernabei, R., Marzetti, E., 2014. Sarcopenia and physical frailty: two sides of the same coin. Front. Aging Neurosci. 6, 192.
Cruz-Jentoft, A.J., Landi, F., Schneider, S.M., Zuniga, C., Arai, H., Boirie, Y., Chen, L.K., Fielding, R.A., Martin, F.C., Michel, J.P., Sieber, C., Stout, J.R., Studenski, S.A., Vellas, B., Woo, J., Zamboni, M., Cederholm, T., 2014. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing 43, 748–759.
Da Boit, M., Sibson, R., Sivasubramaniam, S., Meakin, J.R., Greig, C.A., Aspden, R.M., Thies, F., Jeromson, S., Hamilton, D.L., Speakman, J.R., Hambly, C., Mangoni, A.A., Preston, T., Gray, S.R., 2017. Sex differences in the effect of fish-oil supplementation on the adaptive response to resistance exercise training in older people: a randomized controlled trial. Am. J. Clin. Nutr. 105, 151–158.
Dal Negro, R.W., Testa, A., Aquilani, R., Tognella, S., Pasini, E., Barbieri, A., Boschi, F., 2012. Essential amino acid supplementation in patients with severe COPD: a step towards home rehabilitation. Monaldi Arch. Chest Dis. 77, 67–75.
Denison, H.J., Cooper, C., Sayer, A.A., Robinson, S.M., 2015. Prevention and optimal management of sarcopenia: a review of combined exercise and nutrition interventions to improve muscle outcomes in older people. Clin. Interv. Aging 10, 859–869.
Dhesi, J.K., Jackson, S.H., Bearne, L.M., Moniz, C., Hurley, M.V., Swift, C.G., Allain, T.J., 2004. Vitamin D supplementation improves neuromuscular function in older people who fall. Age Ageing 33, 589–595.
Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315, 629–634 Clinical research ed.
Englund, D.A., Kirn, D.R., Koochek, A., Zhu, H., Travison, T.G., Reid, K.F., von Berens, Å., Melin, M., Cederholm, T., Gustafsson, T., 2017. Nutritional supplementation with physical activity improves muscle composition in mobility-limited older adults, the VIVE2 study: a randomized, double-blind, placebo-controlled trial. J. Gerontol. A Biol. Sci. Med. Sci. 73, 95–101.
Fiatarone, M.A., O'Neill, E.F., Ryan, N.D., Clements, K.M., Solares, G.R., Nelson, M.E., Roberts, S.B., Kehayias, J.J., Lipsitz, L.A., Evans, W.J., 1994. Exercise training and nutritional supplementation for physical frailty in very elderly people. N. Engl. J. Med. 330, 1769–1775.
Flakoll, P., Sharp, R., Baier, S., Levenhagen, D., Carr, C., Nissen, S., 2004. Effect of beta-hydroxy-beta-methylbutyrate, arginine, and lysine supplementation on strength, functionality, body composition, and protein metabolism in elderly women. Nutrition 20, 445–451.
Fulton, R.L., McMurdo, M.E., Hill, A., Abboud, R.J., Arnold, G.P., Struthers, A.D., Khan, F., Vermeer, C., Knapen, M.H., Drummen, N.E., Witham, M.D., 2016. Effect of vitamin K on vascular health and physical function in older people with vascular disease–A randomised controlled trial. The journal of nutrition. Health Aging 20, 325–333.
Gall, M.J., Harmer, J.E., Wanstall, H.J., 2001. Prescribing of oral nutritional supplements in Primary Care: can guidelines supported by education improve prescribing practice? Clin. Nutr. 20, 511–515.
Glendenning, P., Zhu, K., Inderjeeth, C., Howat, P., Lewis, J.R., Prince, R.L., 2012. Effects of three-monthly oral 150,000 IU cholecalciferol supplementation on falls, mobility, and muscle strength in older postmenopausal women: a randomized controlled trial. J. Bone Miner. Res. 27, 170–176.
Grieger, J.A., Nowson, C.A., Jarman, H.F., Malon, R., Ackland, L.M., 2009. Multivitamin supplementation improves nutritional status and bone quality in aged care residents. Eur. J. Clin. Nutr. 63, 558–565.
Higgins, J.P.T., Green, S., 2008. Cochrane Handbook for Systematic Reviews of.
Higgins, J.P., Altman, D.G., Gotzsche, P.C., Juni, P., Moher, D., Oxman, A.D., Savovic, J., Schulz, K.F., Weeks, L., Sterne, J.A., Cochrane Bias Methods, G., Cochrane Statistical Methods, G., 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343, d5928.
Hutchins-Wiese, H.L., Kleppinger, A., Annis, K., Liva, E., Lammi-Keefe, C.J., Durham, H.A., Kenny, A.M., 2013. The impact of supplemental n-3 long chain polyunsaturated fatty acids and dietary antioxidants on physical performance in postmenopausal women. The journal of nutrition. Health Aging 17, 76–80.
Jadad, A.R., 2009. The merits of measuring the quality of clinical trials: is it becoming a Byzantine discussion? Transpl. Int. 22 1028–1028.
Jadad, A.R., Moore, R.A., Carroll, D., Jenkinson, C., Reynolds, D.J., Gavaghan, D.J., McQuay, H.J., 1996. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control. Clin. Trials 17, 1–12.
Kenny, A.M., Biskup, B., Robbins, B., Marcella, G., Burleson, J.A., 2003. Effects of vitamin D supplementation on strength, physical function, and health perception in older, community-dwelling men. J. Am. Geriatr. Soc. 51, 1762–1767.
Kim, H., Suzuki, T., Kim, M., Kojima, N., Ota, N., Shimotoyodome, A., Hase, T., Hosoi, E., Yoshida, H., 2015. Effects of exercise and milk fat globule membrane (MFGM) supplementation on body composition, physical function, and hematological parameters in community-dwelling frail Japanese women: a randomized double blind, placebo-controlled, follow-up trial. PLoS One 10, e0116256.
Latham, N.K., Anderson, C.S., Lee, A., Bennett, D.A., Moseley, A., Cameron, I.D., 2003. A randomized, controlled trial of quadriceps resistance exercise and vitamin D in frail older people: the Frailty Interventions Trial in Elderly Subjects (FITNESS). J. Am. Geriatr. Soc. 51, 291–299.
Levis, S., Gomez-Marin, O., 2017. Vitamin d and physical function in sedentary older men. J. Am. Geriatr. Soc. 65, 323–331.
Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gøtzsche, P.C., Ioannidis, J.P.A., Clarke, M., Devereaux, P.J., Kleijnen, J., Moher, D., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 6 e1000100-e1000100.
Lips, P., Binkley, N., Pfeifer, M., Recker, R., Samanta, S., Cohn, D.A., Chandler, J., Rosenberg, E., Papanicolaou, D.A., 2010. Once-weekly dose of 8400 IU vitamin D(3) compared with placebo: effects on neuromuscular function and tolerability in older adults with vitamin D insufficiency. Am. J. Clin. Nutr. 91, 985–991.
Liu, X., Machado, G.C., Eyles, J.P., Ravi, V., Hunter, D.J., 2017. Dietary supplements for treating osteoarthritis: a systematic review and meta-analysis. Br. J. Sports Med.
Nieuwenhuizen, W.F., Weenen, H., Rigby, P., Hetherington, M.M., 2010. Older adults and patients in need of nutritional support: review of current treatment options and factors influencing nutritional intake. Clin. Nutr. 29, 160–169.
Rondanelli, M., Opizzi, A., Antoniello, N., Boschi, F., Iadarola, P., Pasini, E., Aquilani, R., Dioguardi, F.S., 2011. Effect of essential amino acid supplementation on quality of life, amino acid profile and strength in institutionalized elderly patients. Clin. Nutr. 30, 571–577.
Rondanelli, M., Klersy, C., Terracol, G., Talluri, J., Maugeri, R., Guido, D., Faliva, M.A., Solerte, B.S., Fioravanti, M., Lukaski, H., Perna, S., 2016. Whey protein, amino acids, and vitamin D supplementation with physical activity increases fat-free mass and strength, functionality, and quality of life and decreases inflammation in sarcopenic elderly. Am. J. Clin. Nutr. 103, 830–840.
Sánchez-Rodríguez, D., Marco, E., Ronquillo-Moreno, N., Miralles, R., Vázquez-Ibar, O., Escalada, F., Muniesa, J.M., 2017. Prevalence of malnutrition and sarcopenia in a post-acute care geriatric unit: applying the new ESPEN definition and EWGSOP criteria. Clin. Nutr. 36, 1339–1344.
Singh, D.K.A., Manaf, Z.A., Yusoff, N.A.M., Muhammad, N.A., Phan, M.F., Shahar, S., 2014. Correlation between nutritional status and comprehensive physical performance measures among older adults with undernourishment in residential institutions. Clin. Interv. Aging 9, 1415–1423.
Songpatanasilp, T., Chailurkit, L.O., Nichachotsalid, A., Chantarasorn, M., 2009. Combination of alfacalcidol with calcium can improve quadriceps muscle strength in elderly ambulatory Thai women who have hypovitaminosis D: a randomized controlled trial. J. Med. Assoc. Thai. 92 (Suppl. 5), S30–41.
Stout, J.R., Smith-Ryan, A.E., Fukuda, D.H., Kendall, K.L., Moon, J.R., Hoffman, J.R., Wilson, J.M., Oliver, J.S., Mustad, V.A., 2013. Effect of calcium beta-hydroxy-beta-methylbutyrate (CaHMB) with and without resistance training in men and women 65 + yrs: a randomized, double-blind pilot trial. Exp. Gerontol. 48, 1303–1310.
Strike, S.C., Carlisle, A., Gibson, E.L., Dyall, S.C., 2016. A high Omega-3 fatty acid multinutrient supplement benefits cognition and mobility in older women: a randomized, double-blind, placebo-controlled pilot study. J. Gerontol. A Biol. Sci. Med. Sci. 71, 236–242.
Stroup, D.F., Berlin, Ja., Morton, S.C., Olkin, I., Williamson, G.D., Rennie, D., Moher, D., Becker, B.J., Sipe, Ta., Thacker, S.B., 2000. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283, 2008–2012.
Tarnopolsky, M., Zimmer, A., Paikin, J., Safdar, A., Aboud, A., Pearce, E., Roy, B., Doherty, T., 2007. Creatine monohydrate and conjugated linoleic acid improve strength and body composition following resistance exercise in older adults. PLoS One 2, e991.
Tieland, M., Dirks, M.L., van der Zwaluw, N., Verdijk, L.B., van de Rest, O., de Groot, L.C., van Loon, L.J., 2012a. Protein supplementation increases muscle mass gain during prolonged resistance-type exercise training in frail elderly people: a randomized, double-blind, placebo-controlled trial. J. Am. Med. Dir. Assoc. 13, 713–719.
Tieland, M., van de Rest, O., Dirks, M.L., van der Zwaluw, N., Mensink, M., van Loon, L.J., de Groot, L.C., 2012b. Protein supplementation improves physical performance in frail elderly people: a randomized, double-blind, placebo-controlled trial. J. Am. Med. Dir. Assoc. 13, 720–726.
Uusi-Rasi, K., Patil, R., Karinkanta, S., Kannus, P., Tokola, K., Lamberg-Allardt, C., Sievanen, H., 2015. Exercise and vitamin D in fall prevention among older women: a randomized clinical trial. JAMA Intern. Med. 175, 703–711.
Veronese, N., Stubbs, B., Trevisan, C., Bolzetta, F., De Rui, M., Solmi, M., Sarton, L., Musacchio, E., Zambon, S., Perissinotto, E., Baggio, G., Crepaldi, G., Manzato, E., Maggi, S., Sergi, G., 2017. Poor physical performance predicts future onset of depression in elderly people: Pro.V.A. Longitudinal study. Phys. Ther.
Wouters-Wesseling, W., 2003. The effect of a liquid nutrition supplement on body composition and physical functioning in elderly people. Clin. Nutr. 22, 371–377.
Zak, M., Swine, C., Grodzicki, T., 2009. Combined effects of functionally-oriented exercise regimens and nutritional supplementation on both the institutionalised and free-living frail elderly (double-blind, randomised clinical trial). BMC Public Health 9, 39.
Zdzieblik, D., Oesser, S., Baumstark, M.W., Gollhofer, A., Konig, D., 2015. Collagen peptide supplementation in combination with resistance training improves body composition and increases muscle strength in elderly sarcopenic men: a randomised controlled trial. Br. J. Nutr. 114, 1237–1245.
Zhu, K., Austin, N., Devine, A., Bruce, D., Prince, R.L., 2010. A randomized controlled trial of the effects of vitamin D on muscle strength and mobility in older women with vitamin D insufficiency. J. Am. Geriatr. Soc. 58, 2063–2068.
Zhu, K., Kerr, D.A., Meng, X., Devine, A., Solah, V., Binns, C.W., Prince, R.L., 2015. Two-year whey protein supplementation did not enhance muscle mass and physical function in well-nourished healthy older postmenopausal women. J. Nutr. 145, 2520–2526.