Lead Article

Nutritional interventions to improve muscle mass, muscle strength, and physical performance in older people: an umbrella review of systematic reviews and meta-analyses

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Context: *Sarcopenia is a progressive and generalized skeletal muscle disorder associated with an increased risk of adverse outcomes such as falls, disability, and death. The Belgian Society of Gerontology and Geriatrics has developed evidence-based guidelines for the prevention and treatment of sarcopenia. This umbrella review presents the results of the Working Group on Nutritional Interventions.* ***Objective:*** *The aim of this umbrella review was to provide an evidence-based overview of nutritional interventions targeting sarcopenia or at least 1 of the 3 sarcopenia criteria (ie, muscle mass, muscle strength, or physical performance) in persons aged ≥ 65 years.* ***Data sources:*** *Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, the PubMed and Web of Science databases were searched for systematic reviews and meta-analyses reporting the effect of nutritional supplementation on sarcopenia or muscle mass, strength, or physical performance.* ***Data extraction:*** *Two authors extracted data on the key characteristics of the reviews, including participants, treatment, and outcomes. Methodological quality of the reviews was assessed using the product A Measurement Tool to Assess Systematic Reviews. Three authors synthesized the extracted data and generated recommendations on the basis of an overall synthesis of the effects of each intervention. Quality of evidence was rated with the Grading of Recommendations Assessment, Development and Evaluation approach.* ***Data analysis:*** *A total of 15 systematic reviews were included. The following supplements were examined: proteins, essential amino acids, leucine,*

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β-hydroxy-β-methylbutyrate, creatine, and multinutrient supplementation (with or without physical exercise). Because of both the low amount and the low to moderate quality of the reviews, the level of evidence supporting most recommendations was low to moderate. ***Conclusions:*** *Best evidence is available to recommend leucine, because it has a significant effect on muscle mass in elderly people with sarcopenia. Protein supplementation on top of resistance training is recommended to increase muscle mass and strength, in particular for obese persons and for* $\geq$ *24 weeks. Effects on sarcopenia as a construct were not reported in the included reviews.*

INTRODUCTION

Aging is associated with a progressive and general loss of muscle mass and muscle strength.[1] Loss of muscle mass is estimated at approximately 35%–40% between the ages of 20 and 80 years.[2] The difference in muscle strength between young persons and healthy elderly persons ages 60 to 80 years is 20%–40%, and this difference increases to $\geq$50% when compared with those older than 80 years.[3] There is, however, wide interindividual variation in the peak muscle mass and strength achieved during early life as well as in the rate of decline of muscle mass and strength in adult and older life. This explains the differences in the remaining amount of muscle mass and muscle strength between older individuals.[4] When a threshold of low muscle mass and strength is reached, sarcopenia is defined, predisposing elderly persons to physical disability, mobility limitations, falls, institutionalization, and death.[1]

Since 2009, several expert groups, such as the European Working Group on Sarcopenia in Older People (EWGSOP), have tried to incorporate the concept of sarcopenia into an operational definition, but so far, no consensus definition has been reached.[1,5–9] Common to these definitions of sarcopenia is that they contain a component of low muscle mass and a component of low muscle function, which may be low physical performance or low muscle strength. Recently, the EWGSOP updated its definition of sarcopenia, which now focuses on low muscle strength as the key clinical characteristic of sarcopenia and considers low muscle mass and/or quality to confirm the diagnosis and poor physical performance to determine its severity.[10] On October 1, 2016, sarcopenia received an International Statistical Classification of Diseases and Related Health Problems code (M62.84), which is necessary to diagnose it as a disease. This recognition urges the need to diagnose sarcopenia in clinical practice and to develop guidelines to effectively prevent or counter this condition.[11]

Because of the major clinical and economic burdens of sarcopenia, it is, indeed, critical to find efficient and feasible interventions for sarcopenia. The aforementioned variation in the age-related decline of muscle mass and strength indicates a potential role, not only for sex, height, weight, and genetic heritability but also for physical exercise and nutritional intake over the lifetime as determinants of sarcopenia, and thus as potential leads for intervention.[4]

The role of physical exercise and nutritional interventions has been examined in several randomized controlled trials (RCTs). The Belgian Society of Gerontology and Geriatrics has developed evidence-based guidelines for the prevention and therapy of sarcopenia for use in broad clinical practice,[12] and recently the results of the Working Groups on Pharmacology and on Exercise Interventions have been published.[13,14] This review presents the results of the Working Group on Nutritional Interventions. The aim is to provide an overview of nutritional interventions targeting sarcopenia or at least 1 of the sarcopenia criteria (ie, muscle mass, muscle strength, or physical performance), with a focus on interventions studied in systematic reviews or meta-analyses. Therefore, a systematic umbrella review was performed and specific recommendations for clinical practice were proposed according to the levels of evidence. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed for this review (*Appendix S1 in the Supporting Information online*).[15]

METHODS

Search strategy and selection criteria

Two databases (PubMed, Web of Science) were systematically searched from the earliest date available (1950s for PubMed, 1900 for Web of Science) until November 8, 2017. Keywords corresponded to the PICOS design, as follows: population: older adults; intervention: nutrition; comparison: no nutrition; outcomes: sarcopenia; study design: systematic review and meta-analysis) (Table 1; *see Appendix S2 in the Supporting Information online for full search strategies*).

Table 1 **PICOS criteria for inclusion of studies**

Parameter	Criteria	Description
Study design	1. Is the study a systematic review?	• Only systematic reviews are considered • No narrative reviews are considered
Participants	2. Does the study involve older people?	Adults aged $\geq$ 65 years are considered Groups that may be covered: A. Healthy older people who remain above the cutoff values of the EWGSOP diagnostic criteria B. Older people with muscle mass below the cutoff values of the EWGSOP diagnostic criteria but without impact on muscle strength or physical performance (EWGSOP pre-sarcopenia) C. Older people with low muscle mass plus low muscle strength and/or low physical performance (EWGSOP sarcopenia)
Intervention	3. Does the study evaluate caloric interventions? 4. Are these interventions aimed at prevention or treatment of sarcopenia?	Caloric and protein supplementation including: A. Studies in which the effect of caloric/protein supplementation is compared with no supplementation B. Studies in which caloric/protein supplementation is added to an exercise program and compared with a control group of exercise without supplementation C. Barriers and motivators to initiate, adhere, and change related lifestyle
Outcomes	6. Does the study report effects on sarcopenia-related outcomes?	Relevant outcomes include: A. muscle mass B. muscle strength C. muscle endurance D. flexibility E. morbidity F. disability G. death H. quality of life I. function and participation J. adverse events

Abbreviation: EWGSOP, European Working Group on Sarcopenia in Older People.

Study selection

Systematic reviews in English reporting the effect of caloric or nutritional supplementation (with or without an exercise program) on 1 or more of the 3 criteria of sarcopenia in older adults $\geq$ 65 years (ie, muscle mass, muscle strength, or physical performance) were considered eligible for inclusion in this umbrella review. Original studies, editorials, letters to the editor, and narrative reviews were excluded. Animal studies and studies in patients with ongoing diseases were also excluded (Table 1). Reviews reporting on the effects of vitamin D supplementation were not taken into consideration, because these were investigated and recently published by the Working Group on Pharmacology.[13] Four authors (D.B., E.G., S.D.B., M.V.), blinded to each other's results, screened the titles and abstracts for duplicate studies and for eligibility using the Rayyan web application for systematic reviews.[16] Subsequently, full-text articles were screened by the same authors. Disagreements were resolved by discussion until consensus was reached.

Data extraction and methodological quality assessment

Data extraction was completed by 1 author (A.D.) and verified by a second author (D.B.) using a data extraction form based on a template provided by the Cochrane Collaboration.[17] The authors extracted data regarding the key characteristics of the reviews, including participants, treatment, and outcomes. No assumptions were made on missing or unclear data.

Two authors (D.B., A.D.) assessed the methodological quality of the systematic reviews using the A Measurement Tool to Assess Systematic Reviews (AMSTAR) (*Appendix S3 in the Supporting Information online*).[18,19] This 11-item tool assesses the degree to which review methods avoided bias. The methodological quality was rated as high (score 8–11), moderate (score 4–7) or low (score 0–3). A quality assessment of the studies included in the systematic reviews was not performed.

To organize the evidence, 3 authors (D.B., A.D., E.G.) systematically synthesized the extracted data of

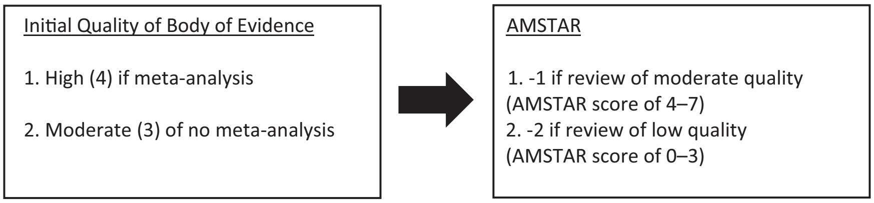

Figure 1 **Method used to rate the quality of the evidence supporting each bottom-line statement.** *Abbreviation:* AMSTAR, A Measurement Tool to Assess Systematic Reviews.[18]

each review. This resulted in standardized effectiveness statements (ie, sufficient evidence, some evidence, insufficient evidence, insufficient evidence to determine) about the treatment effect of the intervention(s) in the individual systematic reviews (*Appendix S4 in the Supporting Information online*). In addition, 2 authors (D.B., E.G.) developed an overall synthesis, beyond a simple summary of the main results of each review. These are the "bottom-line statements" about the main effects of each intervention category. The quality of the evidence (QoE) supporting each bottom-line statement was rated by using a method based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for primary evidence (1 = very low; 2 = low; 3 = moderate; 4 = high) (Figure 1[18]).[20] This method takes into account study design (meta-analysis: yes or no) and AMSTAR rating of the included systematic reviews.

RESULTS

Included studies

A total of 516 studies were screened for eligibility (Figure 2[15]). After removal of duplicates and screening of titles and abstracts, 448 records were excluded and 53 additional records were removed after assessment of the full texts. Eventually, 15 systematic reviews were included,[21–35] of which a meta-analysis had been conducted in 6.[21–24,30,34] In 1 of these, the meta-analysis was performed for body composition but not for muscle strength and physical performance.[24] AMSTAR scores varied between 3[28,31] and 9[22] (Figure 3[18]).

The included reviews examined the effects of nutritional interventions on muscle mass, muscle strength, and/or physical performance. Effects on sarcopenia as a construct were reported in none of the included reviews. The following interventions were examined: supplementation with protein,[23,26–29] essential amino acids (EAAs),[21,25,29] leucine,[22,25,29,30] and β-hydroxy-β-methylbutyrate (HMB)[24,29]; and protein supplementation plus resistance training,[27,32,34,35] creatine supplementation plus resistance training,[28,31,33] protein supplementation plus (various types of) physical exercise,[28,29,31,33] EAA supplementation plus (various types of) physical exercise,[28,29,33] HMB supplementation plus (various types of) physical exercise,[29,33] and multinutrient supplementation plus (various types of) physical exercise.[31,33] "Various types of physical exercise" indicates that, in those reviews, the exercise program was not specified or consisted of a multimodal exercise program (eg, the combination of progressive resistance training with balance training or a walking program).

The following sections start with an evaluation of the effect of different nutritional interventions on muscle mass, muscle strength, and physical performance, leading to bottom-line statements and recommendations within each intervention category. Importantly, for most of the nutritional interventions, this umbrella review could not distinguish the effect in sarcopenic individuals from the effect in healthy subjects, because most of the reviews did not specify the sarcopenia status of the participants.

Table 2[22–35] presents an overview of the included systematic reviews together with the standardized effectiveness statements and AMSTAR score of the individual reviews. The bottom-line statements about the main effects of each intervention together with the QoE supporting each bottom-line statement are presented in Tables 2 and 3. Table 4 gives an overview of the recommendations for each intervention category.

Protein supplementation

Five systematic reviews provided data on protein supplementation only,[23,26–29] of which 1 included a meta-analysis.[23] Four systematic reviews (1 with a meta-analysis[34]) evaluated the combination of protein supplementation and resistance training[27,32,34,35] and 4 (without meta-analyses) evaluated the combination with various types of physical exercise.[28,29,31,33]

Most systematic reviews with, in general, low to moderate AMSTAR scores indicated either insufficient evidence or were unable to determine whether protein supplementation alone is effective to improve muscle mass, strength, and/or physical performance.[26,28,29] One meta-analysis of moderate quality showed, in a small number of participants, some evidence in favor of no

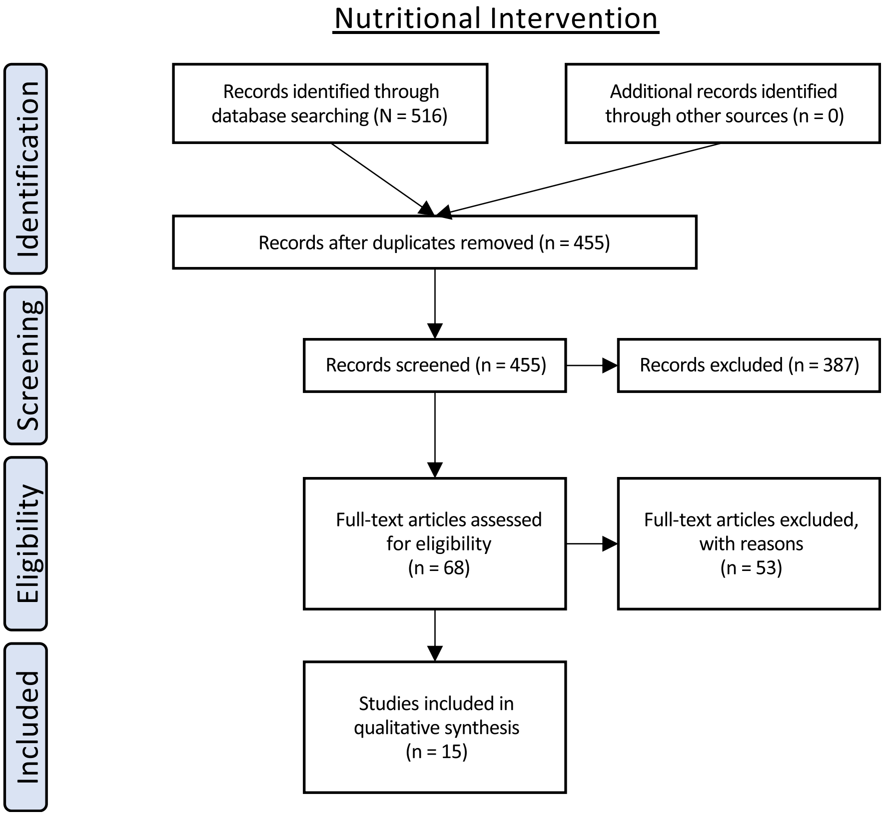

Figure 2 **PRISMA flowchart of study selection process.** *Abbreviation:* PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[15]

difference between protein supplementation and placebo on muscle mass and muscle strength.[23] In contrast, a large systematic review of moderate quality, including 2940 individuals, showed some evidence in favor of protein supplementation on muscle mass.[27] According to this review, a recommended dietary allowance of 0.83 g of good-quality protein per kilogram body weight per day represents the minimum dietary protein need of virtually all healthy elderly persons.[27] Together, the data in this umbrella review suggest a positive effect of protein supplementation on muscle mass, whereas no clear effect has been reported on muscle strength and physical performance. On the basis of the current evidence, proteins may be considered an intervention to increase muscle mass (QoE level, 2).

When combined with resistance training, 2 systematic reviews of moderate to high quality were unable to determine whether this combined intervention is more effective to improve muscle mass than resistance training alone.[27,32] There was some evidence from 2 systematic reviews of moderate quality in favor of no difference between the combined intervention vs resistance training alone on body composition, muscle strength, or physical performance.[34,35] However, 1 of these systematic reviews showed, in a meta-analysis of moderate quality, sufficient evidence in favor of the combined intervention on muscle mass and strength, but only in persons with a body mass index $\geq 30\,\text{kg/m}^2$ and, for muscle mass, also when the duration of the intervention was longer than 24 weeks.[34] Together, the data in this umbrella review show a significant additive effect of protein supplementation on top of resistance training on muscle mass and muscle strength in persons with obesity and, for muscle mass, also in persons with a duration of intervention of $\geq$ 24 weeks, but no clear additive effect on physical performance. In conclusion, to achieve optimal effects on muscle mass and strength in older adults, particularly those who are obese, protein supplementation is recommended in combination with resistance training, with a minimum duration of 24 weeks to increase muscle mass (QoE level, 3).

When combined with a multimodal exercise program, 2 systematic reviews of moderate to low quality found insufficient evidence to determine whether the combination of protein supplementation with physical exercise is more effective than no treatment or than the multimodal exercise program alone to improve muscle mass or muscle strength.[28,29] Most of the reviews showed some evidence in favor of no difference on muscle mass, muscle strength, and/or physical performance.[29,31,33] The quality of these reviews was low to

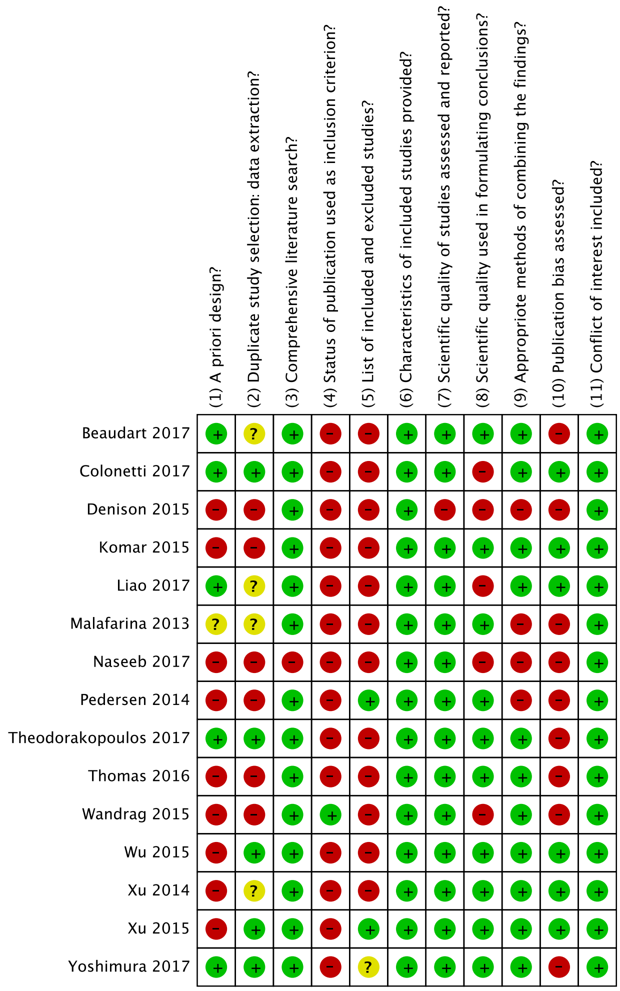

Figure 3 **A Measurement Tool to Assess Systematic Reviews scores.** − indicates "no"; ? indicates "cannot answer/not applicable"; + indicates "yes."

moderate. There was 1 systematic review of low quality that showed some evidence in favor of the combined intervention on muscle mass when compared with an exercise program alone.[28] In the individual trials in these 4 reviews, the exercise intervention varied widely but generally consisted of progressive resistance training with or without additional exercises such as balance training, aerobic exercises, or a walking program,[28,31,33] or was not specified.[29] Together, these data suggest a positive effect of protein supplementation on top of physical exercise on muscle mass, but not on muscle strength or physical performance. In conclusion, proteins on top of physical exercise may be considered to increase muscle mass, but not for improving muscle strength and physical performance (QoE level, 2).

Two systematic reviews examined the adverse effects of proteins alone[28] or combined with resistance training.[32] The intake of 1.0 to 1.4 g of proteins per kilogram body weight per day was not associated with adverse events.[28] In particular, renal function was not affected by a 12-week intervention in which 20 g of whey proteins were consumed directly after resistance training.[36] However, due to the low number of participants in these reviews, the evidence was considered insufficient to determine the adverse effect of protein supplementation.

Essential amino acid supplementation

The reviews included in this section did not specify the content of the EAA supplement. Reviews specifically assessing the effect of leucine, a branched-chain amino acid (AA), are discussed in the next section. Three systematic reviews provided data on supplementation with EAA.[21,25,29] In 1, a meta-analysis was performed.[21] Three systematic reviews (all without meta-analysis) evaluated the combination of EAA supplementation with various types of physical exercise.[28,29,33]

Two systematic reviews of moderate quality showed either insufficient evidence or were unable to determine whether EAA supplementation alone is effective to improve muscle mass, muscle strength, and/or

Table 2 **Results of the individual systematic reviews**

Reference	S	BC	MS	PP	AE	No. of studies (no. of participants)	MA	Results/findings[a]	Standardized effectiveness statement	AMSTAR	Bottom-line statement about the main effects of interventions and recommendation within each intervention category	QoE
Protein supplementation												
Malafarina et al (2013)[29]		v				2 (311)	N	FFM: "Could not find significant differences due to treatment in FFM." FFM: "No change"	Insufficient evidence	5	Data suggest a positive effect of protein supplementation on muscle mass. No clear effect has been reported on muscle strength and physical performance. In conclusion, based on the conflicting evidence, protein supplementation may be considered an intervention to increase muscle mass.	2
Naseeb et al (2017)[28]		v				3 (828)	N	aLM: "Protein intake was a positive predictor of change in aLM over 2.6 y ($P = 0.003$) after adjustment for energy intake. Protein intake was a significant independent positive predictor of change in aLM ($P = 0.007$). In addition, protein intake was negatively associated with the rate of muscle loss and positively associated with muscle mass, but not muscle strength. Consequently, protein reduced the progression of sarcopenia." Muscle mass: "No significant changes in muscle mass" Muscle cross-sectional area: "Protein supplementation (≈20 g twice daily) did not decrease muscle loss (muscle cross sectional area)."	Insufficient evidence	3		
Pedersen et al (2014)[27]		v				3 (2940)	N	3/3 studies in favor of intervention The evidence is assessed as suggestive regarding a positive relation between muscle mass and total protein intake in the range of 13–20 E%. The evidence is assessed as probable for an EAR of 0.66 g good-quality protein/kg BW/day based on nitrogen-balance studies and the subsequent RDA of 0.83 g good-quality protein/kg BW/day representing the minimum dietary protein needs of virtually all healthy elderly persons.	Some evidence in favor of intervention	6		
Theodorakopoulos et al (2017)[26]		v				1 (40)	N	Body composition: "No significant changes were seen in body	Insufficient evidence to determine	8		

(continued)

Table 2 **Continued**

Reference	S	BC	MS	PP	AE	No. of studies (no. of participants)	MA	Results/findings[a]	Standardized effectiveness statement	AMSTAR	Bottom-line statement about the main effects of interventions and recommendation within each intervention category	QoE
								composition, in either experimental or control groups."				
Xu et al (2014)[23]		v				6 (394)	Y	LBM: "Overall difference in mean change in LBM between treatment intervention and placebo was 0.34 kg, which was not significant (95%CI, −0.42 to 1.10 kg, $P = 0.386$)."	Some evidence in favor of no difference	7		
Malafarina et al (2013)[29]			v			2 (311)	N	Handgrip strength: "Improvement in the supplemented group compared with the control group. Handgrip strength: "No change"	Insufficient evidence	5		
Naseeb et al (2017)[28]			v			3 (828)	N	Muscle strength: "No significant association between nutrient intake and muscle strength" Muscle strength: "No significant changes in muscle mass or muscle strength" Muscle strength: "Protein supplementation (≈20 g twice daily) did not decrease muscle loss (muscle strength)"	Insufficient evidence	3		
Theodorakopoulos et al (2017)[26]			v			1 (40)	N	Muscle strength: "The group receiving the extra protein noted a non-significant trend towards an increase in strength (+0.9% relative increase). Although the control group experienced a drop in strength (−3.5%), the difference between the two groups did not achieve statistical significance ($P = 0.06$)."	Insufficient evidence to determine	8		
Xu et al (2014)[23]			v			4 (354)	Y	Leg press: "Overall difference between treatment group and placebo in mean change from baseline to end of study = 2.14 kg (95%CI, −10.92 to 15.20 kg, $P = 0.748$) (3 studies)" Leg extension: "Overall difference between treatment group and placebo in mean change from baseline to end of study = 2.28 kg (95%CI, −1.73 to 6.29 kg, $P = 0.265$) (4 studies)"	Some evidence in favor of no difference	7		
Naseeb et al (2017)[28]				v		1 (65)	N	Physical performance: "Protein supplementation significantly improved physical performance after achieving a daily protein intake from 1.0 to 1.4 g/kg BW/day ($P = 0.02$)."	Insufficient evidence to determine	3		
Malafarina et al (2013)[29]				v		1 (210)	N	Reduction of functional limitations: "There was a tendency to reduce		5		

(continued)

Table 2 **Continued**

Reference	S	BC	MS	PP	AE	No. of studies (no. of participants)	MA	Results/findings[a]	Standardized effectiveness statement	AMSTAR	Bottom-line statement about the main effects of interventions and recommendation within each intervention category	QoE
								functional limitations, although this outcome was not statistically significant."	Insufficient evidence to determine			
Naseeb et al (2017)[28]					v	1 (117)	N	Adverse events: "Consumption of 1.0 to 1.4 g of protein/kg BW/day was not associated with any adverse events."	Insufficient evidence to determine	3		
EAA supplementation												
Malafarina et al (2013)[29]		v				1 (32)	N	FFM: "Dal Negro et al proved a significant increase ($P = 0.05$) of FFM in the group supplemented with EAA but the difference was not significant compared to the control group."	Insufficient evidence to determine	5	No clear effect has been reported of EAA supplementation on muscle mass, muscle strength and physical performance.	4
Yoshimura et al (2017)[21]		v				5 (501)	Y	ASM: WMD = −0.34 kg (95%CI, −0.78 to 0.10, $P = 0.13$) (3 articles) ASMI: WMD = 0.15 kg/m^2 (95%CI, −0.66 to 0.96, $P = 0.72$) (1 article) FFM: WMD = 3.3 kg (95%CI, −0.56 to 7.16, $P = 0.09$) (1 article)	Some evidence in favor of no difference	8	In conclusion, EAA supplementation should not be considered an intervention to increase muscle mass, muscle strength, and physical performance.	
Wandrag et al (2015)[25]		v				2 (26)	N	LBM: "Significantly higher after 3 months of EAA compared to placebo" LBM: "Improvement ($P = 0.038$)"	Insufficient evidence to determine	6		
Yoshimura et al (2017)[21]			v			4 (475)	Y	Grip strength: WMD = −0.36 kg (95%CI, −1.40 to 0.67, $P = 0.49$) (2 articles) Knee extension strength: WMD = 0.11 Nm/kg (95%CI, 0.03–0.20, $P = 0.008$) (1 article) Knee extension strength: WMD = −1.61 Nm (95%CI, −5.43 to 2.20, $P = 0.41$) (2 articles) Knee extension strength: WMD = 2.07 N (95%CI, −18.77 to 22.91, $P = 0.85$) (1 article)	Some evidence in favor of no difference	8		
Wandrag et al (2015)[25]			v			1 (12)	N	Leg strength: "Leg strength improvement ($P < 0.001$)"	Insufficient evidence to determine	6		
Malafarina et al (2013)[29]				v		1 (32)	N	Climbed steps: "In the trials by Dal Negro et al a statistically significant increase of the functional state of the supplemented group, expressed as an increase of steps climbed ($P = 0.01$), was observed."	Insufficient evidence to determine	5		

(continued)

Table 2 **Continued**

Reference	S	BC	MS	PP	AE	No. of studies (no. of participants)	MA	Results/findings[a]	Standardized effectiveness statement	AMSTAR	Bottom-line statement about the main effects of interventions and recommendation within each intervention category	QoE
Yoshimura et al (2017)[21]				v		3 (422)	Y	Usual walking speed: WMD = −0.01 m/s (95%CI −0.06 to 0.04, $P = 0.66$) (3 articles)	Some evidence in favor of no difference	8		
Wandrag et al (2015)[25]				v		2 (53)	N	Physical performance: "The results showed that the EAA mixture significantly improved nutritional status, physical performance, muscle function and levels of depression." Walking speed and functional assessment: "Improvement in walking speed ($P = 0.002$) and functional assessment ($P = .007$)"	Insufficient evidence	6		
Leucine supplementation											A significant effect of leucine supplementation on muscle mass is shown in persons with sarcopenia but not in healthy subjects. No clear effect has been reported on muscle strength and physical performance. In conclusion, leucine supplementation is recommended for sarcopenic older people to increase muscle mass.	3
Komar et al (2015)[30]		v				10 (LBM) (426)	Y	LBM:MD = 0.99 kg (95%CI, 0.43–1.55, $P = 0.0005$) Healthy seniors: MD = −0.05 kg (95%CI, −1.55 to 1.46, $P = 0.95$) Sarcopenic seniors: MD = 1.14 kg (95%CI, 0.55–1.74, $P = 0.0002$) No effect on fat mass or percent body fat	Sufficient evidence in favor of intervention (only sarcopenic seniors)	7		
Xu et al (2015)[22]		v				4 (121)	Y	LBM: Pooled standardized difference in mean changes = 0.18 (95%CI, −0.18 to 0.54, $P = 0.318$ (4 studies) Leg lean mass: Pooled standardized difference in mean changes = 0.006 (95%CI, −0.32 to 0.44, $P = 0.756$ (3 studies)	Some evidence in favor of no difference	9		
Wandrag et al (2015)[25]		v				1 (29)	N	Muscle mass: "No differences after 3 months of supplementation"	Insufficient evidence to determine	9		
Malafarina et al (2013)[29]		v				2 (90)	N	Fat-free mass and fat mass: "In the trials conducted by Leenders et al and Verhoeven et al, the effect of leucine supplementation was assessed, with no change in fat free mass and fat mass (measured with DXA) observed in the supplemented groups over those using a placebo."	Insufficient evidence	5		

(continued)

Table 2 **Continued**

Reference	S	BC	MS	PP	AE	No. of studies (no. of participants)	MA	Results/findings[a]	Standardized effectiveness statement	AMSTAR	Bottom-line statement about the main effects of interventions and recommendation within each intervention category	QoE
Komar et al (2015)[30]			v			5 (hand grip) 6 (knee extension strength) (578)	Y	No effect on handgrip strength or knee extension strength	Some evidence in favor of no difference	7		
Wandrag et al (2015)[25]			v			1 (29)	N	Muscle strength: "No difference after 3 months of supplementation"	Insufficient evidence to determine	9		
Malafarina et al (2013)[29]			v			2 (90)	N	Thigh strength: "Leenders et al found a statistically significant ($P < 0.001$) increase of thigh strength after a 6-month follow-up in both the supplemented and the control group, but the difference between them was not significant. The same outcome was observed by Verhoeven et al."	Insufficient evidence	5		
HMB supplementation												
Malafarina et al (2013)[29]		v				1 (104)	N	FFM: "Baier et al demonstrated a significant increase of FFM in the group supplemented with HMB compared with the control group. 1/1 article in favour of intervention."	Insufficient evidence to determine	5	Data suggest a positive effect of HMB supplementation on muscle mass. No clear effect has been reported on muscle strength and physical performance. In conclusion, based on the conflicting evidence, HMB supplementation may be considered an intervention to increase muscle mass.	4
Wu et al (2015)[24]		v				7 (287)	Y	FM: SMD = −0.08 kg (95%CI, −0.32 to 0.159, $P = 0.511$) Muscle mass: SMD = 0.352 kg (95%CI, 0.11–0.594, $P = 0.004$)	Sufficient evidence in favor of intervention	8		
Malafarina et al (2013)[29]			v			2 (161)	N	Handgrip strength: "Baier et al found a decrease of handgrip strength in both the supplemented and control groups, whereas Flakoll et al observed a statistically significant improvement ($P = 0.04$) of this parameter in the supplemented group."	Insufficient evidence to determine	5		

(continued)

Table 2 **Continued**

Reference	S	BC	MS	PP	AE	No. of studies (no. of participants)	MA	Results/findings[a]	Standardized effectiveness statement	AMSTAR	Bottom-line statement about the main effects of interventions and recommendation within each intervention category	QoE
Wu et al (2015)[24]			v			5 (238)	N	2/5 studies in favor of intervention	Some evidence in favor of no difference	8		
Wu et al (2015)[24]				v		4 (214)	N	2/4 studies in favor of intervention	Insufficient evidence	8		
Protein supplementation + progressive resistance training (PRT)												
Colonetti et al (2017)[32]		v				1 (80)	N	LBM = 0.26 (95%CI, −0.43 to 0.95) (average difference between supplementation + PRT vs control + PRT) Fat mass: −0.12 (95%CI, 0.87–0.64) ($P = 0.41$) (supplementation vs control)	Insufficient evidence to determine	8	A significant additive effect of protein supplementation on top of resistance training on muscle mass and muscle strength is shown in persons with obesity (BMI ≥ 30) and, for muscle mass, also in persons with a duration of intervention of ≥ 24 wk. No clear additive effect has been reported on physical performance.	3
Liao et al (2017)[34]		v				16 (LBM) (802) 8 (aLM) (566) 11 (AFM) (633) 15 (BF%) (752) 6 (muscle volume) (242)	Y	LBM: SMD = 0.58 (95%CI, 0.32–0.84, $P < 0.0001$; $I^2 = 66\%$; $P < 0.0001$) Subgroup duration ≥ 24 wk: SMD = 0.66 (95%CI, 0.35–0.97; $P < 0001$; $I^2 = 41\%$; $P = 0.13$) Subgroup BMI ≥ 30 kg/m^2: SMD = 0.53 (95%CI, 0.19–0.87, $P = 0.002$; $I^2 = 35\%$; $P = 0.19$) aLM: SMD = 0.33 (95%CI, 0.07–0.60, $P = 0.01$; $I^2 = 51\%$, $P = 0.04$) Absolute FM: SMD = −0.61 (95%CI, −0.93 to −0.29, $P = 0.0002$; $I^2 = 72\%$, $P = 0.0001$) BF%: SMD = −1.14 (95%CI −1.67 to −0.60, $P < 0.0001$; $I^2 = 90\%$, $P = 0.00001$) Muscle volume: SMD = 1.23 (95%CI, 0.50–1.96, $P = 0.001$; $I^2 = 83\%$, $P = 0.00001$)	Sufficient evidence in favor of intervention for obese (BMI ≥ 30) or duration of intervention ≥ 24 weeks	7	In conclusion, to achieve optimal effects on muscle mass and muscle strength in older adults, particularly those who are obese, protein supplementation in combination with resistance training is recommended (with a minimum duration of 24 wk to increase muscle mass).	
Pedersen et al (2014)[27]		v				2 (55)	N	Body composition: "The evidence is assessed as *inconclusive* regarding the relation of total protein intake and sources of protein (animal versus vegetable protein) to muscle mass and body composition in combination with resistance training."	Insufficient evidence to determine	6		
Thomas et al (2016)[35]		v				9 (615)	N	LBM/FM/FM%/total MM/FFM/muscle size: "Five measurements from 2 studies (out of 9 studies) indicated significant differences between groups, with greater increases in LBM, leg LTM, appendicular LTM and FM in the supplemented groups compared with the exercise-only controls."	Some evidence in favor of no difference	6		

(continued)

Table 2 **Continued**

Reference	S	BC	MS	PP	AE	No. of studies (no. of participants)	MA	Results/findings[a]	Standardized effectiveness statement	AMSTAR	Bottom-line statement about the main effects of interventions and recommendation within each intervention category	QoE
								Muscle size: "7/8 studies reported significant increases in supplemented (+PRT) and non-supplemented (PRT only) groups, but with no significant differences between the groups."				
Thomas et al (2016)[35]			v			15 (917)	N	Knee extension and hand grip strength: "3/15 reported significant differences between control (PRT only) and supplemented (protein + PRT) groups, with greater improvements in the supplemented groups in measures of knee extension strength and hand grip strength."	Some evidence in favor of no difference	6		
Liao et al (2017)[34]			v			6 (handgrip strength) (357) 13 (leg strength) (668)	Y	Handgrip strength: "No significant difference in the increase in handgrip strength" Leg strength: SMD = 0.69 (95%CI, 0.39–0.98, $P < 0.00001$; $I^2 = 67\%$, $P = 0.0001$) Subgroup men: SMD = 0.87 (95%CI, 0.43–1.31, $P < 0.001$; $I^2 = 51\%$, $P = 0.06$) Subgroup BMI ≥ 30 kg/m^2: SMD = 0.88 (95%CI, 0.42–1.34; $P = 0.0004$; $I^2 = 26\%$, $P = 0.26$)	Sufficient evidence in favor of intervention for leg strength in people with obesity (BMI ≥ 30)	7		
Liao et al (2017)[34]				v		10 (654)	Y	Gait speed, 6-min, or 400-m walk test, chair rise time, stair climbing test, physical activity test, functional reach test, SPPB: "Non-significant treatment effects on gait speed, physical activity, timed up-and go and chair rise time in favour of protein supplementation"	Some evidence in favor of no difference	7		
Colonetti et al (2017)[32]					v	1 (144)	N	Renal function: "Not negatively affected after 20 g of whey protein supplementation"	Insufficient evidence to determine	8		
Creatine supplementation + PRT											Data suggest a positive effect of creatine supplementation on top of progressive resistance training on muscle mass and muscle strength.	2
Beaudart et al (2017)[33]		v				5 (167)	N	Muscle mass: 4/5 studies in favor of an additional effect of creatine supplementation on top of exercises	Some evidence in favor of intervention	7		
Denison et al (2015)[31]		v				2 (69)	N	FFM: 2/2 studies showed greater gains among supplemented participants		3		

(continued)

Table 2 **Continued**

Reference	S	BC	MS	PP	AE	No. of studies (no. of participants)	MA	Results/findings[a]	Standardized effectiveness statement	AMSTAR	Bottom-line statement about the main effects of interventions and recommendation within each intervention category	QoE
								who received exercise training, compared with the placebo groups that only received exercise training.	Some evidence in favor of intervention		No clear effect has been reported on physical performance. Creatine supplementation on top of progressive resistance training may be considered an intervention to increase muscle mass and muscle strength.	
Naseeb et al (2017)[28]		v				2 (78)	N	Muscle mass and FFM: "Creatine supplementation with resistance training increased muscle mass ($\Delta\% = +2.8\%$) and FFM ($\Delta\% = +3.2\%$). The increase was greater than in the exercise only group ($P < 0.05$)." aLM: "Creatine supplementation with resistance training improved aLM. The increase was greater than in the exercise only group."	Some evidence in favor of intervention	3		
Beaudart et al (2017)[33]			v			5 (167)	N	Muscle strength: 4/5 studies in favor of an additional effect of creatine for some strength outcomes	Some evidence in favor of intervention	7		
Denison et al (2015)[31]			v			2 (69)	N	Muscle strength: 2/2 studies showed greater improvements in participants supplemented with creatine, compared with the placebo groups. All groups also received exercise training.	Some evidence in favor of intervention	3		
Naseeb et al (2017)[28]			v			1 (18)	N	1 RM strength: "Creatine supplementation with resistance training increased 1RM strength ($\Delta = +5.1\%$). The	Insufficient evidence to determine	3		

(continued)

Table 2 **Continued**

Reference	S	BC	MS	PP	AE	No. of studies (no. of participants)	MA	Results/findings[a]	Standardized effectiveness statement	AMSTAR	Bottom-line statement about the main effects of interventions and recommendation within each intervention category	QoE
								increase was greater than in the exercise only group ($P < 0.05$)."				
Beaudart et al (2017)[33]				v		4 (147)	N	Physical performance: 1/4 studies in favor of an interactive effect of creatine	Some evidence in favor of no difference	7		
Denison et al (2015)[31]				v		2 (69)	N	Physical performance: 0/2 studies showed evidence of additional benefits arising from supplementation on top of exercise training.	Some evidence in favor of no difference	3		
Nutritional supplementation + physical exercise program												
Protein (or: protein or EAA) supplementation + physical exercise program												
Beaudart et al (2017)[33]		v				12 (1049)	N	Muscle mass: 3/12 studies showed additional effect of protein supplementation on top of exercises	Some evidence in favor of no difference	7	Data suggest a positive effect of protein supplementation on top of physical exercise on muscle mass but not on muscle strength and physical performance. In conclusion, protein supplementation on top of physical exercise may be considered to increase muscle mass, but not for muscle strength and physical performance.	2
Denison et al (2015)[31]		v				7 (646)	N	Muscle size: 5/7 studies showed no interaction between exercise training and protein/EAA supplementation on muscle mass, cross-sectional area, or lean body mass. Lean mass: 1/7 studies showed evidence of increase in lean mass after HMB supplementation (HMB + PRT vs placebo +PRT, $P = 0.08$). Lean body mass: 1/7 studies showed interactive effects when following a resistance exercise training program and consuming protein-supplemented drinks.	Some evidence in favor of no difference	3		
Malafarina et al (2013)[29]		v				1 (149)	N	FFM: "No changes following physical exercise and supplementation, compared with the group with no treatment (no exercise and no supplementation)"	Insufficient evidence to determine	5		
Naseeb et al (2017)[28]		v				2 (162)	N	Lean body mass: "Lean body mass increased in protein supplemented group compared with the placebo group ($P = 0.006$). Both groups performed PRT."	Some evidence in favor of intervention	3		

(continued)

Table 2 **Continued**

Reference	S	BC	MS	PP	AE	No. of studies (no. of participants)	MA	Results/findings[a]	Standardized effectiveness statement	AMSTAR	Bottom-line statement about the main effects of interventions and recommendation within each intervention category	QoE
								Lean tissue mass and fat mass: "Protein intake of 1.3 g/kg BW/day enhanced PRT effects on lean tissue mass ($P < 0.05$) and decreased fat mass ($P < 0.05$) and percent of body fat ($P < 0.01$)."				
Beaudart et al (2017)[33]			v			12 (909)	N	Muscle strength: 3/12 studies showed additional effect of protein on top of exercises	Some evidence in favor of no difference	7		
Denison et al (2015)[31]			v			7 (646)	N	Muscle strength: 6/7 studies: No interaction between protein/EAA supplementation and exercise training 1/7 study: Additional gains from EAA supplementation combined with a multicomponent exercise training program in sarcopenic community-dwelling women older than 75 y	Some evidence in favor of no difference	3		
Naseeb et al (2017)[28]			v			1 (100)	N	Muscle strength: "Protein intake of 1.3 g/kg BW/day enhanced PRT effects on muscle strength ($P < 0.05$)."	Insufficient evidence to determine	3		
Beaudart et al (2017)[33]				v		9 (793)	N	Physical performance: "No additional effect of protein on top of exercises"	Some evidence in favor of no difference	7		
Denison et al (2015)[31]				v		4 (569)	N	Physical performance: 0/4 studies showed additional improvement of the combination of exercise training and protein/EAA supplementation	Some evidence in favor of no difference	3		
Malafarina et al (2013)[29]				v		2 (326)	N	Berg Balance Scale: "Improvement in measurements with the Berg Balance Scale for exercise with and without supplementation, but not specified whether this improvement was significant."	Some evidence in favor of no difference	5		

(continued)

Table 2 **Continued**

Reference	S	BC	MS	PP	AE	No. of studies (no. of participants)	MA	Results/findings[a]	Standardized effectiveness statement	AMSTAR	Bottom-line statement about the main effects of interventions and recommendation within each intervention category	QoE
								Walking speed: "Walking ability decreased in a significant way in the control group (no exercise and no supplementation) compared with the supplemented group. Walking capacity remained constant in trained subjects whereas it declined significantly in non-trained groups, regardless of supplementation."				
EAA supplementation + physical exercise program											No clear additive effect of EAA supplementation on top of physical exercise has been reported on muscle mass, muscle strength and physical performance. In conclusion, EAA supplementation on top of physical exercise should not be considered an intervention to increase muscle mass, muscle strength, and physical performance.	2
Beaudart et al (2017)[33]		v				3 (196)	N	Muscle mass: "No additional effect of EAA on top of exercises"	Some evidence in favor of no difference	7		
Malafarina et al (2013)[29]		v				2 (183)	N	Leg muscle mass: "Significant increase in the group treated with physical exercise and supplementation compared with the group without treatment (only health education) ($P = 0.007$)" FFM: "Significant increase ($P = 0.05$) in the group supplemented with EAA, but not significantly different compared to the control group. Both groups followed an exercise program."	Some evidence in favor of intervention	5		
Naseeb et al (2017)[28]		v				1 (155)	N	Muscle mass: "Exercise with EAA supplementation improved muscle mass in women with sarcopenia > 75y. Exercise only did also improve muscle mass, but EAA only did not."	Insufficient evidence to determine	3		
Beaudart et a. (2017)[33]			v			3 (196)	N	Muscle strength: "No additional effect of EAA on top of exercises"	Some evidence in favor of no difference	7		
Naseeb et al (2017)[28]			v			1 (155)	N	Muscle strength: "Exercise with EAA supplementation improved muscle strength in women with sarcopenia > 75y. EAA only and exercise only did not improve muscle strength."	Insufficient evidence to determine	3		
Beaudart et al (2017)[33]				v		2 (179)	N	Walking speed and SPPB: "No additional effect of EAA on top of exercises"	Some evidence in favor of no difference	7		

(continued)

Table 2 **Continued**

Reference	S	BC	MS	PP	AE	No. of studies (no. of participants)	MA	Results/findings[a]	Standardized effectiveness statement	AMSTAR	Bottom-line statement about the main effects of interventions and recommendation within each intervention category	QoE
Malafarina et al (2013)[29]				v		1 (155)	N	Walking speed: "Significant increase in the groups treated with physical exercise (with or without EAA), compared with the group with no treatment ($P = 0.007$)"	Insufficient evidence to determine	5		
Naseeb et al (2017)[28]				v		1 (155)	N	Walking speed: "Exercise with EAA supplementation improved walking speed in women with sarcopenia > 75y. EAA only and exercise only did also improve walking speed"	Insufficient evidence to determine	3		
HMB supplementation + physical exercise program												
Beaudart et al (2017)[33]		v				3 (103)	N	Muscle mass: 1/3 articles in favor of HMB supplementation on top of exercises	Some evidence in favor of no difference	7	No clear additive effect of HMB on top of physical exercise has been reported on muscle mass, muscle strength, and physical performance. In conclusion, HMB supplementation on top of physical exercise should not be considered an intervention to increase muscle mass, strength and physical performance.	2
Beaudart et al (2017)[33]			v			3 (103)	N	Muscle strength: "No additional effect of HMB supplementation on top of exercises"	Some evidence in favor of no difference	7		
Malafarina et al (2013)[29]			v			1 (31)	N	Leg curl strength: "Vukovich et al showed a significant improvement of leg curl in the HMB supplemented group compared to the control group. Both groups followed an exercise program."	Insufficient evidence to determine	5		
Beaudart et al (2017)[33]				v		2 (72)	N	Timed up-and-go test: "No additional effect of HMB supplementation on top of exercises"	Some evidence in favor of no difference	7		
Multinutrient supplementation + physical exercise program												
Beaudart et al (2017)[33]		v				4 (300)	N	Muscle mass: 0/4 studies showed an additional effect of multinutrient supplementation on top of exercises	Insufficient evidence	7	No clear additive effect of multinutrient supplementation on top of physical exercise has been reported on muscle mass, muscle strength, and physical performance. In conclusion, multinutrient supplementation on top of physical exercise should not be considered an intervention to increase muscle mass, muscle strength, and physical performance.	2
Denison et al (2015)[31]		v				5 (?)	N	Muscle size: 0/6 studies showed evidence of interactive effects of multinutrient supplementation with exercise training	Insufficient evidence	3		
Beaudart et al (2017)[33]			v			5 (379)	N	Muscle strength: 1/5 studies showed an additional effect of multinutrient supplementation on top of exercises	Insufficient evidence	7		
Denison et al (2015)[31]			v			6 (659)	N	Muscle strength: 0/6 studies showed evidence of interactive effects of multinutrient supplementation with exercise training	Insufficient evidence	3		
Beaudart (et al). 2017[33]				v		4 (304)	N	Physical performance: 0/4 studies showed an additional effect of multinutrient intervention on top of exercises	Insufficient evidence	7		

(continued)

Table 2 **Continued**

Reference	S	BC	MS	PP	AE	No. of studies (no. of participants)	MA	Results/findings[a]	Standardized effectiveness statement	AMSTAR	Bottom-line statement about the main effects of interventions and recommendation within each intervention category	QoE
Denison et al (2015)[31]				v		6 (659)	N	Physical performance: 0/6 studies showed evidence of interactive effects of multinutrient supplementation with exercise training	Insufficient evidence	3		

[a]Outcomes are underlined.

Abbreviations: ?, the number of studies was not mentioned in the systematic review/meta-analysis; AE, adverse event; aLM, appendicular lean mass; ASM, appendicular skeletal muscle mass; ASMI, appendicular muscle mass index; BC, body composition; BMI, body mass index (calculated as kg/m^2); BW, body weight; CI, confidence interval; DXA, dual-energy X-ray absorptiometry; E%, energy percent; EAA, essential amino acid; EAR, estimated average requirement; FFM, fat-free mass; FM, fat mass; HMB, β-hydroxy-β-methylbutyrate; LBM, lean body mass; MA, meta-analysis; MD, mean difference; MM, muscle mass; MMI, muscle mass index; MS, muscle strength; PP, physical performance; PRT, progressive resistance training; QoE, quality of evidence; RDA, recommended dietary allowance; RM, repetition maximum; S, sarcopenia; SMD, standardized mean difference; SPPB, short physical performance battery; SR, systematic review; v, indicates the construct that is addressed: sarcopenia (as a construct) or the sarcopenia subdimensions (muscle mass, muscle strength, physical performance) or adverse events; WMD, weighted mean difference.

physical performance.[25,29] There was some evidence from 1 meta-analysis of high quality in favor of no difference between EAA supplementation and placebo.[21] Together, no clear effect has been reported of EAA supplementation only on muscle mass, muscle strength, and physical performance. In conclusion, EAA supplementation should not be considered to increase muscle mass, strength, and physical performance (QoE level, 4).

Regarding the effects of EAA supplementation with physical exercise, 2 systematic reviews of low to moderate quality showed insufficient evidence to determine the effect of the combined intervention on muscle mass, muscle strength, or physical performance compared with the effect of the exercise intervention alone, EAA supplementation alone, or no intervention.[28,29] One systematic review of moderate quality showed some evidence in favor of no difference between EAA supplementation and EAA supplementation on top of exercise, either on muscle mass, muscle strength, or physical performance.[33] In contrast, another systematic review of moderate quality showed some evidence in favor of the combined intervention when compared with no treatment or with exercise alone.[29] In the individual trials in these reviews assessing the combined effect of EAA supplementation and physical exercise, the exercise program was not specified[29] or consisted of progressive resistance training combined with or without balance, gait, or other exercises.[28,33] Together, no clear additive effect of EAA supplementation on top of physical exercise has been reported on muscle mass, muscle strength, and physical performance. In conclusion, EAA supplementation on top of physical exercise should not be considered an intervention to increase muscle mass, muscle strength, and physical performance (QoE level, 2).

Leucine supplementation

Four systematic reviews examined the effect of leucine supplementation only.[22,25,29,30] Of these, a meta-analysis was performed in 2.[22,30] In 1 of these reviews, a subgroup analysis was performed to differentiate between healthy and sarcopenic persons.[30]

One systematic review of high quality was unable to determine whether leucine supplementation alone is effective to improve muscle mass or strength.[25] One systematic review of moderate quality showed insufficient evidence that leucine supplementation is more effective to improve muscle mass and muscle strength compared with the nonsupplemented group,[29] whereas 2 systematic reviews of moderate to high quality showed some evidence in favor of no difference between leucine and placebo.[22,30] However, there was sufficient evidence

Table 3 **Bottom-line statements with quality of evidence about the main effects of interventions within each intervention category**

Intervention	Bottom-line statement about the main effects of interventions within each intervention category	QoE[a]
Nutritional supplementation only		
Protein supplementation	Data suggest a positive effect of protein supplementation on muscle mass. No clear effect has been reported on muscle strength and physical performance.	2
EAA supplementation	No clear effect has been reported of EAA supplementation on muscle mass, muscle strength, and physical performance.	4
Leucine supplementation	A significant effect of leucine supplementation on muscle mass is shown in persons with sarcopenia but not in healthy subjects. No clear effect has been reported on muscle strength and physical performance.	3
HMB supplementation	Data suggest a positive effect of HMB supplementation on muscle mass. No clear effect has been reported on muscle strength and physical performance.	4
Nutritional supplementation + progressive resistance training		
Protein supplementation + progressive resistance training	A significant additive effect of protein supplementation on top of resistance training on muscle mass and muscle strength is shown in persons with obesity (BMI $\geq$ 30) and, for muscle mass, also in persons with a duration of intervention of $\geq$ 24 wk. No clear additive effect has been reported on physical performance.	3
Creatine supplementation + progressive resistance training	Data suggest a positive effect of creatine supplementation on top of progressive resistance training on muscle mass and muscle strength. No clear effect has been reported on physical performance.	2
Nutritional supplementation + (various types of) physical exercise		
Protein supplementation + physical exercise	Data suggest a positive effect of protein supplementation on top of physical exercise on muscle mass, but not on muscle strength and physical performance.	2
EAA supplementation + physical exercise	No clear additive effect of EAA supplementation on top of physical exercise has been reported on muscle mass, muscle strength, and physical performance.	2
HMB supplementation + physical exercise	No clear additive effect of HMB supplementation on top of physical exercise has been reported on muscle mass, muscle strength, and physical performance.	2
Multinutrient supplementation + physical exercise	No clear additive effect of multinutrient supplementation on top of physical exercise has been reported on muscle mass, muscle strength, and physical performance.	2

[a]QoE supporting each bottom-line statement is based on the Grading of Recommendations Assessment, Development and Evaluation approach for primary evidence: 1, very low; 2, low; 3, moderate; 4, high.

Abbreviations: BMI, body mass index (calculated as kg/m^2); BW, body weight; EAA, essential amino acid; HMB, β-hydroxy-β-methylbutyrate; QoE, quality of evidence.

Table 4 **Recommendations with quality of evidence for each intervention category**

Protein supplementation

- **Protein supplementation alone** may be considered as an intervention to increase muscle mass (low QoE).
- **Protein supplementation in combination with progressive resistance training** (with a minimum duration of 24 wk to increase muscle mass) is recommended to achieve optimal effects on muscle mass and muscle strength in older adults, particularly those who are obese (moderate QoE).
- **Protein supplementation on top of physical exercise** may be considered to increase muscle mass, but not muscle strength and physical performance (low QoE).

EAA supplementation

- **EAA supplementation alone** should not be considered an intervention to increase muscle mass, muscle strength, and physical performance (high QoE).
- **EAA supplementation on top of physical exercise** should not be considered an intervention to increase muscle mass, muscle strength, and physical performance (low QoE).

Leucine supplementation is recommended for sarcopenic older people to increase muscle mass (moderate QoE).

HMB supplementation

- **HMB supplementation** alone may be considered an intervention to increase muscle mass (high QoE).
- **HMB supplementation on top of physical exercise** should not be considered an intervention to increase muscle mass, strength and physical performance (low QoE).

Creatine supplementation on top of progressive resistance training may be considered an intervention to increase muscle mass and muscle strength (low QoE).

Multinutrient supplementation on top of physical exercise should not be considered an intervention to increase muscle mass, muscle strength, and physical performance (low QoE).

Abbreviations: EAA, essential amino acid; HMB, β-hydroxy-β-methylbutyrate; QoE, quality of evidence.

from 1 meta-analysis in favor of leucine supplementation on muscle mass, but only in sarcopenic older persons.[30] Together, a significant effect of leucine on muscle mass is shown in persons with sarcopenia but not in healthy subjects. No clear effect has been reported on muscle strength and physical performance.

In conclusion, leucine supplementation alone is recommended for sarcopenic older people to increase muscle mass (QoE level, 3).

β-Hydroxy-*β*-methylbutyrate supplementation

Four systematic reviews examined the effect of HMB supplementation on muscle mass, muscle strength, and/or physical performance. In 2 of these, HMB supplementation was the only intervention,[24,29] whereas HMB was combined with various types of physical exercise in the other 2.[29,33] There was 1 meta-analysis about the effect on body composition.[24]

Two reviews of moderate to high quality showed either insufficient evidence or were unable to determine whether HMB alone is effective to improve muscle mass, muscle strength, and/or physical performance.[24,29] One systematic review of high quality showed some evidence in favor of no difference between HMB and placebo on muscle strength.[24] However, the same systematic review showed, with a meta-analysis, sufficient evidence in favor of HMB supplementation on muscle mass.[24] Together, these data suggest a positive effect of HMB on muscle mass but no clear effect on strength and physical performance. In conclusion, HMB supplementation may be considered an intervention to increase muscle mass (QoE level, 4).

When combined with physical exercise, 1 systematic review of moderate quality showed insufficient evidence to determine the additive effect of this combined intervention compared with exercise alone on muscle strength.[29] Another systematic review of moderate quality showed some evidence in favor of no difference between the combined intervention and the exercise intervention alone on muscle mass, muscle strength, and physical performance.[33] Looking at the individual trials in these systematic reviews, the exercise intervention consisted of progressive resistance training with or without other exercises[33] or was not specified.[29]Together, no clear additive effect of HMB on top of physical exercise has been reported on muscle mass, strength, and physical performance. In conclusion, HMB supplementation on top of physical exercise should not be considered an intervention to increase muscle mass, muscle strength, and physical performance (QoE level, 2).

Creatine supplementation

None of the included systematic reviews examined the effect of creatine supplemenation alone. Therefore, no recommendation can be made about the effect of creatine supplementation alone on muscle mass, muscle strength, and/or physical performance. Three systematic reviews (all without meta-analysis) examined the combined effect of creatine supplementation and progressive resistance training.[28,31,33]

One of these 3 systematic reviews, which was of low quality, showed insufficient evidence to determine the additional effect of creatine supplementation on top of progressive resistance training compared with exercise alone on muscle strength, but there was some evidence in favor of the combined intervention on muscle mass.[28] Two other systematic reviews of low to moderate quality found some evidence in favor of no difference between creatine supplementation combined with progressive resistance training and exercise alone on physical perfomance, whereas on muscle mass and muscle strength, there was some evidence in favor of the combined intervention.[31,33] Together, these data suggest a positive effect of creatine supplementation on top of progressive resistance training on muscle mass and muscle strength, but no clear effect has been reported on physical performance. In conclusion, creatine supplementation on top of progressive resistance training may be considered an intervention to increase muscle mass and muscle strength (QoE level, 2).

Multinutrient supplementation

Although no reviews examined the effect of multinutrient supplementation alone or in combination with resistance training, 2 reviews examined the effect of multinutrient supplementation on muscle mass, muscle strength, and/or physical performance in combination with various types of physical exercise.[31,33]

These systematic reviews, both of moderate to low quality, showed insufficient evidence that multinutrient supplementation combined with physical exercise is more effective to improve muscle mass, muscle strength, and physical performance compared with the exercise intervention alone.[31,33] In these reviews, the multinutrient supplementation consisted of a variety of macronutrients (proteins, carbohydrates, fats) and micronutrients (vitamins, minerals).[31,33] In the individual trials in these systematic reviews, the exercise intervention consisted of progressive resistance training with or without other exercises,[31,33] whereas in 1 trial in the meta-analysis of Beaudart et al, the intervention was a walking program alone.[33] Together, no clear additive effect of multinutrients on top of physical exercise has been reported on muscle mass, muscle strength, and physical performance. In conclusion, multinutrient supplementation on top of physical exercise should not be considered an intervention to increase muscle mass, strength, and physical performance (QoE level, 2).

DISCUSSION

The aim of this umbrella review was to provide a systematic overview of the effect of nutritional interventions targeting sarcopenia or 1 of the 3 sarcopenia components: muscle mass, muscle strength, or physical performance.

As of this writing, best evidence is available to recommend leucine supplementation, because it has a significant effect on muscle mass in persons with sarcopenia. Protein supplementation on top of resistance training is recommended to increase muscle mass and muscle strength, particularly in obese persons and when the intervention lasts at least 24 weeks. Protein supplementation alone, proteins with physical exercise, and HMB supplementation alone may be considered to increase muscle mass, whereas creatine supplementation with progressive resistance training may be considered to increase both muscle mass and strength. Supplementation with EAA and multinutrient supplementation in addition to physical exercise should not be considered, because no sufficient evidence was found for an additional effect of the supplement on muscle mass, strength, or physical performance.

Protein supplementation

Dietary proteins deliver the AAs needed for the synthesis of muscle proteins and form an anabolic stimulus that promotes muscle protein synthesis (MPS).[37] The current recommended dietary allowance for healthy adults is 0.8 g/kg body weight,[38] a recommendation based on nitrogen-balance studies. With respect to the elderly, a systematic review of 23 papers, included in this umbrella review, found probable evidence to recommend 0.83 g good-quality protein/kg body weight per day as the minimum dietary protein need of generally healthy, elderly people aged ≥ 65 years.[27] However, several limitations related to nitrogen-balance studies are likely to result in an underestimation of the true protein need, especially in the elderly, in whom short-term nitrogen-balance studies may be unable to detect the slow rate of muscle protein turnover.[39] Furthermore, neutral nitrogen-balances studies may not detect the reduced ability of elderly to use the available proteins, resulting from subtle changes in protein redistribution due to higher splanchnic extraction and the so-called anabolic resistance in the elderly.[39] Indeed, current evidence suggests that, although the postabsorptive MPS is preserved in elderly persons, the MPS rate in response to protein feeding is blunted, with a postprandial MPS rate that is 16% lower in persons aged ≥ 75 years.[40]

Therefore, several expert groups currently recommend for the elderly a protein intake that is higher than the recommended dietary allowance for adults and that ranges from 1.0 to 1.2 g/kg body weight for healthy elderly persons (> 65 years), to > 1.2 to 1.5 g/kg body weight for elderly persons with an acute or chronic disease, and up to 2.0 g/kg body weight for elderly persons with severe illness, injury, or marked malnutrition.[39,41,42] To maximize the effect of protein supplementation, not only the daily amount of protein intake should be taken into account but also protein quality and timing of ingestion. There is increasing evidence that "fast" proteins (eg, whey, a milk-derived protein) may stimulate MPS more than "slow" proteins (eg, casein, the other milk-derived protein) and that an evenly distributed protein intake during the day, with an intake of ≥ 25 to 30 g of protein per meal, is required to optimize MPS.[43–45] However, despite the well-established effect of proteins on MPS, individual RCTs found inconsistent evidence regarding the effect of long-term (≥ 12 weeks) protein supplementation on muscle mass, muscle strength, and physical performance. Negative findings may be explained, at least partly, by a suboptimal amount of protein intake, protein quality, and distribution over the day. More research is needed to define the optimal protein intake and pattern for the elderly.[46,47]

Likewise, systematic reviews and a meta-analysis included in this umbrella review found mixed evidence regarding the effect of protein supplementation, with standardized effectiveness statements varying between insufficient evidence, insufficient evidence to determine, some evidence in favor of no difference, and some evidence in favor of protein supplementation compared with placebo. Together, these data suggested a positive effect of protein supplementation on muscle mass. However, for muscle strength and physical performance, the evidence was, in general, insufficient or insufficient to determine the difference with placebo. It should be noted that insufficient evidence might reflect a lack of statistical power of the studies in the systematic review to detect an effect of the intervention, thus indicating more likely "no evidence of effect" than "evidence of no effect." This might have been the case for the systematic reviews of Malafarina et al[29] and Naseeb et al,[28] in which the number of studies and the number of the participants included in the studies were rather small. Notwithstanding, based on the current evidence, it was concluded that protein supplementation may be considered an intervention to increase muscle mass, but not for muscle strength and physical performance.

To also obtain an effect on muscle strength, the combination of protein supplementation and resistance training is recommended. In recent years, there has been growing interest in the combination of protein intake and physical exercise, especially progressive resistance training. Resistance training stimulates MPS, although the response is blunted due to aging. When combining both anabolic interventions, physical activity may restore the sensitivity of older muscles to protein or AA intake, thereby increasing the use of the ingested proteins for de novo MPS.[48,49] In turn, the ingestion of sufficient proteins in temporal proximity to exercise produces an anabolic stimulus that increases the MPS in response to exercise in young and old individuals.[50,51]Inconsistent results of the combination of protein intake and exercise intervention in individual RCTs may be explained, at least partly, by an already adequate baseline protein intake by participants in the RCTs as well as by differences in protein source, timing of ingestion, and type and intensity of the exercise program.[31]

In this umbrella review, the large meta-analysis of Liao et al[34] found sufficient evidence in favor of the combination of protein supplementation and resistance training on muscle mass and muscle strength, compared with resistance training alone. Therefore, protein supplementation in combination with resistance training is recommended to achieve optimal effects on muscle mass and muscle strength. Because the heterogeneity of the RCTs in the meta-analysis of Liao et al[34] was only acceptable ($< 50\%$) in the subgroups 'duration of intervention $\geq$ 24 weeks' (for muscle mass) and 'BMI $\geq 30\,kg/m^2$' (for muscle mass and muscle strength), it should be noted that the intervention should last at least 24 weeks to also increase muscle mass and that the available evidence in particular applies to obese elderly. Only 1 systematic review examined, with a meta-analysis, the effect on physical performance and the authors found no significant effects of the combined intervention compared with resistance training alone.[34] Therefore, the recommendation is limited to muscle mass and strength and states that, to achieve optimal effects on muscle mass and muscle strength in older adults, particularly those who are obese, protein supplementation in combination with resistance training (with a minimum duration of 24 weeks to increase muscle mass) is recommended.

Finally, this umbrella review examined the effect of the combination of protein supplementation with various types of physical exercise in systematic reviews that did not explicitly specify the modalities of the exercise program (ie, type, intensity, duration). Looking at the individual trials, the exercise programs varied widely but generally consisted of progressive resistance training with or without additional exercises such as balance training, aerobic exercises, or a walking program. This umbrella review indicated a positive effect of protein supplementation combined with physical exercise on muscle mass. However, for muscle strength and physical performance, most evidence was in favor of no difference between the combined intervention and the control group (mostly exercise only). This might be explained by the fact that most of the systematic reviews in the umbrella review included a limited number of RCTs with small numbers of participants. Therefore, these RCTs might have been underpowered to detect a difference between the groups with respect to muscle strength and physical performance. Together, it was concluded that protein supplementation on top of physical exercise may be considered to increase muscle mass, but not muscle strength and physical performance.

In this respect, questions may arise regarding the optimal timing of protein intake relative to physical exercise therapy, because this might contribute to maximize the exercise-induced MPS. Research has shown that the highest level of MPS is observed approximately 60 minutes after the end of exercise training, suggesting that providing proteins during this period may induce the greatest anabolic response.[50,52] However, the aforementioned exercise-induced increased sensitivity of muscle to protein feeding may persist for up to 24 hours after an exercise bout.[53] Thus, to take advantage of this sensitizing effect of exercise, proteins should be consumed within 24 hours of exercise.[39,50]

Essential amino acid supplementation

Essential (indispensable) AAs are AAs that cannot be synthesized in the human body, in contrast to the nonessential (dispensable) and the conditionally indispensable AAs. These EAAs should, by consequence, be supplied from dietary sources. Nine of the 20 AAs from which human proteins are built are EAAs. Ingestion of EAAs effectively stimulates MPS in the elderly.[54] Even more, when comparing MPS after the ingestion of an isocaloric intact whey protein supplement and the same amount of an EEA supplement, the increase in MPS rate after whey protein was 50% less than that in the EAA group. To obtain an equivalent anabolic effect, a higher dose of whey protein would be needed, resulting in a higher caloric intake and an energetically equivalent reduction in spontaneous food consumption, which should be avoided, especially in the elderly. Thus, supplementation with EAAs is more energetically efficient than with intact proteins.[55]

Yet, systematic reviews and a meta-analysis included in this umbrella-review did not reveal sufficient evidence in favor of EAA supplementation, with standardized effectiveness statements indicating insufficient evidence, insufficient evidence to determine, and some evidence in favor of no difference. Although the latter might be explained by insufficient power, as may have been the case in the meta-analysis of Yoshimura et al,[21] no clear effect has been reported of EAA supplementation on muscle mass, muscle strength, and physical performance. Therefore, it was concluded that EAA supplementation should not be considered an intervention to increase muscle mass, muscle strength, and physical performance.

Leucine supplementation

These negative findings of individual RCTs and meta-analyses about the effect of EAAs on sarcopenia components may be explained by the content of the EAA mixture, with a lack of so-called branched-chain AAs (BCAAs). Three of the 9 EAAs (leucine, isoleucine, and valine) are BCAAs. These BCAAs, especially leucine, have a particular role in MPS.[56] They serve not only as a substrate for MPS but also have specific positive effects on the intracellular signaling pathways involved in MPS.[57,58] Furthermore, enriching the diet with these specific EAAs may overcome the rate-limiting effect of the BCAAs in MPS.[39]

Therefore, research has been done to evaluate the effects of BCAA mixtures and leucine alone. In a systematic evaluation of the evidence, this umbrella review showed that the standardized effectiveness statements for the effect of leucine on muscle mass were insufficient evidence,[29] insufficient evidence to determine the difference between leucine supplementation and placebo,[25] some evidence in favor of no difference,[22] and sufficient evidence in favor of leucine supplementation.[30] The latter was reported for the meta-analysis of Komar et al,[30] leading us to recommend leucine to increase muscle mass. However, because a subanalysis of this meta-analysis showed that leucine was only effective in the subgroup of sarcopenic elderly persons but not in healthy elderly persons, this recommendation only applies for persons with sarcopenia. It should be noted, however, that the meta-analysis of Komar et al[30] did not specify how sarcopenia was defined in the individual RCTs.

For leucine and muscle strength, the standardized effectiveness statements were insufficient evidence,[29] insufficient evidence to determine the difference between leucine supplementation and placebo,[25] and some evidence in favor of no difference.[30] No RCTs, to our knowledge, have assessed the effect on physical performance. So, in contrast to muscle mass in sarcopenic elderly persons, a clear effect of leucine supplementation on muscle strength and physical performance could not be demonstrated.

Thus, BCAAs such as leucine might be promising pharmaconutrients in the prevention and treatment of sarcopenia[39,59] or, at least, as suggested by this umbrella review, to improve muscle mass in sarcopenic individuals. Recently, however, the unique capacity of BCAAs and leucine to enhance MPS has been questioned, and some individual, long-term supplementation studies with leucine did not show a positive effect on muscle mass.[56,57,59,60] A potential explanation, apart from a too-short supplementation period, is that although BCAA have the capacity to stimulate MPS, a full complement of EAAs may be needed to maximize MPS.[56] This is true, in particular, in combination with exercise training, when the difference in MPS after resistance training between BCAAs and whey protein containing the same amount of BCAAs may even be as high as 50%.[61] This umbrella review did not include systematic reviews that examined the combined effect of leucine and resistance training, so this combined effect could not be evaluated. The explanation is that BCAA mixtures may provide too-limited a substrate for MPS due to limited availability of the other EAAs needed for MPS.[56,60] Thus, although BCAA supplementation stimulates MPS, this response may not be maximal, because BCAAs do not increase the supply of all EAAs that may become rate limiting for accelerated MPS.[56,60] As with the BCAA mixtures, leucine supplementation alone does not provide the other EAAs, thereby limiting the maximal stimulation of MPS. Moreover, plasma elevation of leucine leads to oxidation of the other BCAAs, valine and isoleucine, which then become rate limiting for MPS. These elements may explain why some individual trials and systematic reviews included in this umbrella review did not show positive effects of leucine supplementation. However, the umbrella review provided sufficient evidence to recommend leucine supplementation for sarcopenic older people to increase muscle mass, but not for muscle strength or physical performance.

β-Hydroxy-*β*-methylbutyrate supplementation

HMB is a metabolite of leucine that has multiple actions. It stimulates MPS through upregulation of the mTOR pathway and attenuates protein degradation through attenuation of the ubiquitin-proteasome pathway. Furthermore, it may stimulate MPS through changes in the activity of the GH/IGF-1 axis and affects satellite cells in skeletal muscle, resulting in increased proliferation and differentiation of myoblasts.[62]

HMB has been widely used by athletes to enhance muscle mass, muscle strength, muscle power, aerobic performance, and recovery.[62] Studies in the elderly, however, remain limited, which is illustrated by this umbrella review that only included 3 systematic reviews including discussion of HMB.[24,29,33] One of these, a meta-analysis, found “sufficient evidence in favor of HMB supplementation” on muscle mass.[24] However, for muscle strength and physical performance, the evidence was insufficient, insufficient to determine the difference with placebo, or in favor of no difference,[24,29] thus indicating no clear effect on muscle strength and physical performance. Again, due to the limited number of studies and participants included in the studies, both insufficient evidence and insufficient evidence to determine ratings might reflect underpowering and rather indicate no evidence of effect than evidence of no effect. Notwithstanding, on the basis of the current evidence, it was concluded that HMB supplementation may be considered an intervention to increase muscle mass, but not for muscle strength or physical performance. With regard to the optimal dosage of HMB, evidence is not conclusive but most studies advise a daily dose of 3 g.

Creatine supplementation

Creatine is endogenously synthesized by the liver, kidney, and pancreas from the AAs arginine, glycine, and methionine, or consumed in the diet from red meat, fish, and dairy products. The majority of creatine is stored in the skeletal muscle, where it combines with phosphate to form phosphorylcreatine. The latter is involved in the rapid re-synthesis of adenosine triphosphate during muscle contraction, thereby improving high-intensity exercise capacity and leading to greater training adaptations.[63–65]Although creatine monohydrate is the most popular supplement used by athletes, it is increasingly being studied in combination with resistance training to determine the effect on muscle mass and muscle strength in the elderly.[63]

Also, this umbrella review investigated the effect of creatine supplementation in combination with progressive resistance training.[28,31,33] For muscle mass and strength, 3 systematic reviews showed some evidence in favor of the intervention; thus, the creatine supplementation had an additive positive effect on top of the exercise program.[28,31,33] No clear effect has been reported on physical performance.[31,33] Thus, it was concluded that creatine supplementation on top of progressive resistance training may be considered an intervention to increase muscle mass and muscle strength, but not physcial performance. Recently, the International Society of Sports Nutrition concluded along the same line that creatine has a number of therapeutic benefits in elderly people who are healthy and those with disease, suggesting that creatine supplementation can help prevent sarcopenia in the elderly.[65]

Strengths and limitations

The most important strength of an umbrella review is the power to efficiently extract clinical relevant information on which general consensus exists (ie, an umbrella review considers for inclusion the highest level of evidence). The literature search was also systematic, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, and so gives a higher level of evidence than a narrative review. Because an umbrella review depends on the quality of the included systematic reviews and meta-analyses, this quality was assessed by using the AMSTAR criteria. Five of the 13 included systematic reviews were of high quality.

A limitation, inherent to the strict search terms used in this umbrella review, is the low total number of eligible reviews (n = 15), together examining 10 types of interventions (nutrition interventions with or without resistance training or various types of physical exercise). In combination with the often low (n = 2 of 13) to moderate (n = 6 of 13) quality of the included systematic reviews, this results in low to moderate ratings of evidence supporting most bottom-line statements, especially when considering combinations of nutritional intervention and physical exercise. Another limitation, inherent to an umbrella review, is that the quality of the individual RTCs was not evaluated nor were the clinical trials analyzed to the level of the raw data. As such, it was not possible to distinguish studies using optimal supplementation from those using suboptimal supplementation. The methodological quality of the included reviews is, however, an item that is assessed by the AMSTAR method used to rate the quality of the evidence supporting each bottom-line statement. Next, this umbrella review was part of the Sarcopenia Guideline project of the Belgian Society of Gerontology and Geriatrics, which was initiated in 2015 and for which the literature search was completed in 2017. Therefore, databases have been searched until November 2017 and no more recent reviews have been included. Finally, physical exercise interventions alone, which have generally accepted effects against sarcopenia, and pharmacological interventions have been documented recently by other working groups of the Sarcopenia Guideline project and were not in the scope of this review.[13,14]

CONCLUSION

The aim of this review was to provide an evidence-based overview of nutritional interventions for sarcopenia targeting 1 or more of the 3 sarcopenia domains: muscle mass, muscle strength, or physical performance.

On the basis of the results of this umbrella review, it is concluded that, as of this writing, best evidence is available to recommend leucine supplementation, because it has a significant effect on muscle mass in persons with sarcopenia. Protein supplementation on top of resistance training is recommended to increase muscle mass and muscle strength. This supplementation is particularly advised for persons with obesity, and the intervention should be performed at least for 24 weeks to achieve an optimal effect on muscle mass. Protein supplementation alone and HMB supplementation alone may be considered to increase muscle mass, whereas creatine supplementation combined with resistance training may be considered to increase both muscle mass and muscle strength. Except for the recommendation about leucine supplementation, this umbrella review could not distinguish the effect of nutritional interventions in sarcopenic individuals from the effect in healthy older persons, because all but 1[30] of the included reviews did not specify sarcopenia status of the participants. The most important reason for this probably is the lack of universally accepted criteria for the diagnosis of sarcopenia. Therefore, most of the conclusions in this umbrella review focus on the elderly in a broader sense, thus encompassing both the prevention and treatment of sarcopenia. Effects on sarcopenia as a construct were not retrieved.

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Ethical approval. This article does not contain any studies with human participants or animals performed by any of the authors.

Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website:

Appendix S1 **Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist**

Appendix S2 **Full search strategy**

Appendix S3 **A Measurement Tool to Assess Systematic Reviews checklist**

Appendix S4 **Standardized effectiveness statements**

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