SARCOPENIA GUIDELINE -

BVGG-SBGG

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Belgian Society for GERONTOLOGY and GERIATRICS

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1. Introduction

At some point in life, both the loss of muscle mass and strength may cross a 'clinical' boundary, leading to physical disability [1, 2]. Sarcopenia is an important contributing factor to the crossing of this 'clinical' boundary since it is the age-related change in muscle strength, muscle quality and muscle quantity [3]. The consequences of sarcopenia in older people are serious and life-changing: it has an impact on health care costs, disability, morbidity and mortality [3]. A recent update of the European Working Group on Sarcopenia in Older People highlighted the high burdens on personal, social and economic level [3]. They state that in terms of human health, sarcopenia increases risk of falls and fractures [4, 5]; impairs ability to perform activities of daily living [6]; is associated with cardiac disease [7]; respiratory disease[8] and cognitive impairment [9]; leads to mobility disorders [10]; and contributes to lowered quality of life [11], loss of independence or need for long-term care placement [12-14], and death [15].

Not only the person itself could be burdened with the consequences of sarcopenia but also the healthcare system is affected. The prevalence of sarcopenia is highly variable, with a prevalence of 1–29% in community-dwelling populations, 14–33% in long-term care populations and around 10% in the acute hospital-care population [16]. The presence of sarcopenia increases risk for hospitalization and increases cost of care during hospitalization [17, 18]. Among older adults who are hospitalized, those with sarcopenia on admission were more than five-fold more likely to have higher hospital costs than those without sarcopenia [19]. Results of a large, community-based study in the Czech Republic showed that direct healthcare costs were more than two-fold higher for older people with sarcopenia than for those without [20]. These findings underline the importance of preventing sarcopenia to reduce its consequences or treat it appropriate to diminish negative outcomes.

Sarcopenia has been overlooked and undertreated in mainstream general practice [21] , apparently due to the complexity of determining what variables to measure, how to measure them, what cut-off points best guide diagnosis and treatment, and how to best evaluate effects of therapeutic interventions [22]. Recently sarcopenia was acknowledged in the International Classification of Diseases (ICD-10) and received its individual code (M62.84). This is an important progress in the recognition of sarcopenia [23].

2. Epidemiology

Sarcopenia has been suggested in 1988 by Rosenberg to describe an age-related decline in muscle mass [1]. Such atrophy of the skeletal muscle starts around the age of 30 [2] (mostly without symptoms), increases with age and may aggravate in clinical situations (disease, malnutrition, immobilization,..). Primary sarcopenia is defined as 'age-related' without other causes, while secondary sarcopenia may present earlier in life when one or more causes (e.g. sedentary lifestyle, acute inflammatory disease and inadequate dietary intake) are evident [3]. An important consequence of muscle atrophy is the loss of muscle strength. Interestingly, the age-related loss of muscle strength cannot be explained by muscle atrophy alone and thus other factors contribute to sarcopenia [4]. To describe the age-related loss of muscle strength independently from sarcopenia, Manini et al. suggested the term "*dynapenia*" [5, 6]." The European Working Group on Sarcopenia in Older People (EWGSOP) takes into consideration the presence of low muscle strength as the primary parameter of sarcopenia; muscle strength is presently the most reliable clinical measure of muscle function. Specifically, sarcopenia is probable when low muscle strength is detected. A sarcopenia diagnosis is confirmed by the presence of low muscle quantity or quality. When low muscle strength and low muscle quantity/quality are accompanied by low physical performance, sarcopenia is considered severe [3].

Prevalence numbers of sarcopenia range from 1% up to 33 % [16]. Reason for this large variance are the different cut-off points proposed in the consensus statements as well as the various methods proposed to assess muscle mass, muscle strength and physical performance [30]. The new EWGSOP2 definition of sarcopenia (2018) appears to decrease its prevalence as a result of changes in the algorithm and in the thresholds compared to the EWGSOP1 definition (2010) [31]. There is a need for future research to develop a standardized model and standardized cut-off points to allow comparison between studies.

3. Scope of the guideline

3.1. Aim of the guideline

> This work aims to translate the actual scientific body of knowledge regarding sarcopenia into a practice guideline. Therefore, international consensus definitions (including related cut-off scores) will be operationalized for practical use. Hence, this guideline aims to assist healthcare providers in the assessment and interventions (pharmacological, exercise and nutritional) of loss of muscle mass, muscle strength and physical performance. The guideline and accompanying tools are designed for all healthcare providers who work with the target audience as stated below for both the prevention and treatment of sarcopenia.

The recommendations will focus on three levels: recommendations for health care and prevention specialists, summary of evidence and 'information for the public' (Layman's terms). To fit the Belgian context, the summarizing recommendations will be written in English, French and Dutch.

3.2. Blueprint of the project

The topic of this project and the selection of the involved researchers was done by the BSGG Governing Board who kept track of the project progress. A scope statement was generated by the Guideline Development Group (GDG) to outline the extent of the project. This group also selected the working group members and provided feedback. The seven working groups refined and approved the review questions, systematically selected relevant evidence, assessed the quality of this evidence, summarized and interpreted the results and suggested guideline recommendations. Two scientific staff members prepared the work plan, organized meetings, developed search strategies, provided support for the GDG and the Working Groups and prepared the first draft of the guideline.
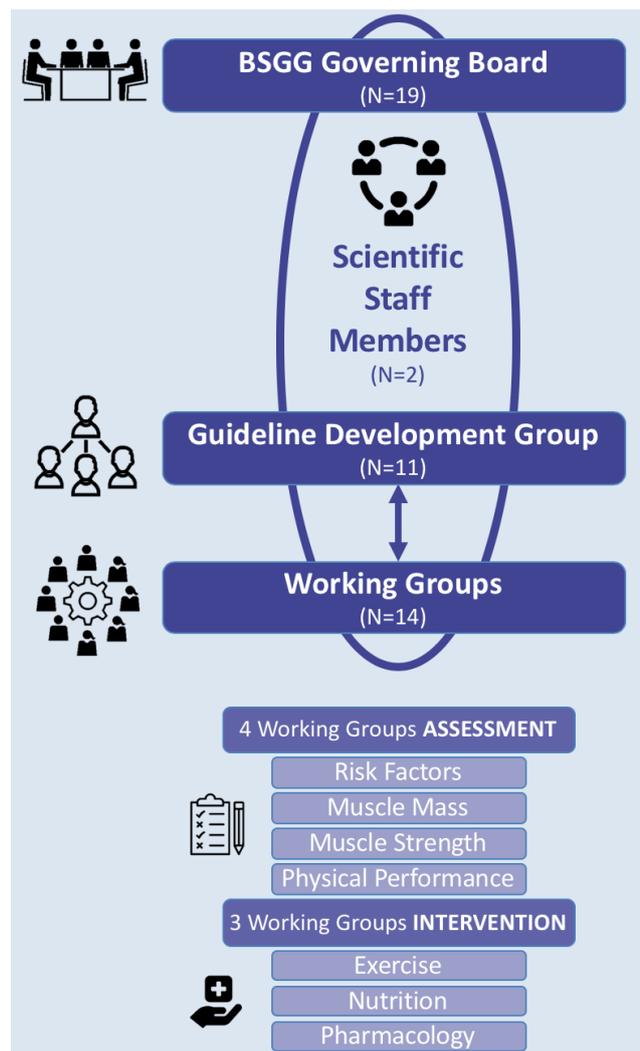
3.3. Target audience

> The target audience of this recommendation are all healthcare providers who work with older people such as general practitioners, physicians, geriatricians, physiotherapists, nurses, occupational therapists, dieticians, social workers, psychologists (from here of labeled as clinicians).

Geriatricians for example can use the guideline to assess an older person who is presumably sarcopenic. Physiotherapists for example could use the guideline to choose a rehabilitation tool to improve muscle strength. Not only clinicians can use these recommendations, but scientific researchers specialized in ageing are target users as well. The guidelines can help at making clinical decisions regarding sarcopenia as well as implementing evidence-based management strategies to prevent or treat sarcopenia.

3.4. Clinical questions

Assessment
- Is there evidence for risk factors to develop sarcopenia?
- How and with which instruments can clinicians assess muscle mass, muscle strength and physical performance of the target population?
- What are the possible clinical actions based on the assessment parameters?

Interventions
- What are the best suitable interventions, that have already been studied in systematic reviews or meta-analyses, to implement in a prevention and or treatment program to reduce or reverse the possible impact of sarcopenia?
  - What are the possible **nutritional interventions** targeting sarcopenia or at least one of the three sarcopenia criteria (muscle mass, muscle strength or physical performance)?
  - What are the possible **exercise interventions** targeting sarcopenia or at least one of the three sarcopenia criteria (muscle mass, muscle strength or physical performance)?
  - What are the possible **pharmacological interventions** targeting sarcopenia or at least one of the three sarcopenia criteria (muscle mass, muscle strength or physical performance)?

3.5. Target population

The target population in this guideline are older men and women who are prone or subject to sarcopenia or severe sarcopenia. Since several consensus papers exist, we divide the target population in two distinct categories.

The first category consists of older people who are either not sarcopenic or pre-sarcopenic. According to the latest EWGSOP statement low muscle strength is the primary parameter for identifying sarcopenia [3]. Non sarcopenic older people are above the cut-off value for this parameter. Previously, these persons were classified as pre-sarcopenic by the EWGSOP when only low muscle mass was present. The IWGS utilizes a binary classification with low gait speed and low muscle mass as parameters [24, 25]. People above their proposed cut-off values are categorized as non-sarcopenic. All persons in this first (non-sarcopenic) category are targeted from a preventive perspective.

The second category consists of older people with sarcopenia. In their latest consensus paper, EWGSOP defines sarcopenia as 'probable' when low muscle strength is present [3]. The diagnosis is confirmed when low muscle quantity or quality is present as well. Severe sarcopenia is present when low muscle strength and low muscle quantity or quality are accompanied by low physical performance. Formerly, the EWGSOP classified persons as either sarcopenic (low muscle mass *and* low muscle strength *or* low physical performance) or severe sarcopenic (low muscle mass *and* low muscle strength *and* low physical performance)[26].

As to the definition of older people, we aimed to include studies/reviews, assessing men and women preferentially older than the age of 65. Older people with specific pathology (e.g. cancer) were not included.

3.6. Settings

All relevant settings that are involved in the promotion of active and healthy ageing and care for older people were taken into account when developing this guideline.
- First line
- Rehabilitation
- Hospitals (general – and specialized)
- Residential care centers

Key issues that were covered are: risk factors, screening and assessment, pharmacological and non-pharmacological treatment. Key issues that were not covered are: the influence of genetic or other non-modifiable factors and metabolic muscle function (non-insulin mediated glucose uptake). Outcomes were all related to sarcopenia and its subdomains. Developers took into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions.

3.7. General methods

Search strategy and selection criteria
The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for this guideline. Pubmed and/or Web of Science were systematically searched for each topic.

Study selection
Systematic reviews and meta-analysis in English reporting on the specific subject were considered eligible for inclusion in the umbrella reviews of this guideline. Original studies, editorials, letters to the editor and narrative reviews were excluded. Animal studies and studies in patients with ongoing diseases were also excluded. Authors blinded for each other's results, screened the titles and abstracts for duplicate studies and for eligibility using the Rayyan web application for systematic reviews. 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 one author and verified by a second author, using a data extraction form based on a template provided by the Cochrane Collaboration. The authors extracted data regarding the key characteristics of the reviews, including participants, treatment/assessment and outcomes. No assumptions were made on missing or unclear data.

The authors assessed the methodological quality of the systematic reviews using either AMSTAR or COSMIN. AMSTAR is A MeaSurement Tool to Assess systematic Reviews (AMSTAR). 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). COSMIN is a modified version of the Interpretability and Generalizability checklists of the 'Consensus-based Standards for the selection of health Measurement Instruments'.

To organize the evidence, the authors systematically synthesized the extracted data of each review. This resulted in 'standardized effectiveness statements' (sufficient evidence, some evidence, insufficient evidence, insufficient evidence to determine) about the treatment effect of the intervention(s) in the individual systematic reviews. In addition, the authors 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. 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). This method takes into account study design (meta-analysis yes/no) and AMSTAR rating of the included systematic reviews.

4. Perspective and patient preferences

Patient perspectives have been extracted from both qualitative (face to face interviews and focus groups) as well as quantitative (survey) studies focusing on the impact of sarcopenia on the quality of life.

4.1. Motivators and barriers for physical activity

4.1.1. PhD Veerle Baert

During the creation of these guidelines, one of the members of the working group (Veerle Baert) completed her Phd in Gerontological Sciences on the topic of 'Motivators and barriers for physical activity at higher age'. These insights were used when drafting this guideline. Key recommendations are that when promoting physical activity for elderly, special attention has to be paid to the health benefits of physical activity, to the subject's fears, individual preferences and social support, and to constraints related to the physical environment.

4.1.2. SPRINT (Senioren Project INtensief Trainen)

Five participants of the SPRINT project (Senioren Project Intensief. Trainen - VUB) were consulted regarding physical activity interventions. Topics of interest were motivators and barriers to start and to persevere in engaging in physical activity. The questionnaire was in Dutch, so the answers are copied exactly as noted. At the end a summary is given in English.

1) Hoe bent u zich bewust geworden van het belang van spierkracht op hogere leeftijd?

   - *Ik beweeg veel thuis (tuinwerk et.) doch het zijn steeds dezelfde spieren die werken, andere spieren komen minder of nooit aan bod. Je leest ook vaak dat spiertraining nodig is. Het project van Prof. Bautmans trok me over de streep.*
   - *Lectuur.*
   - *Door erover te lezen.*
   - *Door het effectief verlies aan kracht te voelen bij klussen en tuinieren.*
   - *Dankzij info over deze studie.*

2) Wat heeft u overhaald om aan spierkrachttraining te beginnen?

   - *Ik ondervond zelf dat ik "te weinig" spieren had en er toh iets moest aan doen maar om alleen zomaar de stap te zetten naar een fitness centrum is veel moed nodig dus resulteert in uitstelgedrag.*
   - *Ikzelf.*
   - *Aankondiging Brussel Deze Week*
   - *Nog alle fysieke activiteiten die ik voorheen kan nog lang te kunnen blijven uitoefenen.*
   - *Zo lang mogelijk proberen gezond en zelfstandig te blijven.*

3) Wat vindt u prettig aan krachttraining?

- *De begeleiding is zeer goed, gemotvieerde fijne mensen. Goede uitleg en motivatie wordt er gegeven. Trainingsomgeving valt best mee, ruim en netjes.*
- *Regelmaat.*
- *Het feit iets lichamelijks te doen.*
- *De winst aan kracht / algemeen goed voelen / beter voelen bij stappen, fietsen, tennis*
- *De vaststelling dat het (voorlopig) positief evolueert.*

4) Wat vindt u minder prettig aan krachttraining?

- *Aan de echte krachttraining eigenlijk niks alleen de moed van jezelf om vol te houden.*
- *Er naar toe komen.*
- *Niets, of toch; angst voor kwetsuur.*
- *De oefeningen met de armen (sommige)*

5) Wat zou helpen om de oefeningen vol te houden?

- *Tot hiertoe niet aan de orde*
- *Variatie.*
- *Er een regelmatig iets van te maken.*
- *Niks speciaal, het samen oefenen met anderen.*
- *Het samen doen met anderen.*

6) Wat zou u verhinderen om de oefeningen verder te zetten?

- *Plots geen zin meer hebben om thuis te vertrekken naar de training.*
- *Blessure.*
- *Blessure*
- *De afstand tot hier.*
- *Het alleen verder moeten doen.*

Summary
When distilling the answers given by the target population it becomes clear that the initial awareness of the importance of muscle strength is initiated by reading on the subject or by experiencing the loss in muscle strength in daily activities. A common barrier to start training is effectively taking the step towards a training facility or engaging in a program. When experiencing success, both during training as well as improvement in daily activities, people are motivated to continue. Variation, regularity and the social interaction of training in group are motivators to continue. An injury and the distance to the training facility are possible barriers in maintaining regular training activity. All these motivators and barriers have to be kept in mind when choosing the appropriate training modality.

4.2. Quality of life- SARQOL

This section discusses in more detail the methodology used to argue the outcome measures of the guideline (muscle strength, mass and function) from the patient's point of view. In particular, the qualitative study in which patients were asked about their quality of life in the context of sarcopenia, is explained. This study was 'on-going' at the time of guideline development but given that the main Principle Investigators (PI) of this study (Olivier Bruyère, Ivan Bautmans and Charlotte Beaudart) were also involved in guideline development, we were able to gain preliminary insight into sarcopenia-related quality of life. These preliminary insights were later confirmed, upon completion of the study, and also published [11, 27-29]. The outcome measures that we have identified in our guideline are therefore supported not only from the international consensus definition of the European Working Group of Sarcopenia in Older People (EWGSOP) but also from the point of view of the quality of life of the patient.

5. Consulting experts / validation

5.1. General

To obtain feedback on the draft guideline among external experts' various actions were undertaken. At several national and international events. these guidelines were presented. The attending audience of these congresses were both clinicians and researchers with a special interest in ageing and sarcopenia. In addition, two scientific papers (pharmacology, exercise) have been published in peer-reviewed journals and a third one (nutrition) accepted for publication.

5.2. Consultation of external experts

In order to obtain relevant information regarding the implementation of the guideline we consulted various experts such as a general practitioner, occupational therapist, international expert on sarcopenia, nurse with expertise on frailty and a psychologist. Below you can find their answers and a brief summary.

Jessie De Cock - Occupational Therapist

1. What is your profession and domain of expertise (clinical and scientific)?
   Occupational therapist (Bach.) – Gerontologist (Ms.)
   Domain of expertise: Comprehensive Geriatric Assessment – functional decline in elderly – cognitive decline in elderly – lifestyle interventions in incontinence – onco-geriatrics.

2. Describe your specific setting in a few words (clinical and scientific).
   Clinical: geriatric day-ward/consultation service at UZ Brussel. It is an ambulatory service for diagnostics and one-day interventions in geriatric patients. The main areas of expertise are comprehensive geriatric consultation, diagnostics of cognitive decline and cognitive rehabilitation, assessment of falls in elderly with ambulatory rehabilitation possibilities if requested, osteoporosis treatment, incontinence, weight loss in elderly.
   Scientific: participation in commercial and academic studies, with interest in onco-geriatrics.

3. Is the rationale and the methodology to develop the guideline, clear for you?
   It is very clearly explained.

4. Are the recommendations clear and understandable?
   Yes

5. Are the recommendations implementable in your setting?
   Yes

6. What are the pro- & cons?
   - *Pro: clear guidelines on assessment and recommendations will help to improve screening for this pathology in a clinical setting.*
   - *Cons: implementation in clinical setting could be made easier by providing assessment-forms or checklists.*

7. Do you have other comments on the guideline?
   No

Sofie Vermeiren - Lecturer and Researcher in Nursing and Frailty

1. What is your profession & domain of expertise (clinical and/or scientific)?
   Lecturer and Researcher in Nursing and Ageing

2. Describe your specific setting in a few words (clinical and/or scientific).
   University College in Antwerp, research performed is rather practical

3. Is the rationale and the methodology to develop the guideline, clear for you?
   Yes

4. Are the recommendations clear and understandable?
   Yes

5. Are the recommendations implementable in your setting?
   Yes, these recommendations could be very useful in our education program, as well as in practical research

6. What are pro- & cons?
   - *Pro: one-pagers are very clear, they stand out. Text in the document is well written, highlights make it pleasant to read.*
   - *Con: /*

7. Do you have other comments on the guideline?
   I did find some spelling mistakes and the lay out in the document is not always consistent.

Ellen Gorus - Clinical Psychologist and Gerontologist

1. What is your profession & domain of expertise (clinical and/or scientific)?
   Clinical Psychologist (MSc) and Gerontologist (PhD)
   clinical expertise: assessment of cognitive and emotional disorders in older persons
   scientific expertise: cognitive frailty, Active Ageing in frail older persons

2. Describe your specific setting in a few words (clinical and/or scientific).
   Clinical setting: ambulatory geriatric dayhospital, multidisciplinary team
   research setting: associate professor at Gerontology department

3. Is the rationale and the methodology to develop the guideline, clear for you?
   Rationale and methodology are clear.

4. Are the recommendations clear and understandable?
   Recommendations on the one pagers are easy to understand. One remark, to me it is not clear from the one pager on muscle strength why one should use the normative values for healthy young people (maybe it is just a question of formulation => the normative values are the same as for healthy young people).

5. Are the recommendations implementable in your setting?
   These recommendations are easy to implement in my clinical setting, there already is a lot of attention for sarcopenia in our multidisciplinary team, but this overview provides the latest state of the art. So, our mode of assessment and clinical recommended interventions can easily be checked against these guidelines. Since I work in a multidisciplinary team as a

clinical psychologist, sarcopenia is not my first interest in geriatric patients. Other professions (physical therapist, geriatrician, dietician,…) from the team are focusing on this issue. But these guidelines certainly raise awareness of the importance of sarcopenia for all other team members.

6. What are pro- & cons?
   /
7. Do you have other comments on the guideline?
   A*re the guidelines applicable to all older people or are there exceptions (certain pathologies eg dementia, …) => not clear from the one pagers*

Dirk Devroey - Family physician and head of department of family practice

1. What is your profession & domain of expertise (clinical and/or scientific)?
   clinical and scientific / Family practitioner and academic

2. Describe your specific setting in a few words (clinical and/or scientific).
   family physician in a private group practice
   head of the department of family practice and chronic care

3. Is the rationale and the methodology to develop the guideline, clear for you?
   Yes

4. Are the recommendations clear and understandable?
   Yes

5. Are the recommendations implementable in your setting?
   Yes

6. What are pro- & cons?
   The evidence on the use of testosterone is rather weak despite the recommendation to use it in all men with low testosterone levels and muscle weakness.

7. Do you have other comments on the guideline?
   - *Pag 0: Intervention: The use of testosterone seems to be supported by very little evidence.*
   - *Considering the pharmacological treatment in general the authors declare that "No distinct pharmacological recommendations for healthy, presarcopenic and sarcopenic older people can be made because specific characterization of the sarcopenia status was lacking from most studies."*
   - *Considering testosterone, the recommendation is mainly based on a review from 2006 (Androgen treatment and muscle strength in elderly men: A meta-analysis. Journal of the American Geriatrics Society. 2006;54(11):1666-73.)*
   - *Thereupon, the authors write in their own review about testosterone: "The less pronounced effects on muscle strength and physical performance can be explained by insufficient treatment duration, low test sensitivity and absence of androgen deficiency at baseline." This suggests a low quality of the cited studies.*
   - *Physical exercise: the references do not mention the year of publication*
   - *The layout of the main documents needs standardization.*

Jürgen Bauer - Geriatrician, medical director and head of research group in Germany

1. What is your profession & domain of expertise (clinical and/or scientific)?
   I am a geriatrician and the medical director of a hospital that is specialized in acute geriatric care and geriatric rehabilitation. The main areas of my expertise are nutrition in older persons, sarcopenia, frailty, electronic monitoring of mobility and physical activity in older persons.

2. Describe your specific setting in a few words (clinical and/or scientific).
   I have to fulfill management duties for the aforementioned hospital, but I am seeing patients every day that I am not traveling. Besides my clinical work I am head of research unit with around 15 members. Our work focuses mostly on physical training, rehabilitation, nutrition, polypharmacy and electronic monitoring.

3. Is the rationale and the methodology to develop the guideline, clear for you?
   I fully agree with the rationale and the methodology which has been clearly presented

4. Are the recommendations clear and understandable?
   The recommendations are very clear for all those that care for the diagnosis and the treatment of sarcopenia. However, for non-experts it may not completely obvious how sarcopenia should be diagnosed, at least not based on the one-pagers. I recommend to make this clearer, maybe to use a flow chart for this purpose.

5. Are the recommendations implementable in your setting?
   DEXA measurements are not available in most clinics in Germany and BIA clearly has its disadvantages in clinical populations. Therefore, we base our diagnosis in clinical routine on strength testing only (handgrip/chair rise).

6. What are the pro- & cons?
   See under 4. Beyond this criticism I am fine with everything else. This is great work that will be relevant to a vast readership.

7. Do you have other comments on the guideline?
   No other recommendations.

Summary

All experts agree on the distinctness of the rationale and the methodology to develop the guideline. Overall it seems that the recommendations are clear for those that have some knowledge of sarcopenia. For people not familiar with sarcopenia the one pagers can be useful but could be improved by adding a flowchart. This remark has been addressed in chapter 10 were we added a flowchart.

The remark of Dirk Devroey regarding the evidence of testosterone was linked back to the experts on the pharmacology guideline (Prof. Mirko Petrovic, Anton De Spiegeleer). Their answer was the following: *"The remark of Prof. Devroey elaborates on the correct interpretation of the recommendation that testosterone can be considered based on the available evidence only in older men with clinical muscle weakness and low serum testosterone levels and provided the preconditions described in the review by De Spiegeleer A. et al. Acta Clin Belgica 2016; 71 (4): 197–205".*

6. Definitions

Sarcopenia: Sarcopenia is a progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality. In 2018, the EWGSOP2 guideline advises low muscle strength as the primary parameter of sarcopenia; muscle strength is presently the most reliable measure of muscle function. Specifically, sarcopenia is probable when low muscle strength is detected. A sarcopenia diagnosis is confirmed by the presence of low muscle quantity or quality. When low muscle strength, low muscle quantity/quality, and low physical performance are all detected, sarcopenia is considered severe [3].

Dynapenia: age related loss of solely muscle strength [32].

Frailty: a multidimensional geriatric syndrome of which the pathogenesis encompasses both physical and social aspects and is characterized by the cumulative decrease in different physiological processes and functions [33]. Sarcopenia is a disorder that is part of this geriatric syndrome.

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ASSESSMENT
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RISK FACTORS
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BVGG-SBGG

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1. Introduction

The assessment of possible risk factors has to be interpreted in the context of the prevention and treatment of sarcopenia. These factors need to be taken into account when sarcopenia is suspected or present and should be subject of investigation and drive for clinical action.

2. Methods

2.1. Search strategy and selection criteria

The PRISMA guidelines were followed in the conduction and reporting of this review [1]. Pubmed was searched systematically from the earliest date available until 08/11/2017. Mesh terms and keywords used focused on risk factors (exposure) and sarcopenia (outcome) (full search strategies see APPENDIX 1).

2.2. Study selection

Systematic reviews and meta-analysis reporting on possible risk factors of sarcopenia in older adults were considered eligible for inclusion. Articles were excluded if studies reported on patients with specific diseases, narrative reviews and studies written in other language than English were excluded (eligibility criteria see APPENDIX 2).

Two reviewers (E.G, M.DSH.), blinded for each other's results, screened the titles and abstracts for eligibility by using the Rayyan web application for systematic reviews [2]. Subsequently, full-text articles of eligible studies were screened. Duplicate selection was done by all researchers. Disagreements were resolved by consensus-based discussion.

2.3. Data extraction and methodological quality assessment

Data extraction was completed by one reviewer using a data extraction form based on a template provided by the Cochrane Collaboration [3]. In case of doubt, a second reviewer was consulted. Data regarding the key characteristics of the reviews were extracted, including population, exposure, outcomes assessed. No assumptions were made on missing or unclear data.

To organize the evidence, one investigator systematically synthesized each review's extracted data, resulting in statements for all reviews. A standardized effectiveness statement, as proposed by Ryan et al was matched to each individual statement [4]. Based on these summaries a 'bottom line statement' about the main effect of the exposures (i.e. risk factors) was developed (see APPENDIX 4). Disagreements were resolved by consensus-based discussion.

Methodological quality of the studies was performed by one reviewer, and verified by a second reviewer, by using the AMSTAR 'Assessment of Methodologic Quality of Systematic Reviews' (see APPENDIX 3) [5, 6]. This 11-item tool assesses the degree to which review methods avoided bias. Methodological quality was rated as high (score 8-11), moderate (score 4-7) or low (score 0-3). Quality assessment of included studies within reviews was not reassessed.

Finally, a rating of the quality of the evidence (1 very low - 2 low - 3 moderate - 4 high) supporting each bottom line statement was assigned by using a method that is based on the GRADE's approach for primary evidence [7]. The methods take into account the 'study design' (meta-analysis yes/no) and the ratings of the quality of evidence of the included systematic reviews (AMSTAR) (see Figure 1).

Initial quality of Body of evidence	AMSTAR
1. high (4) if meta-analysis 2. moderate (3) if no meta-analysis	1. -1 if review of moderate quality (AMSTAR score of 4-7) 2. -2 if review of low quality (AMSTAR score of 0-3)
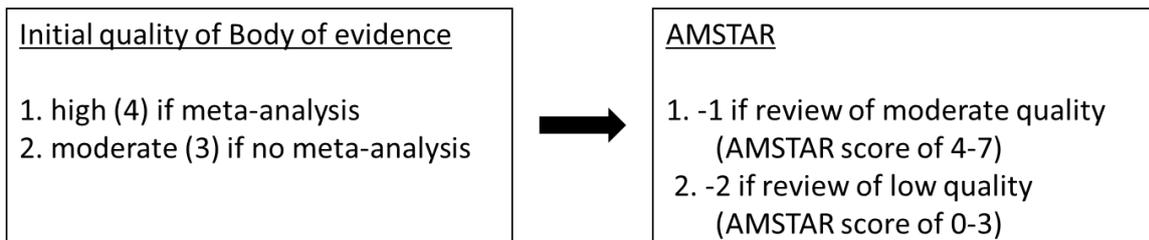
Figure 1: Method used to rate the quality of the evidence supporting each bottom line statement

3. Results

A total of 1086 studies were screened for eligibility (figure 2). After screening for title and abstract, 1034 studies were excluded. Subsequently 52 full-text articles were obtained and screened of which 49 were excluded due to various reasons such as no systematic review (n=42), no risk factors reported (n=6), or specific genetic study (n=1). Eventually, 2 meta-analysis [8] [9] and 1 systematic review [10] were included.
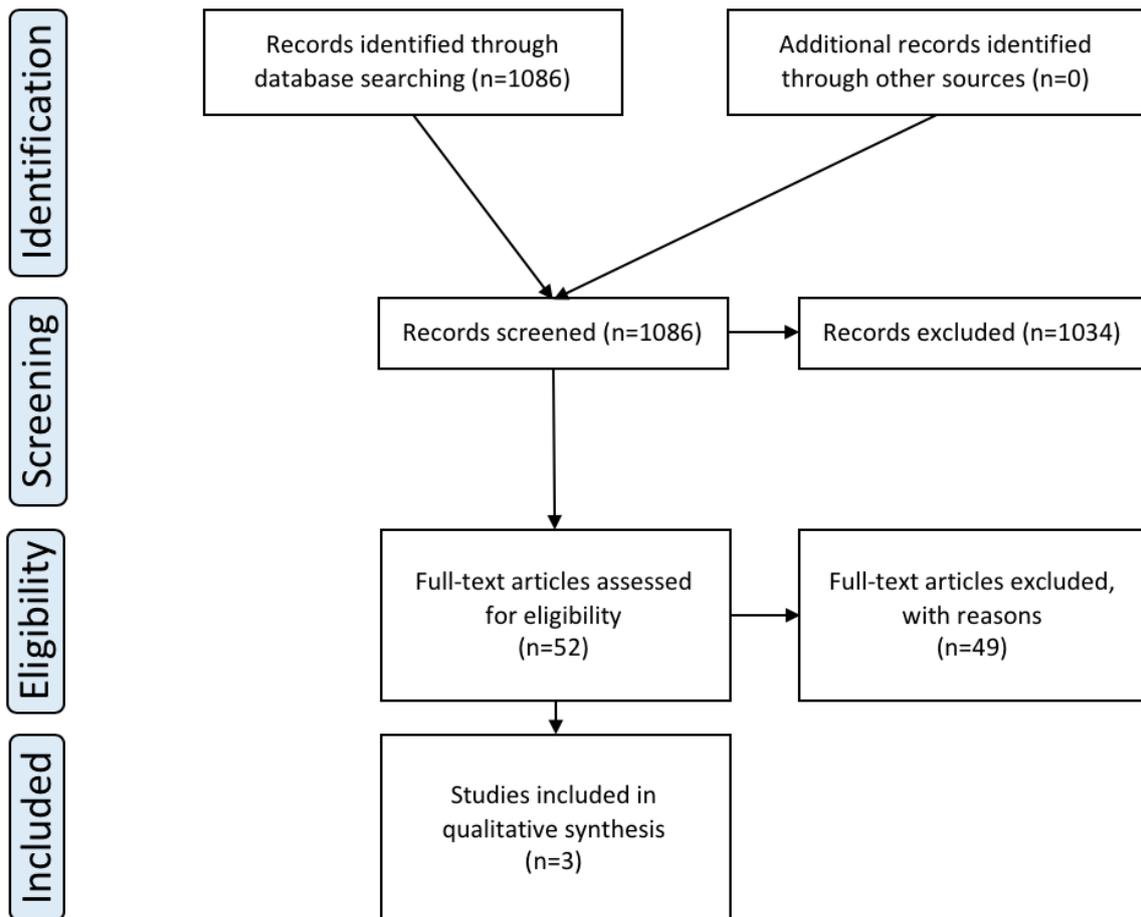
Figure 2 - PRISMA Flowchart
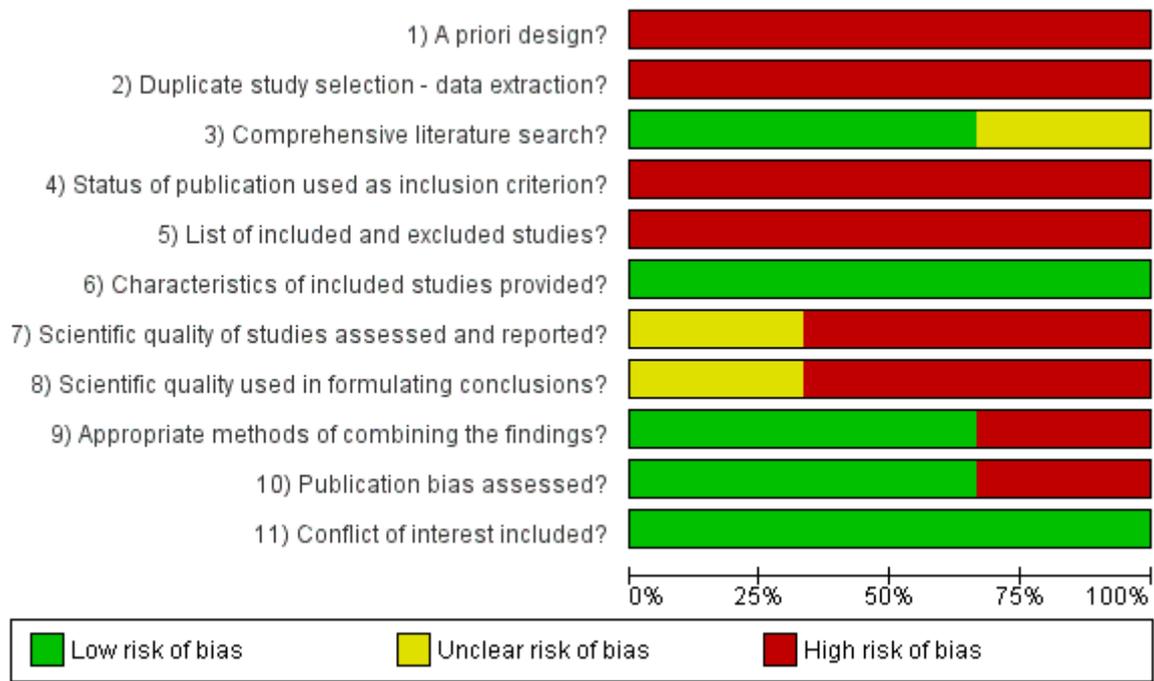
Figure 3 – AMSTAR scores
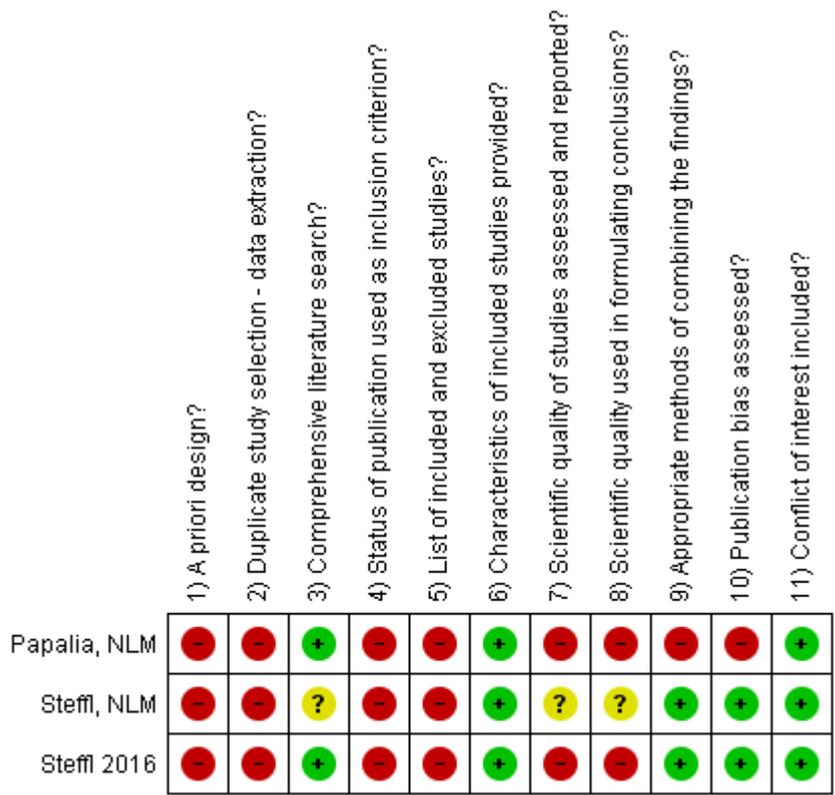
Figure 4 – AMSTAR scores

3.1. Cigarette smoking

A total number of 22.515 participants, spread across twelve studies, were investigated in the meta-analysis of Steffl et al. in 2014 [8]. The population consisted of elderly people with sarcopenia measured via body mass. Subjective evaluation of smoking habits was performed. The results of this meta-analysis suggest that cigarette smoking may increase the chance of developing sarcopenia. Associated odds ratios were calculated: overall 1.12 (95%CI:1.03-1.21), male 1.2 (95%CI: 1.06-1.35), female 1.21 (95%CI: 0.92-1.59). Standardized effectiveness statement consisted of 'some evidence' in favor of smoking as a potential risk factor. AMSTAR score revealed a moderate quality (7/11).

3.2. Osteoarthritis

A total number of 4231 participants, spread across five studies were investigated in the systematic review of Papalia et al. [10]. Participants with a diagnosis of ongoing osteoarthritis were present in all included studies. Neither the thesis of a direct effect of sarcopenia on OA development nor the opposite relation could be confirmed because the literature lacks basic science studies concerning these topics. The absence of clinical studies regarding measurements and tools to compare sarcopenia and OA do not allow to definitely clarify this relationship. Standardized effectives statement consisted of insufficient evidence to determine. AMSTAR score revealed a low quality (3/11).

3.3. Alcohol

Thirteen studies including 13155 participants were selected in the meta-analysis of Steffl et al. [9]. Population consisted of community dwelling elderly aged 65 or older. Status of sarcopenia was dichotomized as well as well as alcohol consumption. Period or intensity of alcohol consumption was not taken into account. The result of this meta-analysis does not support alcohol consumption as a risk factor for sarcopenia. The OR (95 % CI) for sarcopenia among alcohol drinkers was 0.67 (0.54–0.83) for males, 0.89 (0.73–1.08) for females, and 0.77 (0.67–0.88) for the overall population. Standardized effectiveness statement consisted of 'sufficient evidence' to reject alcohol consumption as a possible risk factor. AMSTAR score revealed a moderate quality (5/11).

3.4. Result table

Reference + Exposure	Number of studies (participants)	Population	Results/findings	AMSTAR (maximal score: 11)	Standardized effectiveness statement	Bottom line statement	Rating quality of the evidence 1 Very low 2 Low 3 Moderate 4 High
Steffl 2014 (meta-analysis) **EXPOSURE**: Cigarette smoking	12 studies (n=22,515) - Lau et al (2005) - Vetrano et al (2014) - Rolland et al (2009) - Volpato et al (2013) - Park et al (2013) - Beavers et al (2009) - Goodman et al (2013) - Castillo et al (2003) - Akune et al (2003) - Domiciano et al (2013) - Figueiredo et al (2013) - Lin et al (2013)	older adults with sarcopenia measured via body mass and smoking habits	The results of this meta-analysis suggest that if we followed only the relation between cigarette smoking and sarcopenia, the cigarette smoking may increase the chance of developing sarcopenia. Based on the results of this meta-analysis, it can be concluded that cigarette smoking could have relatively little impact on the development of sarcopenia. However, results are still inconclusive. There have not been many studies performed on the relation of sarcopenia and diverse health factors yet. **Odds Ratio** (OR): 1.12 95%CI: (1.03-1.21) Odds ratio MALE: 1.20 95%CI: (1.06-1.35) Odds ratio FEMALE: 1.21 95%CI: (0.92-1.59) Sarcopenia No Sarcopenia Risk factor present N=2692 N=4839 Risk factor absent N=6026 N=16489	moderate quality (4/11)	**Statement:** some evidence **Direction:** in favor of smoking as potential risk factor **Significant effect**: yes	**Smoking may contribute to the development of sarcopenia (odds ratios = 1.12(95 % CI 1.03-1.21))**	3 - moderate

Papalia 2014 **EXPOSURE:** ongoing osteo-arthritis at some site	5 studies (n=4231 of which 2,983 retrospectively examined) - Toda et al (2000) - Scott et al (2012) - Toda et all (2000) - Santos et al (2011) - Lee et al (2012)	patients with osteoarthritis at knee/hip or other minor joints and sarcopenia (no age restriction, mean age 62)	We cannot support neither the thesis of a direct effect of sarcopenia on OA development nor the opposite relation, because the up-to-date literature lacks basic science studies concerning these topics. The absence of clinical studies regarding measurements and tools to compare sarcopenia and OA do not allow to definitely clarify this relationship. Although several authors have already investigated this relationship, the literature lacks basic science studies concerning the sarcopenia-related molecular pattern and lacks also clinical studies about measurements and tools to compare sarcopenia and OA, analyzing the role of isolated joints OA in the sarcopenia progression in lower limbs	Low quality (3/11)	**Statement:** Insufficient evidence to determine **Direction:** / **Significant effect**: no	**Osteoarthritis could not be identified as a possible risk factor for the development of sarcopenia.**	1 - very low
Steffl 2016 **EXPOSURE**: Alcohol consumption	13 studies (n=13.155) - Akune et al. 2013 - Castillo et al. 2003 - Domiciano et al. 2013 - Figueiredo et al. 2013 - Landi et al. 2013 - Lau et al. 2005 - Lin et al. 2013 - Liu et al. 2014 - Park et al. 2014 - Sampaio et al. 2014 - Silva Alexandre et al. 2014 - Volpato et al. 2014 - Wu et al. 2014	adults aged 65 or older	To sum up, we found out that alcohol consumption was not a risk factor for the development of sarcopenia, even more, according to the results alcohol consumption could have protective character against sarcopenia. The OR (95 % CI) for sarcopenia among alcohol drinkers was 0.67 (0.54–0.83) for males 0.89 (0.73–1.08) for females 0.77 (0.67–0.88) for the overall population.	Moderate quality (5/11)	**Statement:** Sufficient evidence **Direction:** control **Significant effect**: yes	**Alcohol consumption is not a risk factor for sarcopenia. (odds ratios = 0.77(95 % CI 0.67-0.88))**	3 - moderate

4. Recommendation

Smoking may contribute to the development of sarcopenia (odds ratios = 1.12(95 % CI 1.03-1.21)). Evidence suggests that alcohol is not a risk factor for the development of sarcopenia (odds ratios = 0.77(95 % CI 0.67-0.88)). Other possible risk factors mentioned in literature are the following: underweight [11], low BMI [12], physical inactivity [13] [14], malnutrition [15]. These could not be confirmed as risk factors since no systematic review or meta-analysis was found. Literature regarding osteoarthritis as a possible risk factor is lacking, therefore it could not be identified as risk factor.

5. Bibliography

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15. Tay, L., et al., *Sex-specific differences in risk factors for sarcopenia amongst community-dwelling older adults.* Age (Dordr), 2015. **37**(6): p. 121.

6. Appendix

APPENDIX 1 - Full search strategy

Pubmed: (("risk factors"[MeSH Terms] OR ("risk"[All Fields] AND "factors"[All Fields]) OR "risk factors"[All Fields] OR ("risk"[All Fields] AND "factor"[All Fields]) OR "risk factor"[All Fields]) OR "Risk Factors"[Mesh]) AND (("sarcopenia"[MeSH Terms] OR "sarcopenia"[All Fields]) OR "Sarcopenia"[Mesh])

APPENDIX 2 - Eligibility criteria

Domain	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 65 or more are considered Groups that may be covered a. Healthy older people who remain above the cut-off values of the EWGSOP diagnostic criteria b. Older people with muscle mass below the cut-off 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 risk factors regarding sarcopenia?	a. Risk factors regarding
		
		   a. Physical activity
		
		   b. Nutrition
		
		   c. General health

Outcomes	4.Does the study report effects on sarcopenia related outcomes?	Relevant outcomes include: • Muscle mass • Muscle strength • Muscle endurance • Flexibility • Morbidity • Disability • Mortality • Quality of life • Function and participation • Adverse events

ASSESSMENT - MUSCLE STRENGTH - BVGG-SBGG

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1. Introduction

The assessment of muscle strength is interpreted in the context of the prevention and treatment of sarcopenia and thus muscle strength primarily drives clinical action, rather than the diagnosis of sarcopenia. In line with the T-scores of bone mineral density assessments in osteoporosis, this work aims to present cut-off scores for grip strength, based on normative data of young and healthy people, acquired from a systematic review with meta-analyses.

2. Methods

2.1. Search strategy and selection criteria

The PRISMA guidelines were followed in the conduction and reporting of this review [1]. Pubmed was searched systematically for reference values for grip strength from the earliest date available until 05/06/2015 (full search strategy in APPENDIX 1).

2.2. Study selection

Observational studies measuring grip strength in young and healthy subjects (18-39 years) were included. If baseline data was present, interventional studies were included as well. Articles were eligible if data was reported for men and women separately. Studies investigating reference values for grip strength in people with musculoskeletal, neurological, cardiovascular or respiratory diseases were excluded. Studies reporting data on heterogeneous groups regarding age (age below 18 or above 39) and sex (men and women combined) were also excluded (eligibility criteria in APPENDIX 2).

Duplicate selection was done by four reviewers (B.I, D.B.S, B.I, B.D.), blinded for each other's results by using the Rayyan web application for systematic reviews [2]. Disagreements were resolved by a third reviewer or by a consensus-based discussion.

2.3. Data extraction and methodological quality assessment

Data extraction was completed by one reviewer and verified by a second reviewer using a data extraction form based on a template provided by the Cochrane Collaboration [3]. The following key characteristics were extracted: population characteristics, sample size, grip strength measuring instrument, maximal grip strength (mean and standard deviation). No assumptions were made on missing or unclear data. To organize the evidence, one investigator systematically synthesized each article in a data table.

Methodological quality of the studies was performed by one reviewer and verified by a second reviewer using a modified version of the Interpretability and Generalizability checklists of the 'Consensus-based Standards for the selection of health Measurement Instruments' (COSMIN) [4]. This approach has been used previously in a systematic review of studies establishing reference values for walking speed [5].

Meta-analyses were performed for maximal grip strength of both sexes using RevMan 5.3 (Review Manager [computer program], version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). A random effect model was used to account for heterogeneity among studies. To investigate heterogeneity, subgroup analyses were performed for measurement instrument (Jamar, other instruments) and age decade (18-29, 30-39). Forrest plots were generated for the graphical presentation of the outcomes. If possible, grip strength data was converted to kg. Standard error (SE) was calculated as SE=Standard Deviation)/√(N). Based on the pooled estimate and related confidence interval, the pooled standard deviation (SD_{pooled}) was calculated by using the Welch-Satterthwaite equation for pooled degrees of freedom [6, 7]. Finally, based on the pooled grip strength and SD_{pooled}, cut-off scores (T-scores) were calculated for men and women: T_{-1}=pooled grip strength- SD_{pooled} and T_{-2}= pooled grip strength – 2xSD_{pooled}.

3. Results

A total of 912 studies were initially screened for eligibility of which 14 studies were further

analyzed (figure 1) [8-21]. COSMIN scores of these studies are presented in figure 2.

Figure 1 - PRISMA Flowchart

Figure 2 – COSMIN scores of included studies

Most studies used a hydraulic dynamometer to measure grip strength of which Jamar was used in seven studies (see table 1) [10, 11, 14-16, 20, 21].

Author	Measuring instrument	Sex	Age	n	Maximal grip strength (kg)
Backman, 1995	Straing Gauge (Rank Stanley Cox)	M	20-29	12	46,2 (8,0)
			30-39	11	50,4 (7,4)
		V	20-29	10	29,9 (5,5)
			30-39	10	32,8 (5,1)
Berg, 2007	Baseline Hydraulic Hand Dynamometer	M	20-29	10	47,9 (8,8)
Bertovic, 1999	Jamar	M	20-29	19	44 (2)
Budziareck , 2008	Jamar	M	18-30	100	43,4 (8,4)
		V	18-30	100	22,8 (4,9)
Fuster, 1998	NK	M	21-29	69	50,2 (7,1)
		V	21-29	152	30,1 (4,1)
Gunther, 2008	Baseline Digital Hydraulic Dynamometer	M	20-29	66	53 (8)
			30-39	52	54 (10)
		V	20-29	75	32 (5)
			30-39	70	33 (5)
Hanten, 1999	Jamar	M	20-24	74	54,4 (10,0)
			25-29	103	53,1 (10,4)
			30-34	61	52,2 (10,9)
			35-39	60	53,5 (10,4)
		V	20-24	80	31,3 (6,4)
			25-29	90	33,1 (6,4)
			30-34	88	33,1 (6,8)
			35-39	75	33,6 (7,3)
Kamimura, 2001	Jamar	M	20-29	25	50 (10)
		V	20-29	25	34 (4,9)
Klum, 2012	Jamar	M	18-29	60	MW: 42,9 (5,8)
				34	nMW: 42,1 (10,6)
		V	18-29	19	MW: 26,7 (5,6)
				48	nMW: 26,2 (5,6)
Luna-Heredia, 2005	GRIP-D dynamometer	M	30-39	43	50,9 (12,5)
		V	30-39	108	28,2 (5,8)
Montalcini, 2013	Hydraulic hand dynamometer	M	19-25	157	44,8 (6,7)
		V	19-25	178	27,7 4,4)
Nilsen, 2012	Grippit	M	18-29	46	49,6 (8,8)
			30-39	67	52,7 (11,5)
		V	18-29	55	29,1 (6,5)
			30-39	46	29,8 (7,7)
Schlussel, 2008	Jamar	M	18-29	295	45,8 (SE 0,67)
			30-39	244	46,5 (SE 0,47)
		V	18-29	431	27,2 (SE 0,46)
			30-39	397	28,0 (SE 0,39)
Werle, 2009	Jamar	M	20-24	29	53,9 (8,7)
			25-29	30	53,0 (7,5)
			30-34	28	55,0 (7,1)
			35-39	41	55,9 (7,9)
		V	20-24	31	33,4 (5,4)
			25-29	30	34,3 (5,7)
			30-34	30	33,8 (5,9)
			35-39	42	35,8 (6,7)

Table 1: Study, measuring instrument and participant characteristics for studies reporting normative values for maximal handgrip strength.

Based on data of 1755 men and 2194 women, a pooled maximum grip strength of 49.8 (95% confidence interval (CI) [48.1, 51.5]) and 30.6 (95%CI [29.3, 37.8]) was calculated for men and women respectively (see forest plots in figure 3 and 4). Heterogeneity was found high in both sexes ($I^2 > 95\%$) and was not explained by the measuring instrument or age decade (see appendix 4).

Study or Subgroup	Mean (KG)	SE	Weight	Mean (KG) IV, Random, 95% CI
Budziareck 2008 (18-30)	22.8	0.49	4.6%	22.80 [21.84, 23.76]
Bäckman 1995 (20-29)	29.88	1.59	3.7%	29.88 [26.76, 33.00]
Bäckman 1995 (30-39)	32.83	1.54	3.8%	32.83 [29.81, 35.85]
Fuster 1998	30.07	0.33	4.6%	30.07 [29.42, 30.72]
Gunther 2008 (20-29)	32	0.58	4.5%	32.00 [30.86, 33.14]
Gunther 2008 (30-39)	33	0.6	4.5%	33.00 [31.82, 34.18]
Hanten 1999 (20-24)	31.3	0.71	4.5%	31.30 [29.91, 32.69]
Hanten 1999 (25-29)	33.11	0.67	4.5%	33.11 [31.80, 34.42]
Hanten 1999 (30-34)	33.11	0.72	4.5%	33.11 [31.70, 34.52]
Hanten 1999 (35-39)	33.57	0.84	4.4%	33.57 [31.92, 35.22]
Kamimura 2001	34	0.98	4.3%	34.00 [32.08, 35.92]
Klum 2012 (18-29) (manual)	26.7	1.28	4.0%	26.70 [24.19, 29.21]
Klum 2012 (18-29) (non-manual)	26.2	0.81	4.4%	26.20 [24.61, 27.79]
Luna-Heredia 2005	28.2	0.56	4.5%	28.20 [27.10, 29.30]
Montalcini 2013	27.7	0.33	4.6%	27.70 [27.05, 28.35]
Nilsen 2012 (20-29)	29.06	0.88	4.3%	29.06 [27.34, 30.78]
Nilsen 2012 (30-39)	29.78	1.13	4.1%	29.78 [27.57, 31.99]
Schlussel 2008 (20-29)	27.2	0.46	4.6%	27.20 [26.30, 28.10]
Schlussel 2008 (30-39)	28	0.39	4.6%	28.00 [27.24, 28.76]
Werle 2009 (20-25)	33.4	0.97	4.3%	33.40 [31.50, 35.30]
Werle 2009 (25-29)	34.3	1.04	4.2%	34.30 [32.26, 36.34]
Werle 2009 (30-34)	33.8	1.08	4.2%	33.80 [31.68, 35.92]
Werle 2009 (35-39)	35.8	1.03	4.2%	35.80 [33.78, 37.82]
Total (95% CI)			100.0%	30.64 [29.33, 31.94]

Heterogeneity: Tau² = 9.38; Chi² = 539.35, df = 22 (P < 0.00001); I² = 96%
Test for overall effect: Z = 46.13 (P < 0.00001)

Figure 3: Forest plot for maximal grip strength of young and healthy men

Study or Subgroup	Mean (kg)	SE	Weight	Mean (kg) IV, Random, 95% CI
Berg 2007	47.93	2.77	3.1%	47.93 [42.50, 53.36]
Bertovic 1999	44	0.46	4.4%	44.00 [43.10, 44.90]
Budziareck 2008 (18-30)	43.4	0.84	4.3%	43.40 [41.75, 45.05]
Bäckman 1995 (20-29)	46.19	2.3	3.4%	46.19 [41.68, 50.70]
Bäckman 1995 (30-39)	50.37	2.24	3.4%	50.37 [45.98, 54.76]
Fuster 1998	50.22	0.86	4.3%	50.22 [48.53, 51.91]
Gunther 2008 (20-29)	53	0.98	4.2%	53.00 [51.08, 54.92]
Gunther 2008 (30-39)	54	1.39	4.0%	54.00 [51.28, 56.72]
Hanten 1999 (20-24)	54.43	1.16	4.1%	54.43 [52.16, 56.70]
Hanten 1999 (25-29)	53.07	1.03	4.2%	53.07 [51.05, 55.09]
Hanten 1999 (30-34)	52.16	1.39	4.0%	52.16 [49.44, 54.88]
Hanten 1999 (35-39)	53.52	1.41	4.0%	53.52 [50.76, 56.28]
Kamimura 2001	50	2.02	3.6%	50.00 [46.04, 53.96]
Klum 2012 (18-29) (manual)	42.9	0.75	4.3%	42.90 [41.43, 44.37]
Klum 2012 (18-29) (non-manual)	42.1	1.82	3.7%	42.10 [38.53, 45.67]
Luna-Heredia 2005	50.9	1.91	3.7%	50.90 [47.16, 54.64]
Montalcini 2013	44.77	0.53	4.4%	44.77 [43.73, 45.81]
Nilsen 2012 (20-29)	49.56	1.31	4.1%	49.56 [46.99, 52.13]
Nilsen 2012 (30-39)	52.72	1.41	4.0%	52.72 [49.96, 55.48]
Schlussel 2008 (20-29)	45.8	0.67	4.4%	45.80 [44.49, 47.11]
Schlussel 2008 (30-39)	46.5	0.47	4.4%	46.50 [45.58, 47.42]
Werle 2009 (20-25)	53.9	1.61	3.9%	53.90 [50.74, 57.06]
Werle 2009 (25-29)	53	1.37	4.0%	53.00 [50.31, 55.69]
Werle 2009 (30-34)	55	1.34	4.0%	55.00 [52.37, 57.63]
Werle 2009 (35-39)	55.9	1.23	4.1%	55.90 [53.49, 58.31]
Total (95% CI)			100.0%	49.78 [48.08, 51.47]

Heterogeneity: Tau² = 16.72; Chi² = 456.14, df = 24 (P < 0.00001); I² = 95%
Test for overall effect: Z = 57.59 (P < 0.00001)

Figure 4: Forest plot for maximal grip strength of young and healthy women

Subsequently, based on the pooled estimates, the pooled standard deviations were calculated (i.e. 12.2 for men and 9.9 for women) and consequently, the cut-off scores (T-scores) were defined for men (38kg (T_{-1}), 25kg (T_{-2})) and women (21kg (T_{-1}), 11kg (T_{-2})).

Figures 5 visualizes the calculated cut-off scores for men and women compared to the cut-off scores that were recommended by international consensus statements.

MEN-WOMEN		VERY LOW	AT RISK	NORMAL
REFERENCE DATA		M-F	M-F	M-F
Hydraulic dynamometer	[kg]	25-11	38-21	50-31
CUTOFF CONSENSUS STATEMENTS				
EWGSOP 2	[kg]	27-16		
FNIH	[kg]	26-16	32-20	
	[kg/BMI]	1.0-0.56		
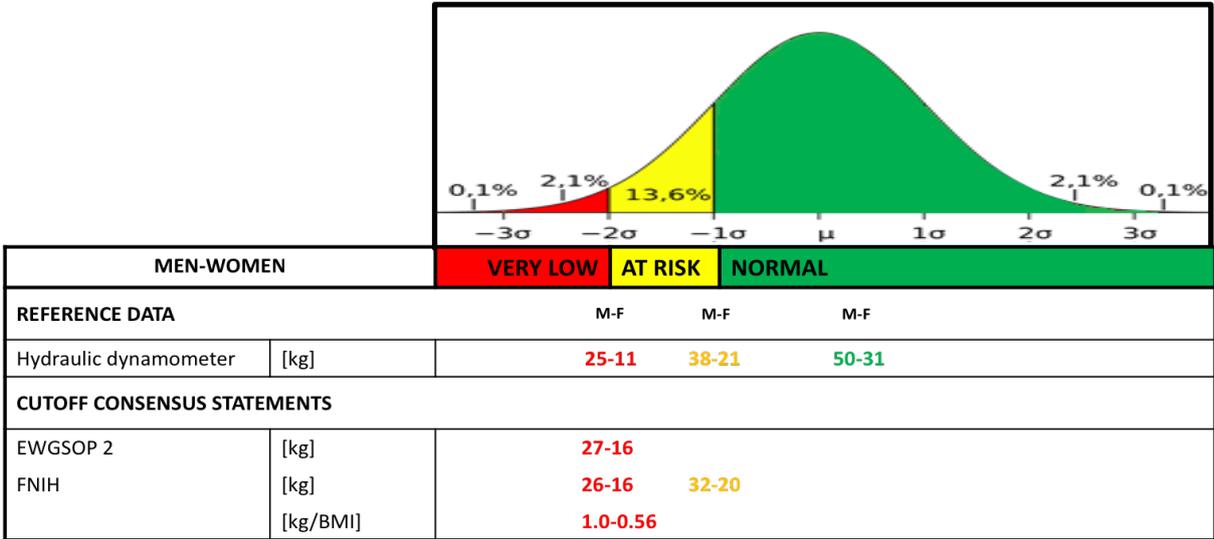
Figure 5: T-1 and T-2 cut-off scores, compared to the cut-off scores of EWGSOP and FNIH in men and women

4. Recommendation

We recommend maximum handgrip strength of the dominant hand to assess general muscle strength. We recommend categorizing patients according to the normative values for healthy young people. We recommend the use of cut-off values for muscle strength that are based on reference values of healthy young people to drive clinical actions. Cut-off scores for men are 38kg (T_{-1}) and 25kg (T_{-2})) and for women 21kg (T_{-1}) and 11kg (T_{-2}).

There are no side effects reported in the retrieved evidence.

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6. Appendix

APPENDIX 1 – Full search strategy

Pubmed: ("Muscle Strength"[Mesh] OR "Hand Strength"[Mesh] OR "Muscle Fatigue"[Mesh]) AND "Reference Values"[Mesh]

APPENDIX 2 – Eligibility criteria

Domain	Criteria	Description
Study design	1.Is the study an observational study?	Observational studies are considered. Interventional studies are considered if baseline data is represented.
Participants	2.Does the study reports on young people?	Healthy adults, aged between 18 and 39 are considered Only data reported for men and woman separately is considered eligible Data is preferably reported in decades
Outcomes	3.Does the study report data on muscle strength?	Relevant outcomes include: • Grip strength • Quadriceps strength • Muscle explosive power • Fatigue resistance Descriptive data are presented in numerical format to enable accurate reporting (N; Mean; SD)
Exclusion criteria		Participants having musculoskeletal, neurological, cardiovascular or respiratory diseases Data reported on heterogeneous group regarding age/sex (<18; >39; men and women combined)

APPENDIX 3 – Subgroup analyses

A. Female - 20-29

Study or Subgroup	Mean (kg)	SE	Weight	Mean (kg) IV, Random, 95% CI	Mean (kg) IV, Random, 95% CI
Budziareck 2008 (18-30)	22.8	0.49	7.5%	22.80 [21.84, 23.76]	
Bäckman 1995 (20-29)	29.88	1.59	6.1%	29.88 [26.76, 33.00]	
Fuster 1998	30.07	0.33	7.6%	30.07 [29.42, 30.72]	
Gunther 2008 (20-29)	32	0.58	7.4%	32.00 [30.86, 33.14]	
Hanten 1999 (20-24)	31.3	0.71	7.3%	31.30 [29.91, 32.69]	
Hanten 1999 (25-29)	33.11	0.67	7.3%	33.11 [31.80, 34.42]	
Kamimura 2001	34	0.98	7.0%	34.00 [32.08, 35.92]	
Klum 2012 (18-29) (manual)	26.7	1.28	6.6%	26.70 [24.19, 29.21]	
Klum 2012 (18-29) (non-manual)	26.2	0.81	7.2%	26.20 [24.61, 27.79]	
Montalcini 2013	27.7	0.33	7.6%	27.70 [27.05, 28.35]	
Nilsen 2012 (20-29)	29.06	0.88	7.1%	29.06 [27.34, 30.78]	
Schlussel 2008 (20-29)	27.2	0.46	7.5%	27.20 [26.30, 28.10]	
Werle 2009 (20-25)	33.4	0.97	7.0%	33.40 [31.50, 35.30]	
Werle 2009 (25-29)	34.3	1.04	6.9%	34.30 [32.26, 36.34]	
Total (95% CI)			**100.0%**	**29.80 [28.10, 31.51]**	

Heterogeneity: Tau² = 9.85; Chi² = 363.95, df = 13 (P < 0.00001); I² = 96%
Test for overall effect: Z = 34.31 (P < 0.00001)

B. Female - 30-39

Study or Subgroup	Mean (kg)	SE	Weight	Mean (kg) IV, Random, 95% CI	Mean (kg) IV, Random, 95% CI
Bäckman 1995 (30-39)	32.83	1.54	9.6%	32.83 [29.81, 35.85]	
Gunther 2008 (30-39)	33	0.6	11.7%	33.00 [31.82, 34.18]	
Hanten 1999 (30-34)	33.11	0.72	11.5%	33.11 [31.70, 34.52]	
Hanten 1999 (35-39)	33.57	0.84	11.3%	33.57 [31.92, 35.22]	
Luna-Heredia 2005	28.2	0.56	11.8%	28.20 [27.10, 29.30]	
Nilsen 2012 (30-39)	29.78	1.13	10.6%	29.78 [27.57, 31.99]	
Schlussel 2008 (30-39)	28	0.39	12.0%	28.00 [27.24, 28.76]	
Werle 2009 (30-34)	33.8	1.08	10.7%	33.80 [31.68, 35.92]	
Werle 2009 (35-39)	35.8	1.03	10.9%	35.80 [33.78, 37.82]	
Total (95% CI)			**100.0%**	**31.95 [29.93, 33.96]**	

Heterogeneity: Tau² = 8.69; Chi² = 140.29, df = 8 (P < 0.00001); I² = 94%
Test for overall effect: Z = 31.05 (P < 0.00001)

C. Female - Jamar

47

Study or Subgroup	Mean (kg)	SE	Weight	Mean (kg) IV, Random, 95% CI	Mean (kg) IV, Random, 95% CI
1.3.1 20-29					
Budziareck 2008 (18-30)	22.8	0.49	7.9%	22.80 [21.84, 23.76]	
Hanten 1999 (20-24)	31.3	0.71	7.8%	31.30 [29.91, 32.69]	
Hanten 1999 (25-29)	33.11	0.67	7.8%	33.11 [31.80, 34.42]	
Klum 2012 (18-29) (manual)	26.7	1.28	7.3%	26.70 [24.19, 29.21]	
Klum 2012 (18-29) (non-manual)	26.2	0.81	7.7%	26.20 [24.61, 27.79]	
Schlussel 2008 (20-29)	27.2	0.46	7.9%	27.20 [26.30, 28.10]	
Werle 2009 (20-25)	33.4	0.97	7.6%	33.40 [31.50, 35.30]	
Werle 2009 (25-29)	34.3	1.04	7.5%	34.30 [32.26, 36.34]	
Subtotal (95% CI)			61.6%	29.35 [26.31, 32.39]	

Heterogeneity: Tau² = 18.54; Chi² = 269.06, df = 7 (P < 0.00001); I² = 97%
Test for overall effect: Z = 18.92 (P < 0.00001)

1.3.2 30-39					
Hanten 1999 (30-34)	33.11	0.72	7.8%	33.11 [31.70, 34.52]	
Hanten 1999 (35-39)	33.57	0.84	7.7%	33.57 [31.92, 35.22]	
Schlussel 2008 (30-39)	28	0.39	8.0%	28.00 [27.24, 28.76]	
Werle 2009 (30-34)	33.8	1.08	7.5%	33.80 [31.68, 35.92]	
Werle 2009 (35-39)	35.8	1.03	7.5%	35.80 [33.78, 37.82]	
Subtotal (95% CI)			38.4%	32.80 [29.50, 36.09]	

Heterogeneity: Tau² = 13.42; Chi² = 103.35, df = 4 (P < 0.00001); I² = 96%
Test for overall effect: Z = 19.51 (P < 0.00001)

| **Total (95% CI)** | | | 100.0% | 30.68 [28.46, 32.90] | |

Heterogeneity: Tau² = 15.98; Chi² = 417.26, df = 12 (P < 0.00001); I² = 97%
Test for overall effect: Z = 27.08 (P < 0.00001)
Test for subgroup differences: Chi² = 2.27, df = 1 (P = 0.13), I² = 55.9%

-100 -50 0 50 100

D. Female - other

Study or Subgroup	Mean (kg)	SE	Weight	Mean (kg) IV, Random, 95% CI	Mean (kg) IV, Random, 95% CI
1.4.1 20-29					
Bäckman 1995 (20-29)	29.88	1.59	7.4%	29.88 [26.76, 33.00]	
Fuster 1998	30.07	0.33	11.6%	30.07 [29.42, 30.72]	
Gunther 2008 (20-29)	32	0.58	11.0%	32.00 [30.86, 33.14]	
Kamimura 2001	34	0.98	9.7%	34.00 [32.08, 35.92]	
Montalcini 2013	27.7	0.33	11.6%	27.70 [27.05, 28.35]	
Nilsen 2012 (20-29)	29.06	0.88	10.0%	29.06 [27.34, 30.78]	
Subtotal (95% CI)			61.3%	30.40 [28.65, 32.15]	

Heterogeneity: Tau² = 4.09; Chi² = 72.70, df = 5 (P < 0.00001); I² = 93%
Test for overall effect: Z = 34.10 (P < 0.00001)

1.4.2 30-39					
Bäckman 1995 (30-39)	32.83	1.54	7.6%	32.83 [29.81, 35.85]	
Gunther 2008 (30-39)	33	0.6	10.9%	33.00 [31.82, 34.18]	
Luna-Heredia 2005	28.2	0.56	11.0%	28.20 [27.10, 29.30]	
Nilsen 2012 (30-39)	29.78	1.13	9.1%	29.78 [27.57, 31.99]	
Subtotal (95% CI)			38.7%	30.88 [28.03, 33.72]	

Heterogeneity: Tau² = 7.43; Chi² = 36.92, df = 3 (P < 0.00001); I² = 92%
Test for overall effect: Z = 21.27 (P < 0.00001)

| **Total (95% CI)** | | | 100.0% | 30.57 [29.18, 31.96] | |

Heterogeneity: Tau² = 4.26; Chi² = 115.01, df = 9 (P < 0.00001); I² = 92%
Test for overall effect: Z = 42.99 (P < 0.00001)
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%

-100 -50 0 50 100

E. Male - 20-29

Study or Subgroup	Mean (KG)	SE	Weight	Mean (KG) IV, Random, 95% CI
Berg 2007	47.93	2.77	4.7%	47.93 [42.50, 53.36]
Bertovic 1999	44	0.46	6.9%	44.00 [43.10, 44.90]
Budziareck 2008 (18-30)	43.4	0.84	6.7%	43.40 [41.75, 45.05]
Bäckman 1995 (20-29)	46.19	2.3	5.2%	46.19 [41.68, 50.70]
Fuster 1998	50.22	0.86	6.7%	50.22 [48.53, 51.91]
Gunther 2008 (20-29)	53	0.98	6.6%	53.00 [51.08, 54.92]
Hanten 1999 (20-24)	54.43	1.16	6.4%	54.43 [52.16, 56.70]
Hanten 1999 (25-29)	53.07	1.03	6.6%	53.07 [51.05, 55.09]
Kamimura 2001	50	2.02	5.5%	50.00 [46.04, 53.96]
Klum 2012 (18-29) (manual)	42.9	0.75	6.8%	42.90 [41.43, 44.37]
Klum 2012 (18-29) (non-manual)	42.1	1.82	5.8%	42.10 [38.53, 45.67]
Montalcini 2013	44.77	0.53	6.9%	44.77 [43.73, 45.81]
Nilsen 2012 (20-29)	49.56	1.31	6.3%	49.56 [46.99, 52.13]
Schlussel 2008 (20-29)	45.8	0.67	6.8%	45.80 [44.49, 47.11]
Werle 2009 (20-25)	53.9	1.61	6.0%	53.90 [50.74, 57.06]
Werle 2009 (25-29)	53	1.37	6.2%	53.00 [50.31, 55.69]
Total (95% CI)			**100.0%**	**48.36 [46.33, 50.39]**

Heterogeneity: Tau² = 15.36; Chi² = 286.20, df = 15 (P < 0.00001); I² = 95%
Test for overall effect: Z = 46.62 (P < 0.00001)

F. Male – 30-39

Study or Subgroup	Mean (KG)	SE	Weight	Mean (KG) IV, Random, 95% CI
Bäckman 1995 (30-39)	50.37	2.24	9.8%	50.37 [45.98, 54.76]
Gunther 2008 (30-39)	54	1.39	11.2%	54.00 [51.28, 56.72]
Hanten 1999 (30-34)	52.16	1.39	11.2%	52.16 [49.44, 54.88]
Hanten 1999 (35-39)	53.52	1.41	11.2%	53.52 [50.76, 56.28]
Luna-Heredia 2005	50.9	1.91	10.4%	50.90 [47.16, 54.64]
Nilsen 2012 (30-39)	52.72	1.41	11.2%	52.72 [49.96, 55.48]
Schlussel 2008 (30-39)	46.5	0.47	12.2%	46.50 [45.58, 47.42]
Werle 2009 (30-34)	55	1.34	11.3%	55.00 [52.37, 57.63]
Werle 2009 (35-39)	55.9	1.23	11.5%	55.90 [53.49, 58.31]
Total (95% CI)			**100.0%**	**52.33 [49.34, 55.33]**

Heterogeneity: Tau² = 18.84; Chi² = 112.52, df = 8 (P < 0.00001); I² = 93%
Test for overall effect: Z = 34.27 (P < 0.00001)

G. Male - Jamar

Study or Subgroup	Mean (kg)	SE	Weight	Mean (kg) IV, Random, 95% CI
1.1.1 20-29				
Bertovic 1999	44	0.46	7.6%	44.00 [43.10, 44.90]
Budziareck 2008 (18-30)	43.4	0.84	7.4%	43.40 [41.75, 45.05]
Hanten 1999 (20-24)	54.43	1.16	7.1%	54.43 [52.16, 56.70]
Hanten 1999 (25-29)	53.07	1.03	7.2%	53.07 [51.05, 55.09]
Klum 2012 (18-29) (manual)	42.9	0.75	7.4%	42.90 [41.43, 44.37]
Klum 2012 (18-29) (non-manual)	42.1	1.82	6.5%	42.10 [38.53, 45.67]
Schlussel 2008 (20-29)	45.8	0.67	7.5%	45.80 [44.49, 47.11]
Werle 2009 (20-25)	53.9	1.61	6.7%	53.90 [50.74, 57.06]
Werle 2009 (25-29)	53	1.37	7.0%	53.00 [50.31, 55.69]
Subtotal (95% CI)			64.5%	48.00 [45.10, 50.91]
Heterogeneity: Tau² = 18.46; Chi² = 200.34, df = 8 (P < 0.00001); I² = 96%				
Test for overall effect: Z = 32.39 (P < 0.00001)				
1.1.2 30-39				
Hanten 1999 (30-34)	52.16	1.39	6.9%	52.16 [49.44, 54.88]
Hanten 1999 (35-39)	53.52	1.41	6.9%	53.52 [50.76, 56.28]
Schlussel 2008 (30-39)	46.5	0.47	7.6%	46.50 [45.58, 47.42]
Werle 2009 (30-34)	55	1.34	7.0%	55.00 [52.37, 57.63]
Werle 2009 (35-39)	55.9	1.23	7.1%	55.90 [53.49, 58.31]
Subtotal (95% CI)			35.5%	52.55 [47.98, 57.12]
Heterogeneity: Tau² = 25.70; Chi² = 95.22, df = 4 (P < 0.00001); I² = 96%				
Test for overall effect: Z = 22.54 (P < 0.00001)				
Total (95% CI)			100.0%	49.61 [47.24, 51.98]
Heterogeneity: Tau² = 19.18; Chi² = 338.83, df = 13 (P < 0.00001); I² = 96%				
Test for overall effect: Z = 40.96 (P < 0.00001)				
Test for subgroup differences: Chi² = 2.71, df = 1 (P = 0.10), I² = 63.1%				

H. Male - other

Study or Subgroup	Mean (kg)	SE	Weight	Mean (kg) IV, Random, 95% CI
1.2.1 20-29				
Berg 2007	47.93	2.77	7.0%	47.93 [42.50, 53.36]
Bäckman 1995 (20-29)	46.19	2.3	7.9%	46.19 [41.68, 50.70]
Fuster 1998	50.22	0.86	10.3%	50.22 [48.53, 51.91]
Gunther 2008 (20-29)	53	0.98	10.2%	53.00 [51.08, 54.92]
Kamimura 2001	50	2.02	8.4%	50.00 [46.04, 53.96]
Montalcini 2013	44.77	0.53	10.7%	44.77 [43.73, 45.81]
Nilsen 2012 (20-29)	49.56	1.31	9.7%	49.56 [46.99, 52.13]
Subtotal (95% CI)			64.2%	48.88 [45.90, 51.87]
Heterogeneity: Tau² = 13.66; Chi² = 72.15, df = 6 (P < 0.00001); I² = 92%				
Test for overall effect: Z = 32.08 (P < 0.00001)				
1.2.2 30-39				
Bäckman 1995 (30-39)	50.37	2.24	8.0%	50.37 [45.98, 54.76]
Gunther 2008 (30-39)	54	1.39	9.6%	54.00 [51.28, 56.72]
Luna-Heredia 2005	50.9	1.91	8.6%	50.90 [47.16, 54.64]
Nilsen 2012 (30-39)	52.72	1.41	9.5%	52.72 [49.96, 55.48]
Subtotal (95% CI)			35.8%	52.52 [50.91, 54.12]
Heterogeneity: Tau² = 0.00; Chi² = 2.79, df = 3 (P = 0.42); I² = 0%				
Test for overall effect: Z = 64.19 (P < 0.00001)				
Total (95% CI)			100.0%	50.03 [47.60, 52.46]
Heterogeneity: Tau² = 14.09; Chi² = 103.76, df = 10 (P < 0.00001); I² = 90%				
Test for overall effect: Z = 40.42 (P < 0.00001)				
Test for subgroup differences: Chi² = 4.41, df = 1 (P = 0.04), I² = 77.3%				

ASSESSMENT

-

MUSCLE MASS

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BVGG-SBGG

Belgian Society
for GERONTOLOGY
and GERIATRICS

1. Introduction

The assessment of muscle mass is interpreted in the context of the prevention and treatment of sarcopenia and thus muscle mass primarily drives clinical action, rather than the diagnosis of sarcopenia. In line with the T-scores of bone mineral density assessments in osteoporosis, this work aims to present cut-off scores for muscle mass as measured by Dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA), based on normative data of young and healthy people, acquired from a systematic review with meta-analyses. Since it has been emphasized that relative muscle mass values should be preferred above absolute values [1], this review aimed to report muscle mass data adjusted for body weight and height.

2. Methods

2.1. Search strategy and selection criteria

The PRISMA guidelines were followed in the conduction and reporting of this review [2]. Pubmed was searched systematically for reference values for muscle mass from the earliest date available until 25/09/2015 (full search strategy in APPENDIX 1).

2.2. Study selection

Observational studies measuring muscle mass with DXA or BIA in young and healthy subjects (18-39 years) were included. If baseline data was present, interventional studies were included as well. Articles were eligible if data was reported for men and women separately. Studies investigating reference values for muscle mass in people with musculoskeletal, neurological, cardiovascular or respiratory diseases were excluded. Studies reporting data on heterogeneous groups regarding age (age below 18 or above 39) and sex (men and women combined) were also excluded.

Duplicate selection was done by three reviewers (S.A., P.S., B.D.), blinded for each other's results by using the Rayyan web application for systematic reviews [3]. Disagreements were resolved by a third reviewer or by a consensus-based discussion.

2.3. Data extraction and methodological quality assessment

Data extraction was completed by one reviewer and verified by a second reviewer using a data extraction form based on a template provided by the Cochrane Collaboration [4]. The following key characteristics were extracted: population characteristics, sample size, measuring instrument, absolute and relative (body mass, body height) muscle mass (mean and standard deviation). No assumptions were made on missing or unclear data. Authors were contacted for missing data regarding relative muscle mass data. To organize the evidence, one investigator systematically synthesized each article in a data table.

Methodological quality of the studies was performed by one reviewer and verified by a second reviewer using a modified version of the Interpretability and Generalizability checklists of the 'Consensus-based Standards for the selection of health Measurement Instruments' (COSMIN) [5]. This approach has been used previously in a systematic review of studies establishing reference values for walking speed [6].

Meta-analyses were performed for muscle mass of both sexes as measured by DXA and BIA respectively using RevMan 5.3 (Review Manager [computer program], version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). A random effect model was used to account for heterogeneity among studies. To investigate heterogeneity, subgroup analyses were performed for age decades (18-29, 30-39). Forrest plots were generated for the graphical presentation of the outcomes. Standard error (SE) was calculated as SE=Standard Deviation)/√(N).

3. Results

A total of 2645 studies were initially screened for eligibility of which 23 studies were further

analyzed (figure 1) [7-29]. COSMIN scores of the included studies are presented in figure 2.

Figure 1 - PRISMA Flowchart

Figure 2 – COSMIN scores of included studies

Most studies reported data regarding *absolute* muscle mass of young and healthy people.

Only four studies reported on *relative* muscle mass (fat free mass Index (height-DXA) ,

appendicular muscle mass index (height-DXA), lean Body Mass index (height-DXA)) [9, 11,

16, 29] (table 1). Due to this low number of studies in combination with a high

heterogeneity, we did not perform meta-analyses. Hence, we recommend the use of cut-off

values for relative muscle mass that are proposed by the EWGSOP [30], EWGSOP2 [31],

IWGS [32] or FNIH [1].

Author	Measuring instrument	Sex	Age	n	Muscle mass
Andreoli 2011	DXA	W	30-39	140	LBM: 42,1kg (6,3)
Boot 2011	DXA	M	20-29	117	LBM:61,3kg (6,4)
		W	20-29	347	LBM:42,5kg (4,4)
Cheng 2014	DXA	M	20-29	198	LBM: 53,8kg (6,9)
					AMM:23,78kg (3,5)
					AMM (height): 7,94 kg/m² (0,9)
			30-39	225	LBM: 54,85kg (7,1)
					AMM: 23,74kg (3,2)
					AMM (height): 7,85 kg/m² (0,8)
		W	20-29	225	LBM:39,06kg (3,9)
					AMM:16,15kg (1,9)
					AMM (height):6,12 kg/m²(0,6)
			30-39	235	LBM: 38,29kg (3,8)
					AMM: 15,4kg (1,8)
					AMM (height): 6,02 kg/m²(0,6)
Coin 2008	DXA	M	20-29	89	FFM: 62,9kg (7,4)
					FFMI:19,7kg/m² (1,8)
			30-39	39	FFM: 62,1kg (12,9)
					FFMI: 19,8kg/m² (3,6)
		W	20-29	105	FFM: 41kg (7,3)
					FFMI: 15,2kg/m² (2,1)
			30-39	54	FFM: 42,7kg (14,4)
					FFMI: 16kg/m² (4,1)
Coin 2012	DXA	M	20-29	67	FFM: 30,76 (-)
		W	30-39	27	FFM: 30,06(-)
			20-29	57	FFM: 17,82(-)
			30-39	26	FFM: 18,67 (-)
DeNino 2011	DXA	W	20-29	88	FFM: 40,0kg (4,1)
Frederiksen 2009	DXA	M	20-29	780	LBM: 63,5kg (-)
Gould 2014	DXA	M	20-39	374	AMM: 28,16kg (3,79)
					AMM (height): 8,8kg/m² (0,93)
					LBM: 60,1kg (7,26)
					LBM (height): 18,79kg/m² (1,73)
		W	20-39	308	AMM: 18,72kg (2,54)
					AMM (height): 6,84kg/m² (0,77)
					LBM: 40,86kg (4,72)
					LBM (height): 14,93kg/m² (1,43)
Lantz 2008	DXA	M	20-29	50	LBM: 59,6kg (6,5)
		W	20-29	56	LBM: 40,6kg (3,6)
Later 2010	DXA	M	20-29	26	MM: 31,6kg (3,7)
		W	20-29	37	MM: 21,7kg (2,9)

Leahy 2012	DXA	M	20-29	236	FFM: 66,1kg (6,8)
		W	20-29	167	FFM: 44,2kg (4,6)
Oliveira 2011	DXA	W	20-29	349	FFM: 38,2kg (4,5)
					AMM: 16,8kg (2,5)
Rico 1994	DXA	M	20-29	45	LBM: 54,1kg (4,9)
		W	20-29	36	LBM: 36,6kg (4)
Seijo 2007	DXA	M	20-30	25	LBM: 56,5kg (3,5)
			30-39	15	LBM: 52,7kg (3,9)
Svendsen 1995	DXA	W	20-29	59	LBM: 43,4kg (4,5)
Sanada 2010	DXA	M	20-39	266	AMM: 26,1kg (3,1)
		W	20-39	263	AMM: 17,5kg (2,3)
Tanko 2002	DXA	W	20-29	97	AMM: 19,4kg (2,3)
					AMM (height): 6,8kg/m² (0,7)
					LBM: 43,4kg (4,3)
					LBM (height): 15,3kg/m² (1,3)
Gaba 2014	BIA	W	20-29	962	FFM: 46,6kg (5,3)
			30-39	113	FFM: 46,5kg (5,7
Gilder 2014	BIA	M	20-29	23	FFM: 63,5kg (5,5)
Leahy 2012	BIA	M	20-29	236	FFM: 66,7kg (6,4)
		W	20-29	167	FFM: 46,2kg (4)
Pichard 2000	BIA	M	25-34	503	FFM: 61,1kg (6,3)
		W		425	FFM: 43,7kg (4,4)
Schutz 2002	BIA	M	20-29	1088	FFM: 59,4kg (5,5)
		W	20-29	1019	FFM: 42,7kg (4)
Strugnell 2014	BIA	M	25-34	507	MM: 33,2kg (3,7)
					FFM: 63,3kg (6,1)
		W		626	MM:23kg (3,1)
					FFM: 41,6kg (4,5)

Table 1: Study, measuring instrument and participant characteristics for studies reporting normative values for maximal handgrip strength.

Figures 5 and 6 visualize the cut-off scores that were recommended by international

consensus statements.

Cutoff consensus statements for Women		
EWGSOP	ALM/h^2 [kg.m^{-2}]	**5,50 - 5,67**
EWGSOP2	ASM [kg]	**15**
	ASM/height^2 [kgm^{-2}]	**6**
IWGS	ALM/h^2 [kg.m^{-2}]	**5,67**
FNIH	ALM [kg]	**15,02**
	ALM/BMI [m^2]	**0,512**
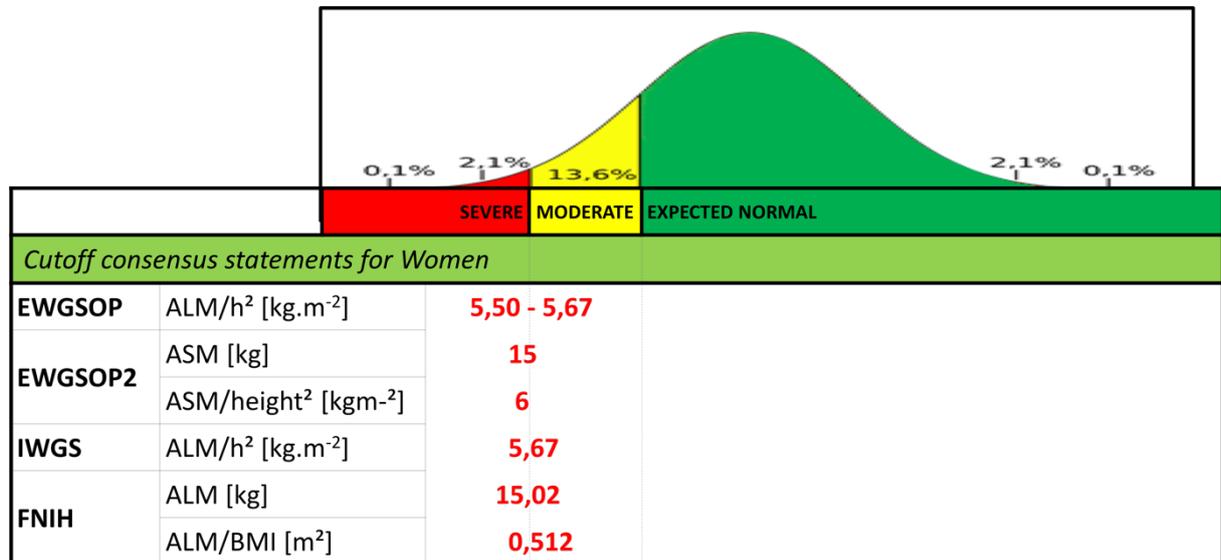
Figure 5: Cut-off scores of EWGSOP1&2, IWGS and FNIH in men

Cutoff consensus statements for Women		
EWGSOP	ALM/h^2 [kg.m^{-2}]	**5,50 - 5,67**
EWGSOP2	ASM [kg]	**15**
	ASM/height^2 [kgm^{-2}]	**6**
IWGS	ALM/h^2 [kg.m^{-2}]	**5,67**
FNIH	ALM [kg]	**15,02**
	ALM/BMI [m^2]	**0,512**
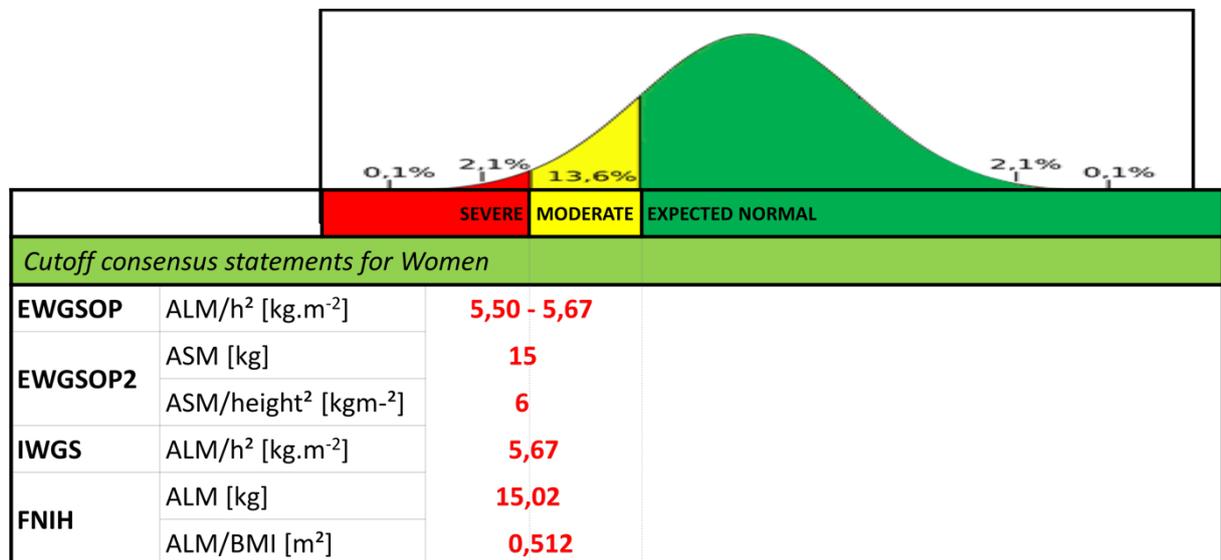
Figure 6: Cut-off scores of EWGSOP1&2, IWGS and FNIH in women

4. Recommendation

We want to warn clinicians that **different components of body composition** are described in literature to estimate muscle mass in the context of sarcopenia. These depend on the techniques and devices that have been used, for example Dual-energy X-Ray absorptiometry (lean body mass, appendicular lean mass) or Bioelectrical impedance analysis (fat free mass (including bone), lean body mass (excluding bone)).

For estimating the muscle mass in the context of sarcopenia, we recommend to use **relative indices** (height, body weight); e.g. appendicular lean mass (ALM, assessed by DXA or BIA) corrected by height² or BMI. For clinical routine, we do not recommend to use other types of medical imagery.

We recommend the use of **cut-off values for relative muscle mass** that are proposed by the **international working groups on sarcopenia** (EWGSOP2 [31], FNIH [1], IWGS [32]).

There are no side effects reported in the retrieved evidence.

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6. Appendix

APPENDIX 1 – Full search strategy

Pubmed: (((((((("Adipose Tissue"[Mesh]) OR "Body Composition"[Mesh])) OR ((((((("fat free mass") OR "lean body mass") OR "intramyocellular lipids") OR "adipose tissue") OR "intermuscular fat") OR "intramuscular fat") OR "muscle mass"))) AND "Reference Values"[Mesh]))

ASSESSMENT

-

PHYSICAL PERFORMANCE

-

BVGG-SBGG

Belgian Society for GERONTOLOGY and GERIATRICS

1. Introduction

The assessment of usual gait speed is interpreted in the context of the prevention and treatment of sarcopenia and thus usual gait speed primarily drives clinical action, rather than the diagnosis of sarcopenia. In line with the T-scores of bone mineral density assessments in osteoporosis, this work aims to present new cut-off scores for usual gait speed, based on normative data of young and healthy people, acquired from a systematic umbrella review (i.e. review of reviews) with meta-analyses.

2. Methods

2.1. Search strategy and selection criteria

The PRISMA guidelines were followed in the conduction and reporting of this review [1]. Pubmed was searched systematically for systematic reviews aiming at reporting reference values for gait speed from the earliest date available until 30/07/2015 (full search strategy in APPENDIX 1).

2.2. Study selection

Systematic reviews reporting data of usual or self-selected overground gait speed in young and healthy subjects (18-39 years) were included. Studies investigating reference values for gait speed on treadmill or in people with musculoskeletal, neurological, cardiovascular or respiratory diseases were excluded. Studies reporting data on heterogeneous groups regarding age (age below 18 or above 39) were also excluded.

Duplicate selection was done by two reviewers (B.C., D.C.A.), blinded for each other's results by using the Rayyan web application for systematic reviews [2]. Disagreements were resolved by a third reviewer or by a consensus-based discussion.

2.3. Data extraction and methodological quality assessment

Data extraction was completed by one reviewer and verified by a second reviewer using a data extraction form based on a template provided by the Cochrane Collaboration [3]. The following key characteristics were extracted: primary source (first author and publication year), population characteristics (sex, age category), gait speed measuring instrument, sample size, usual gait speed (mean and standard deviation). No assumptions were made on missing or unclear data. To organize the evidence, one investigator systematically synthesized each article in a data table.

Methodological quality of the studies was performed by one reviewer and verified by a second reviewer using the AMSTAR tool, a measurement tool to asses methodological quality of systematic reviews [4].

Meta-analyses were performed for usual gait speed by using RevMan 5.3 (Review Manager [computer program], version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). A random effect model was used to account for heterogeneity among studies. To investigate heterogeneity, subgroup analysis was performed for sex. Forrest plots were generated for the graphical presentation of the outcomes. All gait speed data was converted to m/s. Standard error (SE) was calculated as SE=Standard Deviation)/$\sqrt{(N)}$. Based on the pooled estimate and related confidence interval, the pooled standard deviation (SD_{pooled}) was calculated by using the Welch-Satterthwaite equation for pooled degrees of freedom [5, 6]. Finally, based on the pooled gait speed and SD_{pooled}, cut-off scores (T-scores) were calculated: T_{-1}=pooled gait speed – SD_{pooled} and T_{-2}= pooled gait speed – $2xSD_{pooled}$.

3. Results

A total of 60 systematic reviews were initially screened for eligibility of which 2 were further analyzed (figure 1) [7, 8]. AMSTAR scores of both reviews are presented in figure 2. A total of 21 unique primary studies that investigated gait speed in young and healthy subjects were reported in the systematic reviews of which most studies (n=19) used distance-limited walk test protocols ranging from 3 to 40m [9-28]. Two studies used timed-limited walk test protocols (6-minute walk test) [29, 30]. Based on the high number of studies using distance-limited walk test protocols and since these tests are time-efficient and easy-to-use in clinical practice, meta-analysis was performed on data from these studies.

Figure 1 - PRISMA Flowchart

Figure 2 – AMSTAR scores of included reviews

Author	Measuring instrument	Sex	Age	n	Usual gait speed (m/s)
Alameri 2009	6mWT	women		111	1,1 (0,1)
Alameri 2009	6mWT	men		127	1,2 (0,1)
Tsang 2005	6mWT	men	30-39	78	1,8 (0,3)
Tsang 2005	6mWT	women	20-29	85	1,7 (0,2)
Tsang 2005	6mWT	women	30-39	108	1,7 (0,2)
Tsang 2005	6mWT	men	20-29	80	1,8 (0,3)
Al-Obaidi 2003	Dist (3m-30m)	women	20-29	15	1,1 (0,1)
Al-Obaidi 2003	Dist (3m-30m)	men	20-29	15	1,2 (0,2)
Ble 2005	Dist (3m-30m)	women	20-29	24	1,3 (0,2)
Blanke 1989	Dist (3m-30m)	men	30-39	12	1,3 (0,2)
Ble 2005	Dist (3m-30m)	men	20-29	27	1,3 (0,2)
Ble 2005	Dist (3m-30m)	women	30-39	32	1,3 (0,2)
Bohannon 1997	Dist (3m-30m)	women	20-29	22	1,4 (0,2)
Ble 2005	Dist (3m-30m)	men	30-39	30	1,4 (0,2)
Bohannon 1997	Dist (3m-30m)	men	20-29	15	1,4 (0,2)
Bohannon 1997	Dist (3m-30m)	women	30-39	23	1,4 (0,1)
Bohannon 1997	Dist (3m-30m)	men	30-39	13	1,5 (0,1)
Busse 2006	Dist (3m-30m)	men	30-39	11	1,5 (0,2)
Button 2005	Dist (3m-30m)	men	30-39	14	1,4 (0,1)
Busse 2006	Dist (3m-30m)	women	20-29	15	1,5 (0,2)
Busse 2006	Dist (3m-30m)	women	30-39	14	1,4 (0,2)
Button 2005	Dist (3m-30m)	men	20-29	17	1,5 (0,1)
Button 2005	Dist (3m-30m)	women	20-29	22	1,4 (0,3)
El Haber 2008	Dist (3m-30m)	women	20-29	22	1,3 (0,2)
El Haber 2008	Dist (3m-30m)	women	30-39	31	1,3 (0,2)
Delval 2006	Dist (3m-30m)	men	20-29	11	1,4 (0,1)
Hageman 1986	Dist (3m-30m)	women	30-40	13	1,6 (0,2)
Goble 2003	Dist (3m-30m)	men	20-29	20	1,4 (0,2)
Haghani 2000	Dist (3m-30m)	men	20-29	10	1,4 (0,3)
Hansen 2004	Dist (3m-30m)	women	20-29	12	1,4 (0,2)
Hollman 2007	Dist (3m-30m)	women	20-29	10	1,4 (0,1)
Laufer 2003	Dist (3m-30m)	men	20-29	14	1,5 (0,2)
Laufer 2003	Dist (3m-30m)	women	20-29	15	1,4 (0,2)
Mills 2001	Dist (3m-30m)	men	20-29	10	1,4 (0,1)
Oberg 1993	Dist (3m-30m)	men	20-29	15	1,2 (0,1)
Lord 1996	Dist (3m-30m)	women	20-29	21	1,4 (0,2)
Lord 1996	Dist (3m-30m)	women	30-39	20	1,3 (0,2)
Oberg 1993	Dist (3m-30m)	women	20-29	15	1,2 (0,2)
Oberg 1993	Dist (3m-30m)	women	30-39	15	1,3 (0,2)
Oberg 1993	Dist (3m-30m)	men	30-39	15	1,3 (0,2)
Rogers 2005	Dist (3m-30m)	women	20-29	10	1,4 (0,2)
Wilken 2012	Dist (3m-30m)	men		130	1,5 (0,2)
Wilken 2012	Dist (3m-30m)	women		50	1,5 (0,1)
Auvinet 2002	Dist (40m)	women	20-29	25	1,5 (0,1)
Auvinet 2002	Dist (40m)	men	30-39	26	1,5 (0,1)
Auvinet 2002	Dist (40m)	women	30-39	27	1,6 (0,1)
Auvinet 2002	Dist (40m)	men	20-29	24	1,6 (0,1)

Table 1: Study, measuring instrument and participant characteristics for studies reporting normative values for gait speed.

Study or Subgroup	Gait speed	SE	Weight	Gait speed IV, Random, 95% CI	Gait speed IV, Random, 95% CI
Al-Obaidi 2003 (men 20)	1.217	0.051	2.3%	1.22 [1.12, 1.32]	
Al-Obaidi 2003 (women 20)	1.082	0.038	2.5%	1.08 [1.01, 1.16]	
Auvinet 2002 (men 20)	1.6	0.027	2.6%	1.60 [1.55, 1.65]	
Auvinet 2002 (men 30)	1.5	0.024	2.6%	1.50 [1.45, 1.55]	
Auvinet 2002 (women 20)	1.5	0.024	2.6%	1.50 [1.45, 1.55]	
Auvinet 2002 (women 30)	1.6	0.021	2.7%	1.60 [1.56, 1.64]	
Blanke 1989 (men 30)	1.3	0.052	2.3%	1.30 [1.20, 1.40]	
Ble 2005 (men 20)	1.31	0.038	2.5%	1.31 [1.24, 1.38]	
Ble 2005 (men 30)	1.375	0.033	2.5%	1.38 [1.31, 1.44]	
Ble 2005 (women 20)	1.266	0.044	2.4%	1.27 [1.18, 1.35]	
Ble 2005 (women 30)	1.256	0.027	2.6%	1.26 [1.20, 1.31]	
Bohannon 1997 (men 20)	1.393	0.04	2.4%	1.39 [1.31, 1.47]	
Bohannon 1997 (men 30)	1.458	0.026	2.6%	1.46 [1.41, 1.51]	
Bohannon 1997 (women 20)	1.407	0.037	2.5%	1.41 [1.33, 1.48]	
Bohannon 1997 (women 30)	1.415	0.026	2.6%	1.42 [1.36, 1.47]	
Busse 2006 (men 30)	1.538	0.048	2.3%	1.54 [1.44, 1.63]	
Busse 2006 (women 20)	1.499	0.049	2.3%	1.50 [1.40, 1.60]	
Busse 2006 (women 30)	1.381	0.063	2.1%	1.38 [1.26, 1.50]	
Button 2005 (men 20)	1.474	0.033	2.5%	1.47 [1.41, 1.54]	
Button 2005 (men 30)	1.432	0.036	2.5%	1.43 [1.36, 1.50]	
Button 2005 (women 20)	1.448	0.054	2.2%	1.45 [1.34, 1.55]	
Delval 2006 (men 20)	1.353	0.028	2.6%	1.35 [1.30, 1.41]	
El Haber 2008 (women 20)	1.3	0.032	2.5%	1.30 [1.24, 1.36]	
El Haber 2008 (women 30)	1.3	0.038	2.5%	1.30 [1.23, 1.37]	
Goble 2003 (men 20)	1.38	0.036	2.5%	1.38 [1.31, 1.45]	
Hageman 1986 (women 30)	1.6	0.044	2.4%	1.60 [1.51, 1.69]	
Haghani 2000 (men 20)	1.44	0.079	1.8%	1.44 [1.29, 1.59]	
Hansen 2004 (women 20)	1.37	0.064	2.1%	1.37 [1.24, 1.50]	
Hollman 2007 (women 20)	1.387	0.04	2.4%	1.39 [1.31, 1.47]	
Laufer 2003 (men 20)	1.465	0.049	2.3%	1.47 [1.37, 1.56]	
Laufer 2003 (women 20)	1.445	0.043	2.4%	1.45 [1.36, 1.53]	
Lord 1996 (women 20)	1.38	0.035	2.5%	1.38 [1.31, 1.45]	
Lord 1996 (women 30)	1.32	0.038	2.5%	1.32 [1.25, 1.39]	
Mills 2001 (men 20)	1.41	0.04	2.4%	1.41 [1.33, 1.49]	
Oberg 1993 (men 20)	1.23	0.028	2.6%	1.23 [1.18, 1.28]	
Oberg 1993 (men 30)	1.32	0.039	2.5%	1.32 [1.24, 1.40]	
Oberg 1993 (women 20)	1.24	0.044	2.4%	1.24 [1.15, 1.33]	
Oberg 1993 (women 30)	1.28	0.049	2.3%	1.28 [1.18, 1.38]	
Rogers 2005 (women 20)	1.35	0.05	2.3%	1.35 [1.25, 1.45]	
Wilken 2012 (men 2030)	1.5	0.015	2.7%	1.50 [1.47, 1.53]	
Wilken 2012 (women 2030)	1.5	0.02	2.7%	1.50 [1.46, 1.54]	
Total (95% CI)			**100.0%**	**1.39 [1.36, 1.43]**	

Heterogeneity: Tau² = 0.01; Chi² = 497.04, df = 40 (P < 0.00001); I² = 92%
Test for overall effect: Z = 74.98 (P < 0.00001)

Figure 3: Forest plot for usual gait speed of young and healthy subjects, based on distance-limited walk tests

Based on data of 882 subjects, a pooled usual gait speed of 1.39 m/s (95% confidence interval (CI) [1.36, 1.43]) was calculated (see forest plot in figure 3). Heterogeneity was found high (I^2=92%) but was not explained by sex (see appendix 2).

Subsequently, based on the pooled estimate, the pooled standard deviation was calculated (i.e. 0.28) and consequently, the cut-off scores (T-scores) were defined (1.1m/s (T_{-1}), 0.8m/s (T_{-2})).

Figures 5 visualizes the calculated cut-off scores for both men and women respectively compared to the cut-off scores that were recommended by international consensus statements.

	Severe	Moderate	Expected normal		
Reference data [ms^{-1}]	0,8	1,1	1,4		
Cutoff consensus statements					
EWGSOP 1 & 2 [ms^{-1}]	0,8				
IWGS [ms^{-1}]		1,0			
FNIH [ms^{-1}]	0,8				
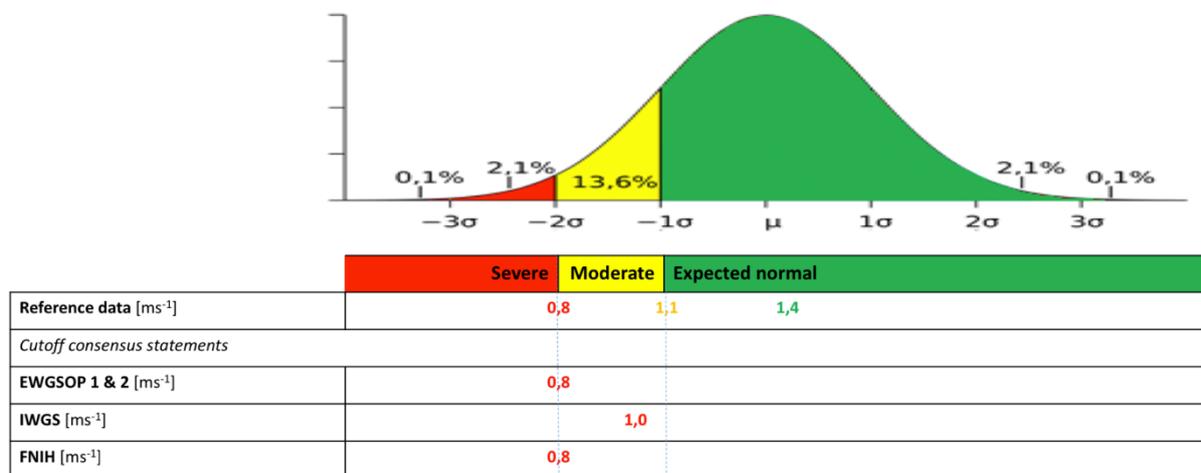
Figure 5: T_{-1} and T_{-2} cut-off scores, compared to the cut-off scores of EWGSOP 1&2, IWGS and FNIH

4. Recommendation

At this moment, best evidence is available for using **gait speed** to appraise physical performance in a clinical setting. Since for gait speed, robust normative values are available, we recommend the use of gait speed to assess physical performance.

Different protocols exist to asses gait speed and we recommend the **4m usual gait speed** protocol since this is considered most feasible in a clinical setting.

We recommend the use of cut-off values for gait speed that are based on reference values of healthy young people to drive clinical actions. Cut-off scores are 1.1m/s (T_{-1}) and 0.8m/s (T_{-2}).

There are no side effects reported in the retrieved evidence.

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6. Appendix

APPENDIX 1 – Full search strategy

Pubmed: (((((walk*[Text Word]) OR gait[Text Word]) OR (("Walking"[Mesh]) OR "Gait"[Mesh]))) AND ((((((("Reference Values"[Mesh]) OR Reference value*[Text Word]) OR reference range*[Text Word]) OR normative research[Text Word]) OR normative standard*[Text Word]) OR normative data[Text Word]) OR normative score*[Text Word]) OR normal range*[Text Word])) AND (("Review"[Publication Type]) OR "Meta-Analysis"[Publication Type])

APPENDIX 2 – Subgroup analyses

Study or Subgroup	Gait speed	SE	Weight	Gait speed IV, Random, 95% CI
10.1.1 Men				
Al-Obaidi 2003 (men 20)	1.217	0.051	2.3%	1.22 [1.12, 1.32]
Auvinet 2002 (men 20)	1.6	0.027	2.6%	1.60 [1.55, 1.65]
Auvinet 2002 (men 30)	1.5	0.024	2.6%	1.50 [1.45, 1.55]
Blanke 1989 (men 30)	1.3	0.052	2.3%	1.30 [1.20, 1.40]
Ble 2005 (men 20)	1.31	0.038	2.5%	1.31 [1.24, 1.38]
Ble 2005 (men 30)	1.375	0.033	2.5%	1.38 [1.31, 1.44]
Bohannon 1997 (men 20)	1.393	0.04	2.4%	1.39 [1.31, 1.47]
Bohannon 1997 (men 30)	1.458	0.026	2.6%	1.46 [1.41, 1.51]
Busse 2006 (men 30)	1.538	0.048	2.3%	1.54 [1.44, 1.63]
Button 2005 (men 20)	1.474	0.033	2.5%	1.47 [1.41, 1.54]
Button 2005 (men 30)	1.432	0.036	2.5%	1.43 [1.36, 1.50]
Delval 2006 (men 20)	1.353	0.028	2.6%	1.35 [1.30, 1.41]
Goble 2003 (men 20)	1.38	0.036	2.5%	1.38 [1.31, 1.45]
Haghani 2000 (men 20)	1.44	0.079	1.8%	1.44 [1.29, 1.59]
Laufer 2003 (men 20)	1.465	0.049	2.3%	1.47 [1.37, 1.56]
Mills 2001 (men 20)	1.41	0.04	2.4%	1.41 [1.33, 1.49]
Oberg 1993 (men 20)	1.23	0.028	2.6%	1.23 [1.18, 1.28]
Oberg 1993 (men 30)	1.32	0.039	2.5%	1.32 [1.24, 1.40]
Wilken 2012 (men 2030)	1.5	0.015	2.7%	1.50 [1.47, 1.53]
Subtotal (95% CI)			46.6%	1.41 [1.36, 1.45]
Heterogeneity: Tau² = 0.01; Chi² = 184.35, df = 18 (P < 0.00001); I² = 90%				
Test for overall effect: Z = 58.42 (P < 0.00001)				
10.1.2 Women				
Al-Obaidi 2003 (women 20)	1.082	0.038	2.5%	1.08 [1.01, 1.16]
Auvinet 2002 (women 20)	1.5	0.024	2.6%	1.50 [1.45, 1.55]
Auvinet 2002 (women 30)	1.6	0.021	2.7%	1.60 [1.56, 1.64]
Ble 2005 (women 20)	1.266	0.044	2.4%	1.27 [1.18, 1.35]
Ble 2005 (women 30)	1.256	0.027	2.6%	1.26 [1.20, 1.31]
Bohannon 1997 (women 20)	1.407	0.037	2.5%	1.41 [1.33, 1.48]
Bohannon 1997 (women 30)	1.415	0.026	2.6%	1.42 [1.36, 1.47]
Busse 2006 (women 20)	1.499	0.049	2.3%	1.50 [1.40, 1.60]
Busse 2006 (women 30)	1.381	0.063	2.1%	1.38 [1.26, 1.50]
Button 2005 (women 20)	1.448	0.054	2.2%	1.45 [1.34, 1.55]
El Haber 2008 (women 20)	1.3	0.032	2.5%	1.30 [1.24, 1.36]
El Haber 2008 (women 30)	1.3	0.038	2.5%	1.30 [1.23, 1.37]
Hageman 1986 (women 30)	1.6	0.044	2.4%	1.60 [1.51, 1.69]
Hansen 2004 (women 20)	1.37	0.064	2.1%	1.37 [1.24, 1.50]
Hollman 2007 (women 20)	1.387	0.04	2.4%	1.39 [1.31, 1.47]
Laufer 2003 (women 20)	1.445	0.043	2.4%	1.45 [1.36, 1.53]
Lord 1996 (women 20)	1.38	0.035	2.5%	1.38 [1.31, 1.45]
Lord 1996 (women 30)	1.32	0.038	2.5%	1.32 [1.25, 1.39]
Oberg 1993 (women 20)	1.24	0.044	2.4%	1.24 [1.15, 1.33]
Oberg 1993 (women 30)	1.28	0.049	2.3%	1.28 [1.18, 1.38]
Rogers 2005 (women 20)	1.35	0.05	2.3%	1.35 [1.25, 1.45]
Wilken 2012 (women 2030)	1.5	0.02	2.7%	1.50 [1.46, 1.54]
Subtotal (95% CI)			53.4%	1.38 [1.32, 1.44]
Heterogeneity: Tau² = 0.02; Chi² = 307.94, df = 21 (P < 0.00001); I² = 93%				
Test for overall effect: Z = 48.04 (P < 0.00001)				
Total (95% CI)			100.0%	1.39 [1.36, 1.43]
Heterogeneity: Tau² = 0.01; Chi² = 497.04, df = 40 (P < 0.00001); I² = 92%				
Test for overall effect: Z = 74.98 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.53, df = 1 (P = 0.47), I² = 0%				

INTERVENTION

-

PHARMACOLOGY

-

BVGG-SBGG

Belgian Society
for GERONTOLOGY
and GERIATRICS

1. Publication details and abstract

This paper was published as

"Pharmacological Interventions to Improve Muscle Mass, Muscle Strength and Physical Performance in Older People: An Umbrella Review of Systematic Reviews and Meta-analyses"

by

De Spiegeleer A, Beckwée D, Bautmans I, Petrovic M; *On behalf of the Sarcopenia Guidelines Development group of the Belgian Society of Gerontology and Geriatrics (BSGG)*

in

Abstract

Background

Sarcopenia, defined as the pathological decline in muscle mass, muscle strength and physical performance with ageing, has become one of the geriatric giants because of its increasing prevalence and devastating health effects. The Belgian Society of Gerontology and Geriatrics (BSGG) is currently developing evidence based guidelines in the prevention and therapy of sarcopenia, which can be used in broad clinical practice. This systematic review summarizes the results of the working group on Pharmacology.

Objective

The objective is to provide an evidence-based overview of the possible pharmacological interventions for sarcopenia with a focus on the interventions that are already studied in systematic reviews or meta-analyses.

Methods

We used the method of a systematic umbrella-review. Using the electronic databases PUBMED and WEB OF SCIENCE, we identified systematic reviews and meta-analyses which assessed the effect of pharmacological interventions on criteria for sarcopenia in subjects aged 65 years and over. Study selection, quality assessment and data extraction were performed by two independent reviewers.

Results

A total of 7 systematic reviews or meta-analyses were identified, encompassing 10 pharmacological interventions: combined estrogen-progesteron, dehydroepiandrosterone, growth hormone, growth hormone releasing hormone, combined testosterone-growth hormone, insulin-like growth factor 1, pioglitazone and angiotensin converting enzyme inhibitors. Of important note is that very few systematic reviews or meta-analyses clearly mentioned baseline status of sarcopenia. Therefore our recommendations are generalised to older people, without specifying if the muscle effect is more effective in healthy, pre-sarcopenic or sarcopenic older people. Vitamin D had a significant effect on muscle strength and physical performance, especially in women with low baseline values (<25nmol/L). Adverse events were rare. Testosterone had a strong effect on muscle mass and a modest to minimal effect on muscle strength and physical performance respectively, when supplementing men with low serum levels (<200-300ng/dL). The adverse events were rare and mild. Insufficient evidence was available to recommend other pharmacological interventions.

Conclusion

Only vitamin D, especially in older women, and testosterone in older men with clinical muscle weakness and low testosterone serum levels, can be justified in daily clinical practice to improve muscle mass, muscle strength and/or physical performance.

2. Introduction

While a progressive and generalised loss of skeletal muscle mass and strength is inherent to ageing, in some older people there is an accelerated muscle decline with a high risk of adverse outcomes. Below a certain clinical threshold, this accelerated muscle decline is called sarcopenia. Sarcopenia has received increasing attention in both the research and public community. Different definitions and cut-offs exist for sarcopenia, but one of the more commonly used is from the European Working Group on Sarcopenia in Older People (EWGSOP) [1]. They recommend using the presence of both low muscle mass and low muscle function (strength or performance) for the diagnosis of sarcopenia. Consequently, diagnosis requires documentation of criterion 1 (low muscle mass) plus documentation of either criterion 2 (low muscle strength) or criterion 3 (low physical performance) [2]. Other definitions, e.g. from the International Working Group on Sarcopenia (IWGS), only need 1 or 2 from the 3 mentioned criteria to diagnose sarcopenia [1].

The *first* reason for this growing attention for sarcopenia derives from its increasing prevalence due to global human ageing. The EWGSOP points out that sarcopenia affects more than 50 million people today worldwide, and that this number will increase to more than 200 million people over the next 40 years [2]. *Secondly,* sarcopenia is a predictor of physical disability, poor quality of life and all-cause mortality, and is an important risk factor for falls in older people [3].

The underlying (patho)physiology of sarcopenia is complex and still insufficiently understood. Inflammation, hormonal dysregulation, changed neuronal activity, (epi)genetics, nutritional changes and immobility have all been shown to be involved, and are highly heterogeneous between individuals [4, 5]. As a consequence of not knowing the

exact pathophysiology, the ultimate (i.e. targeted and highly efficient) therapy for

sarcopenia does not yet exist. However, some interventions are already recognized to have a

positive effectiveness/safety profile or are currently under investigation. Three groups of

interventions can be differentiated at the moment: exercise, nutrition and pharmacological

interventions.

This clinical review presents the results of the working group on Pharmacology within the

Sarcopenia Guidelines Development group of the Belgian Society of Gerontology and

Geriatrics (BSGG) [Electronic Supplementary Material Appendix S1]. The aim is to provide an

overview of the possible pharmacological interventions targeting one or more of the three

sarcopenia-domains (muscle mass, muscle strength or physical performance) - with a focus

on the interventions that are already studied in systematic reviews or meta-analyses.

Therefore, we used the method of a systematic umbrella-review.

3. Methods

a. Search strategy and selection criteria

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for this review [6]. We systematically searched two databases (PubMed and Web of Science) from the earliest date available (1950s for PubMed, 1900 for Web of Science) until October 31st 2017. Keywords used corresponded to the PICOS design (Population: older adults; Intervention: pharmacological; Comparison: non-exposed control; Outcomes: sarcopenia; Study design: systematic review) (see full search strategies in Electronic Supplementary Material Appendix S2).

b. Study selection

Systematic reviews in English regarding the effect of pharmacological interventions on one or more of the three criteria of sarcopenia in older adults (≥ 65y), i.e. muscle mass, muscle strength or physical performance, were eligible for inclusion in the umbrella review. Original studies, editorials, letters to the editor and animal studies were excluded. Two reviewers, blinded for each other's results, screened the titles and abstracts for eligibility by using the Rayyan web application for systematic reviews [7]. Subsequently, the same reviewers screened full-text articles of studies. They resolved mutual disagreements by discussion.

c. Data extraction and methodological quality assessment

Two authors completed data extraction by using a data extraction form based on a template provided by the Cochrane Collaboration. The authors extracted data regarding the key characteristics of the reviews, including: participants, pharmacological treatment, outcomes assessed. No assumptions were made on missing or unclear data. Besides sarcopenia-related outcomes (muscle mass, muscle strength, physical performance), the authors also considered adverse effects.

Two reviewers assessed methodological quality of the studies by using the 'Assessment of multiple systematic reviews' (AMSTAR) [8]. This 11-item tool assesses the degree to which review methods avoided bias. The reviewers rated methodological quality as high (score 8-11), moderate (score 4-7) or low (score 0-3). However, they did not perform quality assessment of included studies within reviews.

To organise the evidence, one investigator systematically synthesized each review's extracted data, resulting in statements for all reviews mapped to that intervention. In addition, two investigators with clinical experience then developed independently an overall synthesis, beyond a simple summary of the main results of each review. We considered these overall syntheses 'bottom line statements' about the main effect of interventions within each intervention. The two investigators resolved mutual disagreements by discussion or by consulting a third investigator. Finally, we assigned a rating of the quality of the evidence (1 very low - 2 low - 3 moderate - 4 high) supporting each bottom line statement by using a method that is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for primary evidence [9]. The methods takes into account the 'study design' (meta-analysis yes/no) and the ratings of the quality of evidence of the included systematic reviews (AMSTAR) (see Figure 1).
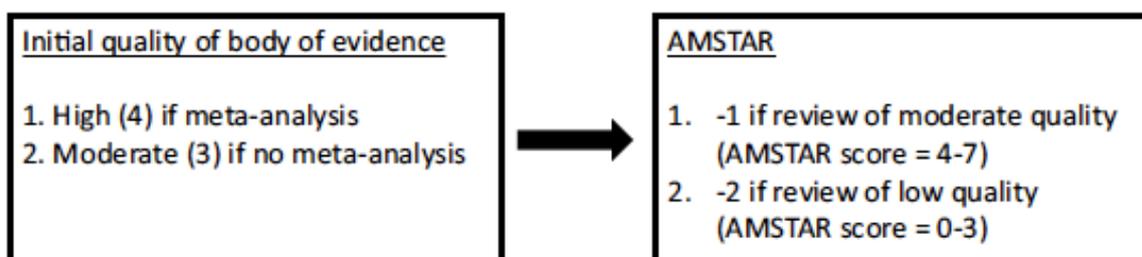
Figure 1: Method used to rate the quality of the evidence supporting each 'bottom line' statement. AMSTAR: Assessment of multiple systematic reviews [8].

4. Results and discussion
a. Included studies

We screened a total of 460 studies for eligibility (Figure 2). After screening the title and

abstract, we excluded 446 studies. Eventually, we included 7 systematic reviews [10-16].

AMSTAR scores varied between 1 [12] and 8 [13] (Figure 3).
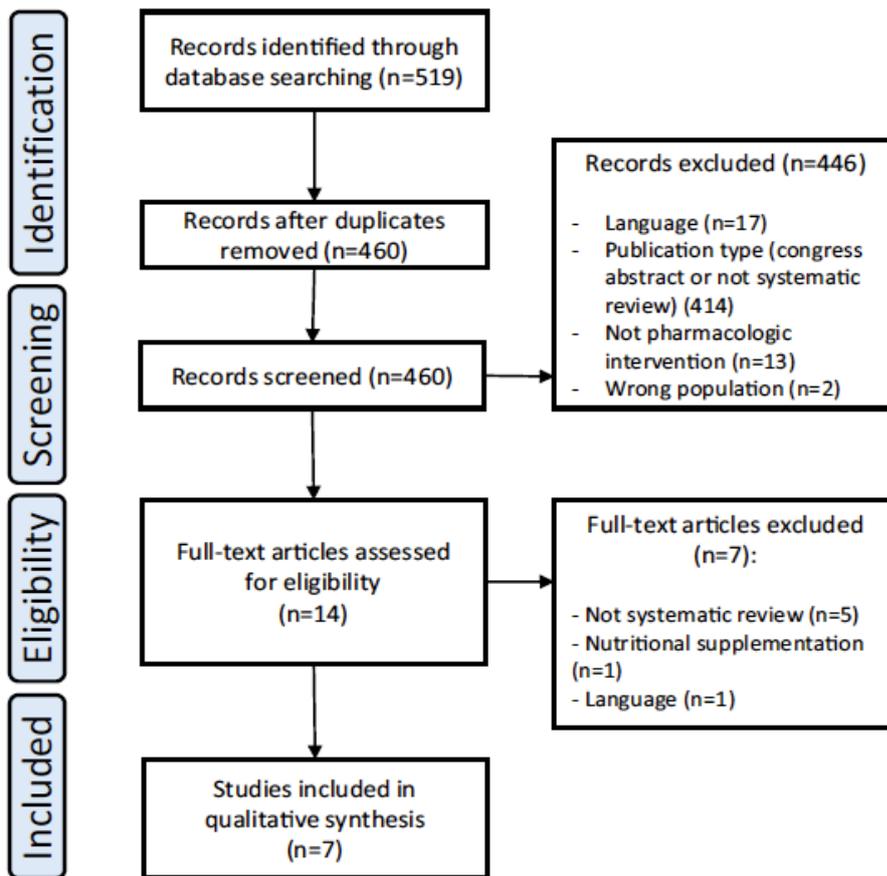
Figure 2: PRISMA flow-chart.

The reviews investigated the effect of the following pharmacological interventions: angiotensin-converting enzyme inhibitors [16], vitamin D [10, 15], beta-estradiol combined with cyclic norethisterone acetate [14], dehydroepiandrosterone (DHEA) [11], growth hormone [11], insulin-like growth factor 1 (IGF 1) [11], pioglitazone [14], testosterone [11-13], testosterone combined with growth hormone [11]. Table 1 presents an overview of all included articles.

	1. Was an 'a priori' design provided?	2. Was there duplicate study selection and data extraction?	3. Was a comprehensive literature search performed?	4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	5. Was a list of studies (included and excluded) provided?	6. Were the characteristics of the included studies provided?	7. Was the scientific quality of the included studies assessed and documented?	8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	9. Were the methods used to combine the findings of studies appropriate?	10. Was the likelihood of publication bias assessed?	11. Was the conflict of interest included?
Anagnostis et al. [10]	−	?	−	?	−	+	+	+	?	−	−
Beaudart et al. [15]	+	+	+	−	−	+	+	+	?	?	−
Borst [11]	−	?	−	?	−	+	−	+	?	−	−
O'Connell et al. [12]	−	?	−	−	−	+	−	−	?	−	−
Ottenbacher et al. [13]	−	−	+	+	−	+	+	+	+	+	+
Poggiogalle et al. [14]	−	?	−	−	−	+	+	−	?	−	−
Zhou et al. [16]	+	+	+	−	−	+	+	+	+	−	−

Figure 3: AMSTAR scores. Legend: Red: no; yellow: can't answer/not applicable; green: yes;
AMSTAR: Assessment of multiple systematic reviews [8].

Table 1: Results of individual Reviews

| Reference	Outcome					N° of Studies included (participants)	Results/findings (outcomes are underlined)	Comments
	S	MM	MS	FP	AE			
Angiotensin converting enzyme inhibitors								
Zhou et al. [16]			x			3 St (499)	-"Grip strength was not significantly different (-0.67, 95 % CI: -1.53 to 0.19; P = 0.12) between ACEIs and placebo or other antihypertensives"	-"Sumukadas2014 had also exercise in the intervention and control associated, but they did not show a significant effect from ACEIs; the reasons for the non-significant results may relate to the short intervening time and limitations of this meta-analysis."
Zhou et al. [16]				x		3 St (337)	-"ACEIs could not significantly improve 6-min walk distance (13.45%, 95 % CI: -16.71 to 43.61; P = 0.38) versus placebo or other antihypertensives""	'-"Sumukadas2014 had also exercise in the intervention and control associated, but they did not show a significant effect from ACEIs; the reasons for the non-significant results may relate to the short intervening time and limitations of this meta-analysis."
Beta-estradiol + cyclic norethisterone acetate								
Poggiogalle et al. [14]		x				1 St (16)	Lean Body Mass: Before intervention: I vs. C: 38.8 kg vs. 39.0 kg (P=0.27) After intervention I vs. C: +0.347 ± 0.858 kg vs. -0.996 ± 1.58 kg (p<0.05) I= "Beta-estradiol (4 mg for 22 days and 1 mg for 6 days) + cyclic norethisterone acetate (1 mg for 10 days); Two 12-week periods separated by a 3-month washout "	Beta-estradiol (4 mg for 22 days and 1 mg for 6 days) + cyclic norethisterone acetate (1 mg for 10 days); Two 12-week periods separated by a 3-month washout
Dehydroepiandrosterone								
Borst [11]			x			G+6:12growth hormone	"No changes were found in a variety of measures of muscle strength." "Small increases in strength were observed in men, but not women."	
Growth hormone								
Borst [11]		x				2 St (?)	- "increase in fat-free mass" - "GH administration improved body composition: 2.4 kg loss of fat mass and a 3.7 kg increase in non-fat mass."	
Borst [11]			x			2 St (?)	- "was not accompanied by an increase in strength." - "...the addition of GH to the training regimen produced no greater strength gains." - "elderly men participating in a 12-week resistance exercise training programme achieved similar strength gains with or without GH replacement" - "the addition of GH to the training regimen produced no greater strength gains."	

Borst [11]					x	6 St (?)	- "Researchers have reported high incidences of adverse effects from GH administration in elderly subjects, including <u>fluid retention</u>, <u>gynaecomastia</u>, <u>orthostatic hypotension</u>, <u>carpal tunnel compression</u>, <u>lower body oedema</u> and <u>general malaise."</u>- "... a drop-out rate of 43%, compared with only 9% in the placebo group. The most common symptoms were <u>carpal tunnel syndrome</u>, <u>gynaecomastia</u> and <u>hyperglycaemia."</u>- "High incidences of <u>carpal tunnel compression</u>, <u>fluid retention</u> and <u>arthralgia."</u>- "<u>Insulin secretion</u> during glucose tolerance testing was increased three-fold" - "Authors also noted that GH causes <u>fluid retention</u>"- "<u>Adverse events</u> were no more common in the treatment group than in controls; however, the lack of serious side-effects may have been due to the short 2-week duration of the study"	
Growth hormone releasing hormone								
Borst [11]		x				1 St (?)	- "They found improved nitrogen balance in both sexes and increased <u>muscle mass</u> in men only."	
Borst [11]			x			1 St (?)	- "<u>Strength</u> was moderately increased in some exercises, but not in others in a longitudinal study without a control group"	
Borst [11]					x	2 St (?)	- "No significant <u>adverse effects</u> were observed." - "The only adverse effect noted was <u>transient hyperlipidaemia</u>, which was resolved by the end of the study."	
IGF 1								
Borst [11]			x			1 St (?)	"Compared to placebo, <u>grip strength </u>was increased and generally, IGF-I/IGFBP-3 was well tolerated."	
Pioglitazone								
Poggiogalle et al. [14]		x				1 St (81)	Lean Body Mass (I vs. C) Before intervention - women: 48.8±1.6 kg vs. 47.8±1.6 kg - men: 68.0±1.3 kg vs. 66.9±1.5 kg After intervention - Women: -1.9±0.3 kg vs.-2.1±0.4 kg - Men: -2.0±0.4 kg vs.-2.5±0.4 kg (P<0.05)	
Testosterone								
Borst [11]		x				9 St (?)	7 out of 9 studies showed increased <u>lean mass</u> and/or decreased fat mass.	"However, the changes in body composition have been small"

Study						N	Findings	Comments
O'Connell et al. [12]	x					16 St	- 12 out of 16 studies showed an increase in <u>lean mass</u>- "Testosterone treatment increases lean body mass in elderly men; in the minority of studies that failed to report a change, this can be explained by insufficient treatment duration, relative inaccuracy of the method to assess body composition and absence of androgen deficiency at baseline"- "Increase in lean body mass varies between 1 and 4kg over the course of testosterone treatment"	Because of the very real risks of side effects in the use of supraphysiologicaldoses of testosterone, especially in the elderly (Bhasin et al., 2005), physiological dosages remain currently the most viable treatment option.- Most impressive gains in lean body mass are seen with injectable testosterone (+4kg), in contrast to other preparations, e.g. transdermal or oral (+1-2kg).
Borst [11]		x				10 St (?)	4 out of 10 studies showed an increase in strength	
O'Connell et al. [12]		x				19 St	- 9 out of 19 studies showed an increase in <u>strength</u> - "A number of studies have reported improvement in <u>grip strength</u> of 3–5 kg following androgen treatment. Others have shown no effect of treatment on this parameter"	- "This discrepancy between studies is not adequately explained by the different gains in muscle mass and may simply reflect the variability in the performance and poor repeatability of this measurement." - there is a smaller size of effect in studies using isokinetic dynamometry techniques
Ottenbacher et al. [13]		x				11 St (474)	- <u>overall strength</u>: ES=0.53, 95% CI=[.21, .86] - <u>upper extremity strength</u>: ES=.47, 95% CI=[.12, .84] - <u>lower extremity strength</u>: ES=.63, 95% CI=[.03, 1.28]	Sensitivity analyses revealed the elimination of one study reduced the mean g-index from 0.53 to 0.23.
O'Connell et al. [12]			x			7 St	- "Studies have failed to show an improvement in a range of functional tasks including tests of <u>balance</u>, <u>gait speed</u>, <u>chair rising</u>, <u>step height</u> and <u>functional reach</u> in response to a variety of androgen treatments." - 3 out of 7 studies showed an improvement in complex functional tasks (e.g. SF36 physical function scale)	"The combination of low test sensitivity and small changes in strength may largely explain the lack of effect of testosterone treatment on physical function."
Borst [11]				x		?	- "Risks of testosterone replacement in older men include <u>fluid retention</u>, <u>gynaecomastia</u>, worsening of <u>sleep apnoea</u>, <u>polycythaemia</u> and acceleration of benign or malignant <u>prostatic tumours</u> [14]. Amongst these risks, the potential effects of testosterone on the prostate are of the greatest concern. - "A retrospective, case-controlled study examined 45 hypogonadal men (mean age=70 years) receiving a replacement dose of testosterone over a 2-year period. Compared to controls, treated individuals had a higher incidence of <u>polycythaemia</u>, but no increase in prostate cancer."	
O'Connell et al. [12]				x		1 M.A. (?)	- <u>prostate events</u>: OR=1.78, 95%CI [1.07, 2.95] - "Testosterone is not considered to cause development of de novo <u>prostate cancer</u>" - "Testosterone treatment was also associated with increased rates of <u>haematocrit >50%</u> (dose-dependently in shorter-acting injectable preparations), but not with <u>cardiovascular events</u>, <u>sleep apnoea</u> or <u>death</u>" - "Testosterone treatment was not associated with significant changes in <u>blood pressure</u>, <u>glycaemia</u> or major <u>lipid fractions</u>" - "physiological testosterone replacement is well <u>tolerated</u> in elderly frail"	"Testosterone is not considered to cause development of de novo prostate cancer " - "the available safety data are largely based on studies in younger hypogonadal patients. However, the recent studies in elderly frail men suggest that physiological testosterone replacement is well tolerated in this group" (Srinivas-Shankar et al., 2010).

Ottenbacher et al. [13]					x	11 St (474)	- "Elevated PSA levels or prostate disease were reported in threestudies out of eleven."- "Four investigations stated that no adverse events were observed in older men receiving testosterone/DHT therapy or placebo."- Other investigations included broad statements such as worsened knee arthritis." (1 study)	
Testosterone + growth hormone								
Borst [11]		x				2 St (?)	- "Combined testosterone and GH produced a 2.7kg increase in lean mass, in healthy elderly men (mean age=68 years). - "GH reduced fat mass and increased lean mass in men and women."	- 1-month duration of treatment and no placebo group. - randomized, double-blind, placebo-controlled study lasting 26 weeks: GH and/or testosterone for men and hormone replacement therapy for women.
Borst [11]			x			2 St (?)	- "Combined testosterone and GH produced no increase in strength in healthy elderly men (mean age=68 years). - "Little if any increase in strength was observed (6% increase in men receiving GH plus testosterone only)."	- 1-month duration of treatment and no placebo group. - randomized, double-blind, placebo-controlled study lasting 26 weeks
Vitamin D								
Anagnostis et al. [10]		x				-1 M.A. (555) -1 St (21)	- Muscle mass: SMD=.058, 95%CI=[-.118, .233],p=.52 - Muscle Fibre size: 'On a molecular level, vitamin D-supplementation with 4000 IU daily for 4 months increased muscle fibre size by 10%.'	umbrella review
Beaudart et al. [15]		x				- 1 St (96)	-lean mass: "No effects of exercise alone or of exercise combined with vitamin D supplementation were observed."	Vitamin D combined with exercise (mainly resistance-type exercise)
Anagnostis et al. [10]			x			- 1 M.A. (626)	- Knee extension: SMD=.05, 95% CI=[.11, .20], P=.04	umbrella review Effect seems absent if baseline 25(OH)D concentrations > 25 nmol/L
						- 1 M.A. (2302)	- 1) Global muscle strength: SMD=.25, 95%CI=[.01, .48] -- institutionalised & hospitalised vs community dwelling: SMD 0.45 vs 0.05;P< .01 2) Grip strength: SMD=.01, 95%CI=[– 0.06, 0.07], P=.87 3) Lower limb muscle strength: SMD=.19, 95%CI=[.05 to .34], P=.01	
						- 1 R (?)	- "no significant effect of vitamin D overall, but significant improvement in strength when starting 25(OH)D≤25nmol/l"	
Beaudart et al. [15]			x			- 2 St (121)	- "Both studies reported significant improvement in muscle strength with exercise but did not report any difference between the exercise-only group and the group with combined exercise and vitamin D supplementation."	Vitamin D combined with exercise (mainly resistance-type exercise)
Anagnostis et al. [10]				x		- 1 M.A. (274) - 1 M.A. (828)	- Timed Up and Go: SMD=-.19, 95%CI=[-.35, .-.02],p=.03 - Gait: "an effect on gait was not found, although the studies that evaluated gait were of lower methodological quality and used low doses of vitamin D"	umbrella review
Beaudart et al. [15]				x		- 2 St (121)	- "Physical performance increased, for some of the physical performance outcomes, in 2/2 RCTs with no additional effect of vitamin D, except for TUG in 1/2 RCTs."	Vitamin D combined with exercise (mainly resistance-type exercise)

Anagnostis et al. [10]					x	- 1 R (42 876)	- Nephrolithiasis: RR=1.17, 95%CI [1.02, 1.34], P=.02, I²=0%"in combination with calcium"	umbrella review- in combination with calcium- Vitamin D3 decreased mortality; a subgroup analysis of trials at high risk of bias suggested that vitamin D2 may increase mortality- Alfacalcidol and calcitriol increased the risk of hypercalcaemia (Vitamin D supplementation in elderly reduces also fall risk, more pronounced when supplementing up to >60nmol/l, in daily doses)
						- 1 R (75 927)	- Mortality: RR=.94 95%CI [.91 to 0.98], P=.002;I²=0%"Vitamin D3 decreased mortality; a subgroup analysis of trials at high risk of bias suggested that vitamin D2 may increase mortality"	
						- 1 R (710)	- Hypercalcaemia: RR=3.18 95%CI [1.17 to 8.68], P=.002;I²=17%"Alfacalcidol and calcitriol increased the risk of hypercalcaemia"	

ACEI: angiotensin converting enzyme inhibitors; AE: adverse events; BC: body composition; C: control; CI: confidence interval; ES: effect size; FP: functional performance; GH: growth hormone; I: intervention; IGF1: insuline-like growth factor 1; IGFBP: insulin-like growth factor-binding protein; kg: kilogram; M.A.: meta-analysis; Mg: milligram; MM: muscle mass; MS: muscle strength; n.a.: not available; nmol: nanomol; OR: odds ratio; R: review; RCT: randomized controlled trial; RR: risk ratio; S: sarcopenia; SMD: standardized mean difference; St: study; TUG: timed up and go; Vit: vitamin; vs.: versus; x: indicates the construct that is addressed: sarcopenia (as a construct) or the sarcopenia sub dimension (muscle mass, muscle strength, physical performance) or adverse events; a question mark (?) indicates that the number was not mentioned in the systematic review/meta-analysis.

It was difficult for this umbrella-review to distinguish subjects with sarcopenia from healthy subjects as most systematic reviews did not characterize the sarcopenia or frailty status of the subjects. The fact that there are no universally accepted criteria for the diagnosis of sarcopenia is probably the most important reason for this. Therefore, in this umbrella-review the conclusions are focused on elderly subjects in a broader sense.

Based on the body of evidence, bottom line statements about the main effects of each intervention- including a rating of the quality of the evidence supporting each bottom line statement- are presented in Table 2. In the text below, consideration of each pharmacological intervention starts with a recommendation based on these bottom line statements, followed by the results of our umbrella review and discussion respectively.

Table 2: Summarizing table about the main effects of interventions.

Intervention	Sarcopenia	Muscle Mass	Muscle Strength	Physical Performance	Adverse events	'Bottom line' statement	QoE
Vitamin D	Insufficient to determine	Insufficient evidence	Sufficient evidence in favour (women)	Some evidence in favour	Nephrolithiasis, hypercalcaemia	In addition to improve muscle strength and physical performance, also a significant decrease in mortality and fall risk is seen when supplementing with vitamin D. The effects are most pronounced when supplementing those with serum levels <10ng/mL. In conclusion we recommend vitamin D supplementation to improve muscle strength and physical performance in older people, especially women, with low baseline serum levels. Monitoring of the serum calcium is needed.	2
Testosterone	Insufficient to determine	Some evidence in favour (men)	Some evidence in favour (men)	Insufficient evidence	Fluid retention, gynaecomastia, worsening of sleep apnoea, polycythemia, acceleration of benign or malignant prostatic tumours; adverse events seem monitorable	Testosterone supplementation may be considered in older men with serum levels <200-300ng/dL and clinical muscle weakness, to improve muscle mass and muscle strength. Monitoring of the Hct, lipid profile and prostatic parameters is needed.	4
GH	Insufficient to determine	Some evidence in favour	Insufficient evidence	Insufficient to determine	Fluid retention, gynaecomastia, orthostatic hypotension, carpal tunnel compression, lower body oedema and general malaise	We do not recommend GH supplementation.	1
Testosterone+GH	Insufficient to determine	Some evidence in favour	Insufficient evidence	Insufficient to determine	Insufficient to determine	We do not recommend the combination of testosterone and GH.	1
GHRH	Insufficient to determine	Some evidence in favour (men)	Insufficient evidence	Insufficient to determine	Transient hyperlipidemia (1 study)	We do not recommend GHRH.	1
IGF-1	Insufficient to determine	Insufficient to determine	Some evidence in favour (women after hip fracture)	Insufficient to determine	Insufficient to determine	We do not recommend IGF-1.	1
DHEA	Insufficient to determine	Insufficient to determine	Insufficient evidence	Insufficient to determine	Insufficient to determine	We do not recommend DHEA.	1
Beta estradiol + cyclic norethisterone acetate	Insufficient to determine	Insufficient evidence	Insufficient to determine	Insufficient to determine	Insufficient to determine	We do not recommend the combination of estrogen and progesterone.	1
ACE-inhibitors	Insufficient to determine	Insufficient to determine	Insufficient evidence	Insufficient evidence	Insufficient to determine	We do not recommend ACE-inhibitors.	3
Pioglitazone	Insufficient to determine	Insufficient evidence	Insufficient to determine	Insufficient to determine	Insufficient to determine	We do not recommend pioglitazone.	1

Sufficient evidence: statistically significant pooled results (meta-analysis); Some evidence: narrative synthesis of review results (based on a majority of studies showing statistically significant results); Insufficient evidence: based on a majority of studies showing statistically non-significant effects (underpowered or no effect); Insufficient (evidence) to determine: not reported in reviews or meta-analyses (reporting gap in evidence); GH: growth hormone; GHRH: growth hormone releasing hormone; IGF-1: insulin-like growth factor 1; DHEA: dehydroepiandrosterone; ACE: angiotensin converting enzyme; QoE: quality of evidence supporting each bottom line statement (1 very low - 2 low - 3 moderate - 4 high); Hct: hematocrit.

b. Vitamin D

We recommend vitamin D supplementation to improve muscle strength and physical performance in older people, especially in older women with very low baseline levels. Monitoring of the serum calcium is needed [low quality of evidence].

Anagnostis et al. summarized the muscle effects of vitamin D supplementation in older women [10]. Although no significant effect was seen of vitamin D supplementation on muscle mass (criterion 1) (pooled standardized mean difference or SMD=0.058, 95% confidence interval (CI)=[-0.118, 0.233]), a small but significant effect was seen on muscle strength (criterion 2) (pooled SMD=0.25, 95%CI=[0.01, 0.48]) and physical performance (criterion 3) (e.g. pooled Timed Up and Go=-0.19, 95%CI=[-0.35, -0.02]). More prominent effects were seen in patients with deficient baseline vitamin D levels (<25nmol/L) and in co-administration with calcium. In addition, a significant decrease in mortality and fall risk was shown when supplementing with vitamin D. Adverse events of vitamin D supplementation described in this review were hypercalcemia (risk ratio or RR 3.18, [1.17;8.68]) and nephrolithiasis (RR 1.17, [1.02;1.34]), both rare. The meta-analysis of Beaudart et al., encompassing other clinical trials, also suggested a small but significant effect on physical performance (gait speed and Timed Up and Go), while not finding a significant effect on muscle mass or muscle strength [17, 18]. It is noteworthy that in both systematic reviews most studies concerned supplementation with the inactive forms of vitamin D, i.e. cholecalciferol (D3) or ergocalciferol (D2).

We hypothesize that the more pronounced effects on functional outcomes in contrast to the lack of effect on muscle mass could be explained by vitamin D causing mostly a gain in muscle quality instead of quantity. Indeed, recent studies suggest that activation of intracellular vitamin D receptors in muscle induces a decline of intramuscular lipids,

enhancing the muscle quality [19, 20]. A recent systematic meta-analysis of Rosendahl-Riise et al. [21], not retrieved in our search because not focusing on the syndrome of sarcopenia, found no significant effect of vitamin D supplementation on muscle strength and physical performance in older people, measured by grip strength and Timed-Up and Go Test respectively. This contrast to our results could be explained by the large heterogeneity of the studies in the meta-analysis ($I^2 \geq 95\%$) and the focus on community-dwelling older people. The heterogeneity was both on the level of patient characteristics as well as on the level of the intervention. Concerning the side-effects of vitamin D, a Cochrane systematic review of vitamin D/calcium supplementation on preventing fractures in older people, found a small but significant increase in gastrointestinal symptoms and renal disease associated with vitamin D and calcium intake, probably related to the hypercalcaemia and nephrolithiasis, in accordance with our results [22]. Interestingly high vitamin D doses (> 1000IU daily) seem to increase the risk of falling in older people [23]. It must be pointed out that most studies so far are conducted in post-menopausal women, and clinical trials in older men are lacking. In conclusion, it seems that vitamin D supplementation, especially in older women, can be beneficial to improve muscle strength or physical performance, mostly when supplementing those with very low baseline vitamin D levels (<25nmol/L), without 'oversupplementing' (< 1000IU daily). However it is clear that more subgroup analyses are needed to find the subjects with a 'good' genetic profile, sarcopenia -, and vitamin D baseline levels that take most advantage of a particular dose and duration of vitamin D/calcium supplementation, in line with the concept of personalized medicine. Indeed current studies are already focusing on subgroups analyses, e.g. the meta-analysis in community-dwelling older people from Rosendahl-Riise et al, and investigating genetic variants responsible for vitamin D status and dose-response [21, 24, 25].

c. Beta estradiol + cyclic norethisterone acetate

We do not recommend the combination of estrogen and progesterone to improve muscle mass, muscle strength or physical performance in older people (very low quality of evidence).

From the included systematic reviews, only the review of Poggiogalle et al. discussed the combination of an estrogen and progesterone [14]. They found a small but significant improvement of muscle mass after sex hormone replacement therapy in post-menopausal women. However, out of this systematic review we did not find results on muscle strength or physical performance, neither on adverse events [14].

A meta-analysis published in 2009, found a beneficial effect on muscle strength of estrogen-based treatments in postmenopausal women [26]. In contrast, a large randomized clinical trial in 2010, found no significant improvement in muscle strength or physical performance of hormone replacement therapy [27]. More subgroup analyses are needed in the future to elucidate this discrepancy.

d. Dehydroepiandrosterone (DHEA)

We do not recommend DHEA supplementation to improve muscle mass, muscle strength or physical performance in older people (very low quality of evidence).

Dehydroepiandrosterone, a steroid that can be transformed into estrogen or testosterone in the body, could possibly have some effect on muscle strength, but the results were inconclusive and data on muscle mass, physical performance and adverse events were lacking [11].

Although the only included systematic review (Borst et al.) dates from 2004, later trials and reviews not included in our umbrella review, remain inconclusive about the muscle effects of DHEA [28]. It needs to be pointed out that no randomized clinical trial of DHEA-supplementation that measures one of the three sarcopenia domains is published in the last

five years. One of the possible reasons could be the status of relatively cheap over-the-counter product of DHEA, making it less interesting for pharmaceutical companies. To make conclusions about the muscle benefits of DHEA in older people, more studies will be needed in the future.

e. Growth hormone

We do not recommend growth hormone (GH) supplementation to improve muscle mass, muscle strength or physical performance in older people (very low quality of evidence).

Borst et al. concluded that growth hormone replacement in older subjects, although increasing muscle mass, does not univocally improve muscle strength nor physical performance and has a high incidence of adverse events, making it inappropriate as a muscle intervention in older people [11]. Adverse events described were fluid retention, gynaecomastia, orthostatic hypotension, carpal tunnel compression, hyperglycaemia, arthralgia and general malaise. Borst et al. reported a drop-out rate in some clinical trials around 40% in the supplemented group vs. 10% in the placebo group, attributed to the adverse events.

A long-term clinical trial (10 years) found a mitigation of the expected age-related decline in muscle strength when supplementing GH to older people with overt pituitary disease [29]. However, this trial was not controlled and the baseline IGF-1 levels, downstream targets of growth hormone, were much lower than expected in older people without overt pituitary disease. No long-term controlled clinical trials in older people without overt pituitary disease exist to recommend growth hormone supplementation.

f. GHRH and IGF-1

We do not recommend GHRH or IGF1 supplementation to improve muscle mass, muscle strength or physical performance in older people (very low quality of evidence).

The GH/IGF-1 pathway is complex, and it may be that a better efficacy/safety profile is obtained when supplementing with other pathway molecules than growth hormone. In the systematic review of Borst et al., besides growth hormone, also growth hormone releasing hormone (GHRH) and insulin-like growth factor 1 (IGF-1) were discussed, upstream and downstream molecules from GH respectively. Muscle mass and muscle strength in some studies were found to be increased when supplementing GHRH in healthy older people, while muscle strength was increased when supplementing IGF-1 in older women after hip fracture. There were no data on physical performance. Both molecules were well tolerated and had a good safety profile, with only transient hyperlipidaemia reported [11].

Recent studies seem to confirm the potency of GHRH to combat muscle ageing in older people, and also of the related growth hormone secretagogue receptor (GHSR) agonists and ghrelin analogues [30-32]. However no firm conclusions can be made today.

g. Pioglitazone

We do not recommend pioglitazone to improve muscle mass, muscle strength or physical performance in older people (very low quality of evidence).

Poggiogalle et al. discussed the effect of pioglitazone, a peroxisome proliferator-activated receptor gamma (PPARγ) agonist, on muscle mass [14]. Although a positive significant effect was seen with pioglitazone on visceral fat loss in obese men, only a small, non-significant effect was measured on muscle mass gain in this population. Our results did not contain data on muscle strength, physical performance or adverse events.

One other randomized clinical trial, not included in the review of Poggiogalle, can be found that investigates the effects of pioglitazone on muscle outcomes in older people [33]. In accordance with our results, this study of Marsh et al. did not show a strong, univocal effect on muscle outcome: only a potentiating effect of pioglitazone on muscle power in women, but not in men, when associated with resistance training [33]. Reasons for this sex difference are not clear. It is thought that the potential positive muscle effects of pioglitazone are mediated by an improved fatty acid metabolism, a known effect of PPARγ agonists besides their hypolipidemic effect [34].

h. Testosterone

We consider testosterone supplementation a possible intervention to improve muscle mass and muscle strength in older men with low serum testosterone levels (< 200-300ng/dL) and clinical muscle weakness. Monitoring of the haematocrit, lipid profile and prostatic parameters is needed.

This is a weak recommendation based on weak evidence (expert opinion for an off-label recommendation, which may have medico-legal implications).

Based on our eligibility criteria, three systematic reviews/meta-analyses with data on testosterone supplementation targeting one or more sarcopenia domains were retained [11-13]. All of them only discussed supplementation in older men. Although a consensus exists about the clear effect on muscle mass, a less pronounced effect was seen on muscle strength and an even less effect on physical performance. The less pronounced effects on muscle strength and physical performance can be explained by insufficient treatment duration, low test sensitivity and absence of androgen deficiency at baseline. Possible

adverse events of testosterone supplementation were fluid retention, virilization, aggressive behaviour, gynaecomastia, worsening of sleep apnoea, thrombotic complications, peripheral oedema, polycythaemia, acceleration of benign or malign prostatic tumours, and a possible risk of hepatic tumours and prostate cancer. An absolute contraindication for testosterone supplementation is a hematocrit >55% [11-13, 39]. However physiological doses of testosterone supplementation both in healthy and older people with frailty were well tolerated: in most studies only a mild polycythaemia was actually seen, while not showing an increase in prostatic or cardiovascular events [11-13].

These results are in agreement with two recent large trials: the Testosterone's Effects on Atherosclerosis Progression in Aging Men or TEAAM trial and the Testosterone Trials or TTrials, where testosterone supplementation in community-dwelling healthy older men was associated with only modest improvements in physical performance and considered safe [35, 36]. Recent studies measuring cardiovascular endpoints in older men supplemented with testosterone, also suggest a beneficial cardiovascular effect when supplementing those with low levels [37, 38]. Further clinical investigations, including pharmacogenomics and other new insights from personalized medicines, are needed to select individuals who benefit most from testosterone supplementation. However, pending the results of such trials, we currently recommend for each older patient with clinical muscle weakness and low serum testosterone levels, a trial phase may be worthwhile. If no clinical effects are seen after 6 months, it is advised to stop supplementation [39]. A practical guide to start testosterone supplementation can be found in the review of De Spiegeleer et al. [39].

In this paper the authors refer to three examples of testosterone formulations for the most frequently used routes of administration as stated in the paper of Bhasin et al. [45]. (see Table 3).

Table 3: Examples of testosterone formulations for the three most frequently used routes of administration

Route of administration	Formulation	Regimen
Intramuscular	T undecanoate	1000 mg every 10-14 weeks
Transdermal	1% testosterone gel	5-10 g every day
Oral	T undecanoate	40-80 mg 2-3 times/day with meals

i. Testosterone + growth hormone

We do not recommend the combination of testosterone and GH supplementation to improve muscle mass, muscle strength or physical performance in older people (very low quality of evidence).

Borst et al. reviewed the effects of testosterone combined with growth hormone. They found an increase in muscle mass in healthy older men, but no significant effect on muscle strength. No data were available on physical performance or on the adverse events. More recent trials do suggest a synergistic effect [11, 40, 41]. However, long-term studies will be needed to elucidate these possible effects, as well as the adverse events.

j. Angiotensin Converting Enzyme (ACE)-inhibitors

We do not recommend ACE-inhibitors to improve muscle mass, muscle strength or physical performance in older people (moderate quality of evidence).

One systematic meta-analysis reported the effects of ACE-inhibitors on muscle strength and physical performance [16]. Three different ACE-inhibitors were used in the included original studies: enalapril, perindopril and fosinopril. The meta-analysis did show a modest positive effect in favour of the intervention; however no significant results were obtained. They attributed the reason for the non-significance to the short intervening times (5-9 months) and limitations of the meta-analysis (high heterogeneity, limited amount of studies, with

only studies from 2000 until 2015). No data on muscle mass or possible adverse events were available.

More recent clinical trials not included in the systematic review, were also not able to find a significant effect of ACE-inhibitors on one of the three sarcopenia criteria [42, 43]. However it is speculated that subgroups of older people, e.g. with heart failure or with a severe sarcopenic status, might benefit from ACE-inhibitors in terms of muscle outcomes [1, 44]. Also it might be that some ACE-inhibitors are superior to others, contradicting the idea of a class effect. Further studies are ongoing. Today there is no evidence to use ACE-inhibitors to improve muscle mass, muscle strength or physical performance in older people.

5. Strengths and limitations

The most important strength using the method of an umbrella-review is the power to efficiently extract clinical relevant information on which general consensus exists in contrast to conclusions of one research group, i.e. an umbrella review considers for inclusion the highest level of evidence. Our literature search is also systematic in nature, in accordance with the PRISMA-guidelines, which gives a higher level of evidence than a narrative review. Because our umbrella review is dependent on the quality of the systematic reviews/meta-analyses, we assessed this quality by using the AMSTAR-criteria.

A limitation, inherent to our strict search terms (see section 2.1), is the low total amount of eligible reviews (seven reviews in total). In combination with the often low quality of the systematic reviews/meta-analyses, this results in low to moderate ratings of evidence supporting most bottom line statements. Another limitation, inherent to an umbrella-review, is that we did not evaluate the quality of the individual randomized clinical trials or analysed the clinical trials to the level of the raw data. Lastly, physical activity and nutrition, two

interventions with generally accepted effects against sarcopenia, and pharmacological interventions not yet discussed in systematic reviews or meta-analyses (e.g. myostatin-inhibitors, selective androgen receptor modulators or SARMs,…) were not in the scope of this review.

6. Conclusion

Based on the results of this umbrella-review we conclude that vitamin D – especially in older women with very low baseline levels (<25nmol/L) - and testosterone - in men with clinical muscle weakness and low serum testosterone levels (<200-300ng/dL) - are the only pharmacological interventions that could be justified in clinical practice to improve one or more of the three sarcopenia-domains (muscle mass, muscle strength and physical performance). For other pharmacological treatments including combined estrogen-progesteron, dehydroepiandrosterone, growth hormone, growth hormone releasing hormone, combined testosterone-growth hormone, insulin-like growth factor 1, pioglitazone and angiotensin converting enzyme inhibitors, there is insufficient scientific evidence.

Key Points
- No distinct pharmacological recommendations for healthy, pre-sarcopenic and sarcopenic older people can be made, due to a lack of specific characterization of the sarcopenia status in most studies. However, recommendations can be made for older people in general.

- Vitamin D – especially in older women with low baseline levels (< 25nmol/L) - and testosterone* - in older men with low baseline levels (< 200-300ng/dL) and clinical muscle weakness - can be justified in clinical practice to improve muscle mass, muscle strength and/or physical performance.
  * This is a weak recommendation based on weak evidence (expert opinion for an off-label recommendation, which may have medico-legal implications).

- Insufficient evidence exists to justify other pharmacological interventions in clinical practice.

7. Recommendation

We recommend **vitamin D supplementation** to improve muscle strength and physical performance in older people, especially in older women with very low baseline levels.

Serum calcium should be monitored. Adverse events were rare.*

(Quality of evidence – 2)

Concerning the side-effects of vitamin D, a Cochrane systematic review of vitamin D/calcium supplementation on preventing fractures in older people, found a small but significant increase in gastrointestinal symptoms and renal disease associated with vitamin D and calcium intake, probably related to the hypercalcaemia and nephrolithiasis, in accordance with our results

We consider **testosterone supplementation** a possible intervention to improve muscle mass and muscle strength in older men with low serum testosterone levels (< 200–300 ng/dl) and clinical muscle weakness. Haematocrit, lipid profile and prostatic parameters should be monitored. An absolute contraindication for testosterone supplementation is a Hct >55%. Adverse events were rare and mild.**

This is a weak recommendation based on weak evidence (expert opinion for an off-label recommendation, which may have medico-legal implication).

(Quality of evidence – 4)

Possible adverse events of testosterone supplementation were fluid retention, virilization, aggressive behaviour, gynaecomastia, worsening of sleep apnoea, thrombotic complications, peripheral oedema, polycythaemia, acceleration of benign or malign prostatic tumours, and a possible risk of hepatic tumours and prostate cancer. An absolute contraindication for testosterone supplementation is a hematocrit >55%. However physiological doses of testosterone supplementation both in healthy and older people with frailty were well tolerated: in most studies only a mild polycythaemia was actually seen, while not showing an increase in prostatic or cardiovascular events

8. Appendix

Appendix S1 - Sarcopenia Guideline Development group of the BSGG

Ivan Bautmans

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Evelien Gielen

Stany Perkisas

Maurits Vandewoude

Appendix S2 – Search strings

Search string PubMed
((((("Review"[Publication Type]) OR "systematic review"[Title/Abstract]))) AND
(((((((((((("Pharmacology"[Mesh]) OR "Testosterone"[Mesh]) OR
"Hormones"[Pharmacological Action]) OR "Angiotensin-Converting Enzyme
Inhibitors"[Pharmacological Action]) OR "Anti-Inflammatory Agents"[Pharmacological
Action]) OR "Immunologic Factors"[Pharmacological Action]) OR "Myostatin"[Mesh]) OR
"Activin Receptors, Type II"[Mesh]) OR "Creatine"[Mesh]) OR ((((("Hormones"[Mesh]) OR
"Angiotensin-Converting Enzyme Inhibitors"[Mesh]) OR "Anti-Inflammatory Agents"[Mesh]
OR "Immunologic Factors"[Mesh]))))) AND ((sarcopenia) OR "Sarcopenia"[Mesh])

Search string Web of Science
1. DOCUMENT TYPES: (Review) OR TITLE: ("systematic review")
2. TOPIC: sarcopen*
3. TOPIC: Pharmaco* OR Testosteron* OR Hormon* OR "Angiotensin-Converting Enzyme
   Inhibitors" OR "Anti-Inflammatory Agents" OR "Immunologic Factor" OR Myostatin OR
   "Activin Receptor" OR "Creatine"
4. #1 AND #2
5. #3 AND #4

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INTERVENTION

-

EXERCISE

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BVGG-SBGG

Belgian Society
for GERONTOLOGY
and GERIATRICS

1. Publication details and abstract

This paper was published as:

"Exercise Interventions for the Prevention and Treatment of Sarcopenia. A Systematic Umbrella Review"

by

Beckwée D, Delaere A, Aelbrecht S, Baert V, Beaudart C, Bruyere O, de Saint-Hubert M, Bautmans I. *On behalf of the Sarcopenia Guidelines Development group of the Belgian Society of Gerontology and Geriatrics (BSGG)*

in

Abstract

Objectives

The aim of this systematic review is to provide an overview of the efficacy of different exercise interventions to counter sarcopenia in older adults. This review will allow the Belgian Society of Gerontology and Geriatrics and other scientific societies to formulate specific exercise recommendations in their Clinical Guidelines for Sarcopenia.

Design

We used the method of a systematic umbrella-review. Based on the level of evidence, we formulated specific recommendations for clinical practice.

Methods

Two databases (Pubmed and Web Of Science) were searched systematically and methodological quality of the reviews was assessed. Extracted data was than mapped to an exercise category and an overall synthesis (bottom line statements) was formulated for each of these exercise categories. Subsequently, we assigned a rating of the quality of the evidence supporting each bottom line statement.

Results

We identified 14 systematic reviews or meta-analyses, encompassing four exercise categories: resistance training, resistance training + nutritional supplementation, multimodal exercise programmes and bloodflow restriction training. Importantly, very few systematic reviews or meta-analyses clearly mentioned baseline sarcopenia status. There is high quality evidence for a positive and significant effect of resistance training on muscle mass, muscle strength, and physical performance. The added effect of nutritional supplementation for resistance training on muscle function appears limited. Blood flow restriction training is a novel training method that has a significant impact on muscle strength.

Conclusion

Since sarcopenia is affecting all skeletal muscles in the body, we recommend training the large muscle groups in a total body approach. Although low-intensity resistance training (≤50% 1RM) is sufficient to induce strength gains, we recommend a high-intensity resistance training program (i.e. 80% 1RM) to obtain maximal strength gains. Multimodal exercises and blood flow restriction resistance training may be considered as well.

KEYWORDS: exercise, sarcopenia, muscle strength, muscle mass, physical performance

2. Introduction

Since the introduction of the term 'sarcopenia' by Rosenberg in 1988 to describe the age-related decline in muscle mass [1], this phenomenon has received increasing attention by researchers and clinicians. In fact, the conceptual definition of sarcopenia has been operationalised into consensus-based diagnostic criteria including besides low muscle mass also muscle weakness and loss of physical functioning (the latter also considered in some definitions to describe the severity of Sarcopenia) [2-7]. The consequences of sarcopenia in older people are serious and life-changing: it has an impact on morbidity, disability, health care costs and mortality [3, 5]. Since 2016, sarcopenia is considered as a disease according to the World Health Organisation's International Statistical Classification of Diseases and Related Health Problems (code ICD-10-CM, M62.84) [8], demonstrating the need for appropriate treatment strategies.

To date, it is well accepted that physical exercise is one of the cornerstones for the prevention and treatment of sarcopenia [3, 5, 9].

However, research in gerontology and geriatrics exploded the last decades, thus leading to fundamentally new insights and knowledge regarding physical exercise in the context of ageing processes, strategies to improve successful ageing and good geriatric practice. In order to implement new strategies in daily practice, there is a need for an appropriate translation of recent scientific findings into realistic and feasible recommendations. The Belgian Society of Gerontology and Geriatrics (BSGG) has developed evidence-based guidelines for the prevention and therapy of sarcopenia for use in broad clinical practice, and recently the results of the Working Group on Pharmacology have been published [10]. Here, we present the results of the Working group on Exercise Interventions. The aim of this review is to provide an overview of the possible exercise interventions for sarcopenia with a focus on the

interventions that are already studied in systematic reviews or meta-analyses. Therefore, we used the method of a systematic umbrella-review. Based on the level of evidence, we formulated specific recommendations for clinical practice.

3. Methods

3.1. Search strategy and selection criteria

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in the conduction and reporting of this review [11]. Two databases (Pubmed and Web Of Science) were searched systematically from the earliest date available until November 08th 2017. Keywords used corresponded to the PICOS design (Population: older adults; Intervention: exercise; Comparison: no exercise or other form of exercise; Outcomes: sarcopenia; Study design: systematic review and meta-analysis) (full search strategy see APPENDIX 2).

3.2. Study selection

English systematic reviews reporting on exercise treatment aimed at the prevention or treatment of sarcopenia in an elderly population were considered eligible for inclusion. When specific sarcopenia outcomes such as muscle mass, muscle strength or physical performance were reported, articles were included as well. Studies focussed on patients with specific diseases and narrative reviews were excluded.

Four reviewers, blinded for each other's results, screened the titles and abstracts for eligibility by using the Rayyan web application for systematic reviews [12]. Subsequently, they screened full-text articles for eligibility. All four researchers did duplicate selection. A third reviewer or consensus-based discussion resolved all disagreements.

3.3.   Data extraction and methodological quality assessment

One reviewer completed data extraction using a data extraction form based on a template provided by the Cochrane Collaboration [13]. The authors extracted data regarding the key characteristics of the reviews, including: participants, exercise modality, outcomes assessed. No assumptions were made on missing or unclear data.

One reviewer assessed the methodological quality of the studies, which was then verified by a second reviewer, using the 'Assessment of Methodologic Quality of Systematic Reviews' (AMSTAR) [14]. This 11-item tool assesses the degree to which review methods avoided bias. The reviewers rated methodological quality as high (score 8-11), moderate (score 4-7) or low (score 0-3). They did not reassess the quality of included studies within reviews.

To organise the evidence, one investigator systematically synthesized each review's extracted data and mapped the result to an exercise modality, resulting in standardized statements for all reviews. In addition, one investigator developed an overall synthesis, beyond a simple summary of the main results of each review for each. We considered these overall syntheses 'bottom line statements' about the main effect of interventions within each intervention. Finally, we assigned a rating of the quality of the evidence (1 very low - 2 Low - 3 Moderate - 4 High) supporting each bottom line statement by using a method that is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for primary evidence [15]. The method takes into account the 'study design' (meta-analysis yes/no) and the ratings of the quality of evidence of the included systematic reviews (AMSTAR) (Figure 1). Finally, the Guideline Development Group of the Belgian Society of Gerontology and Geriatrics, consisting of scientific and clinical experts, developed recommendations based on these bottom line statements.
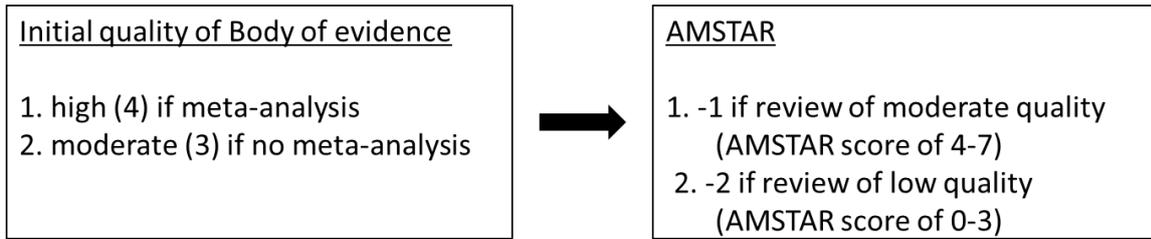
Initial quality of Body of evidence		AMSTAR

1. high (4) if meta-analysis
2. moderate (3) if no meta-analysis
	➡	1. -1 if review of moderate quality
		   (AMSTAR score of 4-7)
		2. -2 if review of low quality
		   (AMSTAR score of 0-3)

Figure 1: Method used to rate the quality of the evidence supporting each bottom line

statement

(AMSTAR: Assessment of multiple systematic reviews) [14]

4. Results

We screened 665 studies for eligibility (Figure 2). After screening the title and abstract, we excluded 509 studies. Eventually, we included 14 systematic reviews [16-29] of which seven performed a meta-analysis [16, 20-22, 26, 27, 29]. AMSTAR scores varied between 2 [19] and 9 [16, 17] (Figure 3).
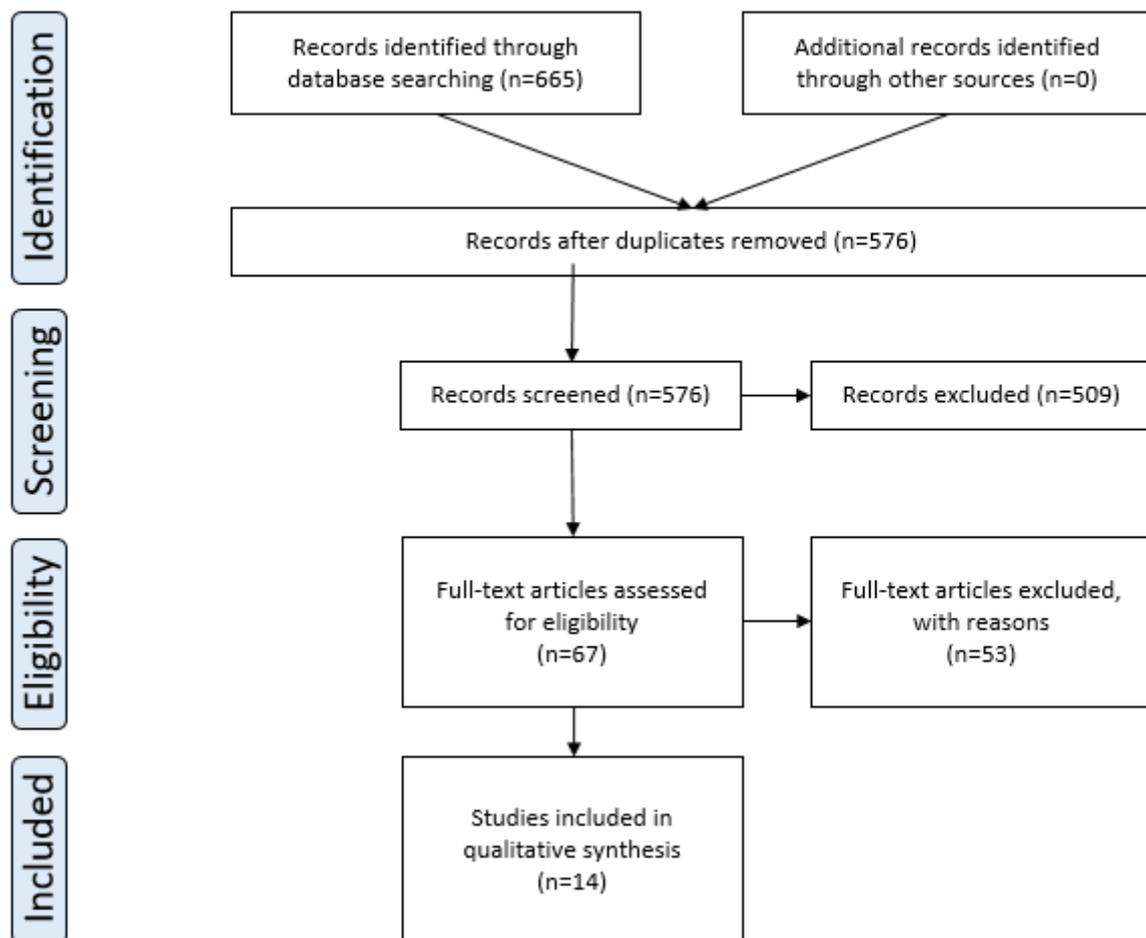
Figure 2: PRISMA Flowchart

(PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [37]

None of the included studies reported effects of exercise on the construct 'sarcopenia'. Consequently, in this umbrella-review the conclusions are focused on elderly subjects in a broader sense since they all investigated at least one of the following outcomes: muscle mass, muscle strength or physical performance.

The included reviews investigated the effect of the following exercise interventions: resistance training [19-21, 24-29], resistance training + nutritional supplementation [16, 17], multimodal exercise programmes (combination of resistance training, balance, walking,…) [18, 23] and bloodflow restriction training [22]. Table 1 presents an overview of all included reviews.

Figure 3: AMSTAR scores

(Red: No; Yellow: can't answer/not applicable; Green: Yes; AMSTAR: Assessment of multiple systematic reviews) [14]

Based on the body of evidence, bottom line statements about the main effects of each exercise modality - including a rating of the quality of the evidence supporting each bottom line statement- are presented in Table 2. In the text below, consideration of each exercise modality starts with a recommendation based on these bottom line statements, followed by the results of our umbrella review.

Reference	Outcome					N° of studies included (participants)	Results/findings (outcomes are underlined)	Comments
	S	BC	MS	PP	AE			
Resistance training								
Buch 2017 [38]		x				1 M.A. (4 st (103))	Lean body mass:	* circuit resistance training
							SMD 0.42 (95% CI;−0.08–0.91; I²= 30%; p for heterogeneity = 0.23)	
							Overall effect 2 kg (95% CI; −0.11–4.11; I²= 37%; p for heterogeneity =	
Csapo 2015 [39]		x				1 M.A. (7 st (213))	Muscle mass:	* moderate vs heavy resistance loads
							Total population effect: μ = 0.136 (CI 0.009-0,259; P = 0.036)	"Both RT at high (~80% 1RM) and lower intensities of load
							High loads μ = 0.199 (CI: 0.046–0.343, P = 0.011) (11% increase)	provoke only minor increases in total muscle size, which
							Low loads μ = 0.108 (CI: −0.050–0.261, P = 0.179) (9% increase)	indicates that the hypertrophic potential of skeletal muscles
Peterson 2011 [27]		x				1 M.A. (49 st (1328))	Muscle mass:	
							LBM: 1.1 kg (95% CI, 0.9 kg to 1.2 kg, p < 0.001)	
							Meta-regression revealed that higher volume interventions were	
							associated (β = 0.05, p < 0.01) with significantly greater increases in	
Theodorakopoulos 2017 [40]		x				1 study (8)	Strength [20, 21, 27-29]	* high-speed resistance training vs normal strength training
							Hypertrophy group and high-speed circuit group:	
							SMI: no significant change	
							BF%: no significant change	
Yoshimura 2017 [41]		x				1 M.A. (3 st (397))	ASMM (kg): 0.38 kg (95% CI 0.01-0.74; P = .04)	
Borst 2004 [42]			x			13 st (/)	Muscle strength: 13/13 studies reported increase in leg strength (1RM	
							(11), isokinetic leg strength (1), thigh muscle volume (1))	
Buch 2017 [38]			x			1 M.A. (4 st (103))	Muscle strength: 4 studies	* circuit resistance training
							Upper body strength:	
							SMD 1.14 kg (95% CI; 0.28–2.00; I2, 65%; p for heterogeneity = 0.04)	
							Lower body strength:	
							SMD 1.81 (95% CI; 1.02–2.61; I2, 59%; p for heterogeneity = 0.06)	
							Overall effect:	
							11.99 kg (95% CI; 2.92–21.06; I2, 96%; p for heterogeneity <0.00001)	

Csapo 2015 [39]			x		1 M.A. (15 st (448))	Muscle strength: Total population effect: μ = 0,430 (CI -0,02-0,735; P=0.06) High loads: μ = 0.778 (CI: 0.447–0.921, P < 0.001) (43% increase) Low loads: μ = 0.663 (CI: 0.396–0.826, P < 0.001) (35% increase)	* moderate vs heavy loads "The present synopsis of current literature demonstrates that RT at lower than traditionally recommended intensities of load (~45% 1RM) may suffice to induce substantial gains in muscle strength in elderly cohorts. Training with heavier loads may still be required to maximize strength gains, although the analysis of a subset of studies in which training was matched for mechanical work suggests that greater training volumes may largely compensate for lower intensities."
Martins 2013 [24]		x			1 M.A. (11 st (834))	Muscle strength: Healthy elderly SMD = 1.30 (95% CI: 0.90, 1.71) (N=152) Elderly with some functional incapacity SMD = 1.01 (95% CI: 0.82, 1.19) (N=591)	* elastic resistance
Peterson 2010 [43]		x			1 M.A. (47 st (1079))	Muscle strength Leg press: 31,63 kg (95% CI, 27.59–35.67 kg, p < 0.001) (32 studies) Chest press: 9.83 kg (95% CI, 8.42–11.24 kg, p < 0.001) (36 studies) Knee extension: 12.08 kg (95% CI, 10.44–13.72 kg, p < 0.001) (28	
Theodorakopoulos 2017 [40]		x			1 st (8)	Strength hypertrophy group: Leg 1RM: significant increase Leg power: significant increase Chest 1 RM: significant increase Chest power: significant increase Handgrip strength: no significant change High speed circuit group Leg 1RM: no significant change; Leg power: significant increase Chest 1 RM: significant increase Chest power: significant increase Handgrip strength: no significant change	* high-speed resistance training vs normal strength training
Yoshimura 2017 [41]		x			1 M.A. (3 st (397))	Knee extension strength: 0.11 Nm/kg (95% CI, 0.03-0.20; P = .01) (1 study) 8.55 Nm (95% CI, 4.70-12.39; P < .01) (1 study) 0.26 N (95% CI, 0.14-0.38; P < .001) (2 studies) Grip strength	
Papa 2017 [44]				x	11 st (-)	Physical performance: 11/11 studies in favour of intervention	

Theodorakopoulos 2018 [40]				x		1 st (8)	Strength hypertrophy group SPPB: no significant change High speed circuit group	* high-speed resistance training vs normal strength training
Yoshimura 2017 [41]				x		1 M.A. (3 st (397))	Usual walking speed: 0.11 m/s (95% CI,0.04-0.19; P = .004) (3 articles) Maximum walking speed: 0.26 m/s (95% CI, 0.03-0.20; P < .001) (2	

Resistance training + nutritional supplementation

Beaudart 2017 [45]		x				Protein: 12 studies (1049) EAA: 3 studies (196) HMB: 3 studies (103) Creatine: 5 studies (167) Multi-nutrient: 4 studies (300) Vitamin D: 1 study (96) Other: 6 studies (670)	Protein: 3/12 studies in favour of intervention Essential amino acids: 0/3 studies in favour of intervention β-hydroxy-β-methylbutyrate:1/3 studies in favour of intervention Creatine: 4/5 studies in favour of intervention Multi-nutrient intervention:0/2 studies in favour of intervention Vitamin D: 0/1 studies in favour of intervention Other: 0/6 studies in favour of intervention "the interactive effect of dietary supplementation on muscle function appears limited"	Other supplementation - green tea in elderly men and women - magnesium oxide in healthy elderly subjects - milk fat globule membrane in frail women - soy isoflavones in frail older women - vitamin and mineralenhanced dairy and fruit products in frail community-dwelling older people - tea catechin in sarcopenic women
Antoniak 2017 [46]			x			1 M.A. (3 st (266))	Muscle strength: Lower limb strength: SMD 0.98 (95%CI 0.73, 1.24), I²=70%, p=.04	* Main supplementation: vit D
Beaudart 2017 [45]			x			Protein: 12 studies (909) EAA: 3 studies (196) HMB: 3 studies (103) Creatine: 5 studies (167) Multi-nutrient: 5 studies (379) Vitamin D: 2 studies (121) Other: 5 studies (648)	Protein: 3/12 studies in favour of intervention Essential amino acids: 2/3 studies in favour of intervention β-hydroxy-β-methylbutyrate: 0/3 studies in favour of intervention Creatine:4/5 articles in favour of intervention Multi-nutrient intervention: 1/5 studies in favour of intervention Vitamin D: 0/2 studies in favour of intervention Other: 0/5 studies in favour of intervention "the interactive effect of dietary supplementation on muscle function appears limited"	* Main supplementation: nutrition supplementation Other supplementation- green tea in elderly men and women - magnesium oxide in healthy elderly subjects - milk fat globule membrane in frail women - soy isoflavones in frail older women- vitamin and mineralenhanced dairy and fruit products in frail community-dwelling older people- tea catechin in sarcopenic women
Antoniak 2017 [46]				x		1.M.A. (2 st (249))	Physical performance TUG: −0.21 (95%CI −0.68; 0.26), I²=0%, p=0.37	* Main supplementation: vit D

Study						Studies (n)	Results	Notes
Beaudart 2017 [45]				x		Protein: 9 studies (793)	Protein: 0/9 studies in favour of intervention	* Main supplementation: nutrition supplementation
						EAA: 2 studies (179)	Essential amino acids: 0/2 studies in favour of intervention	Other supplementation
						HMB: 2 studies (72)	β-hydroxy-β-methylbutyrate: 0/2 studies in favour of intervention	- green tea in elderly men and women
						Creatine: 4 studies (147)	Creatine: 1/4 studies in favour of intervention	- magnesium oxide in healthy elderly subjects
						Multi-nutrient: 4 studies (304)	Multi-nutrient intervention: 0/4 studies in favour of intervention	- milk fat globule membrane in frail women
						Vitamin D: 2 studies (121)	Vitamin D: 1/2 studies in favour of intervention	- soy isoflavones in frail older women
						Other: 5 studies (648)	Other: 2/5 studies in favour of intervention	- vitamin and mineralenhanced dairy and fruit products in
							" the interactive effect of dietary supplementation on muscle function	frail community-dwelling older people
							appears limited"	- tea catechin in sarcopenic women

Multimodal exercise

Study						Studies (n)	Results	Notes
Bibas 2014 [18]		x				3 st (214)	<u>Lean body mass</u>: 2/3 studies in favour of intervention	
Liberman 2017 [47]		x				4 st (162)	1/4 studies in favour of intervention	Population: 65+ frail older people
Liberman 2017 [47]		x				14 st (411)	10/14 studies in favour of intervention	Population: 65+ healthy older people
Bibas 2014 [18]			x			4 st (401)	3/4 studies in favour of intervention	
							(muscle power, muscle strength, isokinetic knee extension force, leg	
							muscle strength)	
Liberman 2017 [47]			x			3 st (147)	2/3 studies in favour of intervention	Population: 65+ frail older people
								Muscle strength seemed to be the most frequently used
								outcome measure, with moderate-to-large effects obtained
								regardless of the exercise intervention studied. Similar
								effects were found in patients with specific diseases.
Liberman 2017 [47]			x			18 st (428)	15/18 studies in favour of intervention	Population: 65+ healthy older people
Bibas 2014				x		9 st (2786)	9/9 studies in favour of intervention	
							(SPPB, Gait speed, mobility measures, PPT score, 400m walk)	
Liberman 2017 [47]				x		3 st (147)	3/3 studies in favour of intervention	Population: 65+ frail older people
Liberman 2017 [47]				x		8 st (221)	5/8 studies in favour of intervention	Population: 65+ healthy older people

Blood flow restriction

Study						Studies (n)	Results	Notes
Hughes 2017 [48]			x			1 M.A. (13 st (341))	Low load BFR (8 studies)	"This review illustrates that the majority of studies do not
							Hedges' g=0.523 (95% CI 0.263 to 0.784, p<0.001) I²=49.8%	report on the presence or absence of adverse events."
							High load BFR (5 studies)	
							Hedges' g=0.674 (95% CI 0.296 to 1.052, p<0.001) I²= 0%	

Table 1: Results of Individual Reviews

ASMM: appendicular skeletal muscle mass; β: standardized regression coefficient estimates; BF: body fat; BFR: blood flow restriction; CI: confidence interval; EAA: essential amino acid; HMB: β-Hydroxy β-methylbutyric acid LBM: lean body mass; I²: heterogeneity; M.A.: meta-analysis; p: p-value; m/s: meter per second; N: Newton; NM:newtonmeter; RT: resistance training; PPT: physical performance test; SMD: smallest mean difference; SMI: skeletal muscle mass index; SPPB: short physical performance battery; st: studies; TUG: timed-up and go test; μ: population mean;

4.1. Resistance training

We recommend resistance training to improve muscle mass, muscle strength and physical performance in older people. [High quality of evidence]

There is high quality evidence for a positive and significant effect of resistance training on muscle mass (five studies of which four meta-analyses [20, 21, 27-29]), muscle strength (seven studies of which five meta-analyses [19-21, 24, 26, 28, 29]) and physical performance (three studies of which one meta-analysis [25, 28, 29]).

The meta-analysis of Peterson et al. (49 studies, 1328 participants) reported a positive effect of resistance training on lean body mass (weighted pooled estimate 1.1 kg (95% confidence interval (CI) [.9, 1.2]) [27]. Meta-regression revealed that higher volume (i.e. total number of sets performed per whole body) interventions were associated with significantly greater increases in lean body mass (β = 0.05, $p < 0.01$), whereas older individuals experienced less increase (β = -0.03, $p = 0.01$). Hence, the authors concluded that resistance training results in superior effectiveness when introduced early in life. In line with the latter, also Csapo et al. reported that the hypertrophic potential of skeletal muscle is blunted at older age [21].

A meta-analysis of 47 studies (1079 participants) showed positive effects of resistance training on strength outcomes of both upper and lower limbs with percent changes of 29±2, 24±2, 33±3, and 25±2, respectively for leg press, chest press, knee extension, and lat pull [26]. Regression revealed that higher intensity training was associated with greater improvement. Intensity was investigated on an ordinal scale, based on the percentage of one repetition maximum (1RM) used for a given exercise: low intensity (< 60% 1RM), low/moderate intensity (60-69% 1RM), moderate/high intensity (70-79% 1RM), and high intensity (≥ 80% 1RM). The mean change in relative strength for an incremental increase in intensity subgroup was 5.5%. Findings of other included reviews supported these conclusions (table 1). For example, Martins et al. reported beneficial effects on muscle strength for resistance training with elastic bands [24]. In addition, one review analysed a subset of studies in which training was matched for mechanical work and suggested that greater training volumes may largely compensate for lower intensities [21].

One meta-analysis (3 studies, 397 participants) reported a significant effect of resistance training on physical performance, measured by usual walking speed (pooled estimate: .11 m/s, 95%CI[.04,.19]) and maximum walking speed (.26 m/s (95%CI[.03,.20]) [29]. In addition, all 11 studies that were included in the systematic review of Papa et al. reported significant

effects of resistance training on physical performance tests including the Timed Up and Go and Functional Reach test [25].

> Thus, since sarcopenia is affecting all skeletal muscles in the body, we recommend resistance training for the large muscle groups in a total body approach. For maximal strength gains, we recommend a high-intensity resistance training program (i.e. 80% 1RM). However, low-intensity resistance training (≤50% 1RM) may be sufficient to induce strength gains. In addition, we recommend the following training parameters: 1-4 sets of 8-15 repetitions during 2-3 training moments a week.

4.2.   Resistance training + nutritional supplementation

We do not recommend nutritional supplementation in addition to resistance training to improve muscle mass, muscle strength or physical performance in older people. We do recommend vitamin D supplementation in addition to resistance training to improve muscle strength but monitoring of the serum calcium is needed. [Low quality of evidence].

Beaudart et al. observed huge variations in the dietary supplementation protocols and remarked that the studies included mainly well-nourished subjects [17]. Subsequently they concluded that "the interactive effect of dietary supplementation on muscle function appears limited".

The meta-analysis of Antoniak et al. reported a significant effect for vitamin D supplementation in addition to resistance training for muscle strength of the lower limb (standardized mean difference (SMD) .98, 95%CI [.73,1.24], I^2=70%, p=.04) but not for the Timed Up and Go tests (SMD −.21, 95%CI [-0.68, 0.26], I^2=0%, p=0.37). However, these authors reported serious inconsistency due to moderate heterogeneity (I^2=70%).

In addition to our findings and based on the work of the guideline development working group *Pharmacology* of the Belgian Society of Gerontology and Geriatrics [30], we recommend to

monitor the serum calcium since a small but significant increase in gastrointestinal symptoms and renal disease was reported to be associated with vitamin D and calcium intake, probably related to the hypercalcaemia and nephrolithiasis [31].

4.3.   Multimodal exercise

We do recommend multimodal exercise therapy to improve muscle mass, muscle strength and physical performance in older people. [Moderate quality of evidence]

Multimodal training encompasses a combination of resistance training, walking, aerobic training, balance training and other types of training. Two systematic reviews reported significant effects of multimodal exercise programs on all subdimensions of sarcopenia in healthy older adults [18, 23, 32]. In addition, Liberman et al. specifically reported the effects on frail older adults and concluded that both muscle strength and physical functioning can be improved after different kinds of exercises [32].

4.4.   Blood flow restriction

We do recommend blood flow restriction training to improve muscle strength in older people. This type of training should be performed under supervision of a trained exercise coach. *[High quality of evidence]*

Blood flow restriction (BFR) strength training is a relatively novel training method, which has a significant positive impact on muscle strength [22]. BFR is defined as muscle resistance training with maintaining arterial blood inflow and restricting the venous blood outflow of the trained muscle. A meta-analysis of 8 studies reported that low intensity (10-30% 1RM) BFR training was more effective in increasing muscle strength compared to low intensity training alone (Hedges' g=0.523, 95%CI [.263,.784], I^2=49.8%). However, low intensity BFR was less effective than heavy-load training (no BFR) (Hedges' g=0.674, 95%CI [.296, 1.052], I^2=0.0%). Since the majority of the studies included in the review of Hughes et al. did not report on the presence or absence of adverse events, we recommend that this type of training should be performed under supervision of a trained exercise coach.

Intervention	Sarcopenia	Muscle Mass	Muscle Strength	Physical Performance	'Bottom line' statement	QoE
Resistance training	Insufficient to determine	Sufficient evidence	Sufficient evidence	Sufficient evidence	A clear and significant effect of resistance training on muscle mass, muscle strength and physical performance is seen in the evidence. For maximal strength gains, a high resistance training (70-80% 1RM) is recommended, but lower intensity (50%) may suffice to induce strength gains. Elastic resistance training is a valid type of resistance training to improve muscle strength that easily can be done at home. In general, we do recommend resistance training, especially to improve muscle strength for healthy, pre-sarcopenic or sarcopenic older people in the prevention or treatment of sarcopenia.	4
Resistance training + supplementation	Insufficient to determine	Insufficient to determine	Some evidence in favour	Insufficient to determine	The added effect of nutritional supplementation for resistance training on muscle function appears limited. However, we do recommend vitamin D supplementation for resistance training since there is some evidence that vitamin D may increase the effect of resistance training on muscle strength. However, monitoring of the serum calcium is needed. Further specifications of vitamin D supplementation can be found in De Spiegeleer et al. 2018 [30].	2
Multimodal exercise	Insufficient to determine	Sufficient evidence	Sufficient evidence	Sufficient evidence	Data shows clear evidence in favor of multimodal exercise therapy on all three sarcopenic parameters. Multimodal training can encompass a combination of resistance training, walking, aerobic training, balance training and other types. To conclude, we do recommend multimodal exercise therapy for healthy, pre-sarcopenic or sarcopenic older people in the prevention or treatment of sarcopenia.	3
Blood Flow Restriction training	Insufficient to determine	Insufficient evidence	Sufficient evidence	Insufficient evidence	Blood flow restriction training is a novel training method which has a significant impact on muscle strength. High or low load BFR training is show to be effective although low load BFR training can be preferred in clinical populations. Since this is a new type of training, we recommend the clinician to be aware of the safety requirements and tailor the method to the individual. In general we do recommend BFR training baring a safe application in mind.	4

Table 2: Bottom line statements

1RM: one repetition maximum; BFR: blood flow restriction; QoE: quality of evidence supporting each bottom line statement (1 very low - 2 low - 3 moderate - 4 high)

Sufficient evidence: statistically significant pooled results (meta-analysis); Some evidence: narrative synthesis of review results (based on a majority of studies showing statistically significant results); Insufficient evidence:

based on a majority of studies showing statistically non-significant effects (underpowered or no effect); Insufficient (evidence) to determine: not reported in reviews or meta-analyses (reporting gap in evidence)

5. Discussion

This systematic umbrella-review aimed to provide an overview of the possible exercise interventions for sarcopenia. High-volume and high-intensity resistance training have the highest level of evidence to improve muscle mass, muscle strength and physical performance in older adults. In addition, multimodal exercises can also be considered for preventing and treating sarcopenia. Low intensity blood flow restriction training was more effective in increasing muscle strength compared to low intensity training alone but was less effective then heavy-load training. By implementing high-intensity resistance training, one can expect increases in muscle mass (+1.1kg [27]), muscle strength (leg press: +31.63kg [26]) and gait speed (+0.11m/s [29]). To reach these effects, we recommend to train the large muscle groups in a total body approach at 70-80% 1RM (4 sets of 8 to 15 repetitions per muscle group; 2-3 times per week) for at least 6-12 weeks. Since these gains are progressively lost during detraining, resistance training should be part of the weekly routine of older persons (which is in line with the physical activity guidelines for adults aged 65 and over of the World Health Organisation) [33].

A strength of our literature study is its systematic approach in accordance with the PRISMA-guidelines, which gives a higher level of evidence than a narrative review. In addition, by using the method of an umbrella-review we were able to efficiently extract clinical relevant information on which general consensus exists in contrast to conclusions of one single article, i.e. an umbrella review considers for inclusion the highest level of evidence, namely other systematic reviews and meta-analyses. Because our umbrella review is dependent on the quality of the included systematic reviews/meta-analyses, we assessed their quality by using the AMSTAR-criteria. Based on these scientific quality assessments, we conclude that our recommendations are supported by the highest level of evidence.

A limitation, inherent to an umbrella-review, is that we did not evaluate the quality of the individual randomized clinical trials or analysed the clinical trials to the level of the raw data. Another limitation, inherent to our strict search terms relating to sarcopenia (see method section) is the low total amount of eligible reviews (fourteen reviews in total). This is also manifested in the fact that none of the included studies reported the effects of exercise on the construct 'sarcopenia'. To counter the latter, we reported effects of exercise on the subdimensions of sarcopenia (i.e. muscle mass, muscle strength and physical performance).

The most important reason for sarcopenia not being considered as an outcome in systematic reviews, is probably the fact that there are no universally accepted criteria for the diagnosis of sarcopenia. Indeed, several working groups have recommended definitions for sarcopenia [2, 4, 34] but these definitions differ slightly. Moreover, within these diagnostic criteria, different cut-off scores and different measuring instruments have been recommended to diagnose sarcopenia. Consequently, prevalence of sarcopenia varies widely depending on the measuring instrument and cut-off score being used [35, 36].

6. Recommendation

Since sarcopenia is affecting all skeletal muscles in the body, we recommend training the large muscle groups in a total body approach.

Evidence shows a positive and significant effect of resistance training on muscle mass, muscle strength, and physical performance. (Quality of evidence – 4)

Multimodal exercises (Quality of evidence – 3) and blood flow restriction resistance training (Quality of evidence – 4) may be considered as well.

Since the majority of the studies included in the review on blood flow restriction resistance training. did not report on the presence or absence of adverse events, we recommend that this type of training should be performed under supervision of a trained exercise coach

There are no side effects reported in the retrieved evidence for the other recommendations.

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8. Appendix

Appendix S1 – Search strings

<u>Search string PubMed</u>

((((((("Review"[Publication Type]) OR "systematic review"[Title/Abstract]))) AND ((((((("Motor Activity"[Mesh]) OR "Exercise Therapy"[Mesh]) OR "Exercise"[Mesh]) OR "Exercise Movement Techniques"[Mesh]) OR "Sports"[Mesh])))) AND ((sarcopenia) OR "Sarcopenia"[Mesh])

<u>Search string Web of Science</u>

1. DOCUMENT TYPES: (Review) OR TITLE: ("systematic review")
2. TOPIC: sarcopen*
3. TOPIC: ("Motor Activity" OR "Exercise Therapy" OR "Exercise" OR "Exercise Movement Techniques" OR "Sports")
4. #1 AND #2
5. #3 AND #4

INTERVENTION

-

NUTRITION

-

BVGG-SBGG

Belgian Society
for GERONTOLOGY
and GERIATRICS

1. Publication details and abstract

This paper will be published as:

Abstract

Aim

The aim of this umbrella review was to provide an evidence-based overview of nutritional interventions, targeting sarcopenia or muscle mass, muscle strength or physical performance.

Methods

PubMed and Web Of Science were systematically searched for systematic reviews and meta-analyses in persons aged ≥ 65 years. Methodological quality of the reviews was assessed using AMSTAR. Recommendations were generated based on an overall synthesis of the effects of each intervention.

Results

15 systematic reviews were included. The following supplements were examined: proteins, essential amino acids, leucine, β-hydroxy-β-methylbutyrate, creatine and multinutrient supplementation (with or without physical exercise). Due to both the low amount and the low to moderate quality of the included reviews, the level of evidence supporting most bottom line statements was low to moderate.

Conclusion

Best evidence is available to recommend leucine since it has a significant effect on muscle mass in sarcopenic elderly. Protein supplementation on top of resistance training is recommended to increase muscle mass and strength, in particular for obese persons and for at least 24 weeks.

2. Introduction

Ageing is associated with a progressive and general loss of muscle mass and muscle strength.[1] Loss of muscle mass is estimated at about 35 to 40% between the age of 20 to 80 years.[2] The difference in muscle strength between young persons and healthy elderly of 60 to 80 years is 20 to 40%, and this difference increases to 50% or more when compared to those older than 80.[3] There is, however, wide inter-individual 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 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, now focusing on low muscle strength as key clinical characteristic of sarcopenia, and considering low muscle mass and/or quality to confirm the diagnosis and poor physical performance to determine its severity (EWGSOP2).[10] On October 1st 2016, sarcopenia received an ICD-10 code (International Statistical Classification of Diseases and Related Health Problems) (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 burden 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 indicate a potential role, not only for gender, height, weight and genetic heritability, but also for physical exercise and nutritional intake over the lifetime as determinants of sarcopenia, and thus potential leads for intervention.[4]

So far, the role of physical exercise and nutritional interventions has been examined in several randomized controlled trials (RCTs). The Belgian Society of Gerontology and Geriatrics (BSGG) has developed evidence-based guidelines for the prevention and therapy of sarcopenia for use in broad clinical practice (https://geriatrie.be/the-bsgg/initiatives/works-and-contributions/sarcopenia-guidelines/), and recently the results of the Working Group on Pharmacology and the Working Group on Exercise Interventions have been published.[12, 13] 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 one of the three sarcopenia criteria (muscle mass, muscle strength or physical performance), with a focus on interventions that have been 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.

3. Methods

3.1. Search strategy and selection criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for this review (Appendix S1).[14] Two databases (PubMed, Web of Science) were systematically searched from the earliest date available (1950s for PubMed, 1900 for Web of Science) until November 08th 2017. Keywords corresponded to the PICOS design (Population: older adults; Intervention: nutrition; Comparison: no nutrition; Outcomes: sarcopenia; Study design: systematic review and meta-analysis) (Appendix S2 for full search strategies).

3.2. Study selection

Systematic reviews in English reporting the effect of caloric or nutritional supplementation (with or without exercise program) on one or more of the three criteria of sarcopenia in older adults (≥ 65 years), i.e. 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 (Appendix S3 for eligibility criteria). Reviews reporting on the effects of Vitamin D supplementation were not taken into consideration since these were investigated and recently published by the Working Group on Pharmacology.[12] Four authors (DB, EG, SD, MV), blinded for each other's results, screened the titles and abstracts for duplicate studies and for eligibility using the Rayyan web application for systematic reviews.[15] Subsequently, full-text articles were screened by the same authors. Disagreements were resolved by discussion until consensus was reached.

3.3. Data extraction and methodological quality assessment

Data extraction was completed by one author (AD) and verified by a second author (DB), using a data extraction form based on a template provided by the Cochrane Collaboration.[16] 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 (DB, AD) assessed the methodological quality of the systematic reviews using A MeaSurement Tool to Assess systematic Reviews (AMSTAR) (Appendix S4).[17, 18] 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, three authors (DB, AD, EG) systematically synthesized the extracted data of each review. This resulted in 'standardized effectiveness statements' (sufficient evidence, some evidence, insufficient evidence, insufficient evidence to determine) about the treatment effect of the intervention(s) in the individual systematic reviews (Appendix S5). In addition, two authors (DB, EG) 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) (Fig. 1).[19] This method takes into account study design (meta-analysis yes/no) and AMSTAR rating of the included systematic reviews.

Fig. 1 Method used to rate the quality of the evidence supporting each 'bottom line statement' (*AMSTAR* = A MeaSurement Tool to Assess systematic Reviews [17])
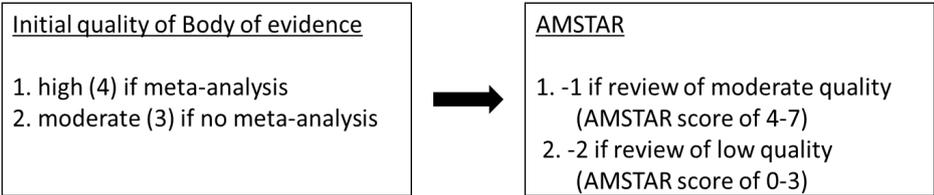
4. Results and recommendations

4.1. Included studies

A total of 516 studies were screened for eligibility (Fig. 2). After removal of duplicates and screening of titles and abstracts, 448 records were excluded. 53 additional records were

removed after assessment of the full-texts. Eventually, 15 systematic reviews were included [20-34] of which six performed a meta-analysis.[20-23, 29, 33] In one of these, the meta-analysis was performed for body composition, but not for muscle strength and physical performance.[23] AMSTAR scores varied between 3 [27, 30] and 9 [21] (Fig. 3).

Fig. 2 PRISMA flowchart of study selection process (*PRISMA* = Preferred Reporting Items for Systematic Reviews and Meta-Analyses [14])

PRISMA flowchart Nutritional Intervention

Identification

Records identified through database searching (n=516)

Additional records identified through other sources (n=0)

Records after duplicates removed (n=455)

Screening

Records screened (n=455)

Records excluded (n=387)

Eligibility

Full-text articles assessed for eligibility (n=68)

Full-text articles excluded, with reasons (n=53)

Included

Studies included in qualitative synthesis (n=15)

Fig. 3 AMSTAR scores. Red indicates 'no'; yellow indicates 'cannot answer/not applicable'; green indicates 'yes' (*AMSTAR* = A MeaSurement Tool to Assess systematic Reviews [17])

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: protein supplementation,[22, 25-28] essential amino acids (EAA) supplementation,[20, 24, 28] leucine supplementation,[21, 24, 28, 29] β-hydroxy-β-methylbutyrate (HMB) supplementation,[23, 28] protein supplementation + resistance training,[26, 31, 33, 34] creatine supplementation + progressive resistance training,[27, 30, 32] protein supplementation + (various types of) physical exercise,[27, 28, 30, 32] EAA supplementation + (various types of) physical exercise,[27, 28, 32] HMB supplementation + (various types of) physical exercise,[28, 32] and multinutrient supplementation + (various types of) physical exercise.[30, 32] '(Various types of) physical exercise' indicates that, in those reviews, the exercise program was not specified or consisted of a multimodal exercise program, *e.g.,* 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 since most of the reviews did not specify the sarcopenia status of the participants.

Table 1 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 1 and 2. Table 3 gives an overview of the recommendations for each intervention category.

Table 1 Results of the individual systematic reviews

Reference	S	BC	MS	PP	AE	N° of studies (n° participants)	MA	Results/findings (outcomes are underlined)	Standardized effectiveness statement	AMSTAR	Bottom line statement about the main effects of interventions and recommendation within each intervention category +	QoE
Protein supplementation												
Malafarina 2013[28]		v				2 studies (311)	N	FFM: "Could not find significant differences due to treatment in FFM." FFM: "No change"	INSUFFICIENT EVIDENCE	5		
Naseeb 2017[27]		v				3 studies (828)	N	ALM: "Protein intake was a positive predictor of change in aLM over 2.6 y (P = .003) after adjusted for energy intake. Protein intake was a significant independent positive predictor of change in aLM (P = .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	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 as an intervention to increase muscle mass.	2
Pedersen 2014[26]		v				3 studies (2940)	N	3/3 studies in favour 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 estimated average requirement (EAR) of 0.66 g good-quality protein/kg BW/day based on nitrogen balance (N-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 favour of INTERVENTION	6		
Theodorakopoulos 2017[25]		v				1 study (40)	N	Body composition: "No significant changes were seen in body composition, in either experimental or control groups."	INSUFFICIENT EVIDENCE TO DETERMINE	8		
Xu 2014[22]		v				6 studies (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 favour of no difference	7		
Malafarina 2013[28]			v			2 studies (311)	N	Handgrip strength: "Improvement in the supplemented group compared with the control group." Hand grip strength: "No change"	INSUFFICIENT EVIDENCE	5		

Author						Studies (N)		Outcome	Conclusion		Overall conclusion	
Naseeb 2017[27]			v			3 studies (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 2017[25]			v			1 study (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 = .06)."	INSUFFICIENT EVIDENCE TO DETERMINE	8		
Xu 2014[22]			v			4 studies (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 favour of no difference	7		
Naseeb 2017[27]				v		1 study (65)	N	Physical performance: "Protein supplementation significantly improved physical performance after achieving a daily protein intake from 1.0 to 1.4g/kg BW/day (P = .02)."	INSUFFICIENT EVIDENCE TO DETERMINE	3		
Malafarina 2013[28]				v		1 study (210)	N	Reduction of functional limitations: "There was a tendency to reduce functional limitations, although this outcome was not statistically significant."	INSUFFICIENT EVIDENCE TO DETERMINE	5		
Naseeb 2017[27]					v	1 study (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		
Essential Amino Acids (EAA) supplementation												
Malafarina 2013[28]	v					1 study (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. In conclusion, EAA supplementation should not be considered as an intervention to increase muscle mass, muscle strength and physical performance.**	4
Yoshimura 2017[20]	v					5 studies (501)	Y	ASM: WMD = -0.34 kg (95% CI -0.78 to 0.10, P = .13) (3 articles) ASMI: WMD = 0.15 kg/m² (95% CI -0.66 to 0.96, P = .72) (1 article) FFM: WMD = 3.3 kg (95% CI -0.56 to 7.16, P = .09) (1 article)	SOME EVIDENCE in favour of no difference	8		
Wandrag 2015[24]	v					2 studies (26)	N	LBM: "Significantly higher after 3 months of EAA compared to placebo" LBM: "Improvement (P = .038)"	INSUFFICIENT EVIDENCE TO DETERMINE	6		
Yoshimura 2017[20]			v			4 studies (475)	Y	Grip strength: WMD = -0.36 kg (95% CI -1.40 t 0.67, P = .49) (2 articles) Knee extension strength: WMD = 0.11 Nm/kg (95% CI 0.03 to 0.20, P = .008) (1 article) Knee extension strength: WMD = -1,61 Nm (95% CI -5,43 to 2.20, P = .41) (2 articles) Knee extension strength: WMD = 2.07 N (95% CI -18,77 to 22.91, P = .85) (1 article)	SOME EVIDENCE in favour of no difference	8		
Wandrag 2015[24]			v			1 study (12)	N	Leg strength: "Leg strength improvement (p < .001)"	INSUFFICIENT EVIDENCE TO DETERMINE	6		
Malafarina 2013[28]				v		1 study (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 = .01), was observed."	INSUFFICIENT EVIDENCE TO DETERMINE	5		

Study					Studies (n)	Y/N	Findings	Evidence	Score	Conclusion	
Yoshimura 2017[20]			v		3 studies (422)	Y	Usual walking speed: WMD = -0.01 m/s (95% CI -0.06 to 0.04, P = .66) (3 articles)	SOME EVIDENCE in favour of no difference	8		
Wandrag 2015[24]			v		2 studies (53)	N	Physical performance: "The results showed that the EAA mixture signficantly improved nutritional status, physical performance, muscle function and levels of depression."Walking speed and functional assessment: "Improvement in walking speed (P = .002) and functional assessment (P=.007) "	INSUFFICIENT EVIDENCE	6		
Leucine supplementation											
Komar 2015[29]	v				10 studies (LBM) Total n = 426	Y	LBM: MD = 0.99 kg (95% CI = 0.43 to 1.55, P = .0005) - healthy seniors: MD = -0.05 kg (95% CI = -1.55 to 1.46, P = .95) - sarcopenic seniors: MD = 1.14 kg (95% CI = 0.55 to 1.74, P = .0002) No effect on fat mass or percentual body fat	SUFFICIENT EVIDENCE in favour of INTERVENTION (only sarcopenic seniors)	7	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, we do recommend leucine supplementation for sarcopenic older people to increase muscle mass.	3
Xu 2015[21]	v				4 studies (121)	Y	LBM: pooled standardised difference in mean changes = 0.18 (95% CI = -0.18 to 0.54, P = .318 (4 studies) Leg lean mass: pooled standardised difference in mean changes = 0.006 (95% CI = -0.32 to 0.44, P = .756 (3 studies)	SOME EVIDENCE in favour of no difference	9		
Wandrag 2015[24]	v				1 study (29)	N	Muscle mass: "No differences after 3 months of supplementation"	INSUFFICIENT EVIDENCE TO DETERMINE	9		
Malafarina 2013[28]	v				2 studies (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		
Komar 2015[29]		v			5 studies (hand grip) 6 studies (knee extension strength) Total n = 578	Y	No effect on hand grip strength or knee extension strength	SOME EVIDENCE in favour of no difference	7		
Wandrag 2015[24]		v			1 study (29)	N	Muscle strength: "No difference after 3 months of supplementation"	INSUFFICIENT EVIDENCE TO DETERMINE	9		
Malafarina 2013[28]		v			2 studies (90)	N	Thigh strength: "Leenders et al found a statistically significant (P < .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		
β-hydroxy-β-methylbutyrate (HMB) supplementation											
Malafarina 2013[28]	v				1 study (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	4
Wu 2015[23]	v				7 studies (287)	Y	FM: SMD = -0.08 kg (95% CI -0.32 to 0.159, P = .511) Muscle Mass: SMD = 0.352 kg (95% CI 0.11 to 0.594, P = .004)	SUFFICIENT EVIDENCE in favour of INTERVENTION	8		
Malafarina 2013[28]		v			2 studies (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 = .04) of this parameter in the supplemented group."	INSUFFICIENT EVIDENCE TO DETERMINE	5		

Study					n (N)	Y/N	Findings	Conclusion	Score	Comments	
Wu 2015[23]			v		5 studies (238)	N	2/5 studies in favour of intervention	SOME EVIDENCE in favour of no difference	8	**considered as an intervention to increase muscle mass**.	
Wu 2015[23]				v	4 studies (214)	N	2/4 studies in favour of intervention	INSUFFICIENT EVIDENCE	8		
Protein supplementation + progressive resistance training (PRT)											
Colonetti 2016[31]	v				1 study (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		
Liao 2017[33]	v				16 studies (LBM) (802) 8 studies (ALM) (566) 11 studies (AFM) (633) 15 studies (BF%) (752) 6 studies (muscle volume) (242)	Y	LBM: SMD 0.58 (95% CI 0.32 to 0.84, P < .0001; I² = 66%; P < .0001) Subgroup duration ≥ 24w: SMD 0.66 (95% CI 0.35 to 0.97; P <.0001; I² = 41%; P = .13) Subgroup BMI ≥ 30 kg/m²: SMD 0.53 (95% CI 0.19 to 0.87, P = .002; I² = 35%; P = .19) ALM: SMD 0.33 (95% CI 0.07 to 0.60, P = .01; I² = 51%, P = .04) Absolute FM: SMD -0.61 (95% CI -0.93 to -0.29, P = .0002; I² = 72%, P = .0001) BF%: SMD -1.14 (95% CI -1.67 to -0.60, P < .0001; I² = 90%, P =.00001) Muscle volume: SMD: 1.23 (95% CI 0.50 to 1.96, P = .001; I² = 83%, P = .00001)	SUFFICIENT EVIDENCE in favour of INTERVENTION for obese (BMI ≥ 30) or duration of intervention ≥ 24 weeks	7	**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 weeks. No clear additive effect has been reported on physical performance.** **In conclusion, to achieve optimal effects on muscle mass and muscle strength in older adults, particularly obese, we recommend protein supplementation in combination with resistance training (with a minimum duration of 24 weeks to increase muscle mass).**	**3**
Pedersen 2014[26]	v				2 studies (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 2016[34]	v				9 studies (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." Muscle size: "7/8 studies studies reported significant increases in supplemented (+PRT) and non-supplemented (PRT only) groups, but with no significant differences between the groups."	SOME EVIDENCE in favour of no difference	6		
Thomas 2016[34]		v			15 studies (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 favour of no difference	6		

Liao 2017[33]		v			6 studies (handgrip strength) (357)
					13 studies (leg strength) (668)
						Y	Handgrip strength: "No significant difference in the increase in handgrip strength"
							Leg strength: SMD 0.69 (95% CI 0.39 to 0.98, P < .00001; I² = 67%, P = .0001)
							  Subgroup Men: SMD 0.87 (95% CI 0.43 to 1.31, P < .001; I² = 51%, P = .06)
							  Subgroup BMI ≥ 30 kg/m²: SMD 0.88 (95% CI 0.42 to 1.34; P = .0004; I² = 26%, p = .26)
								SUFFICIENT EVIDENCE in favour of INTERVENTION for leg strength in people with obesity (BMI ≥ 30)	7		

Liao 2017[33]			v		10 studies (654)	Y	Gait speed, 6min or 400m 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 favour of no difference	7		
Colonetti 2016[31]				v	1 study (144)	N	Renal function: "Not negatively affected after 20 g of whey protein supplementation"	INSUFFICIENT EVIDENCE TO DETERMINE	8		

Creatine supplementation + progressive resistance training (PRT)											
Beaudart 2017[32]	v				5 studies (167)	N	Muscle mass: 4/5 studies in favour of an additional effect of creatine supplementation on top of exercises	SOME EVIDENCE in favour of INTERVENTION	7		
Denison 2015[30]	v				2 studies (69)	N	FFM: 2/2 studies showed greater gains among supplemented participants who received exercise training, compared to the placebo groups that only received exercise training.	SOME EVIDENCE in favour of INTERVENTION	3	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. Creatine supplementation on top of progressive resistance training may be considered as an intervention to increase muscle mass and muscle strength.	2
Naseeb 2017[27]	v				2 studies (78)	N	Muscle mass and FFM: "Creatine supplementation with resistance training increased muscle mass (Δ% = +2.8%) and FFM (Δ% = +3.2%). The increase was greater than in the exercise only group (P < .05)." aLM: "Creatine supplementation with resistance training improved aLM. The increase was greater than in the exercise only group."	SOME EVIDENCE in favour of INTERVENTION	3		
Beaudart 2017[32]		v			5 studies (167)	N	Muscle strength: 4/5 studies in favour of an additional effect of creatine for some strength outcomes	SOME EVIDENCE in favour of INTERVENTION	7		
Denison 2015[30]		v			2 studies (69)	N	Muscle strength: 2/2 studies showed greater improvements in participants supplemented with creatine, compared to the placebo groups. All groups also received exercise training.	SOME EVIDENCE in favour of INTERVENTION	3		
Naseeb 2017[27]		v			1 study (18)	N	1RM strength: "Creatine supplementation with resistance training increased 1RM strength (Δ = +5.1%). The increase was greater than in the exercise only group (P < .05)."	INSUFFICIENT EVIDENCE TO DETERMINE	3		
Beaudart 2017[32]			v		4 studies (147)	N	Physical performance: 1/4 studies in favour of an interactive effect of creatine	SOME EVIDENCE in favour of no difference	7		
Denison 2015[30]			v		2 studies (69)	N	Physical performance: 0/2 studies showed evidence of additional benefits arising from supplementation on top of exercise training.	SOME EVIDENCE in favour of no difference	3		
Nutritional Supplementation + physical exercise program											
Protein (or: protein or EAA) supplementation + physical exercise program											
Beaudart 2017[32]	v				12 studies (1049)	N	Muscle mass: 3/12 studies showed additional effect of protein supplementation on top of exercises	SOME EVIDENCE in favour of no difference	7		
Denison 2015[30]	v				7 studies (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 following HMB supplementation (HMB+PRT vs. placebo +PRT, P = .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 favour of no difference	3	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
Malafarina 2013[28]	v				1 study (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 2017[27]	v				2 studies (162)	N	Lean body mass: "Lean body mass increased in protein supplemented group compared with the placebo group (P = .006). Both groups performed PRT." Lean tissue mass and fat mass: "Protein intake of 1.3 g/kg BW/day enhanced PRT effects on lean tissue mass (P < .05) and decreased fat mass (P < .05) and percent of body fat (P < .01)."	SOME EVIDENCE in favour of INTERVENTION	3		
Beaudart 2017[32]		v			12 studies (909)	N	Muscle strength: 3/12 studies showed additional effect of protein on top of exercises	SOME EVIDENCE in favour of no difference	7		

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Study						N studies (n)	N	Outcome	Conclusion	Score	Summary	
Denison 2015[30]		v				7 studies (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 > 75y	SOME EVIDENCE in favour of no difference	3		
Naseeb 2017[27]		v				1 study (100)	N	Muscle strength: "Protein intake of 1.3 g/kg BW/day enhanced PRT effects on muscle strength (P < .05)."	INSUFFICIENT EVIDENCE TO DETERMINE	3		
Beaudart 2017[32]			v			9 studies (793)	N	Physical performance: No additional effect of protein on top of exercises"	SOME EVIDENCE in favour of no difference	7		
Denison 2015[30]			v			4 studies (569)	N	Physical performance: 0/4 studies showed additional improvement of the combination of exercise training and protein/EAA supplementation	SOME EVIDENCE in favour of no difference	3		
Malafarina 2013[28]			v			2 studies (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." 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 nontrained groups, regardless of supplementation."	SOME EVIDENCE in favour of no difference	5		
Essential Amino Acids (EAA) supplementation + physical exercise program												
Beaudart 2017[32]	v					3 studies (196)	N	Muscle mass: "No additional effect of EAA on top of exercises"	SOME EVIDENCE in favour of no difference	7	**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 as an intervention to increase muscle mass, muscle strength and physical performance.**	**2**
Malafarina 2013[28]	v					2 studies (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 = .007)" FFM: "Significant increase (P = .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 favour of INTERVENTION	5		
Naseeb 2017[27]	v					1 study (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 2017[32]		v				3 studies (196)	N	Muscle strength: "No additional effect of EAA on top of exercises"	SOME EVIDENCE in favour of no difference	7		
Naseeb 2017[27]		v				1 study (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 2017[32]			v			2 studies (179)	N	Walking speed and SPPB: "No additional effect of EAA on top of exercises"	SOME EVIDENCE in favour of no difference	7		
Malafarina 2013[28]			v			1 study (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 = .007)	INSUFFICIENT EVIDENCE TO DETERMINE	5		
Naseeb 2017[27]			v			1 study (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		
β-hydroxy-β-methylbutyrate (HMB) supplementation + physical exercise program												
Beaudart 2017[32]	v					3 studies (103)	N	Muscle mass: 1/3 articles in favour of HMB supplementation on top of exercises	SOME EVIDENCE in favour of no difference	7	**No clear additive effect of HMB on top of physical exercise has**	**2**

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Reference	S	MM	MS	PP	Studies (N)	N	Outcome	Evidence	QoE	Conclusion	
Beaudart 2017[32]			v		3 studies (103)	N	Muscle strength: "No additional effect of HMB supplementation on top of exercises"	SOME EVIDENCE in favour of no difference	7	been reported on muscle mass, muscle strength and physical performance. In conclusion, HMB supplementation on top of physical exercise should not be considered as an intervention to increase muscle mass, strength and physical performance.	
Malafarina 2013[28]			v		1 study (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 2017[32]				v	2 studies (72)	N	Timed up and go test: "No additional effect of HMB supplementation on top of exercises"	SOME EVIDENCE in favour of no difference	7		
Multi-nutrient supplementation + physical exercise program											
Beaudart 2017[32]		v			4 studies (300)	N	Muscle mass: 0/4 studies showed an additional effect of multi-nutrient 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 as an intervention to increase muscle mass, muscle strength and physical performance.	2
Denison 2015[30]		v			5 studies (?)	N	Muscle size: 0/6 studies showed evidence of interactive effects of multinutrient supplementation with exercise training	INSUFFICIENT EVIDENCE	3		
Beaudart 2017[32]			v		5 studies (379)	N	Muscle strength: 1/5 studies showed an additional effect of multi-nutrient supplementation on top of exercises	INSUFFICIENT EVIDENCE	7		
Denison 2015[30]			v		6 studies (659)	N	Muscle strength: 0/6 studies showed evidence of interactive effects of multinutrient supplementation with exercise training	INSUFFICIENT EVIDENCE	3		
Beaudart 2017[32]				v	4 studies (304)	N	Physical performance: 0/4 studies showed an additional effect of multi-nutrient intervention on top of exercises	INSUFFICIENT EVIDENCE	7		
Denison 2015[30]				v	6 studies (659)	N	Physical performance: 0/6 studies showed evidence of interactive effects of multinutrient supplementation with exercise training	INSUFFICIENT EVIDENCE	3		

AE: adverse events; aLM: appendicular lean mass; ASM: appendicular skeletal muscle mass; ASMI: appendicular muscle mass index; BC: body composition; BMI: body mass index; BW: body weight; CI: confidence interval; kg: kilogram; EAA: essential amino acid; E%: energy percent; FM: fat mass; FFM: fat free mass; LBM: lean body mass; MA: meta-analysis; MD: mean difference; MM: muscle mass; MMI: muscle mass index; MS: muscle strength; N: Newton: Nm: Newton meter; PP: physical performance; PRT: progressive resistance training; QoE: quality of evidence; RDA: recommended dietary allowance; RM: repetition maximum; S: sarcopenia; SMD: standardized mean difference; SR: systematic review; vs: versus; WMD: weighted mean difference; y: year v: indicates the construct that is addressed: sarcopenia (as a construct) or the sarcopenia sub-dimensions (muscle mass, muscle strength, physical performance) or adverse events; a question mark (?) indicates that the number was not mentioned in the systematic review/meta-analysis

4.2. Protein supplementation

Five systematic reviews provided data on protein supplementation only,[22, 25-28] of which one performed a meta-analysis.[22] Four systematic reviews (one with a meta-analysis [33]) evaluated the combination of protein supplementation and resistance training [26, 31, 33, 34] and four (without meta-analyses) the combination with (various types of) physical exercise.[27, 28, 30, 32]

Most systematic reviews, with, in general low to moderate AMSTAR scores, showed either insufficient evidence or were unable to determine whether protein supplementation alone is effective to improve muscle mass, strength and/or physical performance.[25, 27, 28] One meta-analysis of moderate quality showed, in a rather small number of participants, some evidence in favour of no difference between protein supplementation and placebo on muscle mass and muscle strength.[22] In contrast, a large systematic review of moderate quality including 2940 individuals showed some evidence in favour of protein supplementation on muscle mass.[26] According to this review, a recommended dietary allowance (RDA) of 0.83 g (gram) good-quality protein/kg (kilogram) body weight/day represents the minimum dietary protein need of virtually all healthy elderly.[26] Together, the data in our umbrella review suggest a positive effect of protein supplementation on muscle mass, while no clear effect has been reported on muscle strength and physical performance. Based on the current evidence, proteins may be considered as an intervention to increase muscle mass (QoE2).

When combined with resistance training, two systematic reviews of moderate to high quality were not able to determine whether this combined intervention is more effective to improve muscle mass than resistance training alone.[26, 31] There was some evidence of two systematic reviews of moderate quality in favour of no difference between the combined intervention *vs.* resistance training alone on body composition, muscle strength or physical performance.[33, 34] However, one of these systematic reviews showed, in a meta-analysis of moderate quality,

sufficient evidence in favour of the combined intervention on muscle mass and strength, but only in persons with a BMI ≥ 30 kg/m² and, for muscle mass, also when the duration of the intervention was longer than 24 weeks.[33] Together, the data in our 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 ≥ 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 obese, we recommend protein supplementation in combination with resistance training (with a minimum duration of 24 weeks to increase muscle mass) (QoE3).

When combined with a multimodal exercise program, two 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.[27, 28] Most of the reviews showed some evidence in favour of no difference on muscle mass, muscle strength and/or physical performance.[28, 30, 32] The quality of these reviews was low to moderate. There was one systematic review of low quality that showed some evidence in favour of the combined intervention on muscle mass when compared with an exercise program alone.[27] In the individual trials in these four 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,[27, 30, 32] or was not specified.[28] 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 muscle strength and physical performance (QoE2).

Two systematic reviews examined the adverse effects of proteins alone [27] or combined with resistance training.[31] The intake of 1.0 to 1.4 g proteins/kg body weight/day was not associated with adverse events.[27] In particular, renal function was not affected by a 12 weeks intervention in which 20 g of whey proteins were consumed directly after resistance training.[35] However, due to the low number of participants in these reviews, the evidence was considered as insufficient to determine the adverse effect of protein supplementation.

4.3. Essential Amino Acid (EAA) 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, will be discussed in the next section. Three systematic reviews provided data on supplementation with EAA.[20, 24, 28] One of these performed a meta-analysis.[20] Three systematic reviews (all without meta-analysis) evaluated the combination of EAA supplementation with (various types) of physical exercise.[27, 28, 32]

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 physical performance.[24, 28] There was some evidence of one meta-analysis of high quality in favour of no difference between EAA supplementation and placebo.[20] 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 (QoE4).

Regarding the effects of EAA supplementation with physical exercise, two 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 to the effect of the exercise intervention alone, EAA supplementation alone or no

intervention.[27, 28] One systematic review of moderate quality showed some evidence in favour of no difference between EAA supplementation and EAA supplementation on top of exercise, neither on muscle mass, muscle strength nor physical performance.[32] In contrast, another systematic review of moderate quality showed some evidence in favour of the combined intervention when compared with no treatment or with exercise alone.[28] In the individual trials in these reviews assessing the combined effect of EAA supplementation and physical exercise, the exercise program was not specified [28] or consisted of progressive resistance training combined with or without balance, gait or other exercises.[27, 32] 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 as an intervention to increase muscle mass, muscle strength and physical performance (QoE2).

4.4.   Leucine supplementation

Four systematic reviews examined the effect of leucine supplementation only.[21, 24, 28, 29] Of these, two performed a meta-analysis.[21, 29] One of these reviews performed a subgroup analysis to differentate between healthy and sarcopenic persons.[29]

One systematic review of high quality was not able to determine whether leucine supplementation alone is effective to improve muscle mass or strength.[24] One systematic review of moderate quality showed insufficient evidence that leucine supplementation is more effective to improve muscle mass and muscle strength compared to the non-supplemented group,[28] while two systematic reviews of moderate to high quality showed some evidence in favour of no difference between leucine and placebo.[21, 29] However, there was sufficient evidence of one meta-analysis in favour of leucine supplementation on muscle mass, but only in sarcopenic older persons.[29] 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, we do recommend leucine supplementation alone for sarcopenic older people to increase muscle mass (QoE3).

4.5. β-hydroxy-β-methylbutyrate (HMB) supplementation

Four systematic reviews examined the effect of HMB supplementation on muscle mass, muscle strength and/or physical performance. In two of these, HMB supplementation was the only intervention,[23, 28] while HMB was combined with (various types of) physical exercise in the other two.[28, 32] There was one meta-analysis about the effect on body composition.[23] 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.[23, 28] One systematic review of high quality showed some evidence in favour of no difference between HMB and placebo on muscle strength.[23] However, the same systematic review showed, with a meta-analysis, sufficient evidence in favour of HMB supplementation on muscle mass.[23] 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 as an intervention to increase muscle mass (QoE4).

When combined with physical exercise, one systematic review of moderate quality showed insufficient evidence to determine the additive effect of this combined intervention compared to exercise alone on muscle strength.[28] Another systematic review of moderate quality showed some evidence in favour of no difference between the combined intervention and the exercise intervention alone on muscle mass, muscle strength and physical performance.[32] Looking at the individual trials in these systematic reviews, the exercise intervention consisted of progressive resistance training with or without other exercises [32] or was not specified.[28] 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 as an intervention to increase muscle mass, muscle strength and physical performance (QoE2).

4.6. 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.[27, 30, 32]

One of these three 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 to exercise alone on muscle strength, but there was some evidence in favour of the combined intervention on muscle mass.[27] Two other systematic reviews of low to moderate quality found some evidence in favour 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 favour of the combined intervention.[30, 32] 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 as an intervention to increase muscle mass and muscle strength (QoE2).

4.7. Multinutrient supplementation

While no reviews examined the effect of multinutrient supplementation alone or in combination with resistance training, two reviews examined the effect of multinutrient

supplementation on muscle mass, muscle strength and/or physical performance in combination with (various types of) physical exercise.[30, 32]

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 to the exercise intervention alone.[30, 32] In these reviews, the multinutrient supplementation consisted of a variety of macronutrients (proteins, carbohydrates, fats) and micronutrients (vitamins, minerals).[30, 32] In the individual trials in these systematic reviews, the exercise intervention consisted of progressive resistance training with or without other exercises,[30 32] while in one trial in the meta-analysis of Beaudart et al it was a walking program alone.[30] 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 as an intervention to increase muscle mass, strength and physical performance (QoE2).

Table 2 '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
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
Essential Amino Acid (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
β-hydroxy-β-methylbutyrate (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 + 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 ≥ 30) and, for muscle mass, also in persons with a duration of intervention of ≥ 24 weeks. No clear additive effect has been reported on physical performance.	3
Creatine supplementation + 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
β-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

BW: body weight; kg: kilogram; QoE: quality of evidence supporting each 'bottom line statement' based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for primary evidence: 1: very low; 2: low; 3: moderate; 4 high.

Table 3 Recommendations with quality of evidence (QoE)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 resistance training** (with a minimum duration of 24 weeks to increase muscle mass) is recommended to achieve optimal effects on muscle mass and muscle strength in older adults, particularly obese (moderate QoE).   • **Protein supplementation on top of physical exercise** may be considered to increase muscle mass, but not for muscle strength and physical performance (low QoE).
Essential Amino Acid supplementation   • **EAA supplementation alone** should not be considered as an intervention to increase muscle mass, muscle strength and physical performance (high QoE).   • **EAA supplementation on top of physical exercise** should not be considered as an intervention to increase muscle mass, strength and physical performance (low QoE).
Leucine supplementation is recommended for sarcopenic older people to increase muscle mass (moderate QoE).
Beta-hydroxy-beta-methylbutyrate (HMB) supplementation   • **HMB supplementation** alone may be considered as an intervention to increase muscle mass (high QoE).   • **HMB supplementation on top of physical exercise** should not be considered as an intervention to increase muscle mass, strength and physical performance (low QoE).
Creatine supplementation on top of progressive resistance training may be considered as an intervention to increase muscle mass and muscle strength (low QoE).
Multinutrient supplementation on top of physical exercise should not be considered as an intervention to increase muscle mass, strength and physical performance (low QoE).

5. Discussion

In this umbrella review we aimed to provide a systematic overview of the effect of nutritional interventions targeting sarcopenia or one of the three sarcopenia components (muscle mass, muscle strength or physical performance).

At this moment, best evidence is available to recommend leucine supplementation since 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, while 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 since no sufficient evidence has been found for an additional effect of the supplement on muscle mass, strength or physical performance.

5.1. Protein supplementation

Dietary proteins deliver the amino acids (AA) needed for the synthesis of muscle proteins and form an anabolic stimulus that promotes muscle protein synthesis (MPS).[36] The current recommended dietary allowance (RDA) for healthy adults is 0.8 g/kg body weight,[37] a recommendation based on nitrogen-balance studies. With respect to the elderly, a systematic review of 23 papers, included in our umbrella review, found *probable* evidence to recommend 0.83 g good-quality protein/kg body weight/day as the minimum dietary protein need of generally healthy elderly aged ≥ 65 years.[26] However, several limitations related to nitrogen-balance studies are likely to result in an under-estimation of the true protein need, especially in the elderly, in whom short-term nitrogen-balance studies may not be able to detect the slow rate of muscle protein turnover.[38] 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.[38] Current evidence indeed suggests that, while the post-absorptive MPS is preserved in elderly, MPS rate in response to protein feeding is blunted, with a post-prandial MPS rate that is 16% lower in persons aged ≥ 75 years.[39]

Therefore, currently, several expert groups recommend for the elderly a protein intake that is higher than the RDA for adults and which ranges from 1.0 to 1.2 g/kg/ body weight for healthy elderly (> 65 years), over 1.2 to 1.5 g/kg/ body weight for elderly with an acute or chronic disease and up to 2.0 g/kg/ body weight for elderly with severe illness, injury or marked malnutrition.[38, 40, 41] 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 indeed growing evidence that 'fast' proteins (such as whey, a milk-derived protein) may stimulate MPS more than 'slow' proteins (such as casein, the other milk-derived protein) and that an evenly distributed protein intake during the day, with an intake of at least 25 to 30 g of proteins per meal, is required to optimize MPS.[42-44] However, despite the well-established effect of proteins on MPS, individual RCTs showed inconsistent evidence regarding the effect of long-term (≥ 12 weeks) protein supplementation on muscle mass, muscle strength and physical performance. Negative findings may, at least partly, be explained 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.[45, 46]

Likewise, systematic reviews and a meta-analysis included in our umbrella review found mixed evidence regarding the effect of protein supplementation, with standardized effectiveness statements varying from 'insufficient evidence', 'insufficient evidence to determine', 'some evidence in favour of no difference' and 'some evidence in favour of protein supplementation

compared to placebo'. Together, our 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 rather indicating 'no evidence of effect' than 'evidence of no effect'. This might have been the case for the systematic reviews of Malafarina et al. and Naseeb et al., in which the number of studies and the number of the participants included in the studies were rather small.[27, 28] Notwithstanding, based on the current evidence, we concluded that *protein supplementation may be considered as 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 is indeed 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 ageing. When combining both anabolic interventions, physical activity may restore the sensitivity of older muscles to protein or amino acid intake, thereby increasing the use of the ingested proteins. In turn, the ingestion of sufficient proteins in close temporal proximity to exercise produces an anabolic stimulus that increases the MPS in response to exercise, with a comparable effect in young and old individuals.[47] Inconsistent results of the combination of protein intake and exercise intervention in individual RCTs may, at least partly, be explained by an already adequate baseline protein intake in participants of the RCTs as well as by differences in protein source, timing of ingestion and type and intensity of the exercise program.[30]

In our umbrella review, the large meta-analysis of Liao et al. found sufficient evidence in favour of the combination of protein supplementation and resistance training on muscle mass and muscle strength, compared with resistance training alone.[33] Therefore, we do recommend protein supplementation in combination with resistance training to achieve optimal effects on muscle mass and muscle strength. Since the heterogeneity of the RCTs in the meta-analysis of Liao was only acceptable (< 50%) in the subgroups 'duration of intervention ≥ 24 weeks' (for muscle mass) and 'BMI ≥ 30 kg/m²' (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 for obese elderly. Only one systematic review examined, with a meta-analysis, the effect on physical performance and found no significant effects of the combined intervention compared to resistance training alone.[33] Therefore, our 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 obese, protein supplementation in combination with resistance training (with a minimum duration of 24 weeks to increase muscle mass) is recommended.*

Finally, our 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 (type, intensity, duration). Looking at the individual trials, we found that 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. Our 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 favour 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 on muscle strength and physical performance. Together, we concluded that *protein supplementation on top of physical exercise may be considered to increase muscle mass, but not for muscle strength and physical performance*.

5.2.   Essential amino acid (EAA) supplementation

Essential (indispensable) AA are AA that can never be synthesized in the human body, in contrast to the non-essential (dispensable) and the conditionally-indispensable AA. These EAA should, by consequence, be supplied from dietary sources. Nine of the 20 AA from which human proteins are built, are EAA. Previous research has shown that the ingestion of EAA effectively stimulates MPS in the elderly.[48] Even more, when comparing MPS following the ingestion of an isocaloric intact whey protein supplement and the same amount of an EEA supplement, the increase in MPS rate following whey protein was 50% less of 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 EAA is more energetically efficient than with intact proteins.[49]

Yet, systematic reviews and a meta-analysis included in our umbrella-review did not reveal sufficient evidence in favour of EAA supplementation, with standardized effectiveness statements indicating 'insufficient evidence', 'insufficient evidence to determine' and 'some evidence in favour 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,[20] currently no clear effect has been reported of EAA on muscle mass, muscle strength and physical performance.

Therefore, we concluded that *EAA supplementation should not be considered as an intervention to increase muscle mass, muscle strength and physical performance.*

5.3. Leucine supplementation

These negative findings of individual RCTs and meta-analyses about the effect of EAA on sarcopenia components may be explained by the content of the EAA mixture, with a lack of so-called branched-chain amino acids. Three of the nine EAAs (leucine, isoleucine and valine) are branched-chain amino acids (BCAA). These BCAA, and especially leucine, have a particular role in the MPS.[50] They do not only serve as a substrate for MPS, but also have specific positive effects on the intracellular signaling pathways involved in MPS.[51, 52] Furthermore, enriching the diet with these specific EAA may overcome the rate-limiting effect of the BCAAs in MPS.[38] Therefore, research has been done to evaluate the effects of BCAA mixtures and leucine alone. In a systematic evaluation of the evidence, our umbrella review showed that the standardized effectiveness statements for the effect of leucine on muscle mass were 'insufficient evidence',[28] 'insufficient evidence to determine the difference between leucine supplementation and placebo',[24] 'some evidence in favour of no difference' [21] and 'sufficient evidence in favour of leucine supplementation'.[29] The latter was reported for the meta-analysis of Komar et al., leading us to recommend leucine to increase muscle mass. However, since a subanalysis of this meta-analysis showed that leucine was only effective in the subgroup of sarcopenic elderly, but not in healthy elderly, our recommendation only applies for persons with sarcopenia. It should be noted, however, that the meta-analysis of Komar et al. did not specify how sarcopenia was defined in the individual RCTs.

For leucine and muscle strength, the standardized effectiveness statements were 'insufficient evidence',[28] 'insufficient evidence to determine the difference between leucine supplementation and placebo' [24] and 'some evidence in favour of no difference'.[29] No RCTs

have assessed the effect on physical performance. So, in contrast to muscle mass in sarcopenic elderly, we could not demonstrate a clear effect of leucine supplementation on muscle strength and physical performance.

Thus, BCAA such as leucine might be promising pharmaconutrients in the prevention and treatment of sarcopenia,[38, 53] or at least, as suggested by our results, to improve muscle mass in sarcopenic individuals. Recently, however, the unique capacity of BCAA and leucine to enhance MPS has been questioned and some individual long-term supplementation studies with leucine have failed to show a positive effect on muscle mass.[50, 51, 53, 54] A potential explanation, apart from a too short supplementation period, is that, although BCAA have the capacity the stimulate MPS, a full complement of EAA may be needed to maximize MPS.[50] This is in particular true in combination with exercise training, when the difference in MPS following resistance training between BCAAs and whey protein containing the same amount of BCAAs may even be as high as 50%.[55] Our umbrella review did not include systematic reviews that examined the combined effect of leucine and resistance training, so we could not evaluate this combined effect. The explanation is that BCAA mixtures may provide too limited substrate for MPS due to limited availability of the other EAA needed for MPS.[50, 54] Thus, although BCAA supplementation stimulates MPS, this response may not be maximal since BCAA do not increase the supply of all EAA that may become rate-limiting for accelerated MPS.[50, 54] As with the BCAA mixtures, leucine supplementation alone does not provide the other EAA, thereby limiting the maximal stimulation of MPS. Moreover, plasma-elevation of leucine leads to oxidation of the other BCAA 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 failed to 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.

5.4.   β-hydroxy-β-methylbutyrate (HMB) supplementation

HMB is a metabolite of leucine with multiple actions. It stimulates MPS through up-regulation of the mTOR pathway and attenuates protein degradation through attenuation of the ubiquitin-proteasome pathway. Further, it may stimulate MPS through changes in the activity of GH/IGF-1 axis and has been shown to affect satellite cells in skeletal muscle resulting in increased proliferation and differentiation of myoblasts.[56]

HMB has been widely used by athletes to enhance muscle mass, muscle strength, muscle power, aerobic performance and recovery. [56] Studies in the elderly, however, remain limited, which is illustrated by our umbrella review that only included 3 systematic reviews with HMB. [23, 28, 32]. One of these, a meta-analysis, found 'sufficient evidence in favour of HMB supplementation' on muscle mass.[23] However, for muscle strength and physical performance, the evidence was 'insufficient', 'insufficient to determine the difference with placebo' or 'in favour of no difference',[23, 28] 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' might reflect underpowering and rather indicate 'no evidence of effect' than 'evidence of no effect'. Notwithstanding, based on the current evidence, we concluded that *HMB supplementation may be considered as an intervention to increase muscle mass, but not for muscle strength or physical performance.* With regards to the optimal dosage of HMB, evidence is not conclusive but most studies advise a daily dose of 3 g.

5.5.   Creatine supplementation

Creatine is endogenously synthesized by the liver, kidney and pancreas from the AA 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 resynthesis of adenosine triphosphate during muscle contraction, thereby improving high-intensity exercise capacity and leading to greater training adaptations.[57-59] While creatine monohydrate is the most popular supplement used by athletes, it is currently increasingly studied in combination with resistance training to determine the effect on muscle mass and muscle strength in the elderly.[57]

Also our umbrella review investigated the effect of creatine supplementation in combination with progressive resistance training.[27, 30, 32] For muscle mass and strength, three systematic reviews showed 'some evidence in favour of the intervention'; thus, the creatine supplementation had an additive positive effect on top of the exercise program.[27, 30, 32] No clear effect has been reported on physical performance.[30, 32] Thus, we concluded that *creatine supplementation on top of progressive resistance training may be considered as an intervention to increase muscle mass and muscle strength, but not physcial performance.* Recently, the International Society of Sports Nutrition (ISNN) concluded along the same line that creatine has a number of therapeutic benefits in both healthy and diseased elderly, suggesting that creatine supplementation can help to prevent sarcopenia in the elderly.[59]

6. 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, i.e. an umbrella review considers for inclusion the highest level of evidence. Our literature search is also systematic in nature, in accordance with the PRISMA-guidelines, which gives a higher level of evidence than a narrative review. Because our umbrella review is dependent on the quality of the included

systematic reviews and meta-analyses, we assessed this quality by using the AMSTAR-criteria. Five of the 13 included systematic reviews were of high quality.

A limitation, inherent to our strict search terms, is the low total amount of eligible reviews (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 (2/13) to moderate (6/13) 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 we did not evaluate the quality of the individual RTCs or analysed the clinical trials to the level of the raw data. As such, we were not able to distinguish studies using 'optimal' from 'suboptimal' supplementation. The methodological quality of the included reviews is, however, an item that is assessed by the AMSTAR method we used to rate the quality of the evidence supporting each 'bottom line statement'. Next, physical exercise interventions alone, which has generally accepted effects against sarcopenia, and pharmacological interventions have been recently documented by other working groups of our consortium and were not in the scope of this review.[12, 13] Finally, this umbrella review was part of the Sarcopenia Guideline project of the Belgian Society of Gerontology and Geriatrics (BSGG) which was initiated in 2015 and of which the literature search was completed in 2017. Therefore, databases have been searched till November 2017 and no more recent reviews have been included.

7. Conclusion

The aim of this review was to provide an evidence-based overview of nutritional interventions for sarcopenia targeting one or more of the three sarcopenia domains (muscle mass, muscle strength or physical performance). Based on the results of this umbrella review, we conclude that, at this moment, best evidence is available to recommend leucine supplementation since 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, while 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 subjects since all but one [29] of the included reviews did not specify sarcopenia status of the participants. Probably, the most important reason for this is the lack of universally accepted criteria for the diagnosis of sarcopenia. Therefore, most of the conclusions in this umbrella review focus on elderly in a broader sense, thus encompassing both the prevention and treatment of sarcopenia. Effects on sarcopenia as a construct were not retrieved.

8. Recommendation

At this moment best evidence is available to recommend leucine supplementation since it has a significant effect on muscle mass in persons with sarcopenia.

(Quality of evidence – 3)

Protein supplementation on top of resistance training is recommended to increase muscle mass and muscle strength. This supplementation is particularly advised for persons with obesitas and should be performed at least for 24 weeks to achieve optimal results.

(Quality of evidence – 3)

No side effects could be retrieved from the evidence.

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10.   Appendix

Appendix S2   Full search strategy

Pubmed:

Search ((("Sarcopenia"[Mesh]) OR sarcopenia)) AND ((((protein suppl*) OR "Dietary Supplements"[Mesh]) OR "Dietary Proteins"[Mesh]) OR ("Diet, Food, and Nutrition"[Mesh])) AND "Review"[Publication Type]

Web of Science:

1. Document types: (Review) OR TITLE: ("systematic review")

2. Topic: (sarcopen*)

3. Topic: ("protein suppl*" OR "Dietary Supplements" OR "Dietary Proteins" OR Diet OR Food OR Nutrition)

4. #3 AND #1

5. #4 AND #2

SUMMARY OF RECOMMENDATIONS

-

ONE PAGERS

-

BVGG-SBGG

Belgian Society
for GERONTOLOGY
and GERIATRICS

Belgian Society for GERONTOLOGY and GERIATRICS

RECOMMENDATIONS
Sarcopenia Guideline 2018-2019

BVGG - SBGG

ASSESSMENT

RISK FACTORS

> **Cigarette smoking** as an isolated factor may contribute to the development of sarcopenia and can be identified as a possible risk factor (odds ratios = 1.12(95 % CI 1.03-1.21)). Alcohol consumption and osteoarthritis are not considered as a possible risk factor.

MUSCLE MASS

> For estimating the muscle mass in the context of sarcopenia, we recommend to use **relative indices** (height, body weight); e.g. appendicular lean mass (ALM, assessed by DXA or BIA) corrected by height^2 or BMI. We recommend the use of **cut-off values for relative muscle mass** that are proposed by the **international working groups on sarcopenia** (EWGSOP, FNIH, IWGS).

MUSCLE STRENGTH

> We recommend **maximum handgrip strength** of the **dominant** hand to assess general muscle strength. We recommend categorising patients according to the **normative values for healthy young people**.

PHYSICAL PERFORMANCE

> At this moment, best evidence is available for using **gait speed** to appraise physical performance in a clinical setting. We recommend categorizing subjects according to the **normative values for healthy young people** as presented in the recommendation by using the **4m usual gait speed** protocol.

INTERVENTION

PHARMACOLOGY

> We recommend **vitamin D supplementation** to improve muscle strength and physical performance in older people, especially women, with low baseline serum levels. **Testosterone supplementation** may be considered in older men with serum levels < 200–300 ng/dl and clinical muscle weakness, to improve muscle mass and muscle strength.

EXERCISE

> We recommend **resistance training and multimodal exercise** to improve muscle strength, muscle mass and physical performance for healthy, pre-sarcopenic or sarcopenic older people since evidence shows a significant and positive effect. We recommend **occlusion training** at a low intensity under supervision of a trained exercise coach to improve muscle strength.

NUTRITION

> At this moment best evidence is available to recommend **leucine** supplementation since is 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 obesitas and should be performed at least for 24 weeks to achieve optimal results.

Belgian Society for GERONTOLOGY and GERIATRICS

PROJECT DESIGN
Sarcopenia Guideline 2018-2019

BVGG – SBGG

RATIONALE

Sarcopenia is a progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality. A range of lifestyle, pharmacological, non-pharmacological and rehabilitation interventions are reported to prevent and/or treat sarcopenia.

OBJECTIVE

The aim of the Sarcopenia Guideline project is to translate the actual scientific body of knowledge regarding sarcopenia into a practice guideline. Recommendations will be tailored to the Belgian context and will be written in English, French and Dutch and will focus on three levels:
1) Recommendations for health care and prevention specialists
2) Summary of evidence
3) Information for the public (Layman's terms)

EXECUTION

The topic of this project and the selection of the involved researchers was done by the BVGG Governing Board who kept track of the project progress. A scope statement was generated by the Guideline Development Group (GDG) to outline the extent of the project. This group also selected the working group members and provided feedback. The seven working groups refined and agreed the review questions, systematically selected relevant evidence, assessed the quality of this evidence, summarized and interpreted the results and suggested guideline recommendations. Two scientific staff members prepared the work plan, organized meetings, developed search strategies, provided support for the GDG and the Working Groups and prepared the first draft of the guideline.

RESULTS

For every working group recommendations were generated and validated by the entire project group. The results of the working groups on intervention are transformed in to publishable papers. The complete guideline will be submitted to CEBAM, the Belgian Centre for Evidence-based Medicine – Cochrane Belgium.

BSGG Governing Board (N=19)

Scientific Staff Members (N=2)

Guideline Development Group (N=11)

Working Groups (N=14)

4 Working Groups ASSESSMENT
- Risk Factors
- Muscle Mass
- Muscle Strength
- Physical Performance

3 Working Groups INTERVENTION
- Exercise
- Nutrition
- Pharmacology

RISK FACTORS
Sarcopenia Guideline 2018-2019 - Assessment
BVGG - SBGG

? WHY?

Identifying possible risk factors for the development of sarcopenia* can provide insights into the origination of sarcopenia. These insights can be used in the prevention or treatment of sarcopenia.

*Sarcopenia was investigated as a construct, no search was done on specific subdimensions .

Smoking
N = 22515
Odds ratios

Overall	1.12 (95% CI 1.03-1.21)
Male	1.20 (95% CI 1.06-1.35)
Female	1.21 (95% CI 0.92-1.59)

HOW?

An umbrella review on risk factors for sarcopenia was performed with the following specifications:
- Population: adults aged 65 or more
- Exposure: possible risk factors
- Outcome: sarcopenia
- Study design: systematic review, meta-analysis
- Quality assessment: AMSTAR checklist

Alcohol
N = 13155
Odds ratios

Overall	0.77 (95% CI 0.67-0.88)
Male	0.67 (95% CI 0.54-0.83)
Female	0.89 (95% CI 0.73-1.08)

DATA HANDLING

Initial search yielded 1054 eligible reviews of which 3 were finally included.

If possible odds ratios were retrieved, if not, narrative conclusions were retrieved.

Osteoarthritis
N = 4231
Narrative conclusion

"We cannot support neither the thesis of a direct effect of sarcopenia on OA development nor the opposite relation, because the up-to-date literature lacks basic science studies concerning these topics." (Papalia et al. 2014)

RECOMMENDATION

- **Cigarette smoking** as an isolated factor may contribute to the development of sarcopenia and can be identified as a possible risk factor.
- **Alcohol consumption** and **osteoarthritis** are not considered as a possible risk factor.
- Various expected risk factors such as physical inactivity, sedentary lifestyle, underweight or malnutrition were not reported in the included studies. This can be due to the fact that only systematic reviews and not primary longitudinal studies were included or due the the fact that sarcopenia was searched as a construct and no search on specific subdimensions was performed.

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MUSCLE MASS
Sarcopenia Guideline 2018-2019 - Assessment

BVGG - SBGG

WHY?

According to the European Working Group on Sarcopenia in Older People (EWGSOP2) the diagnosis of sarcopenia is confirmed by the presence of low muscle quantity or quality. Various components of body composition as well as different measurement techniques to estimate muscle quantity are described in literature. The proposed findings can be seen as a call for more research resulting in relative muscle mass data.

HOW?

A systematic search on reference values for muscle mass was performed:

- *Population*: young/healthy men & women (20-39)
- *Exposure*: muscle mass assessed by DXA or BIA
- *Outcome*: reference values
- *Study design*: observational / RCT (baseline)
- *Quality assessment*: COSMIN checklist

DATA HANDLING

An initial umbrella review revealed no relevant systematic reviews. Subsequently a systematic search was performed and revealed 2645 eligible observational studies of which 22 were finally included.

Mean, standard deviation and number of participants was retrieved. Subsequently, standard error, pooled degrees of freedom and pooled standard deviation was calculated. Due to high heterogeneity and low number of studies we were not able to calculate T-scores.

Mostly data regarding **absolute** muscle mass was found in the included papers. No proper **adjusted** data for height or body weight was reported.

		SEVERE	MODERATE	EXPECTED NORMAL
Cutoff consensus statements for Men				
EWGSOP	ALM/h² [kg.m⁻²]	7,23 - 7,26		
EWGSOP2	ASM [kg]	20		
	ASM/height² [kgm⁻²]	7		
IWGS	ALM/h² [kg.m⁻²]	7,23		
FNIH	ALM [kg]	19,75		
	ALM/BMI [m²]	0,789		

		SEVERE	MODERATE	EXPECTED NORMAL
Cutoff consensus statements for Women				
EWGSOP	ALM/h² [kg.m⁻²]	5,50 - 5,67		
EWGSOP2	ASM [kg]	15		
	ASM/height² [kgm⁻²]	6		
IWGS	ALM/h² [kg.m⁻²]	5,67		
FNIH	ALM [kg]	15,02		
	ALM/BMI [m²]	0,512		

🔴 Out of the norm	→	TREATMENT
🟡 Action should be undertaken to prevent worsening	→	SECONDARY PREVENTION
🟢 Healthy, within the norm	→	PRIMARY PREVENTION

Legend: EWGSOP: European Working Group on Sarcopenia in Older People; EWGSOP2: revised EWGSOP consensus; IWGS: International Working Group on Sarcopenia; FNIH: Foundation for the National Institutes of Health Sarcopenia; DXA: Dual-energy X-ray absorptiometry; BIA: Bioelectrical impedance;

RECOMMENDATION

- We want to warn clinicians that **different components of body composition** are described in literature to estimate muscle mass in the context of sarcopenia. These depend on the techniques and devices that have been used, for example Dual-energy X-Ray absorptiometry (lean body mass, appendicular lean mass) or Bioelectrical impedance analysis (fat free mass (including bone), lean body mass (excluding bone)).
- For estimating the muscle mass in the context of sarcopenia, we recommend to use **relative indices** (height, body weight); e.g. appendicular lean mass (ALM, assessed by DXA or BIA) corrected by height² or BMI. For clinical routine, we do not recommend to use other types of medical imagery.
- We recommend the use of **cut-off values for relative muscle mass** that are proposed by the **international working groups on sarcopenia** (EWGSOP2, FNIH, IWGS).

REFERENCES: Andreoli, A., et al. (2011). "Relationship between body composition, body mass index and bone mineral density in a large population of normal, osteopenic and osteoporotic women." La Radiologia medica 116(7): 1115-1123.; Boot, A. M., et al. (2011). "The relation between 25-hydroxyvitamin D with peak bone mineral density and body composition in healthy young adults." Journal of pediatric endocrinology & metabolism: JPEM 24(5): 355-360.; Cheng, Q., et al. (2014). "A cross-sectional study of loss of muscle mass corresponding to sarcopenia in healthy Chinese men and women: reference values, prevalence, and association with bone mass." Journal of bone and mineral metabolism 32(1): 78-88; and 19 others; icons from thenounproject.com.

Belgian Society for GERONTOLOGY and GERIATRICS

PHYSICAL PERFORMANCE
Sarcopenia Guideline 2018-2019 - Assessment

BVGG - SBGG

[?] WHY?

Physical performance is a measurable parameter to determine the severity of sarcopenia according to the European Working Group on Sarcopenia in Older People (EWGSOP). To assess physical performance in a clinical setting, to date best evidence is available for using gait speed. The proposed recommendation is aimed at the need to drive clinical action.

HOW?

An umbrella review on reference values for gait speed was performed.
- *Population*: young/healthy men and women (20-39 year)
- *Exposure*: gait speed
- *Outcome*: reference values
- *Study design*: systematic review, meta-analysis
- *Quality assessment*: AMSTAR checklist

DATA HANDLING

Initial search yielded 60 eligible reviews of which 2 were finally included.

Mean, standard deviation and number of participants was retrieved. Subsequently, standard error, pooled degrees of freedom and pooled standard deviation was calculated.

Finally, T-scores for both genders together were calculated.

> N = 882

> Gait speed

> T-scores

T-SCORE	
< -2	Out of the norm
-2 < X < -1	Action should be undertaken to prevent worsening
> -1	Healthy, within the norm

MEN & WOMEN	VERY LOW	AT RISK	NORMAL
Reference data			
	0.8	1.1	1.4
Cut-off consensus statements			
EWGSOP 1 & 2 (m/s)	0.8		
IWGS (m/s)	1.1		
FNIH (m/s)	0.8		

VERY LOW	< 0.8 m/s	➢ treatment
AT RISK	0.8 m/s < X < 1.1 m/s	➢ secundary prevention
NORMAL	> 1.1 m/s	➢ primary prevention

Legend: EWGSOP: European Working Group on Sarcopenia in Older People; IWGS: International Working Group on Sarcopenia; FNIH: Foundation for the National Institutes of Health Sarcopenia

RECOMMENDATION

- At this moment, best evidence is available for using **gait speed** to appraise physical performance in a clinical setting. Since for gait speed, robust normative values are available, we recommend the use of gait speed to assess physical performance.
- Different protocols exist to asses gait speed and we recommend the **4m usual gait speed** protocol since this is considered most feasible in a clinical setting.
- We recommend categorizing subjects according to the **normative values for healthy young people as presented above.**

REFERENCES: Bohannon RW, Williams Andrews A. Normal walking speed: a descriptive meta-analysis. Physiotherapy 2011;97(3):182-9. [PubMed: 21820535], Salbach NM, O'Brien KK, Brooks D, Irvin E, Martino R, Takhar P, et al. Reference values for standardized tests of walking speed and distance: a systematic review. Gait & posture 2015;41(2):341-60. [PubMed: 25542397]

MUSCLE STRENGTH
Sarcopenia Guideline 2018-2019 - Assessment

BVGG - SBGG

? WHY?

Muscle strength is the primary parameter of sarcopenia according to European Working Group on Sarcopenia in Older People (EWGSOP).

Muscle strength can be assessed by various measurement methods and on various parameters. To assess general muscle strength in a clinical setting, to date best evidence is available for using maximum handgrip strength of the dominant hand . The proposed recommendation is aimed at the need to drive clinical action.

> N = ♂1755 - ♀2194

> GRIP STRENGTH

> T-SCORES

Hydraulic dynamometer

Pneumatic dynamometer

HOW?

A systematic search on reference values for muscle mass was performed:

- *Population*: young/healthy men & women (20-39)
- *Exposure*: grip strength
- *Outcome*: reference values
- *Study design*: observational / RCT (baseline)
- *Quality assessment*: COSMIN checklist

MEN-WOMEN		VERY LOW	AT RISK	NORMAL
REFERENCE DATA		M-F	M-F	M-F
Hydraulic dynamometer	[kg]	25-11	38-21	50-31
Pneumatic dynamometer	[kPa]	71-41	93-59	114-76
CUTOFF CONSENSUS STATEMENTS				
EWGSOP 2	[kg]	27-16		
FNIH	[kg]	26-16	32-20	
	[kg/BMI]	1.0-0.56		

DATA HANDLING

Initial umbrella review revealed no relevant systematic reviews. Subsequently, a systematic search was performed and revealed 912 eligible reviews of which 14 were finally included.

Mean, standard deviation and number of Participants was retrieved. Subsequently, standard error, pooled degrees of freedom and pooled standard deviation was calculated.

Finally, overall T-scores were calculated.

	MEN	WOMEN	
VERY LOW	< 25 kg	< 11 kg	→TREATMENT out of the norm
	< 71 kPa	< 41 kPa	
AT RISK	25 kg < X < 38 kg	11 kg < X < 21 kg	→SECUNDARY PREVENTION action should be undertaken to prevent worsening
	71 kPa < X < 93 kPa	41 kPa < X < 59 kPa	
NORMAL	> 38 kg	> 21 kg	→PRIMARY PREVENTION healthy, within the norm
	> 93 kPa	> 59 kPa	

RECOMMENDATION

• We recommend **maximum handgrip strength** of the **dominant** hand to assess general muscle strength. We recommend categorising patients according to the **normative values for healthy young people**.

REFERENCES: Bäckman, E., et al. (1995). "Isometric muscle strength and muscular endurance in normal persons aged between 17 and 70 years." Scandinavian Journal of Rehabilitation Medicine 27(2): 109-117.Berg, H. E., et al. (2007). "Hip, thigh and calf muscle atrophy and bone loss after 5-week bedrest inactivity." Eur J Appl Physiol 99(3): 283-289.Bertovic, D. A., et al. (1999). "Muscular strength training is associated with low arterial compliance and high pulse pressure." Hypertension 33(6): 1385-1391.Budziareck, M. B., et al. (2008). "Reference values and determinants for handgrip strength in healthy subjects." Clin Nutr 27(3): 357-362.Fuster, V., et al. (1998). "Anthropometry and strength relationship: male-female differences." Anthropol Anz 56(1): 49-56.Gunther, C. M., et al. (2008). "Grip strength in healthy caucasian adults: reference values.". icons from thenounproject.com.

PHARMACOLOGY
Sarcopenia Guideline 2018-2019 - Intervention

BVGG – SBGG

WHY?

To provide an evidence-based overview of the possible pharmacological interventions for sarcopenia targeting one or more of the three sarcopenia domains (muscle mass, muscle strength or physical performance).

No distinct pharmacological recommendations for healthy, presarcopenic and sarcopenic older people can be made because specific characterization of the sarcopenia status was lacking from most studies. However, recommendations can be made for older people in general.

HOW?

An umbrella review on pharmacological interventions was performed:
- *Population*: older adults (65+)
- *Intervention*: pharmacological
- *Control*: non-exposed control
- *Outcome*: sarcopenia
- *Study design*: systematic review, metaanalysis
- *Quality assessment*: AMSTAR checklist

DATA HANDLING

Initial search yielded 519 eligible reviews of which 7 were finally included.

Key characteristics of the reviews, including participants, pharmacological treatment and outcomes assessed were retrieved. Recommendations were generated based on the overall syntheses about the main effect of interventions within each intervention.

- Muscle mass
- Muscle strength
- Physical performance

VITAMIN D
- ✓ Muscle strenght
- ✓ Physical performance

TESTOSTERONE
- ✓ Muscle strength
- ✓ Muscle mass

- Beta-Estradiol + Cyclic Norethisterone Acetate
- Dehydroepiandrosterone
- Pioglitazone
- Angiotensin-Converting Enzyme Inhibitors
- Growth Hormone
- Testosterone + Growth Hormone
- Growth Hormone-Releasing Hormone
- Insulin-Like Growth Factor 1

RECOMMENDATION

- We recommend **vitamin D supplementation** to improve muscle strength and physical performance in older people, especially women, with low baseline serum levels. Monitoring of the serum calcium is needed
- **Testosterone supplementation** may be considered in older men with serum levels < 200–300 ng/dl and clinical muscle weakness, to improve muscle mass and muscle strength. Monitoring of the hematocrit, lipid profile and prostatic parameters is needed

REFERENCES: Anagnostis P, Dimopoulou C, Karras S, Lambrinoudaki I, Goulis DG. Sarcopenia in post-menopausal women: Is there any role for vitamin D? Maturitas. 2015;82(1):56-64. Beaudart C, Dawson A, Shaw SC, Harvey NC, Kanis JA, Binkley N, et al. Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review. Osteoporosis International. 2017;28(6):1817-33 Ottenbacher KJ, Ottenbacher ME, Ottenbacher AJ, Acha AA, Ostir GV. Androgen treatment and muscle strength in elderly men: A meta-analysis. Journal of the American Geriatrics Society. 2006;54(11):1666-73. icons by the noun project

Belgian Society for GERONTOLOGY and GERIATRICS

PHYSICAL EXERCISE
Sarcopenia Guideline 2018-2019 - Intervention
BVGG - SBGG

? WHY?

To provide an evidence-based overview of the possible physical exercise interventions for sarcopenia targeting one or more of the three sarcopenia domains (muscle mass, muscle strength or physical performance).

HOW?

An umbrella review on physical exercise interventions was performed:
- *Population*: older adults (65+)
- *Intervention*: exercise
- *Control*: non-exposed control
- *Outcome*: sarcopenia
- *Study design*: systematic review, meta-analysis
- *Quality assessment*: AMSTAR checklist

DATA HANDLING

Initial search yielded 665 eligible reviews of which 14 were finally included.

Key characteristics of the reviews, including participants, exercise treatment, outcomes assessed were retrieved.

Recommendations were generated based on the overall syntheses about the main effect of each intervention.

› RESISTANCE TRAINING

✓ Muscle mass
✓ Muscle strength
✓ Physical performance

3 meta-analysis (75 st.)
2 sytematic review
(24 studies - 100% in favour)

- large muscle group training in a total body approach
- 1-4 sets of 8-15 repetitions during 2-3 training moments a week
- elastic bands can be used effectively at home to improve muscle strength

› MULTIMODAL EXERCISE

✓ Muscle mass
✓ Muscle strength
✓ Physical performance

3 systematic reviews
*(70 studies - >80% in favour)*

- can encompass a combination of resistance training, walking, aerobic training, balance training and other types of training

› OCCLUSION TRAINING

✓ Muscle strength

1 meta-analysis (13st.)

- performed under supervision of a trained exercise coach
- low intensity: 10-30% 1RM

RECOMMENDATION

- We do recommend **resistance training** to improve muscle strength, muscle mass and physical performance for healthy, pre-sarcopenic or sarcopenic older people since evidence shows a significant and positive effect.
  - ➢ For maximal strength gains a **high-intensity** resistance training program is recommended, i.e. 70-80% of the maximum weight that a person can lift/move for one repetition (1RM). However, low-intensity resistance training (≤50% 1RM) may be sufficient to induce strength gains.
- We do recommend **multimodal exercise** therapy for healthy, pre-sarcopenic or sarcopenic older people in the prevention or treatment of sarcopenia since data show significant evidence in favour.
- We do recommend occlusion training (=blood flow restriction training (BFR)). **Occlusion training** (i.e. muscle resistance training with maintaining arterial blood inflow and restricting the venous blood outflow of the trained muscle) is a relatively novel training method that has a significant positive impact on muscle strength. Low intensity (10-30% 1RM) BFR training has proven to be more effective in increasing muscle strength compared to low intensity training alone. We recommend that this type of training is performed under supervision of a trained exercise coach.

REFERENCES: Antoniak, A. E. and C. A. Greig "The effect of combined resistance exercise training and vitamin D-3 supplementation on musculoskeletal health and function in older adults: a systematic review and meta-analysis." Bmj Open 7(7). Beaudart, C., et al. "Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review." Osteoporosis International 28(6): 1817-1833. Czapo, R. and L. M. Alegre "Effects of resistance training with moderate vs heavy loads on muscle mass and strength in the elderly: A meta-analysis." Scand J Med Sci Sports 26(9): 995-1006.Hughes, L., et al. "Blood flow restriction training in clinical musculoskeletal rehabilitation: a systematic review and meta-analysis." Br J Sports Med 51(13): 1003-1011. icons from the noun project

NUTRITION
Sarcopenia Guideline 2018-2019 - Intervention

BVGG - SBGG

? WHY?

To provide an evidence-based overview of the possible nutritional interventions for sarcopenia targeting one or more of the three sarcopenia domains (muscle mass, muscle strength or physical performance).

HOW?

An umbrella review on nutritional interventions was performed:
- *Population*: older adults (65+)
- *Intervention*: nutritional supplementation
- *Control*: non-exposed control
- *Outcome*: sarcopenia domains
- *Study design*: systematic review, meta-analysis
- *Quality assessment*: AMSTAR checklist

DATA HANDLING

Initial search yielded 516 eligible reviews of which 15 were finally included.

Key characteristics of the reviews, including participants, nutritional interventions, outcomes assessed were retrieved.

Recommendations were generated based on the overall syntheses about the main effect of each intervention.

〉PROTEIN

Based on the conflicting evidence, protein supplementation may be considered to increase muscle mass. No clear effect has been reported on muscle strength and physical performance. In conclusion, protein supplementation may be considered as an intervention to increase muscle mass.

PROTEIN + RT*

A significant additive effect of protein supplementation on top of resistance training on muscle mass and muscle strength is shown in persons with obesitas (BMI ≥30). This effect is also present for muscle mass, when the intervention had a duration of ≥ 24 weeks. No clear additive effect has been reported on physical performance. To achieve optimal effects on muscle mass and muscle strength in older adults, particularly obese, we do recommend protein supplementation in combination with resistance training (with a minimum duration of 24 weeks to increase muscle mass).

PROTEIN + NS*

Protein supplementation on top of exercise (not specified) may be considered to increase muscle mass, but not for muscle strength and physical performance.

〉EAA*

No clear effect has been reported on muscle mass, muscle strength and physical performance. In conclusion, EAA supplementation should not be considered as an intervention to increase muscle mass, strength and physical performance.

〉LEUCINE

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, we do recommend leucine supplementation for sarcopenic older people to increase muscle mass.

〉HMB*

Based on the conflicting evidence, HMB supplementation may be considered to increase muscle mass. No clear effect has been reported on muscle strength and physical performance. In conclusion, HMB supplementation may be considered as an intervention to increase muscle mass.

〉CREATINE + NS*

Creatine supplementation on top of exercise (not specified) may be considered as an intervention to increase muscle mass and muscle strength.

* EAA = essential amino acids; HMB = B-Hydroxy-B-Methylbutyrate RT = resistance training; NS = not specified exercise program

RECOMMENDATION

- At this moment best evidence is available to recommend **leucine** supplementation since 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 obesitas and should be performed at least for 24 weeks to achieve optimal results.

REFERENCES: Liao CD, Tsauo JY, Wu YT, Cheng CP, Chen HC, Huang YC, Chen HC, Liou TH. Effects of protein supplementation combined with resistance exercise on body composition and physical function in older adults: a systematic review and meta-analysis. Am J Clin Nutr. 2017 Oct;106(4):1078-1091.; Komar B, Schwingshackl L, Hoffmann G. Effects of leucine-rich protein supplements on anthropometric parameter and muscle strength in the elderly: a systematic review and meta-analysis. J Nutr Health Aging. 2015 Apr;19(4):437-46.

11. Implementation of guidelines in clinical practice

We took several measures to make sure that the extensive scientific research can be implemented easily in clinical practice. For each chapter we created a one pager. This one-pager is a short but thorough summary of the underlying evidence. The format of this one-pager can be seen as an infographic were if possible, icons and visual aides were added. One example of these visual support is the traffic light system. This system is uniformly used in all the one-pagers if applicable. Vivid colors matching the traffic light colors assist in verifying at what level the subject is situated and to choose the appropriate action.

To evaluate the guideline, we propose to monitor the following

- The number of patients registered in the EMD with a diagnosis of sarcopenia.
- The number of patients registered in the EMD were therapy in line with our recommendations is initiated (nutritional, pharmacological, exercise).
- Questionnaire during local sessions of consultation platforms of various care providers regarding their knowledge on sarcopenia.

In addition to the one pagers, a flowchart based on the assessment method and the accompanying result was constructed.

First, in line with the consensus definition of the European Working Group on Sarcopenia in Older People (EWGSOP2), it is advised **to start measuring handgrip strength**. Based on these results, treatment can then be initiated by following the principles of the traffic light (see figure 1).

Second, also in line with EWGSOP2 and depending on the setting, consideration can be given to the **assessment of muscle mass** by BIA (primary care) or DXA (secondary care). Based on these results, treatment can then be initiated by following the principles of the traffic light (see figure 2).

Third, also in line with EWGSOP2, the severity of sarcopenia can be determined by assessing the physical performance (**gait speed)**. Based on these results, treatment can then be initiated by following the principles of the traffic light
 (see figure 3).

Since the above-mentioned policy options for the prevention and treatment of sarcopenia, fall within the expertise domain of more than one discipline, an interdisciplinary approach is recommended.

11.1. Muscle strength assessment

1. Muscle Strength Assessment

GREEN

EXERCISE
- Resistance training OR Multimodal exercise
- Occlusion training (supervision of trained exercise coach is necessary)

NUTRITION
- Protein supplementation on top of resistance training (especially for obese people)
- Creatine supplementation (on top of exercise) may be considered

PHARMACOLOGY
- Vitamin D supplementation (especially women with low vitamin D serum levels)

YELLOW

EXERCISE
- Resistance training OR Multimodal exercise
- Occlusion training (supervision of trained exercise coach is necessary)

NUTRITION
- Protein supplementation on top of resistance training (especially for obese people)
- Creatine supplementation (on top of exercise) may be considered

PHARMACOLOGY
- Vitamin D supplementation (especially women with low vitamin D serum levels)

RED

EXERCISE
- Resistance training OR Multimodal exercise
- Occlusion training (supervision of trained exercise coach is necessary)

NUTRITION
- Protein supplementation on top of resistance training (especially for obese people)
- Creatine supplementation (on top of exercise) may be considered

PHARMACOLOGY
- Vitamin D supplementation (especially women with low vitamin D serum levels)
- Testosterone supplementation in older men (in case of low testosterone serum levels)

Figure 4: Interventions based on the results of hand grip strength assessment (traffic light)

11.2.   Muscle mass assessment

2.   Muscle Mass Assessment

GREEN (Primary prevention)

EXERCISE
- Resistance training OR Multimodal exercise

NUTRITION
- Protein supplementation alone or on top of resistance training (≥24weeks)
- Creatine supplementation (on top of exercise) may be considered

YELLOW (Primary prevention)

EXERCISE
- Resistance training OR Multimodal exercise

NUTRITION
- Protein supplementation alone or on top of resistance training (≥24weeks)
- Creatine supplementation (on top of exercise) may be considered

RED (Secondary prevention)

EXERCISE
- Resistance training OR Multimodal exercise

NUTRITION
- Protein supplementation on top of resistance training (especially for obese people)
- Creatine supplementation (on top of exercise) may be considered

PHARMACOLOGY
- Testosterone supplementation in older men (in case of low testosterone serum levels)
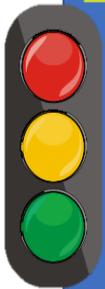
Figure 5: Interventions based on the results of muscle mass assessment (traffic light)

3. **Physical Performance Assessment**

GREEN (Primary prevention)
   EXERCISE
   - Resistance training OR Multimodal exercise
   PHARMACOLOGY
   - Vitamin D supplementation
     (especially women with low vitamin D serum levels)

YELLOW (Primary prevention)
   EXERCISE
   - Resistance training OR Multimodal exercise
   PHARMACOLOGY
   - Vitamin D supplementation
     (especially women with low vitamin D serum levels)

RED (Secundary prevention)
   EXERCISE
   - Resistance training OR Multimodal exercise
   PHARMACOLOGY
   - Vitamin D supplementation
     (especially women with low vitamin D serum levels)

Figure 6: Interventions based on the results of physical performance assessment (traffic light)

12.   Strengths and limitations of the guideline

Strengths
- Comprehensive guideline on both assessment and interventions.
- Available and useful for different professions.
- Strong scientific foundation. (3 peer-reviewed publications)
- Large group of experts contributed to the guideline.
- One pagers and flowchart are useful tools for clinical practice.

Limitations
- Use of umbrella review method. No primary studies were included.
- English language can be a barrier for understanding the guidelines.

13. Members of the guideline working groups

Name Surname	Discipline / place	Expertise	Role in working groups
Gielen Evelien	Prof. Dr. Gielen is a geriatrician specialized in osteoporosis and metabolic bone diseases, sarcopenia and frailty, general geriatrics. She is affiliated with the UZ Leuven	Geriatrics, osteoporosis & sarcopenia	Member of the Guideline Development Group Member of the Working group Nutrition
de Saint-Hubert Marie	Prof. de Saint Hubert is a geriatrician and affiliated with the Université Catholique de Louvain as well as CHU UCL Namur - Site Godinne.	Geriatrics	Board member of the BSGG Member of the Guideline Development Group Member of the Working group Risk Factors Member of the Working group Exercise
Vandewoude Maurits	Prof. Dr. Vandewoude is senior geriatrics professor at Uantwerp, and he is also a consultant in internal medicine / geriatrics at the University Hospital Antwerp.	Geriatrics, sarcopenia, nutrition	Member of the Guideline Development Group Member of the Working group Nutrition
Baert Veerle	Active gerontologist and senior care worker at OCMW Gent	Gerontology, physical exercise in the elderly	Member of the Working group Exercise
Bruyère Olivier	Professor Bruyere is Professor of Clinical Epidemiology at the Department of Health Sciences and Geriatric Rehabilitation at the Department of Sports Sciences at the University of Liège. He is also head of the Research Unit in Public Health, Epidemiology and Health Economics at this university. His most important areas of interest are prevention, rehabilitation and epidemiology in relation to geriatric disorders and musculoskeletal disorders. He is also chairman of the Belgian Aging Muscle Society.	Rehabilitation, epidemiology & Sarcopenia, methodological expert in systematic reviews	Member of the Guideline Development Group Member of the Working group Risk Factors Member of the Working group Exercise
Aelbrecht Senne	Former academic staff member at the VUB. Currently personal trainer at SANO.	Physical activity for the elderly	Member of the Working group Exercise
Mets Tony	Professor Emeritus Mets is affiliated with the Gerontology department of the University of Brussels as well as at UZ Brussel.	Geriatrics & sarcopenia	Board member of the BSGG

Pepersack Thierry	Professor Pepersack works as head of the geriatric department at the Erasmus Hospital and is affiliated as Professor at the Université Libre de Bruxelles	Geriatrics	Assistant Member of the Working group Pharmacologic interventions
Gilles Christian	Dr. Gilles is associated with the Marche Hospital and Bastogne Hospital and specializes in neuropsychiatry, psycho-geriatrics and general geriatrics.	Geriatrics & pharmacology	Assistant Member of the Working group Pharmacologic interventions
Petrovic Mirko	Prof. Dr. Petrovic is head of the department of Geriatrics at the UZ in Ghent, he is also affiliated as Professor at the University of Ghent at the Faculty of Medicine and Health Sciences Department of Internal Diseases	Geriatrics & pharmacology	Member of the Working group Pharmacologic interventions
Beaudart Charlotte	Prof. Dr. Beaudart is affiliated with the University of Liège, she specializes in sarcopenia and geriatric epidemiology.	Sarcopenia, quality of life, epidemiology, methodological expert in systematic reviews	Member of the Guideline Development Group Member of the Working group Functional performance
De Breucker Sandra	Geriatrician, working as head of department in the geriatrics department at the Erasmus Hospital.	Geriatrics, oncogeriatrics, cachexia & sarcopenia	Board member of the BSGG Member of the Guideline Development Group Member of the Working group Risk Factors Member of the Working group Nutrition
Bautmans Ivan	Prof. Dr. Bautmans is Professor of Gerontology and chairman of the research group Frailty in Aging at the Vrije Universiteit Brussel. He is also active as vice-chairman of the Belgian Association for Gerontology and Geriatrics and as General Secretary of the Belgian Aging Muscle Society.	Sarcopenia, physical exercise in the elderly, frailty, methodological expert in systematic reviews	Board member of the BSGG Member of the Guideline Development Group Member of the Working group Exercise Member of the Working group Assessment muscle strength
Beyer Ingo	Prof. Dr. Beyer is the former department head of the department of Geriatrics at the UZ in Brussels. In addition, he also works as a professor in Geriatrics at the Vrije Universiteit Brussel.	Geriatrics & sarcopenia	Board member of the BSGG Member of the Guideline Development Group Member of the Working group Assessment muscle strength
Perkisas Stany	Geriatrician working at the University Hospital of Antwerp.	Geriatrics & sarcopenia	Member of the Guideline Development Group

			Member of the working group muscle mass assessment
Scafoglieri Aldo	Professor Scafoglieri is an expert in body composition research and is associated with the Vrije Universiteit Brussel where he teaches both clinical and (clinical) research. In addition, he also holds the position of the SOMT Chair in Manual Therapy.	Body composition	Member of the working group muscle mass assessment
Baeyens Jean-Pierre	Prof. Dr. Baeyens works as a specialist in geriatrics at AZ Alma.	Geriatrics	Board member of the BSGG
Beckwée David	Prof. Dr. Beckwée is affiliated as a researcher and professor at the Vrije Universiteit Brussel (research groups Frailty in Aging & Rehabilitation Research) and the University of Antwerp. He is also affiliated with the SOMT University of Physiotherapy (The Netherlands).	Physiotherapy for the elderly, sarcopenia, osteoarthritis. Methodological expert in systematic reviews.	Member of the Guideline Development Group Member of the Working group Assessment muscle strength Member of the Working group Exercise Scientific staff, coordinating the guideline development and working groups
De Cock Anne-Marie	Dr. De Cock works as department head of the geriatrics department at Ziekenhuis Netwerk Antwerpen Middelheim. In addition, she is also affiliated with the University of Antwerp.	Geriatrics & gait analysis	Board member of the BSGG Member of the Guideline Development Group Member of the Working group Functional performance
De Spiegeleer Anton	Dr. De Spiegeleer is associated with Ghent University as a researcher at the Department of Internal Medicine.	Geriatrics & pharmacology	Member of the Guideline Development Group Member of the Working group Pharmacologic interventions
Lafosse Christophe	Dr. Lafosse is Director of Strategy and Scientific Policy and a clinical neuropsychologist at the Revalidation Hospital RevArte in Edegem (ww.revarte.be). Here he is also head of the department of neuropsychology and psychological counseling and of the service of speech therapy. He is also guest professor at the Catholic University of Leuven (Faculty of Psychology and Pedagogy), at the Vrije Universiteit Brussel (Faculty of Physiotherapy and Rehabilitation Sciences) and at the Thomas More Hogeschool	Psychogeriatrics	BSGG Board Member

Swine Christian	Professor at the Université catholique de Louvain. In addition, Prof. Dr. Swine is also connected to UCL Saint-Luc hospital as a geriatrician.	Geriatrics	Former BSGG Board member
Van Den Noortgate Nele	Prof. Dr. Van Den Noortgate is leading a research group, investigating the end of life of the elderly in close collaboration with the research group End-of-life Care of the VUB and Ghent University. She is also an expert at various working groups and committees of the Flemish and federal government within the landscape of elderly care. Prof. Van Den Noortgate teaches geriatrics and gerontology at several master's programs at Ghent University.	Geriatrics and care around the end of life	BSGG Board member
Delaere Andreas	Scientific assistant at the Vrije Universiteit Brussel. Independent physiotherapist / manual therapist specialized in rehabilitation of the elderly.	Physiotherapy for the elderly & sarcopenia	Scientific staff, coordinating the guideline development and working groups

14. Update

Regarding the revision, the current Guideline Development Group will be complemented by a broader multidisciplinary stakeholder group. This group will support the revision process. An update will be carried out of the existing literature studies according to the previously described search strategies, including therapy compliance. The results of these updates will

then be added to the current body of evidence. The current approved recommendations will, if necessary, be adjusted based on this new literature

15. Financing

The guideline was not influenced by the ideas or interests of the authority responsible for the funding of this project. The authority who funded this project was the Belgian Society for Gerontology & Geriatrics (BSGG).

16. Conflict of interest

The authors and experts consulted during this project, have no relationship with the pharmaceutical industry or other interest groups. There are no conflicts of interest known. All completed forms of conflict of interest can be found in appendix.

17. Appendix

17.1. Conflict of Interest Statements

Declaration of Interest Statement

-

Sarcopenia Guideline

Belgian Society for GERONTOLOGY and GERIATRICS

The Belgian Society for Gerontology and Geriatrics - BSGG is aware that a high level of scientific expertise is often associated with various interests. Some of these interests could, internally or externally, be considered as potentially affecting the impartiality of the decisions of a group of experts. We therefore strive for transparency in this area and want to take our responsibility in this. That is why we ask you to state **any financial or other interest** in companies, institutions and groups, so that the association is able to apply the procedures regarding conflicts of interest.

If there is doubt about whether an interest is relevant or significant, it is prudent to disclose. Readers will benefit from transparency, including knowing authors' and contributors' affiliations and interests. Sources of funding for research or publication should always be disclosed. Authors should routinely include information about research funding in all papers they prepare for publication. Where a clinical trial registration number is available, this should be included.

Author Name: Olivier Bruyère

Title of manuscript: BVGG Guideline on Sarcopenia

☐ I have no relevant interest(s) to disclose.
☐ I have potentially relevant interest(s) as outlined below (if more space is required, please document the information in an attachment):
Grant research: Biophytis, IBSA, MEDA, Servier, SMB.
Consulting or lecture fees: Amgen, Biophytis, IBSA, MEDA, Servier, SMB, TRB Chemedica, UCB.

With this document I declare, in good faith and conscience, that all direct and indirect interests that I have in companies, institutions and groups related to the activities of the BSGG are mentioned above.

Signature:

Date: 25/10/19

Belgian Society for GERONTOLOGY and GERIATRICS

Declaration of Interest Statement
-
Sarcopenia Guideline

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Author Name: …Tony Mets………………………………………………………………………….
Title of manuscript: BVGG Guideline on Sarcopenia ……………………………………………………
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v I have no relevant interest(s) to disclose.
□ I have potentially relevant interest(s) as outlined below (if more space is required, please document the information in an attachment):
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With this document I declare, in good faith and conscience, that all direct and indirect interests that I have in companies, institutions and groups related to the activities of the BSGG are mentioned above.

Signature: Date: 25/10/2019

Belgian Society for GERONTOLOGY and GERIATRICS

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Sarcopenia Guideline

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Author Name: **Ingo BEYER**
Title of manuscript: **Screening and assessment – muscle function**

☒ I have no relevant interest(s) to disclose.
☐ I have potentially relevant interest(s) as outlined below (if more space is required, please document the information in an attachment):
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With this document I declare, in good faith and conscience, that all direct and indirect interests that I have in companies, institutions and groups related to the activities of the BSGG are mentioned above.

Signature: Date: October 26th, 2019

Belgian Society for GERONTOLOGY and GERIATRICS

Declaration of Interest Statement
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Sarcopenia Guideline

The Belgian Society for Gerontology and Geriatrics - BSGG is aware that a high level of scientific expertise is often associated with various interests. Some of these interests could, internally or externally, be considered as potentially affecting the impartiality of the decisions of a group of experts. We therefore strive for transparency in this area and want to take our responsibility in this. That is why we ask you to state **any financial or other interest** in companies, institutions and groups, so that the association is able to apply the procedures regarding conflicts of interest.

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Author Name: ………SCAFOGLIERI ALDO…………………………………………………………………………………
Title of manuscript: ………..……..

● I have no relevant interest(s) to disclose.
□ I have potentially relevant interest(s) as outlined below (if more space is required, please document the information in an attachment):
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With this document I declare, in good faith and conscience, that all direct and indirect interests that I have in companies, institutions and groups related to the activities of the BSGG are mentioned above.

Signature: Date: 25-10-2019

Declaration of Interest Statement

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Sarcopenia Guideline

The Belgian Society for Gerontology and Geriatrics - BSGG is aware that a high level of scientific expertise is often associated with various interests. Some of these interests could, internally or externally, be considered as potentially affecting the impartiality of the decisions of a group of experts. We therefore strive for transparency in this area and want to take our responsibility in this. That is why we ask you to state **any financial or other interest** in companies, institutions and groups, so that the association is able to apply the procedures regarding conflicts of interest.

If there is doubt about whether an interest is relevant or significant, it is prudent to disclose. Readers will benefit from transparency, including knowing authors' and contributors' affiliations and interests. Sources of funding for research or publication should always be disclosed. Authors should routinely include information about research funding in all papers they prepare for publication. Where a clinical trial registration number is available, this should be included.

Author Name: Vandewoude Maurits, MD, PhD………
Title of manuscript: Sarcopenia Guidelines of the Belgian Society of Gerontology and Geriatrics (BSGG)

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 I have no relevant interest(s) to disclose.
 ~~I have potentially relevant interest(s) as outlined below (if more space is required, please document the information in an attachment~~):
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With this document I declare, in good faith and conscience, that all direct and indirect interests that I have in companies, institutions and groups related to the activities of the BSGG are mentioned above.

Signature: Date: October 24, 2019

Declaration of Interest Statement

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Sarcopenia Guideline

The Belgian Society for Gerontology and Geriatrics - BSGG is aware that a high level of scientific expertise is often associated with various interests. Some of these interests could, internally or externally, be considered as potentially affecting the impartiality of the decisions of a group of experts. We therefore strive for transparency in this area and want to take our responsibility in this. That is why we ask you to state **any financial or other interest** in companies, institutions and groups, so that the association is able to apply the procedures regarding conflicts of interest.

If there is doubt about whether an interest is relevant or significant, it is prudent to disclose. Readers will benefit from transparency, including knowing authors' and contributors' affiliations and interests. Sources of funding for research or publication should always be disclosed. Authors should routinely include information about research funding in all papers they prepare for publication. Where a clinical trial registration number is available, this should be included.

Author Name: .... de SAINT-HUBERT M.A.RIE
Title of manuscript: ....
.... BVGG / SBGG Guidelines on SARCOPENIA

☑ have no relevant interest(s) to disclose.
☐ I have potentially relevant interest(s) as outlined below (if more space is required, please document the information in an attachment):

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With this document I declare, in good faith and conscience, that all direct and indirect interests that I have in companies, institutions and groups related to the activities of the BSGG are mentioned above.

Signature: Date: 24/10/19

Pr. M. de SAINT-HUBERT
Gériatrie
CHU UCL Namur/ Site Godinne
Av. G. Thérasse, 1
B5530 Yvoir (Belgique)
INAMI : 1-58566629-180

Declaration of Interest Statement

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Sarcopenia Guideline

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The Belgian Society for Gerontology and Geriatrics - BSGG is aware that a high level of scientific expertise is often associated with various interests. Some of these interests could, internally or externally, be considered as potentially affecting the impartiality of the decisions of a group of experts. We therefore strive for transparency in this area and want to take our responsibility in this. That is why we ask you to state **any financial or other interest** in companies, institutions and groups, so that the association is able to apply the procedures regarding conflicts of interest.

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Author Name: ......VAN DEN NOORTGATE NELE...

Title of manuscript: ....
.....................BSGG Guideline on Sarcopenia...............................

☒ I have no relevant interest(s) to disclose.

☐ I have potentially relevant interest(s) as outlined below (if more space is required, please document the information in an attachment):

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Signature:

Date: 25/10/2019

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Author Name: **Mirko Petrovic**

Title of manuscript: **Pharmacological Interventions to Improve Muscle Mass, Muscle Strength and Physical Performance in Older People: An Umbrella Review of Systematic Reviews and Meta-analyses. Drugs Aging 2018 Aug;35(8):719-734.**

X I have no relevant interest(s) to disclose.
□ I have potentially relevant interest(s) as outlined below (if more space is required, please document the information in an attachment):

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With this document I declare, in good faith and conscience, that all direct and indirect interests that I have in companies, institutions and groups related to the activities of the BSGG are mentioned above.

Signature: *Mirko Petrovic*   Date: 24th October 2019

Declaration of Interest Statement

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Sarcopenia Guideline

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Author Name: Stany Perkisas

Title of manuscript: BVGG Guideline on Sarcopenia

☒ I have no relevant interest(s) to disclose.

With this document I declare, in good faith and conscience, that all direct and indirect interests that I have in companies, institutions and groups related to the activities of the BSGG are mentioned above.

Signature:

Date: October 25th, 2019

Declaration of Interest Statement

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Sarcopenia Guideline

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Author Name: .....Anton De Spiegeleer..

Title of manuscript: ....

.....................Sarcopenia guidelines..

☒ I have no relevant interest(s) to disclose.
☐ I have potentially relevant interest(s) as outlined below (if more space is required, please document the information in an attachment):

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With this document I declare, in good faith and conscience, that all direct and indirect interests that I have in companies, institutions and groups related to the activities of the BSGG are mentioned above.

Signature: Date:

29/10/2019

Declaration of Interest Statement

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Sarcopenia Guideline

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Author Name: David Beckwée
Title of manuscript: Sarcopenia guideline

X I have no relevant interest(s) to disclose.
□ I have potentially relevant interest(s) as outlined below (if more space is required, please document the information in an attachment):
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With this document I declare, in good faith and conscience, that all direct and indirect interests that I have in companies, institutions and groups related to the activities of the BSGG are mentioned above.

Signature:

Date:
29/10/2019

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Sarcopenia Guideline

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Author Name: *Evelien Gielen*

Title of manuscript: *BSGG guideline on Sarcopenia*

☐ I have no relevant interest(s) to disclose.

☒ I have potentially relevant interest(s) as outlined below (if more space is required, please document the information in an attachment):

consultant for U.C.B. & Alexion
speaker fees from Sandoz & Amgen
travel /accomodation /meeting expenses from UCB & Amgen
Not Related to this manuscript.

With this document I declare, in good faith and conscience, that all direct and indirect interests that I have in companies, institutions and groups related to the activities of the BSGG are mentioned above.

Signature:

Date:
25/10/2019

Declaration of Interest Statement

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Sarcopenia Guideline

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Author Name:

. DE. BREUCKER... SANDRA...
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Title of manuscript:

...... BVGG./SBGG....Guidelines. Sarcopenia.................
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☒ I have no relevant interest(s) to disclose.
☐ I have potentially relevant interest(s) as outlined below (if more space is required, please document the information in an attachment):

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Author Name: ....Ivan....Bautmans...
Title of manuscript: ......Sarcopenia....Guideline....BVGG : SBGG.........
....

☐ I have no relevant interest(s) to disclose.
☒ I have potentially relevant interest(s) as outlined below (if more space is required, please document the information in an attachment):
. Ivan Bautmans Received Speaker fees from Fresenius Kabi.
. Ivan Bautmans' Department participate in a sponsored clinical trial sponsored by Danone Research - Biophytis
. Ivan Bautmans is member of the Scientific Advisory Board of Biomed Resuvenates

With this document I declare, in good faith and conscience, that all direct and indirect interests that I have in companies, institutions and groups related to the activities of the BSGG are mentioned above.

Signature:

Date: 29 October 2019

Belgian Society for GERONTOLOGY and GERIATRICS

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Author Name: .....Andreas Delaere...

Title of manuscript: ...SARCOPENIA   GUIDELINES................................

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☒ I have no relevant interest(s) to disclose.
☐ I have potentially relevant interest(s) as outlined below (if more space is required, please document the information in an attachment):

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Signature:

Date:
23/10/2019

Declaration of Interest Statement

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Author Name: Charlotte Beaudart
Title of manuscript: ...Sarcopenia ...Guidelines.....BSGG.......................

☒ I have no relevant interest(s) to disclose.
☐ I have potentially relevant interest(s) as outlined below (if more space is required, please document the information in an attachment):
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With this document I declare, in good faith and conscience, that all direct and indirect interests that I have in companies, institutions and groups related to the activities of the BSGG are mentioned above.

Signature:

Date: 25|10|2019

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review. *Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."* *Note 2: If a study has an a priori design and thus would receive the answer 'yes', and appears not to have followed this design, it would be scored a "can't answer" or even "no".*	• Yes • No • Can't answer • Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place. *Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.*	• Yes • No • Can't answer • Not applicable
3. Was a comprehensive literature search performed? <u>At least two electronic sources</u> should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. <u>All searches should be supplemented</u> by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found. *Note: If at least 2 electronic sources + one supplementary source is used, select "yes" (Cochrane register and CENTRAL count as 2 separate sources; a grey literature search counts as supplementary).* *Note 2: The elements stated in Question 3 are examples of the items that should be reported in the paper. All these elements do not need to be present to receive a "yes", or vice versa, the absence of one of these elements is not enough to receive a "no". If the databases and methods used to perform the search are reported and are appropriate, then it would receive a "yes". However, when critically appraising a systematic review, it would be good to mention the items that were not addressed.*	• Yes • No • Can't answer • Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	• Yes • No • Can't answer • Not applicable

Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.

Note 2: What is meant with the question is: 'Was grey or unpublished literature included in the search?' The aim of this question is to increase the value of grey and unpublished literature. The paper would receive a "yes" if there was a search for grey literature (or other) and reported those that were excluded. If a search for grey literature is not considered necessary for a specific topic, answer "not applicable".

5. Was a list of studies (included and excluded) provided?	
A list of included and excluded studies should be provided.	• Yes
	• No
	• Can't answer
Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."	• Not applicable

6. Were the characteristics of the included studies provided?	
In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	• Yes
	• No
	• Can't answer
Note: Acceptable if not in table format as long as they are described as above.	• Not applicable

7. Was the scientific quality of the included studies assessed and documented?	
'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	• Yes
	• No
	• Can't answer
	• Not applicable
Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).	
Note 2: The word "and" is imperative, i.e. if a study provides the procedure for quality appraisal, but not the results of this appraisal, it would receive a "no". Because authors are supposed to report results on all findings this includes the quality appraisal of the studies.	

8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations. *Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies." Cannot score "yes" for this question if scored "no" for question 7.*	• Yes • No • Can't answer • Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?). *Note: Indicate "yes" if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.* *Note 2: This question mainly applies to the traditional statistical methods, as used for example by the Cochrane Collaboration.* *Note 3: If a study uses correct statistical methods, although combining the findings was not appropriate in the first place, the item would receive a "no".*	• Yes • No • Can't answer • Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). *Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.* *Note 2: If a study just states 'No publication bias was suspected', it is not enough to receive a "yes". Authors need to state how they assessed it and include graphical aids or statistical tests like the Egger test and funnel plots. An additional method to assess publication bias is by consulting trial registers.*	• Yes • No • Can't answer • Not applicable
11. Was the conflict of interest included? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies. *Note: To get a "yes," must indicate source of funding or support for the systematic review AND for each of the included studies.*	• Yes • No • Can't answer • Not applicable

Quality assessment (~COSMIN):

1. I: Was the **sample size** included in the analysis adequate?
   (>15 in each age- and/or sex-specific category)
   ☐ YES (1)   ☐ NO (0)

2. I: Was the **distribution** of the (total) scores in the study sample described?
   ☐ YES (1)   ☐ NO (0)   ☐ CAN'T TELL (0.5)

3. I: Were scores (i.e. means and SD) presented for **relevant subgroups**
   (healthy young male and/or female)?
   ☐ YES (1)   ☐ NO (0)

4. I: Were there any important flaws in the design or methods of the study? If yes, please
   specify:
   ☐ YES (1)   ☐ NO (0)

   - A

5. G: Was the sample adequately described? In terms of: **median or mean age (with standard deviation or range)?)**
   ☐ YES (1)   ☐ NO (0)

6. G: Was the sample adequately described? In terms of: **distribution of sex?)**
   ☐ YES (1)   ☐ NO (0)

7. G: Was the sample adequately described? In terms of: **setting(s)** in which the study
   was conducted? e.g. general population, educational setting (college students), sport
   setting?
   ☐ YES (1)   ☐ NO (0)

8. G: Was the sample adequately described? In terms of: **countries** in which the study
   was conducted? (can be derived from the text of the article or the authors' affiliations)
   ☐ YES (1)   ☐ NO (0)
   If yes, please specify country:

9. G: Was the **method used to select** patients adequately described? e.g. convenience,
   consecutive, or random.
   ☐YES (1)   ☐ NO (0)
   Important flaws: For example, if in a study patients were only included in the analyses
   if their data were complete, this could be considered a methodological flaw because
   selection bias might have occurred. Bias may also occur, for example, when a long version of
   a questionnaire is compared to a short version, while the scores of the short version were
   computed using the responses obtained with the longer version.

17.4.   Standardized effectiveness statements

Summary statement	Translation
A. Sufficient evidence	Evidence to make a decision about the effect of the intervention(s) in relation to a specific outcome(s). This includes evidence of an effect in terms of (i) benefit or (ii) harm. Statistically significant results are considered to represent sufficient evidence on which to base decisions, but a judgement of sufficient evidence is also made based on the number of studies/participants included in the analysis for a particular outcome. A rating of sufficient evidence is often based on meta-analysis producing a statistically significant pooled result that is based on a large number of included studies/participants. This judgement may also be made based on the number of studies and/or study participants showing a statistically significant result - for example (in a narrative synthesis) a result where 12 studies of a total of 14 for a specific outcome showed a statistically significant effect of an intervention would be considered to represent sufficient evidence.
B. Some evidence	Less conclusive evidence to make a decision about the effects of a particular intervention(s) in relation to a specific outcome(s). This may be based on narrative syntheses of review results. In this case, the result is qualified according to the findings of the review - for example, 'some evidence (5 studies of 9) reported a positive effect of '.....' (This would be based on a more equivocal set of results than those obtained for 'sufficient evidence' above. For example, while 12/14 statistically significant studies would be classed as 'sufficient evidence', 5/9 statistically significant studies is more equivocal and would be classed as 'some evidence.') This may also be based on a statistically significant result obtained in a small number of studies; a statistically significant result obtained from studies with a small number of participants; or a statistically significant result obtained from studies of low quality.
C. Insufficient evidence	Not enough evidence to support decisions about the effects of the intervention(s) on the basis of the included studies. This should be interpreted as 'no evidence of effect', rather than 'evidence of no effect'. Statistically non-significant results are considered to represent insufficient evidence. Where the number of studies is small, and/or the number of participants included in the studies is small, insufficient evidence might reflect underpowering of the included studies to be able to detect an effect of the intervention. Where the number of studies is large, and/or the number of participants included in these studies is large, 'insufficient evidence' may reflect underlying ineffectiveness of the intervention to affect the outcomes being examined. In such cases the intervention may additionally be described as 'generally ineffective' in order to separate such results from those cases where insufficient evidence is used to describe results, but this is based on a small number of studies and/or participants (where non-significant results may reflect underpowering of studies rather than ineffectiveness).
D. Insufficient evidence to determine	Not enough evidence to be able to determine whether an intervention is effective or not on the basis of the included studies. This statement is about reporting gaps in the evidence (ie where there are too few studies to be able to determine effects), rather than the situation of the summary statement above, which is about ineffectiveness (eg several studies reporting a statistically non-significant result). It is likely to arise when the numbers of included studies is very small.

18. Bibliography

1. De Spiegeleer, A., et al., *Pharmacological Interventions to Improve Muscle Mass, Muscle Strength and Physical Performance in Older People: An Umbrella Review of Systematic Reviews and Meta-analyses.* Drugs Aging, 2018. **35**(8): p. 719-734.
2. Beckwée, D.D., Andreas ; Aelbrecht, Senne ; Baert, Veerle ; Beaudart, Charlotte ; Bruyere, Olivier ; de Saint-Hubert, Marie ; Bautmans, Ivan *Exercise interventions for the prevention and treatment of sarcopenia. A systematic umbrella review.* The journal of nutrition, health & aging, 2019.