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EXERCISE INTERVENTIONS FOR THE PREVENTION AND TREATMENT OF SARCOPENIA. A SYSTEMATIC UMBRELLA REVIEW

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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.

Key words: Exercise, sarcopenia, muscle strength, muscle mass, physical performance.

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-

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review. Based on the level of evidence, we formulated specific recommendations for clinical practice.

Methods

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).

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.

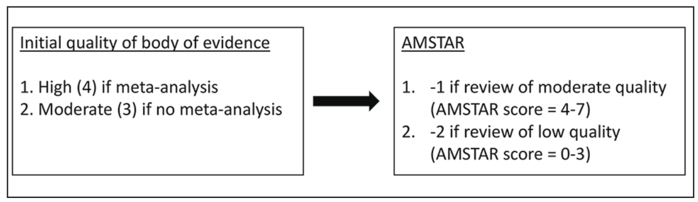
Data extraction and methodological quality assessment

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.

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

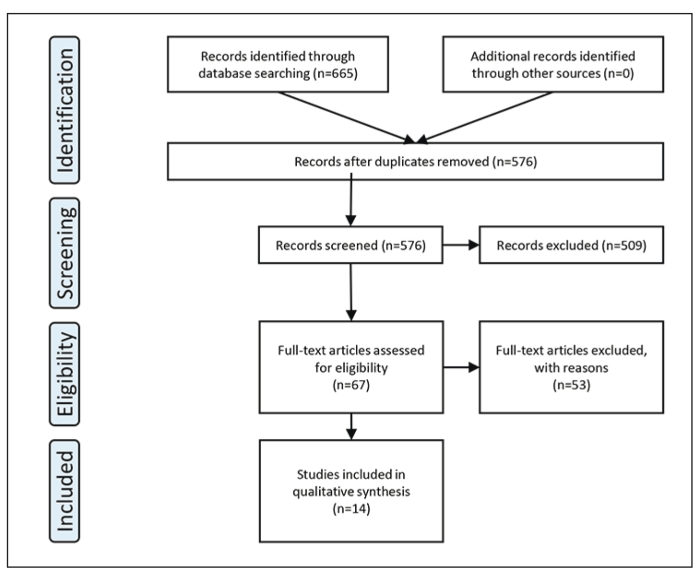


(AMSTAR: Assessment of multiple systematic reviews) (14)

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

	1) A priori design?	2) Duplicate study selection - data extraction?	3) Comprehensive literature search?	4) Status of publication used as inclusion criterion?	5) List of included and excluded studies?	6) Characteristics of included studies provided?	7) Scientific quality of studies assessed and reported?	8) Scientific quality used in formulating conclusions?	9) Appropriote methods of combining the findings?	10) Publication bias assessed?	11) Conflict of interest included?
Antoniak 2017	+	+	+	−	−	+	+	+	+	+	+
Beaudart 2017	+	+	+	−	−	+	+	+	?	?	−
Bibas 2014	−	−	−	−	−	+	−	−	+	−	+
Borst 2004	−	?	−	?	−	+	−	+	?	−	−
Buch 2017	−	+	+	−	−	+	+	+	+	+	+
Csapo 2015	−	+	+	−	−	+	+	?	+	+	+
Hughes 2017	−	+	+	−	−	+	+	−	+	+	+
Liberman 2017	−	+	+	−	−	+	+	?	−	−	+
Martins 2013	−	+	+	−	−	+	+	+	+	+	+
Papa 2017	−	+	+	−	−	+	+	+	−	−	+
Peterson 2010	−	−	−	−	−	+	−	−	+	+	−
Peterson 2011	−	−	+	−	−	+	−	−	+	+	−
Theodorakopoulos 2017	+	+	+	−	−	+	+	+	+	−	+
Yoshimura 2017	+	+	+	?	+	+	+	+	+	−	+

(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.

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 ($\beta = 0.05$, $p < 0.01$), whereas older individuals experienced less increase ($\beta = -0.03$, $p = 0.01$). 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

Table 1
Results of Individual Reviews

Reference	Outcome S	BC	MS	PP	AE	N° of studies included (participants)	Results/findings (outcomes are underlined)	Comments
Resistance training								
Buch 2017 (38)		x				1 M.A. (4 st (103))	Lean body mass: SMD 0.42 (95% CI;–0.08–0.91; I^2= 30%; p for heterogeneity = 0.23) Overall effect 2 kg (95% CI; –0.11–4.11; I^2= 37%; p for heterogeneity = 0.19)	* circuit resistance training
Csapo 2015 (39)		x				1 M.A. (7 st (213))	Muscle mass: Total population effect: μ = 0.136 (CI 0.009-0,259; P = 0.036) High loads μ = 0.199 (CI: 0.046–0.343, P = 0.011) (11% increase) Low loads μ = 0.108 (CI: –0.050–0.261, P = 0.179) (9% increase)	* moderate vs heavy resistance loads «Both RT at high (~80% 1RM) and lower intensities of load provoke only minor increases in total muscle size, which indicates that the hypertrophic potential of skeletal muscles is blunted at older age.»
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 lean body mass, whereas older individuals experienced less increase (β = -0.03, p = 0.01).	
Theodorakopoulos 2017 (40)		x				1 study (8)	Strength (20, 21, 27-29) Hypertrophy group and high-speed circuit group: SMI: no significant change BF%: no significant change	* high-speed resistance training vs normal strength training
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 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)	* circuit resistance training
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) Elderly patients with pathology SMD = 0.54 (95% CI: 0.12, 0.96) (N=91)	* elastic resistance

Table 1
Results of Individual Reviews (continued)

Reference	Outcome S	BC	MS	PP	AE	N° of studies included (participants)	Results/findings (outcomes are underlined)	Comments
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 studies) Lat pulldown: 10.63 kg (95% CI, 8.59–12.67 kg, p < 0.001) (19 studies)	
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 0.42 kg (95% CI, 2.46 to 3.30; P =.78) (2 studies)	
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 SPPB: significant decrease	* 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 articles)	
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), I^2=70%, p=.04	* Main supplementation: vit D

Table 1
Results of Individual Reviews (continued)

Reference	Outcome S	BC	MS	PP	AE	N° of studies included (participants)	Results/findings (outcomes are underlined)	Comments
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), I^2=0%, p=0.37)	* Main supplementation: vit D
Beaudart 2017 (45)				x		Protein: 9 studies (793) EAA: 2 studies (179) HMB: 2 studies (72) Creatine: 4 studies (147) Multi-nutrient: 4 studies (304) Vitamin D: 2 studies (121) Other: 5 studies (648)	Protein: 0/9 studies in favour of intervention Essential amino acids: 0/2 studies in favour of intervention β-hydroxy-β-methylbutyrate: 0/2 studies in favour of intervention Creatine: 1/4 studies in favour of intervention Multi-nutrient intervention: 0/4 studies in favour of intervention Vitamin D: 1/2 studies in favour of intervention Other: 2/5 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 Multimodal exercise
Bibas 2014 (18)		x				3 st (214)	Lean body mass: 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								
Hughes 2017 (48)			x			1 M.A. (13 st (341))	Low load BFR (8 studies) Hedges' g=0.523 (95% CI 0.263 to 0.784, p<0.001) I^2=49.8% High load BFR (5 studies) Hedges' g=0.674 (95% CI 0.296 to 1.052, p<0.001) I^2= 0%	«This review illustrates that the majority of studies do not report on the presence or absence of adverse events.»

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;

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.

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).

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).

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.

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).

Conclusion

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. Multimodal exercises and blood flow restriction resistance training may be considered as well.

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