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Review

Impact of Interventions on Sarcopenia from the Perspective of Older Persons: A Systematic Literature Review

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Abstract

Current interventions targeting sarcopenia are diverse, incorporating a blend of nutritional, exercise, and pharmacological strategies. Although muscle mass, muscle strength, or functional performance typically serve as the primary endpoints, regulatory agencies have recently emphasized integrating Patient-Reported Outcome Measures (PROMs) as primary or secondary outcomes in interventional studies. This shift acknowledges the importance of PROMs and Patient-Reported Experience Measures (PREMs) in assessing intervention effectiveness and aligns with patient-centered healthcare models. The aims of this systematic review are 1) to identify all sarcopenia-designed interventional studies that used PROMs/PREMs as the primary or secondary outcome, 2) to identify the different PROMs/PREMs used within those studies, and 3) to summarize the effects of sarcopenia-designed interventions on PROMs/PREMs of sarcopenic participants. For that, a systematic search of databases (Medline, EMBASE, Review- Cochrane Central of Register of Controlled Trials, and PsychINFO (Via Ovid)) was conducted in September 2023. The review followed the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement, and the protocol was registered on Open Science Framework (https://osf.io/zxgwm/). The systematic review identified 17 RCTs as sarcopenia-designed interventional studies reporting PROMs. PROMs covered the assessment of various aspects, including quality of life, depressive symptoms, loneliness/social isolation, daytime sleepiness, insomnia impact, and sleep quality/disturbance. Only one sarcopenia-specific PROM, namely the SarQoL, was reported. The effect of sarcopenia-designed interventions on PROMs showed considerable heterogeneity, underscoring the need for standardization in sarcopenia research by developing a Core Outcome Set (COS). COS in sarcopenia studies would ensure consistent and comparable findings, ultimately enhancing the reliability and effectiveness of interventions.

Key words: Patient-reported outcome measure, quality of life, clinical trials, patient-centered care, Sarcopenia.

Introduction

In 2016, sarcopenia was recognised as a disease with an International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) code (1). As global life expectancy continues to rise, sarcopenia presents itself as a significant public health challenge (2). The various consequences of sarcopenia, ranging from the development of physical disability to nursing home admission, depression, hospitalisation, and mortality, are anticipated to significantly impact the quality of life for affected individuals (3, 4). Within the context of health systems shifting towards a more patient-centred model of care, it is crucial to consider the impact of diseases, such as sarcopenia, on patients' quality of life and directly perceived outcomes, (5). In this context, patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs) emerge as invaluable tools for capturing patients' perspectives on their health and experiences. PROMs and PREMs aim to report on diseases and symptoms, treatment side effects (such as pain, fatigue, or anxiety), functional outcomes (physical, sexual, social, role, emotional, or cognitive functioning), or multidimensional constructs like HRQoL or health utility (6).

Using PROMs and PREMs as endpoints in clinical studies may improve the understanding of patient's experience by providing information that may not be captured through biomedical methods due to the difficulty of observing certain aspects and their subjective nature (6). This approach may support healthcare professionals and future patients in choosing the most suitable treatment by giving a clearer view of patient's experiences and identify any unmet needs or areas in healthcare that require improvement (6). Therefore, using PROMs and PREMs in interventional clinical studies on sarcopenia contribute to a more comprehensive understanding of clinically perceived benefits, fostering an assessment of treatment efficacy. Government regulatory agencies, including the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (7, 8), have advocated for the incorporation of PROMs as primary or secondary outcomes in interventional studies. The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) working group further also recommends using co-primary endpoints, combining a measure of physical performance with PROMs in all phases III clinical trials for sarcopenia (9).

The current approach to managing sarcopenia involves a multifaceted strategy to mitigate its impact on individuals' health and well-being. Interventions are diverse, incorporating a blend of nutritional, exercise, and pharmacological strategies. Many of these approaches raise numerous questions regarding their effectiveness, particularly in patient-centred management.

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Although several studies demonstrate improvements in various parameters such as muscle mass, strength, and physical performance, there are still uncertainties about their impact on enhancing patients' overall HRQoL (10).

This systematic review addresses the need to understand the impact of sarcopenia interventions from patient's perspective. We therefore aimed 1) to identify all sarcopenia-designed interventional studies that used a PROMs/PREMs as the primary or secondary outcome; 2) to identify the different PROMs/PREMs used within those studies and 3) to summarize the effects of sarcopenia-designed interventions on PROMs/PREMs of sarcopenic participants.

Methods

The 2020 Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (11) has been followed throughout the whole procedure of this systematic review (completed PRISMA checklist available in Appendix 1). The review protocol has been registered on the Open Science Framework (https://osf.io/zxgwm/).

Literature Search

The electronic databases MEDLINE, EMBASE, Review-Cochrane Central of Register of Controlled Trials, and APA PsycINFO (via OVID platform for all the mentioned bibliographic databases) were searched in September 2023 for any study who have used a PROMs/PREMs in a clinical trial aiming at the management of sarcopenia. The search strategy employed for searching in Medline (Ovid) is available in Appendix 2. The search strategy was further adapted to fit the requirements of each database. Additionally, a manual search within the bibliography of relevant papers was performed in order to complete the bibliographic search. Moreover, we also conducted forward references searching of included studies using Web of Science to identify other research that has referenced any article of interest. We also searched on clinical trial registries (www.clinicaltrial.gov) for potential unpublished studies.

Study selection

The search results from the electronic sources and hand searching were imported into Covidence software for data management. Covidence is a web-based collaboration software platform that streamlines the production of systematic and other literature reviews (https://support.covidence.org/help/how-can-i-cite-covidence). During the initial screening phase, three reviewers (G.L.D., F.O.F, V.S.) independently assessed the title and abstract of each obtained reference to eliminate articles irrelevant to the systematic review. Rigorous inclusion criteria were applied, as outlined in Table 1. In the subsequent step, the three reviewers individually examined the full text of each article that had not been excluded in the initial stage, selecting studies that fulfilled the inclusion criteria. Any discrepancies in article selection were resolved through discussion and consensus.

Studies were excluded if they included individuals with acute sarcopenia or diagnosed sarcopenia based solely on a single biomarker (e.g., muscle mass only). Additionally, exclusion criteria applied to studies that relied only on a screening tool (e.g., the SARC-F) without further diagnosing the condition, studies that recruited pre-/post-operative hospitalised or disease-specific participants, studies exclusively focused on the diagnosis of sarcopenic obesity, and studies that examined PROMs/PREMs using qualitative research methods.

Data extraction

Data extraction was carried out by three independent reviewers (G.L.D., F.O.F, V.S.) using a standardised form, which had been pretested on a sample of 4 studies.

The following data were extracted: article information (authors, journal name, years of publication, title, country), study description (objective, design, and duration), population characteristics (general description and sarcopenia diagnosis), outcomes (type of PROMs/PREMs), funding details, information on conflicts of interest, and the study's conclusion. To include as many studies as possible in our systematic review, we systematically contacted authors or co-authors when information was missing in the full-text paper.

Risk of Bias Assessment

The same three independent reviewers assessed trials' risk of bias using the Cochrane Risk of Bias Tool 2.0 (12). This tool assesses five domains for each study: randomisation process, deviation from intended interventions, missing outcome data, measurement of the outcome and selection of the reported results. When a study included various PROMs, the focus was primarily on assessing the quality-of-life outcome. For studies featuring a single PROM, the assessment specifically targeted that particular outcome. In case of conflicts, resolution was achieved through consensus, with the option of involving a third party (C.B.).

Data Synthesis

Due to the diverse range of treatments included in this systematic review, conducting a direct comparison using meta-analytic statistics was impossible. Consequently, the findings were summarised and explained narratively.

Results

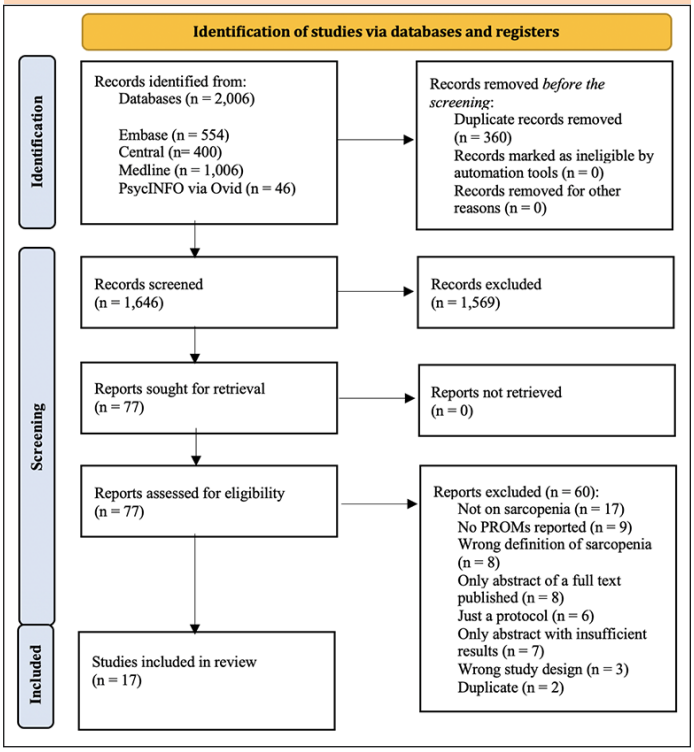
The search strategy initially identified 2,006 records, with 1,646 records remaining after removing duplicates. Upon screening the titles and abstracts of these records, 77 were considered potentially eligible. Following a thorough evaluation of the full texts of these 77 articles, 60 were excluded and a total of 17 studies met the eligibility criteria and were included in this systematic review. A list of excluded studies and their reasons for exclusion is available on the Open Science

Table 1. Inclusion criteria

Patients	Community-dwelling, hospitalised or residents in assisted living facilities They should be 60 years or older, or the mean or median age of the sample should be ≥ 60 years. Diagnosis of sarcopenia relying on a minimum of two parameters (muscle mass, muscle strength, and/or physical performance)
Interventions	All interventions studied in randomised controlled trials (including nutrition, exercise, pharmacological treatments, etc.).
Comparators	All comparators studied in randomised controlled trial.
Outcomes	Any validated patient-reported outcome measure (including health-related quality of life). The instrument must capture the patient experience (i.e., function as a PROM or PREM) and should not be based on observer assessments.
Study design	Randomised controlled trials
Languages	All languages, no restriction

Framework deposit (https://osf.io/zxgwm/). Authors from three included paper were contacted by email for additional information or details about their analyses. They all responded positively to our request, providing us enough information to ensure the inclusion of their paper in the current manuscript. Manual search yielded no new reference. Flowchart of study selection is available in Figure 1.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) flowchart of study selection



Studies characteristics

The 17 randomized-controlled trials (RCTs) included, published between 2015 and 2023, are detailed in Table 3 and Table 4 (13–24). Trial durations ranged widely, spanning 8 (18) to 156 (20) weeks, and study design comprised 2 to 5 groups. The intervention was singular or combined, including medications (n=2, 11.76% (25, 26)), nutritional supplementation (n=6; 35.3% (13–18)), exercise program (n=4, 23.53% (23, 24, 27, 28)) and a combination of exercise and nutritional supplements (n=5, 29.41% (19–22, 29)). At the same time, the control group received isocaloric products/placebos, isocaloric products/placebo combined with an exercise program, or exercise programs alone. The number of participants ranged from 28 (23) to 1519 (20). Only one study exclusively enrolled females (19). Although the targeted population across included studies was sarcopenic, variations were observed in age categories (≥ 60 years, ≥ 65 years, ≥ 70 years) and living conditions encompassing community-dwelling individuals (76.47%), residents of care institutions (11.76%), and candidates for in-patient rehabilitation (5.88%). Regarding sarcopenia diagnosis, 13 studies adhered to a recommended definition by scientific societies, with 4 using AWGS (13, 21, 25, 29), 8 using EWGSOP 1 or 2 (16, 18, 19, 22, 23, 26–28), and 1 using FNIH criteria (20). Other studies used at least two biomarkers to diagnose sarcopenia but did not mention their adherence to a scientific-societies consensual definition.

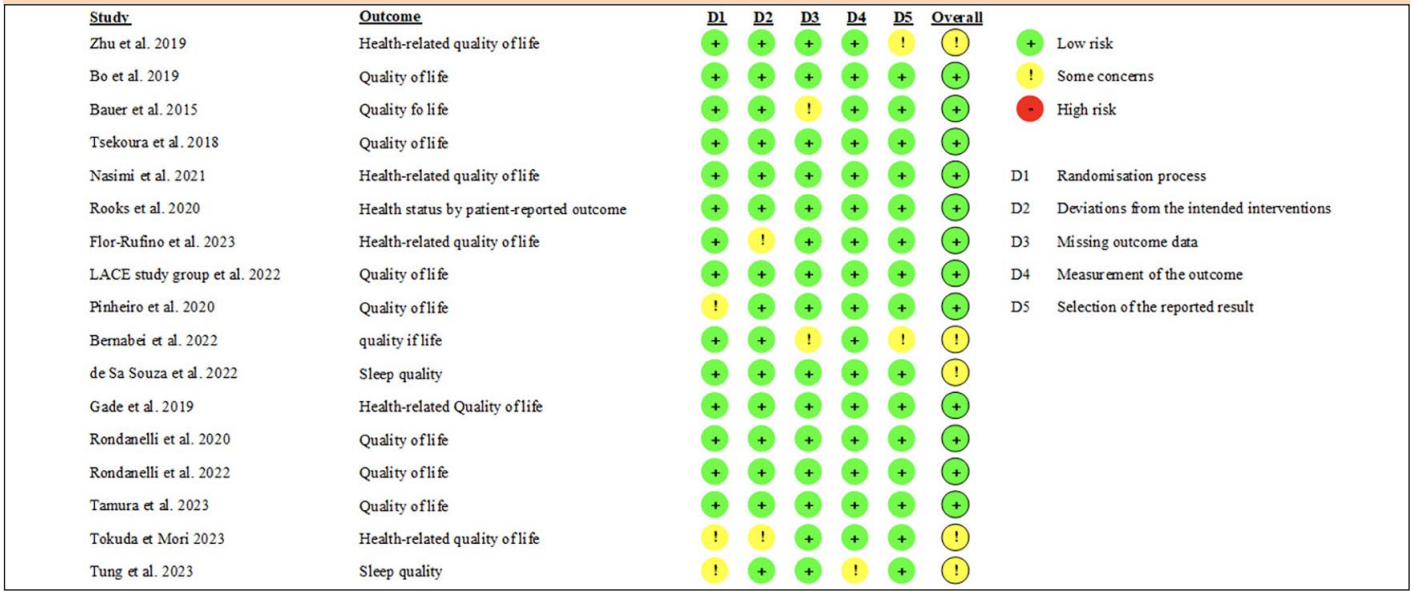
None of the included studies presented any high risk of bias for any of the investigated domain (Figure 2).

PROMs/PREMs characteristics

The 17 included studies reported PROMs as outcomes, but none of them reported any PREMs. PROMs utilized in the studies covered assessments of various concepts including HRQoL (SF-12, SF-36, EQ-5D, SarQoL) (13–22, 24–29), depressive symptoms (GDS, BDI) (17, 30), loneliness/social isolation (UCLA) (30), daytime sleepiness (ESS) (23), insomnia impact (ISI) (23), and sleep quality/disturbance (PSQI) (23, 24). The majority of PROMs employed in these studies were generic, with the exception of one study that utilized a sarcopenia-specific PROM called SarQoL (27). Table 2 provides a brief overview of these various PROMs.

PROMs were mainly used as secondary outcomes. Nevertheless, 5 studies listed multiple primary outcomes among which one or more PROMs were listed. Only Pinheiro et al. (19) used exclusively PROMs as primary endpoint (i.e. depression, loneliness and HRQoL).

Figure 2. Results of risk of bias assessment of included studies



Results of interventions on primary endpoint

The nature of the primary endpoint varied widely across trials, but in the majority of trials, primary outcome was defined by a physical measurement (i.e. change in gait speed, change in SPBB test, etc.). Further details are provided in Table 3 and Table 4.

Nine RCT reported a significant improvement of the primary endpoint following exercise-based intervention (20, 23, 24, 27, 28), nutrition-based intervention (15, 18, 31) or a combination of exercise and nutrition-based intervention (21) (Table 3). In four of these studies, no further improvement was observed on PROMs (neither HRQoL (18, 20, 21, 31) nor depression (31)). The other five RCTs highlighted both an improvement in the primary endpoint and in PROMs, reflecting that the proposed intervention may be effective in counteracting sarcopenia and its impact on PROMs. De Sa Souza et al. (23) reported a significant effect of a 12-week intervention with resistance exercise training on the Insomnia Severity Index (ISI) and the Sleep Quality Disturbance (PSQI) compared to the control group. Flor-Rufino et al. (28) reported that 26 weeks of high-intensity resistance training may improve muscle strength, gait speed, maximum expiratory pressure alongside the EQ-5D VAS, despite reporting no effect on the EQ-5D utility index. Tsekoura et al. (27) reported that a 12-week group-based exercise and individualized home-based exercise may be effective in improving calf circumference, Time up and Go test, 4-meter gait speed, muscle mass index, muscle strength, and HRQoL PROM, as reported by the SarQoL questionnaire. Tung et al. (24) reported that a 26-week vital acupunch exercise program may be effective in improving muscle mass, muscle strength, and sleep quality as reported by the PSQI PROM. Finally, one nutrition-based intervention, published by Bo et al. (15), using a 24-week intervention with supplements containing whey protein, vitamin D and vitamin E, reported a significant improvement in muscle strength and muscle mass index alongside a significant improvement in HRQoL physical and mental component scales of the SF36 questionnaire.

The other 8 RCTs did not report any significant improvement on the primary endpoint (i.e. SMI, handgrip strength, SPPB test 30-second chair stand test, gait speed) nor on the PROMs either (Table 4). None of the pharmacological intervention-based RCTs (i.e. using Bimagrumab 700mg monthly (25) or perindopril/leucine (26)) reported improvement in the primary endpoint or in PROMs.

Discussion

The objective of this study was to identify sarcopenia-focused interventional studies utilizing PROMs and PREMs as primary or secondary outcomes. This systematic literature review aimed to provide a comprehensive overview of the impact of sarcopenia-designed interventions on outcomes directly considered as relevant by patients suffering from sarcopenia. Seventeen sarcopenia-designed RCTs encompassing interventions such as medication (11.76%), nutritional supplementation (35.3%), exercise programs (23.53%), and a combination of exercise and nutritional supplements (29.41%) were identified. Surprisingly, none of the 17 studies incorporated PREMs but all of them utilized PROMs, mainly as secondary outcomes. The selected PROMs covered diverse concepts, including HRQoL (88.23%), depressive symptoms (17.65%), loneliness/social isolation (5.88%), and sleep quality/disturbance (11.76%).

Out of the 17 sarcopenia-targeting RCTs utilizing PROMs as primary or secondary endpoints, half of them (i.e., 9/17) reported a positive impact of the intervention on sarcopenia parameters (i.e., improvement of muscle mass, muscle strength, or physical performance), and approximately 30% of them (i.e., 5/17) further reported an improvement in PROMs. One hypothesis that could explain these results might be that, with the exception of one study employing a sarcopenia-specific PROM called SarQoL, most reported PROMs were generic. Generic instruments provide a broad assessment of HRQoL in populations and enable comparisons with other conditions, but their generic nature makes them less likely to reflect the

Table 2. General description of the 9 that showed an improvement of the primary outcome following the intervention

Reference	Study Description	Population and sample size included in the analysis	Diagnosis of sarcopenia	Type of PROMs/PREMs	Primary endpoint	Effect on primary endpoint	Results of interventions on PROMs/ PREMs
Exercise-based intervention							
Bernabei et al. 2022 (20) (results of HRQoL presented in a separate paper Rapp et al. 2023)(43)	RCT 156 weeks Two groups: Intervention: Multicomponent Intervention (MCI) Control: Healthy Aging Lifestyle Education (HALE)	Community-dwelling older men and women with physical frailty and sarcopenia (≥ 70 years) 1519 participants Women 1088 (71.63%)	FNIH Low muscle mass (ALM Men < 19.75 kg, Women < 15.02 kg) Low physical performance (SPPB score between 3 and 9 or gait speed ≤ 0.8 m/s)	Quality of life: EQ-5D index EQ-5D Vas	Mobility disability (inability to independently walk 400 m in < 15 minutes)	Significantly lower incidence in mobility disability in the intervention group as compared with control.	Quality of life: no significant improvement compared to the control group
de Sá Souza et al. 2022(23)	RCT 12 weeks Two groups: Intervention: Resistance exercise training (RET) Control: No exercise	Community-dwelling older adult with sarcopenia (≥ 65 years) 28 participants Women 18 (64.28%)	EWGSOP Low muscle mass (SMI Men <7.27 g/m², Women: < 5 g/m²) Low muscle strength (handgrip strength Men <40 kg, Women: <30 kg) Low physical performance (SPPB score < 6)	Daytime sleepiness Epworth Sleepiness Scale (ESS) Insomnia impact: Insomnia Severity Index (ISI) Sleep quality and disturbance: Pittsburgh Sleep Quality Index (PSQI)	Polysomnography, Pitsburgh Sleep Quality Index, Evaluation of sleep-wake cycle actigraphy, biochemical assessments, SPPB, Manual grip strength, body composition	Significant improvement of time to sleep onset, apnea/hour, subjective sleep quality and interleukin-1 receptor antagonist in the intervention group.	ESS: no significant difference compared to the control group ISI and PSQI : significant improvement compared to the control group
Flor-Rufino et al. 2023(28)	RCT 26 weeks Two groups: Intervention: High-intensity resistance training (HIRT) Control: No exercise	Community-dwelling older women with sarcopenia (≥ 70 years) 38 participants Women (100%)	EWGSOP Low muscle mass (SMI < 6.68 kg/m²) Low muscle strength (handgrip strength < 20 kg) Low physical performance SPPB score ≤ 8 Gait speed < 0.8 m/s	Quality of life EQ-5D index EQ-5D Vas	Muscle volume, bone volume, relative volume of intramuscular fat, extra muscular subcutaneous fat, microscopic fat fraction, descriptors of muscle texture, diffusion coefficient.	Significant improvement of muscle strength, gait speed, maximum expiratory pressure	Quality of life: EQ-5D index – No significant difference EQ-5D VAS – Significant difference compared to the control group
Tsekoura et al. 2018(27)	RCT 12 Weeks Three groups: Interventions: - Group-based exercise (I1) - Individualized home-based exercise (I2) Control: Educational leaflet about sarcopenia	Older adults living independently in the community with sarcopenia (≥ 60 years) 54 participants Women: 47 (87.3%)	EWGSOP1 Low muscle mass (SMI Men <7.23 kg/m², Women < 5.67 kg/m²) Low muscle strength (handgrip strength Men <30 kg, Women <30kg)	Quality of life: SarQoL	Muscular, functional/physical performance and quality of life	Significant improvement of calf circumference, timed up and Go test, 4m test, chair stand test, muscle mass index and muscle strength.	Quality of life : I1 – significant improvement in 4 domains of SarQoL (locomotion, functionality, activity of daily living, and fears) I2 – Significant improvement in 2 domains of SarQoL (Functionality, activity of daily living)
Tung et al. 2023 (24°)	RCT 26 Weeks Two groups: Intervention: Vitaly acupunch (VA) exercise program Control: Usual care routine	Older adults from 12 voluntary long-term care institutions who had lived there for at least three months (≥ 65 years) 103 participants Women 59 (57.3%)	Low muscle mass (Calf circumference Men <34 cm, Women: <33cm) Low muscle strength (handgrip strength Men <28 kg, Women: <18 kg)	Sleep Quality: Pittsburgh Sleep Quality Index (PSQI)	Muscle mass, handgrip strength and sleep quality	Significant improvement of muscle mass and handgrip strength.	PSQI: Significant improvement in sleep quality
Nutrition-based intervention							
Bo et al. 2019(15)	RCT 24 weeks Two group: Intervention: Whey protein, vitamin D and E supplements control: Isocaloric product	Community-dwelling older adults with sarcopenia (≥ 65 years) 60 participants Women 33 (55%)	Low muscle mass (SMI Men <7.00 kg/m², Women <5.4 kg/m²) Low muscle strength (handgrip strength Men <26 kg, Women: <18 kg) Low physical performance (gait speed ≤ 0.8 m/s)	Quality of life : SF-36	Body composition, relative muscle mass index, handgrip strength, serum IGF-1, IL-2, vitamin D3, vitamin E compared to the control group	Significant improvement of relative muscle mass index, handgrip strength, serum IGF-1, IL-2, vitamin D3, vitamin E compared to the control group	Quality of life: Significant improvement of physical and mental component scales of the SF36 questionnaire compared to the control group
Rondanelli et al. 2020(18)	RCT 8 weeks Two groups: Intervention: Experimental protein-based nutritional formula enriched with leucine and vitamin D Control: Isocaloric placebo	Older adult candidates for in-patient rehabilitation who were found to have sarcopenia (≥ 65 years) 127 participants Women 84 (66.14%)	EWGSOP (handgrip strength Men <26 kg, Women <18kg) Low physical performance (gait speed ≤ 0.8 m/s)	Quality of life: SF-12	Change in 4meter gait speed per month	Significantly greater increase in mean gait speed compared to the control group. Significant effect was also found for muscle mass and all key secondary functional endpoints.	Quality of life: No significant improvement compared to the control group
Rondanelli et al. 2022(31)	RCT 8 Weeks Two groups: Intervention: Novel food composed of leucine, omega-3 fatty acids and probiotic Lactobacillus Paracasei PS23 (OLEP) Control: Isocaloric placebo	Community-dwelling Adult with sarcopenia (≥ 55years) * 50 participants (gender distribution NR) *This study is included because the mean age of participants is ≥ 60 years: Mean +/- SD 78.84 ± 5.80 -Intervention 80.50 ± 3.74 - Placebo	EWGSOP Low muscle mass (SMI) Low muscle strength (handgrip strength) Low physical performance (SPPB score)	Quality of life: SF-12 Depression: Geriatric Depression Scale (GDS)	Appendicular lean mass	Significant improvement of SMI index compared to the control group. Significant improvement of muscle strength and physical performance as well.	Quality of life and depression: No significant improvement compared to the control group
Combined exercise and nutrition-based intervention							
Tokuda et Mori 2023(21)	RCT 24 weeks Three groups: Interventions: - Resistance exercise + essential amino acids + tea catechins (RE + EAA + TCC) (I1) - Resistance exercise + essential amino acids (RE + EAA) (I2) Control: Resistance exercise (RE)	Older adults with sarcopenia residing in either a community or a care facility (≥ 65 years) 46 participants Women 40 (86.96%)	AWGS Low muscle mass (SMI (Men <7.0 kg/m² Women <5.7 kg/m²) Low muscle strength (handgrip strength Men < 28 kg, Women < 18 kg) Low physical performance (gait speed < 1m/s)	Quality of life : SF-36	Skeletal muscle mass	Significant improvement in the I1 et I2 compared to the control group. Higher improvement in I1 compared to I2.	Quality of life: No significant improvement compared to the control group.

RCT: Randomized Controlled Trial, ALM: Appendicular Lean Mass; SPPB: Short Physical Performance Battery; SMI: Skeletal Muscle Index; MCI: Multicomponent Intervention; HALE: Healthy Aging Lifestyle Education ; RET: Resistance exercise training; ESS: Epworth Sleepiness Scale; ISI: Insomnia Severity Index ; PSQI: Pittsburgh Sleep Quality Index; SD: Standard Deviation ;GDS: Geriatric Depression Scale

Table 3. General description of the 8 RCTs that showed no improvement of the primary outcome following the intervention

Reference	Study Description	Population and sample size included in the analysis	Diagnosis of sarcopenia	Type of PROMs/PREMs	Primary endpoint	Effect on primary endpoint	Results of interventions on PROMs/ PREMs
Nutrition-based intervention							
Tamura et al. 2023(17)	RCT 12 weeks Five groups: Interventions: - ALA 50/SFC 29 - ALA 100/SFC 29 - ALA 150/SFC 29 - ALA 100/SFC 57 Control: ALA 0/SFC 29	Community-dwelling older adults with sarcopenia (≥ 65 years) 90 participants Women 64 (71.1%)	Low muscle mass (SMI Men <7 kg/m^2 Women: <5.7 kg/m^2) Low muscle strength (handgrip strength Men <25 kg ; Women: <20 kg) Low physical performance (gait speed < 1 m/s)	Quality of life: SF36 EQ-5D index EQ-5D Vas Depression : Beck Depression Inventory (BDI)	Change in SMI from baseline	No significant difference between groups. Significant improvement of handgrip strength compared to control.	Quality of life and depression: No significant improvement compared to the control group. Only a significant improvement of EQ-5D VAS was observed in the ALA100/SFC29 group compared to the control group.
Bauer et al. 2015(44)	RCT 13 week Two groups: Intervention: Vitamin D and leucine-enriched whey protein nutritional supplement Control: Isocaloric product	Sarcopenic primarily independent-living older adults (≥ 65 years) 380 participants Women 249 (65.53%)	Low muscle mass (Skeletal muscle mass/ body weight) *100 - Men <37%, Women <28%) Low muscle strength (handgrip strength Men <30 kg, Women <30kg) Low physical performance (gait speed ≤ 0.8 m/s)	Quality of life: EQ-5D index EQ-5D VAS	Handgrip strength, SPPB test	No significant improvement of muscle strength and SPPB test compared to the control group	Quality of life: No significant improvement compared to the control group
Nasimi et al. 2021(13)	RCT 12 weeks Two groups: Intervention: Yogurt fortified with 3 g beta-hydroxy beta-methyl butyrate (HMB), vitamin D, and vitamin C Control: Plain yoghurt.	Community-dwelling older adults with sarcopenia (≥ 65 years) 64 participants Women 16 (25%)	AWGS Low muscle mass (SMI Men <7.00 kg/m^2, Women <5.4 kg/m^2) Low muscle strength (handgrip strength Men <26 kg, Women <18 kg) Low physical performance (gait speed ≤ 0.8 m/s)	Quality of life: SF-12	Lean mass and appendicular lean mass	No improvement of primary outcome but significant improvement of handgrip strength and gait speed compared to the control group.	Quality of life: Significant improvement of Physical component scale, no significant improvement of mental component scale compared to the control group
Combined exercise and nutrition-based intervention							
Gade et al. 2019 (22)	RCT 12 weeks Two groups: Intervention: Resistance training and protein supplementation (PrS) Control: Resistance training and placebo	Geriatric older adult with sarcopenia (≥ 70 years) 148 participants Women 100 (67.57%)	EWGSOP Low muscle mass (SMI) Low muscle strength (handgrip strength) Low physical performance (gait speed)	Quality of life: EQ-5D index EQ-5D Vas	30-s chair stand test	No significant improvement compared to the control group.	Quality of life: No significant improvement compared to the control group
Pinheiro et al. 2020(19)	RCT 12 Weeks Three groups: Interventions: - Functional exercise (I1) - Functional exercise and nutritional intervention (I2) Control: Health guidance	Community-dwelling older women with sarcopenia (Mean age: 80.3 ± 6.8) 30 participants Women (100%)	EWGSOP Low Muscle mass (calf circumference Women ≤ 31cm) Low muscle strength (handgrip strength Women ≤ 20 kg) Low physical performance (gait speed < 0.8 m/s	Quality of life : EQ-5D Depression: GDS Loneliness/social isolation: UCLA loneliness scale	Depression, loneliness and quality of life	See column on PROM/PREM as they are the primary outcome	Depression, loneliness and quality of life: Significant improvement in the nutritional intervention group (I2) but no comparison with the control group – impossible to conclude.
Zhu et al. 2019(29)	RCT 24 weeks Three Groups: Intervention: - Combined exercise program and nutrition supplement - Exercise program alone Control group: Waitlist	Community-dwelling older Chinese people with sarcopenia (≥ 65 years) 113 participants Women 87 (77%)	AWGS Low muscle mass (SMI Men <7.00 kg/m^2, Women <5.4 kg/m^2) Low muscle strength (handgrip strength Men <26 kg, Women <18 kg) Low physical performance (gait speed ≤ 0.8 m/s)	Quality of life: SF-12	Gait speed	No significant improvement of gait speed	Quality of life: No significant improvement compared to the control group
IMP-based interventions							
Rooks et al. 2020(25)	RCT 26 weeks Two groups: Intervention: Bimagrumab 700 mg monthly with adequate diet and home-based exercise. Control: Placebo	Community-dwelling older men and women meeting gait speed and skeletal muscle criteria for sarcopenia. (≥ 70 years) 180 participants Women 109 (60.56%)	EWGSOP or AWGS Low muscle mass (SMI – European cut-off Men ≤ 7.26 kg/m^2, Women ≤ 5.5 kg/m / Asian cut-offs: Men ≤ 7.0 kg/m^2, Women ≤ 5.4 kg/m^2) Low physical performance (PPB score <9 or gait speed over 4 meters ≤ 0.8 m/s)	Quality of life: SF-36 EQ-5D	Change in SPPB test	No significant improvement compared to the control group.	Quality of life: No significant improvement compared to the control group
LACE study group et al. 2022(26)	RCT two-by-two factorial trial 52 weeks Four groups: Interventions: - Perindopril + placebo - Leucine + perindopril - perindopril + Leucine Control: Placebo + Placebo	Older adults with low muscle strength and mass (≥ 70 years) 145 participants Women 78 (53.79%)	EWGSOP Low muscle mass (cut-off value varied with BMI) Low muscle strength (handgrip strength Men <30 kg, Women <20 kg) Low physical performance (gait speed < 0.8 m/s)	Quality of life : EQ-5D EQ-VAS	Change in SPPB test	No significant improvement compared to the control group.	Quality of life: Perindopril - Significant negative effect on EQ-VAS compared to the control group Leucine – Significantly worse score on EQ-5D compared to the control group

ALA: 5 aminolevulinic acid; SFC: sodium ferrous citrate; BDI; Beck Depression Inventory ;

Table 4. Overview of PROMs used within included studies

PROMs	Description
Short Form – 36 health survey (SF-36)	Generic PROMs Measure general health and well-being (HRQoL), including the impact of all illnesses of a broad range of functional domain 8 domains: general health, physical functioning, role limitation physical, mental health, role limitation-emotional, social functioning, bodily pain, vitality
Short Form – 12 health survey (SF-12)	Generic PROMs Alternative to the SF-36 developed to be much shorter Measure the same domain but improve wording and response choice to cover a broader range of health.
EuroQoL-5 Dimension (EQ-5D)	Generic PROMs To describe and value health-related quality of life (HRQoL) Based on a descriptive system that defines health in terms of 5 dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression.
Sarcopenia Quality of Life (SarQoL)	Disease-specific PROMs Design for community-dwelling older persons (≥ 65 years) to measure the quality of life of a patient suffering from sarcopenia. 7 domains: physical and mental health, locomotion, body composition, activity of daily living, leisure activity, and fear.
Geriatric Depression Scale (GDS)	Generic PROMs To assess depressive symptoms and screen depression among older people
Beck Depression Inventory (BDI)	Generic PROMs Designed to assess the level of depression in adults.
UCLA loneliness scale	Generic PROMs A 20-item scale designed to measure one's subjective feelings of loneliness and social isolation.
Epworth sleepiness Scale (ESS)	Generic PROMs Measure a person's general level of daytime sleepiness or their average sleep propensity in daily life
Insomnia Severity Index (ISI)	Generic PROMs Designed to assess the nature, severity, and impact of insomnia.
Pittsburgh Sleep Quality Index (PSQI)	Generic PROMs Designed to assess sleep quality and disturbance over a one-month interval.

impact of the intervention compared to a specific instrument. Specific questionnaires are more sensitive to change. Currently, only three specific PROMs for sarcopenia are documented in the scientific literature, which explains their limited utilization in clinical trials. First, the Age-Related Muscle Loss Questionnaire (ARMLQ - SARCOPRO) has been developed by Evans et al. (32) in 2011 to assess functional impacts of reduced muscle strength. Only the content validity of this PROM has been reported, leaving the other psychometric properties, such as validity, reliability and responsiveness to change unexplored. Second, the Patient-Reported Outcomes Measurement Information System (PROMIS) Physical function item bank, funded by the NIH (33), has been validated for measuring physical function. However, the appropriate context of use and the fit-for-purpose measurement in sarcopenia have not been reported thus far. Thirdly, the SarQoL, a specific quality of life questionnaire for sarcopenia, stands as the only validated PROM currently available. Translated into more than 35 languages and validated across 19 different populations, this PROM is recommended for use in both clinical and research practices (34–36).

The international COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) initiative (37) provides guidelines for selecting the most appropriate PROM in research and clinical settings. COSMIN taxonomy covers key psychometric properties, including reliability (such as reliability, measurement error, and internal consistency), validity (such as content validity, criterion validity, and construct validity), and responsiveness. However, the mere existence of a PROM doesn't ensure its suitability for measuring a specific concept related to PROMs. In clinical trials targeting sarcopenia management using a PROM as a primary or secondary endpoint, it is crucial to verify that the PROM has been properly developed and validated according to established guidance. In the context of interventional studies, the PROM's responsiveness to change of a PROM is paramount. The instrument should be sensitive enough to detect any change in the measured concept. For this reason, an ESCEO working group, composed by key experts in the field of clinical trials for sarcopenia, recommends the use of specific PROMs in clinical trials aiming at the management of sarcopenia (9).

The existing diversity in outcome measures underlined in this systematic review also underscores the critical need for standardization in sarcopenia research. The development and adoption of a Core Outcome Set (COS) play a pivotal role in achieving this standardization. The absence of a COS for sarcopenia significantly contributes to the observed variability in PROMs across studies. The COMET (Core Outcome Measures in Effectiveness Trials, https://www.comet-initiative.org/) initiative actively promotes the creation and use of COS, recognizing its numerous advantages (38). COS serves as a valuable tool in averting ineffective interventions and addressing outcome-reporting bias by providing a predefined list of essential outcomes for measurement in Randomized Controlled Trials (RCTs) (39). Its implementation enhances the ability to conduct more consistent systematic reviews or meta-analyses, facilitating robust comparisons across studies and improving the reliability and generalizability of research findings (39). Developing a COS specific to sarcopenia is indispensable not only for establishing uniformity in outcome reporting but also for enhancing the validity and reliability of study results.

This review also brings to light a significant aspect of sarcopenia research: Patient-Reported Experience Measures (PREMs) were not reported in any of the included studies. The underreporting of PREMs in sarcopenia can be attributed to several factors, including researchers' skepticism, resource limitations, insufficient funding, reluctance to overburden patients, uncertainties about how to utilize PREMs results, and an evident lack of standardization (40). However, addressing the underreporting of PREMs in sarcopenia research requires a broader recognition of the importance of patient perspectives in evaluating intervention effectiveness. Adopting a patient-centered approach is crucial, as neglecting the patient's experience during an interventional trial can impede shared decision-making in sarcopenia research. Shared decision-making (SDM) explicitly involves patients and clinicians in decisions regarding diagnostic and treatment options (41) by integrating patients' values and preferences (42). Developing a standardized tool to address this issue could overcome barriers to PREMs implementation and contribute to a more comprehensive and patient-centered approach to sarcopenia studies.

Limitations

This study is constrained by its reliance solely on published literature, potentially overlooking additional interventional studies that are either ongoing or completed but unpublished. Furthermore, our inclusion criteria focused on interventional studies explicitly reporting PROMs or PREMs as primary or secondary outcomes, preventing us from offering a comprehensive prevalence of studies employing such outcomes. Consequently, it remains uncertain whether the use of PROMs is a common or less widespread practice in sarcopenia research. Additionally, the substantial variability in the PROMs used across these studies posed a challenge to conducting a meta-analysis. The differences in outcome measurement instruments between studies created obstacles in synthesizing quantitative data. This emphasizes the critical need for heightened standardization of measurement tools in sarcopenia research. Enhancing standardization would not only facilitate future meta-analyses but also promote comparability across studies, addressing a significant challenge in the current landscape.

Conclusion

In addressing the impact of sarcopenia intervention on PROMs/PREMs, this study identified 17 sarcopenia-designed interventional trials employing diverse strategies such as medication, nutritional supplementation, and exercise. None of these studies used a PREM as primary or secondary outcome. PROMs were exclusively use in those studies covering aspects like HRQoL, depressive symptoms, loneliness and sleep quality. The varied effect on PROMs highlights the need for standardization in sarcopenia research. Developing a Sarcopenia Core Outcome Set is important to ensure consistent, comparable findings, enhancing the intervention's reliability and effectiveness.

Data availability and transparency: All materials related to this work are freely available on the Open Science Framework deposit.

Conflict of Interest: Charlotte Beaudart is stakeholder of SARQOL SRL, a spin-off of of the University of Liège, in Belgium, in charge of the interests of SarQoL, a specific health-related quality of life questionnaire for sarcopenia. However, she has never received any financial compensation for this role.

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Authors contribution: C.B. designed the study, the protocol, run the different search strategies. G.L.D, F.O.F and V.S. screened the studies and extracted the data. S.vH. helped in the interpretation of data, manual search and risk of bias assessment. G.L.D and C.B. wrote the manuscript. All authors read and approved the final version of the manuscript.

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