Systematic Review

Effects of Probiotics, Prebiotics, and Synbiotics on Sarcopenia Parameters in Older Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Maria Besora-Moreno[1], Elisabet Llauradó[1,2,*], Rosa M. Valls[1,*], Anna Pedret[1], Rosa Solà[1,2,3]

[1]Universitat Rovira i Virgili, Facultat de Medicina i Ciències de la Salut, Departament de Medicina i Cirurgia, Functional Nutrition, Oxidation, and Cardiovascular Diseases Group, 43201 Reus, Spain; [2]Institut Investigació Sanitària Pere i Virgili, 43204 Reus, Spain; [3]Hospital Universitari Sant Joan de Reus, 43204 Reus, Spain

*Corresponding author: *Elisabet Llauradó*, Functional Nutrition, Oxidation, and Cardiovascular Diseases Group, Facultat de Medicina i Ciències de la Salut, Universitat Rovira i Virgili, C/Sant Llorenç 21, 43201, Reus, Spain (elisabet.llaurado@urv.cat); *Rosa M. Valls*, Functional Nutrition, Oxidation, and Cardiovascular Diseases Group, Facultat de Medicina i Ciències de la Salut, Universitat Rovira i Virgili, C/Sant Llorenç 21, 43201, Reus, Spain (rosamaria.valls@urv.cat).

Context: *There is scarce evidence about which probiotic, prebiotic, or synbiotic supplementation is the most appropriate to improve sarcopenia parameters, and this presents a challenge.* ***Objective:*** *The effects of consumption of probiotics, prebiotics, and synbiotics on sarcopenia, muscle strength, muscle mass, and physical performance and function were assessed in this study. In addition, another aim of the study was to determine the best probiotic, prebiotic, and/or synbiotic for the management of sarcopenia in older adults.* ***Data Sources:*** *A systematic search was conducted in the MEDLINE/PubMed, Cochrane Library, SCOPUS databases, and other sources (eg, references obtained from articles identified in databases).* ***Data Extraction:*** *The search was limited from 2000 to 2023 and was based on sarcopenia parameters, and probiotics, prebiotics, or synbiotics supplementation. The quality of each included study also was assessed.* ***Data Analysis:*** *A meta-analysis was performed with the Review Manager program and publication bias and sensitivity analysis were performed.* ***Results:*** *Eight randomized controlled trials (RCTs) were included in the systematic review and 4 in the meta-analysis. Results showed that probiotics supplementation improved muscle strength and physical performance and function and suggested a beneficial effect on muscle mass. Prebiotics are suggested to be effective on muscle strength. The meta-analysis also determined that probiotic interventions were effective in increasing muscle strength by handgrip strength (mean difference [MD], 2.50 kg [95% CI, 1.33-3.66]; $P < .0001$) and physical performance and function by gait speed (MD, 0.10 m/s [95% CI, 1.33-3.66]; $P < .0001$) and physical performance and function by gait speed (MD, 0.10 m/s [95%CI, 0.03-0.16]; $P = .003$), but when sensitivity analysis was applied, the effectiveness was only maintained for gait speed.* ***Conclusion:*** *Nutritional strategies based on probiotic supplementation seem to improve muscle strength and physical function. More robust research is needed with high-quality RCTs to confirm probiotics' effects. There is still limited evidence about prebiotic*

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and synbiotic strategies, and more evidence is needed to elucidate their effects on sarcopenia parameters.
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Key words: *probiotic, prebiotic, synbiotic, sarcopenia, aged.*

INTRODUCTION

Sarcopenia is a multifactorial, progressive, and generalized musculoskeletal disorder related to the aging process.[1,2] The European Working Group on Sarcopenia in Older People (EWGSOP2) in 2019 defined sarcopenia as low muscle strength, low muscle quantity or quality, and low physical performance.[1] Probable sarcopenia is considered with low muscle strength.[1] The diagnosis of sarcopenia is confirmed with low muscle strength and low muscle quantity or quality.[1] Sarcopenia is categorized as severe when the 3 sarcopenia parameters are identified.[1] There are different classifications and cutoff points of sarcopenia parameters; thus, the global prevalence of sarcopenia ranges from 10% to 27% in people aged ≥60 years.[3] In 2016, the prevalence of sarcopenia among adults older than 65 years in Europe was around 11.1%-20.2% and is projected to increase to 12.9%-22.3% in 2045.[4] The World Health Organization defines older adults as people aged ≥60 years[5]; however, leg muscle mass and strength decrease by 1%-2% and 1.5%-5% per year, respectively, starting at the age of 40 years.[6,7] Additionally, sarcopenia negatively affects health by increasing the risk of fractures,[1] falls,[1,8] and death[1,9,10]; enhancing other comorbidities; and increasing hospitalizations[9] and health care costs,[9,11] all of which are associated with a loss of independence.[9]

The gut microbiota seems to have some relationship with the onset of sarcopenia in older adults. The diversity and composition of microbiota of older individuals are reduced; there are fewer beneficial bacteria and an increase of harmful and opportunistic bacteria.[12,13] This gut microbiota dysregulation is called dysbiosis and is associated with increased intestinal permeability, which, consequently, facilitates the entry of endotoxins and other microbial products into the circulation that promote and inflammatory condition and changes in skeletal muscle mass.[14] Additionally, related to dysbiosis, there is a reduction of short-chain fatty acid (SCFA) producers that is related to aging-associated diseases.[13] In this context, dysbiosis is associated with low muscle mass and low physical performance and function.[15] So, the microbiota could be related to sarcopenia pathogenesis,[16] probably via the gut-muscle axis by the regulation of inflammation, reactive oxygen species production, and mitochondrial function in muscle.[16]

Different strategies can modify the microbiota composition, such as nutritional interventions and the supplementation of SCFAs, probiotics, prebiotics, and synbiotics.[16,17] Nutritional interventions based on a diet rich in fruits and vegetables, high protein intake (in particular, leucine), correct hydration, and physical exercise were the best strategies to improve sarcopenia.[18] Additionally, a diet rich in protein or protein supplementation improved appendicular skeletal muscle mass index (ASMI). Also, in the early elderly population (<75 years old), protein supplementation enriched with leucine and vitamin D increased ASMI and gait speed (GS).[19]

Probiotics, prebiotics, and synbiotics act directly on the gut microbiota, providing live microorganisms and/or substrates used selectively by the host's microorganisms, generating health benefits.[20–22] It remains unknown which nutritional strategies, such as probiotic, prebiotic, and synbiotic supplementation, are the most appropriate to improve sarcopenia parameters. Thus, the present systematic review and meta-analysis were conducted to address this gap in the literature considering probiotic, prebiotic, and synbiotic supplementation as a novel nutritional strategy for the prevention and treatment of sarcopenia.

The main objective of the present systematic review and meta-analysis of randomized controlled trials (RCTs) was to assess the effects of probiotic, prebiotic, and synbiotic consumption on sarcopenia, muscle strength, muscle mass, and physical performance and function by the gut-muscle axis. Also, we wanted to determine which is the best probiotic, prebiotic, and/or synbiotic for the management of sarcopenia in older adults (ie, ≥60 years old).

METHODS

A systematic review and meta-analysis of RCTs about probiotic, prebiotic, and synbiotic consumption and their effects on sarcopenia were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis.[23] The review was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42022360514).

Search Strategy

A systematic search was conducted of electronic databases (MEDLINE/PubMed, Cochrane Library, and SCOPUS) and other sources (ie, references from articles included in this review). The search strategies were based on the following keywords: probiotic, prebiotic, synbiotic, sarcopenia, muscle strength, muscle mass, physical performance, physical function, frailty, gut-muscle axis, elderly, older adults, and geriatrics; and limited to publication from 2000 to 2023, in the English language, and human studies. The search was started with publication in 2000 because no articles were identified before 2000 in any database based on the search strategy we defined. The full search strategies are listed in Table S1.

Eligibility Criteria

The inclusion criteria for articles were the following: (1) RCTs; (2) including a population ≥60 years old; (3) about probiotic, prebiotic, and synbiotic consumption and their effects on sarcopenia, sarcopenia parameters (namely, muscle strength, muscle mass, and physical performance and function) assessed with any assessment tool according to the different sarcopenia consensus and diagnostic criteria; (4) published in English; and (5) published from 2000 to 2023.

Articles reporting on studies that included a population with skeletal muscle disorders (eg, osteoporosis, fibromyalgia, rheumatoid arthritis) or populations with cancer in bone or muscle mass, and studies that did not meet all the aforementioned inclusion criteria were excluded. The RCTs were defined according to the Population, Intervention, Comparison, Outcomes, and Study (PICOS) criteria (Table 1).

Diagnostic Criteria for Sarcopenia

According to the revised European consensus EWGSOP2, the sarcopenia cutoff points for the diagnosis were as follows: (1) muscle strength based on a grip strength <27 kg for men, <16 kg for women; (2) muscle quantity or quality based on appendicular skeletal muscle mass <20 kg for men, <15 kg for women; ASMI <7.0 kg/m^2 for men, <5.5 kg/m^2 for women; and (3) physical performance based on GS ≤0.8 m/s, or Short Physical Performance Battery score ≤8 points, and either 3-m timed up-and-go test (TUG) ≥20 seconds or 400-m walk test ≥6 min or noncompletion.[1] The grip strength measured with a calibrated handheld dynamometer is the gold standard for assessing muscle strength, and magnetic resonance imaging and computed tomography are gold standard assessment tools for muscle mass.[1] However, bioimpedance analysis is the most used tool in clinical practice.[1] Finally, GS, short physical performance battery (SPPB), 3 m-TUG, and 400-m walk test are the most used tools to assess physical performance and function, according to the EWGSOP2.[1]

Table 1. PICOS Criteria for Inclusion of Studies

Population	Adults aged >60 y
Intervention	Consumption of probiotics, prebiotics, and synbiotics
Comparison	Placebo consumption or no consumption of probiotics, prebiotics, and synbiotics
Outcomes	Sarcopenia, muscle strength, muscle mass, and physical performance or function
Study type	Randomized controlled trials

Study Selection and Data Extraction

The study selection was carried out using the Covidence web-based software platform to produce systematic reviews to facilitate the study selection process (Veritas Health Innovation, Melbourne, Australia; www.covidence.org). First, title and abstract screening was done based on the eligibility criteria. Second, the full texts of those studies accepted were assessed. Finally, the RCTs that met all the screening criteria were included for data extraction and quality assessment. Data extraction was performed by 2 researchers (M.B.-M. and E.L.) and any disagreement or discrepancies were resolved through discussion with other authors (R-M.V. and A.P). If any necessary information was missing, the article's authors were contacted to request it.

In the data extraction process, information on the following variables was collected: author names; title; year of publication; type of study; country; number of participants; age and sex of participants; duration of the intervention; probiotics, prebiotics, and synbiotics (product description); dose of probiotics, prebiotics, and synbiotics; sarcopenia, muscle strength, muscle mass, and physical performance and function assessment; effects on sarcopenia of consumption of probiotics, prebiotics, and synbiotics; and risk of bias of the included studies.

Quality Assessment by Risk of Bias in Individual Studies

The quality of each included study was assessed using the Cochrane risk-of-bias tool for RCTs (RoB2).[24] According to the RoB2, based on 5 domains, the risk-of-bias classification was as follows: (1) low risk of bias (low risk of bias for all domains); (2) some concerns (some concerns in at least 1 domain without high risk of bias for any domain); and (3) high risk of bias (high

risk of bias in at least 1 domain or some concerns about multiple domains). Two authors evaluated the risk of bias in each RCT (M.B.-M. and E.L.), and any disagreement between these authors regarding the risk of bias in a study was resolved through discussion with the other authors.

Data Synthesis and Statistical Analysis

Statistical analyses were performed using Review Manager (RevMan; version 5.4; The Cochrane Collaboration).

In the systematic review, the RCTs results are reported as mean and SD, mean and SEM, median and IQR, or mean difference (MD) and the 95% CI to enable comparison among the studies included. To assess the change in RCTs, it was preferable to have the MD and 95% CI values whenever possible; otherwise, they were calculated with RevMan if all the necessary data were available.

For the meta-analysis, the effect size was represented by MD and the 95% CI from continuous outcomes and risk ratios (RRs) for dichotomous outcomes. The meta-analysis inclusion criteria were (1) RCTs about the same sarcopenia variable; (2) using the same tool to assess each sarcopenia variable; (3) with the complete information about the outcome with means and SD or the change of the sarcopenia variables from baseline to the end of the intervention; and (4) only those sarcopenia variables for which at least 3 articles met the inclusion criteria. To include a study in the meta-analysis, the article needed to report the mean and SD of the sarcopenia parameters analyzed or the change of the sarcopenia parameter from baseline to the end of the intervention.

Additionally, the heterogeneity was evaluated using the I^2 statistic. When the heterogeneity was 0% (no heterogeneity) the results were analyzed with the fixed-effects method, although the results using the random-effects method were the same.[25] In case of high heterogeneity (>75%), the results were analyzed with the random-effects method as long as the results of smaller studies were not systematically different from the results of larger ones.[25] A random-effects method would aggravate the effects of bias, whereas a fixed-effects method would be less affected, although it would not be entirely appropriate.[25] If any information results were missing, the authors of the publication were asked to provide them, and if they did not answer, the MD and the 95% CI were calculated whenever possible based on the mean ± SD or mean ± SEM of baseline and end of intervention data. Additionally, sensitivity analyses were performed excluding higher-weight studies and studies with high risk of bias. A P value <0.05 was considered statistically significant.

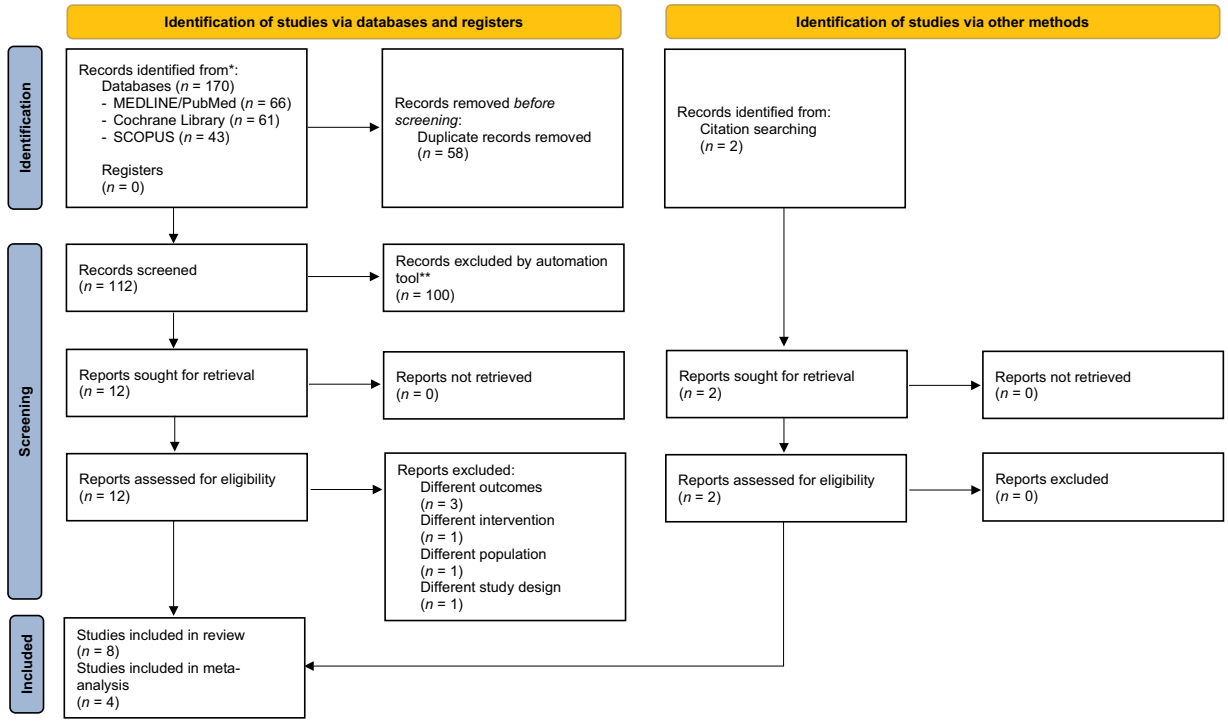
The publication bias of the meta-analysis was assessed by funnel plot[26] and Egger's test,[27] using SPSS Statistics for Windows, version 29.0.1.0 (IBM Corp., Armonk, NY). There is no publication bias when the funnel plot is symmetric; however, when the funnel plot is asymmetric, there is a publication bias.[26] Also, when Egger's test is statistically significant, publication bias is detected.[27] An Egger's test with a P value <0.10 is considered statistically significant.[27]

RESULTS

A total of 170 RCTs were identified from electronic databases. Of these, 58 duplicate RCTs were removed before screening and 100 were excluded according to the inclusion and exclusion criteria based on review of titles and abstracts. The full texts of the remaining 12 RTCs were assessed and 6 of them were excluded for the following reasons: different outcomes ($n=3$)[28–30], different intervention ($n=1$)[31], different population ($n=1$)[32], and different study design ($n=1$)[33] than detailed in the inclusion and exclusion criteria of the present systematic review. Despite the aforementioned age-related inclusion and exclusion criteria, 3 RCTs that had as inclusion criteria people aged ≥55 years[34,35] or ≥58 years[36] were included in the present systematic review because all the volunteers included were ≥60 years old. In addition, 2 RCTs were identified from other sources.[36,37] Finally, 8 articles were included in the systematic review,[34,35,37–41] of which 4 were included in the meta-analysis (Figure 1).[34,36,37,41]

Characteristics of the Studies Included in the Systematic Review

All 8 studies included were RCTs[34–41] (Tables 2[34–41] and 3[34–37,40,41]) (Table S2[34–36,39,41]). The study population was women and men in 6 studies[34,35,37–40] and only men in 2 studies;[36,41] all participants were aged ≥60 years. The sample size of the included studies ranged from 18[39] to 396 participants.[38] Of the total of 8 RCTs, 2 were carried out in Spain,[37,40] 2 in Pakistan[36,41], and 1 each from Brazil,[39] Taiwan,[34] Italy,[35] and China.[38] Supplementation was with probiotics in 6 studies,[34–38,41] prebiotics in 1 study,[40] and synbiotics in 1 study.[39] In addition, the intervention duration ranged from 8 weeks[35] to 24 weeks[38] in the different studies. All the studies used a placebo product as a control. Related to sarcopenia assessment, 8 studies assessed muscle strength,[34–41] 5 studies assessed muscle mass,[34–36,39,41] and 6 studies assessed physical performance and function[34–37,40,41] (Figure S1).



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis Flow Diagram of the Studies Included in the Systematic Review and Meta-Analysis[51]

Sarcopenia Variables Assessment

Muscle strength was assessed with a handgrip dynamometer in all 8 studies.[34–41] In 3 studies in which muscle mass was assessed, researchers used bioelectrical impedance analysis,[36,39,41] and 2 studies used dual-energy X-ray absorptiometry.[34,35] Physical performance and function were assessed with the following tools: GS and SPPB in 2 articles[36,41]; 3 m-TUG, 10-m walk test, and 30-second chair-stand test (30 s-CST) in 1 article[34]; 3 m-TUG, and GS in 1 article[37]; time to walk 4.6 m[40] in 1 article; and the Tinetti scale and SPPB in 1 article.[35]

Quality of the Studies in the Systematic Review

The quality of the 8 RCTs included in the systematic review according to the RoB2[24] is shown in Figure 2.[34–41] One article reported on a study that had a high risk of bias in domain 3 (missing outcome data),[40] and 2 reported on RCTs that had a high risk of bias in domains 2 (deviations from intended interventions) and 3.[34,35] Furthermore, 4 RCTs had a low risk of bias,[36–38,41] and 1 had some concerns for bias.[39]

Probiotic, Prebiotic, and Synbiotic Supplementation

Effects on Muscle Strength. The 8 RCTs assessed muscle strength (Table 2).[34–41] Focusing on probiotics supplementation and based on the MD (95% CI) and *P* for group × time, 3 RCTs had statistically significant results favoring the probiotic intervention group compared with the placebo group.[35,36,41] Two articles reporting on RCTs involving probiotics[34,37] did not show significance. And 1 article reporting on an RCT about probiotic supplementation did not report results between groups.[38] Additionally, 1 RCT on prebiotic supplementation[40] and another on synbiotic supplementation[39] did not show significance, based on the MD with 95% CI and *P* for group × time.

One of the effective interventions was studied in a 16-week, 2-arm RCT. Participants took either 1 capsule/d of Vivomixx (Vivomix food supplements, UAE) probiotic based on 112 billion live bacteria (*Streptococcus thermophilus* DSM 24731; *Bifidobacterium longum* DSM 24736; *B. breve* DSM 24732, DSM 24737; *Lactobacillus* DSM 24735, DSM 24730, DSM 24733; *L. delbrueckii* subsp. *bulgaricus* DSM 24734) or 1 capsule/d of placebo with inactive agents (not reported).[41] The RCT results showed that, compared

Table 2. Characteristics From Included Articles on Randomized Controlled Trials of Interventions Based on Probiotic, Prebiotic, and Synbiotic Supplementation, and Muscle Strength

Author; year	Study design; country	Participant sex; age (y)[a]	Total no. of participants	Type of supplementation		Duration of intervention; dose	Baseline HGS (kg)[b]	End HGS (kg)[c]	Change in HGS (kg)[d]
				PRO/PRE/SYN	Placebo				
Karim et al, (2022)[41]	R, DB, PL, PC Pakistan	M; 63-73	104	Probiotic (Vivomixx; *S. thermophilus*, bifidobacteria, and lactobacilli)[f]	Inactive agents[e]	16 wk 1 capsule/d[f]	CG 21.09 ± 3.2; $n = 53$ IG 20.77 ± 2.9; $n = 47$	CG 21.55 ± 3.2; $n = 53$ IG 23.50 ± 3.3*; $n = 47$	MD (95% CI) 2.27 (0.52, 4.02) ***P* = .01** for group × time
Lee et al, (2021)[34]	R, DB, PL, PC Taiwan	M/W; 55-85[a]	55	Probiotic (*L. plantarum* TWK10)[g]	Maltodex. and microcrys. cellul.	18 wk 2 capsules/d[g]	Left hand[b,h] CG 17.90 ± 6.1; $n = 17$ IG (TWK10-L) 19.60 ± 5.8; $n = 12$ IG (TWK10-H) 18.30 ± 5.7; $n = 13$	Left hand[b,h] CG 17.60 ± 5.1; $n = 17$ IG (TWK10-L) 19.50 ± 3.5; $n = 12$ IG (TWK10-H) 20.60 ± 6.2*; $n = 13$	Left hand TWK10-H baseline vs 18 wk 1.13-fold increased (***P* = .02**) Placebo vs TWK10-L[d] MD (95% CI) 0.20 (−5.18, 5.58) $P = .94$ for group × time Placebo vs TWK10-H[d] MD (95% CI) 2.60 (−3.34 to 8.54) $P = .39$ for group × time TWK10-L vs TWK10-H[d] MD (95% CI) 2.40 (−3.57 to 8.37) $P = .43$ for group × time
Lei et al, (2016)[38]	R, DB, PL, PC China	M/W; ≥60	396	Probiotic Skimmed milk containing LcS[i]	Skimmed milk	24 wk 2 servings/d[i]	HGS[b] CG NI IG NI	HGS[b] CG NI IG NI	Significantly higher at 2-5 mo in LcS group compared with the placebo group (***P* < .05**) No MD (95% CI) and *P* for group × time values compared with placebo
Neto et al, (2013)[39]	R, DB, PT, PL, PC Brazil	M/W; 60-75	18	Synbiotic (FOS, *L. paracasei*, *L. rhamnosus*, *L. acidophilus*, and *B. lactis*)[j]	Maltodex.	12 wk 1 dose/d[j]	HGS[b] CG 15.90 ± 2.7; $n = 8$ IG 15.00 ± 5.2; $n = 9$	HGS[b] CG 17.20 ± 3.9; $n = 8$ IG 15.70 ± 5.3; $n = 9$	HGS[d] MD (95% CI) −0.60 (−6.46 to 5.26) $P = .84$ for group × time
Román et al, (2019)[37]	R, DB, PL, PC Spain	M/W; >61.4	36	Probiotic (Vivomixx or Visbiome; *S. thermophilus, Bifidobacterium breve, B. longum, B. infantis, L. paracasei, L. acidophilus, L. delbrueckii* subsp. *bulgaricus*, and *L. plantarum*)[k]	Inactive agents (maltose and silicon dioxide)	12 wk 2 sachets diluted/d[k]	HGS[c] CG 20.98 ± 2.28; $n = 18$ IG 20.76 ± 2.27; $n = 17$	HGS[c] CG 20.24 ± 2.05; $n = 18$ IG 20.62 ± 2.05; $n = 17$	HGS[d] MD (95% CI) 0.60 (−7.89 to 9.09) $P = .89$ for group × time

(continued)

Table 2. Continued

Author; year	Study design; country	Participant sex; age (y)[a]	Total no. of participants	Type of supplementation		Duration of intervention; dose	Baseline HGS (kg)[b]	End HGS (kg)[c]	Change in HGS (kg)[d]
				PRO/PRE/SYN	Placebo				
Rondanelli et al, (2022)[35]	R, DB, PL, PC Italy	M/W; ≥55[a]	60	Omega-3 fatty acid, leucine, probiotic *L. paracasei* PS23 + nutritional and physical activity recommendations[l]	Isocaloric placebo[e]	8 wk 1 serving/d[l]		CG MD [95% CI] −0.76 [−1.63 to 0.12] IG MD [95% CI] 3.33 [2.40, 4.26]*	MD (95% CI) 4.09 (2.78, 5.39) **$P < .05$** for group × time
Buigues et al, (2016)[40]	R, DB, PL, PC Spain	M/W; ≥65	60	Prebiotic (Darmocare Pre; inulin and FOS)[m]	Maltodex.	13 wk 1 level spoon/d[m]	Right hand[b] CG 11.50 ± 5.7; $n = 22$ IG 10.60 ± 8.2; $n = 28$ Left hand[b] CG 10.20 ± 5.8; $n = 22$ IG 10.10 ± 7.6; $n = 28$	Right hand[b] CG 10.20 ± 4.1; $n = 22$ IG 12.40 ± 3.2*,**; $n = 28$ Left hand[b] CG 9.10 ± 3.7; $n = 22$ IG 9.80 ± 3.5; $n = 28$	Right hand[d] MD (95% CI) 3.10 (−1.29 to 7.49) $P = .17$ for group × time Left hand[d] MD (95% CI) 0.80 (−3.43 to 5.03) $P = .71$ for group × time
Karim et al, (2022)[36]	R, DB, PL, PC Pakistan	M; 58-73[a]	108	Probiotic (Vivomixx; *S. thermophilus*, bifidobacteria, and lactobacilli)[f]	Inactive agents[e]	12 wk 1 capsule/d[f]	HGS[b] CG 22.45 ± 2.87; $n = 48$ IG 23.11 ± 3.18; $n = 44$	HGS[b] CG 22.09 ± 2.18; $n = 48$ IG 25.78 ± 3.56*; $n = 44$	HGS[d] MD (95% CI) 3.03 (1.29, 4.77) **$P < .001$** for group × time

In each trial, sarcopenia assessment was conducted with a dynanometer.

[a]Despite the inclusion age, all included volunteers were ≥ 60 years old.

[b]Values are mean ± SD unless indicated.

[c]Mean ± SEM.

[d]MD (95% CI) calculated by researchers.

[e]Not reported.

[f]Each capsule contained 112 billion live bacteria (*Streptococcus thermophilus* DSM 24731; *Bifidobacterium longum* DSM 24736; *B. breve* DSM 24732, DSM 24737; *Lactobacillus* DSM 24735, DSM 24730, DSM 24733; *L. delbrueckii* subsp. *bulgaricus* DSM 24734).

[g]Each capsule of *L. plantarum* TWK10 contained either 1×10^{10} CFU (TWK10-L) or 3×10^{10} CFU (TWK10-H).

[h]No significant results for the right hand.

[i]Each serving of skimmed milk contained a minimum of 6×10^9 CFU *L. casei* Shirota.

[j]Each dose contained 6 g of FOS, 10^8-10^9 CFU *L. paracasei*, 10^8-10^9 CFU *L. rhamnosus*, 10^8-10^9 CFU *L. acidophilus*, and 10^8-10^9 CFU *B. lactis*.

[k]Each sachet (4.4 g) contained 450 billion live bacteria (*S. thermophilus* DSM 24731, *B. breve* DSM 24732, *B. longum* DSM 24736, *B. infantis* DSM 24737, *L. paracasei* DSM 24733, *L. acidophilus* DSM 24735, *L. delbrueckii* subsp. *bulgaricus* DSM 24734, and *L. plantarum* DSM 24730).

[l]One serving contained omega-3 fatty acid (500 mg, consisting 64.71% eicosapentaenoic acid, 29.41% docosahexaenoic acid, and 5.88% omega-3 in general), leucine (2.5 g), probiotic *L. paracasei* PS23 in powder format.

[m]Each spoon (7.5 g) contained inulin (minimum 3375 mg) and FOS (minimum 3488 mg).

*Statistically significant between baseline and end of intervention ($P < .05$).

**Statistically significant between the control group and intervention group ($P < .05$). In the change, the *P* value of the statistically significant results is in bold.

Abbreviations: cellul., cellulose; CG, control group; DB, double blind; FL, frailty level; FOS, fructooligosaccharides; HGS, handgrip strength; IG, intervention group; LcS, *Lactobacillus casei* Shirota; M, men; maltodex., maltodextrin; MD, mean difference; microcrys., microcrystalline; NI, no information; PC, placebo controlled; PL, parallel; PRE, prebiotic; PRO, probiotic; PT, pilot study; R, randomized; SYN, synbiotic; TWK10-H, high-dose *L. plantarum* TWK10; TWK10-L, low-dose *L. plantarum* TWK10; W, women.

Table 3. Characteristics From Each Included Randomized Controlled Trial of Interventions Based on Probiotic, Prebiotic, and Synbiotic Supplementation, and Physical Performance and Function

Author; year	Study design; country	Sex; age (y)	Total (n)	Type of supplementation		Duration of intervention; dose	SA	Baseline	End	Change
				PRO/PRE/SYN	Placebo					
Karim et al, (2022)[41]	R, DB, PL, PC Pakistan	M; 63-73	104	Probiotic (Vivomixx; *S. thermophilus*, bifidobacteria, and lactobacilli)[a]	Inactive agents[b]	16 wk 1 capsule/d[a]	GS SPPB[c]	GS (m/s)[d] CG 0.86 ± 0.17; $n = 53$ IG 0.94 ± 0.18; $n = 47$ 4MWT (score 0-4)[d] CG 2.86 ± 0.25; $n = 53$ IG 3.01 ± 0.34; $n = 47$ Balance (score 0-4)[d] CG 2.95 ± 0.31; $n = 53$ IG 2.83 ± 0.30; $n = 47$ 5-STS (score 0-4)[d] CG 2.26 ± 0.26; $n = 53$ IG 2.21 ± 0.28; $n = 47$	GS (m/s)[d] CG 0.86 ± 0.17; $n = 53$ IG 1.06 ± 0.18*; $n = 47$ 4MWT (score 0-4)[d] CG 2.93 ± 0.27; $n = 53$ IG 3.19 ± 0.39*; $n = 47$ Balance (score 0-4)[d] CG 2.87 ± 0.28; $n = 53$ IG 3.04 ± 0.29*; $n = 47$ 5-STS (score 0-4)[d] CG 2.15 ± 0.23; $n = 53$ IG 2.53 ± 0.37*; $n = 47$	GS (m/s)[e] MD (95% CI) 0.13 (0.03, 0.22) **$P = .01$** for group × time 4MWT (score 0-4)[e] MD (95% CI) 0.11 (−0.07 to 0.29) $P = .23$ for group × time Balance (score 0-4)[e] MD (95% CI) 0.29 (0.13, 0.45) **$P < .001$** for group × time 5-STS (score 0-4)[e] MD (95% CI) 0.43 (0.27, 0.59) **$P < .001$** for group × time
Lee et al, (2021)[34]	R, DB, PL, PC Taiwan	M/W; 55-85[f]	55	Probiotic (*L. plantarum* TWK10)[g]	Maltodex. and microcrys. cellul.	18 wk 2 capsules/d[g]	3m-TUG 10m-WT 30s-CST	3m-TUG (s)[d] CG 9.40 ± 3.9 IG (TWK10-L) NI IG (TWK10-H) 9.60 ± 3.2 10m-WT (sec)[d] CG NI IG (TWK10-L) NI IG (TWK10-H) NI 30s-CST (times)[d] CG NI IG (TWK10-L) NI IG (TWK10-H) NI	3m-TUG (s)[d] CG 11.70 ± 4.0* IG (TWK10-L) NI IG (TWK10-H) 8.00 ± 1.8*,** 10m-WT (sec)[d] CG NI* IG (TWK10-L) NI* IG (TWK10-H) NI 30s-CST (times)[d] CG NI IG (TWK10-L) NI* IG (TWK10-H) NI*	3m-TUG (s) Placebo baseline vs 18 wk 1.25-fold increased ($P < .001$) TWK10-H baseline vs 18 wk 16.80% lower ($P = .01$) At 18 wk placebo vs TWK10-H 31.66% lower ($P < .01$) 10m-WT (s) Placebo baseline vs 18 wk 1.15-fold increased ($P < .01$) TWK10-L baseline vs 18 wk 9.09% decreased ($P < .01$) 30s-CST (times) TWK10-L baseline vs 18 wk 1.37-fold increased ($P < .001$) TWK10-H baseline vs 18 wk 1.51-fold increased ($P < .001$) No MD (95% CI) *P* for group × time) values compared with placebo
Román et al, (2019)[37]	R, DB, PL, PC Spain	M/W; >61.4	36	Probiotic (Vivomixx or Visbiome; *S. thermophilus, B. breve, B. longum, B. infantis, L. paracasei, L. acidophilus, L. delbrueckii* subsp. *bulgaricus*, and *L. plantarum*)[h]	Inactive agents (maltose and silicon dioxide)	12 wk 2 sachets diluted/d[h]	3m-TUG GS	3m-TUG (s)[i] CG NI 11.90 ± 0.9; $n = 18$ IG 11.40 ± 0.6; $n = 16$ GS (m/s)[i] CG 0.88 ± 0.07: N =18 IG 0.90 ± 0.05; $n = 16$	3m-TUG (s)[i] CG 12.30 ± 0.7; $n = 18$ IG 10.00 ± 0.5*; $n = 16$ GS (m/s)[i] CG 0.95 ± 0.06; $n = 18$ IG 1.12 ± 0.10; $n = 16$*	3m-TUG (s)[e] MD (95% CI) −1.80 (−4.51 to 0.91) $P = .19$ for group × time GS (m/s)[e] MD (95% CI) 0.15 (−0.13 to 0.43) $P = .30$ for group × time

(continued)

Table 3. Continued

Author; year	Study design; country	Sex; age (y)	Total (n)	Type of supplementation		Duration of intervention; dose	SA	Baseline	End	Change
				PRO/PRE/SYN	Placebo					
Rondanelli et al, (2022)[35]	R, DB, PL, PC Italy	M/W; ≥55[f]	60	Omega-3 fatty acid, leucine, probiotic *L. paracasei* PS23 + nutritional and physical activity recommendations[j]	Isocaloric placebo[b]	8 wk 1 serving/d[k]	Tinetti[l] SPPB[c]		Tinetti (score 0-40) CG MD (95% CI) −0.45 (−1.34 to 0.45) IG MD (95% CI) 1.94 (0.99, 2.89)* SPPB (score 0-12) CG MD (95% CI) 0.45 (−0.08 to 0.97) IG MD (95% CI) 2.67 (2.11, 3.23)*	Tinetti (score 0-40) MD (95% CI) 2.39 (1.05, 3.72) **$P < .05$** for group × time SPPB (score 0-12) MD (95% CI) 2.22 (1.44, 3.00) **$P < .05$** for group × time
Buigues et al, (2016)[40]	R, DB, PL, PC Spain	M/W; ≥65	60	Prebiotic (Darmocare Pre; inulin and FOS)[j]	Maltodex.	13 wk 1 level spoon/d[j]	4.6 m-WT	Slow walk (s)[d] CG 8.60 ± 9.0; $n = 22$ IG 8.40 ± 6.0; $n = 28$	Slow walk (s)[d] CG 8.70 ± 4.2; $n = 22$ IG 7.90 ± 4.5; $n = 28$	Slow walk (s)[e] MD (95% CI) −0.60 (−5.59 to 4.39) $P = .81$ for group × time
Karim et al, (2022)[36]	R, DB, PL, PC Pakistan	M; 58-73[f]	108	Probiotic (Vivomixx; *S. thermophilus*, bifidobacteria, and lactobacilli)[a]	Inactive agents[b]	12 wk 1 capsule/d[a]	GS SPPB[c]	GS (m/s)[d] CG 0.77 ± 0.12; $n = 48$ IG 0.83 ± 0.14; $n = 44$ SPPB (score)[m] CG 18 (37.5); $n = 48$ IG 14 (31.8); $n = 44$	GS (m/s)[d] CG 0.85 ± 0.15; $n = 48$ IG 0.98 ± 0.19*; $n = 44$ SPPB (score)[m] CG 20 (41.6); $n = 48$ IG 12 (27.2); $n = 44$	GS (m/s)[e] MD (95% CI) 0.07 (−0.02 to 0.16) $P = .12$ for group × time

[a]Each capsule contained 112 billion live bacteria (*Streptococcus thermophilus* DSM 24731; *Bifidobacterium longum* DSM 24736; *B. breve* DSM 24732, DSM 24737; *Lactobacillus* DSM 24735, DSM 24730, DSM 24733; *L. delbrueckii* subsp. *bulgaricus* DSM 24734).

[b]Not reported.

[c]SPPB: Each test score ranged from 0 (worst performers) to 4 (best performers). The total score ranged from 0 to 12; sarcopenia was diagnosed with a score ≤8.

[d]Values are mean ± SD unless indicated.

[e]MD (95% CI) calculated by researchers.

[f]Despite the inclusion age, all included volunteers were ≥60 years old.

[g]Each capsule of *L. plantarum* TWK10 contains 1×10^{10} CFU TWK10-L or 3×10^{10} CFU TWK10-H).

[h]Each sachet (4.4 g) contains 450 billion live bacteria (*S. thermophilus* DSM 24731, *B. breve* DSM 24732, *B. longum* DSM 24736, *B. infantis* DSM 24737, *L. paracasei* DSM 24733, *L. acidophilus* DSM 24735, *L. delbrueckii* subsp. *bulgaricus* DSM 24734, and *L. plantarum* DSM 24730).

[i]Data reported as mean ± SEM.

[j]Each spoon (7.5 g) contains inulin (minimum 3375 mg) and FOS (minimum 3488 mg).

[k]One serving contains omega-3 fatty acid (500 mg, consisting of 64.71% eicosapentaenoic acid, 29.41% docosahexaenoic acid, and 5.88% omega-3 in general), leucine (2.5 g), probiotic *L. paracasei* PS23 in powder format.

[l]Tinetti scale: total score ranged from 0 (worst performance) to 40 (best performance).

[m]Data reported as no. (%).

*Statistically significant between baseline and end of intervention ($P < .05$).

**Statistically significant between the control group and intervention group ($P < .05$). In the change, the *P* value of the statistically significant results is in bold.

Abbreviations: 3 m-TUG, 3-m timed up-and-go test; 4MWT, 4-m walking test; 4.6 m-WT, 4.6-m walk test; 5-STS, 5 times chair-stand test; 10 m-WT, 10-m walk test; 30 s-CST, 30-second chair-stand test; CG, control group; DB, double blind; FL, frailty level; FOS, fructooligosaccharides; GS, gait speed; IG, intervention group; M, men; maltodex, maltodextrin; MD, mean difference; microcrys cellul, microcrystalline cellulose; NI, no information; PC, placebo controlled; PL, parallel; PRE, prebiotic; PRO, probiotic; R, randomized; SA, sarcopenia assessment; SPPB, short physical performance battery; SYN, synbiotic; TWK10-H, high-dose *L. plantarum* TWK10; TWK10-L, low-dose *L. plantarum* TWK10; W, women.

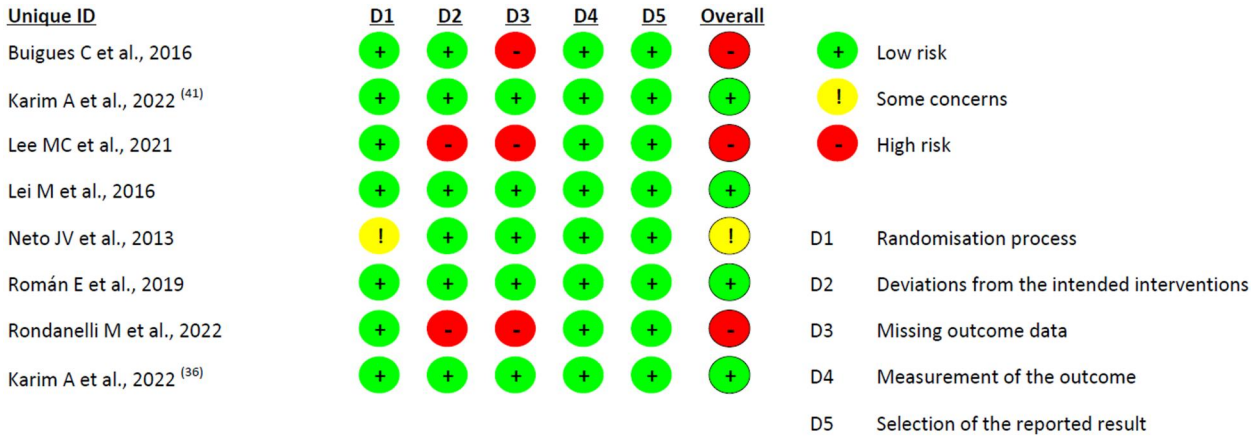


Figure 2. Quality of the Randomized Controlled Trials in the Systematic Review. Abbreviation: D, domain.

with the placebo group, the probiotic group had significantly increased handgrip strength (HGS) (MD [95% CI], 2.27 kg [0.52-4.02]; $P = .01$ for group × time).[41]

Another effective probiotic intervention was reported in an article about a 12-week, 2-arm RCT, also with Vivomixx probiotic based on 112 billion live bacteria, and a placebo with inactive agents (not reported).[36] The RCT determined that the probiotic group had significantly increased HGS (MD [95% CI], 3.03 kg [1.29-4.77]; $P < .001$ for group × time) compared with the placebo group.[36]

A third effective probiotic intervention was studied in an 8-week, 2-arm RCT. In this arm, participants received either 1 serving/d omega-3 fatty acid (500 mg, consisting of 64.71% eicosapentaenoic acid, 29.41% docosahexaenoic acid, and 5.88% omega-3 in general), leucine (2.5 g), probiotic *L. paracasei* PS23 ("30 Billion," freeze-dried by Abiogen Pharma) in powder format, and nutritional (1.5 g protein/kg of body weight/d) and physical activity recommendations; or 1 serving/d, in powder format, of isocaloric placebo (not reported).[35] The RCT results indicated HGS was significantly increased in the probiotic group compared with the placebo group (MD [95% CI], 4.09 kg [2.78-5.39] $P < .05$ for group × time).[35]

Conversely, 4 RCTs did not show significant results among groups.[34,37,39,40] One was an 18-week, 3-arm RCT in which participants took 2 capsules/d of probiotic *L. plantarum* TWK10 low-dose group with 1×10^{10} CFU in each capsule; or 2 capsules/day of probiotic *L. plantarum* TWK10 high-dose group (TWK10-H) with 3×10^{10} CFU in each capsule; or 2 capsules/day of placebo based on maltodextrin and microcrystalline cellulose.[34] Although the findings were not significant, the HGS of the left hand in the TWK10-H group was 1.13-fold higher at the end of the intervention compared with baseline ($P = .02$).[34] A second RCT without significant results among groups was a 12-week, 2-arm probiotic Vivomixx (Europe) or Visbiome (United States) intervention. In that study, participants took either 2 diluted sachets/d (4.4 g/sachet) with 450 billion live bacteria (*S. thermophilus* DSM 24731, *B. breve* DSM 24732, *B. longum* DSM 24736, *B. infantis* DSM 24737, *L. paracasei* DSM 24733, *L. acidophilus* DSM 24735, *L. delbrueckii* subsp. *bulgaricus* DSM 24734, and *L. plantarum* DSM 24730), or 2 diluted sachets/d placebo with inactive agents (maltose and silicon dioxide).[37] A third RCT without significant results among groups was a 13-week, 2-arm RCT based on prebiotic supplementation intervention. Participants took either 1 level spoon/d (7.5 g) of Darmocare Pre (Bonusan Besloten Vennootschap (BV), Numansdorp, The Netherlands), based on inulin (minimum 3375 mg) and fructooligosaccharides (FOS; minimum 3488 mg) per each spoon; or 1 level spoon/d (7.5 g) placebo (maltodextrin).[40] The MD (95% CI) and *P* values were not significant; however, there was a statistically significant improvement of HGS of the right hand in the intervention group compared with the placebo group at the end of the intervention.[40] Also, there was a statistically significant improvement at the end of the intervention compared with the baseline in the prebiotic group.[40] Finally, a fourth RCT without significant results among groups was a synbiotic 12-week, 2-arm RCT in which participants took either 1 dose/d of a synbiotic based on 6 g FOS, 10^8-10^9 CFU *L. paracasei*, 10^8-10^9 CFU *L. rhamnosus*, 10^8-10^9 CFU *L. acidophilus*, and 10^8-10^9 CFU *B. lactis;* or 1 dose/d placebo (maltodextrin).[39]

It was not possible to obtain the MD (95% CI) *P* for group × time values for a 24-week, 2-arm RCT (intervention: 2 servings/d skimmed milk containing a minimum of 6×10^9 CFU *L. casei* Shirota probiotic; control: skimmed milk as a placebo).[38] However, the article on this RCT reported significantly higher HGS at 2-5 months in the intervention group compared with the placebo group ($P < .05$).[38]

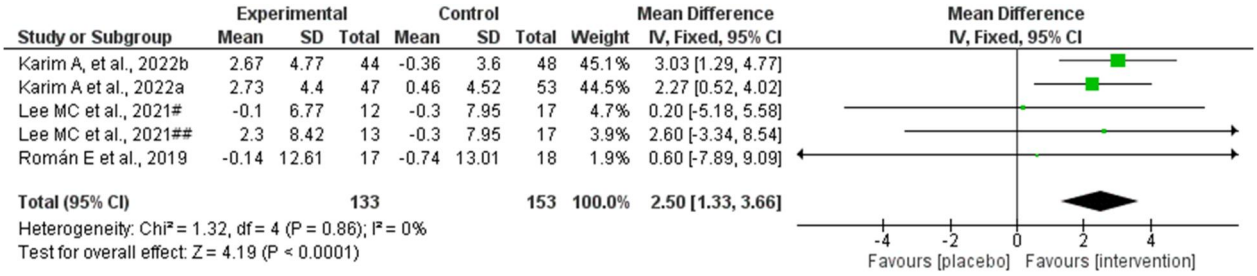


Figure 3. Forest Plot of the Meta-Analysis of Randomized Controlled Trials Based on Supplementation with Probiotics, Prebiotics, and Synbiotics, and Muscle Strength (as measured by handgrip strength). (#) low-dose group (TWK10-L) $1x10^{10}$ CFU; (##) high-dose group (TWK10-H) $3x10^{10}$ CFU. Abbreviation: IV, inverse variance.

Additionally, 4 RCTs were included in the meta-analysis about muscle strength.[34,36,37,41] This meta-analysis, with a sample of 286 individuals, revealed a statistically significant increase in HGS (MD [95% CI], 2.50 kg [1.33-3.66], $P < .001$; $I^2 = 0\%$, $P = .86$ for heterogeneity) (Figure 3[34,36,37,41]). However, Egger's test indicated a publication bias ($P = .062$) and the funnel plot appeared asymmetric (Figure S2). Furthermore, a sensitivity analysis was performed. First, when the 2 studies with higher weight were excluded from the meta-analysis,[36,41] the meta-analysis result was not significant (for HGS, MD [95% CI], 1.16 kg [−2.45 to 4.77]; $P = .53$; $I^2 = 0\%$, $P = .83$ for heterogeneity) (Figure S3[34,37]). Another sensitivity analysis was performed, excluding the study with a high risk of bias,[34] and in this case, the meta-analysis could not be performed, and the results could not be replicated.

Effects on Muscle Mass. A total of 5 RCTs assessed muscle mass (Table S2).[34–36,39,41] Three RCTs did not report statistically significant results for probiotics interventions, based on the MD (95% CI) *P* for group × time values,[35,36,41] and 1 RCT did not show results between groups.[34] Also, 1 RCT of synbiotic supplementation did not report statistically significant results based on the MD (95% CI) and *P* for group × time.[39]

One RCT that included an intervention based on omega-3 fatty acid, leucine, and probiotic *L. paracasei* PS23 supplementation with nutritional and physical activity recommendations, although not significance was not reported among groups, indicated that appendicular lean mass was reduced in the placebo group compared with baseline (MD [95% CI], −1.27 g [−2205.44 to −332.26]; $P < .05$).[35] The other RCTs without significant results among groups studied Vivomixx probiotic supplementation (*S. thermophilus* DSM 24731; *B. longum* DSM 24736; *B. breve* DSM 24732, DSM 24737; *Lactobacillus* DSM 24735, DSM 24730, DSM 24733; *L. delbrueckii* subsp. *bulgaricus* DSM 24734),[36,41] and about synbiotic supplementation (FOS; *L. paracasei*, *L. rhamnosus*, *L. acidophilus*, and *B. lactis*).[39]

Additionally, despite being unable to obtain the MD (95% CI) values among groups, 1 RCT of probiotic supplementation with *L. plantarum* TWK10 showed that muscle mass of the TWK10-H group, compared with the baseline, was 1.03-fold higher at 18 weeks ($P = .002$).[34]

Effects on Physical Performance and Function. Six of the included articles in this review each reported on an RCT that assessed physical performance and function (Table 3).[34–37,40,41] Focusing on probiotics supplementation and based on the MD (95% CI) and *P* for group × time values, 2 RCTs reported statistically significant results favoring the probiotic intervention group compared with the placebo group,[35,41] and 2 RCTs did not show significance.[36,37] However, 1 RCT of probiotic supplementation did not show results between groups.[34] Additionally, 1 RCT of prebiotic supplementation did not show significance based on the MD (95% CI) and *P* for group × time values.[40]

One effective RCT intervention involving the Vivomixx probiotic based on 112 billion live bacteria showed an improvement, compared with placebo, in GS in the probiotic group (MD [95% CI], 0.13 m/s [0.03-0.22]; $P = .01$ for group × time).[41] Additionally, the RCT revealed a statistically significant improvement in some components of SPPB in the probiotic group compared with the placebo group, such as balance score (MD [95%CI], 0.29 [0.13-0.45]; $P < .001$ for group × time) and 5 times chair-stand test score (MD [95% CI], 0.43 [0.27-0.59]; $P < .001$ for group × time).[41] Nevertheless, the RCT did not show significant results in the 4-m walking test score, among groups.[41]

Another effective probiotic RCT of omega-3 fatty acid, leucine, and probiotic *L. paracasei* PS23 supplementation with nutritional and physical activity recommendations determined a statistically significant improvement in Tinetti score (MD [95% CI], 2.39 [1.05-3.72]; $P < .05$ for group × time) and SPPB score (MD [95% CI], 2.22 [1.44-3.00] $P < .05$) for group ×

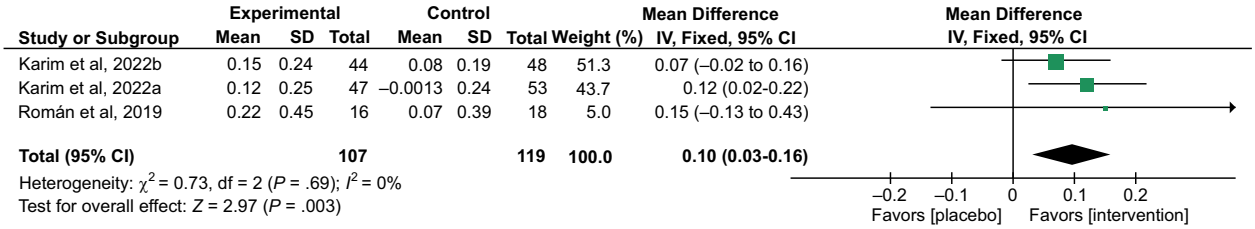


Figure 4. Forest Plot of the Meta-Analysis of Randomized Controlled Trials Based on Supplementation with Probiotics, Prebiotics, and Synbiotics, and Physical Performance and Function (as measured by gait speed). Abbreviation: IV, inverse variance.

time) in the probiotic group compared with the placebo group.[35]

In contrast, 1 RCT, neither Vivomixx (Europe) nor Visbiome (United States) probiotic (*S. thermophilus, B. breve, B. longum, B. infantis, L. paracasei, L. acidophilus, L. delbrueckii* subsp. *bulgaricus*, and *L. plantarum*) achieved significance among groups.[37] Even though the RCT showed a reduction of 3 m-TUG (11.38 ± 0.57 seconds vs 10.00 ± 0.49 seconds; $P < .05$) and an improvement in GS (0.90 ± 0.05 m/s vs 1.12 ± 0.10 m/s; $P < .05$) in the probiotic group at the end of the intervention compared with baseline.[37] Additionally, another article on an RCT of Vivomixx (112 billion live bacteria probiotic supplementation) reported there were no significant results.[36] Nevertheless, showed an improvement in GS between baseline and end of the intervention in the probiotic group (0.83 ± 0.14 m/s vs 0.98 ± 0.19 m/s; $P < .05$).[36] In this context, another prebiotic RCT of Darmocare Pre, based on inulin and FOS supplementation, did not achieve significance among groups.[40]

Furthermore, in 1 RCT based on probiotic supplementation with *L. plantarum* TWK10, although it was not possible to obtain the MD (95% CI) values among groups, researchers revealed statistically significant results both in the intervention and placebo groups at 18 weeks.[34] Related to the placebo group, compared with baseline, the results of the 3 m-TUG and the 10-m walk test were significantly increased by 1.25-fold ($P < .001$) and 1.15-fold ($P < .01$), respectively, at 18 weeks.[34] Moreover, in the TWK10 low-dose group, compared with baseline, the 10-m walk test was significantly decreased by 9.09% ($P < .01$), and the 30 s-CST was significantly increased by 1.37-fold ($P < .001$), at the end of the intervention.[34] Also, in the TWK10-H group, compared with the baseline, the 30 s-CST was significantly increased by 1.51-fold ($P < .001$) at the end of the intervention.[34] Additionally, at the end of the intervention, the 3 m-TUG of the TWK10-H group, compared with the placebo group, was significantly lower by 31.66% ($P < .01$).[34]

A total of 3 RCTs were included in the meta-analysis about physical performance and function.[36,37,41] This meta-analysis, with a sample of 226 individuals, revealed a statistically significant increase in GS (MD [95% CI], 0.10 m/s [0.03-0.16], $P = .003$; $I^2 = 0\%$, $P = .69$ for heterogeneity) (Figure 4[36,37,41]). Egger's test indicated no publication bias ($P = .603$), although the funnel plot appeared asymmetric (Figure S4). A sensitivity analysis could not be performed.

DISCUSSION

The present systematic review and meta-analysis of RCTs showed that nutritional strategies based on probiotic supplementation had statistically significant positive effects on the improvement of muscle strength and physical function. However, in the meta-analysis, considering the studies using probiotic supplementation for muscle strength, statistical significance was lost when the sensitivity analysis was applied, and the effectiveness disappeared. This analysis was conducted to address the heterogeneity of the articles included in the systematic review and meta-analysis, because 2 RCTs about the same probiotic Vivomixx (112 billion live bacteria) had the largest sample size of the studies included and were the only ones that showed effectiveness in the meta-analysis. Therefore, this heterogeneity in the sample size among studies affected the reliability of the results.

There are still limited studies about prebiotics and synbiotics, and more evidence is needed to elucidate their effects on sarcopenia parameters. However, prebiotic supplementation is suggested to be effective on muscle strength. On the other hand, neither strategy seems to be effective in improving muscle mass. Figure 5 and Table 4[35,36,41] provide a summary integration of the effects of probiotics, prebiotics, and synbiotics on sarcopenia parameters.

Despite limited information on probiotic supplementation (Figure 5), the systematic review and meta-analysis determined that Vivomixx probiotic, based on 112 billion live bacteria (*S. thermophilus* DSM 24731; *B. longum* DSM 24736; *B. breve* DSM 24732, DSM 24737; *Lactobacillus* DSM 24735, DSM 24730, DSM

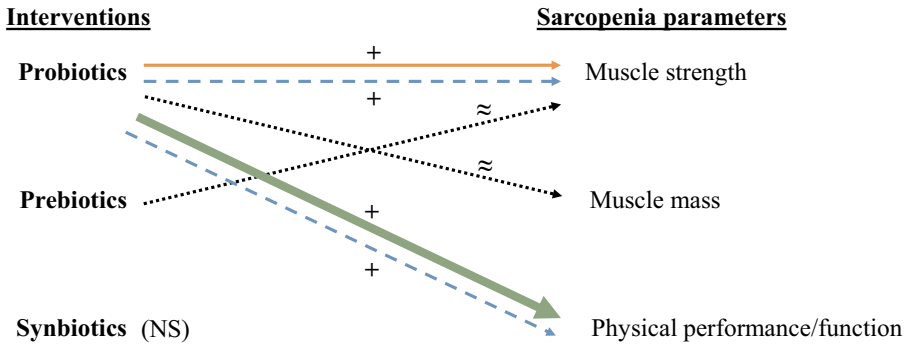


Figure 5. Summary of Probiotics, Prebiotics, and Synbiotics Results on Sarcopenia Parameters. Orange arrow (thin arrow): statistically significant meta-analysis results, but without significance after sensitivity analysis. Blue arrow (dashed arrow): statistically significant systematic review results are based on mean difference (95% CI) and *P* for group × time. Green arrow (thick arrow): statistically significant meta-analysis results. Black arrow (dotted arrow): statistically significant systematic review results based on the comparison between groups. + indicates results favoring intervention; ≈ indicates results that suggest a trend favoring intervention. NS, no statistically significant results.

Table 4. Probiotics Supplementation Recommendation According to the Statistically Significant Studies Based on Mean Difference and the 95%CI from the Systematic Review and Meta-Analysis of Muscle Strength and Physical Performance and Function

Author; year	Study duration (wk)	Sarcopenia parameters	Characteristics of probiotics	Dose
Karim et al (2022)[41]	16	MS PP/F	Vivomixx[a]	1 capsule/d
Karim et al (2022)[36]	12	MS PP/F	Vivomixx[a]	1 capsule/d
Rondanelli et al (2022)[35,b]	8	MS PP/F	1 serving (powder format) contains omega-3 fatty acid (500 mg, consisting of 64.71% eicosapentaenoic acid, 29.41% docosahexaenoic acid, and the remaining 5.88% omega-3 in general), leucine (2.5 g), probiotic *L. paracasei* PS23 plus nutritional and physical activity recommendations	1 serving/d

[a]Each capsule contains 112 billion live bacteria (*Streptococcus thermophilus* DSM 24731; *Bifidobacterium longum* DSM 24736; *B. breve* DSM 24732, DSM 24737; *Lactobacillus* DSM 24735, DSM 24730, DSM 24733; *L. delbrueckii* subsp. *bulgaricus* DSM 24734).
[b]Results only from systematic review.
Abbreviations: MS, muscle strength; PP/F, physical performance and function.

24733; *L. delbrueckii* subsp. *bulgaricus* DSM 24734) seems to be the most effective for improving muscle strength as measured by HGS and physical performance and function by GS.[36,41] Along this line, another 12-week RCT that used the same probiotic (Vivomixx) showed less effectiveness, although the probiotic included 450 billion live bacteria, a larger dose.[37] The different effectiveness of Vivomixx probably is due to the shorter intervention duration (12 weeks vs 16 weeks) and the difference in probiotic format (capsule or sachets). However, the heterogeneity of the included studies made it difficult to obtain definitive results.

Furthermore, based on the results of the systematic review on muscle strength and physical performance and function, supplementation with omega-3 fatty acid, leucine, and probiotic *L. paracasei* PS23, in addition to nutritional and physical activity recommendations, resulted in improved muscle strength and physical performance and function compared with placebo.[35] Nevertheless, the isolated effects of *L. paracasei* PS23 could not be appreciated because the intervention included other components, such as omega-3 fatty acids, leucine, and nutritional and physical activity interventions.[35] For this reason, it could be interesting to assess the effects of the probiotic alone to determine if they are attributable to the probiotic or to the other nutritional and physical activity components of the intervention. However, the implementation of nutritional recommendations allows us to emphasize the importance of diet, especially promoting the consumption of foods rich in protein and leucine, and physical activity for sarcopenia management reported in the scientific literature.[18]

There were no statistically significant results between groups in terms of prebiotics in the different sarcopenia parameters (Figure 5). However, the

systematic review showed that prebiotic supplementation based on Darmocare Pre containing inulin and FOS statistically improved HGS in the intervention group compared with the placebo group at the end of the intervention.[40] Also, the scientific evidence related to prebiotic and synbiotic supplementation is still scarce, probably because they are less studied than probiotics, and more research with high-quality RCTs is needed to explore the role of these nutritional strategies on sarcopenia management.

The present review determined that the sarcopenia variables of physical performance and function and muscle strength have more evidence of improvement after probiotic supplementation, whereas muscle mass is less enhanced. In this context, resistance training and mixed training by adults with sarcopenia improve muscle strength, such as knee extension strength,[42] HGS, and CST,[43] and physical performance and function, such as TUG and GS.[42,43] Nevertheless, muscle mass has not been evaluated because of differences in assessment criteria and tools[42] or because there were no statistically significant differences.[43]

As the evidence shows, there is a more rapid loss of muscle strength and physical performance and function than of muscle mass in aging; indeed, these changes can be seen with a minimal reduction in muscle mass.[44,45] This may be due to the loss of muscle quality instead of quantity with age.[44–46] Additionally, sarcopenia is characterized by the loss of type I and type II fibers, with an atrophy of type II fibers.[47] This highlights the importance of assessing muscle quality in clinical practice using phase angle by bioimpedance analysis to show little changes in muscle fibers due to the aging process,[46,48] or ultrasound to obtain muscle thickness and muscle cross-sectional area.[46,48,49]

The present systematic review and meta-analysis suggested that probiotics could influence sarcopenia parameters via the gut-muscle axis; however, the specific mechanisms of action on skeletal muscle are not specified. Because of microbiota dysbiosis, there are a systematic chronic low-grade inflammation, a reduction of autophagic activity that increases reactive oxygen species production, a dysregulation of the endocrine system, a negative muscle protein balance, and a mitochondrial and neuromuscular connectivity dysfunction.[50] These physiological and pathological conditions negatively affect muscle mass and physical performance and function, and alter muscle growth and development.[50] Although there is evidence for the gut-muscle axis, more studies are needed to demonstrate the causal link.

The present systematic review and meta-analysis have some strengths. First, we focused the results on all sarcopenia parameters with the scientific evidence from the past 2 decades. Moreover, considering the certainty of evidence, in the meta-analysis of physical performance and function, all included RCTs had a low risk of bias without publication bias, whereas 3 of 4 RCTs included in the meta-analysis about muscle strength had a low risk of bias, although there was a publication bias. Also, the 2 RCTs with the highest weight in the meta-analysis had a low risk of bias. For this reason, the results supported that the favorable effects of probiotics on muscle strength and physical performance and function could be considered a certainty due to the majority low risk-of-bias RCTs.

Despite the strengths, the present systematic review and meta-analysis had some limitations. First, there was small number of studies included in the systematic review and in the meta-analysis, which limited the evidence of the results. Second, there is language bias because the search was only for English-language publications, and possible publications in other languages are not included. Also, the search was limited from 2000 to 2023; there may be some articles published prior to 2000 that were not identified with the current search strategy. Third, the inclusion of older adults with different diseases and the inclusion of RCTs with an inclusion age of <60 years could increase heterogeneity and affect the results' interpretability (although the mean age (± SD) was >60 years in these studies). Therefore, future research should focus on each disease to reduce the heterogeneity of the included studies. Fourth, the wide range of sample sizes of the RCTs and geographic diversity affected the generalizability of the results, due to the increased heterogeneity of the studies. Fifth, there is scarce evidence of nutritional intervention studies about sarcopenia effects that involve all sarcopenia parameters. Future studies should include all sarcopenia parameters to tackle all aspects of sarcopenia. Sixth, the variability in sarcopenia assessment tools might complicate the comparison across studies. The use of different tools to evaluate muscle mass made it difficult to perform a meta-analysis on this parameter of sarcopenia. For this reason, it is important to use the gold standard assessment tools from the EWGSOP2.[1] Seventh, some articles did not report enough information about placebo. Eighth, 3 RCTs included in the systematic review and meta-analysis presented a high risk of bias, according to the RoB2 tool. Ninth, the meta-analysis of muscle strength showed a publication bias. Tenth, the sensitivity analysis showed that results could not be reproduced when high-weight studies and high risk-of-bias publications were excluded. And last, the studies included in the meta-analysis did not control the diet of participants, such as protein intake, branched-chain amino acids, or essential amino acids consumption, and the exercise parameters (intensity, frequency and duration).

These uncontrolled variables could significantly influence the outcomes, considering the existing evidence in the literature on the impact of diet and exercise on sarcopenia parameters. Thus, more rigorous studies are necessary to establish clear guidelines on the use of specific types of probiotics, prebiotics, and synbiotic, doses, and duration of supplementation for sarcopenia parameters enhancement in older adults.

CONCLUSION

In conclusion, the present systematic review and meta-analysis revealed that probiotic supplementation seems to be effective in improving muscle strength and physical function, particularly in HGS and GS. Results of prebiotic supplementation suggested beneficial effects on muscle strength. In contrast, there was no significant evidence for the effects of probiotics, prebiotics, and synbiotics on muscle mass. The heterogeneity of studies included made it difficult to obtain solid results. More robust research is needed with high-quality RCTs with large sample sizes, different bacterial strains, matrices, doses, duration of intervention, and controlling for relevant aspects such as diet and physical activity of participants, to confirm the probiotics' effects and to elucidate the role of the gut-muscle axis. Currently, there is still a lack of evidence on prebiotic and synbiotic strategies, and further research is needed to elucidate their effects on sarcopenia parameters.

Author Contributions

M.B.-M., E.L., R.M.V., A.P., and R.S. all contributed to the study design; data collection, interpretation, and analysis; and writing and critical revision of the article. All authors have read and approved the final manuscript and share responsibility for ensuring the manuscript complies with the journal's style requirements and terms of consideration.

Supplementary Material

Supplementary Material is available at *Nutrition Reviews* online.

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Conflict of Interest

None declared.

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