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Review

Improving sarcopenia in older adults: a systematic review and meta-analysis of randomized controlled trials of whey protein supplementation with or without resistance training

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ABSTRACT

Objectives: The aim of the study was to comprehensively analyze the effects of whey protein (WP)-enriched supplement intake with or without resistance training (RT) in older patients, either from the community or hospital, who were diagnosed with sarcopenia according to the EWGSOP or AWGS criteria.

Methods: This meta-analysis study was registered in PROSPERO (CRD42023407885). We searched the PubMed, Embase, Web of Science, and Cochrane Library databases for RCTs up to June 1, 2023. Standardized mean differences (SMD) with 95% confidence intervals (CI) were used to estimate the pooled results.

Results: Ten RCT studies, including 1154 participants, were included and analyzed. The primary outcomes were the changes in muscle mass, strength, and physical performance. In WP group versus (vs.) Isocaloric placebo (PLA)/ Routine consultation (RC) group, WP significantly increased the appendicular skeletal muscle mass index (SMD: 0.47, 95%CI: 0.23, 0.71), appendicular skeletal muscle mass (SMD: 0.28, 95%CI: 0.11, 0.45) and gait speed (SMD: 1.13, 95%CI: 0.82, 1.44) in older patients with sarcopenia. In WP with RT group vs. PLA/ RC group, there was significant increase in handgrip strength (SMD: 0.67, 95%CI: 0.29, 1.04). In addition, in the secondary outcomes, WP significantly reduced interleukin-6, significantly increased insulin-like growth factor-1 and albumin, promoted participants' intake of total energy and protein, enhanced activities of daily living scores in patients, and had no significant effect on BMI, weight, or fat mass.

Conclusion: This review confirms that WP can improve various aspects of older adult with sarcopenia, thereby enhancing their overall physical condition. More studies should be conducted to validate this result and further explore the effects of WP and RT in patients with sarcopenia.

1. Introduction

Sarcopenia, an age-related syndrome, is characterized by reduced muscle mass, decreased muscle strength, and/or loss of physical function. Currently, there are at least eight accepted consensus criteria for sarcopenia diagnosis within the scientific community [1], with varying diagnostic thresholds owing to differences in ethnic population characteristics [2–5]. The general understanding of sarcopenia encompasses three main aspects: muscle strength, mass, and function. Muscle strength can be measured using handgrip strength (HGS) and the 5-time chair stand test

Abbreviations: ADL, the Activities of Daily Living score; ASM, appendicular skeletal muscle mass; AWGS, the Asian Working Group on Sarcopenia; BMI, body mass index; Carbohydrate (g/day), carbohydrate intake per day; CI, confidence intervals; CRP, C-reactive protein; EWGSOP, the European Working Group on Sarcopenia; Fat (g/day), fat intake per day; FM, fat mass; FTCST, 5-time chair stand test; GS, gait speed; HGS, handgrip strength; IGF-1, Insulin-like Growth Factor-1; IL-6, Interleukin-6; OS, osteosarcopenia; PRISMA, Program Guidelines for Systematic Reviews and Meta-analyses; Protein (g/day), protein intake per day; Protein (g/kg/day), protein intake per kilogram (Kg) of body weight per day; RCT, randomized controlled trials; RoB2, the Cochrane Risk of Bias Tool 2; RT, resistance training; SD, standard deviation; SF-36 MCS, Short-form 36-item Health Survey Mental Component Summary scores; SF-36 PCS, Short-form 36-item Health Survey Physical Component Summary scores; SMDs, standardized mean differences; SPPB, Short Physical Performance Battery scores; TC, total cholesterol; TEI, total energy intake; WP, whey protein /whey protein-rich supplementation; WP with RT, combining whey protein-rich supplementation with resistance training.

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(FTCST). Muscle mass can be assessed using methods such as bioelectrical impedance analysis, dual-energy X-ray absorptiometry, magnetic resonance imaging, and computed tomography to evaluate whole-body skeletal muscle mass (SMM), appendicular skeletal muscle mass (ASM), or the cross-sectional area of specific muscle groups or body regions. Physical function can be assessed through tests such as the gait speed (GS), short physical performance battery (SPPB), and timed-up and go (TUG) test [6]. Globally, 10–27% of older adults suffer from sarcopenia. Age-related inflammation, inactivity, malnutrition, and chronic diseases can exacerbate the condition [7,8]. However, there are currently no approved drugs specifically targeting sarcopenia [6]. Given the inevitability of aging and the growing population affected by sarcopenia, implementing essential interventions is paramount to alleviate the disease burden.

Sarcopenia can be ameliorated through dietary [9] and exercise [10] interventions [2]. Protein supplements are widely employed as a dietary intervention [11]. Consuming high-quality protein has proven to be beneficial for preventing muscle loss and maintaining healthy weight. However, the protein intake of older adults may not meet the optimal requirements for preserving SMM [12,13]. Whey protein (WP), casein, and soy protein are the three principal proteins that stimulate muscle protein synthesis [14,15]. WP is particularly effective at promoting systemic muscle protein anabolic metabolism [16] electing a more pronounced response compared to others [14,17]. Furthermore, it plays a proactive role in preventing and treating conditions such as type 2 diabetes [18], obesity [19], blood pressure regulation [20], anti-inflammatory responses [21], and resistance to oxidative stress [22]. Because of its high digestibility, fast absorption rate, and rich essential amino acid content, WP has gained popularity as a nutritional supplement [23]. Exercise has consistently been demonstrated to improve muscle mass, strength, and physical function in older adults, particularly when individualized progressive long-term resistance training (RT) regimens are employed [24,25].

However, there are conflicting results regarding the role of WP supplementation alone [26–29] or WP with RT [2,3,30,31] in patients with sarcopenia. Recently, several meta-analyses relevant to our topic have been published, some of which specifically focus on the effects of WP supplementation [26,32,33], and another that includes comparisons of WP in combination with RT versus RT alone [34], all of which primary focused on muscle strength, muscle mass, and physical performance. Therefore, in addition to conducting separate analyses for WP supplementation, we also considered a combined analysis of WP with RT to explore potential synergistic effects that could substantially improve sarcopenia in older adults. Considering the complexity of sarcopenia and the impact of the aforementioned interventions on patients, our study used a comprehensive approach to evaluate multiple aspects of improvement in patients with sarcopenia after intervention. This included primary outcome analyses of muscle strength, muscle mass, and physical performance in patients with muscle wasting, in addition to secondary outcome analyses of inflammatory markers, nutritional intake, mental status, and certain basic physical indicators. Thus, our comprehensive approach facilitated the assessment of the overall impact of therapies beyond their conventional muscle-related effects.

2. Materials and methods

2.1. Guidance protocol

This review is reported in accordance to the Nutrition Research Guidelines [35], the Cochrane Manual of Systematic Reviews on Interventions [36], and the 2020 Preferred Program Guidelines for Systematic Reviews and Meta-analyses (PRISMA) [37,38] (Table S1 supplementary materials). We registered our protocol in PROSPERO (National Institutes of Health, International Prospective Systematic Review Registry, https://www.crd.york.ac.uk/PROSPERO) under the number CRD42023407885.

The main processes of the literature search and selection, data collation, quality assessment, statistical analysis, and evidence grading for this review were conducted independently by two researchers (ML-L and LT-H), and disagreements were resolved through discussion and negotiation. In instances where no agreement was reached, a third researcher (JH-W) was involved in resolving the issues.

2.2. Literature search strategies

In this study, the Population, Intervention, Comparison, Outcome, Study Design (PICOS) model was utilized to formulate the search strategy as follows: (i) 'Population (P)' pertains to older patients diagnosed with sarcopenia without pre-existing heart, kidney, or liver disease, or any other disease or condition that might affect the results of the study; (ii) 'Intervention (I)' refers to the intake of WP with or without RT in the experimental groups, and the consumption of isocaloric placebo supplements (PLA) or a routine consultation (RC) in the control groups; (iii) 'Comparison (C)' refers to the contrasts between the experimental and control groups, or within the experimental groups themselves; (iv) 'Outcome (O)' encapsulates changes in muscle mass, muscle strength, physical performance, laboratory indicators, general anthropometric parameters, and nutritional intake metrics in patients with sarcopenia; and (v) 'Study Design (S)' involves randomized controlled trials (RCT). Advanced searches in the PubMed, Embase, Web of Science, and Cochrane Library databases were performed for RCT published until June 1, 2023, followed by a subsequent search on June 20, 2023, to avoid omitting newly published research. The complete search strategy and terms used are listed in Table S2. To broaden the search scope, relevant studies were selected from the 'similar articles' listed in databases, and manual searches were conducted on the references cited in the chosen articles.

2.3. Eligibility criteria and study selection

Eligible studies met the following inclusion criteria: (i) RCT published in English; (ii) participants in the study were $\geq$ 60 years old and diagnosed with sarcopenia according to the European Working Group on Sarcopenia in Older People (EWGSOP) or Asian Working Group for Sarcopenia (AWGS) criteria sourced from the community or hospital (Table 1); (iii) including experimental and control groups ('I' and 'C' above); (iv) the study result included the use of validated tools to assess muscle mass, muscle strength, physical performance, laboratory indicators, nutritional intake indicators, and general parameters of the human body; and (v) the duration of the intervention was not $<$4 weeks. Articles that met at least one of the following exclusion criteria were not considered: (i) study types other than RCT ; (ii) non-human research; (iii) insufficient data; (iv) data from previous publications of the same trial; and (v) reviews, case reports, letters, editorials, meta-analyses, and conference reports.

2.4. Data extraction and risk of bias assessment

Information extracted from the studies included comprised name of the first author, year of study, country or region, type of blinding of study design, diagnostic criteria for sarcopenia, number of participants, age and average age of the population included, sex ratio, mean and standard deviation (SD) of body mass index (BMI), intervention groups setting, leucine, vitamin D and calcium content in the experimental group, duration of the intervention, outcome measures, mean and SD of change between baseline and endpoint of outcome measures, and other basic information. If data on outcome measures were analyzed in studies with different intervention timings, they were recorded separately.

The risk of bias for each study was assessed using the Cochrane Risk of Bias Tool 2 (RoB2, Version 9) (www.riskobias.info) [39] for RCT,

Table 1
Characteristics of included studies.

Author	Year	Country/ Region	Blind design	Diagnostic criteria	Patient recruitment setting	Sample size (n)	Age (Years, Mean)	Sex (% Female)	BMI (Kg/ m^2, mean ± standard deviation)	Intervention group	Proportion of whey protein in the protein dose and total dose of supplements in the experimental group (%, %)	Leucine and Vitamin D dose in the experimental group (g, IU)	Duration	Outcome measures
H. Mori et al. [47]	2022	Japan	Double-blind RCT	AWGS 2014	Community	70	≥65, 77.70	84.29%	20.23 ± 2.78	Experimental group: RT + WP group (n = 23). RT group (n = 23). WP group (n = 24). Control group: NA.	100, 27.8	2.3, not contain	24 weeks	ASMI, BMI, HGS, GS
Zhuo Li et al. [48]	2021	China	RCT	AWGS 2014	Community	169	>60, 71.80	58.58%	23.11 ± 2.82	Experimental group: WP group (n = 51). RT group (n = 37). WP + RT group (n = 48). Control group: RC group (n = 33).	100, 95.2	not contain, 250	12 weeks	ASMI, ASM, FM
Mariangela Rondanelli et al. [49]	2020	Italy	Double-blind RCT	EWGSOP 2010	Hospital	127	≥65, 81.50	66.2%	21.55 ± 2.78	Experimental group: WP group (n = 64). Control group: PLA group (n = 63). .	100, 50	2.8, 800	8 weeks	ASM, HGS, FTCST, GS, SPPB, Albumin, TC, IGF-1, CRP, 25-hydroxyvitamin D, Fat, TEI, Protein, Body weight, ADL, SF-36 MCS, SF-36 PCS
Mikko P. Björkman et al. [50]	2020	Finland	Double-blind RCT	EWGSOP 2010	Community	180	>74, 83.80	67.9%	26.13 ± 3.97	Experimental group: WP group (n = 65). Control group: RC group (n = 52).	48, 48	not contain,800	6 months and 12 months	HGS, ASM
Wolfgang Kemmler et al. [51]	2020	Germany	Double-blind RCT	EWGSOP 2010	Community	38	≥72, 78.52	0%	24.74 ± 2.48	Experimental group: WP + RT group (n = 19). Control group: RC group (n = 19).	80, 80	9, 400	18 months	ASMI, HGS, GS
Keliane Liberman et al. [23]	2019	Belgium, Germany, Ireland, Italy, Sweden and the United Kingdom	Double-blind RCT	EWGSOP 2010	Community	227	≥65, 77.72	64.93%	26.12 ± 2.68	Experimental group: WP group (n = 103). Control group: PLA group (n = 124). .	87, 87	3, 800	13 weeks	IL-6, CRP
Tom R. Hill et al. [52]	2019	Belgium, Germany, Ireland, Italy, Sweden, and the United Kingdom	Double-blind RCT	EWGSOP 2010	Community	380	>65, 77.71	65.53%	26.10 ± 2.66	Experimental group: WP group (n = 184). Control group: PLA group (n = 196).	100, 56.3	3, 800	13 weeks	25-hydroxyvitamin D

(continued on next page)

Table 1 *(continued)*

Author	Year	Country/ Region	Blind design	Diagnostic criteria	Patient recruitment setting	Sample size (n)	Age (Years, Mean)	Sex (% Female)	BMI (Kg/ m^2, mean ± standard deviation)	Intervention group	Proportion of whey protein in the protein dose and total dose of supplements in the experimental group (%, %)	Leucine and Vitamin D dose in the experimental group (g, IU)	Duration	Outcome measures
Yacong Bo et al. [53]	2019	China	Double-blind RCT	AWGS 2014	Community	60	60−85, 74.03	55%	20.54 ± 3.42	Experimental group: WP group (n = 30). Control group: PLA group (n = 30).	100, 61	not contain, 702	6 months	ASMI, ASM, FM, HGS, FTCST, GS, Albumin, IL-6, TC, IGF-1, CRP, 25-hydroxyvitamin D, Fat, TEI, Carbohydrate, Protein, BMI, Body weight, SF-36 MCS, SF-36 PCS
Mariangela Rondanelli et al. [54]	2016	Italy	Double-blind RCT	EWGSOP 2010	Hospital	130	≥65, 80.30	59.29%	23.89 ± 4.1	Experimental group: WP group (n = 69). Control group: PLA group (n = 61). .	100, 66.7	4, 100	12 weeks	ASMI, FM, HGS, IGF-1, CRP, Fat, TEI, Carbohydrate, Protein, BMI, Body weight, ADL, SF-36 MCS, SF-36 PCS
Jürgen M. Bauer et al. [55]	2015	Belgium, Germany, Ireland, Italy, Sweden, and the United Kingdom	Double-blind RCT	EWGSOP 2010	Community	380	≥65, 77.71	65.53%	26.10 ± 2.66	Experimental group: WP group (n = 184). Control group: PLA group (n = 196).	100, 57.1	3, 800	13 weeks	ASM, HGS, FTCST, SPPB, IGF-1, 25-hydroxyvitamin D, TEI, Protein

Note: ADL: Activities of daily living score; ASM: Appendicular skeletal muscle mass; ASMI: Appendicular skeletal muscle mass index; AWGS: Asian Working Group for Sarcopenia; BMI: Body mass index; CRP: C-reactive protein; EWGSOP: European Working Group on Sarcopenia in Older People; FM: Fat mass; FTCST: 5-time chair stand test; GS: Gait speed; HGS: Handgrip strength; IGF-1: Insulin like growth factor-1; IL-6:Interleukin-6; PLA: Isocaloric placebo group; RC: Routine consultation group; RT + WP: resistance training intervention with leucine enriched whey protein supplementation group; SPPB: Short Physical Performance Battery (SPPB) score; SF-36 MCS: Short-form 36-item health survey Mental component summary score; SF-36 PCS: Short-form 36-item health survey Physical component summary score; TC: Total Cholesterol; TEI: Total energy intake.

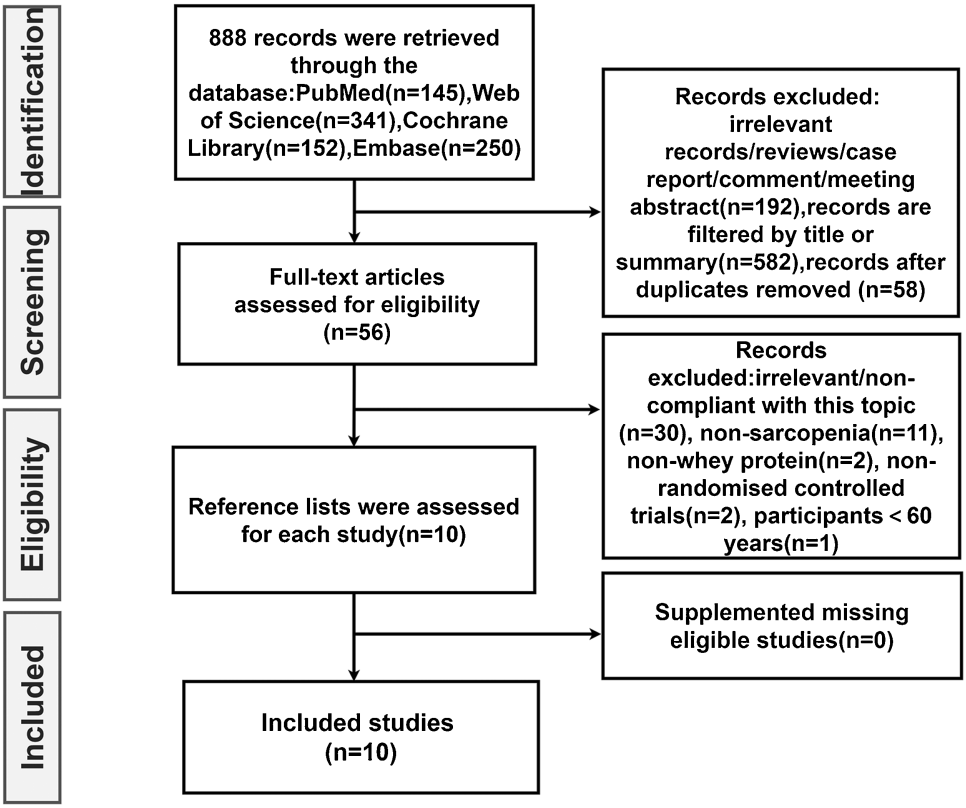

Fig. 1. The detailed screening process of the literature.

considering five areas of bias [1]: risk of bias arising from the randomization process [2], risk of bias due to deviation from the intended intervention [3], risk of bias due to missing outcome data [4], risk of bias in the measurement of the results, and [5] risk of bias in the selection of reported results.

2.5. Data synthesis and statistical analysis

The primary outcomes of this review were the changes in muscle mass, strength, and physical performance. Secondary outcomes were changes in laboratory indicators, general parameters (body weight and BMI), nutritional intake indicators, and activities of daily living (ADL) [40] scores and simple mental and physical health scores. Due to differences in measurements across studies, continuous results were expressed as standardized mean differences (SMDs) with 95% confidence intervals (CI). When the mean and SD data were missing from the original study, they were obtained using formula calculations or data conversion tools [36,41,42]. Inconsistent units of measurement were converted to the common units required for the analysis.

Meta-analyses were performed when at least two studies compared the results of participants who received and did not receive WP. Simultaneously, the experimental group with combined RT was analyzed to explore whether the combined effect was statistically significant. Subgroup analyses were performed to explore the sources of heterogeneity. According to the Corens'd effect size, for statistically significant SMD results, the effect intensity of the results was categorized as low, moderate, high, or very high, based on cutoffs of 0.2, 0.5, and 0.8, respectively [43]. Data heterogeneity was assessed using Cochran's Q test and I^2 test. The random-effects model was used when statistical heterogeneity was significant ($I^2 > 50\%$ [44]), otherwise, the fixed-effects model was used. Funnel charts, the Begg rank correlation test, and Egger's linear regression test were used to detect publication bias [45]. To examine the effects of the individual studies on the overall pooled results, sensitivity analyses were performed to verify the robustness of the results by sequentially omitting each study. Statistical significance was set at $P < 0.05$. All analyses were performed using Stata 15.0 software.

2.6. Confidence in evidence

The certainty of the evidence was assessed using the NutriGrade scoring system [46]. This tool considers seven meta-analysis items: risk of bias, study quality and limitations, precision, heterogeneity, directness, publication bias, funding bias, and study design. The corresponding levels of the total score calculated are as follows: 0–3.99: very low-level meta-evidence; 4–5.99: low-level meta-evidence; 6–7.99: intermediate meta-evidence; and ≥8: high-level meta-evidence.

3. Results

3.1. Search results and basic trial characteristics

The detailed literature screening process is represented in Fig. 1. A total of ten RCTs [21,47–55] were included in our review for quantitative analysis. Apart from one study [48] that did not mention its blinding design, the remaining studies were all double-blind. These studies were conducted across nine different countries in Asia and Europe, spanning 8 weeks–18 months. One study specifically included patients with osteosarcopenia (OS) — a condition of concurrent osteoporosis and sarcopenia [51]. Three studies utilized the AWGS diagnostic criteria, and seven employed the EWGSOP. Detailed study characteristics and data are presented in Table 1.

3.2. Participants' characteristics

A total of 1761 participants were included in the study. However, three studies [21,52,55] were derived from the same trial, although with different primary outcomes. Therefore, the actual number of participants across the ten included RCTs was 1154. All patients were ≥60, with a

mean age of 72–84 years. The mean BMI of the patients was 20.5–26.1 kg/m^2, and five studies included patients who were overweight or obese. One trial [51] exclusively recruited male participants, whereas in the remaining studies, the prevalence of females was 55–84%.

3.3. Characteristics of supplements

Across all experimental groups from the studied research, the average proportion of WP in the total nutritional supplement and protein content was 62.91% and 91.50%, respectively. Patients received oral doses of 9.6–40 g of WP per intake. Furthermore, the frequency of administration varied across studies, with one study [54] administering the protein supplement once a day, seven studies administering it twice a day, one study [48] administering it three times a day, and another study [51] describing only the total daily intake. Significantly, all the studies implemented supplements rich in WP. In three studies [49,51,52], the experimental groups' supplements were augmented with leucine, vitamin D, and calcium. Furthermore, three other studies [21,54,55] added leucine and vitamin D, while one study [47] only added leucine, and three other studies only incorporated vitamin D. However, in a comprehensive view, vitamin D, leucine, and calcium were added in nine, seven, and three studies, respectively. The dose of leucine is 2.3–9 g, vitamin D is 100–800 IU, and calcium is 500–1200 mg.

Across the control group, seven studies consumed PLA, consisting mainly of carbohydrates similar to those in the experimental group, one study [48] was an RC group in which dietitians designed personalized diets to achieve the basic nutrients required, and one study [47] was a cross-control between experimental groups because no blank or PLA control group was available. Another study [51] included WP with RT, where WP was 1.5–1.6 g/kg/day, while the control group was supplemented with WP at 1.2 g/kg/day. The above grouping was performed under the premise of the patients' regular diet, and intake was guaranteed to meet the daily needs of the human body.

3.4. RT characteristics

Across the ten studies, six implemented systematic whole-body RT. Among these, three studies [47,48,51] primarily incorporated moderate-to-high-intensity RT in their protocols, typically conducted 2–3 times per week, with each session lasting approximately 30 min. The other three studies [49,50,54] guided patients through low-to-moderate-intensity basic exercise training, scheduled 3–5 times per week, with each session lasting approximately 30 min. The training duration was designed to match the timeline of nutritional intervention for each study. Conversely, the remaining four studies did not incorporate RT into their experimental design.

3.5. Group design characteristics

Six of the ten studies exclusively focused on contrasting groups supplemented with WP against PLA groups. Additionally, one study [50] compared an intervention group with an RC group. Three other studies included data from groups that underwent a combination of WP and RT. Two of these studies [47,48] incorporated multiple control groups, whereas one study [51] merely compared WP with RT against the PLA group. Moreover, the research conducted by Mikko P. Björkman et al. [50] included data from interventions spanning 6 and 12 months.

3.6. Meta-analysis results

The pooled results for each study outcome used in the meta-analysis are presented in Table 2.

3.7. Effects of WP supplements with or without RT on muscle mass

In the WP group, we included appendicular skeletal muscle mass index (ASMI), ASM, and fat mass (FM) in our muscle mass assessment. Participants in the WP group exhibited a significant increase in ASMI (SMD: 0.47, 95% CI: 0.23, 0.71) and ASM (SMD: 0.28, 95% CI: 0.11, 0.45) compared to those in the PLA or RC (PLA/RC) groups who consumed an equivalent number of calories, while there were no differences observed in changes to FM (SMD: −0.02, 95% CI: −0.26, 0.22). In the WP with RT group, there was no significant difference in ASMI compared to the RT group (SMD: 0.24, 95% CI: −0.11, 0.59) (Figures S1–S3).

3.8. Effects of WP supplements with or without RT on muscle strength

In the WP group, we analyzed HGS and FTCST scores to evaluate muscle strength. In comparison with the PLA/RC group, no significant changes were observed in HGS (SMD: 0.40, 95% CI: −0.28,1.07) and FTCST (SMD: −0.04, 95% CI: −1.33,1.24). In the WP with RT group, muscle strength was assessed using HGS, which showed a significant increase compared to PLA/RC (SMD: 0.67, 95% CI: 0.29, 1.04) groups. However, no significant difference was observed when compared to the RT group (SMD: 0.22, 95% CI: −0.13, 0.56) (Figures S4 and S5).

3.9. Effects of WP supplements on physical performance

Participants' physical performance was evaluated by measuring their GS and SPPB scores. Participants in the WP group exhibited a significant increase in GS (SMD: 1.13, 95% CI: 0.82, 1.44) compared to the PLA/RC group (Figures S6 and S7).

3.10. Effects of WP supplements on laboratory indicators

Laboratory indicators in both the experimental and control groups, revealed that compared to the PLA/RC group, albumin (SMD: 0.60, 95% CI: 0.30, 0.89), insulin-like growth factor-1 (IGF-1) (SMD: 0.77, 95% CI: 0.33, 1.22), and 25-hydroxyvitamin D (SMD: 2.14, 95% CI: 1.07, 3.21) were significantly elevated in the WP group, while interleukin-6 (IL-6) (SMD: −0.32, 95% CI: −0.55, −0.09) was notably reduced. Nevertheless, the alterations in total cholesterol (TC) (SMD: 0.00, 95% CI: −0.28, 0.29) and C-reactive protein (CRP) (SMD: −0.11, 95% CI: −0.53, 0.30) had no statistical significance (Figures S8 and S9).

3.11. Effects of WP supplements on daily dietary nutrient intake

Fat intake per day (fat [g/d]), total energy intake (TEI), carbohydrate intake per day (carbohydrate [g/day]), protein intake per day (protein [g/day]), and protein intake per kilogram (kg) of body weight per day (protein [g/kg/day]) were used to evaluate changes in nutrient intake between the WP and PLA/RC groups. The results indicated that the experimental group exhibited a significant increase in TEI (SMD: 0.16, 95%CI: 0.02, 0.29) and protein intake (g/day) (SMD: 0.97, 95%CI: 0.37, 1.58) compared to the control group, while no significant differences were observed in the intact of fat (g/day) (SMD: 0.05, 95%CI: −0.24, 0.33), carbohydrate (g/day) (SMD: 0.85, 95%CI: −0.94, 2.64), and protein (g/kg/day) (SMD: 1.26, 95%CI: −0.59, 3.11). (Figures S10 and S11).

3.12. Effects of WP supplements on fundamental physical parameters

The fundamental parameters of body weight and BMI were analyzed. No significant changes were observed in the BMI (SMD: 0.25, 95%CI: −0.04, 0.54) and body weight (SMD: 0.14, 95%CI: −0.08, 0.36) of the WP group compared to the PLA/RC group (Figure S12).

3.13. Effects of WP supplements on other relevant assessment scales

Three additional relevant assessment scales were used to compare the WP and PLA/RC groups. The ADL score (SMD: 0.80, 95%CI: 0.55, 1.06) significantly increased in the WP group compared to the control group, while there was no significant difference between groups for Short-form

Table 2
Basic characteristics of each outcome, meta-analysis results, publication bias assessments and sensitivity analyses.

Outcome	Number of Studies (n)	Total Samples (n)	Model of effect	Standardized Mean Differences, with 95% Confidence Interval	P-value	I^2 (%)	P-value of Egger linear regression test	P-value of Begg rank correlation test	Sensitivity analyses
Muscle mass related items									
WP vs. PLA/RC									
Appendicular skeletal muscle mass index (ASMI) (kg/m^2)	3	274	Fixed	0.47 (0.23, 0.71)	<0.0005	0.0	0.292	1.000	Robust
Appendicular skeletal muscle mass (ASM)(kg)	4	530	Random	0.28 (0.11, 0.45)	0.002	57.0	0.850	1.000	Robust
Fat mass (FM) (kg)	3	274	Random	−0.02 (−0.26, 0.22)	0.851	66.7	0.452	0.296	Robust
WP with RT vs. RT									
Appendicular skeletal muscle mass index (ASMI) (kg/m^2)	2	131	Fixed	0.24 (−0.11, 0.59)	0.174	0.0	–	1.000	Robust
Muscle strength related items									
WP vs. PLA/RC									
Handgrip Strenght (Kg)	9	1184	Random	0.40 (−0.28, 1.07)	0.246	96.7	0.754	0.417	Robust
5-time chair stand test (s)	3	451	Random	−0.04 (−1.33, 1.24)	0.948	97.3	0.644	1.000	Robust
WP with RT vs. □PLA/RC □RT									
Handgrip Strenght (Kg)□	2	119	Fixed	0.67 (0.29, 1.04)	<0.0005	0.0	–	1.000	Robust
Handgrip Strenght (Kg)□	2	131	Fixed	0.22 (−0.13, 0.56)	0.218	0.0	–	1.000	Robust
Physical performance related items									
WP vs. PLA/RC									
Gait speed (m/s)	2	187	Fixed	1.13 (0.82, 1.44)	<0.0005	6.5	–	1.000	Robust
Short Physical Performance Battery (SPPB) score	6	918	Random	0.38 (−0.16, 0.92)	0.171	93.6	0.296	0.024	Less Robust
Laboratory indicators related items									
WP vs. PLA/RC									
Albumin (g/L)	2	187	Fixed	0.60 (0.30, 0.89)	<0.0005	40.1	–	1.000	Robust
Interleukin-6(IL-6) (pg/mL)	2	287	Fixed	−0.32 (−0.55, −0.09)	0.007	0.0	–	1.000	Robust
Total Cholesterol (TC) (mmol/L)	2	187	Fixed	0.00 (−0.28, 0.29)	0.979	0.0	–	1.000	Robust
Insulin like growth factor-1 (IGF-1) (ng/mL)	3	490	Random	0.77 (0.33, 1.22)	<0.0005	77.9	0.455	1.000	Robust
C-reactive protein (CRP) (mg/L)	4	544	Random	−0.11 (−0.53, 0.30)	0.786	81.8	0.298	0.734	Robust
25-hydroxyvitamin D (ng/mL)	4	867	Random	2.14 (1.07, 3.21)	<0.0005	97.2	0.621	1.000	Robust
Nutrient intake indicators related items									
WP vs. PLA/RC									
Fat (g/day)	2	198	Fixed	0.05 (−0.24, 0.33)	0.734	20.0	–	1.000	Robust
Total energy intake (kcal/day)	5	830	Fixed	0.16 (0.02, 0.29)	0.023	0.0	0.037	0.221	Robust
Carbohydrate (g/day)	2	198	Random	0.85 (−0.94, 2.64)	0.352	96.7	–	1.000	Robust
Protein (g/day)	3	326	Random	0.97 (0.37, 1.58)	0.002	83.9	0.783	1.000	Robust
Protein (g/Kg/day)	3	564	Random	1.26 (−0.59, 3.11)	0.181	98.8	0.688	1.000	Robust
Basic Physical indicators related items									
WP vs. PLA/RC									
Body Mass Index (BMI) (Kg/m^2)	2	198	Fixed	0.25 (−0.04, 0.54)	0.087	0.0	–	1.000	Robust
Body weight (kg)	3	326	Fixed	0.14 (−0.08, 0.36)	0.223	0.0	0.897	1.000	Robust
Other relevant assessment scales related items									
WP vs. PLA/RC									
Activities of daily living (ADL) score	2	257	Fixed	0.80 (0.55, 1.06)	<0.0005	31.6	–	1.000	Robust
Short-form 36-item health survey Mental component summary (SF-36 MCS) score	3	317	Random	0.44 (−0.15, 1.03)	0.146	84.4	0.418	0.296	Robust
Short-form 36-item health survey Physical component summary (SF-36 PCS) score	3	317	Random	0.32 (−0.36, 1.00)	0.360	88.3	0.007	0.296	Robust

Notes: WP vs. PLA/RC: Whey protein group vs. Isocaloric placebo/ Routine consultation group.
WP with RT vs. □PLA/RC □RT: Whey protein with resistance training group vs. □Isocaloric placebo/ Routine consultation group □Resistance training group.

36-item Health Survey Mental Component Summary (SF-36 MCS) (SMD: 0.44, 95%CI: −0.15, 1.03) and Physical Component Summary (SF-36 PCS) scores (SMD: 0.32, 95%CI: −0.36, 1.00) (Figures S13 and S14).

3.14. Publication bias and sensitivity analyses

The results of the publication bias and sensitivity analyses are shown in Figures S15–S21. Using the images in each row as a unit, a publication bias funnel plot, an Egger test plot, a Begg test plot, and a sensitivity analysis plot were constructed from left to right. To avoid bias in the assessment of the publication bias funnels, we performed individual analyses for each study. In the physical performance group, we identified a significant bias (Begg analysis P-value = 0.024) and the sensitivity analysis results were not robust. In addition, the TEI's publication bias analysis showed an Egger analysis P-value of 0.037 and an SF-36 PCS Begg analysis P-value of 0.007. However, for the remaining studies, no significant bias was detected, and sensitivity analyses suggested robust results.

3.15. Risk of bias assessment

The results of the RoB2 bias risk assessment of the studies included in this review are shown in Fig. 2. One study [51] was assessed as high

Fig. 2. The results of the RoB2 bias risk assessment of the studies included in this review.

risk because the experimental and control groups used different criteria for common measures (domain 5), and some of the remaining potential sources of bias were mainly due to a lack of information on randomization or concealment methods (domain 1), a lack of double-blind design, or an inability to blind resistance movements (domain 2). Ninety percent of the overall assessments for all studies were judged to have a low risk of bias. The full rationale for RoB2's decision can be found in Excel file S1.

3.16. Quality of evidence assessment using NutriGrade

The certainty of the evidence was assessed in seven categories based on the groupings used in this study. According to NutriGrade, the overall quality of the meta-evidence for this study was considered to be high, with a score of 8.3 out of 10. The seven main analysis categories had a score between 7.5 and 9.1 points. The quality of results in the categories of physical performance and basic physical indicator outcomes was downgraded to intermediate meta-evidence, attributed to the risk of bias, heterogeneity, publication bias, and the insufficient number of included studies. The remaining five outcome categories were assessed with scores >8 points, considered high-level meta-evidence. The full rationale for determining the results of the nutrient-level quality assessment is shown in Table S3.

4. Discussion

4.1. Main findings

We divided the relevant indicators affecting patients with sarcopenia into seven categories consisting of 25 indicators. We conducted a comprehensive and thorough meta-analysis of the overall effects of WP with or without RT in older people with sarcopenia. Notably, all included studies were RCT, and we used the latest RoB2 tool for literature quality assessment, thus ensuring the credibility of our compiled results. Finally, we assessed outcome indicators using NutriGrade, a tool specifically developed to evaluate evidence in nutritional research.

Our study found that WP supplementation significantly increased ASM, ASMI, and GS, but not in the HS, in older patients with sarcopenia compared to those in the PLA/RC group. However, there was a significant increase in HS in the WP with RT group compared to that in the PLA/RC group, suggesting that the improvement in muscle strength may be primarily due to RT. In addition, WP with RT had no significant effect on ASMI compared to RT alone, suggesting that the combined effect did not enhance the effectiveness of RT. Our secondary outcomes found that, compared to the PLA/RC group, the WP group had significantly reduced inflammatory markers (IL-6), significantly increased IGF-1 and albumin levels, significantly improved TEI and protein intake, and enhanced ADL in patients.

Effects of WP supplementation, with or without RT, on muscle mass, strength, and physical performance

The WP intervention demonstrated significant efficacy in improving physical performance but showed only moderate or non-significant effects in improving muscle mass and strength, and this positive effect may be attributed primarily to RT. Firstly, WP, owing to its high biological availability, is considered a premium source of protein. Particularly for older populations that exhibit decreased physiological nutrient absorption efficiency and diminished protein synthesis capacity, WP supplementation may have a greater positive impact on their muscle health [56]. This could provide a theoretical basis for its role in muscle synthesis and resistance to muscle atrophy [57], and it might be a key factor in the positive effect of WP on improving muscle mass and function [58]. Additionally, studies have found that the intake of 20–40 g of WP per meal (approximately 1.5–1.6 g/kg/day) could maximize the stimulation of muscle protein synthesis [59], and older adults with sarcopenia may need a higher dose as a result of anabolic resistance [60].

Secondly, RT is undoubtedly beneficial for patients with sarcopenia. The World Health Organization recommends that adults aged 65 years and above engage in 150 min of moderate-intensity or 75 min of vigorous-intensity aerobic physical activity per week, along with muscle-strengthening activities on 2 or more days a week (i.e., strength training/RT) [61]. The U.S. Department of Health and Human Services suggests engaging in a multi-component exercise program, including balance training and muscle-strengthening exercises (at least 2 days per week), as well as performing moderate-intensity aerobic activity for at least 30−45 min, three or more times per week, for a minimum of 3–5 months. This has proved to be most effective in improving functional capacity in frail older adults [61]. While high-load resistance training has proved effective in older adults, its implementation may be challenging for individuals with muscle and skeletal disorders, coronary artery disease, diabetes, and other comorbidities, because of joint pain, decreased cardiopulmonary reserve and so on. For patients with sarcopenia, moderate- or low-load resistance training or adherence to the basic founding principles of DeLorme, using "unconventional" progressive overload in strength exercises, is considered an effective approach [61–63]. Future research should focus on understanding ways to increase exercise participation and long-term adherence to exercise [25]. RT has been proven to stimulate muscle growth [64] and enhance nutrient uptake [65]. Protein supplementation can also enhance the adaptive response of skeletal muscles to RT [66], and their combined effect may enhance muscle mass and function by activating muscle growth signaling pathways [67].

However, protein supplementation alone has shown a lot of contradictory results in clinical trials, or rather, its effects are less pronounced [26,32,33]. Similarly, it is still inconclusive whether WP combined with RT causes a "1 + 1 > 2" or "1 + 1 < 2" effect in clinical trials. Although the therapeutic effects of WP and RT on sarcopenia have been corroborated in numerous studies, their effects in clinical studies may be uncertain because of a variety of factors, including the patient's baseline nutritional status, disease severity, supplement dosage, and exercise regimen [68,69].

4.2. Effects of WP supplements on laboratory indicators

In the current meta-analysis, we concurrently analyzed laboratory indicators, particularly inflammatory indicators. This is crucial, as two key processes are involved in the onset of age-related sarcopenia: the accumulation of senescent cells in skeletal muscle and adipose tissue, and systemic low-grade chronic inflammation [70]. Furthermore, inflammation substantially increases the risk of mortality due to sarcopenia [71]. Major inflammatory molecules worsening muscular conditions through promoting infiltration of inflammatory cells via NF-κB are TNF-α, IL-6, IL-1, and chemokines [72]. Concurrently, inflammation associated with cellular senescence may lead to the senescence-associated secretory phenotype, and the accumulation of this phenotype may induce chronic inflammation and changes in the cellular microenvironment, thus significantly promoting sarcopenia [73–75]. Particularly, persistent levels of IL-6 can impair muscle integrity and function, leading to muscle degeneration and atrophy [76]. Our study indicated that WP supplementation can significantly reduce IL-6 levels and increase IGF-1 levels. IGF-1 plays a pivotal role in muscle growth, differentiation, and regeneration by promoting muscle synthesis and resisting progressive muscle loss [77]. It also negatively regulates interleukin levels and counteracts inflammation [78]. Additionally, vitamin D deficiency and limited physical activity are closely associated with reduced muscle mass, strength, physique, and weight loss [79,80]. We observed a significant increase in 25-hydroxyvitamin D levels in the experimental group. While this may be linked to the presence of vitamin D in the WP supplement consumed by the experimental group, evidence suggests that merely supplementing with vitamin D does not improve the muscle loss index in community-dwelling older adults and might even impair certain physiological functions [81]. This implies that a combination of WP and vitamin D supplements could be more beneficial for older people with sarcopenia, a perspective supported by previous studies [26,32]. Furthermore, it is worth noting that the marked increase in albumin and the unchanged TC in our experimental group also underscore the advantages of WP supplementation.

4.3. Effects of WP supplements on daily dietary nutrient intake

Daily dietary nutrient intake was considered one of the outcomes to investigate the impact of daily supplementation on macronutrient and energy intake in this study. Overall, WP consumption did not significantly increase fat and carbohydrate intake in the experimental group, but increased TEI and protein intake. This could be associated with the concurrent RT undertaken by participants in the experimental group. Although co-ingestion of WP and carbohydrates may not increase the rate of muscle protein synthesis [82], protein intake has a beneficial impact on muscle synthesis.

4.4. Effects of WP supplements on fundamental physical parameters

The two most fundamental metrics of human health, BMI and body weight, are crucial criteria for assessing obesity in older populations. Diminishing muscle mass inherent to aging can potentially lead to a decrease in the basal metabolic rate, resulting in obesity. Obesity can exacerbate muscle loss through inflammatory responses and endocrine alterations. The coexistence of muscle loss and obesity could lead to a more severe condition, known as sarcopenic obesity [83,84]. Therefore, the potential adverse effects of this level should be considered when contemplating nutritional supplementation therapy for sarcopenia. Our findings indicate that WP does not have a significant effect on BMI and body weight in patients with sarcopenia. Finally, it is worth mentioning that we found that WP can significantly improve ADL scores, indicating an overall improvement in the patient's ability to perform activities in daily life.

4.5. Heterogeneity, publication bias, and sensitivity analyses

Firstly, in our analysis of publication bias, we observed its presence in the outcome measures of the SPPB, TEI, and SF-36 PCS, with the sensitivity analysis for the SPPB yielding inconsistent results. However, after excluding the study conducted by Rondanelli et al. [49], subsequent publication bias analysis for the SPPB revealed no significant bias (Figures S17 [b] and [b']). This could be attributed to the study incorporating medium-intensity RT five times a week for all participants, an intervention that likely overshadows the effects of WP, thereby introducing bias into the results. In terms of the remaining two indicators, owing to the limited number of studies included in our analysis and the robustness of the results suggested by the sensitivity analysis, we were unable to further investigate the causes of publication bias. Secondly, the

heterogeneity in this study may be attributable to multiple factors, such as the selection of the population in the ten included studies, the research design, and the outcome measures analyzed. Within the subgroup analysis (muscle strength-related items, as shown in Table 2), we observed that when comparing WP with RT with the PLA or RT groups, only the former showed significant changes, further confirming that RT may be a source of heterogeneity in the observed outcomes. Additional large-scale RCTs are required to verify the accuracy of these findings.

4.6. Comparison of similar studies

Some recent studies relevant to our topic were identified. A meta-analysis conducted by Chang et al. [26] investigated the effects of supplementation with WP, leucine, and vitamin D on sarcopenia. The analysis included three RCTs, and the findings suggested that the blend supplement effectively increased ASM. However, it did not significantly improve the HGS or SPPB scores unless combined with RT. Kamińska et al. [33] conducted a meta-analysis on the effects of WP on individuals with sarcopenia. They included ten RCTs but had a similar yet less comprehensive focus compared to our study and did not include an analysis of RT. They demonstrated that WP had no significant effect on ASM, HGS, FTCST, SPPB, or body weight. Nasimi et al. [32] investigated the effects of WP supplementation (with or without vitamin D supplementation) on measures related to sarcopenia. They showed that WP significantly improved ASM and physical performance in patients with sarcopenia; however, these improvements were not observed in healthy individuals. Supplementation with WP and vitamin D significantly improved muscle strength, mass, and physical performance in the entire study population. Furthermore, a meta-analysis conducted by Cuyul-Vásquez et al. [34] examined the effects of WP supplementation during RT on muscle mass and strength in patients with sarcopenia in seven studies. Studies have demonstrated that WP supplementation during RT significantly increases ASM and HGS compared to RT alone, but the strength of the effect is small and the GRADE evidence is very low. Overall, there are some discrepancies between the items analyzed in recently published studies and our results, and additional research is required to verify the validity of our results.

4.7. Limitations

This study had certain limitations. First, the literature search was confined to English publications. Second, although two independent authors evaluated the quality of literature and evidence using the RoB2 and NutriGrade systems, some studies were difficult to fully randomize or double-blind, making evaluation challenging and introducing an inevitable element of subjectivity. Third, the studies included in our analysis demonstrated inconsistent diagnostic criteria for sarcopenia. At the research level, several trials have small sample sizes and short durations. Moreover, the limited number of studies included in this review prevented subgroup analysis for some outcome measures, such as analyses of different WP dosages, the presence or absence of leucine, vitamin D, or calcium in WP, and analysis of various RT intensities. Future research should aim to design studies that explore the impact of these factors.

5. Conclusions

The results demonstrate that WP can improve muscle mass and physical performance but does not have a significant effect on muscle strength. A significant increase in muscle strength was observed when WP was combined with RT. However, further research is required to validate these findings. Additionally, WP supplementation showed significant benefits in enhancing ADL, increasing IGF-1 and albumin levels, promoting participants' adherence to TEI and protein intake, and reducing inflammation marker levels. Furthermore, WP had no significant effect on BMI, body weight, or FM. These findings provide new insights into the clinical applications of WP.

Institutional review board statement

Ethical review and approval were waived due to this study being a systematic review and meta-analysis.

Informed consent statement

Patient consent was waived due to this study being a systematic review and meta-analysis.

Data availability statement

Data were available within the article and its supplementary materials.

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jnha.2024.100184.

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