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Review

Protein supplementation alone or combined with exercise for sarcopenia and physical frailty: A systematic review and meta-analysis of randomized controlled trials

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HIGHLIGHTS

- Combined protein and exercise significantly improved muscle mass and grip strength.
- Protein supplementation alone showed modest strength gains but limited performance benefits.
- Evidence quality for all outcomes was rated as very low, requiring further robust trials.
- Results highlight the potential of protein for managing sarcopenia in older adults.

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ABSTRACT

Background: Sarcopenia and physical frailty are age-related syndromes characterized by progressive loss of muscle mass and function, significantly impacting mortality and quality of life in older adults. This systematic review evaluated the effectiveness of protein supplementation interventions for these conditions.
Methods: We systematically searched Medline, CENTRAL, and Ichushi Web from January 2000 to March 2023, with additional manual searching extended to March 2024. Randomized controlled trials investigating protein supplementation, alone or combined with exercise, in adults aged ≥65 years with sarcopenia or physical frailty were included. The primary outcomes were changes in muscle mass, strength, and physical performance.
Results: The systematic literature search identified 1,506 records through database searching (Medline: 357, CENTRAL: 275, Ichushi Web: 639) and 235 additional records through hand searching. Finally, 13 randomized controlled trials (n=1,057) met the inclusion criteria. Combined protein and exercise interventions demonstrated significant improvements in skeletal muscle index (MD = 0.89 kg/m^2, 95 % CI: 0.45 to 1.33) and handgrip strength (MD: +2.64 kg, 95 % CI: +0.75 to +4.53) compared to exercise alone. Protein supplementation alone showed modest benefits in muscle strength but limited effects on physical performance. No serious adverse events were reported.
Conclusions: While protein supplementation combined with exercise shows promising effects on muscle mass and strength in older adults with sarcopenia or physical frailty, the evidence quality was consistently rated as very low. Further high-quality trials are needed to establish optimal supplementation strategies.
Registration: PROSPERO: CRD42023408529

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1. Introduction

Sarcopenia and physical frailty represent significant age-related syndromes characterized by progressive loss of muscle mass, strength, and physical function that substantially impact mortality, hospitalization risk, and quality of life among older adults (Sayer et al., 2024, Kirk et al., 2024, Chen et al., 2020, Dent et al., 2019, Chew et al., 2024). The global prevalence of sarcopenia ranges from 10 % to 40 % in community-dwelling older adults (Weng et al., 2025, Petermann-Rocha et al., 2022), while physical frailty affects approximately 10–15 % of the older population (Walsh et al., 2023, Ofori-Asenso et al., 2019). These syndromes are not only major contributors to increased risks of falls, functional decline, and institutionalization but also key drivers of escalating healthcare costs (Álvarez-Bustos et al., 2022), as they often necessitate prolonged rehabilitation and long-term care (Sánchez-Rodríguez et al., 2014, Yoshimura et al., 2019a).

Protein supplementation has emerged as a potential therapeutic strategy, given its crucial role in muscle protein synthesis and maintenance (Negm et al., 2022, Negm et al., 2019, Sun et al., 2023, Sirikul, Buawangpong, Pinyopornpanish & Siviroj, 2024, Yoshimura et al., 2017). Current evidence suggests that older adults may require higher protein intake than younger individuals due to anabolic resistance, a condition where the muscle's response to protein intake is blunted with aging (Deane, Cox & Atherton, 2024, Campbell, Deutz, Volpi & Apovian, 2023). While exercise, particularly resistance training, remains a cornerstone intervention, growing evidence indicates that combining exercise with nutritional supplementation may yield superior outcomes in addressing the complex pathophysiology of these conditions (Whaikid & Piaseu, 2024, Cuyul-Vásquez et al., 2023). Several recent meta-analyses have explored the effects of protein supplementation combined with resistance training on sarcopenia-related outcomes (Whaikid & Piaseu, 2024, Cuyul-Vásquez et al., 2023, Li et al., 2024). However, these studies often include heterogeneous populations, such as those with secondary sarcopenia due to ICU stays, malnutrition, or acute illnesses. Additionally, many earlier reviews were limited in scope, with narrower outcome assessments and outdated search periods. Our study focuses exclusively on adults aged 65 years and older diagnosed with primary sarcopenia or physical frailty, as outlined in our PROSPERO-registered protocol. This updated meta-analysis addresses these gaps by including recently published randomized controlled trials (RCTs) and expanding the scope to evaluate a broader range of outcomes, including functional performance measures.

The primary objective of this updated meta-analysis was to evaluate the therapeutic effects of protein-based nutritional interventions, alone or combined with exercise, on sarcopenia and physical frailty outcomes in older adults. We specifically examine the impact on muscle mass, strength, physical performance, and adverse health outcomes including mortality, hospitalization, and functional decline. Despite the theoretical benefits, the optimal protein supplementation strategy, including timing, dosage, and combination with exercise, remains unclear, particularly in specific populations such as those who are hospitalized or institutionalized (Deane, Cox & Atherton, 2024). While the majority of the included studies focused on community-dwelling older adults, our analysis also incorporated studies involving nursing home residents who met the criteria for primary sarcopenia or physical frailty. By including diverse settings, our study provides a broader perspective on the applicability of protein interventions across different populations.

2. Materials and methods

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study protocol was prospectively registered in the PROSPERO database (CRD42023408529).

2.1. Review questions

This systematic review and meta-analysis addresses two primary questions:

1. Is protein supplementation effective for improving sarcopenia and physical frailty in older adults?
2. Does protein supplementation reduce adverse outcomes such as disability, hospitalization, and mortality?

2.2. Search strategy

A comprehensive literature search was conducted in PubMed, the Cochrane Library (The Cochrane Database of Systematic Reviews and The Cochrane Central Register of Controlled Trials), and The Igaku Chuo Zasshi (ICHUSHI) of the Japan Medical Abstracts Society (Japanese) databases from January 1, 2000, to March 31, 2023. Additional relevant studies were identified through manual searching of reference lists from January 1, 2000, to March 31, 2024. No language restrictions were applied to the search strategy. The search strategy was devised with a medical information specialist's help (Supplementary Table 1).

2.3. Eligibility criteria

1. Types of Studies

Only randomized controlled trials (RCTs) were included in this meta-analysis to ensure high-quality evidence.

2. Types of Participants

The inclusion criteria were defined as adults aged 65 years and older diagnosed with primary sarcopenia (loss of skeletal muscle mass combined with reduced muscle strength or physical function) or physical frailty based on the phenotype model. To maintain population homogeneity, we excluded studies involving:

- Secondary sarcopenia due to ICU stays, acute illness, malnutrition, organ failure, cachexia, or other conditions.
- Sarcopenia or frailty due to specific diseases, including diabetes mellitus and organ failure (renal, liver, heart, or respiratory insufficiency).
- Frailty defined by the deficit accumulation model.
- Hospitalized populations, as secondary sarcopenia in these settings could confound the effects of protein-based interventions.

The majority of the included studies focused on community-dwelling older adults, though studies involving nursing home residents were included if they met the criteria for primary sarcopenia or frailty.

3. Types of Interventions and Controls

Interventions included:

- Protein supplementation
- Combined interventions (protein supplementation with exercise)
- Other nutritional interventions involving energy-producing nutrients, amino acids, and micronutrients

To isolate the effects of protein supplementation, we excluded studies where additional bioactive compounds (e.g., DHA, EPA, vitamin D, fish oil omega-3, and carbohydrates) may have significantly influenced the outcomes. However, RCTs in which protein was the predominant active ingredient with only minimal additional nutrients were retained.

Control conditions comprised:

- No intervention
- Exercise alone

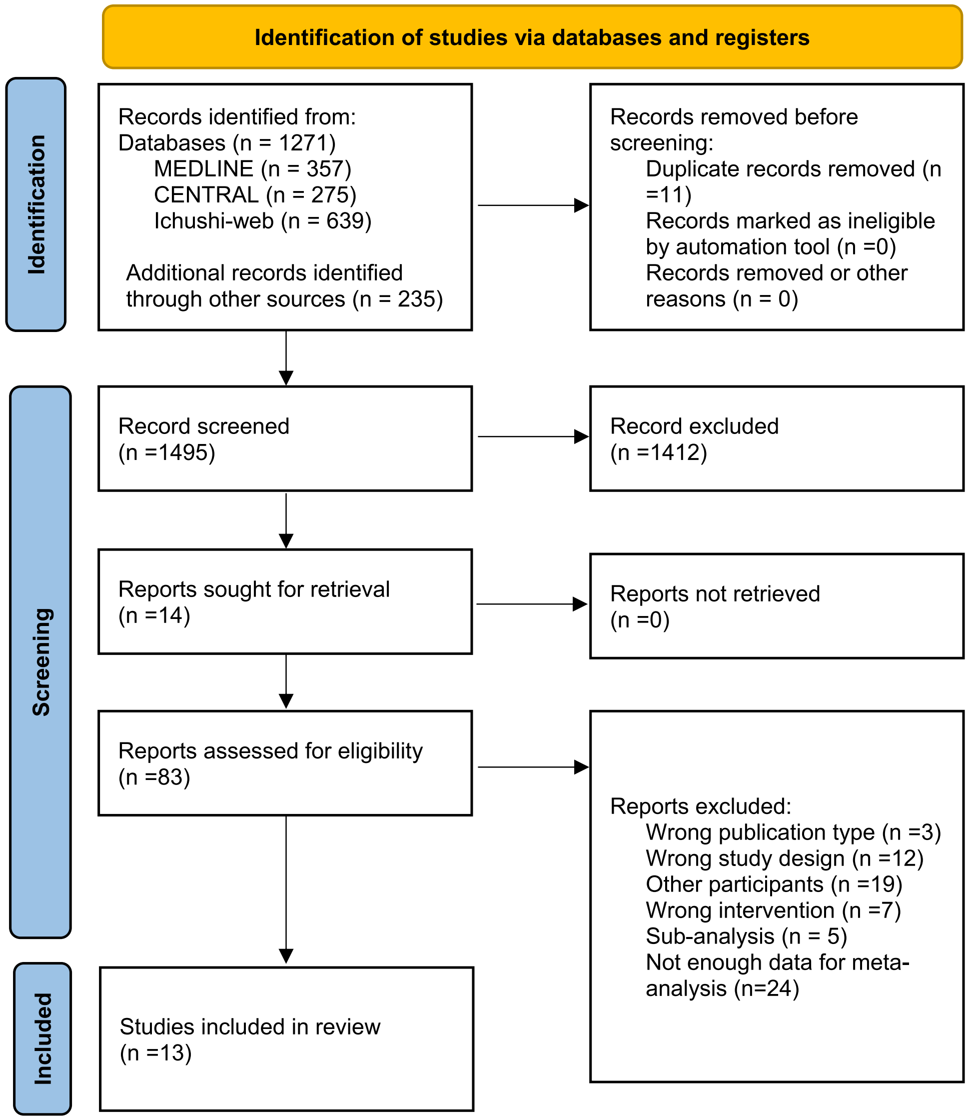

Fig. 1. PRISMA diagram of patient inclusion and exclusion flowchart.

- Placebo supplementation

2.4. Outcome measures

1. ***Primary outcomes***:
   - Changes in sarcopenia diagnostic parameters (e.g., skeletal muscle mass, strength, function).
   - Changes in frailty status.
2. ***Secondary outcomes***:
   - Mortality
   - Hospitalization
   - Functional decline
   - Quality of life

2.5. Data extraction and quality assessment

Two independent researchers (each from AM, TI and MO) extracted data and evaluated the eligibility of the retrieved full-text studies. The extracted data included study characteristics (journal, author, year, country), participant demographics, intervention details, and outcome measures. Consensus on inclusion was reached through discussion among the reviewers, with any disagreements resolved through further deliberation. Studies that did not meet the inclusion criteria were documented along with their specific reasons for exclusion.

The methodological quality and risk of bias were assessed using the Cochrane Risk of Bias tool for RCTs (RoB 2) and GRADE methodology for evidence quality (Mathes et al., 2022). At least two independent reviewers evaluated each study by examining six key domains: randomized sequence generation, treatment allocation concealment, blinding, completeness of outcome data, selective outcome reporting, and other potential sources of bias. For each domain, reviewers made independent judgments categorizing the risk as high, low, or unclear, with any discrepancies resolved through discussion to reach consensus.

2.6. Strategy for data synthesis

The meta-analysis employed:

- Random-effects model for data combination
- Standardized mean differences for continuous outcomes
- Risk ratios for binary outcomes
- 95 % confidence intervals and two-sided P values
- Heterogeneity assessment using $\chi 2$ test and I2 statistic

Table 1
Characteristics of the studies included.

Author	Country	Study design	Setting	Patients	Sample size	Intervention	Intervention period	Control	Outcomes	Main findings
Maltais ML, 2016	Canada	RCT	Community-dwelling	Sarcopenic men	26	(a) RE + EAA supplement[1] (b) RE + milk supplement[2]	4 months	RE + placebo[3]	BW, BMI, MM, AMMI, LP, BP, NWS, MWS, TUG, CST, PASE	LBM increased significantly in all groups, with no significant differences between groups.
Boutry-Regard C, 2020	France	Single-center, parallel, double-blind RCT	Community-dwelling	Elderly with mobility limitations	37	(1) WPI[4] (2) WPI+BIO[5] + EMS	12 weeks	CHO[6] + EMS	MT, KES, GS (6MWT), TLM, MNA	KES improved significantly by 13 % in WPI+BIO vs CHO ($p = 0.025$). GS increased by 8 % in WPI+BIO ($p = 0.032$). MT increased 3–5 % in all groups.
Biesek S, 2021	Brazil	RCT	Community-dwelling	Pre-frail older women	90	(1) ETG[7] (2) PSG[8] (3) ETPSG[9] (4) ETISG[10]	12 weeks	No intervention	PFS, BC (ASM, ASMI), GMA, PI, IL-6, IPT, HGS	ETG showed reduction in ASM and ASMI. ETPSG increased DPT by 11.4 %. ETG increased HGS by 13.7 %. PFS reversed in 73.3 % of ETG, 55.6 % of ETPSG, and 43.8 % of ETISG.
Li Z, 2021	China	RCT	Two medical centers	Sarcopenic elderly (≥60 years)	241	(1) Nutr[11] (2) Ex[12] (3) Nutr+Ex	12 weeks	Routine consultation	AMM, GS, FM, AMM/H², AMM/W, AMM/BMI, AMM/FM	AMM and GS significantly higher in all intervention groups vs control ($p < 0.001$). FM significantly lower in Nutr and Nutr+Ex vs control and Ex ($p < 0.001$).
Park W, 2023	South Korea	Community-based RCT	Community-dwelling	Pre-frail older women (≥65 years)	60	(1) Diet group[13] (2) AE+D[14] (3) AE+EMS+D[15]	8 weeks	No intervention	BP, PF (GS, SPPB, 6MWD), CVB, PWV, FMD	GS significantly increased in all intervention groups ($p < 0.05$). SPPB, 6MWD, and FMD significantly increased in AE+D and AE+EMS+D groups ($p < 0.05$). BP and PWV decreased in exercise groups.
Kwok T, 2001	Hong Kong	RCT	Nursing homes	Frail older Chinese	47	Low lactose milk powder supplement[16]	7 weeks	No supplement	24-h FR, BW, BMI, TSF, BSF, MAC, GS, BI, AMTS	Intervention group showed trend towards weight gain (NS). Significant increases in intake of Ca, vit D, vit A, riboflavin, and K in supplemented group. No significant differences in GS, MF, or DL.
Roschel H, 2021	Brazil	Parallel-group, double-blind, RCT	Community-dwelling	Pre-frail and frail older adults	168	(1) Leucine[17] vs placebo (2) Whey[18] vs soy[19] vs placebo (3) Creatine[20] vs placebo (4) Vitamin D^3 [21] vs placebo	16 weeks	Placebo	1-RM LP, 1-RM BP, KEPT, HGS, TUG, TST, TLM, ALM, TFM, VLCSA	Whey and soy protein supplementation did not enhance effects of RT. Leucine, creatine, or vitamin D^3 supplementation did not augment adaptations to RT. No sex-specific effects of whey protein supplementation observed.
Wu SY, 2018	Taiwan	Single-blind, parallel group RCT	Community-dwelling	Pre-frail or frail elderly (≥65 years)	36	(1) MMS[22] (2) MMS+ISP[23] (3) INE[24]	3 months	No intervention	FS, RHG, LHG, GS, IPAQ-SF, DI, UUN, GDS	INE significantly increased intake of vegetables, dairy, and nuts, and increased UUN. Significant reduction in FS ($p < 0.05$) and borderline reduction in GDS ($p = 0.063$) in INE group. No significant changes in other intervention groups.
Tieland M, 2012	Netherlands	RCT, double-blind, placebo-controlled	Community-dwelling	Frail elderly	62	RT + protein supplementation[25]	24 weeks	RT + placebo	BW, LBM, ALM, FM, BMD, LPS, LES, HGS, SPPB, GS, CST	LBM increased in protein group (1.3 ± 0.4 kg) but not in placebo group (–0.2 ± 0.5 kg). MS and PP improved significantly in both groups, with no differences between groups.
Payette H, 2002	Canada	Prospective RCT	Community-dwelling	Frail undernourished elderly receiving long-term home care	83	Commercial liquid nutrition supplement[26]	16 weeks	Usual care	BW, MAC, TSF, SIS, SSS, CC, TUG, IEF, LES, LEF, SPHS, FS, SF-36	Supplement group had higher total energy intake (1772 vs 1440 kcal; $p < 0.001$) and weight gain (1.62 vs 0.04 kg; $p < 0.001$) compared to control group. No significant changes in other anthropometric indicators, muscle strength, or physical function.
Mori H, 2020	Japan	RCT	Community-dwelling	Sarcopenic elderly	54	(1) WHEY[27] (2) EX+WHEY[28]	24 weeks	EX[29]	SP, BW, SMI, HGS, KES, SF-8	SMI increased significantly in all groups ($p < 0.05$). KES increased significantly in EX+WHEY and EX groups ($p < 0.05$). No significant differences in SMI and KES

(*continued on next page*)

Table 1 (*continued*)

Author	Country	Study design	Setting	Patients	Sample size	Intervention	Intervention period	Control	Outcomes	Main findings
										increase rates between EX+WHEY and EX groups.
Zhu LY, 2019	China	Prospective parallel group, single-blind RCT	Community-dwelling	Sarcopenic older adults (≥60 years)	113	(1) ExS[30] (2) Ex[31]	12 weeks	WC[32]	GS, UFM, USMM, LSMM, ASMI, MHG, LES, 5STS, 6MWD, PASE, SF-12, IADL	LES and 5STS improved significantly in ExS and Ex groups, with improvements persisting at 24 weeks. PASE improved in ExS and Ex groups, with improvement persisting at 24 weeks only in ExS. LSMM and TSMM increased significantly in ExS group but did not persist at 24 weeks.
Alemán-Mateo H, 2012	Mexico	RCT	Community-dwelling	Sarcopenic elderly (≥60 years)	40	210 g/day ricotta cheese[33]	3 months	Habitual diet	TASM, MS, BW, LBM, FI, IGF-1	Percentage of relative change in TASM not significant between groups. MS improved in intervention group, but only showed tendency towards significance ($p = 0.06$). Secondary analysis showed men in intervention group gained 270 g in TASM compared to control group, and improved FI levels ($p = 0.05$), MS, LBM in arms, and BW.

Footnotes:

[1] EAA powder: 12 g protein, 7 g EAA (3.5 g leucine), 39 g carbohydrate, 5.3 g fat, 252 kcal
[2] Milk supplement: 375 ml, 13.53 g protein, 7 g EAA (3.5 g leucine), 37.5 g carbohydrate, 3.8 g fat, 270 kcal
[3] Rice milk, no protein
[4] WPI: 20 g whey protein isolate + placebo capsules
[5] WPI+BIO: 20 g whey protein isolate + bioactive capsules (500 mg rutin, 1.5 g fish oil omega-3, 500 mg curcumin)
[6] CHO: 20 g carbohydrate + placebo capsules
[7] ETG: Exergames training
[8] PSG: Protein supplementation (20 g whey protein/day)
[9] ETPSG: Exergames + protein supplementation
[10] ETISG: Exergames + isoenergetic supplementation
[11] Nutr: Whey protein powder (10 g) 3 times/day, EPA (300 mg), DHA (200 mg), vitamin D3 (250 IU) 2 tablets twice daily
[12] Ex: Resistance exercise and outdoor activities
[13] Diet group: Protein-added meals twice daily on weekdays
[14] AE+D: Aerobic exercise (45 min stepping exercise at 50–70 % max HR, 3 days/week) + protein-added meals
[15] AE+EMS+D: Aerobic exercise with electromyostimulation + protein-added meals
[16] 87.5 kcal, 9.4 g protein, 12.4 g carbohydrate, 0.2 g fat, 120 IU vitamin D3 per serving, twice daily
[17] Leucine: 10 g/day
[18] Whey protein: 30 g/day
[19] Soy protein: 30 g/day
[20] Creatine: 5 g/day
[21] Vitamin D3: 2000 IU/day
[22] MMS: Multiple micronutrient supplements
[23] ISP: Isolated soy protein
[24] INE: Individualized nutrition education with customized dishware and food supplements (mixed nuts and skimmed milk powder)
[25] 15 g protein twice daily
[26] Ensure, 2 cans (235 ml each) per day
[27] WHEY: Whey protein supplementation (160 kcal, 11.0 g protein, 2.2 g fat, 24.0 g carbohydrate, 2300 mg leucine)
[28] EX+WHEY: Resistance exercise + whey protein supplementation
[29] EX: Resistance exercise only
[30] ExS: Combined exercise program and nutritional supplementation (231 kcal, 8.61 g protein, 1.21g β-hydroxy-β-methylbutyrate, 130 IU vitamin D, 0.29 g omega-3 fatty acids)
[31] Ex: Exercise program only
[32] WC: Control group

[33] 15.7 g protein (including 8.6 g essential amino acids), 18.4 g fat, 10.4 g carbohydrates, total 267 kcal/day

Abbreviations: RCT: randomized controlled trial; RE: resistance exercise; EAA: essential amino acids; BMI: body mass index; MM: muscle mass; AMMI: appendicular muscle mass index; LP: lat pulldown; BP: bench press; NWS: normal walking speed; MWS: maximum walking speed; TUG: timed up and go; CST: chair stand test; PASE: physical activity scale for the elderly; LBM: lean body mass; WPI: whey protein isolate; EMS: electrical muscle stimulation; CHO: carbohydrate; MT: muscle thickness; KES: knee extension strength; GS: gait speed; 6MWT: 6-meter walking test; TLM: total lean mass; MNA: mini nutritional assessment; BC: body composition; ASM: appendicular skeletal muscle; ASMI: appendicular skeletal muscle mass index; GMA: gastrocnemius muscle architecture; PI: protein intake; IL-6: interleukin-6; IPT: isokinetic peak torque; HGS: handgrip strength; DPT: dorsiflexion peak torque; AMM: appendicular muscle mass; FM: fat mass; H: height; W: weight; FR: food record; BW: body weight; TSF: triceps skinfold; BSF: biceps skinfold; MAC: mid-arm circumference; BI: Barthel index; AMT: abbreviated mental test; RT: resistance training; 1-RM: one-repetition maximum; KEPT: knee extension peak torque; TST: timed stands test; ALM: appendicular lean mass; TFM: total fat mass; VLCSA: vastus lateralis cross-sectional area; FS: frailty score; RHG: right handgrip; LHG: left handgrip; IPAQ-SF: International Physical Activity Questionnaire-Short Form; DI: dietary intake; UUN: urinary urea nitrogen; GDS: geriatric depression score; MFS: muscle fiber size; MS: muscle strength; PP: physical performance; SIS: suprailiac skinfold; SSS: subscapular skinfold; CC: calf circumference; IEF: isometric elbow flexion; LES: leg extension strength; LEF: lower extremity function; SPHS: self-perceived health status; FS: functional status; SF-36: short form-36 health survey; SP: sarcopenia prevalence; SMI: skeletal muscle mass index; UFM: upper limb fat mass; USMM: upper limb skeletal muscle mass; LSMM: lower limb skeletal muscle mass; MHG: maximum handgrip strength; 5STS: 5-time sit-to-stand; 6MWD: 6-minute walking distance; IADL: instrumental activities of daily living; TASM: total appendicular skeletal muscle; FI: fasting insulin; IGF-1: insulin-like growth factor-1.

2.7. Definition of outcome parameters

To ensure consistency in outcome assessment, we standardized definitions as follows:

- **Skeletal Muscle Mass Index (SMI):** Measured using bioelectrical impedance analysis (BIA) or dual-energy X-ray absorptiometry (DXA) as appendicular skeletal muscle mass relative to height squared (kg/m^2).
- **Grip Strength:** Assessed using a handgrip dynamometer, with values reported in kilograms (kg).
- **Walking Speed:** Measured as gait speed over a predefined distance (e.g., 4 m or 6 m), expressed in meters per second (m/s).
- **Knee Extension Strength:** Evaluated using an isometric dynamometer or manual muscle testing, reported in Newtons (N) or kilograms (kg).
- **Body Weight (BW) and Body Mass Index (BMI):** Recorded using standard anthropometric measurements.
- **Short Physical Performance Battery (SPPB):** A composite test including balance, gait speed, and chair rise, scored from 0 to 12.
- **Quality of Life (QOL):** Assessed using validated tools such as SF-36 or EQ-5D.

2.8. Summary of the findings tables

Results were presented using:

- GRADE evidence profiles
- Forest plots for meta-analyses
- Subgroup analyses based on:
  - Population characteristics
  - Intervention types
  - Duration of follow-up

3. Results

3.1. Study selection

The systematic literature search identified 1506 records through database searching (Medline: 357, CENTRAL: 275, Ichushi Web: 639) and 235 additional records through hand searching. After removing 11 duplicates, 1495 articles were screened by title and abstract, resulting in the exclusion of 1412 records. Full-text assessment was conducted for 83 articles, of which 70 were excluded for the following reasons: ineligible study design (n=12), inappropriate population (n=19), non-relevant intervention (n=7), and wrong outcomes (n=24), *etc.*. Finally, 13 randomized controlled trials met all inclusion criteria and were included in both qualitative and quantitative synthesis (Fig. 1).

3.2. Study characteristics

The 13 included randomized controlled trials were published between 2001 and 2023, with sample sizes ranging from 26 to 241 participants (Table 1). The studies were conducted across multiple countries: Canada (2 studies), France (1), Brazil (2), China (2), South Korea (1), Hong Kong (1), Netherlands (1), Mexico (1), Japan (1), and Taiwan (1). Study durations varied from 7 weeks to 24 weeks. The interventions included protein supplementation alone (4 studies), protein combined with exercise (5 studies), and multi-nutrient supplementation (4 studies).

The study populations comprised community-dwelling older adults (11 studies) and nursing home residents (2 studies), with participants' ages ranging from 60 to 95 years. The protein supplementation protocols varied widely, from 10 g to 30 g of protein per day, delivered through different sources including whey protein isolate, essential amino acids, milk products, and ricotta cheese. Exercise interventions included

Table 2
Certainty of the evidence (GRADE).

Outcome	No. of studies	Design	Certainty assessment					Certainty of the evidence (GRADE)
			Risk of bias	Inconsistency	Indirectness	Imprecision	Others	
SMI: Multi-nutrient with protein vs. Control	2	Randomized trial	Very serious	Very serious	Serious	Serious	Very serious	⊕◯◯◯ Very low
SMI: Protein + Exercise vs. Control	4	Randomized trial	Serious	Not serious	Serious	Serious	Not serious	⊕◯◯◯ Very low
SMI: Protein + Exercise vs. Exercise	4	Randomized trial	Serious	Not serious	Not serious	Serious	Not serious	⊕◯◯◯ Very low
Muscle strength (Grip strength): Multi-nutrient vs. Control	7	Randomized trial	Very serious	Very serious	Very serious	Serious	Not serious	⊕◯◯◯ Very low
Muscle strength (Grip strength): Protein + Exercise vs. Control	3	Randomized trial	Serious	Not serious	Serious	Very serious	Not serious	⊕◯◯◯ Very low
Muscle strength (Grip strength): Protein + Exercise vs. Exercise	5	Randomized trial	Serious	Serious	Serious	Serious	Not serious	⊕◯◯◯ Very low
Muscle strength (Grip strength): Protein vs. Control	2	Randomized trial	Very serious	Not serious	Not serious	Very serious	Not serious	⊕◯◯◯ Very low
Muscle strength (Knee extension strength): Protein + Exercise vs. Exercise	3	Randomized trial	Serious	Not serious	Serious	Serious	Not serious	⊕◯◯◯ Very low
Physical function (Gait speed): Multi-nutrient vs. Control	3	Randomized trial	Very serious	Not serious	Very serious	Very serious	Not serious	⊕◯◯◯ Very low
Physical function (Gait speed): Protein + Exercise vs. Control	2	Randomized trial	Very serious	Not serious	Serious	Very serious	Not serious	⊕◯◯◯ Very low
Physical function (Gait speed): Protein + Exercise vs. Exercise	2	Randomized trial	Serious	Not serious	Serious	Very serious	Not serious	⊕◯◯◯ Very low
Physical function (Gait speed): Protein vs. Control	2	Randomized trial	Very serious	Not serious	Not serious	Very serious	Not serious	⊕◯◯◯ Very low
Physical function (SPPB): Protein + Exercise vs. Control	2	Randomized trial	Very serious	Not serious	Serious	Very serious	Not serious	⊕◯◯◯ Very low
QOL (Physical): Multi-nutrient + Exercise vs. Exercise	2	Randomized trial	Very serious	Serious	Serious	Very serious	Not serious	⊕◯◯◯ Very low
QOL (Mental): Multi-nutrient + Exercise vs. Exercise	2	Randomized trial	Very serious	Serious	Serious	Very serious	Not serious	⊕◯◯◯ Very low
Physical activity (PASE): Multi-nutrient + Exercise vs. Control	2	Randomized trial	Serious	Not serious	Very serious	Very serious	Not serious	⊕◯◯◯ Very low
Body weight: Multi-nutrient + Exercise vs. Control	4	Randomized trial	Very serious	Not serious	Very serious	Serious	Not serious	⊕◯◯◯ Very low
Body weight: Multi-nutrient + Exercise vs. Exercise	3	Randomized trial	Serious	Not serious	Serious	Serious	Not serious	⊕◯◯◯ Very low
BMI: Multi-nutrient vs. Control	2	Randomized trial	Serious	Not serious	Serious	Very serious	Not serious	⊕◯◯◯ Very low

Abbreviations: SMI: Skeletal Muscle Index; SPPB: Short Physical Performance Battery; QOL: Quality of Life; PASE: Physical Activity Scale for the Elderly; BMI: Body Mass Index; RCT: Randomized Controlled Trial
Note: Certainty of evidence was rated as very low for all outcomes due to various limitations in the included studies. The symbol ⊕◯◯◯ represents very low certainty of evidence according to the GRADE system.

resistance training, aerobic exercise, and combined training programs. Primary outcome measures included muscle mass, muscle strength (grip strength, knee extension strength), physical performance (walking speed, SPPB), and frailty status, while secondary outcomes included body composition, quality of life, and functional status.

3.3. Risk of Bias assessment

The Risk of Bias (RoB) assessment, conducted using the GRADE system, revealed significant limitations across the included studies, leading to very low certainty of evidence for all outcomes (Table 2). Skeletal muscle index (SMI), muscle strength (including grip and knee extension strength), and physical function outcomes (such as gait speed and the Short Physical Performance Battery) were all rated as very low certainty. The main factors contributing to these ratings included serious or very serious risks of bias, imprecision, and indirectness, stemming from methodological weaknesses like poor randomization, inadequate blinding, small sample sizes, and inconsistent interventions. Quality of life (QOL) outcomes, physical activity, body weight, and BMI were similarly affected, with very low certainty due to pervasive risks of bias, indirectness, and imprecision. The variability in study designs and population characteristics further reduced the reliability and generalizability of findings. These results highlight the urgent need for high-quality randomized controlled trials with robust methodologies to better evaluate the effectiveness of nutritional and exercise interventions for sarcopenia and frailty.

3.4. Effects of interventions

The effects of nutritional and exercise interventions on sarcopenia-related outcomes, including skeletal muscle index (SMI), handgrip strength (HGS), gait speed, and quality of life (QOL), were synthesized across included studies. Forest plots for these outcomes (Figs. 2, 4, 6, 8) illustrate the intervention effects alongside their effect sizes and 95 % confidence intervals (CIs).

For **SMI**, three meta-analyses evaluated the effects of different interventions: (a) multi-nutrient supplements including protein vs control, (b) protein supplements vs control, and (c) combined intervention of protein supplements and exercise vs exercise (Fig. 2) (Biesek et al., 2021, Li et al., 2021, Maltais, Ladouceur & Dionne, 2016, Zhu et al., 2019, Mori et al., 2020). Multi-nutrient supplements showed a mean difference (MD) of +0.03 kg/m^2 (95 % CI: –1.03 to +1.09) with substantial heterogeneity (I^2 = 84 %), indicating no statistically significant improvement in SMI. In contrast, protein supplements alone demonstrated a small but statistically significant effect, with an MD of +0.32 kg/m^2 (95 % CI: +0.01 to +0.62) and low heterogeneity (I^2 = 12 %), suggesting

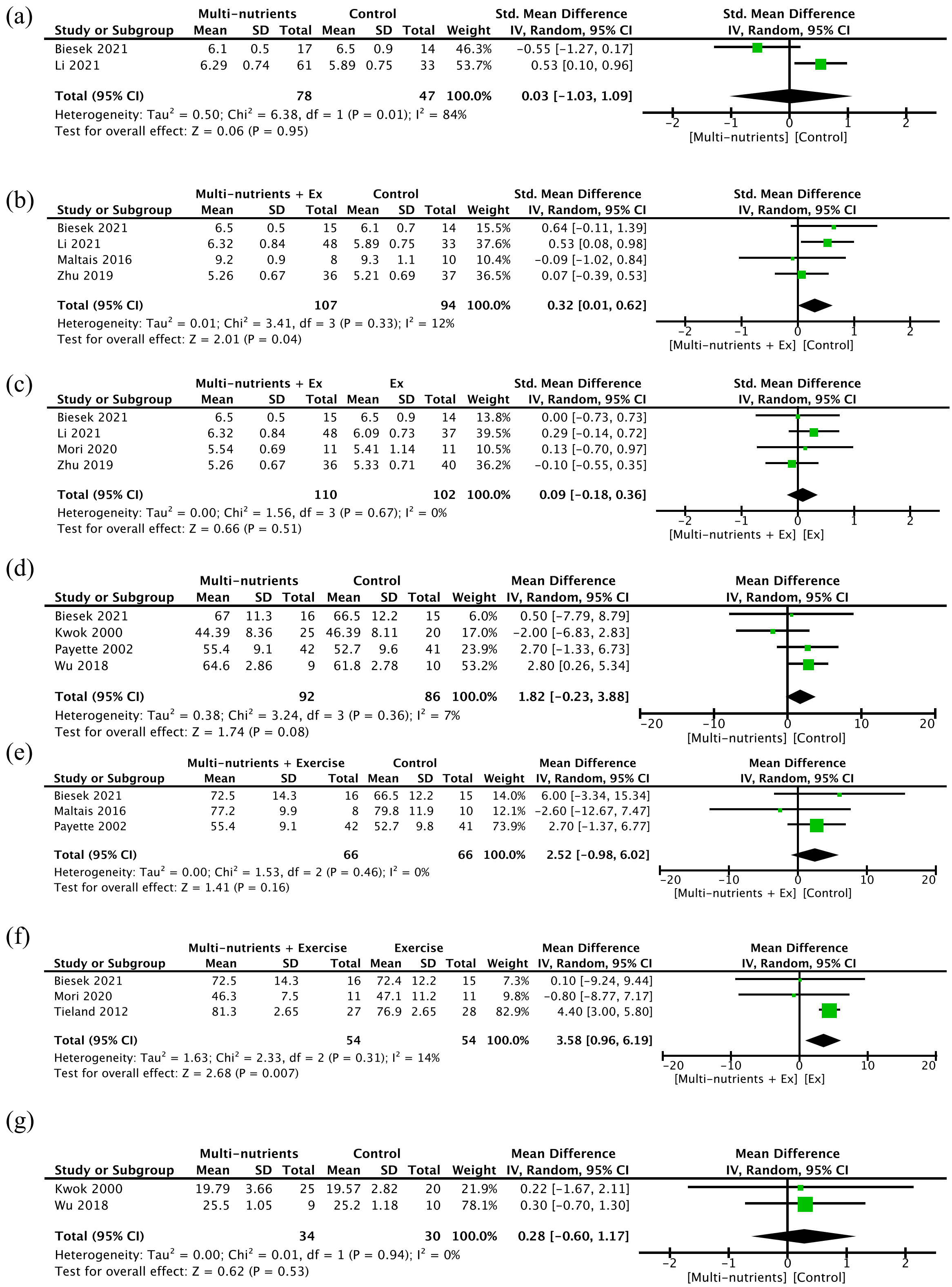

Fig. 2. Forest plot for SMI, BW, BMI
(a) Multi-nutrient supplements including protein vs control for SMI (b) Protein supplement vs control for SMI (c) Combined intervention of protein supplements and exercise vs exercise for SMI (d) Multi-nutrient supplements including protein vs control for BW (e) Combined intervention of multi-nutrient supplements including protein and exercise vs control for BW (f) Combined intervention of multi-nutrient supplements including protein and exercise vs exercise for BW (g) Multi-nutrient supplements including protein vs control for BMI
Abbreviation: BMI: body mass index; BW: body weight; SMI: skeletal muscle mass.

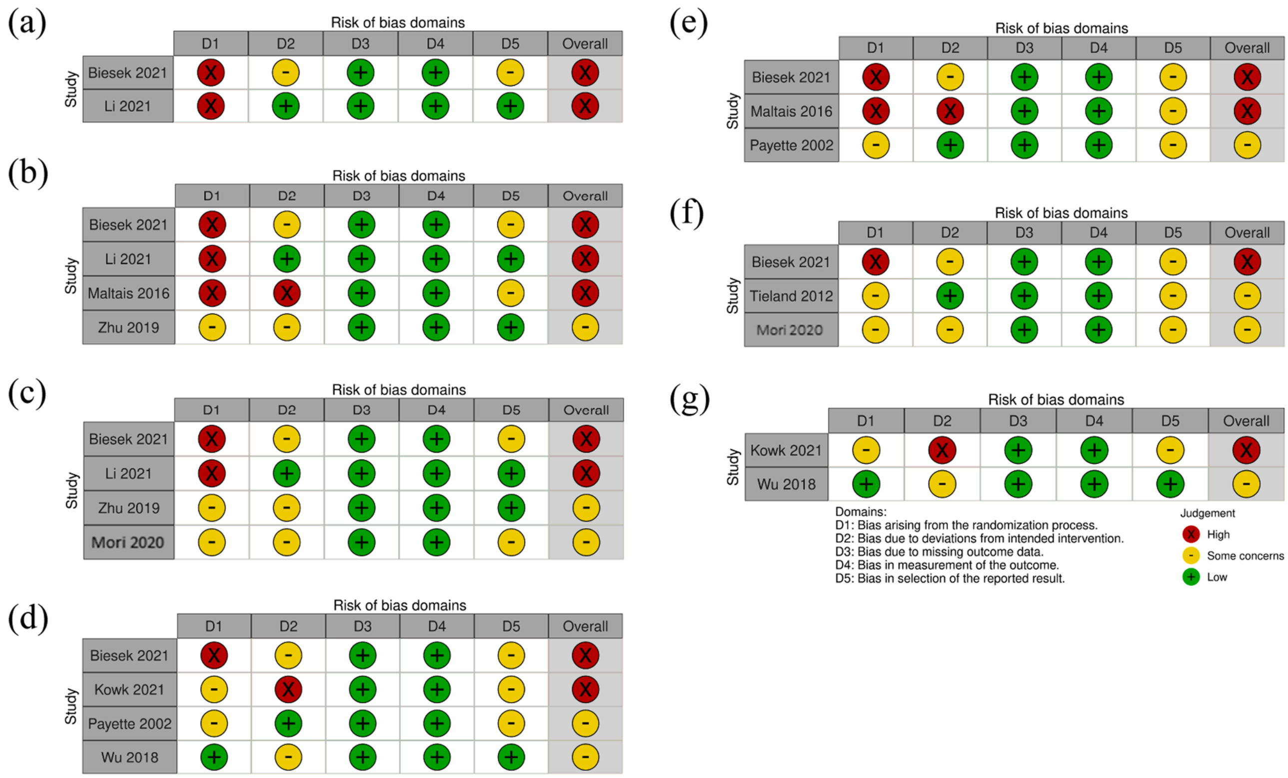

Fig. 3. Risk of Bias for SMI, BW, BMI
(a) Multi-nutrient supplements including protein vs control for SMI (b) Protein supplement vs control for SMI (c) Combined intervention of protein supplements and exercise vs exercise for SMI (d) Multi-nutrient supplements including protein vs control for BW (e) Combined intervention of multi-nutrient supplements including protein and exercise vs control for BW (f) Combined intervention of multi-nutrient supplements including protein and exercise vs exercise for BW (g) Multi-nutrient supplements including protein vs control for BMI
D1: Bias arising from the randamization process
D2: Bias due to deviations from intended intervation
D3: Bias due to missing outcome data
D4: Bias in measurement of the outcome
D5: Bias in selection of the reported result
Abbreviation: BMI: body mass index; BW: body weight; SMI: skeletal muscle mass.

consistent benefits across studies. However, the combined intervention of protein supplements and exercise resulted in an MD of +0.09 kg/m^2 (95 % CI: –0.18 to +0.36) with no observed heterogeneity ($I^2 = 0$ %), but the result was not statistically significant.

For **BW**, three meta-analyses evaluated the effects of different interventions: (d) multi-nutrient supplements including protein vs control, (e) combined intervention of multi-nutrient supplements including protein and exercise vs control, and (f) combined intervention of multi-nutrient supplements including protein and exercise vs exercise (Fig. 2) (Biesek et al., 2021, Maltais, Ladouceur & Dionne, 2016, Mori et al., 2020, Kwok, Woo & Kwan, 2001, Payette, Boutier, Coulombe & Gray-Donald, 2002, Wu et al., 2018, Tieland et al., 2012). Multi-nutrient supplements alone (d) resulted in a mean difference (MD) of +1.82 kg (95 % CI: –0.23 to +3.88) with low heterogeneity ($I^2 = 7$ %), but the confidence interval included zero, indicating no statistically significant improvement in body weight. The combined intervention of multi-nutrient supplements and exercise compared to control (e) showed a slightly larger MD of +2.52 kg (95 % CI: –0.98 to +6.02) with no observed heterogeneity ($I^2 = 0$ %); however, this result was also not statistically significant. In contrast, the combined intervention compared to exercise alone (f) demonstrated a statistically significant MD of +3.58 kg (95 % CI: +0.96 to +6.19) with low heterogeneity ($I^2 = 14$ %).

For **BMI**, the meta-analysis evaluated the effects of multi-nutrient supplements including protein compared to control (g) (Fig. 2) (Kwok, Woo & Kwan, 2001, Wu et al., 2018). The reported mean difference (MD) was +0.28 kg/m^2 (95 % CI: –0.60 to +1.17), with no observed heterogeneity ($I^2 = 0$ %). Despite the low heterogeneity indicating consistency across studies, the confidence interval included zero, rendering the result statistically non-significant.

For **HGS**, four meta-analyses assessed the effects of different interventions: (a) multi-nutrient supplements including protein vs control, (b) combined intervention of protein supplements and exercise vs control, (c) combined intervention of protein supplements and exercise vs exercise, and (d) protein supplements vs control (Fig. 4) (Biesek et al., 2021, Li et al., 2021, Zhu et al., 2019, Mori et al., 2020, Kwok, Woo & Kwan, 2001, Wu et al., 2018, Tieland et al., 2012, Alemán-Mateo et al., 2012, Park et al., 2023, Roschel et al., 2021). Multi-nutrient supplements alone (a) showed no significant improvement (MD: +0.22 kg, 95 % CI: –1.81 to +2.25; $I^2 = 70$ %). In contrast, both protein supplementation combined with exercise (b) (MD: +2.64 kg, 95 % CI: +0.75 to +4.53; $I^2 = 2$ %) and protein supplementation alone (d) (MD: +1.84 kg, 95 % CI: +0.83 to +2.85; $I^2 = 10$ %) demonstrated statistically significant improvements compared to control. However, the combined intervention of protein supplementation and exercise compared to exercise alone (c) did not yield significant benefits (MD: +0.56 kg, 95 % CI: –0.34 to +1.45; $I^2 = 8$ %).

For **knee extension strength**, the meta-analysis evaluated the effects of a combined intervention of protein supplements and exercise compared to exercise alone (e) (Fig. 4) (Zhu et al., 2019, Mori et al., 2020, Tieland et al., 2012). The mean difference (MD) was –0.35 kg (95 % CI: –0.72 to +0.01) with low heterogeneity ($I^2 = 20$ %).

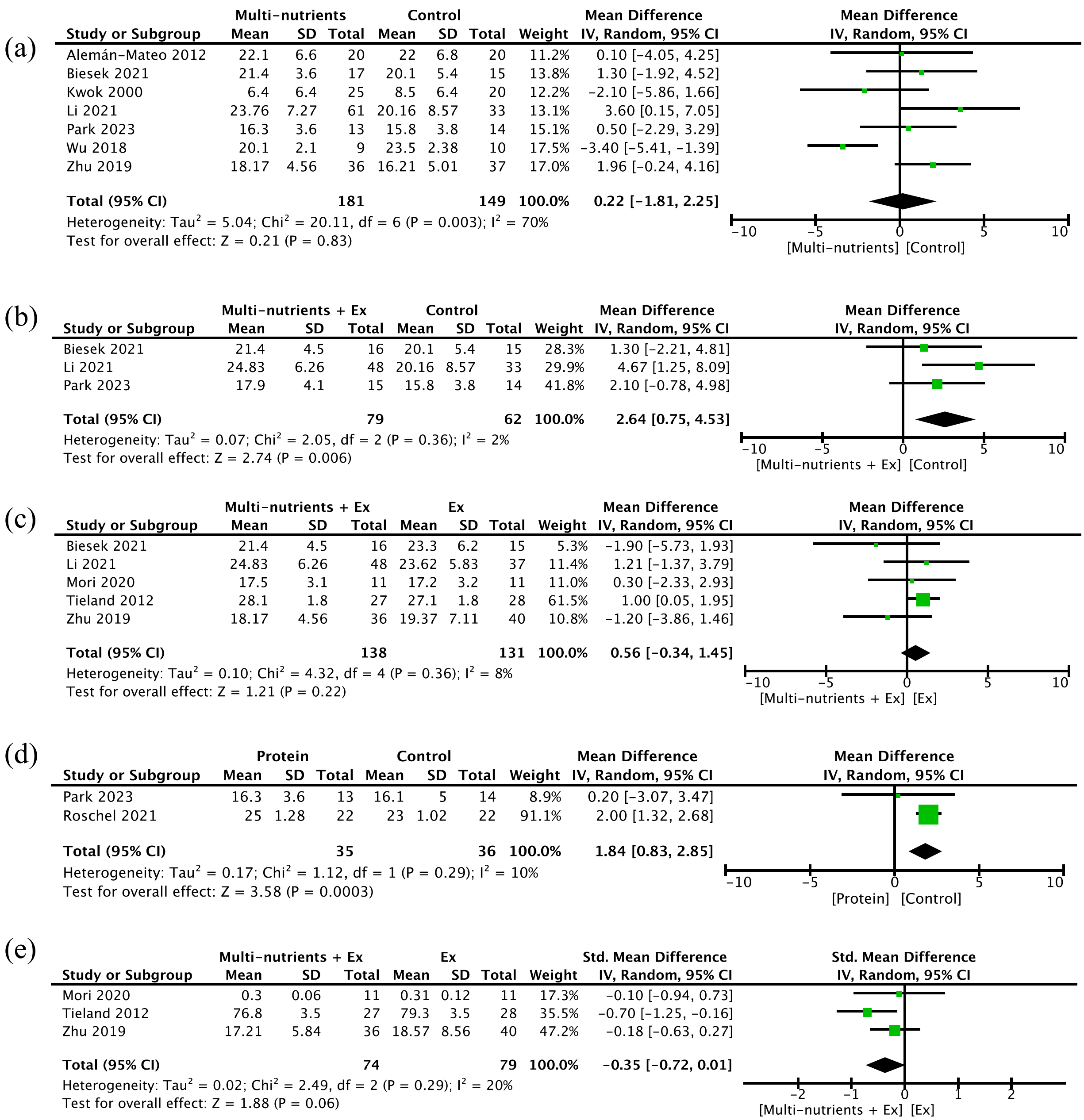

Fig. 4. Forest plot for handgrip strength and knee extension strength
(a) Multi-nutrient supplements including protein vs control for handgrip strength (b) Combined intervention of protein supplements and exercise vs control for handgrip strength (c) Combined intervention of protein supplements and exercise vs exercise for handgrip strength (d) Protein supplements vs control for handgrip strength (e) Combined intervention of protein supplements and exercise vs exercise for knee extension strength.

For **gait speed**, three meta-analyses assessed the effects of different interventions: (a) protein supplements including protein vs control, (b) combined intervention of protein supplements and exercise vs control, and (c) combined intervention of protein supplements and exercise vs exercise (Fig. 6) (Maltais, Ladouceur & Dionne, 2016, Mori et al., 2020, Wu et al., 2018, Tieland et al., 2012, Park et al., 2023, Boutry-Regard, Vinyes-Parés, Breuillé & Moritani, 2020). Multi-nutrient supplements alone (a) showed a mean difference (MD) of +0.01 m/s (95 % CI: –0.07 to +0.10) with no observed heterogeneity ($I^2 = 0$ %). The confidence interval included zero, indicating no statistically significant improvement in gait speed. Similarly, the combined intervention of protein supplements and exercise vs control (b) resulted in an MD of +0.10 m/s (95 % CI: –0.11 to +0.31) with no heterogeneity ($I^2 = 0$ %), but this result was also not statistically significant. When comparing the combined intervention to exercise alone (c), the MD was +0.02 m/s (95 % CI: –0.01 to +0.05), again with no heterogeneity ($I^2 = 0$ %) and no statistical significance.

For **physical function** assessed by Short Physical Performance Battery (SPPB), a single meta-analysis evaluated the effects of a combined intervention of protein supplements and exercise compared to control (d) (Fig. 6) (Tieland et al., 2012, Park et al., 2023). The reported mean difference (MD) was +0.60 score (95 % CI: –0.23 to +1.44) with moderate heterogeneity ($I^2 = 64$ %). Although the MD suggested a potential improvement in physical performance, the confidence interval included zero, indicating that the result was not statistically significant.

For **physical activity** assessed by the Physical Activity Scale for the Elderly (PASE), the meta-analysis evaluated the effects of a combined intervention of multi-nutrient supplements including protein and

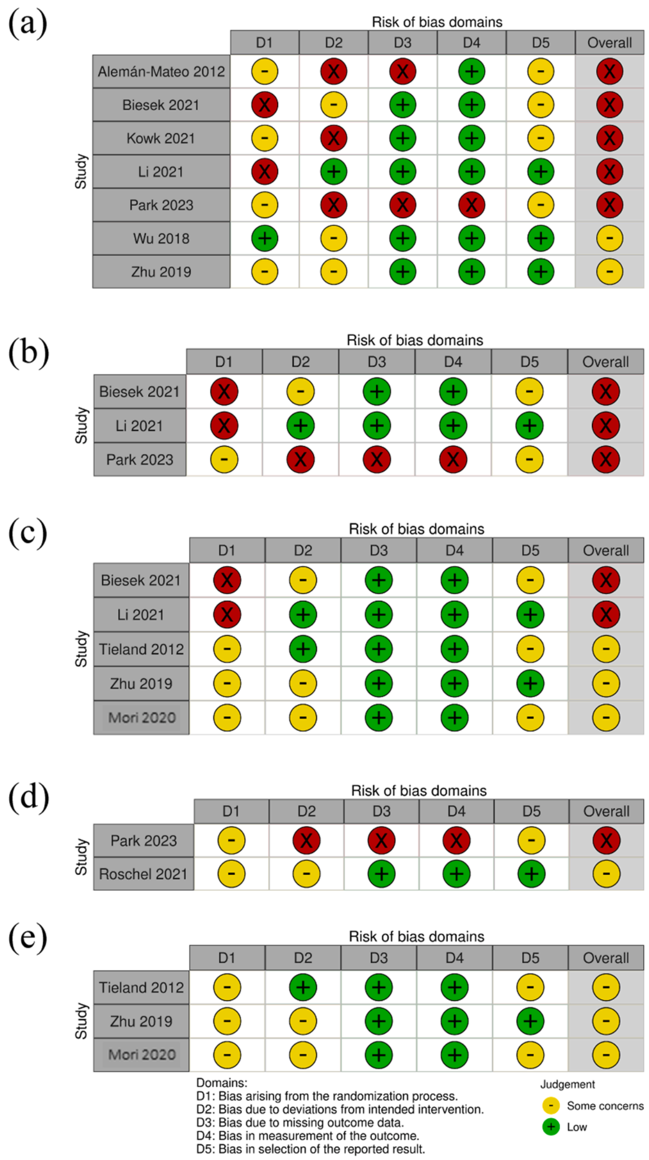

Fig. 5. Risk of Bias for handgrip strength and knee extension strength
(a) Multi-nutrient supplements including protein vs control for handgrip strength (b) Combined intervention of protein supplements and exercise vs control for handgrip strength (c) Combined intervention of protein supplements and exercise vs exercise for handgrip strength (d) Protein supplements vs control for handgrip strength (e) Combined intervention of protein supplements and exercise vs exercise for knee extension strength.

exercise vs control (e) (Fig. 6) (Maltais, Ladouceur & Dionne, 2016, Zhu et al., 2019). The reported mean difference (MD) was +10.36 points (95 % CI: –4.43 to +25.16) with no observed heterogeneity (I^2 = 0 %). However, the confidence interval included zero, indicating that the result was not statistically significant.

For quality of life (QoL) assessed by SF-8 and SF-12, two meta-analyses evaluated the effects of a combined intervention of protein supplements and exercise compared to exercise alone for physical and mental QoL assessed using SF-12 (Fig. 8) (Zhu et al., 2019, Mori et al., 2020). For physical QoL (a), the mean difference (MD) was +0.35 score (95 % CI: –0.32 to +1.02) with moderate heterogeneity (I^2 = 52 %). While the MD indicated a slight improvement, the confidence interval included zero, rendering the result not statistically significant. For mental QoL (b), the MD was +0.15 score (95 % CI: –0.49 to +0.80) with moderate heterogeneity (I^2 = 49 %), again showing no statistically significant effect.

The risk of bias (RoB) assessment for the meta-analyses across outcomes, including SMI, HGS, gait speed, and QoLs, revealed notable methodological limitations. For SMI, BW and BMI (Fig. 3), many studies were rated as having high or unclear risk of bias due to concerns with randomization, blinding, and incomplete outcome data. Similar issues were observed for HGS and knee extension strength (Fig. 5), with a substantial number of studies demonstrating bias related to deviations from intended interventions. For gait speed, SPPB and Physical Activity Scale for the Elderly (Fig. 7), while the risk of bias was slightly lower, concerns remained regarding measurement and reporting of outcomes. Lastly, for QoL (Fig. 9), bias was particularly noted in participant blinding and selective outcome reporting. These findings indicate that methodological limitations across the included studies may have impacted the reliability of the meta-analyses, underscoring the need for more rigorously designed trials to strengthen the evidence base.

3.5. *Adverse effects*

While protein supplementation suggested potential benefits for improving muscle mass and strength, concerns exist regarding its effects on renal function. However, none of the included randomized controlled trials reported serious adverse events related to protein supplementation. It is noteworthy that a large cross-sectional study of 3302 community-dwelling elderly twins, though not included in our systematic review, found that high protein intake (≥1.3 g/kg/day) was associated with increased risk of sarcopenia (Ni Lochlainn et al., 2023). These findings suggest that protein supplementation alone may be insufficient for improving outcomes in sarcopenia and frailty, and potential negative effects cannot be ruled out. Further research is needed to establish the safety and optimal dosage of protein supplementation in this population.

4. Discussion

This systematic review and meta-analysis evaluated the effectiveness of protein-based nutritional interventions, including both supplementation and dietary intake, in improving sarcopenia and physical frailty outcomes among older adults. By synthesizing evidence from 13 randomized controlled trials published through March 31, 2024, we provide an updated and comprehensive assessment of these interventions. The majority of the included studies focused on community-dwelling older adults, though nursing home residents were also included if they met the criteria for primary sarcopenia or frailty. This broader inclusion enhances the applicability of our findings across different living environments. However, hospitalized populations were excluded to maintain a homogeneous study sample and avoid confounding effects from secondary sarcopenia due to acute illness or malnutrition.

Protein supplementation has shown consistent yet modest benefits in improving muscle mass and handgrip strength. These findings support the role of protein supplementation in stimulating muscle protein synthesis and counteracting the anabolic resistance commonly observed in aging populations (D'Souza et al., 2019, Drummond et al., 2008). Specific amino acids, such as leucine, and its derivative β-hydroxy β-methylbutyrate, have been identified as particularly effective in activating the mTOR pathway and reducing muscle protein breakdown, respectively (Duan et al., 2016, Wilkinson et al., 2013, Yoshimura et al., 2019b). However, when combined with exercise, the additional benefits of protein supplementation over exercise alone were less clear, with results suggesting limited incremental improvements (Whaikid & Piaseu, 2024). This highlights the potential of protein supplementation as an accessible and effective standalone strategy for managing sarcopenia, especially in populations with limited access to structured exercise programs. Future research should aim to refine supplementation protocols, including the dosage, timing, and delivery method of protein, while also exploring the characteristics of populations that may derive the greatest benefit from such combined strategies.

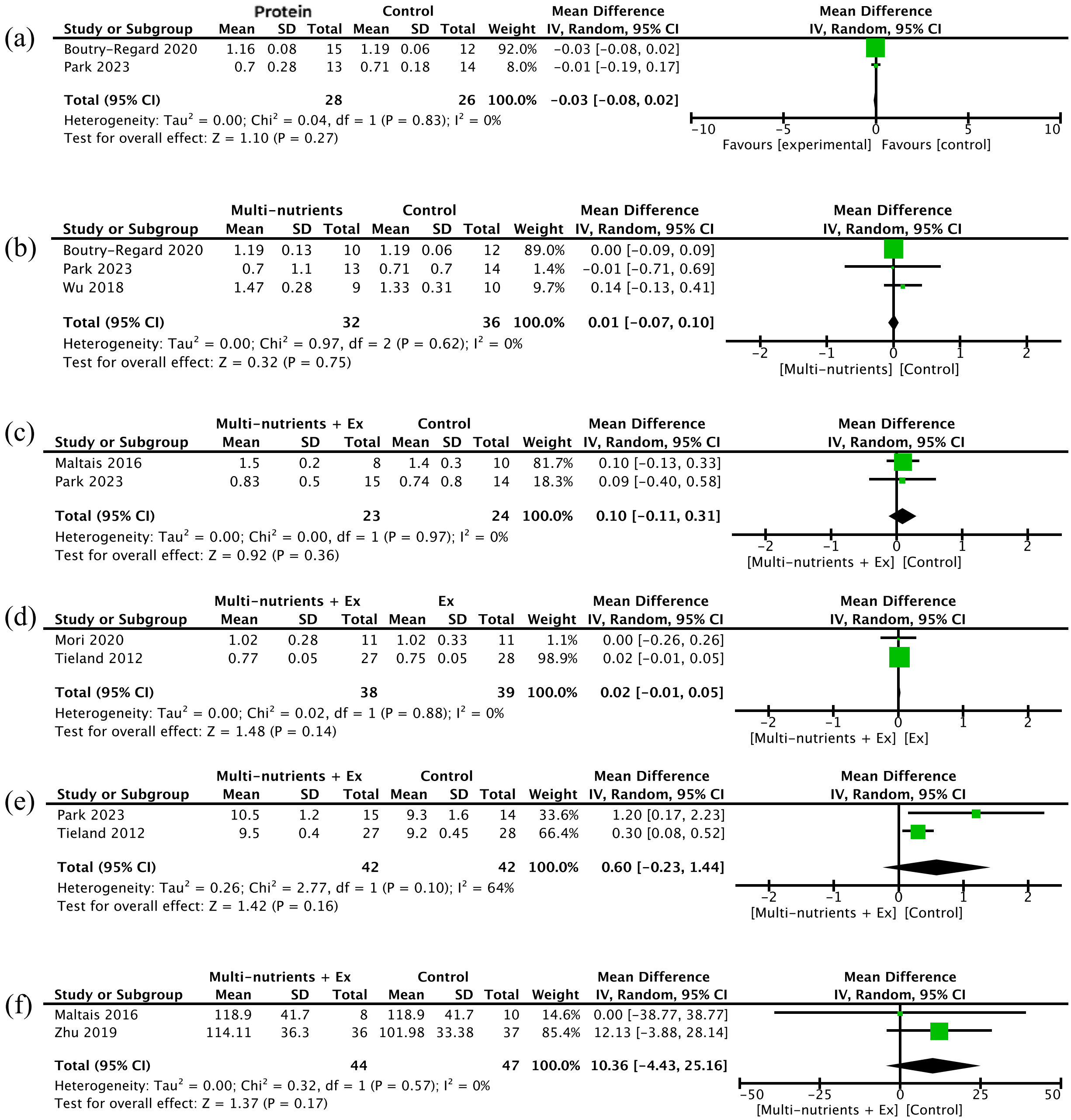

Fig. 6. Forest plot for gait speed, SPPB and Physical Activity Scale for the Elderly
(a) Protein supplements including protein vs control for gait speed (b) Combined intervention of protein supplements and exercise vs control for gait speed (c) Combined intervention of protein supplements and exercise vs exercise for gait speed (d) Combined intervention of protein supplements and exercise vs control for SPPB (e) Combined intervention of multi-nutrient supplements including protein and exercise vs control for Physical Activity Scale for the Elderly
Abbreviation: SPPB: Short Physical Performance Battery.

While protein supplementation alone provided consistent benefits, combined interventions involving protein and exercise showed limited incremental improvements. Meta-analyses revealed that these combined interventions did not consistently enhance muscle strength or functional performance beyond the effects of exercise alone. These findings suggest that, while protein supplementation can be beneficial as a standalone strategy, particularly for those unable to engage in regular exercise, its additional effects when paired with exercise require further exploration. Future trials should investigate whether specific subgroups—such as frail individuals with lower baseline protein intake—derive greater benefits from combined interventions.

Multi-nutrient supplementation, including protein combined with other bioactive compounds such as DHA, EPA, vitamin D, and omega-3 fatty acids, yielded inconsistent or non-significant effects on physical function outcomes, including gait speed, SPPB, and QoL. To ensure a precise evaluation of protein's role, we refined our inclusion criteria and excluded studies where additional bioactive compounds may have confounded the results. While multi-nutrient interventions may offer synergistic benefits, future research should examine their independent effects through well-controlled trials.

Although sarcopenia and physical frailty have different diagnostic definitions, they are interrelated conditions that contribute to age-related declines in physical function. Both conditions share common risk factors and therapeutic strategies, particularly protein-based nutritional interventions. A combined meta-analysis allows for a broader evaluation of intervention efficacy while maintaining statistical

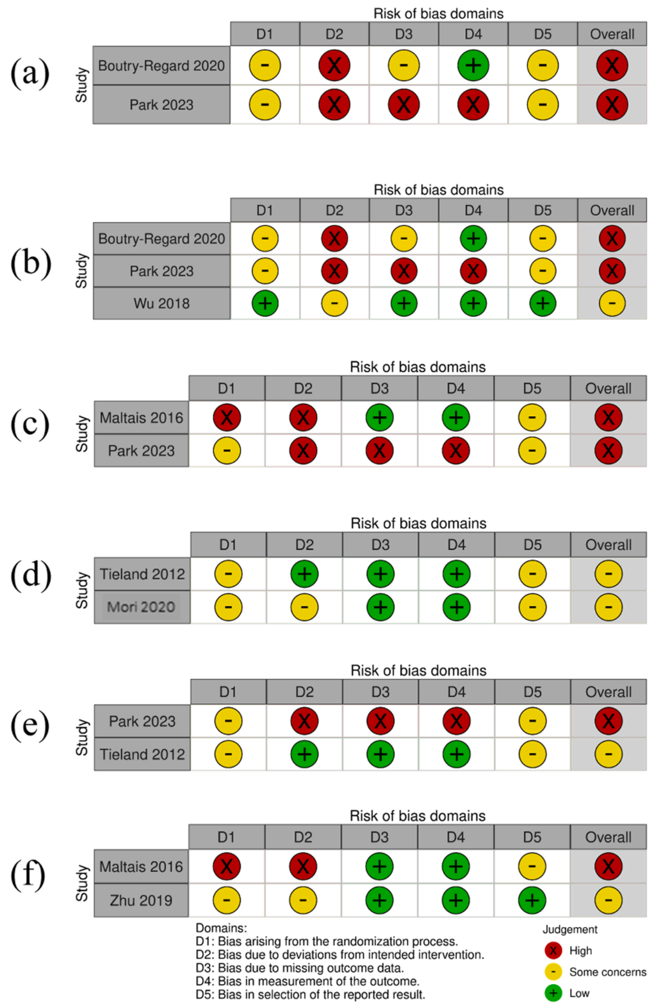

Fig. 7. Risk of Bias for gait speed, SPPB and Physical Activity Scale for the Elderly
(a) Multi-nutrient supplements including protein vs control for gait speed (b) Combined intervention of protein supplements and exercise vs control for gait speed (c) Combined intervention of protein supplements and exercise vs exercise for gait speed (d) Combined intervention of protein supplements and exercise vs control for SPPB (e) Combined intervention of multi-nutrient supplements including protein and exercise vs control for Physical Activity Scale for the Elderly
Abbreviation: SPPB: Short Physical Performance Battery.

power. While we did not conduct a formal subgroup analysis distinguishing sarcopenia from frailty, we carefully examined the characteristics of included studies. Future research should explore separate analyses to provide condition-specific insights and optimize intervention strategies. Further, significant heterogeneity was observed across studies in terms of intervention protocols, study populations, and outcome measures. Differences in protein dosages, nutrient compositions, exercise regimens, and participant characteristics (e.g., age, baseline sarcopenia severity, comorbidities, and nutritional status) may have contributed to variability in responses. Moreover, inconsistent methodologies for measuring sarcopenia-related outcomes further complicated cross-study comparisons. These challenges underscore the need for harmonized protocols and standardized assessment tools in future clinical trials to enhance comparability and clinical translation.

Although several interventions demonstrated statistical significance, their clinical relevance remains uncertain. Our meta-analysis identified significant improvements in SMI, body weight, and handgrip strength across different intervention comparisons. However, the extent to which these improvements translate into meaningful functional benefits is unclear. For instance, while increased SMI is associated with better muscle health, its direct impact on mobility and disability risk reduction requires further validation. Similarly, handgrip strength improvements are promising but may not necessarily equate to enhanced functional independence. Future research should establish the minimum clinically important difference (MCID) for these outcomes to better assess the real-world impact of protein-based interventions.

Our meta-analysis builds upon existing evidence by addressing key gaps in prior reviews. Unlike earlier meta-analyses that included heterogeneous populations, our study exclusively targeted older adults diagnosed with primary sarcopenia or physical frailty, ensuring a more homogeneous population. The inclusion of trials published through March 31, 2024, allowed us to incorporate the most up-to-date evidence. Although the number of included RCTs (13) may seem limited, this reflects the current state of high-quality research in this area. The limited number of studies highlights the need for future trials to further validate the effectiveness of protein supplementation, alone or combined with exercise, in managing sarcopenia and frailty.

The optimal dosage of protein supplementation for nutritional interventions remains uncertain, as the 13 studies included in this review demonstrated a wide range of intervention amounts, from 10 to 40 g per day. For instance, Biesek et al. (2021) utilized 21 g/day of whey protein (Biesek et al., 2021), Zhu et al. (2019) implemented 22 g/day[27], and Li et al. (2021) employed 30 g/day[25], with many studies converging around 20–25 g/day of protein supplementation, demonstrating consistent efficacy. While specific recommendations cannot yet be established, the findings suggest that supplementing with approximately 20–25 g/day of protein, in addition to regular dietary intake, could be effective when combined with exercise therapy for older adults with sarcopenia or frailty. However, it is crucial to tailor supplementation to the individual, taking into account comorbidities, particularly renal function, and other clinical factors (Narasaki et al., 2021). Future research should focus on refining dosage guidelines to maximize therapeutic benefits while ensuring safety in diverse patient populations.

The findings of this review highlight the potential of protein-based nutrition supplementation as an accessible and practical strategy for managing sarcopenia and physical frailty (Dent et al., 2019, Dent et al., 2018), offering measurable benefits in muscle mass and strength, particularly when used independently (Liu, Zhang & Li, 2023). However, the variability in outcomes and limited evidence on combined interventions underscore the need for a more nuanced understanding of how nutritional and exercise strategies can be optimized. A key limitation of this meta-analysis is the inconsistent reporting of total protein and energy intake across studies. While some trials monitored dietary intake, others did not provide this information, potentially influencing the observed effects. Future research should incorporate detailed dietary assessments to ensure that total nutrient intake is adequately accounted for. Another limitation is the exclusion of hospitalized populations, which limits the generalizability of our findings to patients experiencing secondary sarcopenia. Future studies should address this gap by investigating protein interventions in diverse clinical settings.

Additionally, mortality and hospitalization—critical clinical outcomes—were not explicitly reported or were insufficiently documented in the included RCTs, preventing their inclusion in this meta-analysis. This underscores the need for systematic reporting of these endpoints to provide a more comprehensive evaluation of protein supplementation's long-term effects. Furthermore, the limited number of included RCTs highlights the need for additional high-quality trials to strengthen the evidence base and validate findings across diverse populations.

5. Conclusions

This meta-analysis underscores the potential of protein supplementation as an effective intervention for managing sarcopenia and physical frailty, particularly in improving muscle mass and strength. However, the benefits of combining it with exercise remain uncertain, and

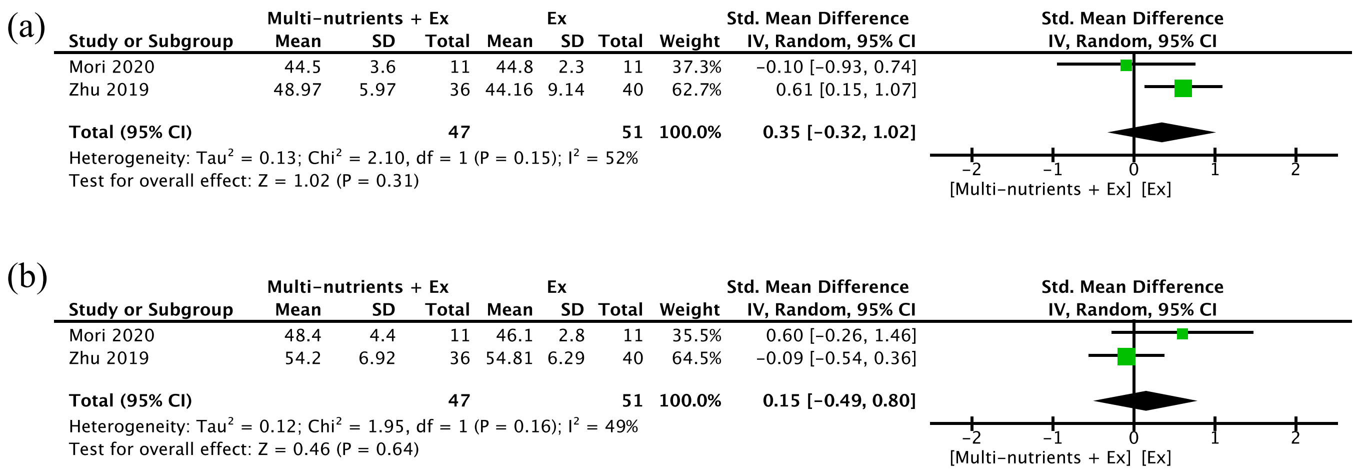

Fig. 8. Forest plot for QoL
(a) Combined intervention of protein supplements and exercise vs exercise for physical QoL
(b) Combined intervention of protein supplements and exercise vs exercise for mental QoL
Abbreviation: QoL: quality of living.

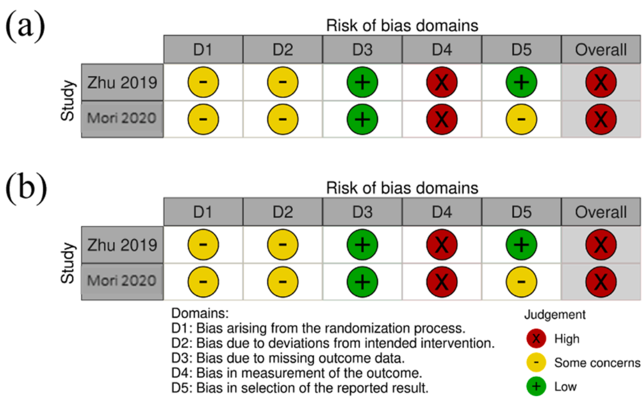

Fig. 9. Risk of Bias for QoL
(a) Combined intervention of protein supplements and exercise vs exercise for physical QoL (b) Combined intervention of protein supplements and exercise vs exercise for mental QoL
Abbreviation: QoL: quality of living.

methodological limitations in existing studies call for more rigorous research. Addressing these gaps is essential to develop evidence-based strategies that enhance the health and independence of aging populations worldwide.

CRediT authorship contribution statement

Yoshihiro Yoshimura: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Conceptualization. **Ayaka Matsumoto:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Tatsuro Inoue:** Writing – review & editing, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Masatsugu Okamura:** Writing – review & editing, Software, Formal analysis, Data curation, Conceptualization. **Masafumi Kuzuya:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.archger.2025.105783.

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