REVIEW

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Exercise for sarcopenia in older people: A systematic review and network meta-analysis

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Abstract

Background Sarcopenia is a serious public health concern among older adults worldwide. Exercise is the most common intervention for sarcopenia. This study aimed to compare the effectiveness of different exercise types for older adults with sarcopenia.

Methods Randomized controlled trials (RCTs) that examined the effectiveness of exercise interventions on patient-important outcomes for older adults with sarcopenia were eligible. We systematically searched MEDLINE, Embase and Cochrane Central Register of Controlled Trials via Ovid until 3 June 2022. We used frequentist random-effects network meta-analyses to summarize the evidence and applied the Grading of Recommendations, Assessment, Development, and Evaluations framework to rate the certainty of evidence.

Results Our search identified 5988 citations, of which 42 RCTs proved eligible with 3728 participants with sarcopenia (median age: 72.9 years, female: 73.3%) with a median follow-up of 12 weeks. We are interested in patient-important outcomes that include mortality, quality of life, muscle strength and physical function measures. High or moderate certainty evidence suggested that resistance exercise with or without nutrition and the combination of resistance exercise with aerobic and balance training were the most effective interventions for improving quality of life compared to usual care (standardized mean difference from 0.68 to 1.11). Moderate certainty evidence showed that resistance and balance exercise plus nutrition (mean difference [MD]: 4.19 kg) was the most effective for improving handgrip strength (minimally important difference [MID]: 5 kg). Resistance and balance exercise with or without nutrition (MD: 0.16 m/s, moderate) were the most effective for improving physical function measured by usual gait speed (MID: 0.1 m/s). Moderate certainty evidence showed that resistance and balance exercise (MD: 1.85 s) was intermediately effective for improving physical function measured by timed up and go test (MID: 2.1 s). High certainty evidence showed that resistance and aerobic, or resistance and balance, or resistance and aerobic exercise plus nutrition (MD from 1.72 to 2.28 s) were intermediately effective for improving physical function measured by the five-repetition chair stand test (MID: 2.3 s).

Conclusions In older adults with sarcopenia, high or moderate certainty evidence showed that resistance exercise with or without nutrition and the combination of resistance exercise with aerobic and balance training were the most effective interventions for improving quality of life. Adding nutritional interventions to exercise had a larger effect on handgrip strength than exercise alone while showing a similar effect on other physical function measures.

Keywords evidence synthesis; exercise; network meta-analysis; older adults; sarcopenia

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Introduction

In geriatric research and clinical settings, sarcopenia is a major public health issue among older adults.[1] The prevalence of sarcopenia increases with age, ranging from 5–13% in those aged 60–70 years to 11–50% in those 80 years and older.[2] A systematic review reported that the prevalence of sarcopenia varies by sex and among different settings: 12.9%, 26.3% and 29.7% for men and 11.2%, 33.7% and 23.0% for women in the community, nursing homes and hospitals, respectively.[3] According to a conservative estimate, more than 50 million people are now affected by sarcopenia, which is predicted to rise to 200 million in the next 40 years.[4] In recent years, the direct expense of sarcopenia has accounted for 1.5% of overall medical costs. Sarcopenia is associated with poor quality of life.[5,6] Older adults with sarcopenia are at a higher risk of many adverse outcomes, including falls,[7,8] fractures,[8] disability,[7] hospitalization[9] and death.[10,11]

There are no specific drugs approved to treat sarcopenia, and physical exercise is the most effective intervention for sarcopenia.[12–14] Evidence-based clinical practice guidelines usually provide strong recommendations for physical activity as a primary treatment for sarcopenia.[15] In practice, exercise is the fundamental intervention for sarcopenia, but evidence for the most effective type of exercise is conflicting.[16–20] However, exercise programmes for sarcopenia vary widely in type (resistance, aerobic, balance training or multicomponent, etc.), and the best types of exercise for this population have not been established because the effect sizes of different exercise types on patient-important outcomes are unclear.[21] For example, one systematic review proved that resistance training had positive effects on body fat mass, handgrip strength, knee extension strength, gait speed and the timed up and go (TUG) test,[22] whereas another review reported that aerobic exercise was most effective to improve muscle strength and physical performance.[23]

Network meta-analysis (NMA), also known as mixed-treatment comparison or meta-analysis of multiple treatment comparisons, provides methods to compare and rank the effect sizes of different exercise types for sarcopenia by estimating direct and indirect comparisons.[24] Although we identified two previously published NMAs,[23,25] one review reported the effects of mixed exercise interventions, without further classification of the specific type of exercise.[25] The two reviews and NMAs did not provide the overall quality of evidence.[23,25] There is one large randomized controlled trial (RCT)[26] including 1519 older adults with sarcopenia available but was not included in the two NMAs. Moreover, our team previously conducted an umbrella review of systematic reviews trying to summarize the evidence for exercise as a treatment for sarcopenia and found that the quality of existing systematic reviews was low and, crucially, did not report on quality of life or all-cause mortality.[27]

Therefore, the objective of this study was to conduct a systematic review and NMA of RCTs to compare the effect of different types of exercise on patient-important outcomes among older adults with sarcopenia. This information is critical for informing clinical practice guidelines on the optimal exercise interventions for older people living with sarcopenia.

Methods

Protocol registration

This systematic review followed the reporting guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and PRISMA 2020 and the extension statement for NMA (PRISMA-NMA)[28,29] and was registered on web PROSPERO with CRD42021278038.

Guideline panel involvement

This study supported a clinical practice guideline for the diagnosis and treatment of sarcopenia. A guideline panel composed of geriatricians, endocrinologists, kinesiologists, general internists, dietitians, cardiologists and methodologists provided critical oversight for this study. The panel reviewed the protocol, identified the population, formulated the clinical questions and selected and ranked patient-important outcomes.

Search strategy

We searched MEDLINE, Embase and Cochrane Library (Cochrane Central Register of Controlled Trials) via Ovid until 3 June 2022. We cross-checked the reference lists of the key reviews. We formed the searching strategy by combining the keywords and Medical Subject Headings (MeSH) terms, including sarcopenia, exercise, physical activity and RCTs (see details in *Appendix S1*).

Eligibility criteria

We included RCTs with parallel arms if they compared any type of exercise with any type of nutrition, placebo or usual care in older adults (age ≥60 years) with sarcopenia. We did not restrict the diagnostic assessment to a specific criterion and followed the study-reported definition of sarcopenia, including but not limited to the European Working Group on Sarcopenia in Older People (EWGSOP) and the Asian Working Group for Sarcopenia (AWGS). The criteria for sarcopenia at least include low muscle mass or low muscle strength/poor physical performance. We decided to include studies published only in English due to feasibility and most high-quality RCTs were published in English. Studies published in some Chinese journals did not provide the details of randomization, and most of these studies are likely not real RCT[30]; moreover, a systematic review[31] noted that restricted English language probably would not introduce systematic bias for treatment effect estimations in the conventional medicine field. We also excluded cross-over trials. Two reviewers independently performed the title/abstract screening and then conducted full-text manuscripts using EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA). We resolved discrepancies by discussion, if needed, by consulting a third reviewer.

Data extraction

Two researchers independently extracted the data using a standardized form, which a third researcher further checking the extracted data. We resolved disagreements by discussion and extracted the following information: (1) study characteristics (publication year, author, region and setting, sample size, diagnostic criteria and severity of sarcopenia, follow-up and treatment duration, and treatment strategy); (2) patients' characteristics (age and sex); and (3) outcome data (mean and standard deviation of results for all continuous, proportion or event rates for binary outcomes). When multiple times of follow-ups for each outcome measure were recorded in eligible studies, we used the data with the longest follow-up period. We privileged intent-to-treat (ITT) analysis results over per-protocol results. When ITT analysis was not available for most continuous outcomes, we used data from the per-protocol analysis. For missing data in reported outcome measures, we calculated the required effect size in our analysis. For example, if eligible studies had reported the mean and standard deviation before and after the intervention, we followed the formulas recommended by the Cochrane Handbook to estimate the missing absolute outcomes change (mean difference [MD]) using the baseline data and post-treatment data.[32] When we did not get all information required in the formula, we excluded this study from the outcome-specific analysis.

Outcomes

Panels judged and rated the patient-important outcomes as follows: (1) critical outcomes: all-cause mortality, quality of life, falls, any adverse events, muscle strength (handgrip strength) and physical performance (usual gait speed, TUG test and five-repetition chair stand test) and (2) important but surrogate outcomes: knee extension strength, maximal gait speed and muscle mass (appendicular skeletal muscle mass index [ASMI], skeletal muscle mass index [SMI], appendicular skeletal muscle mass [ASM], fat-free mass and fat mass, and skeletal muscle mass [SMM]). We adopted the study-reported definition for these outcomes.

Risk-of-bias assessment

Two reviewers independently assessed risk of bias, with adjudication by a third reviewer using a modified Cochrane risk-of-bias tool[33] for assessing risk of bias in randomized trials, which includes random-sequence generation, allocation concealment, blinding, missing outcome data and selective reporting of outcomes. Each domain was answered with 'definitely yes' (low risk of bias), 'probably yes', 'probably no' or 'definitely no' (high risk of bias). The major reason to choose the modified version of the Cochrane risk-of-bias tool is that existing instruments frequently include items that do not address the risk of bias.[34] We judged an overall high risk of bias if any domain had a high risk of bias.

Data analysis

This study performed a frequentist NMA with a graph-theoretical method by R package *netmeta*. If eligible studies reported outcomes (quality of life and knee extension strength) measured by different scales or instruments/units, we used standardized MD (SMD) to pool the improvement following the intervention. For other outcomes, we can get the effect size with the same unit; we used MD to pool the effects of the interventions. The treatment effect heterogeneity was defined by the generalized methods of moments estimate of variance. We used forest plots and league tables to display the network estimations and P score to rank the interventions. Cochran's Q was used to assess the global and local statistical heterogeneity. To examine network loop structure and assess inconsistency, we used the node-splitting method. We assessed the potential incoherence by calculating the ratio or difference of direct and indirect estimates and corresponding 95% confidence intervals (CIs) as well as the P value for the inconsistency. We also evaluated whether there is a clinically important difference between direct and indirect estimates by comparing the overlap of the point and interval estimates. We used the comparison-adjusted funnel plot and Begger and Egger's test to detect publication bias.

We also conducted six subgroup analyses, including (1) sex (female and male; large effect in female group), (2) setting (hospital and community; large effect in hospital group), (3) co-obesity or not (obesity and non-obesity; large effect in obesity group), (4) duration (intervention over 6 months and within 6 months; large effect in over 6 months group), (5) nutrition (antioxidants vs. amino acid supplements vs. protein supplements vs. comprehensive nutrition; large effect in comprehensive nutrition group) and (6) diagnosis criteria for sarcopenia (AWGS, EWGSOP or other criteria; large effect in AWGS or EWGSOP criteria). If there was a positive result, we used Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN)[35] to assess the credibility of the subgroup effect.

To assess whether the study's effect was important for the patients, we used the minimally important difference (MID) for important sarcopenia outcomes. The MID for grip strength, usual walking speed, five-repetition chair stand test and TUG test was 5.0 kg (grip strength),[36] 0.10 m/s (usual walking speed),[37] 2.3 s (chair stand test)[38] and 2.1 s (TUG test),[39] respectively.

Assessment of evidence certainty

We followed the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) method to rate the certainty of the evidence for direct, indirect and network estimates as high, moderate, low and very low certainty. Seven issues were considered for rating down the certainty, including the risk of bias, inconsistency, indirectness, publication bias, intransitivity, incoherence and imprecision.[40,41]

This study adopted the minimally contextualized framework to rate the imprecision and draw conclusions from an NMA.[42–44] We used the null effect as the decision threshold and usual care as the reference group. The interventions were categorized into three groups: among the most effective, intermediately effective and among the least effective, as well as the high/moderate certainty and low/very low certainty groups.[42]

Role of the funding source

The funder of this study had no role in the study's design, data collection, data analysis, data interpretation, report writing or decision to submit for publication.

Results

Description of included studies

We identified 5988 records for initial screening and 120 records for full-text screening. Of them, 42 RCTs that included 3728 older adults proved eligible (*Figure 1*). The median age was 72.9 (inter-quartile range [IQR]: 69–79.5) years, median female proportion was 73.3% (50–100%), median length of follow-up was 12 (12–16) weeks and duration of treatment in the trials ranged from 8 to 144 weeks (*Appendix S3*). Nine studies (20.9%) had a high risk of bias downrated by

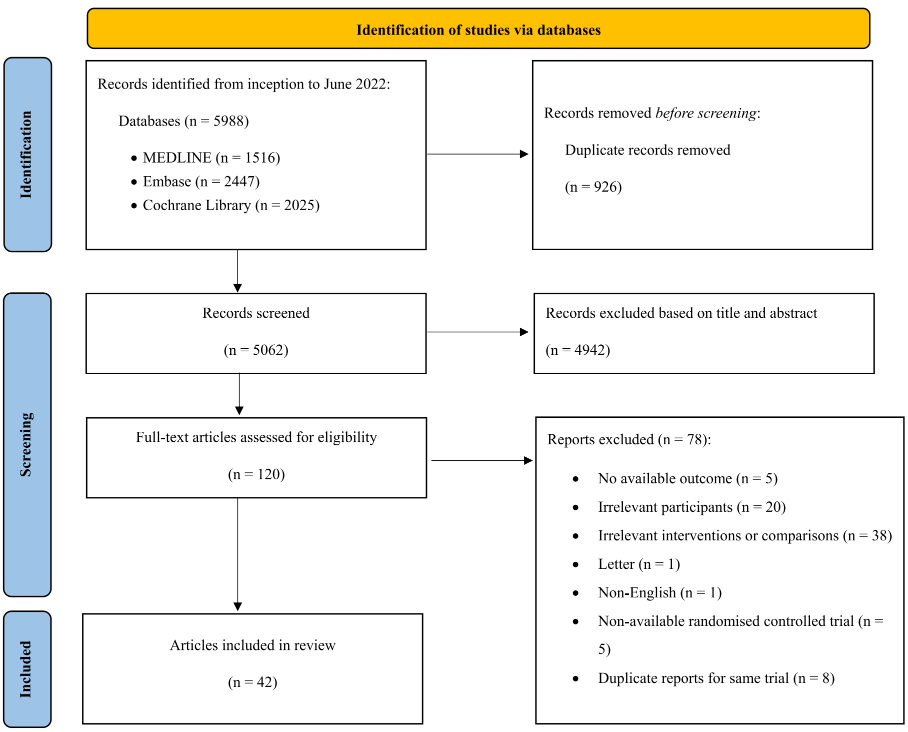

Figure 1 Flow chart.

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allocation concealment or missing outcome (*Appendix S4*). *Appendices S5.5* and *S6.1* show the heterogeneity and inconsistency of the NMA.

Figure 2 shows the network for quality of life and handgrip strength in the available trials. All other network plots are in *Appendix S5.1*. *Figure 3* shows the league table for quality of

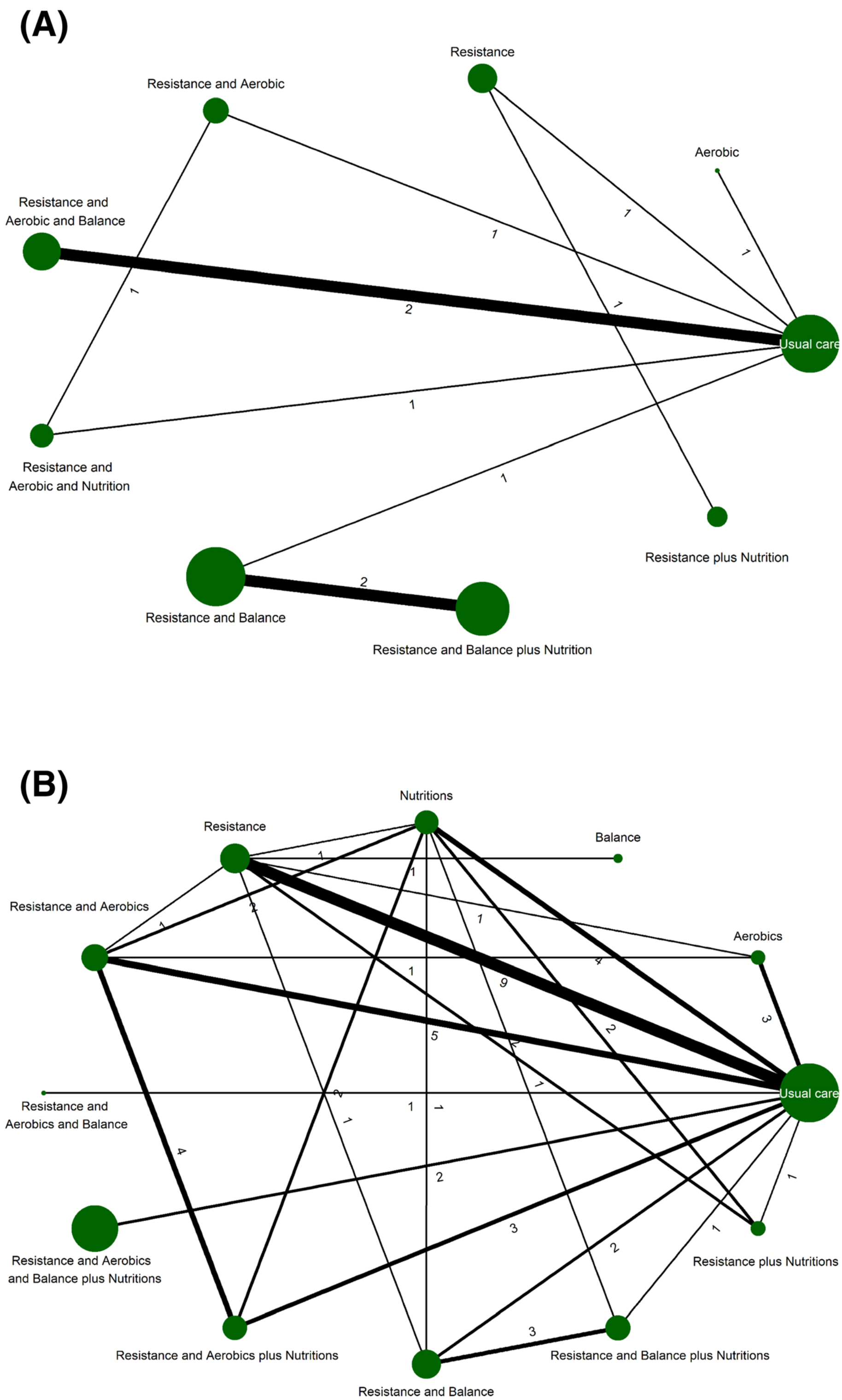

Figure 2 Network plots of (A) quality of life and (B) handgrip strength.

High | Moderate | Low | Very low

Aerobic								
-0.52 (-1.39, 0.34)	Resistance							
0.65 (-0.14, 1.44)	**1.18 (0.45,1.90)**	Resistance and Aerobic						
-0.10 (-0.84, 0.65)	0.43 (-0.25, 1.10)	**-0.75 (-1.32, -0.18)**	Resistance and Aerobic and Balance					
0.47 (-0.33, 1.26)	**0.99 (0.26, 1.72)**	-0.19 (-0.64, 0.26)	0.56 (-0.02, 1.14)	Resistance and Aerobic plus Nutrition				
0.57 (-0.29, 1.43)	**1.09 (0.29, 1.89)**	-0.08 (-0.81, 0.64)	0.67 (0.00, 1.34)	0.10 (-0.63, 0.83)	Resistance and Balance			
0.23 (-0.67, 1.12)	0.75 (-0.09, 1.59)	-0.43 (-1.19, 0.34)	0.32 (-0.39, 1.04)	-0.24 (-1.01, 0.53)	**-0.34 (-0.59, -0.10)**	Resistance and Balance plus Nutrition		
-0.48 (-1.54, 0.58)	0.04 (-0.58, 0.66)	**-1.13 (-2.09, -0.18)**	-0.39 (-1.30, 0.53)	-0.95 (-1.90, 0.01)	**-1.05 (-2.06, -0.04)**	-0.71 (-1.75, 0.33)	Resistance plus Nutrition	
0.58 (-0.06, 1.23)	**1.11 (0.54, 1.68)**	-0.07 (-0.52, 0.38)	**0.68 (0.32, 1.04)**	0.12 (-0.34, 0.58)	0.02 (-0.55, 0.58)	0.36 (-0.26, 0.98)	**1.07 (0.23, 1.91)**	Usual care

Figure 3 League tables of quality of life. The league tables show the absolute effects of each intervention and usual care (the column's treatment vs. the row's treatment). The absolute effects are measured as a standardized mean difference for outcomes along with 95% confidence intervals. Bold indicates statistical significance. The colour of each cell indicates the certainty of evidence according to the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE). All tables list the treatments in alphabetical order.

life. *Appendix S5.3* shows the league tables for the network estimates of all other comparisons. *Table 1* shows the summary of findings. *Figure 4* presents the categorization of interventions from among the best to among the worst—when compared with usual care and the certainty of the evidence on main outcomes; other outcomes are in *Appendix S5.7*. We presented the results of the subgroup analyses in *Appendix S7* and the certainty of evidence for direct, indirect and network estimates in *Appendix S6.1*.

All-cause mortality

One study[26] published in the BMJ in 2022 reported that death occurred in 31 of the 605 (5.1%) participants in intervention group (moderate-intensity exercise including aerobic, resistance and balance exercise plus nutrition) and 25 of the 600 (4.2%) participants in the lifestyle education control group (risk ratio [RR]: 1.23, 95% CI: 0.74 to 2.06).

Quality of life

Nine trials, including 694 patients, reported on quality of life. Eligible studies used the following scales to assess quality of life: Euro quality of life, Japanese version of the Euro quality of life, Euro quality-of-life questionnaire five-dimensional classification, sarcopenia quality-of-life questionnaire, short form-12 physical questionnaire and short form-36 physical component summary. Overall, exercise with nutrition (SMD: 0.60, 95% CI: 0.17 to 1.03) or without nutrition (SMD: 0.44, 95% CI: 0.13 to 0.75) is effective for improving quality of life compared to intervention without exercise (*Appendix S5.4*). Resistance exercise with or without nutrition and the combination of resistance and aerobic and balance exercise are the most effective interventions for improving the quality of life compared to usual care (e.g., resistance exercise alone vs. usual care: SMD: 1.11, 95% CI: 0.54 to 1.68, high certainty; details in *Figures 3* and *4*).

Muscle strength: handgrip strength

Twenty-seven trials, including 2883 patients, reported on handgrip strength. Moderate certainty evidence showed that resistance exercise alone (MD: 2.69 kg, 95% CI: 1.78 to 3.61) and the combination of resistance and aerobic exercise with nutrition (MD: 3.02 kg, 95% CI: 1.64 to 4.4) are the most effective interventions for improving handgrip strength. Nutrition added to exercise shows larger effect sizes than exercise alone. The effect sizes of nutrition added to resistance exercise alone (MD: 3.93 kg, 95% CI: 2.22 to 5.65, high certainty) or the combination of resistance and balance exercise (MD: 4.19 kg, 95% CI: 2.55 to 5.83, moderate) may exceed the pre-set MID threshold for handgrip strength (*Figure 4* and *Appendix S5.3*).

Table 1 Summary of findings to illustrate absolute effects based on outcomes of exercise compared with usual care

1.1. All-cause mortality

Intervention	Subgroup (sex)	Relative effects (risk ratio; 95% CI)	Time frames	Anticipated absolute effect (95% CI) Without intervention[a]	With intervention	Risk differences (95% CI)	Certainty of evidence	Reason for rating down/up
Resistance and aerobic and balance plus nutrition	Female	1.23 (0.74 to 2.06)	3-year	85 per 1000 patients	105 per 1000 patients (63 to 175)	20 more per 1000 patients (22 fewer to 90 more)	Moderate	Rating down due to imprecision
(1 RCT; 1205 participants)	Male	1.23 (0.74 to 2.06)	3-year	223 per 1000 patients	274 per 1000 patients (165 to 459)	51 fewer per 1000 patients (58 fewer to 236 more)	Moderate	Rating down due to imprecision

1.2. Quality of life

Interventions		Estimated risk or estimated score/value with placebo	Certainty of evidence
Resistance	Resistance (1 RCT; 56 participants)	The quality-of-life score in the intervention group was on average 1.11 SDs (0.54 to 1.68) higher than in the usual-care group.	High
	Resistance plus nutrition (indirect estimation)	The quality-of-life score in the intervention group was on average 1.07 SDs (0.23 to 1.91) higher than in the usual-care group.	High
Resistance and balance	Resistance and balance (1 RCT; 54 participants)	The quality-of-life score in the intervention group was on average 0.02 SDs (−0.55 to 0.58) higher than in the usual-care group.	Moderate
	Resistance and balance plus nutrition (indirect estimation)	The quality-of-life score in the intervention group was on average 0.36 SDs (−0.26 to 0.98) higher than in the usual-care group.	Low
Resistance and aerobic	Resistance and aerobic (1 RCT; 77 participants)	The quality-of-life score in the intervention group was on average −0.07 SDs (−0.52 to 0.38) higher than in the usual-care group.	Moderate
	Resistance and aerobic plus nutrition (1 RCT; 73 participants)	The quality-of-life score in the intervention group was on average 0.12 SDs (−0.34 to 0.58) higher than in the usual-care group.	Moderate
Resistance and aerobic and balance	Resistance and aerobic and balance (2 RCTs; 130 participants)	The quality-of-life score in the intervention group was on average 0.68 SDs (0.32 to 1.04) higher than in the usual-care group.	Moderate
Aerobic	Aerobic (1 RCT; 38 participants)	The quality-of-life score in the intervention group was on average 0.58 SDs (−0.06 to 1.23) higher than in the usual-care group.	Moderate

1.3. Muscle function

Outcomes	Interventions		Usual care (MD)	Adding intervention (MD)	Intervention vs. usual care (MD)	Certainty of evidence
Handgrip strength	Resistance	Resistance (9 RCTs; 308 participants)	0.55 lower	2.14 higher	2.69 higher (1.78 higher to 3.61 higher)	Moderate
		Resistance plus nutrition (1 RCT; 17 participants)	0.55 lower	3.38 higher	3.93 higher (2.22 higher to 5.65 higher)	High
	Resistance and balance	Resistance and balance (2 RCTs; 118 participants)	0.55 lower	0.68 higher	1.23 higher (0.16 lower to 2.62 higher)	Low
		Resistance and balance plus nutrition (1 RCT; 64 participants)	0.55 lower	3.64 higher	4.19 higher (2.55 higher to 5.83 higher)	Moderate
	Resistance and aerobic	Resistance and aerobic (5 RCTs; 347 participants)	0.55 lower	1.39 higher	1.94 higher (0.79 higher to 3.08 higher)	Low
		Resistance and aerobic plus nutrition (3 RCTs; 277 participants)	0.55 lower	2.47 higher	3.02 higher (1.64 higher to 4.4 higher)	Moderate
	Resistance and aerobic and balance	Resistance and aerobic and balance (2 RCTs; 1205 participants)	0.55 lower	0.35 lower	0.2 higher (3.5 lower to 3.9 higher)	Low

(*Continues*)

Table 1 (continued)

1.3. Muscle function

Outcomes	Interventions		Usual care (MD)	Adding intervention (MD)	Intervention vs. usual care (MD)	Certainty of evidence
		Resistance and aerobic and balance plus nutrition (2 RCTs; 1205 participants)	0.55 lower	0.75 higher	1.3 higher (0.14 lower to 2.73 higher)	Moderate
	Aerobic	Aerobic (3 RCTs; 224 participants)	0.55 lower	0.09 lower	0.46 higher (1.13 lower to 2.04 higher)	Low
	Balance	Balance (indirect estimation)	0.55 lower	0.17 lower	0.38 higher (2.32 lower to 3.09 higher)	Low
Usual gait speed	Resistance	Resistance (6 RCTs; 220 participants)	0	0.11 higher	0.11 higher (0.04 higher to 0.18 higher)	Moderate
		Resistance plus nutrition (indirect estimation)	0	0.13 higher	0.13 higher (0.01 higher to 0.25 higher)	Moderate
	Resistance and balance	Resistance and balance (3 RCTs; 196 participants)	0	0.16 higher	0.16 higher (0.08 higher to 0.24 higher)	Moderate
		Resistance and balance plus nutrition (2 RCTs; 141 participants)	0	0.16 higher	0.16 higher (0.06 higher to 0.26 higher)	Moderate
	Resistance and aerobic	Resistance and aerobic (2 RCTs; 147 participants)	0	0.1 higher	0.1 higher (0.01 lower to 0.22 higher)	Moderate
		Resistance and aerobic plus nutrition (2 RCTs; 143 participants)	0	0.06 higher	0.06 higher (0.06 lower to 0.18 higher)	Moderate
	Resistance and aerobic and balance	Resistance and aerobic and balance (1 RCT; 40 participants)	0	0.04 higher	0.04 higher (0.14 lower to 0.22 higher)	Low
Timed up and go test	Resistance	Resistance (6 RCTs; 246 participants)	0.07 higher	0.9 higher	0.83 lower (1.68 lower to 0.02 higher)	Very low
		Resistance plus nutrition (1 RCT; 31 participants)	0.07 higher	0.84 higher	0.77 lower (2.16 lower to 0.63 higher)	Moderate
	Resistance and balance	Resistance and balance (2 RCTs; 118 participants)	0.07 higher	1.92 higher	1.85 lower (0.49 lower to 3.22 lower)	Moderate
		Resistance and balance plus nutrition (1 RCT; 64 participants)	0.07 higher	1.61 higher	1.54 lower (3.33 lower to 0.25 higher)	Moderate
	Resistance and aerobic and balance	Resistance and aerobic and balance (1 RCT; 90 participants)	0.07 higher	1.77 higher	1.7 lower (3.99 lower to 0.59 higher)	Low
Five-repetition chair stand test	Resistance	Resistance (1 RCT; 16 participants)	0.78 lower	0.47 higher	0.4 lower (2.21 lower to 1.41 higher)	Moderate
		Resistance plus nutrition (1 RCT; 17 participants)	0.78 lower	0.82 higher	0.75 lower (2.58 lower to 1.07 higher)	Low
	Resistance and balance	Resistance and balance (1 RCT; 54 participants)	0.78 lower	1.86 higher	1.79 lower (0.6 lower to 2.97 lower)	High
	Resistance and aerobic	Resistance and aerobic (1 RCT; 77 participants)	0.78 lower	1.79 higher	1.72 lower (0.27 lower to 3.17 lower)	High
		Resistance and aerobic plus nutrition (1 RCT; 76 participants)	0.78 lower	2.35 higher	2.28 lower (0.83 lower to 3.73 lower)	High

Abbreviations: CI, confidence interval; MD, mean difference; RCT, randomized controlled trial; SDs, standard deviation units.
[a]The baseline risks were derived from a large national cohort study (Akihiko Kitamura, Journal of Cachexia, Sarcopenia and Muscle 2021; 12: 30–38).

Physical performance

Seventeen trials, including 1151 patients, reported on usual gait speed. Adding nutrition to exercise showed similar effect sizes to exercise alone on physical performance measures. Moderate certainty evidence showed that resistance and balance exercise with or without nutrition are the most effective interventions for improving physical function measured by usual gait speed. Their effect size (MD: 0.16 m/s, 95% CI: 0.06 to 0.26) probably exceeds the MID threshold (0.1 m/s). Resistance exercise with or without nutrition are the intermediately effective interventions for improving usual gait speed, and their effect size (MD: ~0.10 m/s, 95% CI: 0.01 to 0.25) probably exceeds the pre-set MID threshold (0.10 m/s) with moderate certainty evidence.

Eleven trials, including 636 patients, reported on TUG test. Moderate certainty evidence showed that resistance and balance exercise is the intermediately effective intervention for

Categories	Outcomes	
	High/Moderate Certainty Evidence	Low/Very low Certainty Evidence
Among the most effective	More effective than at least one intervention in intermediately effective	Might be superior to at least one intervention in intermediately effective
Intermediately effective	Inferior to the most effective or superior than the least effective	Might be inferior to the most effective or superior than the least effective
Among the least effective	Not convincingly different than usual care	Might be similar to usual care.

Intervention		**Quality of life**	**Muscle strength**	**Physical performance**		
		Quality of life (scale, SMD, 95% CI)	**Handgrip strength (MD, 95% CI)**	**Usual gait speed (MD, 95% CI)**	**Timed up and go (MD, 95% CI)**	**Chair stand test (MD, 95% CI)**
Resistance	Resistance	**1.11 (0.54 to 1.68)**	**2.69 (1.78 to 3.61)**	**0.11 (0.04 to 0.18)**	-0.83 (-1.68 to 0.02)	-0.4 (-2.21 to 1.41)
	Resistance plus Nutrition	**1.07 (0.23 to 1.91)**	**3.93 (2.22 to 5.65)**	**0.13 (0.01 to 0.25)**	-0.77 (-2.16 to 0.63)	-0.75 (-2.58 to 1.07)
Resistance and Balance	Resistance and Balance	0.02 (-0.55 to 0.58)	1.23 (-0.16 to 2.62)	**0.16 (0.08 to 0.24)**	**-1.85 (-3.22 to -0.49)**	**-1.79 (-2.97 to -0.6)**
	Resistance and Balance plus Nutrition	0.36 (-0.26 to 0.98)	**4.19 (2.55 to 5.83)**	**0.16 (0.06 to 0.26)**	-1.54 (-3.33 to 0.25)	
Resistance and Aerobic	Resistance and Aerobic	-0.07 (-0.52 to 0.38)	**1.94 (0.79 to 3.08)**	0.1 (-0.01 to 0.22)		**-1.72 (-3.17 to -0.27)**
	Resistance and Aerobic plus Nutrition	0.12 (-0.34 to 0.58)	**3.02 (1.64 to 4.4)**	0.06 (-0.06 to 0.18)		**-2.28 (-3.73 to -0.83)**
Resistance and Aerobic and Balance	Resistance and Aerobic and Balance	**0.68 (0.32 to 1.04)**	0.2 (-3.5 to 3.9)	0.04 (-0.14 to 0.22)	-1.7 (-3.99 to 0.59)	
	Resistance and Aerobic and Balance plus Nutrition		1.3 (-0.14 to 2.73)			
Aerobic	Aerobic	0.58 (-0.06 to 1.23)	0.46 (-1.13 to 2.04)			
Balance	Balance		0.38 (-2.32 to 3.09)			

Figure 4 Summary of effects of interventions on critical outcomes. We categorized the interventions and rated the certainty of outcomes by whether the intervention was better or worse than usual care and some other interventions (the 95% confidence interval [CI] not crossing null effect). The best, intermediate and worst categories show the effect for each intervention, whereas the certainty of evidence shows whether the effect is trustworthy or not. Bold text represents statistical significance. MD, mean difference; SMD, standardized mean difference.

improving physical function measured by TUG test (MD: −1.85 s, 95% CI: −3.22 to −0.49), and the CIs of the effect size crossed the MID threshold (2.1 s).

Four trials, including 227 patients, reported on five-repetition chair stand test. High certainty evidence showed that resistance exercise combined with balance or aerobic training are the intermediately effective interventions for improving physical performance measured by the chair stand test. The 95% CIs of these effect sizes (MD: around −1.70 s for exercise alone and −2.28 s for adding nutrition to resistance and aerobic exercise) cross the pre-set MID threshold (2.3 s) (*Figure 4* and *Appendix S5.3*).

Any adverse events

Seventeen studies reported no adverse events associated with the intervention. Falls were recorded in 80 of the 605 (13.2%) participants in the multicomponent intervention group and 49 of the 600 (8.2%) participants in the lifestyle education group (RR: 1.62, 95% CI: 1.16 to 2.27).[26] One study[45] reported no fall associated with intervention. A study published in the BMJ[26] in 2022 reported that 337 of the 605 (55.7%) participants in the intervention group and 297 of the 600 (49.5%) participants in the lifestyle education group experienced at least one adverse event (including any adverse event defined by the trial) during the trial (RR: 1.13, 95% CI: 1.01 to 1.25).

See *Appendix S5.7* for other outcomes.

Subgroup analyses

We used meta-regression to examine the effects of subgroups and did not identify any subgroup effects except for settings and sex for some outcomes (*Appendix S7.1*). Resistance and balance exercise plus nutrition had a larger effect on handgrip strength in hospitalized patients than in community-dwelling older adults (MD: 9.24 kg, 95% CI: 3.85 to 14.25 for hospitalized patients; MD: 1.71 kg, 95% CI: −1.41 to 4.83 for community-dwelling older adults; coefficients: 7.53, 95% CI: 1.34 to 13.53) (*Appendix S7.2*). Resistance exercise plus nutrition had a larger effect on usual gait speed among males than females (MD: 0.74 m/s, 95% CI: 0.23 to 1.25 vs. MD: 0.09 m/s, 95% CI: −0.15 to 0.3, respectively; coefficients: 0.66, 95% CI: 0.06 to 1.24) (*Appendix S7.2*). However, we rated the credibility of the subgroup effects of setting and sex as low credibility.

Discussion

Principal findings

This systematic review and NMA is the most thorough examination of currently available evidence on exercise interventions in sarcopenic older adults. We analysed direct and indirect comparisons from 42 RCTs that compared multiple exercise intervention arms in ~3728 older people with sarcopenia. We found that adding nutritional interventions to exercise had little effect on quality of life and physical performance (such as usual gait speed, TUG test and the chair stand test). Still, adding nutritional interventions improved handgrip strength compared to exercise alone in terms of both quality of evidence and effect size. With respect to the optimal type of exercise, resistance exercise alone has the largest effect on quality of life; however, it is better to add balance or aerobic training to resistance exercise to improve other physical function measures.

Strengths and limitations

In this review, we conducted a broad search that included the most comprehensive synthesis of evidence to date on exercise for older adults with sarcopenia. A nationwide multidisciplinary guideline panel contributed to formulating the review questions, subgroup analyses and identifying patient-important outcomes. This review included a considerable sample size of older adults with sarcopenia. We used the GRADE framework to assess the overall quality of evidence and presented our main findings according to GRADE guidance for NMA.[42,46]

The major limitations of this review are the limited currently available evidence on all-cause mortality and the inconsistency in the definition of adverse events across trials. Although we included a considerable sample size of older adults with sarcopenia, only a few eligible studies were included in the analyses for some specific interventions and outcomes. For example, although nine studies in total reported quality of life, only one study provided direct comparisons for almost every intervention. Four studies in total reported chair stand test, and only one study provided direct comparisons of each intervention. In this review, we found 42 eligible studies with 3728 participants, but we did not further explore grey literature and contact experts to review the search strategy, which is one of the limitations of this review. When interpreting the results, we should consider the heterogeneity in participants across eligible studies that include various diagnostic criteria for sarcopenia and some participants also with osteoporosis or receiving dialysis as comorbidity. In addition, we used a modified Cochrane risk-of-bias tool to assess the risk of bias, which was not formally validated. A number of credible alternatives are available for assessing risk of bias. For many years, Cochrane RoB 1.0 was widely used. It does, however, have an important limitation: The 'unclear' option was widely used and is uninformative. As it turns out, information is usually available that demonstrates that, for blinding, reviewers can make accurate inferences even when authors' statements regarding blinding are not completely explicit.[47] Thus, response options that include 'probably yes' and 'probably no' are desirable and are included in the revised RoB 1.0 we used in our study. Cochrane RoB 2 recognized this issue and includes the 'probably yes' and 'probably no' options. The revised Cochrane RoB 2 has demonstrated low interrater reliability, challenges in its application and no demonstration that it improves the validity of risk-of-bias assessment beyond RoB 1.0. For these reasons, we chose the revised RoB 1.0 to address risk of bias in our study.

Comparison with other studies

Recently, there are two other systematic reviews with NMAs on interventions for sarcopenia published in 2021[25] and 2022.[23] Wu et al. reported that a comprehensive exercise intervention has beneficial effects on muscle strength (handgrip strength) and physical performance (dynamic balance).[25] This study was limited to only including participants over the age of 65, which yielded 26 eligible studies with 2561 participants. In their review, the definition of sarcopenia was based on only one criterion (only muscle mass, only muscle strength, muscle mass and muscle strength, or physical performance). Furthermore, this study used a broader classification of interventions, which makes it difficult to draw conclusions about specific exercise types; comprehensive exercise included whole-body vibration, resistance exercise, mixed exercise and other types of exercise, with substantial clinical heterogeneity. In the review by Negm et al.,[23] aerobic exercise was the most effective intervention to improve muscle strength and physical performance, and resistance combined with aerobic exercise were suggested as the most effective intervention for improving muscle mass, muscle strength and physical performance, which yield different conclusions with our review. Our review only included studies with older adults. In contrast, the review conducted by Negm et al.[23] also did not restrict their population to older people with some participants aged $<$55, which may be one of the reasons for the discrepancies in results of the two reviews.

In addition, the clinical practice guideline published by Dent et al.[15] recommended that prescribed exercise with resistance-based training improved muscle strength, skeletal muscle mass and physical function (grade: strong recommendation, moderate certainty of evidence). However, most of the evidence behind this recommendation comes from two background meta-analyses published in 2014[18] and 2017,[16] which included relatively few RCT studies. Our study, with expanded sample size, found that both resistance exercise and resistance plus nutrition were the most effective intervention for improving quality of life and handgrip strength and the intermediately effective intervention for usual gait speed with effect sizes that may exceed the MID threshold. Further, we found that adding balance training to resistance exercise is the most effective method for improving most physical function measures, such as usual gait speed, TUG test and chair stand test. The finding is consistent with single RCTs. For example, Liang et al.[45] conducted an RCT of patients with sarcopenia aged 80–99 years and confirmed that balance exercise plus resistance exercise significantly improved usual gait speed, handgrip strength and short physical performance battery (SPPB) scores compared to resistance exercise alone. Runge et al.[48] explored the effects of a balance training programme alone compared to a strength training programme. The results showed that balance training was more effective in increasing muscle strength as well as achieving muscular equalization, which may partially explain why adding balance training to resistance exercise seems more favourable than resistance alone.

Muscle mass decreases with age, and strength and power decrease as well. After age 30, the rate of mass muscle decline is ~3–8% per decade, and it is even more rapid after age 60.[49,50] Muscle loss, strength loss and function loss in older people are fundamental causes of disability. A large, randomized trial[26] demonstrated that a multicomponent intervention (exercise and nutritional counselling) could reduce the incidence of mobility disability for people aged 70 years or older with frailty and sarcopenia. Participants in the multicomponent intervention arm also experienced handgrip strength or muscle mass reductions over 36 months of follow-up. These results indicate that multicomponent interventions may not be able to compensate for the loss of muscle and function that occurs over years in older adults. Early targeted interventions (such as resistance exercise alone or combined with balance or aerobic exercise) may be necessary for mitigating later-life muscle and functional loss among older adults.

Conclusion

In conclusion, high or moderate certainty evidence shows that resistance exercise with or without nutritional intervention and the combination of resistance and balance or aerobic exercise are the most effective interventions for improving quality of life in older adults with sarcopenia. Adding nutritional interventions to exercise had a larger effect on handgrip strength than exercise alone while showing a similar effect on other physical function measures to exercise alone. Moderate certainty evidence showed that adding balance training to resistance exercise was the most effective intervention for improving physical function measures. These findings can be used to guide the optimal exercise prescription for improving patient-important outcomes among older adults with sarcopenia.

Conflict of interest statement

The authors declare no conflicts of interest.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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