Review

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Association between sarcopenia with incident cardio-cerebrovascular disease: A systematic review and meta-analysis

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SUMMARY Sarcopenia is an age-associated skeletal muscle disease characterized by the progressive loss of muscle mass and function. The objective of this systematic review and meta-analysis was to evaluate the associations between sarcopenia and cardio-cerebrovascular disease (CCVD). A comprehensive search of the PubMed/Medline, Embase, Web of Science, Scopus, and Cochrane Library databases was conducted from their inception to April 1st, 2023. A total of eight cross-sectional studies involving 63,738,162 participants met the inclusion criteria. Pooled estimates of odds ratios (ORs) were calculated using random-effects models. The findings demonstrated a significant association between sarcopenia and an increased risk of CCVD (OR: 1.33, 95% CI: 1.18 - 1.50, I^2 = 1%; $p < 0.001$). Subgroup analyses indicated that sarcopenia was associated with a 1.67-fold increase in the risk of stroke and a 1.31-fold increase in the risk of CVD. Four studies included in this review examined the association between sarcopenic obesity and the risk of CCVD, and the results revealed that sarcopenic obesity was associated with a higher risk of CCVD (OR: 1.64, 95% CI: 1.08 - 2.49, I^2 = 69%; $p < 0.001$). Meta-regressions and sensitivity analyses consistently supported the robustness of the overall findings. In conclusion, sarcopenia and sarcopenic obesity are significantly associated with an elevated risk of developing CCVD. However, further prospective cohort studies are warranted to validate this relationship while controlling for confounding factors.

Keywords Sarcopenia; cardio-cerebrovascular disease risk; meta-analysis.

1. Introduction

Sarcopenia is an age-associated skeletal muscle disease characterized by the progressive loss of muscle mass and function. It has been consistently linked to adverse functional and health outcomes, including frailty, falls, nutritional deficiencies, and increased mortality rates (*1*). The prevalence of sarcopenia is heavily influenced by the criteria used for its definition and the measurement tools employed to assess its markers. Different definitions yield varying prevalence rates, providing us with a range of estimates. For instance, the European Working Group on Sarcopenia in Older People criterion suggests a prevalence of around 5%, while the International Working Group on Sarcopenia criteria indicate a higher estimate of about 17%. However, even within these definitions, the prevalence values can vary significantly based on the specific tools utilized to evaluate muscle mass, strength, and physical performance. To illustrate this, the prevalence values can range from as low as 1% to as high as 7% for muscle mass, 1% to 12% for strength, and even span from 0% to 22% for physical performance, respectively (*1*). Among specific populations, the prevalence of sarcopenia is reported to be between 4% and 33% in long-term care settings (*2*) and approximately 14.7% in hospitalized elderly patients (*3*). Moreover, the prevalence of sarcopenia varies across different regions. In Oceania, for example, the reported prevalence ranges from 1% to 40%. In South America, it ranges from 13% to 35%, while in Europe, the prevalence is around 1%. Importantly, sarcopenia frequently coexists with other medical conditions, such as cardiovascular disease (31.4% prevalence) (*4*), chronic obstructive pulmonary disease (COPD) patients (27.5% prevalence) (*5*), heart failure patients (34% prevalence) (*6*), stroke patients (42% prevalence) (*7*), and diabetes (18% prevalence) (*8*). These high rates of comorbidity emphasize the clinical significance of sarcopenia in various disease contexts.

The increasing global aging population and the high

prevalence of sarcopenia have positioned sarcopenia as a focal point of interest within geriatric research and clinical practice. Various sociodemographic, lifestyle, and behavioral factors have been found to be significantly associated with sarcopenia among older adults. These factors include age, marital status, disability in activities of daily living, underweight status, smoking, physical inactivity, risk of malnutrition, sleep duration (either long or short), living alone, presence of diabetes, cognitive impairment, heart diseases, respiratory diseases, osteoporosis, osteoarthritis, depression, history of falls, anorexia, and anemia (*9*). These associations highlight the multifactorial nature of sarcopenia and underscore the need for comprehensive assessment and management strategies in addressing this condition.

Except for the well-established increased risks of frailty, falls, nutritional status, and mortality, emerging evidence suggests that sarcopenia may also contribute to an elevated risk of cardio-cerebrovascular disease (CCVD). CCVD, recognized as the leading global cause of mortality, arises from a complex interplay of various factors (*11*). Investigating the associations between sarcopenia and CCVD, particularly in the elderly population, holds significant relevance. To address this knowledge gap, we conducted a rigorous systematic review, meta-analysis, and synthesis of available published research. This study aims to provide an insightful overview of the association between sarcopenia and CCVD, enabling a better understanding of this important clinical relationship.

2. Materials and Methods

This systematic review and meta-analysis were performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines (*12*). The study protocol was registered in the International Prospective Register of Systematic Reviews Database (PROSPERO) under the registration number CRD42023426047.

2.1. Inclusion and exclusion criteria

The inclusion criteria for this study were as follows: (1) observational studies, including case-control studies, cohort studies, and cross-sectional studies; (2) studies investigating the relationship between sarcopenia and the risk of CCVD (cardiovascular disease (CVD) and stroke); (3) studies reporting the association between sarcopenia and CCVD using measures such as odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) with corresponding 95% confidence intervals (CIs); (4) original articles published in the English language. Exclusion criteria encompassed: 1) nonhuman studies; 2) clinical trials or experimental studies; 3) studies that did not present primary data analyses (*e.g.*, letters, editorials, or narrative reviews); and 4) studies lacking clear methods for data extraction, including ORs, RRs, or HRs.

2.2. Literature search and selection

All records identified in the initial search underwent an independent screening for relevance by two reviewers (Fang M and Liu CH), starting from the titles, abstracts, and full texts. Disagreements were arbitrated by a third reviewer (Guo L). Relevant literature was systematically searched in multiple literature databases, including PubMed/Medline, Embase, Web of Science, Scopus, and the Cochrane Library, from inception to April 1st, 2023. The search terms employed a combination of free-text terms and controlled vocabulary pertaining to sarcopenia and CCVD. The complete search strategy is available in Table S1 (*http://www.biosciencetrends.com/action/getSupplementalData.php?ID=149*).

Following the removal of duplicates, two researchers (Liu Y and Tang G) independently reviewed the titles of the remaining studies. After further elimination of irrelevant articles, they proceeded to evaluate the abstracts of the remaining studies. Subsequently, they assessed the full texts of the remaining studies, excluding those that did not meet the inclusion criteria. Disagreements were resolved through consensus. The same authors conducted the full-text screening to determine the final selection.

2.3. Data extraction

Two independent researchers (Fang M and Liu CH) utilized a standardized form to extract data from the included studies (an example of the data extraction form is provided in the supplementary materials, Table S2, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=149*). The following data points were extracted: (1) first author's name; (2) year of publication; (3) study design; (4) study location; (5) age range and sex distribution; (6) sample size; (7) diagnostic method of sarcopenia and sarcopenic obesity; (9) outcome measures, including CVD and stroke; CVD was defined using the International Classification of Diseases (ICD), 10th Revision (ICD-10, CD-10 code 053-075) (*13*). (10) reported risks of CCVD in relation to sarcopenia (including ORs, RRs, HRs, and 95% CIs).

The effect sizes representing the most comprehensive adjustment for potential confounders were extracted. In studies with different exposure or disease subgroups, data from distinct subgroups was pooled using a fixed-effects model. In cases where an outcome of interest was reported without providing estimates, the corresponding article's author was contacted for further information. Any discrepancies or disagreements regarding data extraction were resolved through discussion and, if necessary, by reviewing the original data with the involvement of a third researcher (Guo L).

2.4. Quality assessment

The quality assessment of the included studies was conducted independently by two researchers (Fang M and Tang G) using the Newcastle-Ottawa Scale (NOS) (*14*). The NOS checklist consists of three sections: selection, comparability, and outcome. Each section can be awarded a maximum of four, two, and three points, respectively. Based on the NOS criteria, studies were categorized as having poor quality (1-3 points), fair quality (4-6 points), or high quality (7-9 points).

2.5. Data synthesis and statistical analyses

All statistical analyses were performed using R software (version 3.4.0; R: The R-Project for Statistical Computing, Vienna, Austria). The primary outcome of this meta-analysis was the association between sarcopenia and CCVD risk, evaluated using a common measure of association: ORs for cross-sectional studies. In cases where ORs were not reported, we included RRs and HRs as proxies for ORs in the pooled analysis. This is because when event rates are low, ORs, HRs, and RRs tend to approximate one another.

Heterogeneity was assessed using the Q test (*15*) and I2 score (*16*), quantifying the extent of heterogeneity. Random-effects models were utilized to calculate pooled effect sizes and test the significance of deviations from zero ($P < 0.05$, 2-tailed). Additionally, subgroup analyses and meta-regressions were conducted to analyze the sources of heterogeneity. Subgroup analyses using the random-effect models were conducted based on the following factors: sample size (< 5,000 or > 5,000), country (Korea or China), and outcomes (CVD or stroke). Furthermore, sensitivity analyses were conducted to assess the stability of the results by excluding each study individually and recalculating the combined effect size based on the remaining studies. To evaluate publication bias among the included articles, funnel plots, Egger's test, and the trim-and-fill method were employed in the current meta-analysis. A *P*-value less than 0.05 indicated the presence of potential small-study effects.

3. Results

3.1. Study selection

A total of 1,241 articles were identified through the aforementioned database search. In the comprehensive literature search, 863 relevant articles were yielded when duplications were excluded. After removing duplicates, the comprehensive literature search yielded 39 relevant articles. Following a thorough examination of the full texts, 21 records were excluded, resulting in the inclusion of eight studies for our meta-analysis. No additional eligible articles were found through the assessment of reference lists (Figure 1).

3.2. Study and patient characteristics

As shown in Table S3 (*http://www.biosciencetrends.com/action/getSupplementalData.php?ID=149*), the eight included studies were published between 2005 and 2022 and encompassed a total of 63,738,162 human participants (*17-24*). The mean age of the participants was 54 years, with a majority being women (57%). The studies were conducted in Asia, with six originating from Korean institutes and the remaining two from China.

Among the eight studies, sarcopenia was investigated as an exposure variable, while four of them also examined sarcopenic obesity as an exposure variable. The most common CCVD reported outcomes were CVD ($n = 8$), followed by stroke ($n = 2$). The study-specific and maximally adjusted ORs were extracted from the selected studies and pooled for the meta-analysis.

3.3. Methodological quality

To assess the quality of all studies, the NOS score was employed. Scores ranging from 0 to 3, 4 to 6, and 7 to 9 were considered indicative of low, fair, and high quality, respectively. Among the eight studies, all attained a high-quality rating with an average NOS score of 8, indicating good methodological quality (Table S4, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=149*).

3.4. Association between sarcopenia and CCVD risk

The association between sarcopenia and the risk of CCVD was assessed in all eight eligible studies. The meta-analysis revealed that sarcopenia was significantly associated with an increased risk of CCVD (OR: 1.33, 95% CI: 1.18 - 1.50, $I^2 = 1\%$; $p < 0.001$; Figure 2) using a random effect model.

3.5. Subgroup analysis of sarcopenia and CCVD

Subgroup analyses were conducted based on various factors, including sample size (> 5,000 or < 5,000), country (Korea or China), and disease (CVD or stroke), to investigate the impact of different population characteristics on the relationship between sarcopenia and the risk of CCVD. The results of the subgroup analysis for sarcopenia and CCVD risk are summarized in Figure 3.

In studies with large sample sizes (> 5,000), the pooled OR for CCVD risk was 1.36 (95% CI: 1.14 - 1.61, $p < 0.001$). However, no significant association was found between sarcopenia and CCVD (OR = 1.36, 95% CI: 0.99 - 1.87) in studies with small sample sizes (< 5,000). Additionally, we found that sarcopenia increased the risk of CCVD in Korea (OR = 1.15, 95% CI = 1.03 -

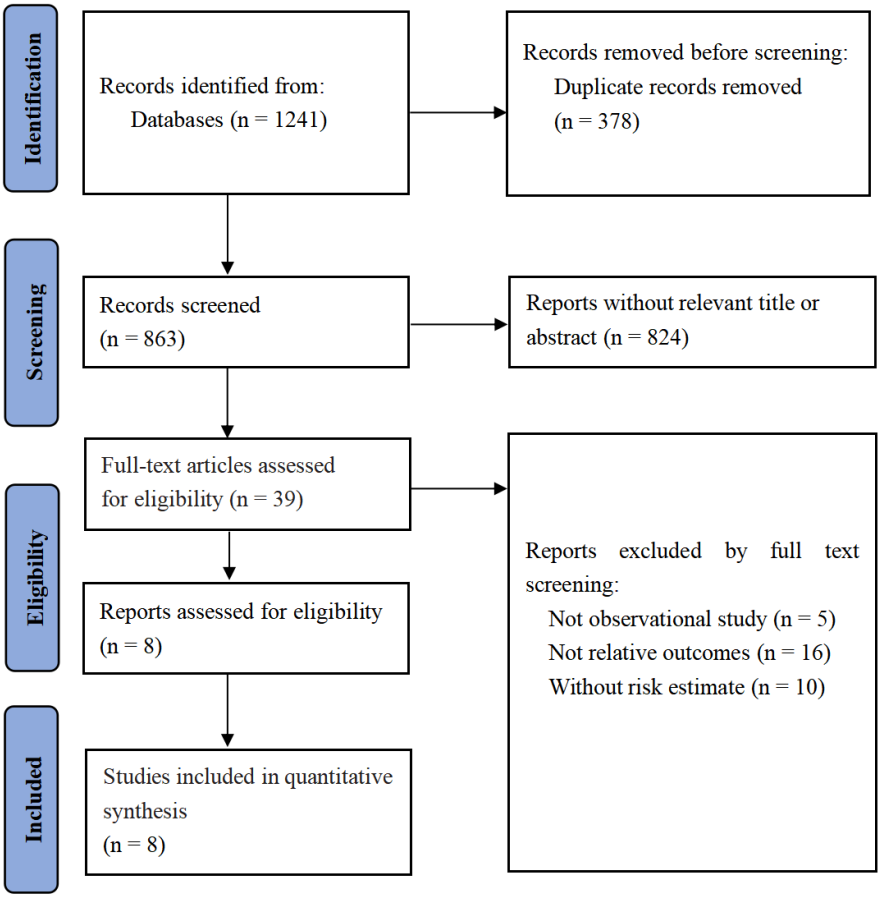

Figure 1. Literature search flow chart. Flowchart of the literature search and selection for systematic review and neta-analysis.

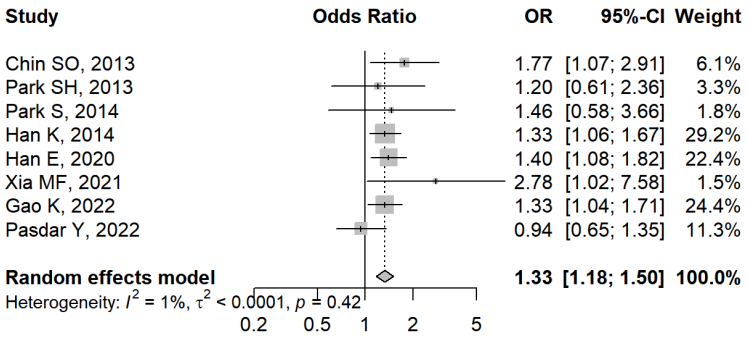

Figure 2. Forest plot of the association between sarcopenia and cardio-cerebrovascular disease. Forest plot for the meta-analysis examining the overall association between sarcopenia and cardiovascular disease (OR and 95% CIs) using a random effects model. OR, odds ratio; CI, confidence interval.

1.28, n = 6) but not in China (OR: 1.63, 95% CI: 0.85 - 3.01, n = 2). Moreover, participants with sarcopenia had a higher risk of stroke (OR = 1.67, 95% CI = 1.18 - 2.37, p = 0.004) compared to CVD (OR = 1.31, 95% CI = 1.14 - 1.49, p < 0.001).

3.6. Association between sarcopenia obesity and CCVD risk

Four studies reported an association between sarcopenic obesity and the risk of CCVD. The meta-analysis demonstrated that the presence of sarcopenic obesity was significantly associated with an increased risk of CCVD (OR: 1.64, 95% CI: 1.08 - 2.49, I^2 = 69%; p < 0.001; Figure 4) using a random effect model.

3.7. Meta-regression and sensitivity analyses

A meta-regression analysis was performed to explore potential sources of heterogeneity. However, the meta-

Subgroup	No. of reports	Odds Ratio (95% CI)	Odds Ratio (95% CI)	*P* for test	I^2 (%)	*P* for heterogeneity
Overall	8		1.33 (1.18 - 1.50)	<0.001	1%	0.42
Sample size						
>5000	4		1.36 (1.14 - 1.61)	0.06	33%	0.971
<5000	4		1.36 (0.99 - 1.87)	<0.001	41%	0.081
Country						
Korea	6		1.15 (1.03 - 1.28)	<0.001	0%	0.872
China	2		1.63 (0.85 - 3.01)	0.138	48%	0.162
Disease						
CVD	8		1.31 (1.14 - 1.49)	<0.001	4%	0.397
Stroke	2		1.67 (1.18 - 2.37)	0.004	0%	0.99

Figure 3. Subgroup analysis of the association between sarcopenia and cardio-cerebrovascular disease.

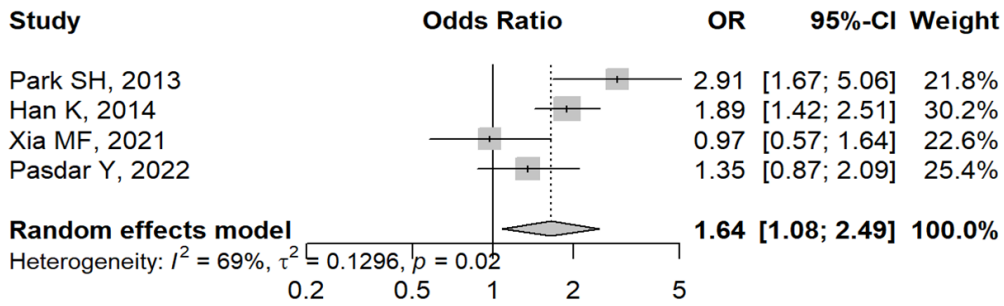

Figure 4. Forest plot of the association between sarcopenic obesity and cardio-cerebrovascular disease. Forest plot for the meta-analysis examining the overall association between sarcopenic obesity and cardiovascular disease (OR and 95% CIs) using a random effects model. OR, odds ratio; CI, confidence interval.

regression analysis of publication year, age, and sample size did not identify any obvious contributors to the heterogeneity (Table S5, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=149*).

To ensure the robustness of our findings and account for the significant heterogeneity observed among the included studies, sensitivity analyses were performed using random-effects models. These analyses involved sequentially excluding each study from the meta-analysis and examining the impact on the combined OR. The sensitivity analyses indicated no significant variation in the combined OR ($P > 0.05$), suggesting the reliability of our results (Figures. 5A and 5B).

3.8. Publication bias

In the current meta-analysis, publication bias among the included articles was assessed using a funnel plot, Egger's test, and the trim and fill method. The funnel plot displayed an asymmetric distribution (Figure S1, A, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=149*). However, Egger's test did not suggest the presence of publication bias ($p = 0.463$). The trim-and-fill analysis indicated that two studies might be missing (Figure S1, B, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=149*). Nevertheless, after adjusting for these potentially missing studies using the trim-and-fill method, the significance of the effect sizes was attenuated but remained statistically significant (OR = 1.29; 95% CI = 1.14 - 1.45).

4. Discussion

4.1. Summary of main results

In this systematic review and meta-analysis, we conducted a comprehensive evaluation of eight studies involving a total of 63,738,162 participants to investigate the association between sarcopenia and incident CCVD. Our findings indicate that sarcopenia is significantly associated with an increased risk of cardiovascular disease and cerebrovascular disease. To the best of our knowledge, this is the first systematic review and meta-analysis specifically examining the relationship between sarcopenia and CCVD.

4.2. Comparison between this and other meta-analyses

Several mechanisms, including inflammatory cell

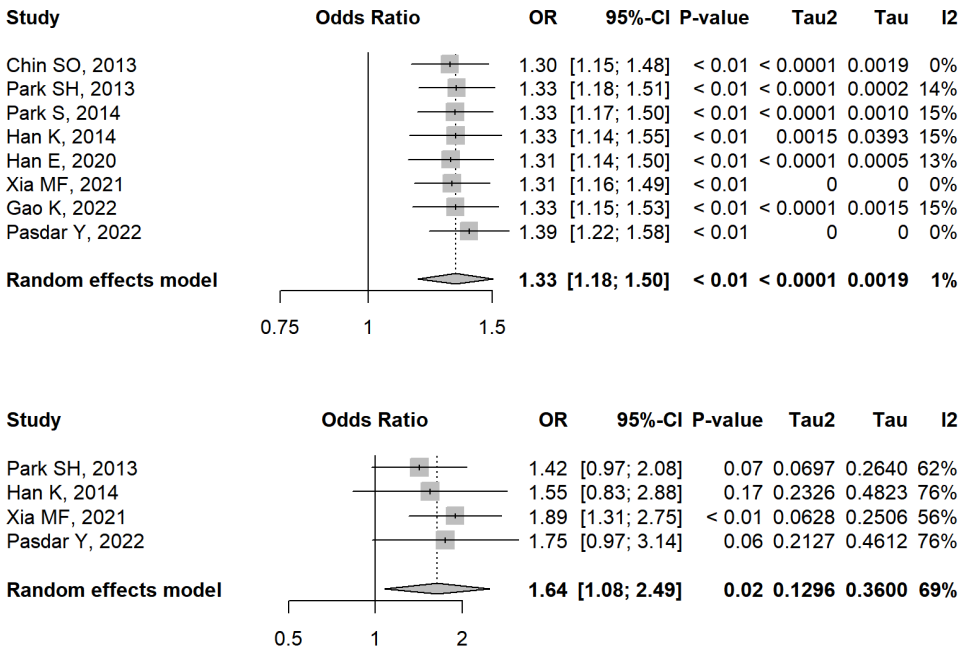

Figure 5. Sensitivity analysis. (A) Association between sarcopenic and CCVD. (B) Association between sarcopenic obesity and CCVD. Sensitivity analysis showed that there was no significant variation in the combined OR after omitting any one of the studies.

infiltration, hormonal dysfunction, impaired capillary blood flow, and reduced repair and regeneration capacity, have been associated with sarcopenia and may explain its relationship with CCVD (*25,26*). Considering the involvement of inflammation in the development of sarcopenia, recent studies have explored the association between the dietary inflammatory index and sarcopenia, highlighting its potential as a biomarker (*27*). Further investigations are needed to determine whether targeting the dietary inflammatory index could be a potential therapeutic approach for sarcopenia.

As an age-related musculoskeletal disorder, previous meta-analyses have primarily centered on investigating the impact of sarcopenia on frailty, falls (*28*) and mortality (*29*) in older populations and suggested that sarcopenia is associated with several harmful outcomes. This focus is reasonable because reduced muscle mass and the function of sarcopenia can easily contribute to falls and the development of frailty. Furthermore, meta-analyses of observational studies have demonstrated that sarcopenia is not only associated with an increased risk of metabolic syndrome and diabetes (*30*), but also other neurological diseases, such as depression, cognitive impairment, and dysphagia in the general population (*31*).

Sarcopenia, as a comorbid condition, is highly prevalent in numerous non-communicable diseases and has been shown to have a negative impact on the prognosis of affected patients. Among patients with cirrhosis, a meta-analysis has revealed a strong and independent association between sarcopenia and a higher risk of hepatic encephalopathy (*24*)(*32*) and mortality (*33*). Similarly, in septic patients, sarcopenia has been associated with increased mortality risk at 3-6 months and 1 year (*34*). Among dialysis patients, sarcopenia is significantly associated with higher mortality risk and cardiovascular events (*35*). Additionally, in patients undergoing mechanical ventilation, sarcopenia is related to increased mortality, a longer duration of mechanical ventilation, and a prolonged hospital stay (*36*). Therefore, sarcopenia imposes a substantial burden not only on society but also on public health.

Our meta-analysis yielded a significant finding, indicating a 33% higher risk of CCVD in patients with sarcopenia compared to those without sarcopenia. This relationship was particularly prominent in the subgroup analysis with a sample size larger than 5000. Furthermore, subgroup analyses examining different outcomes revealed that sarcopenia is associated with a 1.67-fold increase in the risk of stroke and a 1.31-fold increase in the risk of CVD. Moreover, when considering different countries, the subgroup analysis indicated that sarcopenia is associated with an increased risk of developing CCVD in Korean populations. However, this association was not observed in Chinese populations. To obtain a comprehensive understanding of sarcopenia and its impact on CCVD risk, future studies should investigate sarcopenia across diverse countries.

Age-related changes in body composition, such as an increase in fat mass and a loss of muscle mass, or sarcopenia, contribute to the high prevalence of sarcopenic obesity among the elderly. Previous studies have suggested the existence of a vicious cycle between fat accumulation and skeletal muscle loss, as increased visceral fat leads to inflammation, which in turn contributes to the development of sarcopenia

(*37*). In our meta-analysis, we have investigated the association between sarcopenic obesity and CCVD. The findings revealed that the risk of CCVD associated with sarcopenic obesity (1.64 times) was higher than the risk of CCVD associated with sarcopenia alone (1.33 times). This indicates that both sarcopenia and sarcopenic obesity can increase the risk of CCVD and should be given adequate attention.

Despite the limited evidence available for the treatment of sarcopenia, significant efforts are being made to identify an effective therapy. Angiotensin-converting enzyme inhibitors appear to increase muscle blood flow to improve muscle contraction, strength, and function (*38*). However, meta-analyses have indicated that angiotensin-converting enzyme inhibitors (ACEIs) do not significantly improve walking distance or mitigate the age-related decline in muscle strength among older participants in clinical trials (*39*). The role of vitamin D supplementation in sarcopenia remains a topic of debate. An umbrella review of systematic reviews and meta-analyses (*40*) on pharmacological interventions for sarcopenia has examined ten different interventions, including vitamin D, combined estrogen-progesterone, dehydroepiandrosterone, growth hormone, growth hormone-releasing hormone, combined testosterone-growth hormone, insulin-like growth factor-1, pioglitazone, testosterone, and ACEIs. Nevertheless, the most recent meta-analysis by Prokopidis *et al*. suggests that vitamin D supplementation does not improve sarcopenia indices and may even have detrimental effects on older adults (*41*). Future studies should focus on examining the impact of vitamin D supplementation on sarcopenia.

According to evidence-based medical research conducted by Yoshimura *et al*., exercise and physical activity, particularly resistance training, combined with nutritional supplementation have been identified as the most effective interventions for sarcopenia (*42*). This finding has been further supported by a recent network meta-analysis (*43*). Additionally, a recent meta-analysis of randomized controlled trials suggested that Tai Chi may also have beneficial effects for individuals with sarcopenia (*44*). However, aerobic exercise has not shown a positive effect on improving sarcopenia (*45*). Regarding dietary patterns, supplementation with branched-chain amino acids among older individuals has been associated with beneficial effects on muscle mass and strength (*46)*. However, the role of dairy protein in sarcopenia remains inconclusive (*47*). Therefore, it is essential to recognize the importance of gaining a better understanding of the underlying pathological mechanisms to facilitate the development of targeted treatments for sarcopenia.

4.3. Strengths and limitations of the study

The strength of this study lies in its extensive inclusion of a large number of patients, allowing for a robust assessment of the relationship between sarcopenia and incident CCVD. However, it is important to acknowledge the limitations of the methods employed in this study. These limitations are primarily attributable to the low quality and high heterogeneity of the individual participant data used in the meta-analysis. Although several potential confounders were identified, and sensitivity analyses were conducted, residual confounding remains a possibility. Additionally, the retrospective design of most of the included studies resulted in selection bias and limited the generalizability of the findings. Ultimately, we did not perform subtypes of CVD and cerebrovascular diseases as insufficient data were available.

5. Conclusion

In conclusion, our meta-analysis highlights the significant association between sarcopenia and sarcopenic obesity and the risk of developing CCVD. However, it is important to acknowledge the limitations inherent in the studies included in this review. To validate our findings and provide more robust evidence, prospective trials with large sample sizes are warranted. If future research strengthens the evidence, it may be prudent for current guidelines to consider incorporating early and regular cardio-cerebrovascular assessments for patients with sarcopenia.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

Author statement: Lei Guo conceived and designed the study. Miao Fang and Guo Tang carried out the literature search and screening of articles; Chunhua Liu and Chunling Li analyzed data. Miao Fang and Chunhua Liu wrote the manuscript. Lei Guo provided critical revision of the manuscript for important intellectual content. All authors have read and approved the final manuscript.

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