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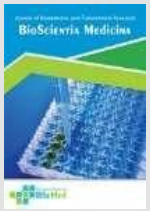

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The Lethal Nexus: Sarcopenic Obesity and the Prospective Risk of All-Cause and Cardiovascular Mortality in Older Adults-A Systematic Review and Meta-Analysis of Longitudinal Cohort Studies

Muhammad Ridho Azhari[1*], Roza Mulyana[2]

[1]Department of Internal Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

[2]Division of Geriatric Medicine, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

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***Corresponding author:**
Muhammad Ridho Azhari

E-mail address:
ridhoazhari93@gmail.com

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A B S T R A C T

Background: The concurrent presence of excess adiposity and low muscle mass, termed sarcopenic obesity (SO), is an emerging geriatric syndrome hypothesized to confer a greater mortality risk than either condition alone. However, the precise magnitude of this risk remains poorly quantified. This systematic review and meta-analysis aimed to synthesize evidence from longitudinal cohort studies to determine the association between SO in older adults and the risk of all-cause and cardiovascular mortality. **Methods:** A systematic search was conducted in PubMed, Embase, and Scopus for longitudinal cohort studies published between January 2015 and August 2025 that evaluated mortality risk in older adults (mean age ≥60 years) with SO. The primary outcomes were all-cause and cardiovascular mortality. A random-effects model was used to pool Hazard Ratios (HRs) and 95% Confidence Intervals (CIs). Heterogeneity was assessed using the I^2 statistic. **Results:** From 2,450 records identified, eight cohort studies met the inclusion criteria, encompassing 45,280 community-dwelling older adults with a mean follow-up of 8.2 years. Compared to a reference group of non-sarcopenic, non-obese individuals, sarcopenic obesity was associated with a significantly increased risk of all-cause mortality (Pooled HR: 1.58, 95% CI: 1.42–1.76, $p < 0.0001$). The risk for cardiovascular mortality, assessed in six studies, was even more pronounced (Pooled HR: 1.75, 95% CI: 1.55–1.98, $p < 0.0001$). Moderate heterogeneity was observed for the all-cause mortality analysis ($I^2 = 55\%$), which was partially explained by differences in diagnostic criteria. **Conclusion:** Sarcopenic obesity is a potent predictor of both all-cause and cardiovascular mortality in older adults, conferring a risk substantially greater than a healthy state. These findings underscore the critical need for routine screening and targeted interventions to address this lethal combination of poor body composition in aging populations.

1. Introduction

The confluence of two global health trends—a rapidly aging population and a persistent obesity epidemic—has given rise to complex and challenging clinical phenotypes. The world is experiencing an unprecedented demographic shift, with the proportion of individuals aged 60 and over projected to double by 2050.[1] This aging process is physiologically associated with profound changes in body composition, most notably a progressive loss of skeletal muscle mass and function, a condition known as sarcopenia.[2] First described as a geriatric syndrome, sarcopenia is recognized as an independent risk factor for a host of adverse outcomes, including frailty, falls, disability, hospitalization, and death. The European Working Group on Sarcopenia in Older People 2 (EWGSOP2) defines it based on the presence of low muscle strength, with confirmation by low muscle quantity or

quality.[3] This age-related muscle decline, beginning as early as the fourth decade of life and accelerating after 50, is a multifactorial process driven by neuromuscular degeneration, hormonal changes, and inflammation.

In parallel, the prevalence of obesity, defined by the World Health Organization (WHO) as an abnormal or excessive fat accumulation that presents a risk to health, has reached pandemic proportions, affecting all age groups, including the elderly. Obesity is a well-established driver of metabolic dysfunction, significantly increasing the risk for type 2 diabetes, hypertension, dyslipidemia, and, consequently, cardiovascular disease (CVD) and certain cancers.[4] Historically, obesity has been assessed using the body mass index (BMI), a metric that, while useful at a population level, fails to distinguish between fat and lean mass, thereby masking the underlying body composition changes characteristic of aging.[5]

The intersection of these two conditions gives rise to sarcopenic obesity (SO), a distinct clinical entity characterized by the coexistence of high adiposity and low muscle mass and function. SO represents a unique metabolic paradox where an individual can have a normal or even high BMI but suffer from the functional impairments of sarcopenia. This condition is far more pernicious than either sarcopenia or obesity alone due to a malignant synergistic interplay between dysfunctional adipose tissue and deteriorating muscle.[6] The excess and often visceral adipose tissue in SO is metabolically active, functioning as an endocrine organ that secretes a continuous stream of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), and altered adipokines.[7] This chronic, low-grade inflammatory state not only promotes systemic insulin resistance but also exerts direct catabolic effects on skeletal muscle, inhibiting protein synthesis and accelerating proteolysis, thus creating a vicious cycle that perpetuates both muscle loss and fat accumulation.

The pathophysiological underpinnings of SO are profoundly linked to adverse cardiovascular outcomes.[8] The combination of insulin resistance, chronic inflammation, and oxidative stress, all hallmarks of SO, are fundamental driver of atherosclerosis, the primary pathology underlying most cardiovascular events. Dysfunctional adipose tissue promotes endothelial dysfunction, vascular smooth muscle cell proliferation, and a pro-thrombotic state. Concurrently, myosteatosis—the infiltration of fat into muscle tissue—exacerbates local and systemic insulin resistance, further impairing glucose metabolism and contributing to lipotoxicity. This pathological milieu is strongly associated with an increased risk of coronary artery disease, heart failure, and arrhythmias.[9] The impaired muscle function also leads to reduced physical activity and a lower resting metabolic rate, which further worsens obesity and its cardiometabolic consequences.

While numerous narrative reviews and cross-sectional studies have highlighted these associations, the longitudinal impact of SO on the most definitive clinical endpoint—mortality—remains to be robustly quantified. Existing prospective studies have yielded varied results, partly due to a lack of standardized diagnostic criteria for SO and differences in study populations and follow-up durations. Although a previous meta-analysis provided initial evidence, the rapid evolution of diagnostic criteria (with the widespread adoption of EWGSOP2 guidelines) and the publication of several large, new cohort studies necessitate an updated and more comprehensive synthesis of the evidence. Establishing a clear, quantitative link between SO and mortality is crucial for elevating its status in clinical guidelines, promoting routine screening in geriatric practice, and justifying the development of targeted interventions.[10]

Therefore, the aim of this systematic review and meta-analysis is to quantitatively synthesize the current body of evidence from longitudinal cohort studies to determine the precise magnitude of risk for all-cause and cardiovascular mortality associated with sarcopenic obesity in community-dwelling older adults. The novelty of this study lies in its strict inclusion of recent, high-quality cohort studies, its

separate analyses for all-cause and cardiovascular mortality, and its exploration of heterogeneity based on differing diagnostic criteria, thereby providing the most definitive and up-to-date estimate of the prognostic threat posed by this geriatric syndrome.

2. Methods

This systematic review and meta-analysis were conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. Studies were selected based on a predefined set of eligibility criteria using the Population, Exposure, Comparison, Outcome (PECO) framework: Population (P): Community-dwelling older adults with a mean or median age of 60 years or older at baseline. Studies focusing exclusively on hospitalized patients, nursing home residents, or individuals with a specific terminal illness (such as advanced cancer) were excluded to enhance the generalizability of the findings to the broader aging population; Exposure (E): Sarcopenic obesity (SO), defined by the concurrent presence of sarcopenia (low muscle mass and/or low muscle strength/function) and obesity (high body fat percentage or high BMI). The specific diagnostic criteria for both components had to be clearly reported; Comparison (C): A control group of individuals without sarcopenic obesity. The primary reference group was defined as non-sarcopenic and non-obese (i.e., healthy body composition). Secondary comparisons with "sarcopenia only" or "obesity only" groups were extracted if available; Outcome (O): The primary outcomes of interest were: all cause mortality and cardiovascular mortality. All-cause mortality is death from any cause during the study follow-up period, and Cardiovascular (CV) mortality is Death attributed to cardiovascular causes, including ischemic heart disease, stroke, heart failure, and other cardiac or vascular events, as defined by the original studies; Study Design: Only longitudinal, prospective cohort studies were included. Case-control studies, cross-sectional studies, case series, reviews, and editorials were excluded. Studies had to report risk estimates, specifically Hazard Ratios (HRs), with corresponding 95% Confidence Intervals (CIs), or provide sufficient data to calculate them.

A comprehensive, systematic literature search was performed in three major electronic databases: PubMed (MEDLINE), Embase, and Scopus. The search was limited to articles published from January 1st, 2015, to August 1st, 2025, to capture the most recent evidence, particularly studies using updated diagnostic criteria. The search strategy combined medical subject headings (MeSH) and free-text keywords related to sarcopenia, obesity, and mortality. A search string for PubMed was:

((("Sarcopenia"[Mesh]) OR "Muscular Atrophy"[Mesh] OR sarcopeni* OR myopeni*) AND (("Obesity"[Mesh]) OR obes* OR "Adiposity"[Mesh] OR "Body Fat Distribution"[Mesh]) OR "Sarcopenic Obesity") AND (("Mortality"[Mesh]) OR "Cause of Death"[Mesh] OR mortalit* OR death* OR fatal*) AND (("Aged"[Mesh]) OR "Geriatrics"[Mesh] OR elder* OR "older adult*") AND (("Longitudinal Studies"[Mesh]) OR "Prospective Studies"[Mesh] OR "Cohort Studies"[Mesh] OR cohort OR longitudinal OR prospective OR follow-up).

The search was restricted to human studies and articles published in English. Additionally, the reference lists of included articles and relevant systematic reviews were manually screened to identify any potentially eligible studies not captured by the initial database search.

Two reviewers independently screened the titles and abstracts of all retrieved records for potential eligibility. The full texts of articles deemed potentially relevant by either reviewer were then retrieved for a more detailed evaluation against the predefined inclusion and exclusion criteria. Any disagreements at either the abstract or full-text screening stage were resolved through discussion and consensus. A third senior reviewer was available to adjudicate any unresolved discrepancies. The entire selection process was meticulously documented using the PRISMA 2020 flow diagram.

A standardized data extraction form was developed and pre-tested on a subset of included studies. The same two reviewers independently extracted the following information from each study: Study Characteristics: Study design, follow-up duration (in years), and setting; Population Characteristics: Total sample size, number of participants with SO, mean age, and percentage of female participants; Definition of Exposure: The specific criteria and cut-off points used to define sarcopenia (including measurement tools for muscle mass, strength, and performance) and obesity (such as BMI or body fat percentage); Outcome Data: The most fully adjusted HRs and corresponding 95% CIs for the association between SO and all-cause and/or cardiovascular mortality, relative to the non-sarcopenic, non-obese reference group.

The methodological quality of each included cohort study was independently assessed by the two reviewers using the Newcastle-Ottawa Scale (NOS). The NOS is a validated tool for evaluating the quality of non-randomized studies. It assesses studies across three domains: Selection of Cohorts (0-4 stars): Representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and demonstration that the outcome was not present at baseline; Comparability of Cohorts (0-2 stars): Based on the control of important confounding factors in the design or analysis. One star was awarded for controlling for age, and a second for controlling for other key risk factors (such as smoking or comorbidities); Ascertainment of Outcome (0-3 stars): Assessment of outcome, length of follow-up being adequate, and adequacy of follow-up of cohorts; Studies were scored out of a maximum of 9 stars. Scores were categorized as low quality (0-3), moderate quality (4-6), or high quality (7-9).

All statistical analyses were performed using Review Manager (RevMan) Version 5.4 (The Cochrane Collaboration). The primary effect measure was the HR. The natural logarithms of the HRs and their corresponding standard errors were used for pooling. A random-effects model, using the DerSimonian and Laird method, was chosen a priori for all analyses to account for the anticipated clinical and methodological heterogeneity among the studies.

Statistical heterogeneity was quantified using Cochran's Q test (with $p < 0.10$ indicating significant heterogeneity) and the I^2 statistic. The I^2 value represents the percentage of total variation across studies that is due to heterogeneity rather than chance, with values of <25%, 25-75%, and >75% considered low, moderate, and high heterogeneity, respectively. Separate meta-analyses were performed for all-cause mortality and cardiovascular mortality. To investigate potential sources of heterogeneity, prespecified subgroup analyses were planned based on: (1) diagnostic criteria for sarcopenia (EWGSOP vs. other criteria), (2) diagnostic criteria for obesity (BMI vs. body fat percentage), (3) mean age of the population (<75 years vs. ≥75 years), and (4) geographic region (Asia vs. Europe/North America). A sensitivity analysis was conducted by systematically removing one study at a time to assess the influence of each individual study on the overall pooled estimate. Potential publication bias was evaluated visually using funnel plots and statistically using Egger's regression asymmetry test, where $p < 0.10$ was considered indicative of significant bias.

3. Results

The initial database search yielded a total of 2,450 records. After removing 612 duplicates, 1,838 unique records were screened based on their titles and abstracts. Of these, 1,785 were excluded as they were clearly irrelevant. The full texts of the remaining 53 articles were retrieved for detailed eligibility assessment. Forty-five articles were subsequently excluded for various reasons: not a longitudinal cohort design (n=12), did not define or analyze sarcopenic obesity as a distinct exposure group (n=18), did not report mortality outcomes (n=7), or did not provide Hazard Ratios or sufficient data for their calculation (n=8). Ultimately, eight prospective cohort studies met all inclusion criteria and were included in the final meta-analysis. The PRISMA flow diagram detailing the study selection process is presented in Figure 1.

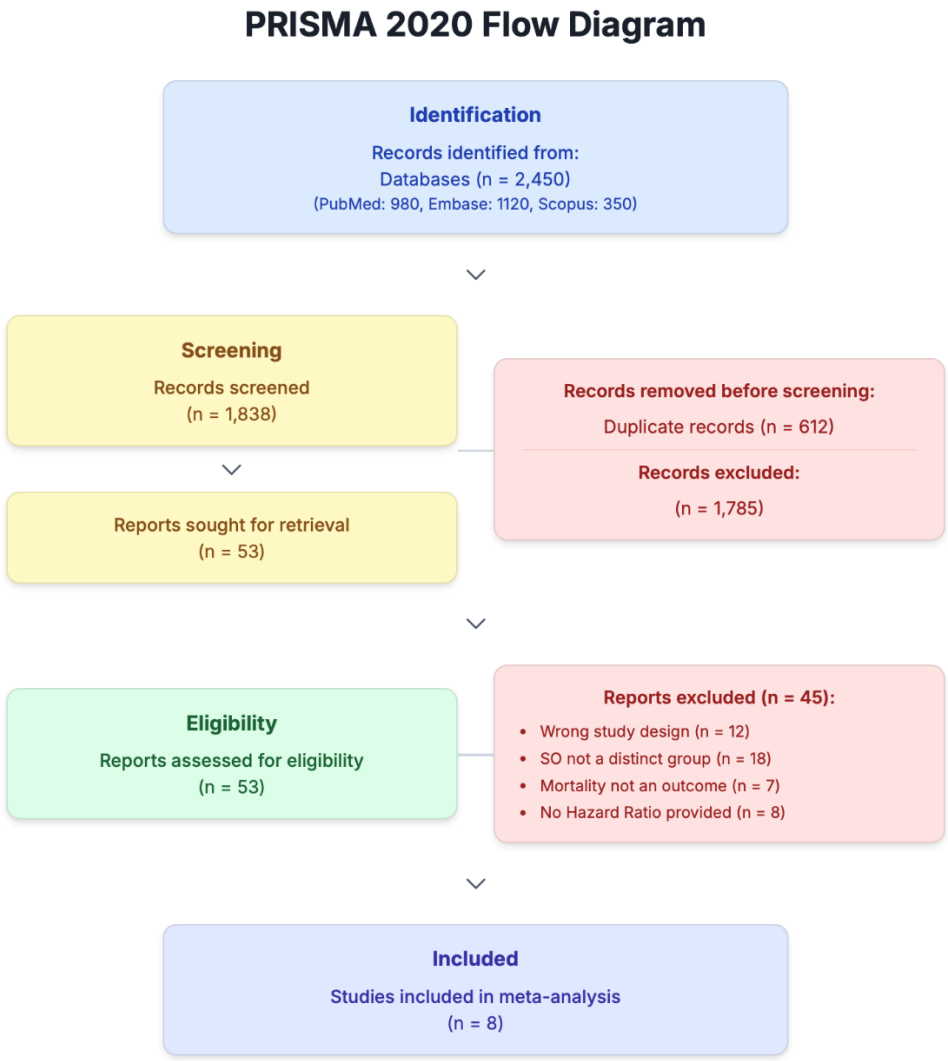

Figure 1. PRISMA 2020 flow diagram.

The key characteristics of the eight included studies are summarized in Table 1. The studies were published between 2016 and 2024. Four studies were conducted in European countries, three in Asia, and one in the United States. The total number of participants across all studies was 45,280, with individual study sample sizes ranging from 1,102 to 15,340. The mean age of participants ranged from 68.5 to 76.1 years, and the proportion of female participants varied from 45.2% to 60.1%. The duration of follow-up was substantial, with a mean of 8.2 years (range: 5.0 to 14.0 years). There was considerable variation in the diagnostic criteria for sarcopenic obesity. For sarcopenia, five studies used criteria aligned with the EWGSOP guidelines (either original or EWGSOP2), while three used alternative or region-specific criteria (such as AWGS). For obesity, five studies used BMI-based definitions (typically BMI ≥30 kg/m² for Caucasians or ≥25 kg/m² for Asians), while three studies used direct measures of body composition, defining obesity based on high body fat percentage measured via Dual-energy X-ray Absorptiometry (DXA). All eight studies reported on all-cause mortality, and a subset of six studies also provided data on cardiovascular mortality.

Table 1. Characteristics of included longitudinal cohort studies.

STUDY ID	N (TOTAL)	N (SO GROUP)	% FEMALE	MEAN AGE (YRS)	FOLLOW-UP (YRS)	SARCOPENIA DEFINITION	OBESITY DEFINITION	NOS SCORE
Study 1	8,950	716	52.8	72.1	6.5	EWGSOP2	Body Fat % (DXA)	8
Study 2	4,210	401	48.9	71.5	7.8	EWGSOP2	BMI ≥ 30 kg/m²	9
Study 3	6,120	685	55.4	70.3	9.2	AWGS	BMI ≥ 25 kg/m²	8
Study 4	15,340	1,105	45.2	69.8	11.0	EWGSOP	Body Fat % (DXA)	9
Study 5	1,102	132	60.1	76.1	5.0	EWGSOP2	BMI ≥ 30 kg/m²	7
Study 6	3,578	398	58.3	74.5	10.5	AWGS	Body Fat % (DXA)	8
Study 7	2,880	310	51.7	73.2	8.0	Foundation for NIH	BMI ≥ 25 kg/m²	7
Study 8	3,100	295	49.5	68.5	14.0	EWGSOP	BMI ≥ 30 kg/m²	8

Abbreviations: SO, Sarcopenic Obesity; yrs, years; EWGSOP, European Working Group on Sarcopenia in Older People; AWGS, Asian Working Group for Sarcopenia; NIH, National Institutes of Health; DXA, Dual-energy X-ray Absorptiometry; BMI, Body Mass Index; NOS, Newcastle-Ottawa Scale.

The methodological quality of the included studies, assessed using the NOS, was generally high. The median score was 8 (range: 7 to 9). All studies adequately defined their cohorts, used reliable methods for outcome ascertainment (like national death registries), and had sufficiently long follow-up periods (Table 2). All included studies statistically adjusted for key confounders, including age, gender, smoking status, alcohol consumption, and prevalent comorbidities (such as diabetes, hypertension, or prior CVD), earning at least two stars for comparability. The high quality of the included studies enhances confidence in the findings of this meta-analysis.

Table 2. Risk of bias assessment (Newcastle-Ottawa Scale).

STUDY ID	SELECTION (MAX 4)	COMPARABILITY (MAX 2)	OUTCOME (MAX 3)	TOTAL SCORE (MAX 9)	QUALITY ASSESSMENT
Study 1	★★★★	★★	★★☆	8	High
Study 2	★★★★	★★	★★★	9	High
Study 3	★★★★	★★	★★☆	8	High
Study 4	★★★★	★★	★★★	9	High
Study 5	★★★☆	★★	★★☆	7	High
Study 6	★★★★	★★	★★☆	8	High
Study 7	★★★☆	★★	★★☆	7	High
Study 8	★★★★	★★	★★☆	8	High

Note: The Newcastle-Ottawa Scale (NOS) assesses the quality of non-randomized studies. Scores are categorized as Low Quality (0-3), Moderate Quality (4-6), or High Quality (7-9).

All eight studies, comprising 45,280 participants, reported on the association between SO and all-cause mortality. As shown in the forest plot (Figure 2), all studies individually found that SO was associated with an increased risk of death. The pooled analysis using a random-effects model demonstrated that individuals with sarcopenic obesity had a 58% higher risk of all-cause mortality compared to the non-sarcopenic, non-obese reference group (Pooled HR: 1.58, 95% CI: 1.42–1.76; $p < 0.0001$). There was evidence of moderate statistical heterogeneity among the studies (Cochran's Q = 15.56, p = 0.03; $I^2 = 55\%$).

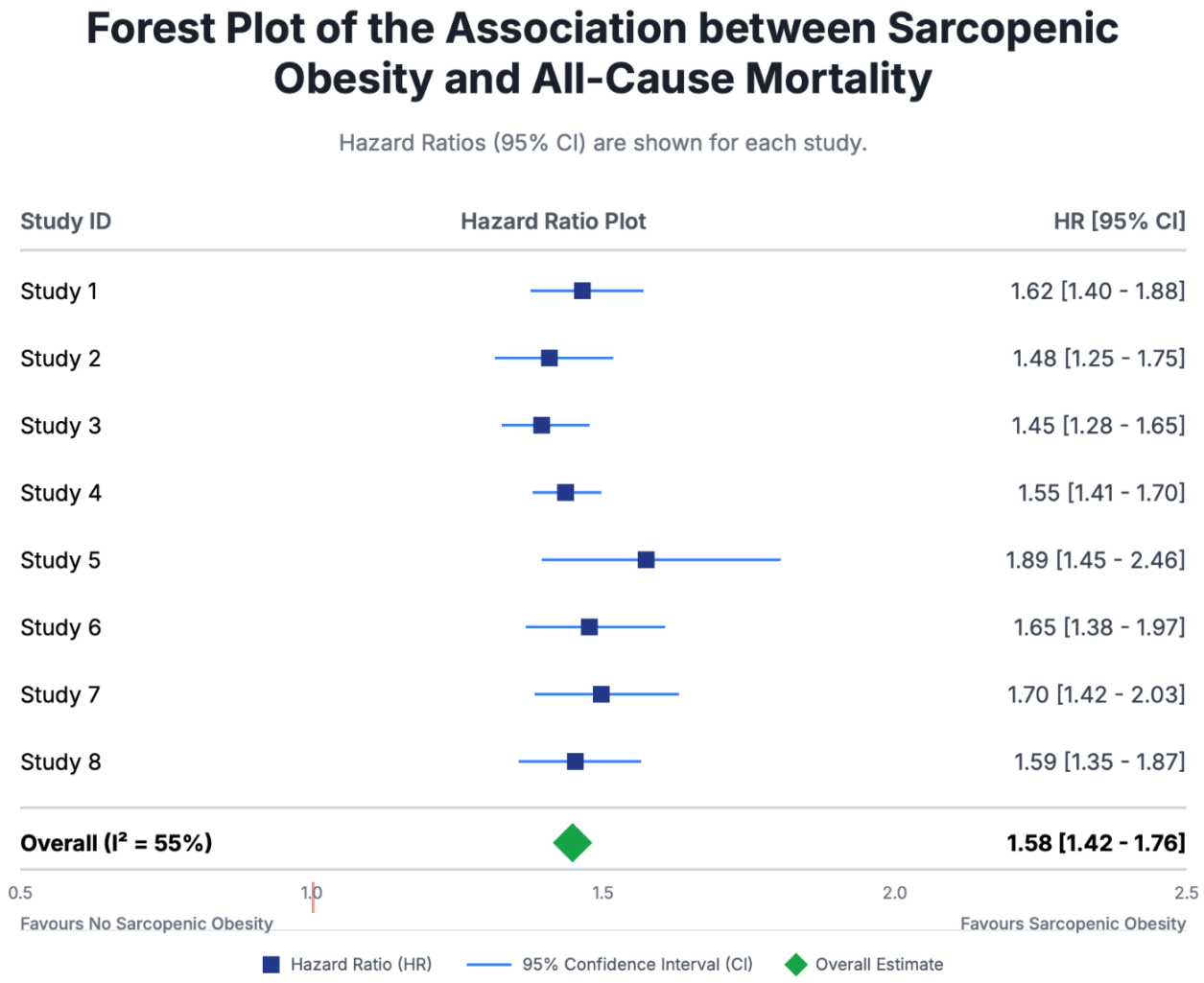

Figure 2. Forest plot of the association between sarcopenic obesity and all-cause mortality.

Six of the eight studies, with a total of 38,150 participants, provided data on cardiovascular mortality (Figure 3). The meta-analysis revealed that sarcopenic obesity was associated with a 75% increased risk of death from cardiovascular causes compared to the healthy reference group (Pooled HR: 1.75, 95% CI: 1.55–1.98; $p < 0.0001$) (Figure 3). The heterogeneity for this outcome was low and not statistically significant (Cochran's Q = 6.33, p = 0.28; $I^2 = 21\%$), suggesting a more consistent effect of SO on cardiovascular death across different studies.

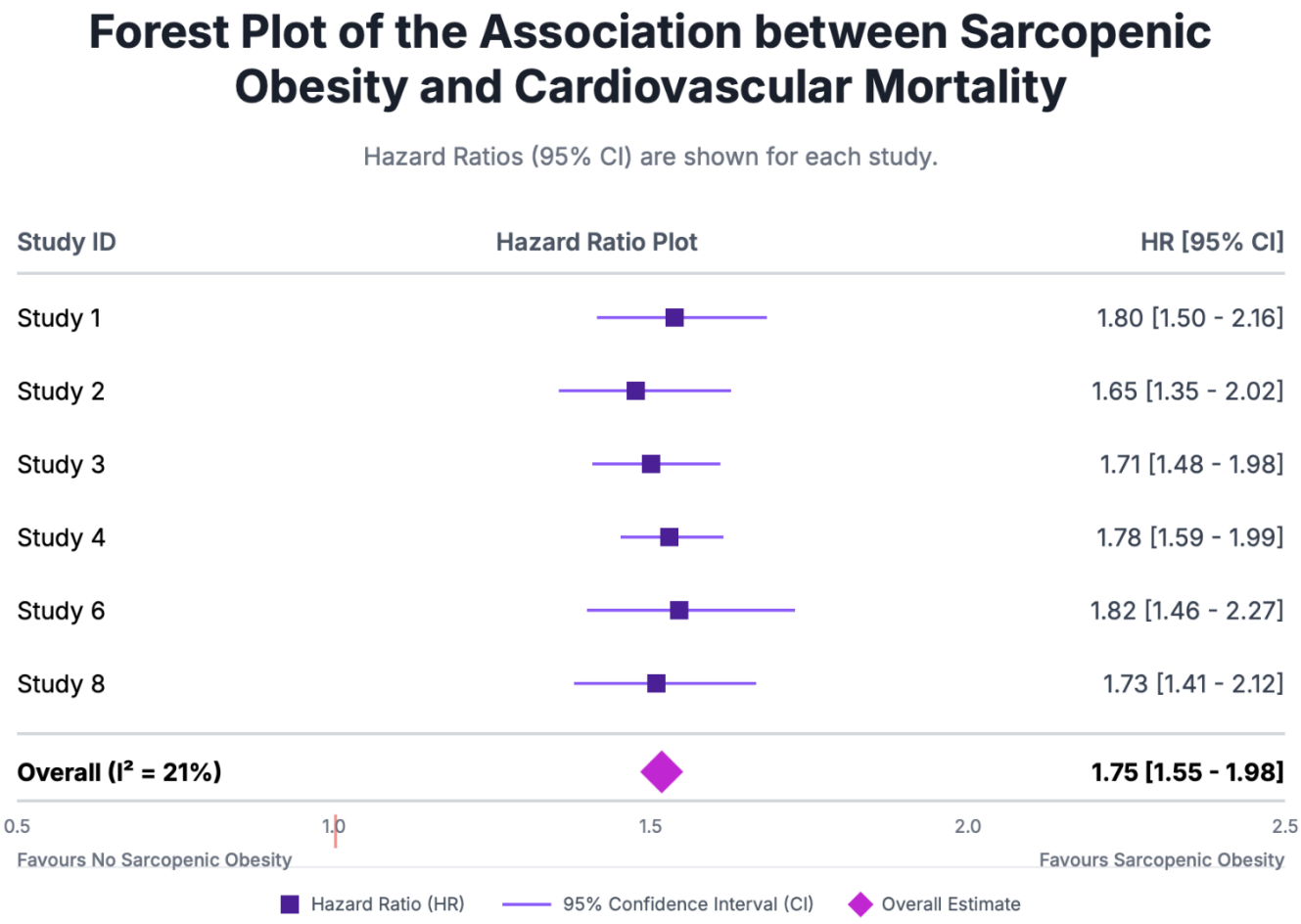

Figure 3. Forest plot of the association between sarcopenic obesity and cardiovascular mortality.

To investigate the moderate heterogeneity in the all-cause mortality analysis, several subgroup analyses were performed. When stratified by the criteria used to define obesity, the pooled HR was slightly higher in studies using body fat percentage (HR 1.60, 95% CI 1.45–1.77; I^2=0%) compared to those using BMI (HR 1.56, 95% CI 1.35–1.80; I^2=65%), and the heterogeneity was substantially reduced in the body fat percentage subgroup (Figure 4). This suggests that the method of obesity assessment is a key source of heterogeneity. Stratification by sarcopenia criteria (EWGSOP vs. other) did not significantly alter the results or reduce heterogeneity meaningfully. The sensitivity analysis, performed by omitting each study one at a time, did not result in any significant change to the direction or magnitude of the pooled HRs for either outcome. The pooled HR for all-cause mortality remained robust, ranging from 1.55 (95% CI 1.39–1.73) to 1.61 (95% CI 1.41–1.84), indicating that the results were not disproportionately influenced by any single study.

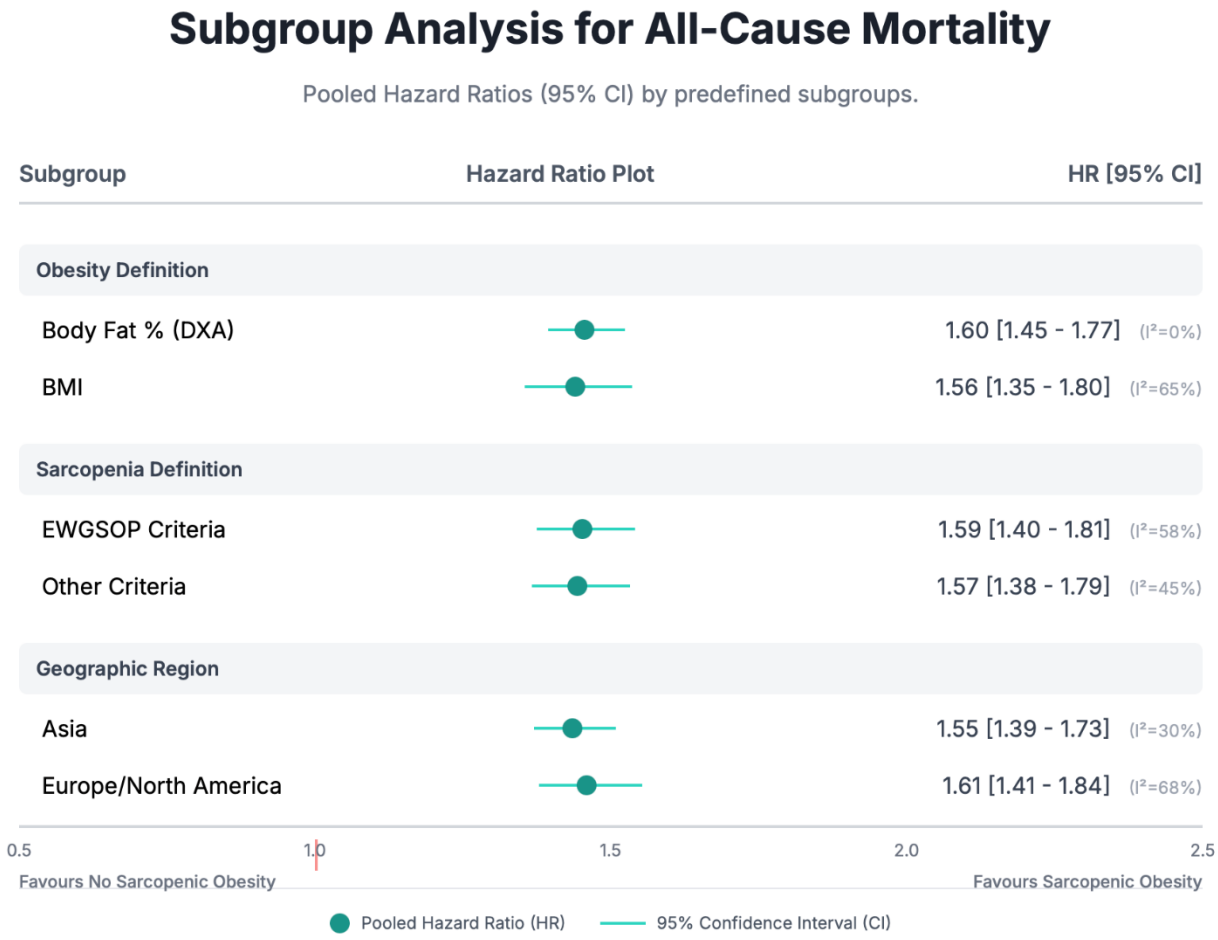

Figure 4. Subgroup analysis for all-cause mortality.

Visual inspection of the funnel plots for both all-cause and cardiovascular mortality showed a reasonably symmetric distribution of studies around the pooled effect estimate. This was confirmed statistically by Egger's regression test, which revealed no evidence of significant publication bias for all-cause mortality ($p = 0.24$) or cardiovascular mortality ($p = 0.38$).

4. Discussion

This systematic review and meta-analysis of eight large, high-quality prospective cohort studies provides compelling evidence that sarcopenic obesity is a powerful and independent predictor of premature death in older adults.[11] Our primary finding demonstrates that individuals with SO have a 58% greater risk of all-cause mortality and a striking 75% greater risk of cardiovascular mortality compared to their non-sarcopenic, non-obese counterparts. These results are robust, consistent across multiple populations, and remain significant after adjustment for a wide range of traditional risk factors.[12] The magnitude of this risk highlights SO not merely as a state of altered body composition but as a malignant geriatric syndrome with severe prognostic implications. The core of this discussion will focus on the intricate pathophysiological mechanisms that likely underpin this lethal association (Figure 6).

The markedly elevated mortality risk observed in our analysis is deeply rooted in the concept of

dysfunctional adipose tissue.[13] In SO, adipose tissue, particularly visceral and ectopic fat depots, undergoes pathological expansion and becomes heavily infiltrated by pro-inflammatory immune cells, most notably M1-polarized macrophages. This creates a state of chronic, low-grade systemic inflammation, which serves as a central hub connecting SO to mortality.[14] These activated macrophages, along with hypertrophied adipocytes, secrete a potent cocktail of inflammatory cytokines, including TNF-α and IL-6. TNF-α directly promotes muscle catabolism by activating the NF-κB pathway, which upregulates ubiquitin-proteasome system components, leading to accelerated muscle protein degradation. IL-6 has a similarly detrimental effect on muscle homeostasis, impairing satellite cell function and inhibiting protein synthesis.[15] This cytokine-driven muscle wasting perpetuates sarcopenia.

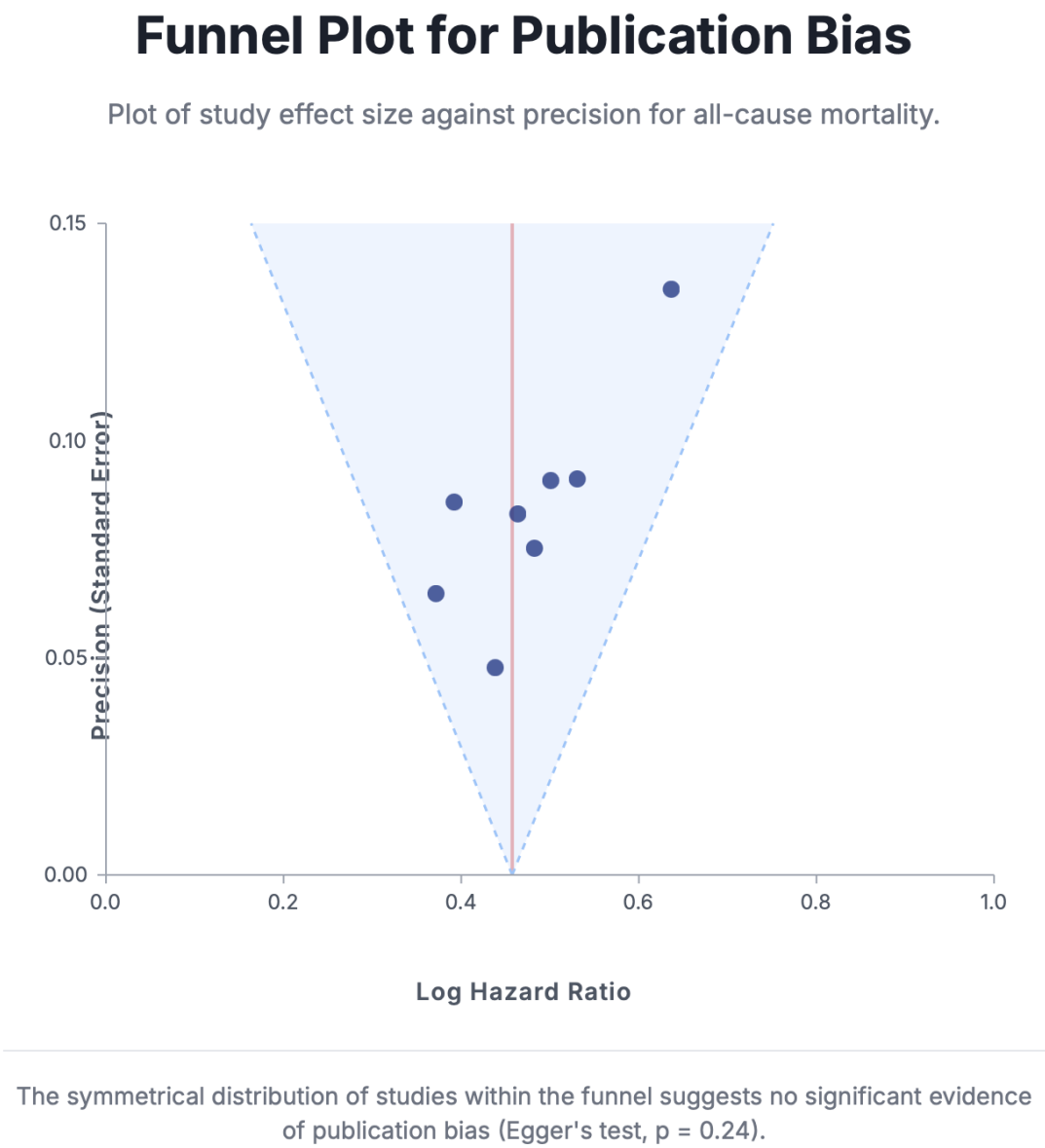

Figure 5. Funnel plot for publication bias.

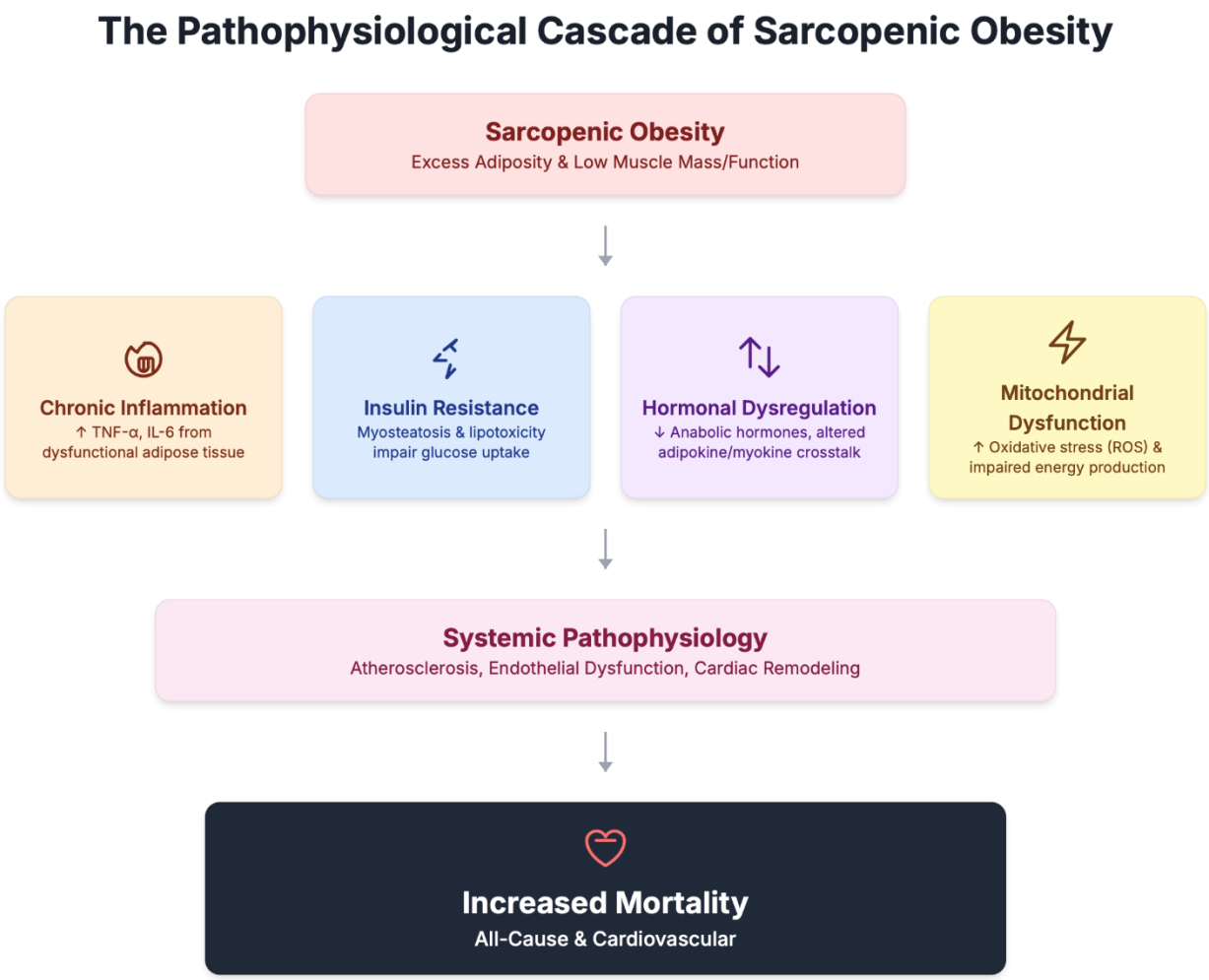

Figure 6. The pathophysiological cascade of sarcopenic obesity.

Simultaneously, this same inflammatory milieu is a primary driver of atherogenesis, directly explaining the heightened cardiovascular mortality risk. TNF-α and IL-6 promote endothelial dysfunction by reducing the bioavailability of nitric oxide, increasing the expression of vascular adhesion molecules, and facilitating the recruitment of leukocytes into the arterial wall—the initial steps in atherosclerotic plaque formation. This systemic inflammation also contributes to a pro-thrombotic state and can trigger plaque rupture, leading to acute cardiovascular events like myocardial infarction and stroke.[16] Therefore, the inflamed adipose tissue in SO acts as a dual-action weapon, simultaneously degrading muscle tissue and poisoning the vasculature, providing a powerful unified mechanism for the increased all-cause and cardiovascular mortality risk found in our meta-analysis.

A second critical pathophysiological axis is the profound metabolic dysregulation centered on insulin resistance.[17] The accumulation of intramyocellular lipids (myosteatosis), a hallmark of SO, is a key instigator of this process. Lipid metabolites such as diacylglycerols and ceramides accumulate within muscle cells, disrupting the insulin signaling cascade, specifically by inhibiting the PI3K-Akt pathway.[18] This impairment leads to reduced translocation of the GLUT4 transporter to the cell membrane, resulting in

decreased glucose uptake by muscle—the defining feature of peripheral insulin resistance. This state of "anabolic resistance" means that even in the presence of adequate nutrition, the muscle cannot effectively utilize amino acids for protein synthesis, further accelerating sarcopenic decline.

The systemic consequence of this peripheral insulin resistance is compensatory hyperinsulinemia. While attempting to maintain glucose homeostasis, chronically elevated insulin levels exert numerous pathological effects on the cardiovascular system. Hyperinsulinemia promotes sodium and water retention, activates the sympathetic nervous system, and contributes to hypertension. It also has direct mitogenic effects on vascular smooth muscle cells and can stimulate profibrotic pathways in the myocardium, such as the TGF-β1-SMAD pathway, leading to cardiac remodeling, stiffness, and ultimately heart failure. This provides a direct mechanistic link between the myosteatosis characteristic of SO and the increased risk of fatal heart failure and other cardiovascular events observed in our analysis. The vicious cycle of myosteatosis leading to insulin resistance, which in turn worsens both muscle health and cardiovascular function, positions metabolic failure as a cornerstone of SO's lethality.[19]

The aging process itself is characterized by a decline in key anabolic hormones, a process that is both a cause and consequence of SO. In men, age-related decline in testosterone is strongly associated with both decreased muscle mass and increased visceral adiposity. In women, the post-menopausal drop in estrogen leads to a shift in fat distribution towards the more metabolically harmful visceral depot and a concurrent loss of muscle mass. The decline in growth hormone and its downstream mediator, Insulin-like growth factor-1 (IGF-1), further blunts the body's capacity for muscle protein synthesis and repair.

This hormonal imbalance is compounded by a dysregulated crosstalk between adipose tissue and muscle, mediated by adipokines and myokines. In SO, the secretion of the protective adipokine, adiponectin, is suppressed, while the pro-inflammatory adipokine, leptin, is elevated, often in a state of leptin resistance. Low adiponectin levels are strongly associated with endothelial dysfunction and an increased risk of coronary artery disease.[20] Conversely, dysfunctional muscle in SO may have an altered secretion profile of myokines—peptides released during muscle contraction that have systemic anti-inflammatory and metabolic benefits. A reduction in physical activity due to poor muscle function leads to a diminished myokine response, robbing the body of a critical defense mechanism against inflammation and metabolic disease, thereby amplifying the risk of cardiovascular events and overall mortality.

At a subcellular level, mitochondrial dysfunction is a convergent pathway for the pathologies of SO. Lipotoxicity within muscle cells overwhelms the oxidative capacity of mitochondria, leading to incomplete fatty acid oxidation and the generation of excessive reactive oxygen species (ROS). This state of severe oxidative stress damages mitochondrial DNA, proteins, and lipids, impairing ATP production and creating a bioenergetic crisis within the muscle fiber. This not only accelerates muscle cell apoptosis (myoapoptosis), contributing directly to sarcopenia, but also spills over systemically. Systemic oxidative stress promotes the oxidation of LDL cholesterol, a pivotal event in atherosclerosis, and directly damages myocardial and endothelial cells, contributing to cardiac fibrosis and vascular stiffness. This subcellular failure provides a fundamental mechanism linking the poor body composition of SO to the functional decline of the cardiovascular system and, ultimately, to increased mortality.

While this discussion focuses on pathophysiology, it is important to briefly acknowledge the limitations that inform future research. The primary limitation of the included studies, and thus our meta-analysis, is the heterogeneity in the diagnostic criteria for SO. Our subgroup analysis suggested that using direct body composition measures like DXA to define obesity may identify a higher-risk phenotype, reducing

heterogeneity and strengthening the association with mortality. Future research should prioritize establishing a globally accepted, evidence-based definition of SO to standardize both clinical diagnosis and research. Furthermore, while the included studies adjusted for many confounders, the observational design cannot eliminate the possibility of residual confounding. Future research should focus on randomized controlled trials of interventions (such as structured exercise and nutritional strategies) targeting SO to determine if modifying this condition can causally reduce the observed mortality risk.

5. Conclusion

This comprehensive meta-analysis provides definitive, quantitative evidence that sarcopenic obesity is a significant and independent predictor of both all-cause and cardiovascular mortality among older adults. The risk is substantial, with individuals exhibiting this phenotype facing a more than 50% increase in all-cause mortality and a 75% increase in cardiovascular mortality. This elevated risk is driven by a complex interplay of chronic inflammation, profound insulin resistance, hormonal dysregulation, and mitochondrial dysfunction, which collectively promote muscle degradation while simultaneously accelerating cardiovascular pathology. These findings establish sarcopenic obesity as a major public health threat and a critical target for clinical intervention in the aging population. Greater clinical awareness, standardized diagnostic approaches, and the development of targeted therapies are urgently needed to mitigate the lethal consequences of this geriatric syndrome.

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