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Exploring the association between sarcopenic obesity and cardiovascular risk: a summary of findings from longitudinal studies and potential mechanisms

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Abstract

It is estimated that more than one-tenth of adults aged ≥60 years are now classified as having sarcopenic obesity (SO), a clinical condition characterised by the concurrent presence of sarcopenia (low muscle mass and weakness) and obesity (excessive fat mass). Independently, sarcopenia and obesity are associated with a high risk of numerous adverse health outcomes including CVD and neurological conditions (e.g. dementia), but SO may confer a greater risk, exceeding either condition alone. This imposes a substantial burden on individuals, healthcare systems and society. In recent years, an increasing number of observational studies have explored the association between SO and the risk of CVD; however, results are mixed. Moreover, the pathophysiology of SO is governed by a complex interplay of multiple mechanisms including insulin resistance, inflammation, oxidative stress, hormonal shifts and alteration of energy balance, which may also play a role in the occurrence of various CVD. Yet, the exact mechanisms underlying the pathological connection between these two complex conditions remain largely unexplored. The aim of this review is to examine the association between SO and CVD. Specifically, we seek to: (1) discuss the definition, epidemiology and diagnosis of SO; (2) reconcile previously inconsistent findings by synthesising evidence from longitudinal studies on the epidemiological link between SO and CVD and (3) discuss critical mechanisms that may elucidate the complex and potentially bidirectional relationships between SO and CVD.

Introduction

People aged 65 years and older, currently constitute 10% of the total global population. This number is expected to reach 16% by 2050[1]. In the context of this unprecedented population ageing phenomenon, there has been heightened attention on ageing-related health conditions, one of which is sarcopenia. Sarcopenia, now recognised as a distinct disease with its own International Classification of Disease, ICD-10 code (M62.84)[2], is characterised by the loss of muscle mass, strength and/or physical performance, with the specific diagnostic criteria varying[3–8]. Notably, sarcopenia may coexist with excessive fat mass (FM), namely obesity[9]. Both sarcopenia and obesity independently pose increased risk for adverse health outcomes such as fall, CVD and dementia[10–12]. The co-existence of these two body composition phenotypes in the same individual (i.e. sarcopenic obesity: SO) may be linked to an amplified risk, surpassing the risks posed by sarcopenia or obesity in isolation[11,13,14]. SO becomes more prevalent with advancing age, with estimates suggesting that over one-tenth of adults aged ≥60 years are now classified with this condition[15]. This imposes a substantial burden on individuals, healthcare systems and society. In the present review, we aim to discuss the definition, epidemiology and diagnosis of SO. Furthermore, by synthesising findings from longitudinal observational studies, we aim to elucidate the epidemiological and pathogenetic link between SO and CVD—the leading cause of death globally and a major global public health concern[16].

Definition of *sarcopenic obesity*

SO was initially defined as the concurrent presence of reduced lean mass and excess body fat[17]. Over the past two decades, numerous definitions of sarcopenia have been proposed, including

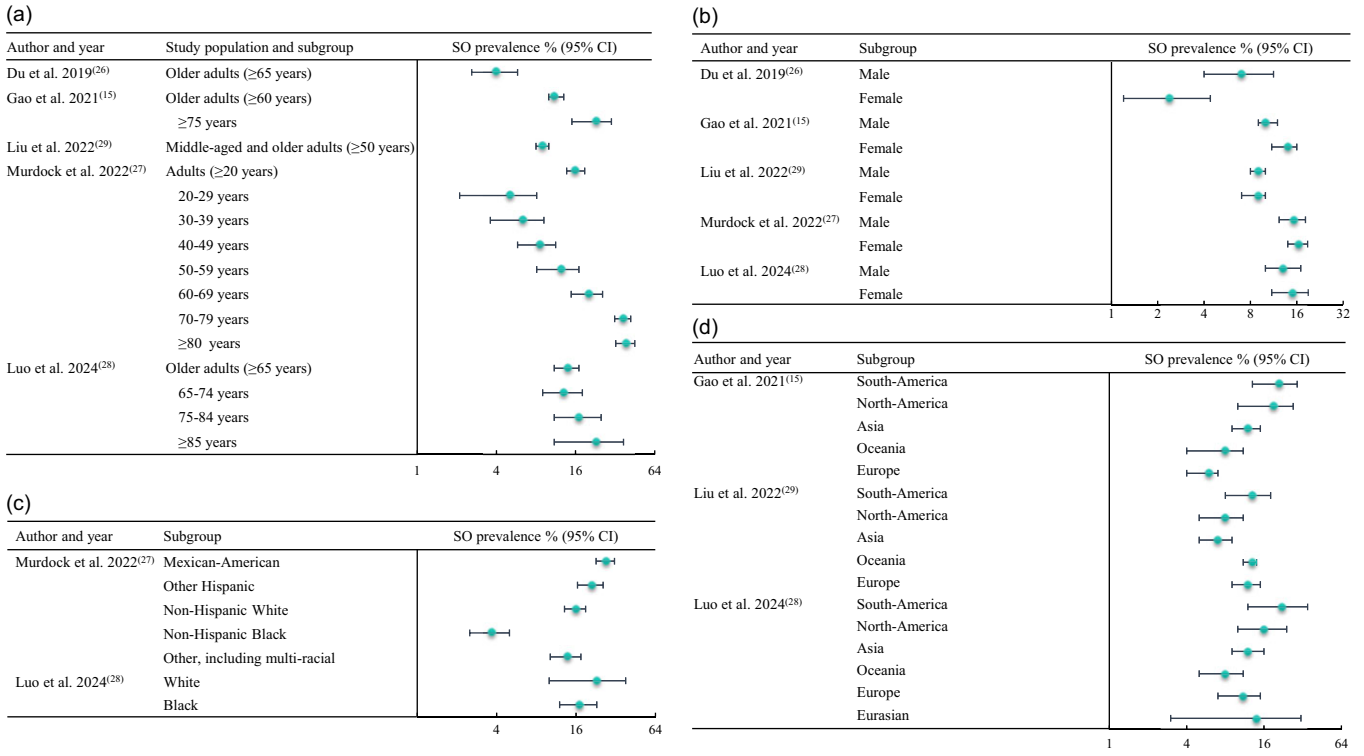

Figure 1. SO prevalence in populations with different demographic characteristics. We report findings from three recent meta-analyses and two cross-sectional studies to present the varied prevalence of SO across populations with different demographic characteristics[15,26–29]. Overall SO prevalences reported by these five studies (part a). Subgroup SO prevalences by age (part a), sex (part b), race/ethnicity (part c) and region (part d). The study conducted by Du et al. did not provide the 95% CI for SO prevalence[26]; we estimate the 95% CI for SO prevalence utilizing the Clopper–Pearson confidence interval method. SO, sarcopenic obesity.

those by the International Working Group on Sarcopenia (IWGS)[8], the Foundation for the National Institutes of Health (FNIH)[5], the Asian Working Group for Sarcopenia (AWGS)[7], the Sarcopenia Definitions and Outcomes Consortium (SDOC)[6], the European Working Group on Sarcopenia in Older People (EWGSOP2) and the Global Leadership Initiative in Sarcopenia (GLIS)[4,18]. These efforts have expanded the diagnostic criteria to encompass diminished muscle function to define SO[19]. In 2022, an initiative led by the European Society for Clinical Nutrition and Metabolism and the European Association for the Study of Obesity (ESPEN-EASO) achieved consensus on the definition and diagnostic criteria for SO, recommending the integration of ESPEN-EASO criteria into clinical and research practice[20,21]. The recently proposed consensus statement recommends that SO be diagnosed as the combination of obesity, defined by high body fat percentage, and sarcopenia, defined by deficits in skeletal muscle mass (SM) and function[20,21].

Epidemiology of *sarcopenic obesity*

SO poses a persistent and escalating threat to global population health, currently impacting approximately 40-80 million individuals and anticipated to affect 100-200 million individuals by 2050[22]. Prevalence rates for SO vary across demographic characteristics such as age, sex, region and race/ethnicity (Fig. 1). SO is highly prevalent in older adults mainly due to changes in body composition and hormone levels associated with ageing[23,24]. Indeed, a meta-analysis estimated that the global prevalence of SO among older adults (≥60 years) is 11%, but it varies according to specific diagnostic criteria used, as discussed later[15]. However, SO is not exclusive to the older aged population; it can also manifest in middle-aged and younger individuals with obesity, particularly if associated with other metabolic complications (e.g. type 2 diabetes)[25], or following weight loss treatments[20].

Both men and women are susceptible to SO, with some studies also indicating between-sex differences in prevalence rates. In a Chinese cross-sectional study of community-dwelling older adults (>65 years), the prevalence of SO was found to be 7.0% in males and 2.4% in females[26]. On the contrary, analysis of a nationally representative sample of adults (aged ≥20 years) in the United States reported a SO prevalence of 15.3% in males and 16.4% in females[27]. Notably, this study revealed an overall SO prevalence of 15.9%, with a significantly higher prevalence of 27.0% in Mexican Americans[27]. Additionally, regional differences in SO global prevalence have also been reported, with a meta-analysis suggesting that among older adults (≥65 years) SO prevalence is higher in South (22%) and North America (16%) compared to Eurasian (14%), Asia (12%), Europe (11%) and Oceania (8%)[28]. Another meta-analysis in middle-aged and older adults (≥50 years) reported a pooled prevalence of 13% in Oceania and South America, 12% in Europe, 8% in North America, and 7% in Asia[29].

Heterogeneity in the definition and diagnostic criteria for SO, involving different assessment methods for body composition including anthropometry, dual-energy X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA) and computerised tomography (CT), diverse body composition parameters such as BMI, waist circumference (WC), SM, appendicular skeletal muscle mass (ASM) and appendicular lean mass (ALM), as well as varied cut-point values for body composition parameters contribute to the divergent findings regarding the prevalence of SO[19,20,30,31].

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Kemmler et al. highlighted that the overlap in sarcopenia diagnosis, as per three different criteria, is less than 50%, based on their research utilising BIA-assessed body composition[32]. The study conducted by Vieira et al. investigated the varied SO prevalence rates among individuals in the mid-to long-term stages post-bariatric surgery using BIA and DXA to assess body composition; these prevalences were respectively: 7.9% and 23.0% (ESPEN-EASO criteria); 0.7% and 3.3% (EWGSOP2 criteria); and 27.0% and 30.3% (SDOC criteria)[33]. In a study employing DXA-assessed body composition, Batsis et al. applied eight diagnostic criteria to identify SO, revealing up to a 26-fold variation in sex-specific prevalence rates[23].

Diagnosis

Body composition assessment methods

The identification of SO hinges on diagnosing sarcopenia and obesity, typically necessitating a quantitative assessment of body composition. Various methods have been employed for quantitative body composition assessment, including non-anthropometric techniques (e.g. DXA, BIA, CT and MRI) and anthropometric indices (e.g. BMI, WC, mid-arm muscle circumference (MAMC) and calf circumference)[14,19,34]. Among the non-anthropometric techniques, DXA is considered a reliable option for SO identification in both research and clinical practice due to its availability, sensitivity, repeatability and safety[20]. However, it is imperative to acknowledge its limitations such as the inability to measure body composition directly, potential interference from changes in tissue hydration status and challenges encountered when scanning individuals with large body sizes that may exceed the scanner's specifications[20,35,36]. Another non-anthropometric method, BIA, is valued for its quickness and portability[37]. Nonetheless, caution is warranted in its use, as hydration status may also affect its diagnostic accuracy[37]. For accurate BIA measurements, it is assumed that tissue hydration remains constant and body shape is cylindrical; however, these assumptions are challenged in individuals with sarcopenia and obesity[14,38]. Furthermore, despite CT and MRI being deemed gold standard methods for precise body composition analysis, the high cost, limited availability and X-ray exposure associated with CT preclude their routine use in SO diagnosis[39], while MRI is limited to research settings due to similar constraints regarding cost and availability. Regarding anthropometric approaches used in SO diagnosis, they are generally less sensitive than precise analytical techniques[20]. In a study utilising DXA-assessed percentage fat mass (%FM) as the gold standard for identifying obesity, BMI incorrectly classified 19.2% of males and 21.5% of females as having obesity, while WC yielded percentages of 35.8% and 19%, respectively[40]. For further details on body composition assessment, we direct readers to additional literature on the subject[41,42].

Parameters and cut-point values

Mainstream definitions and diagnostic criteria for SO, as discussed previously, involve identifying obesity and the loss of SM and function (e.g. skeletal muscle strength). According to a systematic review, the assessment of SM commonly relies on parameters measured through DXA or BIA; these parameters include ALM adjusted by weight, ASM divided by weight (ASM/W), ASM adjusted by height in meters squared (ASM/h^2) and ASM adjusted by BMI (ASM/BMI)[19]. Regarding the evaluation of muscle function, hand grip strength (HGS), gait speed and chair-stand time have been recommended[4,5,8,20]. Nevertheless, the existing body of evidence does not conclusively indicate the superiority of any specific muscle function parameter[20]. On the other hand, as mentioned previously, adiposity can be identified using anthropometric parameters such as BMI and WC, as well as non-anthropometric body composition parameters such as %FM[24]. Although anthropometric parameters have relatively modest sensitivity, they are frequently employed in adiposity diagnosis due to their simplicity and widespread availability[19]. Notably, the cut-offs for the same parameters used in SO diagnosis may vary across studies as few universally accepted cut-off values for most of these parameters exist. Previous studies predominantly adhered to established guidelines, such as a BMI of ≥30 kg/m^2 denoting obesity, or adopted population-specific cut-offs derived from statistical measures such as n-tiles, SD or z scores based on individual parameter values[19]. For further information regarding the various cut-point values for these parameters, we refer readers to the ESPEN-EASO consensus statement, which provides a detailed summary of these cut-offs[20,21].

So and risk of CVD

In recent years, the roles of sarcopenia and its concurrence with obesity—a well-established risk factor for CVD—have received increasing attention in the development of CVD[43]. Analysis of data from a nationally representative sample of middle-aged and older adults (≥45 years) in China revealed that sarcopenia was associated with an increased risk of CVD, as demonstrated in both cross-sectional and longitudinal analyses (with a follow-up period of 3.6 years)[44]. Furthermore, a cross-sectional study of Korean older adults (≥65 years) found a positive association between sarcopenia and CVD risk[45]. To date, a small number of observational studies have investigated the association between SO and the risk of CVD; however, the current body of evidence remains inconclusive[11,46]. In addition to the SO diagnostic criteria and definition discrepancies between studies, different sample sizes, populations, study designs and statistical approaches used to assess CVD risk could further contribute to contradictory findings. Furthermore, most investigations are cross-sectional, thereby limiting the ability to discern long-term associations or causality. Therefore, to reconcile previously inconsistent findings, we synthesised evidence from previously published longitudinal studies that quantitatively assessed the association between SO and CVD risk.

Findings from these longitudinal studies are summarised in Table 1[47–52], four of which revealed a significant association between SO and an elevated risk of overall CVD[49–52]. Atkins et al., leveraging data from a British prospective cohort over an average follow-up duration of 11.3 years, reported no significant association between SO and CVD risk[48]. In their study, sarcopenia was defined solely by anthropometrics (MAMC and WC) or BIA-estimated muscle mass (fat mass index (FMI) and fat free mass index (FFMI)), without consideration of muscle function. On the contrary, using data from an American prospective cohort with an 8-year follow-up, Stephen and Janssen suggested that SO, when sarcopenia was assessed based on HGS, was modestly associated with an elevated risk of overall CVD (HR = 1.23; 95% CI = 0.99–1.54) and significantly associated with the a higher coronary heart disease (CHD) risk (HR = 1.42; 95% CI = 1.05–1.91)[47]. Notably, this association was not observed when sarcopenia was defined by SM, highlighting the importance

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Table 1. Summary of longitudinal studies assessing the association between SO and CVD risk

Author, Year	Subject Characteristics	Study Type and Region	SO Measurement	SO Definition	Main Findings*
Stephen & Janssen, 2009[47]	3366 older adults (≥65 years) who were free of CVD at baseline	Prospective cohort with 8-year follow-up. United States	Anthropometry (WC), BIA (SMM) and muscle function (HGS)	Obesity†: subjects in the high WC tertile and the moderate/high muscle mass tertiles. Sarcopenia†: (1) subjects with the low SM tertile and the low/moderate WC tertile or (2) subjects with the low HGS tertile and the low / moderate WC.	SO (sarcopenia identified by assessing muscle function but not SM) was modestly associated with a higher risk of CVD risk (HR = 1.23; 95% CI = 0.99–1.54); moreover, a significant association was observed between SO and a heightened risk of CHD (HR = 1.42; 95% CI = 1.05–1.91).
Atkins et al., 2014[48]	4252 males (≥60 years)	Prospective cohort with a mean follow-up time of 11.3 years. United Kingdom	Anthropometry (MAMC and WC) and BIA (FMI and FFMI)	**Anthropometrics** Obesity: WC >102 cm Sarcopenia: MAMC ≤25.9 cm. **BIA** Obesity: FMI >11.1 kg/m^2. Sarcopenia: FFMI ≤16.7 kg/m^2.	SO (identified either by anthropometric or BIA) was not associated with an increased risk of CVD events.
Fukuda et al., 2018[49]	716 type 2 diabetes patients (mean age 65 ± 13 years)	Retrospective cohort with a median follow-up time of 2.6 years. Japan	Anthropometry (BMI) and DXA (SMI)	Obesity was defined in four different ways: (1) A/G ration >0.80 for males and >0.62 for females; (2) AF >2.16 kg for males and >1.95 kg for females; (3) %FM >31.8% for males and >38.8% for females; or (4) BMI ≥25 kg/m^2. Sarcopenia: SMI less than 7.0 kg/m^2 (males) or 5.4 kg/m^2 (females).	SO was significantly associated with an elevated risk of incident CVD when obesity was defined using the A/G ratio HR = 2.63; 95% CI = 1.10–6.28 and AF (HR = 2.57; 95% CI = 1.01–6.54). Notably, neither obesity nor sarcopenia alone was significantly associated with an increased risk of incident CVDs.
Farmer et al., 2019[50]	452 931 middle-aged and older adults (40-69 years)	Prospective cohort with a mean follow-up time of 5.1 years. United Kingdom	Anthropometry (BMI and WHR), BIA (SMM and FM) and muscle function (HGS)	Obesity was defined in three different ways: (1) BMI >30 kg/m^2; (2) WHR ≥0.95 for males and ≥0.80 for females; and (3) %FM (differences between quintiles were compared without identifying cut-off for obesity). Sarcopenia was identified in two different ways: (1) the bottom 40% of the SMI distribution; and (2) HGS <30 kg for males and <20 kg for females.	SO was significantly associated with a higher risk of CVD than either obesity or sarcopenia in isolation, as defined by HGS and BMI. This association was consistent among participants regardless of their CVD history, with an HR of 1.37 (95% CI = 1.26–1.49) for those with a history of CVD and 1.42 (95% CI = 1.31–1.55) for those without.
Chuan et al., 2022[51]	386 older adults with type 2 diabetes (≥60 years)	Retrospective cohort study with a mean follow-up time of 3.46 years. China	Anthropometry (BMI), DXA (SMI, FM, VFA and AF) and muscle function (HGS and GS)	Obesity was identified in five different ways: (1) BMI ≥25 kg/m^2; (2) BMI ≥28 kg/m^2; (3) %FM ≥25% for males or ≥35% for females; (4) VFA ≥100 cm^2; or 5) AF >1.69 kg for male and >1.75 kg for females. Sarcopenia: SMI <7.0 kg/m^2 in males or <5.4 kg/m^2 in females plus HGS <28 kg in males and <18 kg in females.	SO, with obesity identified by %FM, was significantly associated with an elevated risk of CVD compared to either obesity or sarcopenia alone (HR = 6.02; 95% CI = 1.56–23.15); a similar association was observed when obesity was defined by BMI ≥25 kg/m^2 (HR = 10.84; 95% CI = 1.57–75.1).
Jiang et al., 2024[52]	7703 middle-aged and older adults (≥45 years)	Prospective cohort with 7-year follow-up. China	Anthropometry (BMI, and WC), muscle function (not mentioned)	Obesity was defined in two different ways: (1) BMI ≥28.0 kg/m^2; or (2) WC ≥85 cm for males or ≥ 80 cm for females. Sarcopenia: specific criteria were not mentioned.	SO was significantly related to increased risks of CVD (HR= 1.47; 95% CI = 1.2–1.8) when obesity was defined based BMI; SO was significantly related to increased risks of CVD (HR=1.38; 95% CI = 1.13–1.68) when obesity was defined based on WC.

SO, sarcopenic obesity; WC, waist circumference; SM, skeletal muscle mass; BIA, bioelectrical impedance analysis; HR, hazard ratio; MAMC, mid-arm muscle circumference; FMI, fat mass index; FFMI, fat free mass index; DXA, dual-energy X-ray absorptiometry; SMI, skeletal muscle index; A/G ratio, android to gynoid ratio; AF, android fat mass; FM, fat mass; WHR, waist:hip ration; HGS, hand grip strength; ASM, appendicular skeletal muscle mass; VFA, visceral fat area.
*In all studies, the group of "normal, i.e. without obesity and without sarcopenia" was regarded as the reference group.
†The specific cut-off values were not mentioned.

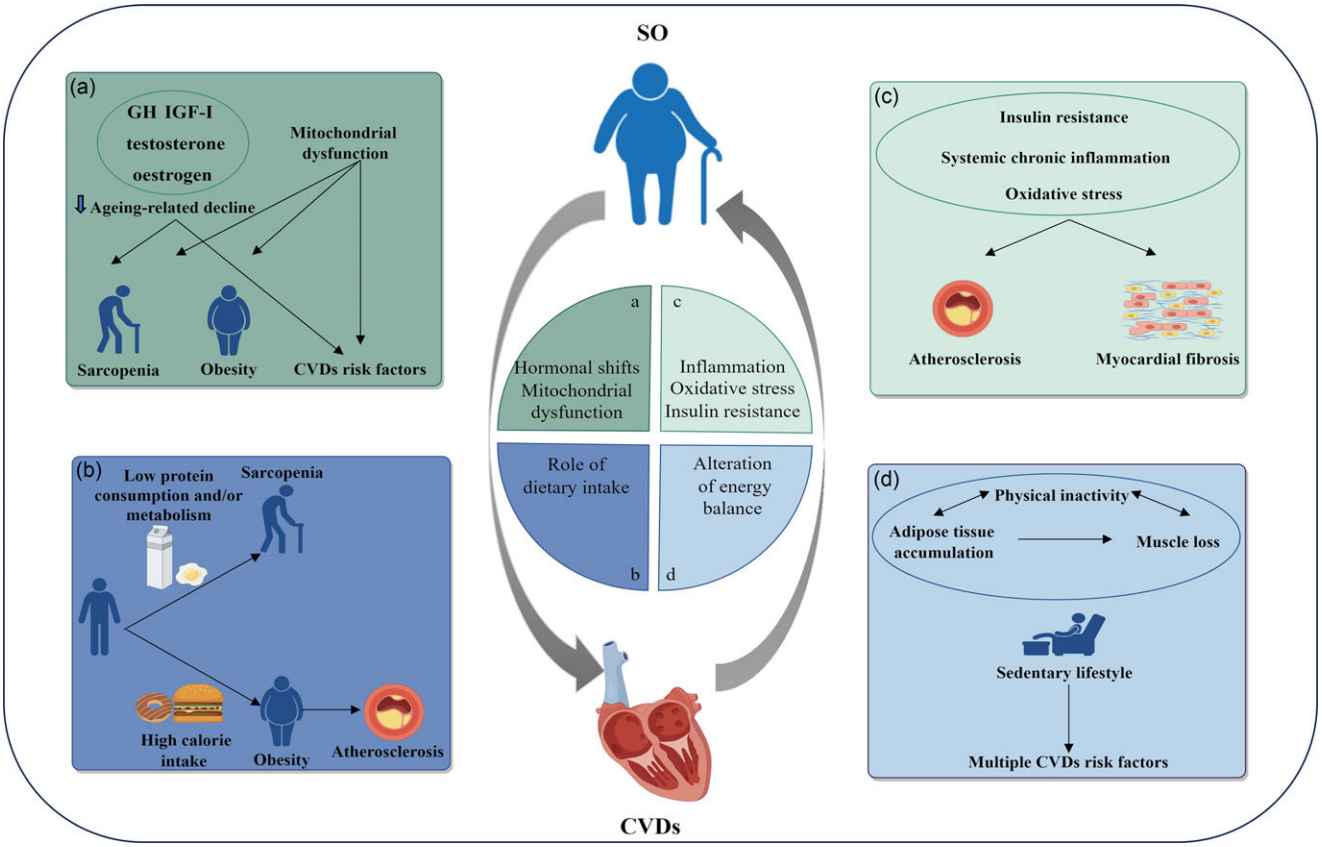

Figure 2. Potential mechanisms underlying the pathogenetic association between SO and CVD risk. The pathogenetic link between SO and CVD may be explained by several underlying mechanisms, suggesting a complex and potentially bidirectional relationship between these two conditions. These mechanisms include: (a) hormonal shifts (ageing-related decline in levels of GH, IGF-1, testosterone and oestrogen) and mitochondrial dysfunction; (b) role of dietary intake; (c) inflammation, oxidative stress and insulin resistance; and (d) alteration of energy balance. SO, sarcopenic obesity; GH, growth hormone; IGF-I, insulin-like growth factor-I. The figure was drawn by Figdraw (www.figdraw.com).

of incorporating muscle function assessments in SO diagnosis[47]. Using data from a Japanese retrospective cohort with a median follow-up of 2.6 years, Fukada et al. reported that SO (obesity was identified based on the android to gynoid ratio (A/G ratio) and android fat mass (AF) but not BMI and %FM) was significantly associated with elevated risk of incident CVD, whereas neither sarcopenia nor obesity alone was linked to a significant increase in risk[49]. Furthermore, two studies suggested that SO had a stronger association with CVD risk than either sarcopenia or obesity alone[50,51].

Pathogenetic link of so with cardiovascular health

The relationship between SO and CVD is complex and multifaceted, with several potential mechanisms underlying the association. The pathophysiology of SO encompasses intricate interactions between multiple factors including inflammation, oxidative stress, insulin resistance, hormonal shifts, mitochondrial dysfunction, improper dietary habits and altered energy balance[53]. These factors may also contribute to the development of CVD, indicating a shared pathogenetic pathway (Fig. 2).

Insulin resistance, inflammation and oxidative stress

Insulin resistance, chronic inflammation and oxidative stress are associated with vascular endothelial dysfunction, potentially precipitating atherosclerosis—a dominant contributor to various CVD such as myocardial infarction, heart failure and stroke[54]. Skeletal muscle serves as a primary site for glucose uptake, storage and myokine secretion. In the context of SO, both obesity and decline of skeletal muscle mass may decrease insulin sensitivity, leading to insulin resistance[55]. This condition can cause hyperinsulinemia, which in turn diminishes the release of nitric oxide (NO), a critical regulator of vascular homeostasis[56]. NO plays an essential role in regulating vascular tone and local blood flow, platelet aggregation and adhesion and leukocyte-endothelial cell interactions[57]. A reduction in NO availability can impair vasodilation and endothelial function, thereby accelerating atherosclerosis[58]. Furthermore, as SO progresses, fat accumulation can lead to the dysregulated production of adipokines and the infiltration of macrophages and other immune cells into adipose tissue[59]. This results in the production of a variety of pro-inflammatory cytokines such as IL-6 and TNF-α, exacerbating systemic, chronic low-grade inflammation in the absence of infection[60]. Concurrently, the decline in muscle mass may reduce myokine secretion, further deteriorating inflammation and insulin resistance[61]. These alterations in humoral factors could induce or amplify oxidative stress[62], a phenomenon characterised by an imbalance between production and accumulation of oxygen reactive species (ROS) in cells and tissues and the biological system's ability to detoxify these reactive products[63]. Oxidative stress can lead to the oxidation of low-density lipoprotein, obstruction of cholesterol efflux and the aggregation of collagen fibres in fibroatheroma plaques. Collectively, these processes

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exacerbate endothelial dysfunction and accelerate atherogenesis[64].

On the other hand, myocardial fibrosis, another well-recognized cardiac condition, and significant risk factor for CVD, is likewise linked to SO. The chronic low-grade inflammatory activity may be involved in myocardial fibrosis, with evidence indicating that inflammatory cells may secrete profibrogenic cytokines such as transforming growth factor-β (TGF-β)[65]. During the pathophysiological development of SO, hyperinsulinemia, induced by insulin resistance, may trigger the renin-angiotensin-aldosterone system[58]. This activation leads to elevated levels of angiotensin II and aldosterone, which in turn activate the angiotensin II type 1 and mineralocorticoid receptors. The engagement of these receptors initiates the TGF-β1-SMAD signaling pathway, ultimately leading to the development of myocardial fibrosis[58]. Moreover, research has highlighted that the augmentation of myocardial oxidative stress, induced by angiotensin II, is a pivotal factor in the onset and progression of myocardial fibrosis[66].

Hormonal shifts and mitochondrial dysfunction

Hormonal changes associated with ageing play a crucial role in the onset and progression of SO. An ageing-related decline in growth hormone (GH) levels leading to numerous adverse consequences for skeletal muscle structure and strength; such decline also reduces liver-derived insulin-like growth factor-I (IGF-I), a principal regulator of muscle mass[67,68]. Both GH and IGF-I are considered atheroprotective, with evidence suggesting IGF-1 promotes a more stable status of atherosclerotic plaques and GH improves endothelial dysfunction[69,70]. Concurrently, the reduction in sex hormone levels (testosterone and oestrogen) associated with ageing leads to diminished muscle mass and strength[71]. These sex hormones also modulate CVD risk factors and vascular biology in a gender-specific manner. For instance, oestrogen is known to lower systemic vascular resistance and enhance endothelial function in coronary vessels in postmenopausal women[72,73]. On the other hand, mutations that leads to impaired oestrogen synthesis or dysfunctional oestrogen receptors are associated with impaired endothelial function and the premature development of atherosclerosis in males[74]. Additionally, testosterone can improve vascular functions and risk factors in men; however, in women, the effects of testosterone are contingent upon estrogen levels[75].

Mitochondrial dysfunction represents a common risk factor among SO and CVD. As the primary sites of aerobic respiration within cells, mitochondria are crucial for generating the energy required through the oxidative phosphorylation system and for regulating cellular metabolism[76]. Mitochondrial dysfunction, arising from mutations in either mitochondrial DNA or nuclear DNA, as well as from ageing, various diseases and environmental stressors, can induce significant cellular disturbances[77]. These include excessive production of ROS, impaired energy production, dysregulated autophagy and activated apoptosis, all of which may contribute to the pathogenesis of CVD and SO[78–81].

Role of dietary intake

Numerous research has reported that adherence to certain dietary patterns, such as the Mediterranean diet and the Dietary Approach to Stop Hypertension diet, is associated with a lower risk of CVD[82,83]. On the contrary, unbalanced dietary patterns such as low protein consumption and excessive high-calorie food intake, may increase the risk of CVD[84]. These dietary patterns may also play a crucial role in the development and progression of SO. The underlying pathophysiologic mechanisms are twofold: First, older adults are susceptible to low protein consumption (both quantity and quality) and/or metabolism, potentially leading to inadequate levels of amino acids essential for muscle protein synthesis and, consequently, the onset of sarcopenia[85]. Second, excessive consumption of high-calorie foods, which leads to obesity, may induce abnormal surges in serum free fatty acids and glucose levels. These changes are associated with an increased production of ROS, resulting in elevated levels of oxidative stress—a key factor in the development and progression of SO[86,87].

Alteration of energy balance

The link between SO and an increased CVD risk could also be partially attributed to disruptions in energy expenditure observed in both conditions. In SO, decreased muscle mass results in a lower basal metabolic rate and consequently, leading to decreased energy expenditure; this reduction creates an energy surplus that favours adipose tissue accumulation[53]. Sarcopenia-related muscle loss and dysfunction make physical activity challenging, while insulin resistance, induced by physical inactivity, further intensifies obesity-related muscle loss[88]. Consequently, the cycle of reduced physical activity, muscle loss and increased fat accumulation may perpetuate a sedentary lifestyle. This lifestyle is linked to complications such as diabetes, hypertension, and dyslipidaemia, all of which are well-recognised risk factors for CVD[89]. Additionally, individuals with CVD may also experience difficulties in maintaining physical activity due to symptoms such as shortness of breath and fatigue. This can lead to obesity-related muscle loss[88], thereby contributing to the development of SO.

Implications for future research

Despite the growing interest in the relationship between SO and CVD risk over the past two decades, much of the research has focused on the association between SO and established CVD risk factors, rather than directly examining the link between SO and CVD incidence or prevalence. To date, only a limited number of studies have delved into the longitudinal relationship between SO and CVD risk. The heterogeneity among these studies in terms of study populations, sample sizes, follow-up periods, definitions and diagnostic criteria for SO, and statistical methods limits the ability to draw definitive conclusions about this relationship. Therefore, there is a pressing need for future observational research to leverage data from longitudinal cohorts with robust designs and to adopt universally recognised definitions and diagnostic criteria for SO to deepen our understanding of this association. Furthermore, the development and progression of SO are governed by a complex interplay of multiple factors, many of which also play a role in the occurrence of various CVD. Yet, the exact mechanisms underlying the pathological connection between these two complex conditions remain largely unexplored. Thus, more efforts are needed to further elucidate the pathophysiology of SO, which could pave the way for a comprehensive strategy for the prevention and treatment of these conditions.

Conclusions

SO poses a persistent and escalating threat to global population health, particularly among older adults. This review synthesises

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findings from previous longitudinal studies, offering suggestive evidence that SO is associated with an increased risk of CVD, higher than that associated with either sarcopenia or obesity alone. The exact mechanisms behind this association remain unclear and may involve common etiological factors shared by these two complex conditions. Additionally, there are also inconsistencies in the observed associations that might be explained by the heterogeneity between studies.

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