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## Conference on 'Nutrition and age-related muscle loss, sarcopenia and cachexia' Symposium 4: Sarcopenia and cachexia and social, clinical and public health dimensions

# Muscle loss and obesity: the health implications of sarcopenia and sarcopenic obesity

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This paper reviews the health implications of obesity, sarcopenia and sarcopenic obesity on CVD and mortality in older adults and discusses the obesity paradox seen in patients with CVD. Obesity is a major public health problem with increasing prevalence worldwide. It is an established risk factor for cardiovascular morbidity and mortality in adult populations. However, there is controversy surrounding the effects of obesity as measured by BMI in older people, and overweight and obesity (BMI ⩾ 25 kg/m$^2$) are apparently associated with increased survival in those with CVD (obesity paradox). Ageing is associated with an increase in visceral fat and a progressive loss of muscle mass which have opposing effects on mortality. Thus BMI is not a good indicator of obesity in older adults. Sarcopenia, the age-associated loss of skeletal muscle mass, is a major concern in ageing populations and has been associated with metabolic impairment, CVD risk factors, physical disability and mortality. Sarcopenia often coexists with obesity. Sarcopenic obesity is a new category of obesity in older adults who have high adiposity coupled with low muscle mass. To fully understand the effect of obesity on mortality in the elderly it is important to take muscle mass into account. The evidence suggests that sarcopenia with obesity may be associated with higher levels of metabolic disorders and an increased risk of mortality than obesity or sarcopenia alone. Efforts to promote healthy ageing should focus on both preventing obesity and maintaining or increasing muscle mass.

**Obesity: Muscle: Sarcopenia: CVD: Mortality: Older adults**

Obesity, i.e. excess body fat usually defined as BMI ⩾ 30 kg/m$^2$, is a major public health problem and is well recognised as a risk factor for cardiovascular morbidity and mortality in adult populations. Obesity prevalence in middle-aged and older adults continues to increase worldwide and has doubled since 1980[1,2]. However, there is controversy surrounding the effects of overweight and obesity in older people, with many studies showing that being overweight, as defined by BMI of 25–29 kg/m$^2$, does not appear to be as harmful in the elderly as in middle-aged populations and may even be associated with lower, rather than higher, mortality[3–5]. In addition, a large body of evidence indicates that overweight and obesity (BMI ⩾ 25 kg/m$^2$) are associated with increased survival in patients with CVD and in particular those with heart failure, an unexpected finding termed the obesity paradox[6–10]. The mechanisms of these paradoxical association remain largely unexplained but a number of explanations have been proposed[11,12]. Part of the explanation may be that BMI is an imprecise measure of body fat and does not distinguish between fat and lean body mass, the latter having been negatively associated with increased mortality[13]. Important changes in body composition occur with age, including a relative increase in fat tissue and a gradual decline in muscle mass, meaning that overall body weight and

**Abbreviations:** BIA, bioelectrical impedance analysis; DXA, dual energy X-ray absorptiometry; HF, heart failure; WC, waist circumference.
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BMI may remain relatively unchanged[3,14,15]. Since BMI does not distinguish between fat mass and fat-free mass, which have opposing effects on the risk of morbidity and mortality, the use of BMI in the elderly may have limitations. Therefore to fully understand the effect of obesity in the elderly, it is important to also take both fat mass and lean mass into account.

Sarcopenia, the age-associated loss of muscle mass and function, is a major concern in ageing populations and is often associated with visceral fat[15]. A new concept of sarcopenic obesity refers to sarcopenia coupled with increased body fat[14,15]. Recent reviews have highlighted the impact of sarcopenic obesity on general health outcomes and metabolic risk[15–20]. The present paper discusses the health implications of obesity and sarcopenia and sarcopenic obesity on CVD and mortality in older adults and discusses the obesity paradox seen in patients with CVD, highlighting the role of diminished muscle mass (sarcopenia) in explaining the obesity paradox.

## Obesity and mortality in older adults

The most commonly used measure of overweight and obesity is BMI, defined by WHO as cut-off points of $\geqslant$25 and $\geqslant$30 kg/m$^2$, respectively[21]. However, the relationship between BMI and mortality in older age is controversial. A systematic review of older adults aged $\geqslant$65 years found that BMI in the overweight range is not associated with a significantly increased mortality risk, and BMI in the moderately obese range is only associated with a modest increase in mortality risk[4]. Similarly, a more recent large meta-analysis of nearly 200 000 individuals aged 65 or older showed a U-shaped relationship between BMI and mortality, with the lowest risk seen in those with a BMI between 24·0 and 30·0 kg/m$^2$ and risk only began to increase when BMI exceeded 33 kg/m$^2$ [5]. Ageing is associated with significant changes in body composition with a substantial reduction in fat-free mass and muscle mass and an increase in visceral fat, even if the body weight remains unchanged[3,14,15]. Thus BMI depends not only on adiposity but also on the loss of muscle mass which has opposing effects on mortality[13], so that BMI may not be a good indicator of obesity in the elderly. It is suggested that measures of adiposity such as waist circumference (WC) or the waist:hip ratio, which better reflect visceral fat, may be more useful at assessing obesity risk as they are better at predicting CVD and mortality in older subjects[22–26]. Central obesity has been defined as a WC > 102 cm for men and >88 cm for women, or a waist:hip ratio $\geqslant$0·9 for men and $\geqslant$0·85 for women[27].

## Sarcopenia

Sarcopenia, the age-related loss of muscle mass and decline in muscle strength, is strongly associated with physical disability, poor quality of life and frailty[28]. Several different definitions of sarcopenia have been used in the literature but to date no consensus definition has been universally adopted[29]. Measurement methods such as computerised tomography, dual energy X-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA) have been used to assess total or skeletal muscle mass[15]. Sarcopenia was originally defined on the basis of appendicular skeletal muscle mass, assessed by DXA and adjusted for height. Those whose height-adjusted appendicular skeletal muscle mass were two standard deviations below the reference for healthy younger persons were considered to be sarcopenic[28]. Subsequently, the definition of sarcopenia has evolved from a focus on muscle mass to muscle strength and physical function. Recently, a definition of sarcopenia has been suggested by The European Working Group on Sarcopenia in Older People which proposed the presence of both low muscle mass and low muscle function (strength or performance)[29].

## Sarcopenia and mortality and cardiovascular risk

Prospective studies have shown consistent associations between low muscle mass (as measured by DXA), BIA and mid-arm muscle circumference) or muscle strength as measured by hand grip and an increased risk of mortality[30–37]. Some studies suggest that decline in muscle strength is a stronger independent risk factor for mortality compared with muscle mass[38,39].

Several mechanisms underlying age-related muscle loss have been recognised, including neuronal and hormonal changes, poor nutrition, physical inactivity and inflammation[15,40]. Thus sarcopenia shares many pathological mechanisms with atherosclerosis, including insulin resistance and inflammation[15]. Population studies have shown sarcopenia to be associated with metabolic impairments, including insulin resistance[15,28,39]. Low muscle mass has also been associated with CVD risk factors, including arterial stiffness and blood pressure[41,42]. However, the association with CVD disease is uncertain and few studies have examined the association between sarcopenia and CVD [43,44]. In those that have there is suggestion that sarcopenia is associated with increased risk of CVD mortality[43].

## Sarcopenic obesity

Given the age-related changes in body composition, sarcopenia often coexists with an increase in fat mass (Fig. 1). Visceral fat and muscle mass are known to be interrelated from a pathogenic point of view and are reported to share common inflammatory pathways[15]. In addition, sarcopenia reduces physical activity which results in decreased energy expenditure leading to increased risk of obesity[15]. Alternatively, visceral fat induces inflammation which may contribute to the development of sarcopenia[45]. The interplay between sarcopenia and rising trends in obesity in an ageing population is emerging as an important public health concern in the elderly. The term sarcopenic obesity was first introduced by Baumgartner[14] and is defined by the combination of

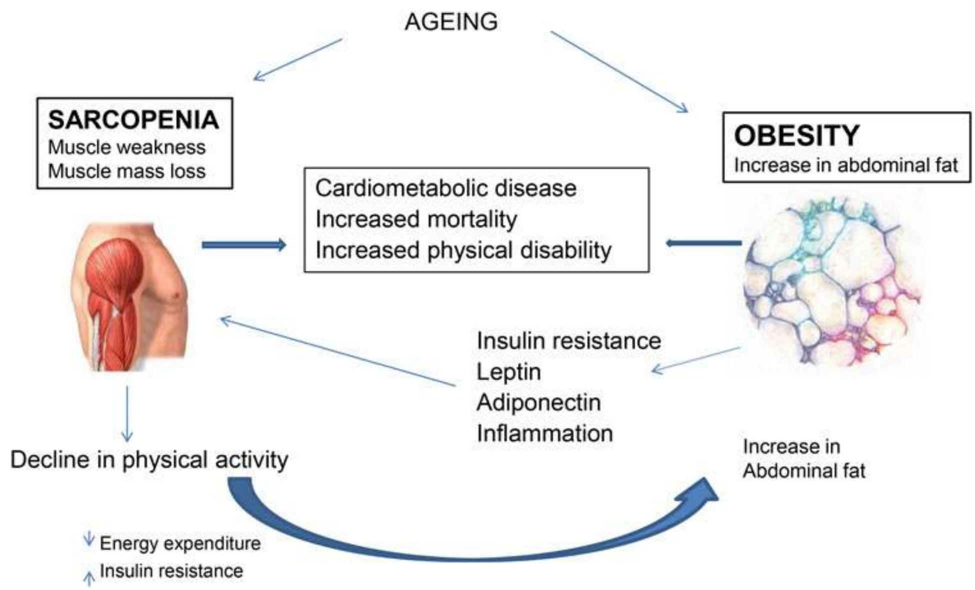


**Fig. 1.** (Colour online) Sarcopenic obesity with ageing. The interplay between sarcopenia and obesity. Adapted from Zamboni *et al.* [15].

sarcopenia and obesity. Both obesity and sarcopenia are associated with metabolic disorders and are important causes of disability, morbidity and mortality[15]. Therefore it is hypothesised that obesity and sarcopenia may act synergistically; sarcopenic obesity may have a greater effect on metabolic disorders, CVD and mortality than either obesity or sarcopenia alone. However, there are limited studies which have investigated the joint effect of sarcopenia and obesity on CVD and mortality, the majority of which have been cross-sectional studies or have focused on disability or physical function as outcomes[15,19,20,46].

### Sarcopenic obesity and mortality

Only a few population prospective studies have examined the association between sarcopenic obesity and the risk of all-cause mortality and there is suggestion that sarcopenic obese adults have the highest mortality risk. In an earlier report from the British Regional Heart study involving over 4000 men, aged 60–79 years followed up for 6 years, men with high WC (>102 cm) and low mid-arm muscle circumference (sarcopenic obese) showed a 55 % increase in mortality risk compared with non-sarcopenic, non-obese individuals[33]. Similar findings were observed with extended 11-year follow-up with the sarcopenic obese group showing the highest mortality risk[43] (Fig. 2). A 14-year prospective study of participants from the National Health and Nutrition Examination Survey III found a similar association in sarcopenic obese women (based on skeletal muscle mass and body fat measurement from BIA), with a 29 % increase in mortality risk compared with those without sarcopenia or obesity[47]. However, no significant association was seen in this cohort between sarcopenic obesity and mortality in men. In the InCHIANTI study of 934 male and female participants aged 65 years and over followed for 6 years, no significant difference in mortality risk was reported across six sarcopenic obesity groups (defined using calf skeletal muscle and BMI) although sarcopenic obese adults showed the lowest survival[35]. A study which defined sarcopenic obesity using a measure of muscle strength instead of muscle mass showed a significant association between sarcopenic obesity and risk of mortality; adult men who were overweight (BMI ⩾ 25) and in the lowest grip strength tertile had the highest mortality risk[36].

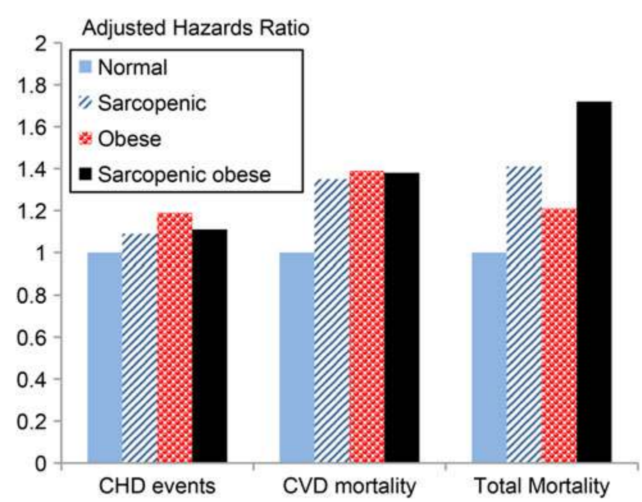


**Fig. 2.** (Colour online) Adjusted hazards ratio for major CHD events, cardiovascular mortality and total cause mortality according to sarcopenic obesity groups (defined according to waist circumference (>102 cms) and mid-arm muscle circumference (lowest 2 quintiles)). Hazards ratios adjusted for age, smoking status, alcohol intake, physical activity and social class. The British Regional Heart Study. Data extracted from Atkins *et al.*[43].

### Sarcopenic obesity and cardiovascular risk factors

Numerous studies have examined the association of sarcopenic obesity with established cardiovascular risk factors. Several cross-sectional studies in Korean populations of older adults have found that sarcopenic obese individuals had the worse cardiovascular risk profile. Sarcopenic obesity (based on skeletal muscle assessed by DXA and obesity measured by either computerised tomography, DXA, BMI or WC) was associated with lower cardiorespiratory fitness, higher fasting glucose levels, a higher risk of hypertension, dyslipidaemia and insulin resistance, and up to an 8-fold increase in risk of the metabolic syndrome compared with non-sarcopenic, non-obese[48–55]. Similar findings were reported in a community-dwelling sample of Taiwanese older adults; sarcopenic obesity (defined by BIA-measured muscle mass and BMI) was associated with the highest risk of metabolic syndrome[56]. In a large cross-sectional analysis of over 14 000 adults from the National Health and Nutrition Examination Survey III, the sarcopenic obese group (defined by BIA-measured muscle mass and BMI) had the highest risk of insulin resistance and dysglycaemia[57]. However, not all studies have shown sarcopenic obese individuals to have the worst profile and some cross-sectional studies have suggested that obese older adults may have higher cardiovascular risk factors than sarcopenic obese subjects[58–60]. Conflicting results have also been shown regarding the relationship between inflammatory markers and sarcopenic obesity. While some cross-sectional studies have shown sarcopenic obese adults to have the highest level of inflammatory markers as measured by C-reactive protein[47,61] others have found no found no significant interactions between sarcopenia and obesity with C-reactive protein[62].

### Sarcopenic obesity and CVD

Despite evidence on the relationships between sarcopenic obesity and cardiovascular risk factors, the association between sarcopenic obesity and CVD has been less studied. Two cross-sectional studies reported that older adults with sarcopenic obesity (based on appendicular skeletal muscle mass and per cent body fat from DXA) did not show significantly higher prevalence of CVD compared with non-sarcopenic, non-obese adults[58,63]. Prospective studies examining the association between sarcopenic obesity and CVD are limited and we have identified only two such studies to date. In the Cardiovascular Health Study, a large prospective study of community-dwelling older men and women (age ⩾ 65 years), sarcopenic obesity based on WC and muscle strength, was associated with the highest risk of CVD and congestive heart failure. Sarcopenic obese adults showed a 23 % increase in risk of CVD and a 42 % increase in risk of congestive heart failure over 8 years of follow-up compared with non-obese non-sarcopenic subjects[44]. However, the risk of CVD events was not significantly greater in the sarcopenic obese group, when defined using BIA-measured muscle mass, implying that muscle strength may be more important than muscle mass. These results are broadly comparable with a prospective study of older men (age 60–79 years), from the British Regional Heart Study which also showed no excess risk of CHD events (fatal or non-fatal myocardial infarction) in sarcopenic obese men (defined by WC and mid-arm muscle circumference) over 11 years of follow-up (Fig. 2)[43]. Sarcopenic obese men showed increased risk of CVD mortality but risk of CVD mortality was similar to those with sarcopenia or obesity alone. However, this study did not consider muscle strength in defining sarcopenic obesity. Overall, findings from cross-sectional and prospective studies do not provide strong evidence for a synergistic effect of sarcopenic obesity on risk of developing CVD.

The inconsistencies in the observed associations of sarcopenic obesity with cardiovascular risk and mortality risk may be explained by the large variability between studies in their sample size and population characteristics, and also due to the heterogeneity in the definition and classification of sarcopenic obesity. To further assess the association between sarcopenic obesity and risk of CVD and mortality there is a need for larger, prospective studies to be carried out which use a standardised definition of sarcopenic obesity.

### The obesity paradox in those with CHD

Despite the potential adverse effects of overweight and obesity on CVD risk factors and incidence, numerous investigators and meta-analysis of studies in cohorts with CHD have shown increased survival in those who are overweight or obese[6–10] when defined by high BMI, the obesity paradox, although this has not been seen in all studies after adjustment for confounders[64,65]. In the RICO Survey, a study of over 2000 patients with acute myocardial infarction, an inverse association was seen between BMI and mortality but this was attenuated after adjustment for factors associated with survival, including prior myocardial infarction, hypertension, diabetes, hyperlipidaemia, smoking and left ventricular ejection fraction[64]. In the Secondary Manifestations of ARTerial disease study no association was seen at all between BMI and mortality in patients with CVD [65]. Part of the explanation for the obesity paradox may be due to the use of BMI to define obesity, which does not take into account lean muscle mass. BMI is a poor marker of body fat and does not distinguish between fat and lean body mass which has been associated with increased mortality[13]. Abdominal obesity has been suggested as a better marker of obesity risk. Indeed, meta-analysis of cohorts in CHD has shown positive associations between WC and mortality[66]. However, few population studies to date have examined the possible role of lean muscle mass in explaining the obesity paradox in those with CHD. In a recent report from the British Regional Heart Study, it was shown that the vast majority of men with normal body weight had low muscle mass and the prevalence of low muscle mass increased appreciably in the presence of CHD and heart failure (HF)



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**Table 1.** BMI and adjusted hazards ratio (95% CI) total mortality in men by CHD and heart failure (HF) status

| | BMI (kg/m²) | | | |
|---|---|---|---|---|
| | 18·5–24·9 | 25–29·9 | 30+ | *P* for trend |
| No CHD and no HF (*n* 3174) | | | | |
| % low muscle mass | 56·7 | 20·9 | 7·8 | |
| Model 1 | 1·00 | 0·88 (0·76, 1·02) | 1·01 (0·83, 1·24) | *P* = 0·67 |
| Model 2 | 1·00 | 0·99 (0·84, 1·16) | 1·25 (1·00, 1·59) | *P* = 0·13 |
| CHD and no HF (*n* 860) | | | | |
| % low muscle mass | 66·4 | 26·4 | 7·3 | |
| Model 1 | 1·00 | 0·71 (0·56, 0·91) | 0·77 (0·57, 1·04) | *P* = 0·04 |
| Model 2 | 1·00 | 0·80 (0·62, 1·03) | 0·96 (0·68, 1·35) | *P* = 0·60 |
| HF (*N* 86) | | | | |
| % low muscle mass | 73·9 | 31·1 | 27·8 | |
| Model 1 | 1·00 | 0·57 (0·28, 1·16) | 0·41 (0·16, 1·09) | *P* = 0·04 |
| Model 2 | 1·00 | 0·66 (0·29, 1·52) | 0·47 (0·17, 1·35) | *P* = 0·09 |

Model 1=adjusted for age, smoking, alcohol intake, social class, physical activity, prevalent diabetes and stroke.
Model 2=Model 1 + low muscle mass.
Low muscle mass defined as lowest quartile of mid-arm muscle circumference.
Source: adapted from Wannamethee *et al.*[67].

(Table 1). Low muscle mass was shown to be associated with increased mortality in those without HF irrespective of CHD status. The lower risk associated with overweight and obesity in those with CHD was attenuated after adjustment for muscle mass suggesting that the lower risk of mortality associated with excess body weight in men with CHD without HF appears largely associated with higher muscle mass (Table 1)[67]. The inverse association seen in those with HF persisted after adjustment for muscle mass. Although one study showed the obesity paradox to persist in those with CHD even after taking into account muscle mass[8], patients with CHD in that study included those with HF. Thus the persistence of lower risk associated with obesity may have been due to the high prevalence of patients with HF in this group. In HF, the obesity paradox may be driven by the deleterious effects of cardiac cachexia (wasting) reflecting the combined loss of muscle and adipose tissue[68]. Cardiac cachexia observed in end stage HF is associated with a decrease of fat mass in addition to a reduced lean muscle mass[69]. It has also been postulated that several physiologic mechanisms may explain the protective effect of a higher BMI on mortality[11]. NT-proBNP levels, a marker of cardiac dysfunction, are lower in overweight and obese patients; lower NT-proBNP predicts lower mortality[66,70]. Another possible explanation for the obesity paradox directly involves the functions of adipose tissue[11,66]. Adipose tissue produces leptin which experimental studies suggest may have protective effects in HF[71] and adiponectin is decreased in obesity; lower concentrations of adiponectin have been associated with lower mortality in patients with CHD or HF[72–74].

The association between WC and mortality in CHD patients in contrast to BMI have found to be positive[67] or null[65]. The positive association between central adiposity and mortality in those with CHD is in keeping with the findings that the inverse association seen for BMI in those with CHD may reflect reduced muscle mass.

## Conclusions

BMI is not a good indicator of obesity in older adults because it does not take into account the loss of muscle mass with increasing age. Muscle mass and visceral fat have opposing effects on mortality. The increased mortality in normal weight subjects compared with overweight and obese subjects in those with CHD (obesity paradox) appears to be associated to some extent with low muscle mass. Sarcopenia is associated with increased mortality and is often associated with visceral obesity. Sarcopenic obesity is a new category of obesity in older adults and there is some evidence that it is associated with higher levels of cardiovascular risk factors and an increased risk of mortality than obesity or sarcopenia alone. This highlights the need to take muscle mass and function into account when assessing the effects of obesity in older adults. Several different definitions of sarcopenia have been used in the literature but to date no consensus definition has been agreed. There is a need for a universal standardised definition of sarcopenia and sarcopenic obesity to improve identification and management in clinical practice. Efforts to promote healthy ageing and to reduce the risk of morbidity and mortality should focus not only on preventing obesity but also on maintaining or increasing muscle mass and strength.

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## Conflicts of Interest

None.

## Authorship

S. G. W. initiated the design of the manuscript. J. L. A. carried out the literature review on the influence of sarcopenic obesity on cardiovascular risk. S. G. W. and J. L. A. both contributed to the writing of the manuscript.

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