TITLE: Associations of Sarcopenic Obesity with the Metabolic Syndrome and Insulin Resistance over Five Years in Older Men: The Concord Health and Ageing in Men Project

AUTHORS: David Scott[1,2], Robert Cumming[3,4,5] Vasi Naganathan[4], Fiona Blyth[4], David G Le Couteur[6], David J Handelsman[7], Markus Seibel[8] , Louise M Waite[4], Vasant Hirani [5,9]

AFFILIATIONS:

1 School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia

2 Department of Medicine and Australian Institute of Musculoskeletal Science, Melbourne Medical School – Western Campus, The University of Melbourne, St Albans, Victoria, Australia

3 School of Public Health, University of Sydney, New South Wales, Sydney, Australia.

4 Centre for Education and Research on Ageing, Concord Hospital, University of Sydney, New South Wales, Sydney, Australia.

5 The ARC Centre of Excellence in Population Ageing Research, University of Sydney, New South Wales, Sydney, Australia.

6 ANZAC Research Institute & Charles Perkins Centre, University of Sydney, New South Wales, Sydney, Australia.

7 Department of Andrology, Concord Hospital & ANZAC Research Institute, University of Sydney, New South Wales, Sydney, Australia.

8 Bone Research Program, ANZAC Research Institute, and Dept of Endocrinology & Metabolism, Concord Hospital, The University of Sydney, New South Wales, Sydney, Australia.

9 School of Life and Environmental Sciences, Charles Perkins Centre, University of Sydney, New South Wales, Sydney, Australia.

CORRESPONDING AUTHOR:

Dr. David Scott

School of Clinical Sciences at Monash Health, Monash University

Clayton, Victoria, Australia 3168

Email: david.scott@monash.edu

Telephone: +61 3 8572 2397

Fax: +61 3 9594 6437

FUNDING: This work was supported by the National Health and Medical Research Council (project grant number 301916) and the Ageing and Alzheimer's Institute. DS acknowledges fellowship funding from the National Health and Medical Research Council (GNT1123014).

ROLE OF THE FUNDING SOURCE: The funding body had no role in the design of the study, collection and analysis of data or decision to publish.

CONFLICTS OF INTEREST: None.

AUTHOR CONTRIBUTIONS: DS and VH completed data analysis and interpretation and drafted the manuscript; RC, VS, FB, DGLC, DJH MS and LMW contributed to study conception and design and revised the manuscript.

Abstract

Purpose: Previous cross-sectional studies investigating associations of sarcopenic obesity with metabolic syndrome (MetS) and insulin resistance have not utilised consensus definitions of sarcopenia. We aimed to determine associations of sarcopenic obesity with MetS and insulin resistance over five years in community-dwelling older men.

Methods: 1,231 men aged ≥70 years had appendicular lean mass (ALM) and body fat percentage assessed by dual-energy X-ray absorptiometry and hand grip strength and gait speed tests. Sarcopenia was defined as low ALM/height (m^2) and low hand grip strength or gait speed (European Working Group definition); obesity was defined as body fat percentage ≥30%. MetS was assessed at baseline and 5-years later. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was assessed at 5-years only.

Results: Men with sarcopenic obesity (odds ratio, 95% CI: 2.07, 1.21-3.55) and non-sarcopenic obesity (4.19, 3.16-5.57) had higher MetS likelihood than those with non-sarcopenic non-obesity at baseline. Higher gait speed predicted lower odds for prevalent MetS (0.45, 0.21-0.96 per m/s). Higher body fat predicted increased odds for prevalent and incident MetS (1.14, 1.11-1.17 and 1.11, 1.02-1.20 per kg, respectively) and deleterious 5-year changes in MetS fasting glucose, high-density lipoprotein cholesterol and triglycerides (all $P<0.05$). Compared with non-sarcopenic non-obesity, estimated marginal means for HOMA-IR at 5-years were higher in non-sarcopenic obesity only (1.0, 0.8-1.1 vs 1.3, 1.2-1.5; $P<0.001$). Similar results were observed when sarcopenic obesity was defined by waist circumference.

Conclusions: Sarcopenic obesity does not appear to confer greater risk for incident MetS or insulin resistance than obesity alone in community-dwelling older men.

KEYWORDS: sarcopenia; obesity; metabolic syndrome; insulin resistance; ageing

1.0 Introduction

Sarcopenia, the age-related decline in skeletal muscle mass and function, is associated with increased disability in older adults (1). There is growing interest in the effects of sarcopenia on cardiometabolic health, particularly given the important role that skeletal muscle plays in insulin sensitivity (2). Sarcopenia has been associated with increased risk for the metabolic syndrome (MetS) (3), type 2 diabetes (4) and cardiovascular disease (5).

Since obesity is a primary risk factor for poor cardiometabolic health it is possible that risk is increased further in the presence of sarcopenia ("sarcopenic obesity"). In cross-sectional studies, Korean older adults with sarcopenic obesity (defined as low appendicular lean mass [ALM] and high visceral fat area) are eight times as likely to develop MetS compared with obesity or sarcopenic alone (6), and have increased risk of insulin resistance, MetS, and cardiovascular disease (7). In contrast, other studies have reported that sarcopenic obesity confers lower risk for cardiovascular disease risk factors (8) and MetS (9) compared with obesity alone, and no increased risk for cardiovascular disease mortality after adjusting for lifestyle factors (10).

A limitation of previous studies is their cross-sectional designs which limit comments on causality in the relationship between sarcopenic obesity and cardiometabolic health. Furthermore, inconsistent findings are likely attributable to considerable heterogeneity in measurements and thresholds used to assess sarcopenia. In recent years, expert groups have provided consensus definitions for sarcopenia which allow investigators to apply consistent methods to explore the relationship between sarcopenia and health outcomes (11). The aim of the present study was to investigate cross-sectional and longitudinal associations between sarcopenic obesity categories and both MetS and insulin resistance in community-dwelling older men, using the current consensus definition of sarcopenia.

2.0 Materials and Methods

2.1 Study design and population: CHAMP is an epidemiological study of Australian men aged 70 years and over. The selection of study subjects has been described in detail elsewhere (12). Briefly, men living in a defined urban geographical region (the Local Government Areas of Burwood, Canada Bay and Strathfield) near Concord Hospital in Sydney, Australia, were recruited. The sampling frame was the New South Wales Electoral Roll, on which registration is compulsory. The only exclusion criterion was living in a residential aged care facility. Eligible men were sent a letter describing the study and, if they had a listed telephone number, were telephoned about one week later. Of 2,815 eligible men with whom contact was made, 1,511 agreed to participate in the study (54%). An additional 194 eligible men heard about the study from friends or the local media and were recruited after contacting the study investigators, yielding a cohort of 1,705 subjects.

Baseline data were collected between January 2005 and June 2007. Men completed questionnaires at home including questions on demographics, health status, and physical activity. Subsequently, participants attended a study clinic at Concord Hospital for assessment of body composition, physical performance, medication use and blood biochemistry. These measurements were repeated at follow-up clinics conducted two (January 2007 - October 2009) and five years (January 2012 - October 2013) after baseline, however for the purposes of this study only 5-year data was included in longitudinal analyses. Trained staff collected data and the same equipment was used for all measurements and assessments, which were carried out in a single clinic. All participants gave written informed consent. The study complied with the Declaration of Helsinki and was approved by the Sydney South West Area Health Service Human Research Ethics Committee, Concord Repatriation General Hospital, Sydney, Australia.

2.2 Anthropometrics, body composition and muscle function: Height was measured using a Harpenden stadiometer and weight using Wedderburn digital scales; BMI was calculated as kg/m^2. Waist circumference was measured around the narrowest point between ribs and hips when viewed from the front after exhaling. Two consecutive recordings were made for each site to the nearest 1 cm using a metal tape on a horizontal plane without compression of skin. The mean of the two values was used in the analysis. Whole-body dual-energy X-ray absorptiometry (DXA) scans were performed using a Hologic Discovery-W scanner (Hologic Inc., Bedford, MA, USA). The same DXA scanner was used for all scans. Quality control scans were conducted daily using the Hologic whole-body phantom and indicated no shifts or drifts. ALM was calculated as the sum of lean mass of arms and legs (kg), and absolute and percentage of total body fat percentage was determined. Hand grip strength (kg) of the dominant hand (best of two trials) was assessed using a Jamar dynamometer (Promedics, Blackburn, UK).

2.3 Sociodemographic and health assessments: Sociodemographic variables included age, education and smoking status. Physical activity was measured using the Physical Activity Scale for the Elderly (PASE) (13). Trained personnel conducted a medication inventory of each participant during the baseline clinic visit. Participants were instructed to bring all the prescription and over-the-counter medications they were taking to the clinic visit for review. They were also asked whether they had taken any prescription or non-prescription medications during the past month. Details of all medications and prescription patterns were recorded. Reported medicines were coded using the Iowa Drug Information Service code numbers (14). Data on medical conditions were obtained from self-report of whether a doctor or a health care provider had told participants that they had any of the following: diabetes, thyroid dysfunction, osteoporosis, Paget's disease, stroke, Parkinson's disease, epilepsy,

hypertension, heart attack, angina, congestive heart failure, intermittent claudication, chronic obstructive lung disease, liver disease, cancer (excluding non- melanoma skin cancers), osteoarthritis, and gout.

2.4 Blood pressure and blood tests: Systolic (SBP) and diastolic blood pressure (DBP) was measured by trained staff using a sphygmomanometer. The mean of four readings, taken on the right arm, with the participant in a standing and lying position were used in the analysis. Serum from early morning fasting blood samples was stored at -80°C until assay. Blood tests were performed at the Diagnostic Pathology Unit of Concord RG Hospital, which is a NATA (National Australian Testing Authority) accredited pathology service, using a MODULAR Analytics system (Roche Diagnostics, Castle Hill, Australia). Fasting serum 25-hydroxyvitamin D levels (25(OH)D) were measured by RIA (DiaSorin Inc., Stillwater, MN) (15). The assay for 25(OH)D has a sensitivity of <3.75 nmol/L with an intra-assay precision of 7.6% and an inter-assay precision of 9.0%. Fasting blood samples for cholesterol and high-density lipoprotein (HDL) cholesterol analysis were performed on a Roche Cobas 8000 analyser using a standard automated enzymatic methodology. Fasting blood samples for glucose measurement were collected in fluoride-oxalate (anticoagulant) tubes. Plasma glucose was measured using the Hexokinase method. Fasting blood results were recorded at baseline and follow-up for LDL and HDL cholesterol, triglycerides, and glucose, but insulin was only measured at 5 year follow up. Homeostasis Model Assessment - Insulin Resistance (HOMA IR) was calculated at 5 years using HOMA calculator v 2.2.3 (© Diabetes Trials Unit, University of Oxford) (16).

2.5 Definition of MetS: Metabolic syndrome was defined using the National Cholesterol Education Program (NCEP) Adult Treatment Panel III criteria, which require presence of

three or more of: waist circumference >102 cm; fasting glucose ≥5.6 mmol/L and/or on anti-diabetic medications; triglycerides ≥1.7 mmol/L, high-density lipoprotein cholesterol (HDL-C) <1.03 mmol/L; and systolic blood pressure (SBP) ≥130 mm Hg and/or diastolic blood pressure (DBP) ≥85 mm Hg and/or on antihypertensive medications (17).

2.6 Definition of sarcopenic obesity: There are currently no internationally-accepted consensus definitions for sarcopenic obesity. The European Working Group on Sarcopenia (EWGSOP) criteria were used to define sarcopenia in this study (11). The EWGSOP defines sarcopenia in men as low ALM/height (<7.26kg/m^2) combined with low hand grip strength (<30kg) and/or low gait speed (≤0.8m/s). Obesity was defined in this study as body fat percentage ≥30%, as body fat percentage is a more appropriate indicator of obesity than BMI (18). Participants were categorised as *non-sarcopenic non-obesity (referent), non-sarcopenic obesity, sarcopenic non-obesity, and sarcopenic obesity.*

***2.7 Statistical analyses*:** Independent samples t-tests compared baseline characteristics for included participants with those excluded at baseline due to missing data and those lost to follow-up. Descriptive characteristics were compared across categories of sarcopenic obesity using one-way ANOVA for continuous variables and Chi-square tests for categorical variables. Bonferroni post-hoc tests identified between-group differences. Multivariable binary logistic regression analyses, adjusted for baseline age, physical activity, smoking, 25(OH)D, statin use, and number of comorbidities, examined odds for prevalent MetS and each MetS component according to sarcopenic obesity categories. Covariates were selected based on potential confounding of the relationship between sarcopenic obesity and MetS and retained in the model if they had a significance level of P<0.2, although age and PASE scores were included in the models regardless of significance level.

Multivariable binary logistic regression examined associations of baseline and change in value of each component of sarcopenic obesity (ALM, hand grip strength, gait speed and body fat) with prevalent and incident MetS. Multivariable generalised linear models adjusting for the above potential confounders obtained estimated marginal means for HOMA IR (measured at 5-year follow-up only) according to sarcopenic obesity status at baseline. Generalised linear models also investigated associations between baseline and 5-year change values for the components of sarcopenic obesity, with 5-year changes in the values for each component of MetS. Finally, a sensitivity analysis was conducted to determine whether associations of sarcopenic obesity with baseline MetS and its components (with the exception of high waist circumference), and insulin resistance at five years, differed when obesity was defined using high waist circumference (>102 cm) as an indicator of central obesity.

P values <0.05 or 95% confidence intervals not including the null point were considered statistically significant. Analyses were performed in SPSS Statistics 23 (IBM, NY, USA).

3.0 Results

Of 1,705 men enrolled at baseline, 32 did not attend a clinic appointment, and 45 had incomplete anthropometric and 139 had incomplete physical performance data. The majority of exclusions were due to missing data for fasting glucose (N=258). Thus, 1231 (72%) participants were included in baseline data analyses. Compared with excluded participants, included participants were younger (77.5±5.8 vs 76.7±5.3 years; P=0.009), had fewer comorbidities (2.8±1.9 vs 2.4±1.7; P<0.001), and lower grip strength (32.7±8.1 vs 34.8±7.3; P<0.001) and gait speed (0.86±0.23 vs 0.90±0.20; P=0.003) but there were no differences in ALM or body fat percentage (both P>0.05). Amongst included participants, 190 (15%) had sarcopenia and 525 (43%) had obesity. In total, 596 (48.5%) men had non-sarcopenic non-obesity, 445 (36%) had non-sarcopenic obesity, 110 (9%) had sarcopenic non-obesity, and 80 (6.5%) had sarcopenic obesity.

Table 1 presents baseline characteristics according to sarcopenic obesity categories. Men with sarcopenic obesity were significantly older than those with non-sarcopenic non-obesity and non-sarcopenic obesity, but there were no differences in education status. Men with sarcopenic obesity had higher numbers of comorbidities and lower physical activity than those with non-sarcopenic non-obesity, but the highest proportion of diabetes, hypertension and statin medication users were observed in non-sarcopenic obesity. The overall prevalence of MetS at baseline was 34%, and men with sarcopenic obesity demonstrated significantly lower prevalence than those with non-sarcopenic obesity, but higher prevalence than those with non-sarcopenic non-obesity and sarcopenic non-obesity (Table 1). Amongst components of MetS, men with non-sarcopenic obesity consistently demonstrated the worst values, and only triglycerides levels were significantly higher in sarcopenic obesity compared with non-sarcopenic non-obesity and sarcopenic non-obesity.

Table 1. Baseline characteristics according to sarcopenic obesity status

	Non-sarcopenic non-obesity N=596	Non-sarcopenic obesity N=445	Sarcopenic non-obesity N=110	Sarcopenic obesity N=80
Age (years)	75.9±4.8[c,d]	75.9±4.7[c,d]	81.2±6.3[a,b]	80.3±6.5[a,b]
Education beyond school (%)	84.6	83.6	86.4	91.1
Current smoker (%)*	5.8[c]	4.3[c]	13.8[a,b]	3.8
Number of comorbidities	2.2±1.6[b,c,d]	2.6±1.7[a]	2.7±1.8[a]	3.0±1.7[a]
PASE score	140.5±57.3[b,c,d]	129.4±59.8[a,c,d]	96.9±56.3[a,b]	88.4±54.9[a,b]
Diabetes medication (%)	8.4[b,c]	16.4[a]	18.2[a]	16.3
Hypertension medication (%)	62.2[b]	71.2[a]	64.5	70.0
Statins (%)	40.4[b]	50.3[a]	40.0	43.8
25(OH)D (nmol/L)	59.0±23.1[b]	55.0±20.4[a]	58.8±23.4	54.6±22.6
BMI (kg/m^2)	26.5±2.9[b,c]	30.7±3.4[a,c,d]	23.3±2.4[a,b,d]	27.2±2.3[b,c]

Total body fat (%)	24.9±3.9[b,d]	33.9±3.1[a,c]	24.4±4.4[b,d]	34.8±3.5[a,c]
ALM (kg)	22.5±2.8[c,d]	22.9±2.9[c,d]	18.6±2.1[a,b]	19.0±2.0[a,b]
Hand grip strength (kg)	36.4±6.8[c,d]	36.2±6.1[c,d]	26.7±5.8[a,b]	27.4±6.9[a,b]
Gait speed (m/s)	0.96±0.19[b,c,d]	0.91±0.18[a,c,d]	0.76±0.17[a,b]	0.70±0.20[a,b]
Waist circumference (cm)	98.6±83.7[b,c,d]	110.6±86.8[a,c,d]	92.9±82.7[a,b,d]	104.1±76.0[a,b,c]
SBP (mmHg)	146.4±18.7[b]	149.7±18.5[a]	146.1±21.1	144.2±21.2
DBP (mmHg)	78.0±9.7	79.2±9.7[c,d]	75.5±11.0[b]	75.5±11.0[b]
Fasting glucose (mmol/L)	5.4±1.2[b]	5.7±1.1[a]	5.3±1.4	5.4±0.9
HDL-C (mmol/L)	1.5±0.4[b]	1.4±0.3[a,c]	1.6±0.5[b]	1.5±0.4
Triglycerides (mmol/L)	1.2±0.6[b,d]	1.5±0.7[a,c]	1.1±0.5[b,d]	1.4±0.6[a,c]
MetS (%)	21.5[b,d]	55.1[a,c,d]	11.8[b,d]	37.5[a,b,c]

*± standard deviation; all tests are one-way ANOVA except *(Chi-square tests).*

[a]Significant difference to non-sarcopenic non obesity; [b]significant difference to non-sarcopenic obesity; [c]significant difference to sarcopenic non-obesity; [d]Significant difference to sarcopenic obesity (Bonferroni post-hoc tests).

Table 2 reports odds ratios for prevalent MetS and its components at baseline according to sarcopenic obesity status. After adjustment for confounders, compared with non-sarcopenic non-obesity, non-sarcopenic obesity and sarcopenic obesity were associated with greater likelihood, and sarcopenic non-obesity with lower likelihood, of overall MetS. With the exception of low HDL cholesterol, non-sarcopenic obesity was associated with increased likelihood for all MetS components, whereas sarcopenic obesity was associated with increased likelihood of high waist circumference only.

Table 2. Odds ratios (95% CI) for baseline MetS and its components according to sarcopenic obesity status.

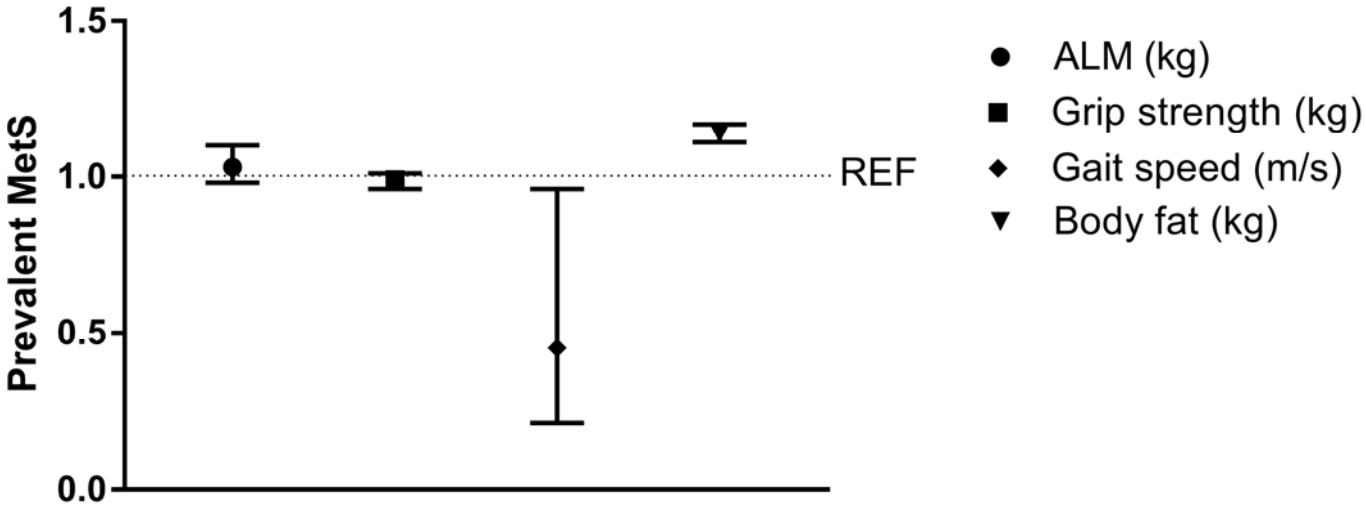
	Non-sarcopenic non-obesity N=596	Non-sarcopenic obesity N=445	Sarcopenic non-obesity N=110	Sarcopenic obesity N=80
High waist circumference	*N=193*	*N=387*	*N=14*	*N=46*
Unadjusted	REF	**14.32 (10.31, 19.90)**	**0.31 (0.17, 0.55)**	**3.08 (1.89, 5.00)**
Adjusted*	REF	**14.37 (10.14, 20.36)**	**0.32 (0.17, 0.59)**	**3.26 (1.90, 5.60)**
High fasting glucose or diabetes meds	*N=162*	*N=177*	*N=33*	*N=29*

Unadjusted	REF	**1.77 (1.36, 2.30)**	**1.15 (0.74, 1.79)**	1.52 (0.93, 2.49)
Adjusted*	REF	**1.61 (1.22, 2.12)**	1.09 (0.66, 1.78)	1.39 (0.81, 2.39)
High triglycerides	*N=107*	*N=144*	*N=11*	*N=18*
Unadjusted	REF	**2.20 (1.65, 2.94)**	**0.51 (0.26, 0.98)**	1.33 (0.76, 2.35)
Adjusted*	REF	**2.09 (1.55, 2.84)**	0.54 (0.27, 1.07)	1.41 (0.78, 2.57)
Low HDL cholesterol	*N=67*	*N=73*	*N=8*	*N=10*
Unadjusted	REF	**1.56 (1.09, 2.23)**	0.62 (0.29, 1.33)	1.13 (0.56, 2.30)
Adjusted*	REF	1.35 (0.93, 1.97)	0.62 (0.28, 1.39)	0.89 (0.41, 1.93)
High BP or BP meds	*N=560*	*N=437*	*N=104*	*N=74*
Unadjusted	REF	**3.41 (1.57, 7.43)**	1.30 (0.50, 3.40)	0.77 (0.31, 1.90)
Adjusted*	REF	**2.76 (1.24, 6.14)**	1.27 (0.45, 3.59)	0.67 (0.24, 1.87)
MetS	*N=128*	*N=245*	*N=13*	*N=30*
Unadjusted	REF	**4.48 (3.42, 5.87)**	**0.49 (0.27, 0.90)**	**2.19 (1.34, 3.59)**
Adjusted*	REF	**4.19 (3.16, 5.57)**	**0.50 (0.26, 0.95)**	**2.07 (1.21, 3.55)**

**Adjusted for baseline age, physical activity, smoking, 25(OH)D, statin use, and number of comorbidities.*

Associations of individual components of sarcopenic obesity with prevalent MetS at baseline are presented in Figure 1. After adjustment for age, physical activity, smoking, 25(OH)D, statin use, and number of comorbidities, and for the other components of sarcopenic obesity, a 1kg increase in body fat was associated with 14% increased likelihood of prevalent MetS and a 1m/s increase in gait speed was associated with less than half the likelihood of MetS. There was no association for ALM or hand grip strength with likelihood of MetS

Figure 1. Associations of components of sarcopenic obesity with prevalent MetS at baseline



Data are odds ratios and 95% confidence intervals (error bars) per unit increase in sarcopenic obesity component. Error bars that do not cross the reference line (REF) are significant at P<0.05. All analyses adjusted for baseline age, physical activity, smoking, 25(OH)D, statin use, and number of comorbidities, and for the other components of sarcopenic obesity.

Six hundred and ninety-seven (57%) men completed the 5-year follow-up and had complete data for MetS with the primary reason for loss to follow-up being death. Significantly greater proportions of men with sarcopenic obesity (64%) and sarcopenic non-obesity (61%) did not complete the 5-year assessment compared with those with non-sarcopenic non-obesity and non-sarcopenic obesity (38 and 43%, respectively; both P<0.0015). At baseline, men who did not complete the 5-year follow-up were older (78.3±5.9 vs 75.4±4.5 years; P<0.001) and had more comorbidities (2.7±1.8 vs 2.2±1.6; P<0.001) than men who participated. Associations of individual components of sarcopenic obesity (and their changes over five years) with incident MetS at 5-year follow-up are presented in Table 3. There were no associations between baseline components of sarcopenic obesity and likelihood of incident MetS. However, a 1kg increase in body fat from baseline to follow-up was associated with approximately 11% increased likelihood of incident MetS.

Table 3. Associations between sarcopenic obesity components (baseline and 5 -year change) and incident MetS at five years.

	Adjusted OR (95% CI)*

Baseline sarcopenic obesity components	ALM (kg)	1.10 (0.99, 1.22)
	Grip strength (kg)	0.99 (0.95, 1.03)
	Gait speed (m/s)	0.51 (0.13, 2.06)
	Body fat (kg)	1.00 (0.96, 1.04)
Change in sarcopenic obesity components (Δ from baseline to year 5)	ALM (kg)	0.97 (0.77, 1.21)
	Grip strength (kg)	1.03 (0.98, 1.08)
	Gait speed (m/s)	1.68 (0.52, 5.46)
	Body fat (kg)	**1.11 (1.02, 1.20)**

**Adjusted for baseline age, physical activity, smoking, 25(OH)D, statin use, and number of comorbidities, and for the other components of sarcopenic obesity. Excludes participants with MetS at baseline.*

Table 4 reports associations between baseline and 5-year changes in sarcopenic obesity components with 5-year changes in components of MetS over five years. Higher hand grip strength at baseline was associated with lower SBP and DBP at follow-up, while higher body fat was associated with a decrease in trigylcerides only. Furthermore, increases in ALM from baseline to follow-up were associated with increases in SBP and DBP, while increases in body fat were associated with increases in fasting glucose, HDL cholesterol and triglycerides. An increase in

grip strength was significantly associated with increased HDL cholesterol levels and increase in gait speed was associated with a decrease in SBP and DBP, but also an increase in fasting glucose.

Table 4. Associations between sarcopenic obesity components (baseline and 5-year change) and 5-year changes in MetS components.

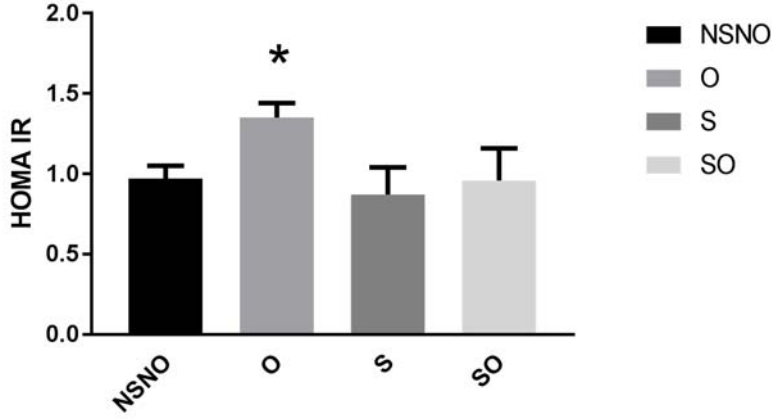
		Change in MetS components (Δ from baseline to year 5) B (95% CI)				
		SBP	**DBP**	**GLU**	**HDL**	**TG**
*Baseline sarcopenic obesity components**	ALM (kg)	-0.41 (-1.00, 0.19)	0.08 (-0.25, 0.41)	-0.01 (-0.05, 0.02)	-0.01 (-0.01, 0.01)	-0.01 (-0.02, 0.02)
	Grip strength (kg)	**-0.40 (-0.63, 0.17)**	**-0.15 (-0.28, -0.03)**	0.01 (-0.01, 0.02)	-0.01 (-0.01, 0.01)	0.01 (-0.01, 0.01)
	Gait speed (m/s)	2.50 (-5.37, 10.36)	2.69 (-1.64, 7.01)	-0.32 (-0.79, 0.15)	0.05 (-0.06, 0.16)	0.07 (-0.17, 0.31)

	Body fat (kg)	-0.12 (-0.36, 0.12)	-0.13 (-0.26, 0.01)	-0.01 (-0.02, 0.01)	-0.01 (-0.01, 0.01)	**-0.01 (-0.02, -0.01)**
*Change in sarcopenic obesity components (Δ from baseline to year 5)**	ALM (kg)	**1.64 (0.37, 2.91)**	**0.86 (0.17, 1.54)**	0.01 (-0.07, 0.08)	0.01 (-0.01, 0.02)	0.01 (-0.03, 0.04)
	Grip strength (kg)	0.24 (-0.04, 0.52)	-0.03 (-0.18, 0.13)	0.01 (-0.01, 0.03)	**0.01 (0.01, 0.01)**	-0.01 (-0.01, 0.01)
	Gait speed (m/s)	**-7.92 (-14.53, -1.31)**	**-7.50 (-11.07, -3.92)**	**0.58 (0.18, 0.98)**	-0.03 (-0.11, 0.05)	-0.12 (-0.32, 0.07)
	Body fat (kg)	-0.02 (-0.49, 0.44)	0.20 (-0.06, 0.45)	**0.05 (0.02, 0.08)**	**-0.02 (-0.02, -0.01)**	**0.04 (0.03, 0.06)**

*Adjusted for baseline age, physical activity, smoking, 25(OH)D, statin use, and number of comorbidities. *Further adjusted for the other components of sarcopenic obesity. Abbreviations: NSNO; non-sarcopenic non-obesity, O; non-sarcopenic obesity, S; sarcopenic non-obesity, SO; sarcopenic obesity, SBP; systolic blood pressure, DBP; diastolic blood pressure, GLU; fasting glucose, HDL; high-density lipoprotein cholesterol, TG; triglycerides, ALM; appendicular lean mass.*

Fasting insulin pmol/L (median [interquartile range]: 44.0 [31.0-62.8]) and HOMA IR (0.8 [0.6-1.2]) were measured at 5-year follow-up only. As demonstrated by the estimated marginal means presented in Figure 2, after adjustment for potential confounders, HOMA IR was signifcantly higher in non-sarcopenic obesity compared with non-sarcopenic non-obesity (P<0.001). A trend was also observed for higher HOMA IR in non-sarcopenic obesity compared with sarcopenic non-obesity (P=0.054), but no other significant differences were observed between groups.

Figure 2. Estimated Marginal Means (+SEM) for HOMA IR levels at five years according to baseline sarcopenic obesity status.



*All analyses adjusted for baseline age, physical activity, smoking, 25(OH)D, statin use, and number of comorbidities. * indicates significantly different to non-sarcopenic non-obese.*

Finally, a sensitivity analysis was conducted to determine whether associations of sarcopenic obesity with MetS and insulin resistance differed when obesity was defined using high waist circumference as an indicator of central obesity. Supplementary Table 1 demonstrates that similar associations with MetS and its components at baseline were observed when sarcopenic obesity was defined by waist circumference as previously observed when defined by body fat percentage; in adjusted models non-sarcopenic obesity only was associated with increased likelihood of high fasting glucose, high triglycerides and low HDL cholesterol, compared with non-sarcopenic non-obesity. Both sarcopenic obesity and non-sarcopenic obesity were associated with significantly increased likelihood of overall MetS (12- and 18-fold increased odds, respectively) with the magnitude of association stronger for non-sarcopenic obesity. Furthermore, estimated marginal means (EMM) from generalised linear models indicated that, compared with non-sarcopenic non-obesity (EMM: 0.96, 95% CI 0.80-1.12), only non-sarcopenic obesity (1.27, 1.11-1.43, P=0.001) was associated with significantly higher HOMA IR levels at year 5 (sarcopenic non-obesity: 0.80, 0.46-1.14, P=0.382; sarcopenic obesity: 1.06, 0.65-1.48, P=0.633).

4.0 Discussion

This 5-year study demonstrated that community-dwelling older men with sarcopenic obesity have increased likelihood of prevalent MetS compared with counterparts with healthy body habitus. However, men with non-sarcopenic obesity and those who demonstrate increases in body fat over time appear to have the greatest risk for prevalent and incident MetS. Nevertheless, changes in physical function were associated with improved HDL cholesterol and blood pressure and these findings may inform future trials investigating benefits of weight loss and maintenance of muscle mass and function in sarcopenic obesity.

To the best of our knowledge, this is the first study to prospectively investigate associations between sarcopenic obesity and MetS in older adults. Our findings suggest that sarcopenic obesity has little influence on incident MetS and MetS components over five years in older men. While higher gait speed was associated with reduced prevalence of MetS and increases in gait speed and hand grip strength were associated with reductions in some MetS components over time, we also observed conflicting findings including positive associations for change in ALM with blood pressure and for change in gait speed with fasting glucose. Conversely, increases in body fat increased likelihood of incident MetS and were associated with significant increases in fasting glucose and triglycerides, and significant decreases in HDL cholesterol. These findings suggest current, rather than previous, body habitus is the strongest predictor of MetS risk as illustrated in the British Regional Heart Study, in which weight reduction, regardless of initial BMI, was associated with reduced risk of MetS at follow-up (19). Thus, avoiding body fat gains during ageing may be more important than preventing sarcopenia progression for reducing incident MetS in older adults. While this is somewhat contradictory to evidence indicating that associations of weight loss with increased mortality during ageing are attributable to loss of muscle (20), it supports the concept that

reducing fat in older adults is likely to be beneficial for cardiometabolic health even in older adults (21).

In the present study we assessed insulin resistance, measured by HOMA IR, at follow-up only. Similar to the findings for MetS, only participants with non-sarcopenic obesity had significantly higher HOMA IR than those with non-sarcopenic non-obesity, whereas those with sarcopenic obesity were not different to controls. A previous analysis of the Korean Sarcopenic Obesity Study reported increased HOMA IR levels in participants with sarcopenic obesity compared with all other participants (22), and so further research is required to explore this relationship. Factors including fatty infiltration and inflammation of skeletal muscle, AMP-activated protein kinase, myostatin and low vitamin D status have been implicated in the association of sarcopenic obesity with insulin resistance (23). Indeed, we reported that fatty infiltration of skeletal muscle is associated with increased fasting glucose and C-reactive protein levels (24), and it is likely that muscle fat infiltration is increased in sarcopenic obesity (25).

We observed significantly lower waist circumference and BMI in men with sarcopenic obesity compared with those with non-sarcopenic obesity. However, while it is possible that these differences also explained the stronger associations of non-sarcopenic obesity with MetS and insulin resistance, our sensitivity analyses in which obesity was defined by high waist circumference similarly indicated that non-sarcopenic obesity was associated with greater likelihood of MetS at baseline, and higher HOMA-IR at year 5, than sarcopenic obesity. These similar findings suggest that body fat distribution does not necessarily explain the poorer cardiometabolic health associated with non-sarcopenic obesity compared to sarcopenic obesity in older men.

We have reported that low lean mass is associated with approximately 80% increased likelihood of MetS in Australian, but not Korean, older adults (3). A separate study

demonstrated no association between low muscle mass and MetS after adjustment for fat mass in Korean older adults (26). In Japanese older adults, lower muscle mass and grip strength was associated with MetS, particularly in men aged 65 to 74 years, but these associations were explained by abdominal obesity (27). The present study similarly indicated that only changes in body fat, not sarcopenia components, was predictive of development of MetS over five years in community-dwelling older men. Furthermore, older men with sarcopenia alone had similar HOMA-IR levels at five years, and also had significantly lower likelihood of MetS at baseline, compared with those non-sarcopenic non-obesity. This difference appears to be largely explained by the fact that men with sarcopenic non-obesity had reduced likelihood for high waist circumference, which is a component of MetS. Thus, sarcopenia in the absence of obesity in older men may reduce the likelihood of MetS due to lower prevalence of abdominal obesity.

A cross-sectional study of 600 Taiwanese older adults which assessed sarcopenia using bioelectrical impedance analysis and obesity according to BMI demonstrated that odds for MetS were greater in sarcopenic obesity (11-fold) than sarcopenia (two-fold) and obesity (seven-fold) alone (28). Similarly, in the Korean National Health and Nutrition Examination Survey, odds ratios for MetS were 6.3 in sarcopenic obesity (defined by DXA-assessed ALM and BMI), compared with 1.9 in sarcopenia alone and 4.6 in obesity alone (29) and in the Korean Longitudinal Study on Aging, odds ratios for MetS were 8.3 in sarcopenic obesity (defined by DXA-assessed ALM and computed tomography-assessed visceral fat area), 2.6 in sarcopenia alone and 5.5 in obesity alone (6). A recent study in Brazilian older adults used hand grip strength and waist circumference measurements to define sarcopenic obesity and reported odds for MetS that were 10- and 12-fold higher for obesity and sarcopenic obesity compared with controls (11). In contrast, a Korean study reported only 30% increased risk for MetS in men with sarcopenic obesity, defined by weight-adjusted muscle mass and total body

fat percentage, compared to those without sarcopenic obesity (30). Our own results suggest that the likelihood for MetS is not increased by the same magnitude in sarcopenic obesity as they are for non-sarcopenic obesity in older men. Clearly, associations of sarcopenic obesity with MetS are substantially influenced by measurements and thresholds applied.

While the present study does not support the hypothesis that sarcopenic obesity increases risk of incident MetS and insulin resistance more than obesity or sarcopenia alone, they provide important considerations for clinicians in managing patients with sarcopenic obesity. Our findings support the beneficial effect of fat loss for cardiometabolic health, but weight loss can result in declines in muscle mass which may reduce physical function particularly in sarcopenic obesity (31). Thus, older adults with sarcopenic obesity may require specialised weight loss programs that incorporate careful management of dietary intake and resistance training interventions to minimise loss of muscle mass and function (18).

These results are subject to several limitations. Participants with missing data at baseline and who did not complete the follow-up assessment were generally of poorer health than those included in the study, and given that the sample population exclusively consisted of community-dwelling older men, the results may not be generalisable to older women or institutionalised older men. Fasting insulin was assessed only at follow-up and so changes in HOMA IR could not be investigated. Furthermore, factors such as medical conditions and medication use were not monitored throughout the five-year follow-up period and changes in these may have influenced changes in MetS and insulin resistance outcomes. Finally, as highlighted above, we preferentially selected body fat percentage as an indicator of obesity as it a more direct estimate of adiposity than anthropometric indices such as BMI or waist circumference, and also given waist circumference in also included in the definition of MetS.

As a result, our findings may not be directly comparable to previous studies which have used differing definitions of sarcopenic obesity.

5.0 Conclusions

Older men with sarcopenic obesity have increased likelihood of prevalent MetS compared with counterparts with healthy body habitus. However, increases in body fat, rather than sarcopenia-associated changes in muscle mass and function, appear to be more predictive of incident MetS in community-dwelling older men.

6.0 Acknowledgements: We thank all the staff working on CHAMP and the participants in the project.

7.0 References

1. Marzetti E, Calvani R, Tosato M, Cesari M, Di Bari M, Cherubini A, et al. Sarcopenia: an overview. Aging Clin Exp Res. 2017:1-7.

2. Bahat G, İlhan B. Sarcopenia and the cardiometabolic syndrome: A narrative review. European Geriatric Medicine.

3. Scott D, Park MS, Kim TN, Ryu JY, Hong HC, Yoo HJ, et al. Associations of low muscle mass and the metabolic syndrome in Caucasian and Asian middle-aged and older adults. J Nutr Health Aging. 2016;20(3):248-55.

4. Cuthbertson DJ, Bell JA, Ng SY, Kemp GJ, Kivimaki M, Hamer M. Dynapenic obesity and the risk of incident Type 2 diabetes: the English Longitudinal Study of Ageing. Diabet Med. 2015:doi: 10.1111/dme.12991.

5. Chin SO, Rhee SY, Chon S, Hwang Y-C, Jeong I-K, Oh S, et al. Sarcopenia Is Independently Associated with Cardiovascular Disease in Older Korean Adults: The Korea National Health and Nutrition Examination Survey (KNHANES) from 2009. PLoS ONE. 2013;8(3):e60119.

6. Lim S, Kim JH, Yoon JW, Kang SM, Choi SH, Park YJ, et al. Sarcopenic obesity: prevalence and association with metabolic syndrome in the Korean Longitudinal Study on Health and Aging (KLoSHA). Diabetes Care. 2010;33(7):1652-4.

7. Chung J-Y, Kang H-T, Lee D-C, Lee H-R, Lee Y-J. Body composition and its association with cardiometabolic risk factors in the elderly: A focus on sarcopenic obesity. Arch Gerontol Geriatr. 2013;56(1):270-8.

8. Aubertin-Leheudre M, Lord C, Goulet ED, Khalil A, Dionne IJ. Effect of sarcopenia on cardiovascular disease risk factors in obese postmenopausal women. Obesity. 2006;14(12):2277-83.

9. Baumgartner RN, Wayne SJ, Waters DL, Janssen I, Gallagher D, Morley JE. Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. Obes Res. 2004;12(12):1995-2004.

10. Atkins JL, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. Sarcopenic Obesity and Risk of Cardiovascular Disease and Mortality: A Population-Based Cohort Study of Older Men. J Am Geriatr Soc. 2014;62:253-60.

11. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412-23.

12. Cumming RG, Handelsman D, Seibel MJ, Creasey H, Sambrook P, Waite L, et al. Cohort Profile: The Concord Health and Ageing in Men Project (CHAMP). Int J Epidemiol. 2009;38(2):374-8.

13. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. J Clin Epidemiol. 1993;46(2):153-62.

14. IDIS Drug Vocabulary and Thesaurus Description: Division of Drug Information Service, College of Pharmacy, University of Iowa; [Available from: http://itsnt14.its.uiowa.edu/.

15. Hirani V, Naganathan V, Cumming RG, Blyth F, Le Couteur DG, Handelsman DJ, et al. Associations Between Frailty and Serum 25-Hydroxyvitamin D and 1,25-Dihydroxyvitamin D Concentrations in Older Australian Men: The Concord Health and Ageing in Men Project. J Gerontol A Biol Sci Med Sci. 2013;68(9):1112-21.

16. HOMA calculator The Oxford Centre for Diabetes. Endocrinology & Metabolism. Diabetes Trial Unit [Available from: https://www.dtu.ox.ac.uk/ToolsSoftware/.

17. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome. An American Heart

Association/National Heart, Lung, and Blood Institute scientific statement. Circulation. 2005;112(17):2735-52.

18. Scott D, Daly RM, Sanders KM, Ebeling PR. Fall and Fracture Risk in Sarcopenia and Dynapenia With and Without Obesity: the Role of Lifestyle Interventions. Curr Osteoporos Rep. 2015;13(4):235-44.

19. Wannamethee SG, Shaper AG, Whincup PH. Modifiable Lifestyle Factors and the Metabolic Syndrome in Older Men: Effects of Lifestyle Changes. J Am Geriatr Soc. 2006;54(12):1909-14.

20. Allison D, Zannolli R, Faith M, Heo M, Pietrobelli A, Vanltallie T, et al. Weight loss increases and fat loss decreases all-cause mortality rate: results from two independent cohort studies. Int J Obes. 1999;23(6):603-11.

21. Chapman IM. Obesity paradox during aging. In: Mobbs C, Hof P, editors. Body Composition and Aging. 37. New York: Karger Publishers; 2010. p. 20-36.

22. Kim TN, Park MS, Lim KI, Choi HY, Yang SJ, Yoo HJ, et al. Relationships between Sarcopenic Obesity and Insulin Resistance, Inflammation, and Vitamin D Status: The Korean Sarcopenic Obesity Study (KSOS). Clin Endocrinol (Oxf). 2012.

23. Cleasby ME, Jamieson PM, Atherton PJ. Insulin resistance and sarcopenia: mechanistic links between common co-morbidities. J Endocrinol. 2016;229(2):R67-R81.

24. Scott D, Trbojevic T, Skinner E, Clark R, Levinger P, Haines T, et al. Associations of calf inter-and intra-muscular adipose tissue with cardiometabolic health and physical function in community-dwelling older adults. J Musculoskelet Neuronal Interact. 2015;15(4):350-7.

25. Zamboni M, Mazzali G, Fantin F, Rossi A, Di Francesco V. Sarcopenic obesity: A new category of obesity in the elderly. Nutr Metab Cardiovasc Dis. 2008;18(5):388-95.

26. Koo HS, Kim MJ, Kim K-M, Kim Y-S. Decreased muscle mass is not an independent risk factor for metabolic syndrome in Korean population aged 70 or older. Clin Endocrinol (Oxf). 2015;82(4):509-16.

27. Ishii S, Tanaka T, Akishita M, Ouchi Y, Tuji T, Iijima K, et al. Metabolic Syndrome, Sarcopenia and Role of Sex and Age: Cross-Sectional Analysis of Kashiwa Cohort Study. PLoS ONE. 2014;9(11):e112718.

28. Lu C-W, Yang K-C, Chang H-H, Lee L-T, Chen C-Y, Huang K-C. Sarcopenic obesity is closely associated with metabolic syndrome. Obesity research & clinical practice. 2013;7(4):e301-e7.

29. Kang S-Y, Lim GE, Kim YK, Kim HW, Lee K, Park T-J, et al. Association between Sarcopenic Obesity and Metabolic Syndrome in Postmenopausal Women: A Cross-sectional Study Based on the Korean National Health and Nutritional Examination Surveys from 2008 to 2011. Journal of Bone Metabolism. 2017;24(1):9-14.

30. Lee J, Hong Y-p, Shin HJ, Lee W. Associations of Sarcopenia and Sarcopenic Obesity With Metabolic Syndrome Considering Both Muscle Mass and Muscle Strength. J Prev Med Pub Health. 2016;49(1):35-44.

31. Thomas DR. Weight loss in older adults. Rev Endocr Metab Disord. 2005;6(2):129-36.