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Sex-specific differences in risk factors for sarcopenia amongst community-dwelling older adults

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Abstract With considerable variation including potential sex-specific differential rate of skeletal muscle loss, identifying modifiable factors for sarcopenia will be pivotal to guide targeted interventions. This study seeks to identify clinical and biological correlates of sarcopenia in community-dwelling older adults, with emphasis on the role of anabolic and catabolic stimuli, and special reference to gender specificity. In this cross-sectional study involving 200 community-dwelling and functionally independent older adults aged ≥50 years, sarcopenia was defined using the Asian Working Group for Sarcopenia criteria. Comorbidities, cognitive and functional performance, physical activity and nutritional status were routinely assessed. Biochemical parameters included haematological indices, lipid panel, vitamin D level, anabolic hormones [insulin-like growth factor-1 (IGF-1), free testosterone (males only)] and catabolic markers [inflammatory markers (interleukin-6, C-reactive protein) and myostatin]. Multiple logistic regression was performed to identify independent predictors for sarcopenia. Age was associated with sarcopenia in both genders. Malnutrition conferred significantly higher odds for sarcopenia in women (OR=5.71, 95 % CI 1.13–28.84.44, p=0.035) while higher but acceptable range serum triglyceride was protective in men (OR=0.05, 95 % CI 0.00–0.52, p=0.012). Higher serum myostatin independently associated with higher odds for sarcopenia in men (OR=1.11, 95 % CI 1.00–1.24, p=0.041). Serum IGF-1 was significantly lower amongst female sarcopenic subjects, with demonstrable trend for protective effect against sarcopenia in multiple regression models, such that each 1 ng/ml increase in IGF-1 was associated with 1 % decline in odds of sarcopenia in women (p=0.095). Our findings support differential pathophysiological mechanisms for sarcopenia that, if corroborated, may have clinical utility in guiding sex-specific targeted interventions for community-dwelling older adults.

Keywords Sarcopenia · Nutrition · Insulin-like growth factor-1 · Myostatin

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Introduction

Age-related decline in skeletal muscle mass eventually culminating in loss of strength and function is now recognized as a distinct clinical phenotype referred to as sarcopenia (Fielding et al. 2011). The implications of sarcopenia in the older adult have been reported extensively, including impairment in physical performance, mobility limitations, frailty and its consequences of falls, fractures and hospitalizations Clark and Manini (2010). Although progressive loss of muscle mass appears inevitable, with annual rate of decline of 1–2 % from as early as age 50, and muscle strength decline of 1.5 % per year between ages 50 and 60 increasing to 3 % annually thereafter (von Haehling et al. 2010), there exists considerable variation in the rate of skeletal muscle mass loss (Korostishevsky et al. 2015) which, importantly, remains potentially reversible as even the most frail of older adults had exhibited improvements with exercise interventions (Fiatarone et al. 1994).

There is emerging evidence for sarcopenia being a multi-factorial process, driven by hormonal alterations, nutritional factors, inflammation and disease states (Cruz-Jentoft et al. 2014; Landi et al. 2012). Myostatin, a member of the transforming growth factor-β superfamily, has also received attention for its role as an inhibitor of skeletal muscle growth and satellite cell proliferation (Trendelenburg et al. 2009). Further, it has been postulated that the progressive loss of muscle mass may be consequent to the imbalance between muscle tissue anabolism and catabolism, although the specific contribution of individual pathways in the complex pathogenesis of muscle wasting remains to be delineated. With an ageing population and estimated direct healthcare cost attributable to sarcopenia amounting to $18.5 billion in the USA in the year 2000 (Janssen et al. 2004), the identification of modifiable factors for sarcopenia will be pivotal to developing therapeutic interventions to counteract the cascade from sarcopenia through frailty and eventual disability.

Epidemiological data for discordance in sarcopenia prevalence between older men and women have been conflicting (Landi et al. 2012; Patel et al. 2013; Lee et al. 2013). Several studies had suggested differential sex-specific rate of absolute muscle loss, being greater in men than in women, which could not be attributed merely to the larger initial muscle mass in men (Payette et al. 2003). The need for improved insights into potential differential sex-specific mechanisms driving sarcopenia is further heightened by the recently observed higher mortality risk conferred by sarcopenia in older women despite its lower prevalence compared to their male counterparts (Batsis et al. 2014). Indeed, data from the Framingham Heart Study had suggested that longitudinal decline in fat-free mass was consequent to a withdrawal of anabolic stimuli in men but reflecting an increase in catabolic stimuli represented by interleukin-6 (IL-6) in women (Payette et al. 2003).

This study sought to identify clinical and biological correlates of sarcopenia in a representative cohort of community-dwelling and functionally independent older adults, with emphasis on the role of anabolic hormones [insulin-like growth factor-1 (IGF-1) and free testosterone (in men)] and catabolic stimuli (inflammation and myostatin), and special reference to sex specificity.

Methods

Study population

The "Longitudinal Assessment of Biomarkers for characterization of early Sarcopenia and predicting frailty and functional decline in community-dwelling Asian older adults Study" (GERI-LABS) is a prospective cohort study involving cognitively intact and functionally independent adults aged 50 years and older residing within the community. We have completed the study's target recruitment of 200 subjects between August 2013 and July 2014, with all subjects having undergone baseline clinical and blood biomarker assessments.

Informed written consent was obtained from the participant, and the study was approved by the Domain Specific Review Board (DSRB) of the National Healthcare Group (NHG).

Eligibility criteria

Subjects were eligible if they were (i) aged 50 to 99 years at study enrollment, (ii) community-dwelling, and (iii) independent in both activities of daily living (ADLs) and instrumental ADLs (iADLs). We excluded subjects with a known history of dementia or evidence of cognitive impairment [defined as Chinese Mini-Mental State Examination (CMMSE) score ≤21] (Sahadevan et al. 2000), and inability to walk at least 4.5 m independently.

Residents of sheltered or nursing homes were similarly excluded.

Data collection

Clinical assessments

Demographic data and comorbid vascular risk factors—hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, peripheral vascular disease, smoking and alcohol history, stroke or transient ischemic attack and ischemic heart disease—were captured at baseline, based on self-report or the use of disease-specific medications. The presence of chronic inflammatory disease and active treatment with steroids or immunosuppressant medication, malignancy, other endocrine disorders and evidence of advanced organ failure was routinely documented.

Standing height, body weight and waist circumference were measured, and body mass index (BMI) was calculated. With increasing recognition for the limitation of BMI as an indicator of obesity as it includes lean mass in its calculation without discriminating between muscle and fat distribution, A Body Shape Index (ABSI) was calculated for each individual [ABSI=Waist circumference/($BMI^{2/3}Height^{1/2}$)], which allows for better representation of central body volume (Krakauer and Krakauer 2012).

The locally validated CMMSE was administered for assessment of cognitive performance. Functional ability was evaluated using Barthel's basic activities of daily living (ADL) index and Lawton and Brody's instrumental ADL (iADL) index (Mahoney and Barthel 1965; Barberger-Gateau et al. 1992). Physical activity level was captured using the Frenchay activity scale (Wade et al. 1985). Nutrition was systematically assessed using the locally validated Mini Nutritional Assessment (MNA) questionnaire (Chan et al. 2010).

Grip strength was measured using the hydraulic hand dynamometer (North Coast@ Hydraulic Hand Dynamometer), with two trials of grip strength for each hand and all four trials averaged to yield strength. Gait speed was based on the time to walk 3 m, and physical performance was measured using the Short Physical Performance Battery (SPPB) (Guralnik et al. 1994).

Laboratory investigations

Fasting venous blood sample was obtained at baseline for measurement of serum albumin, glucose, lipid profile, C-reactive protein, full blood count and 25-hydroxy vitamin D, with additional analysis for free testosterone level in male subjects, performed within the clinical laboratory of Tan Tock Seng Hospital, Singapore. Vitamin D deficiency was defined as serum concentration <20 ng/ml based on modified Holick's classification (Thacher and Clarke 2011), while C-reactive protein levels in excess of 5 mg/l were considered elevated.

In addition, serum obtained following centrifugation at 3000 rpm for 10 min was aliquoted and stored at −80 °C until analysis for Interleukin-6 (IL-6) (eBioscience, San Diego, CA, USA), myostatin *(Immundiagnostik AG, Bensheim)* and insulin-like growth factor-1 (IGF-1) *(BioVendor, Ceska republika)*. All assays were performed according to the manufacturers' recommendations, and measured in duplicates, with detection limits of 0.04 pg/ml for IL-6, 0.6 ng/ml for myostatin and 1 ng/ml for IGF-1.

Muscle and fat measures

Percentage body fat and lean mass measures were obtained via a dual-energy X-ray absorptiometry system (Discovery™ APEX 13.3; Hologic, Bedford, MA, USA). Appendicular skeletal mass was derived from the summation of muscle mass measurements in the four limbs.

Sarcopenia was defined using the Asian Working Group for Sarcopenia criteria, employing recommended gender specific cut-off values for muscle mass as measured on DXA, as well as grip strength and gait speed (Chen et al. 2014).

Statistical analyses

Descriptive data are presented as means (±SD) or median (interquartile range, IQR) for quantitative variables and as absolute and relative frequencies for categorical variables. We performed univariate analyses comparing sarcopenic and non-sarcopenic subjects in baseline demographics, clinical measures of cognitive, functional and physical performance, nutritional status, comorbid medical conditions and biochemical parameters using independent-sample *t* test and Wilcoxon rank-sum test for parametric and non-parametric continuous variables, respectively, and chi-square and Fisher's exact tests for categorical variables. Analyses were first performed on the whole cohort, followed by subgroup analyses

according to gender. To identify independent factors contributing to sarcopenia, we performed multiple logistic regression, adjusting for age and significant univariate variables.

Statistical analyses were performed using STATA version 12 (Stata Corp., College Station, TX). All statistical tests were two-tailed, with p value ≤0.05 considered statistically significant.

Results

Clinical characteristics of study cohort

Two hundred and thirty-one healthy older adults fulfilled eligibility criteria, of whom 200 provided written informed consent and were recruited. The mean age of enrolled subjects was 67.9±7.9 years, with female predominance (68.5 %) and majority of Chinese ethnicity (92 %). There was no difference in age and gender distribution between study participants and non-participants.

Fifty (25 %) subjects fulfilled criteria for sarcopenia at baseline (Fig. 1), and they were significantly older than their non-sarcopenic counterparts (72.0±8.1 vs 66.6±7.3, $p<0.001$), but gender distribution was similar between groups. Amongst the individual medical comorbidities, only cerebrovascular disease was significantly different, being higher in prevalence amongst sarcopenic subjects (8 vs 0.7 %, $p=0.014$). While serum albumin level was similar and none of the participants was overtly malnourished based on MNA total score <17, sarcopenic subjects were significantly more likely to be at risk of malnutrition (MNA total score 17–23.5: 14 % vs 4.7 %, $p=0.025$). Sarcopenic subjects had significantly lower BMI (21.7±2.4 vs 24.7±3.8, $p<0.001$), but their ABSI was higher than their non-sarcopenic counterparts (8.55±0.64 vs 8.27±0.47, $p=0.002$) (Table 1). Functional ability and physical performance was similar between sarcopenic and non-sarcopenic subjects, but sarcopenic subjects exhibited significantly lower physical activity level (FAI: 29.9±5.6 vs 32.8±4.7, $p=0.0003$).

Biochemical parameters of study cohort

Haemoglobin level was significantly lower in sarcopenic subjects (12.9±1.3 vs 13.3±1.2 g/dl, $p=0.038$), who also had lower serum triglyceride levels (0.97±0.41 vs 1.27±0.61 mmol/l, $p=0.001$) despite there being no difference in prevalence of dyslipidaemia or use of cholesterol-lowering medications. Total cholesterol, fasting glucose and serum vitamin D levels were similar between groups.

Serum markers of inflammation were similar between sarcopenic and non-sarcopenic subjects (even following exclusion of subjects with inflammatory disease or immunosuppressant therapy), and there was no significant difference in myostatin levels. However, sarcopenic subjects had significantly lower serum levels of IGF-1 [100.1 (IQR 77.7–117.6) vs 117.6 ng/ml (IQR 88.2–147), $p=0.007$] (Table 2).

Clinical and biochemical parameters associated with sarcopenia: gender-specific)

The prevalence of sarcopenia was 24.8 % in women and 25.4 % in men. While the risk of malnutrition was significantly higher in female sarcopenic subjects (17.7 vs 2.9 %, $p=0.007$), nutritional status was not associated with sarcopenia in men. Additionally, we observed that female sarcopenic subjects had significantly higher ABSI (8.52±0.75 vs 8.22±0.53, $p=0.012$) despite their significantly lower BMI, while sarcopenia was associated with ABSI but not BMI in men (Table 3). In both genders, serum triglyceride level was significantly lower in sarcopenic subjects. There was no association between vitamin D and sarcopenia in both genders.

Male sarcopenic subjects had significantly lower haemoglobin and lymphocyte counts than their non-sarcopenic counterparts, a difference that was not observed in women. Amongst the individual biomarkers representative of a catabolic state, there was a trend for higher serum myostatin in male sarcopenic subjects [30.72 (IQR 23.75–34.05) vs 25 (21–32.27)ng/ml, $p=0.057$], but without demonstrable difference in women (Table 4). Serum levels of inflammatory cytokine (IL-6) were similar between sarcopenic and non-sarcopenic subjects in both genders, with no observed association with CRP.

Within hormonal pathways, serum IGF-1 was significantly lower in female sarcopenic subjects [94.11 (IQR 75.6–112.35) vs 117.6 ng/ml (IQR 88.2–141.71), $p=0.002$]. However, neither IGF-1 nor free testosterone level differentiated between male sarcopenic and non-sarcopenic subjects.

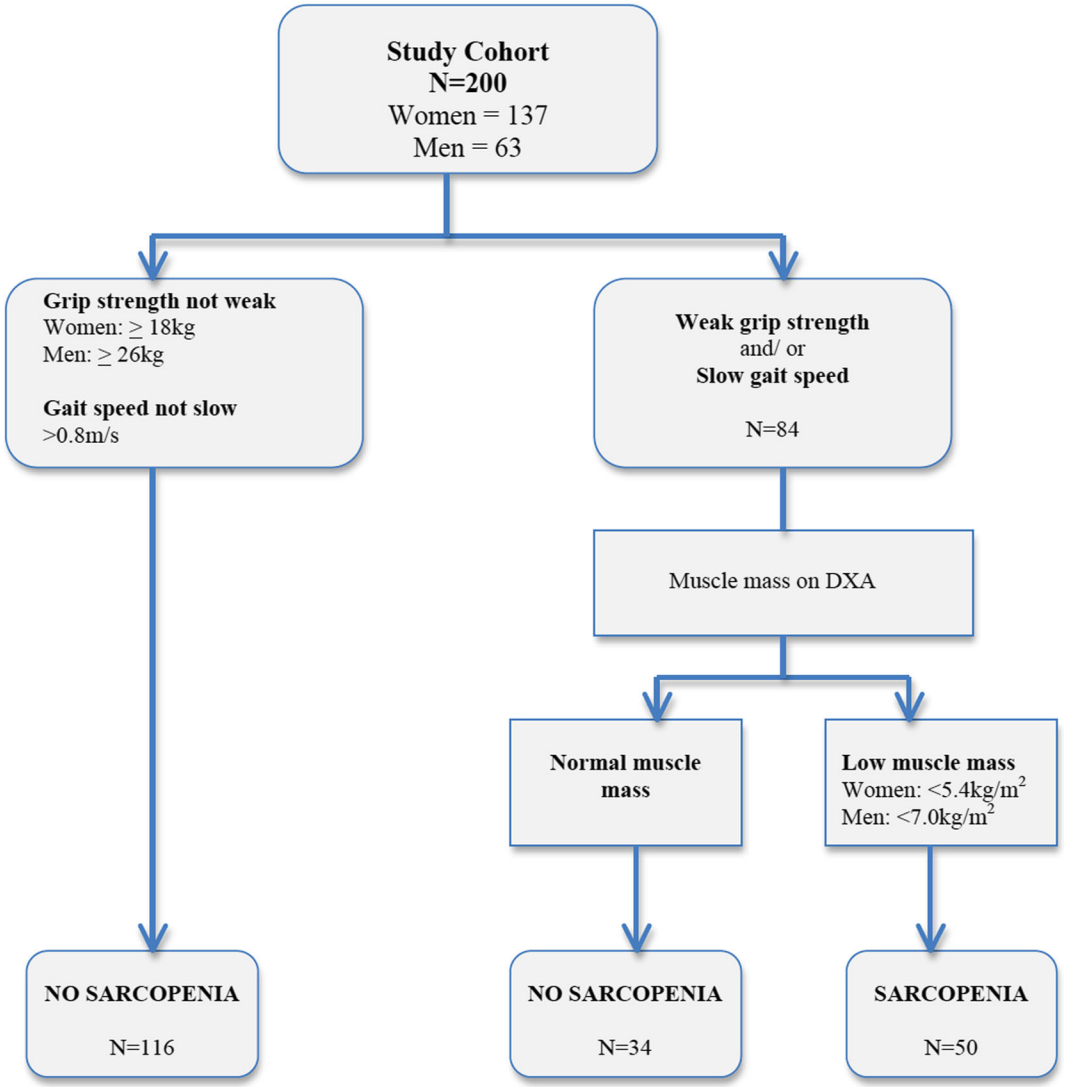

Fig. 1 Application of the Asian Working Group Algorithm for Sarcopenia

Differential predictors for sarcopenia: gender-specific

As individual factors contributing to sarcopenia were different in men and women, separate multiple logistic regression models were performed according to gender.

In women, we performed multiple logistic regression for sarcopenia as the outcome variable, selecting as independent variables age, risk for malnutrition, serum IGF-1 level, and triglyceride level. BMI and ABSI were excluded owing to collinearity with MNA score. In the first model, the odds for sarcopenia increased significantly with age (OR=1.08, 95 % CI 1.02–1.15), while being at risk of malnutrition conferred sixfold higher odds for sarcopenia (OR=6.23, 95 % CI 1.13–34.44) (Table 5). Neither serum IGF-1 nor triglyceride significantly associated with the odds of being sarcopenic. However, as earlier studies had linked IGF-1 to alterations in lipid metabolism (Eggert et al. 2014), we excluded triglyceride from the final model to delineate the independent effect of serum IGF-1 on sarcopenia status. Age and nutritional status remained significant predictors of sarcopenia, while each 1 ng/ml increase in serum IGF-1 was associated with 1 % decline in odds of sarcopenia, although not achieving statistical significance (p=0.095).

In the first-step multiple logistic regression model in men, we included age and significant univariate variables of ABSI, triglyceride level, serum myostatin,

Table 1 Clinical characteristics of study cohort (N=200)

	Sarcopenic (n=50)	Non-sarcopenia (n=150)	p value
Demographics			
Age (years), mean (SD)	72.0 (8.1)	66.6 (7.3)	<0.001
Gender (female), n (%)	34 (68 %)	103 (68.7 %)	0.930
Race (Chinese), n (%)	50 (100 %)	134 (89.3 %)	0.294
Comorbidities (n, %)			
Hypertension	27 (54 %)	69 (46 %)	0.327
Hyperlipidaemia	32 (64 %)	99 (66 %)	0.797
Diabetes mellitus	10 (20 %)	35 (23.3 %)	0.625
IHD	2 (4 %)	2 (1.3 %)	0.261
Atrial fibrillation	2 (4 %)	7 (4.7 %)	1.00
Stroke/TIA	4 (8 %)	1 (0.7 %)	0.014
Smoker	7 (14 %)	14 (9.3 %)	0.510
Ethanol use	5 (10 %)	6 (4 %)	0.013
Inflammatory disease[a]	2 (4 %)	1 (0.7 %)	0.155
Advanced organ failure	0	1 (0.7 %)	1.00
Malignancy	3 (6 %)	9 (6 %)	1.00
Other endocrine	5 (10 %)	9 (6 %)	0.337
Cognitive performance			
CMMSE (median, IQR)	27 (26–28)	27 (25–28)	0.577
Functional performance			
MBI (median, IQR)	100 (100–100)	100 (100–100)	0.487
iADL (median, IQR)	9 (9–9)	9 (9–9)	0.245
Physical activity and performance			
FAI (mean, SD)	29.9 (5.6)	32.8 (4.7)	<0.001
SPPB (median, IQR)	12 (10–12)	12 (11–12)	0.120
Nutritional status			
BMI (kg/m^2), mean (SD)	21.7 (2.4)	24.7 (3.8)	<0.001
ABSI, mean (SD)	8.55 (0.64)	8.27 (0.49)	0.002
Albumin (g/l), mean (SD)	38.3 (2.4)	39.2 (2.6)	0.369
MNA total, mean (SD)	26.1 (2.0)	27.3 (1.9)	<0.001
At risk of malnutrition, n (%)	7 (14 %)	7 (4.7 %)	0.025

ABSI a body shape index, *BMI* body mass index, *CMMSE* Chinese Mini-Mental State Examination, *FAI* Frenchay Activity Index, *iADL* Lawton and Brody's instrumental activities of daily living, *IHD* ischemic heart disease, *MBI* modified Barthel Index, *MNA* Mini Nutrition Assessment, *SPPB* short physical performance battery

[a] Inflammatory disease: myasthenia gravis, on immunosuppressant therapy (n=2); ulcerative colitis (n=1)

haemoglobin and lymphocyte count. Taking into consideration the limited sample size in men, only age and variables with p value of <0.10 (myostatin and triglyceride) were retained in the final model (model 2). The odds for sarcopenia increased significantly with age (OR=1.12, 95 % CI 1.01–1.25), with protective effect conferred by incremental serum triglyceride level (p=0.012). Each 1 ng/ml increase in serum myostatin increased the odds for sarcopenia by 11 % (p=0.041) (Table 6). Nearly 28 % of the variance in likelihood of being sarcopenic in an older male adult could be attributed to the combination of age, serum myostatin and triglyceride level.

Discussion

This study contributes to the evolving literature for sarcopenia etiopathogenesis, thereby confirming the sex-specific differences in mechanisms underlying age-related sarcopenia. While older age is a common risk factor, sarcopenia appears to be driven by the catabolic influence of myostatin in men, with anabolic decline represented by reduced IGF-1 potentially contributing to sarcopenia in women. Additionally, we observed a protective effect conferred by nutrition in women and serum triglyceride in men.

The growth hormone/IGF-1 axis has been widely examined as a potential mediator of skeletal muscle loss (Perrini et al. 2010; Harridge 2003; Scicchitano et al. 2009). In a recent application of the EWGSOP criteria for sarcopenia in community-dwelling older people, IGF-1 in the lowest tertile was associated with approximately fourfold higher odds for sarcopenia, a finding that was initially corroborated in our study (Volpato et al. 2014). However, subgroup analysis by gender revealed that IGF-1 was associated with sarcopenia only in women, with similar levels being observed in sarcopenic and non-sarcopenic male subjects, although subsequent multiple regression models suggested that the observed influence of IGF-1 in women was largely driven by the effect of age. The gender-specific association between body composition and IGF-1 has been contradictory (Payette et al. 2003; Hofmann et al. 2015; Goodman-Gruen and Barrett-Connor 1997; Harris et al. 1997) . Contrary to the earlier studies that had defined sarcopenia based simply on muscle mass measurements, we had incorporated performance-based measures in defining sarcopenia, and our observed sex-specific influence of IGF-1, albeit not fulfilling statistical significance in the multiple regression models, is in line with an earlier study demonstrating correlation between muscle power and IGF-1 in older women but not in men (Kostka et al. 2000). There is thus greater impetus to

Table 2 Biochemical correlates of sarcopenia (N=200)

	Sarcopenic (n=50)	Non-sarcopenia (n=150)	p value
Full blood count, mean (SD)			
Haemoglobin (g/dl)	12.9 (1.3)	13.3 (1.2)	0.038
White blood cell count ($\times 10^9$/l)	5.7 (1.7)	5.8 (1.3)	0.628
Neutrophils ($\times 10^9$/l)	3.4 (1.3)	3.4 (1.0)	0.852
Lymphocytes ($\times 10^9$/l)	1.7 (0.7)	1.8 (0.5)	0.132
Monocytes ($\times 10^9$/l)	0.41 (0.13)	0.41 (0.12)	0.675
Fasting glucose (mmol/l), median (IQR)	5.2 (4.9–5.8)	5.4 (5–6.3)	0.094
Lipid panel (mmol/l), mean (SD)			
Total cholesterol	4.95 (1.05)	5.13 (1.00)	0.274
Low density lipoprotein	2.93 (0.84)	3.11 (0.83)	0.191
High density lipoprotein	1.58 (0.42)	1.47 (0.37)	0.079
Triglyceride	0.97 (0.41)	1.27 (0.61)	0.001
Inflammatory markers			
Raised C-reactive protein (>5 mg/l), n (%)	4 (8 %)	4 (8 %)	1.00
Interleukin-6 (pg/ml), median (IQR)	1.07 (0.60–1.54)	1.0 (0.64–1.7)	0.762
Myostatin (ng/ml), median (IQR)	29.75 (22.5–33.5)	27.68 (22.3–32.51)	0.257
Hormonal			
Vitamin D (μg/l), mean (SD)	29.5 (9.6)	29.3 (9.6)	0.930
Insulin-like growth factor-1 (ng/ml), median (IQR)	100.1 (77.7–117.6)	117.6 (88.2–147)	0.007

examine the differential effects of IGF-1, potentially remediable through exercise and nutritional interventions (Yamada et al. 2015).

Myostatin has received recognition as a potent inhibitor of skeletal muscle growth (Elliot et al. 2012), further supported by animal models evidencing muscle hypertrophy with myostatin gene deletion (McPherron and Lee 1997; McPherron et al. 1997) while its overexpression in transgenic mice was associated with lower muscle mass (Reisz-Porszasz et al. 2003). Indeed, myostatin is already emerging as a promising therapeutic target for muscle health, with myostatin antibody demonstrating increase in muscle mass amongst persons with muscle dystrophy, and its pharmacological inhibition leading to improved lean mass in patients undergoing androgen deprivation therapy for prostate cancer (Wagner et al. 2008; Padhi et al. 2014). Yet, data for the relationship between circulating myostatin and age-related muscle loss have been scarce and conflicting. While an earlier study reported significant elevations in serum myostatin levels with advancing age and declining lean mass (Yarasheski et al. 2002), more recent studies had failed to support these findings (Hofmann et al. 2015; Ratkevicius et al. 2011). Intriguingly, we have observed myostatin to confer deleterious effects for sarcopenia only in older male adults that, if corroborated, has important clinical significance in selection of individuals most likely to benefit from myostatin blocking therapy.

The influence of nutritional status for optimal muscle performance has been further reinforced, evident by the clearly detrimental impact of malnutrition conferring greater than fivefold higher risk for sarcopenia in women. Interestingly, we observed that higher serum triglyceride was independently associated with reduced odds for sarcopenia in men even after adjusting for the use of lipid-lowering agents, running contrary to prior hypotheses for the negative impact of adiposity on muscle quality and physical performance (Kleevil et al. 2015; Newman et al. 2003), and the observed univariate associations between central adiposity represented by ABSI and sarcopenia. Nonetheless, our findings parallel the recently observed linear relationship between a composite profile comprising measures of adiposity and metabolic markers (including total cholesterol and triglycerides) with skeletal muscle mass (Perna et al. 2015).

Table 3 Gender-specific clinical parameters associated with sarcopenia—female (N=137) and male (N=63)

	Female (N=137)		p value	Male (N=63)		p value
	Sarcopenia (n=34)	Non-sarcopenia (n=103)		Sarcopenia (n=16)	Non-sarcopenia (n=47)	
Demographics						
Age, mean (SD)	70.7 (8.7)	65.2 (6.7)	<0.001	74.8 (5.7)	69.5 (7.9)	0.016
Race (Chinese)	34 (100 %)	93 (90.3 %)	0.478	16 (100 %)	41 (87.2 %)	1.00
Comorbidities						
Hypertension	18 (52.9 %)	42 (40.8 %)	0.215	9 (56.3 %)	27 (57.5 %)	0.933
Hyperlipidaemia	22 (64.7 %)	68 (66.0 %)	0.889	10 (62.5 %)	31 (66.0 %)	1.00
Diabetes mellitus	5 (14.7 %)	23 (22.3 %)	0.339	5 (31.3 %)	12 (25.5 %)	0.747
IHD	2 (5.9 %)	0	0.060	0	2 (4.3 %)	1.00
Atrial fibrillation	2 (5.9 %)	3 (2.9 %)	0.598	0	4 (8.5 %)	0.564
Stroke/TIA	0	1 (0.97 %)	1.00	4 (25 %)	0	0.003
Smoker	2 (5.8 %)	2 (1.9 %)	0.117	5 (31.3 %)	12 (25.5 %)	0.872
Ethanol use	2 (5.9 %)	0	0.060	3 (18.8 %)	5 (10.6 %)	0.214
Inflammatory disease[a]	0	1 (0.97 %)	1.00	2 (12.5 %)	0	0.061
Advanced organ failure	0	1 (1.0 %)	1.00	0	0	–
Malignancy	2 (2.9 %)	6 (5.8 %)	0.681	2 (12.5 %)	3 (6.4 %)	0.594
Other endocrine	5 (14.7 %)	6 (5.8 %)	0.098	0	3 (6.4 %)	0.564
Cognitive						
CMMSE (median, IQR)	27 (26–28)	27 (25–28)	0.880	27 (26–28)	27 (25–27)	0.413
Functional						
MBI (median, IQR)	100 (100–100)	100 (100–100)	0.534	100 (100–100)	100 (100–100)	0.746
iADL (median, IQR)	9 (9–9)	9 (9–9)	0.408	9 (9–9)	9 (9–9)	0.420
Physical activity and performance						
FAI (mean, SD)	32.0 (3.7)	33.3 (4.3)	0.116	25.3 (6.2)	31.7 (5.4)	<0.001
SPPB (median, IQR)	12 (11–12)	12 (11–12)	0.265	12 (10–12)	12 (11–12)	0.245
Nutritional						
BMI (mean, SD)	21.4 (2.1)	24.9 (3.9)	<0.001	22.6 (2.8)	24.4 (3.6)	0.076
ABSI (mean, SD)	8.52 (0.75)	8.22 (0.53)	0.012	8.60 (0.26)	8.37 (0.37)	0.027
Albumin (mean, SD)	39.0 (2.3)	39.0 (2.6)	0.938	38.6 (2.4)	39.7 (2.6)	0.143
MNA total (mean, SD)	25.8 (2.0)	27.2 (1.8)	<0.001	26.8 (1.6)	27.4 (2.0)	0.298
At risk of malnutrition, n (%)	6 (17.7 %)	3 (2.9 %)	0.007	1 (6.3 %)	4 (8.5 %)	1.00

ABSI a body shape index, *BMI* body mass index, *CMMSE* Chinese Mini-Mental State Examination, *FAI* Frenchay Activity Index, *iADL* Lawton and Brody's instrumental activities of daily living, *IHD* ischemic heart disease, *MBI* modified Barthel Index, *MNA* Mini Nutrition Assessment, *SPPB* short physical performance battery

[a] Inflammatory disease: myasthenia gravis, on immunosuppressant therapy (n=2); ulcerative colitis (n=1)

However, it is worthy to mention that the serum lipid parameters in our male cohort as well as the previous study had been within appropriate reference ranges, suggesting that the observed influence of serum triglyceride may therefore merely reflect its role as a mediator of the effect of malnutrition on muscle mass loss (Rondanelli et al. 2014).

Contrary to the widely recognized role of chronic inflammation in driving sarcopenia and frailty (Brinkley et al. 2009; Michaud et al. 2013), we failed to confirm the detrimental effect of inflammatory biomarkers, even after taking into consideration the presence of chronic inflammatory conditions or immunosuppressant treatment, although this will need to be clarified in our

Table 4 Gender-specific biochemical parameters associated with sarcopenia—female (N=137) and male (N=63)

	Female (N=137)		p value	Male (N=63)		p value
	Sarcopenia (n=34)	Non-sarcopenia (n=103)		Sarcopenia (n=16)	Non-sarcopenia (n=47)	
FBC, mean (SD)						
Hb (g/dl)	12.6 (1.3)	12.9 (1.1)	0.242	13.4 (1.0)	14.2 (1.1)	0.013
WBC ($\times 10^9$/l)	5.81 (1.86)	5.73 (1.23)	0.768	5.51 (1.33)	6.04 (1.42)	0.197
Neutrophils	3.40 (1.43)	3.27 (0.92)	0.548	3.41 (1.02)	3.59 (1.13)	0.590
Lymphocytes	1.81 (0.76)	1.86 (0.47)	0.665	1.42 (0.45)	1.74 (0.53)	0.034
Monocytes	0.41 (0.14)	0.38 (0.11)	0.230	0.41 (0.14)	0.38 (0.11)	0.230
Glucose, mmol/l, median (IQR)	5.2 (4.7–5.6)	5.4 (5–6.1)	0.066	5.6 (4.9–5.9)	5.6 (4.9–6.4)	0.710
Lipid panel, mmol/l, mean (SD)						
Total cholesterol	5.17 (1.08)	5.25 (0.96)	0.686	4.47 (0.80)	4.86 (1.06)	0.178
LDL	3.09 (0.91)	3.15 (0.83)	0.698	2.61 (0.59)	3.03 (0.83)	0.068
HDL	1.65 (0.43)	1.53 (0.38)	0.126	1.44 (0.36)	1.34 (0.32)	0.331
TG	0.96 (0.44)	1.28 (0.62)	0.011	0.94 (0.34)	1.26 (0.59)	0.043
Inflammatory						
Raised CRP (>5 mg/l), n (%)	2 (5.6 %)	9 (8.7 %)	0.731	2 (12.5 %)	3 (6.4 %)	0.594
IL-6, pg/ml, median (IQR)	1.06 (0.60–1.5)	0.96 (0.59–1.58)	0.921	1.12 (0.671–1.69)	1.2 (0.7–3.8)	0.372
Myostatin, ng/ml, median (IQR)	28.86 (22.1–33.5)	28.5 (22.8–32.74)	0.992	30.72 (23.75–34.05)	25 (21–32.27)	0.057
Hormonal						
Vitamin D, ug/l, mean (SD)	27.8 (10.3)	27.8 (9.0)	0.987	33.13 (6.94)	32.70 (10.17)	0.878
IGF1, ng/ml, median (IQR)	94.11 (75.6–112.35)	117.6 (88.2–141.71)	0.002	111.87 (94.35–143.85)	117.6 (88.2–151.2)	0.740
Free testosterone, pmol/l, mean (SD)				23.02 (7.10)	25.99 (6.47)	0.136

FBC full blood count, *CRP* C-reactive protein, *Hb* haemoglobin, *HDL* high density lipoprotein, *IGF-1* insulin-like growth factor-1, *IL-6* interleukin-6, *LDL* low density lipoprotein, *TG* triglyceride, *WBC* white blood cell count

ongoing follow-up. Further, we failed to detect significant correlations between ABSI which is representative of adiposity and serum IL-6 levels. The longitudinal tracking of inflammatory markers with sarcopenic status will be especially pertinent given the pleiotropic nature of IL-6 (Fontes et al. 2015), along with its recognition as a myokine, being secreted by skeletal muscle with potential benefits that include improved skeletal muscle glucose uptake and insulin sensitivity in response to exercise (Pal et al. 2014).

Our study's strengths include a well-characterized cohort of older adults with complete clinical, imaging and biochemical parameters, incorporating functional performance measures beyond mere muscle mass in

Table 5 Multiple logistic regression model for sarcopenia in women (N=137)

	Model 1		Model 2	
	OR (95 % CI)	p value	OR (95 % CI)	p value
Age	1.08 (1.02–1.15)	0.014	1.08 (1.02–1.15)	0.013
MNA-risk of malnutrition	6.23 (1.13–34.44)	0.036	5.71 (1.13–28.84)	0.035
Triglyceride	0.40 (0.16–1.03)	0.058		
IGF-1	0.99 (0.98–1.00)	0.212	0.99 (0.98–1.00)	0.095

Model 1: R^2 =16.7 %; model 2: R^2 =14.4 %

Table 6 Multiple logistic regression model for sarcopenia in men (N=63)

	Model 1		Model 2	
	OR (95 % CI)	p value	OR (95 % CI)	p value
Age	1.08 (0.96–1.22)	0.219	1.12 (1.01–1.25)	0.040
ABSI	5.29 (0.54–52.27)	0.154		
Myostatin	1.11 (0.99–1.23)	0.065	1.11 (1.00–1.23)	0.041
Triglyceride	0.10 (0.01–1.33)	0.081	0.05 (0.00–0.52)	0.012
Haemoglobin	0.61 (0.30–1.24)	0.174		
Lymphocytes	0.51 (0.11–2.43)	0.400		

Model 1: R^2 =33.9 %; model 2: R^2 =27.6 %

defining sarcopenia, thereby according due recognition that mere measurement of quantitative muscle mass may not accurately reflect important changes impacting muscle performance. However, several limitations are acknowledged, including the cross-sectional design that does not allow us to definitively conclude the temporal relationship between sarcopenia and its risk factors, limiting confidence in dismissing potential for alterations in the measured blood biomarkers being consequent to changes in body composition. Further, it has been suggested that measured serum myostatin levels may not reflect myostatin activity, owing to its secretion as a precursor protein and regulation by its antagonist follistatin (White and LeBrasseur 2014). Our sample size of 200 subjects had been calculated for the longitudinal follow-up of adverse outcomes associated with sarcopenia, and we acknowledge that this may not be adequately powered for the cross-sectional analysis due to the limited number of participants fulfilling sarcopenia criteria at baseline, with consequent type II error in the multiple regression models. We have also recruited a cohort of relatively well and functionally independent older adults residing within the community, warranting caution in generalizability to a wider population of heterogeneous older adults including those at the end of the frailty spectrum.

In conclusion, our findings support sex-specific pathophysiological mechanisms for sarcopenia, that have potential important clinical utility in guiding targeted interventions for older men and women, respectively. Malnutrition appears to be a common modifiable risk factor for sarcopenia, reflected in different surrogate measures of MNA score in women and higher but appropriate range serum triglyceride levels in men. While therapies that block myostatin signalling may be relevant in older male adults, the role of IGF-1 agonists may hold greater promise in women. Finally, differing underlying physiology supports examining therapeutic effects by gender in clinical trials for the prevention and treatment of sarcopenia.

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Compliance with ethical standards Informed written consent was obtained from the participant, and the study was approved by the Domain Specific Review Board (DSRB) of the National Healthcare Group (NHG).

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Conflict of interest The authors declare that they have no competing interests.

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