Table 3. Adjusted* Associations Between Body Mass Index and Incident Fracture Before and After Controlling for Different Pathways[a]

| | Normal (22 ≤ BMI < 25) | | Overweight (25 ≤ BMI < 30) | | Obese (30 ≤ BMI) | | BMI as continuous predictor | |
| | Ref: Low weight | | Ref: Low weight | | Ref: Low weight | | Per unit BMI increment (kg/m²) | |
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Base model[b]	0.91 (0.58, 1.41)	0.67	1.02 (0.66, 1.59)	0.93	1.01 (0.64, 1.59)	0.97	1.01 (0.98, 1.03)	0.58
Model 2a	1.06 (0.68, 1.67)	0.79	1.32 (0.84, 2.08)	0.22	1.89 (1.14, 3.14)	0.01	1.05 (1.02, 1.07)	<.001
Model 2b	1.03 (0.66, 1.62)	0.89	1.27 (0.81, 1.99)	0.30	1.50 (0.93, 2.42)	0.10	1.03 (1.005, 1.06)	0.02
Model 3a	0.70 (0.44, 1.10)	0.12	0.59 (0.36, 0.97)	0.04	0.43 (0.24, 0.76)	0.004	0.96 (0.93, 0.99)	0.006
Model 3b	0.76 (0.48, 1.20)	0.24	0.72 (0.45, 1.16)	0.18	0.59 (0.35, 0.99)	0.048	0.98 (0.95, 1.003)	0.08
Model 3c	0.71 (0.45, 1.13)	0.15	0.63 (0.38, 1.03)	0.07	0.47 (0.26, 0.84)	0.01	0.96 (0.93, 0.99)	0.02
Model 4	0.71 (0.45, 1.13)	0.15	0.62 (0.37, 1.02)	0.06	0.43 (0.23, 0.81)	0.009	0.95 (0.92, 0.99)	0.005
Model 5	0.76 (0.48, 1.22)	0.26	0.72 (0.42, 1.23)	0.23	0.65 (0.31, 1.40)	0.27	0.98 (0.91, 1.04)	0.47

Abbreviations: BMI, body mass index; HR, hazard ratio; CI, confidence intervals.

[a]Results of Cox proportional hazards analysis with BMI as categorical predictor (reference group: low weight category, BMI < 22kg/m²) and as continuous predictor in separate models.

[b]Base model: age, menopause transition stage, race/ethnicity, study site, physical activity, smoking status and alcohol consumption, history of fracture since age 20, baseline use of medications (supplementary vitamin D, supplementary calcium, bone-active medications, central nervous system active medications, ever/previous use of oral steroids, and ever/previous use of sex steroids) and use of medications during the follow-up (sex steroid hormones, osteoporosis medications, oral steroids, and other bone-active medications).

Model 2a: adjusted for covariates in base model plus femoral neck BMD. Model 2b: adjusted for covariates in base model plus lumbar spine BMD. Model 3a: adjusted for covariates in base model plus compression strength index. Model 3b: adjusted for covariates in base model plus bending strength index. Model 3c: adjusted for covariates in base model plus impact strength index.

Model 4: adjusted for covariates in model 3a plus diabetes status and log (C-reactive protein). Model 5: adjusted for covariates in model 4 plus a surrogate measure of hip soft tissue.

indices of femoral neck strength relative to load (Table 3, models 3a and 3c). Similarly, the linear and negative relationship between BMI (as a continuous predictor) and fracture hazard became nonsignificant when hip soft tissue was added to the model (Table 3, model 5).

Association between baseline BMI and incident minimum trauma fracture

After the 9-year follow-up, 82 women (4.3%) had at least one minimum trauma fracture, at a rate of 5.1 per 1000 person-years. Findings for minimum trauma fracture were similar to the ones for all fracture with respect to the direction and magnitude of the associations with BMI (Table 4). However, reflecting the smaller number of events, fewer associations reached levels of statistical significance.

Discussion

This study was designed to test multiple hypothesized pathways by which obesity might affect fracture risk: (1) increased BMD in response to greater skeletal loading, (2) increased impact forces in a fall (load), (3) deleterious effects of chronic inflammation and diabetes (common in obesity) on bone mass, and (4) absorption of impact forces by soft tissue padding. Using data from a multi-ethnic cohort of 1924 women going through the menopause transition, we demonstrated that although higher BMI was indeed associated with higher BMD (consistent with previous studies[2,3]), it is in fact associated with lower indices of bone strength relative to load. These associations between BMI and the bone strength estimates were monotonic. These findings suggest that although obesity may increase BMD, the increase in bone strength is not commensurate with the increase in fall impact forces. Further adjustment for the detrimental effects of diabetes and inflammation did not substantially alter the associations between high BMI and low bone strength.

We also demonstrated that adjusted for BMD, obesity was associated with increased fracture hazard. Increased fracture hazard in obesity, when adjusted for BMD, has been seen in previous studies[10,26] and is consistent with the hypothesis that larger fall impact forces in obesity increase fracture risk. We also demonstrated that obesity was associated with decreased fracture hazard after adjustment for any of the three composite indices of bone strength relative to fall impact forces. Since controlling for the composite indices statistically eliminates the effects of obesity on both bone strength and fall impact forces without eliminating the effect of soft tissue padding, this is consistent with a fracture protection effect of soft tissue padding. Such a protective role is further supported by the observation that additional adjustment for a surrogate marker for hip soft tissue padding attenuated the remaining obesity–fracture association and made it statistically nonsignificant.

Taken together, these findings provide empirical evidence for the hypothesized pleiotropic effects of obesity on fracture risk. First, bone mass increases in response to the excess weight. Second, obesity increases fracture risk by increasing impact forces in a fall. The increase in bone mass in obesity is not commensurate with the increased fall impact forces. Third, the reduction in bone strength relative to load is to some degree offset by the protection conferred by increased soft tissue padding. The balance between these factors determines the overall fracture risk in an individual.

Because the magnitude of these competing effects can vary from body site to body site, the relationship between obesity and fracture will be both site-specific and person-specific. For instance, the adaptive increase in BMD due to greater skeletal loading will be more pronounced at weight-bearing sites such as the hip and spine than in the forearm and wrist. Similarly, the protection conferred by soft tissue mass will be greatest at body sites where it is most abundant, and the localization of soft tissue can vary from person to person. For instance, gynecoid obesity, where most fat accumulation is around the hip, should provide

Table 4. Adjusted* Associations Between Body Mass Index and Incident Minimum Trauma Fracture Before and After Controlling for Different Pathways[a]

| | Obese (30 ≤ BMI) | | BMI as continuous predictor | |
| | Ref: Low weight | | Per unit BMI increment (kg/m²) | |
	HR (95% CI)	p	HR (95% CI)	p
Base model[b]	1.06 (0.49, 2.28)	0.88	1.02 (0.98, 1.05)	0.35
Model 2a	1.78 (0.77, 4.13)	0.18	1.05 (1.01, 1.09)	0.01
Model 2b	1.58 (0.71, 3.51)	0.26	1.04 (1.004, 1.08)	0.03
Model 3a	0.33 (0.13, 0.87)	0.02	0.96 (0.92, 1.007)	0.10
Model 3b	0.47 (0.20, 1.10)	0.08	0.98 (0.94, 1.02)	0.23
Model 3c	0.39 (0.15, 1.005)	0.051	0.97 (0.93, 1.02)	0.22
Model 4	0.29 (0.10, 0.80)	0.02	0.95 (0.90, 1.001)	0.053
Model 5	0.30 (0.09, 1.03)	0.055	0.95 (0.86, 1.05)	0.31

Abbreviations: BMI, body mass index; HR, hazard ratio, CI, confidence intervals.

[a]Results of Cox proportional hazards analysis with BMI as categorical predictor (reference group: low weight category, BMI < 22kg/m²) and as continuous predictor in separate models.

[b]Base model: age, menopause transition stage, race/ethnicity, study site, physical activity, smoking status and alcohol consumption, history of fracture since age 20, baseline use of medications (supplementary vitamin D, supplementary calcium, bone-active medications, central nervous system active medications, ever/previous use of oral steroids, and ever/previous use of sex steroids) and use of medications during the follow-up (sex steroid hormones, osteoporosis medications, oral steroids, and other bone-active medications). Model 2a: adjusted for covariates in base model plus femoral neck BMD. Model 2b: adjusted for covariates in base model plus lumbar spine BMD. Model 3a: adjusted for covariates in base model plus compression strength index. Model 3b: adjusted for covariates in base model plus bending strength index. Model 3c: adjusted for covariates in base model plus impact strength index. Model 4: adjusted for covariates in model 3a plus diabetes status and log(C-reactive protein). Model 5: adjusted for covariates in model 4 plus a surrogate measure of hip soft tissue.

protection against hip fractures, but not necessarily protect against fractures at other appendicular sites. This is consistent with previous studies which found lower hip fracture risk[4,11,12,14] but higher risk of fractures elsewhere[11-15] in obese compared to non-obese women.

Previous studies have found that both inflammation and diabetes, which are more prevalent in obesity, have deleterious effects on bone strength and fracture risk[6-9] and that diabetes is also associated with increased fall risk.[27,28] The observed negative associations of obesity with both bone strength relative to load and fracture risk independent of inflammation and diabetes in this current study suggests that there are other direct mechanisms by which obesity is deleterious to bone health. Adipose tissue is considered an endocrine organ producing adipokines such as adiponectin and leptin, which have been implicated in bone metabolism.[29] Increased bone marrow fat in obesity may also have deleterious effects on bone.[30] Other possible mechanisms include osteoarthritis (which increases fall risk),[11,31] prediabetes, hyperlipidemia, hypertension, and vascular atherosclerosis (which may reduce blood and oxygen supply to bone), all of which are more prevalent in obese individuals.

It should be noted that the composite strength indices employed in this study are structural measures based on macroscopic measurements from DXA scans and body size derived from structural engineering principles. The indices ignore important microscopic features such as differences in microarchitecture, and a recent case control study did demonstrate that obesity-induced improvements in microarchitecture may also not be commensurate with the increased body weight.[32] In addition, the strength indices were derived using the simplifying assumption that the femoral neck is a simple cylinder and do not take into account other aspects of shape such as femoral neck-shaft angle, which may also be influenced by body composition[4,33] and associated with hip fracture risk.[34] These other pathways from obesity to fracture risk need further investigation.

Our study has other limitations to be noted. First, fractures were self-reported, but fractures after visit 6 were confirmed by medical records review. It is still possible that we overlooked clinically silent vertebral fractures. Also, the exact date of fracture was not recorded until the medical records review process began; thus, fractures that occurred prior to that time were assumed to occur at the midpoint between the current and prior visit. This could bias our estimates.[35] Second, we employed BMI as a measure of obesity and did not assess the role of truncal versus appendicular distribution of fat or distinguish fat mass from lean mass. We also did not differentiate between visceral and subcutaneous adipose tissues, each of which may have different biological implications.[36] Third, the composite strength indices were designed to quantify bone strength in the femoral neck, but fractures in the femoral neck were relatively rare in this cohort of middle-aged women (less than 5% of all fractures). However, just like low or high BMD in the femoral neck is a reflection of low or high bone mass more generally,[22] femoral neck strength indices also reflect bone strength elsewhere in the individual and predict fracture risk more generally.[20,37] Fourth, the incidence of fracture was low in this cohort of middle-aged women, precluding analyses by specific locations of bone fractures and limiting our power to detect residual BMI effects after adjusting for hip soft tissue. Lastly, we did not take into account the change in BMD or bone strength indices during follow-up, which may also be influenced by obesity. Further studies are warranted to assess the generalizability of our findings to other populations, such as men, older postmenopausal women, and younger premenopausal women.

In summary, this study provided empirical evidence for at least three major mechanisms by which obesity may influence fracture risk: adaptive increase in BMD, increased impact forces in a fall, and soft tissue padding to absorb impact forces. Our findings suggest that the assessment of fracture risk has to go beyond measurement of BMD to include assessment of bone strength relative to load and the extent of soft tissue over potential impact sites.

Disclosures

All authors state that they have no conflicts of interest.

Acknowledgments

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Metabolic Syndrome, Sarcopenia and Role of Sex and Age: Cross-Sectional Analysis of Kashiwa Cohort Study

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Abstract

Recent epidemiological evidence suggests that effects of cardiovascular risk factors may vary depending on sex and age. In this study, we assessed the associations of metabolic syndrome (MetS) with sarcopenia and its components in older adults, and examined whether the associations vary by sex and age. We also tested if any one of the MetS components could explain the associations. We conducted a cross-sectional analysis of the baseline data from the cohort study conducted in Kashiwa city, Chiba, Japan in 2012 which included 1971 functionally-independent, community-dwelling Japanese adults aged 65 years or older (977 men, 994 women). Sarcopenia was defined based on appendicular skeletal muscle mass, grip strength and usual gait speed. MetS was defined based on the National Cholesterol Education Program's Adult Treatment Panel-III criteria. The prevalence of sarcopenia was 14.2% in men and 22.1% in women, while the prevalence of MetS was 43.6% in men and 28.9% in women. After adjustment for potential confounders, MetS was positively associated with sarcopenia in men aged 65 to 74 years (odds ratio 5.5; 95% confidence interval 1.9–15.9) but not in older men or women. Among the sarcopenia components, MetS was associated with lower muscle mass and grip strength, particularly in men aged 65 to 74 years. The associations of MetS with sarcopenia and its components were mainly driven by abdominal obesity regardless of sex or age. In conclusion, MetS is positively associated with sarcopenia in older men. The association is modified by sex and age, but abdominal obesity is the main contributor to the association across sex and age.

Introduction

Metabolic syndrome (MetS) is a constellation of cardiovascular risk factors which include abdominal obesity, dyslipidemia, hypertension and elevated glucose [1]. Insulin resistance and chronic inflammation are considered central mechanisms responsible for MetS [2] and inextricably correlate with each other to exert detrimental metabolic effects and lead to cardiovascular morbidity and mortality [3–5]. Accumulating epidemiological evidence suggests that both insulin resistance and chronic inflammation cause adverse effects on skeletal muscle. Diabetes, or even insulin resistance without diabetes, is associated with greater declines in skeletal muscle mass and strength [6,7]. A link between inflammation and muscle weakness has been reported in several studies [8,9]. Therefore, we postulate that MetS can accelerate age-related loss of muscle mass and strength, leading to the development of sarcopenia, a syndrome characterized by loss of skeletal muscle mass and function with a risk of physical disability [10]. Indeed, recent studies showed that MetS is associated with physical capacity impairment and increased risk of developing physical and functional disabilities [11–13].

Several recent studies have suggested that the effects of MetS may vary depending on age and sex. Cardiovascular risk factors, whose adverse effects have been established in younger people, may have different impacts in the elderly or frail population. Obesity did not seem to be a risk factor for increased mortality in elderly hospitalized patients with or without diabetes [14,15]. Elevated blood pressure was associated with lower mortality risk in physically frail elderly adults who could not walk 20 feet [16]. MetS was associated with lower probability of prevalent and incident functional disability in older adults [17]. The association between MetS and cardiovascular events was observed only in patients younger than 75, but not in patients aged 75 or over [18]. With regard to sex-related differences in the effects of MetS, MetS was associated with lower muscle strength in elderly men but not in elderly women [19]. However, data on sex- or age-related differences in the effect of MetS on sarcopenia are still scarce.

In the present study, we assessed the associations of MetS with sarcopenia and its components in functionally-independent community-dwelling Japanese older adults, and examined whether the associations were modified by sex or age. We hypothesized that MetS is positively associated with sarcopenia and its components, and that the associations are more pronounced in relatively young men. We also examined whether any of the individual MetS components could explain the associations and if the same MetS components contributed to the associations across sex and age.

Methods

Subjects

The Kashiwa study is a prospective cohort study designed to characterize the biological, psychosocial and functional changes associated with aging in a community-based cohort of 2044 older adults (1013 men, 1031 women). Those aged 75 and older accounted for 36.3% of men and 35.0% of women. The sampling and data collection process has been described in detail elsewhere [20]. Briefly, the inclusion criteria were age equal to or older than 65 years and functional independence (i.e., not requiring nursing care provided by long-term care insurance). The subjects were randomly selected from the resident register of Kashiwa city, Chiba, Japan, enrolled in 2012, and followed annually. The current study is a cross-sectional analysis of the Kashiwa study baseline data. Seventy three subjects who did not undergo bioimpedance analysis (BIA), usual gait speed or hand grip strength measurements were excluded, leaving an analytic sample of 1971 older adults (977 men, 994 women). Those excluded from the analysis were older compared to those included in the analysis (mean age 75.9 years vs. 72.9 years, p = 0.001), but did not significantly differ with respect to other characteristics including sex, height, weight, and prevalence of MetS.

The study was approved by the ethics committee of the Graduate School of Medicine, The University of Tokyo. All subjects provided written informed consent.

Definition of Sarcopenia

We followed the recommendations of the European Working Group on Sarcopenia in Older People (EWGSOP) for the diagnostic definition of sarcopenia [10]. The proposed diagnostic criteria required the presence of low muscle mass plus the presence of either low muscle strength or low physical performance. Muscle mass was measured by BIA using an Inbody 430 machine (Biospace, Seoul, Korea). Appendicular skeletal muscle mass (ASM) was derived as the sum of the muscle mass of the four limbs [10]. ASM was then normalized by height in meters squared to yield skeletal muscle mass index (SMI) (kg/m^2). SMI values lower than two standard deviations below the mean values of young male and female reference groups were classified as low muscle mass (SMI <7.0 kg/m^2 in men, <5.8 kg/m^2 in women) [21]. Muscle strength was assessed by hand grip strength, which was measured using a digital grip strength dynamometer (Takei Scientific Instruments, Niigata, Japan). Hand grip strength values in the lowest quintile were classified as low muscle strength in this study (cutoff values: 30 kg for men, 20 kg for women). Physical performance was assessed by usual gait speed. Subjects were instructed to walk over an 11-meter straight course at their usual speed. Usual gait speed was derived from 5 meters divided by the time in seconds spent in the middle 5 meters (from the 3-meter line to the 8-meter line) [22]. Usual gait speed values in the lowest quintile were classified as low physical performance in the current study (cutoff values: 1.26 m/s for each sex).

Definition of metabolic syndrome

MetS was defined based on the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria [1]. The presence of any three of the following five abnormalities constitutes a diagnosis of MetS: (i) abdominal obesity; (ii) elevated triglycerides (TG) with fasting plasma triglycerides ≥150 mg/dL; (iii) low high density lipoprotein cholesterol (HDL-C) with fasting HDL-C <40 mg/dL in men and <50 mg/dL in women; (iv) elevated blood pressure with systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg; (v) elevated fasting plasma glucose with fasting plasma glucose ≥100 mg/dL. Abdominal obesity was defined by waist circumference using the thresholds recommended by the Japanese Obesity Society (≥ 85 cm in men and ≥90 cm in women) [1].

Waist circumference was measured at the umbilical level using a measuring tape with the subject in an upright position. Blood pressure was measured using a standard technique with an HEM-7080IT automated measuring device (Omron Co., Tokyo, Japan). Blood samples were obtained after an overnight fast. Total cholesterol, HDL-C and TG were analyzed by enzymatic methods using a JCA-BM8060 automated analyzer (Japan Electron Optics Laboratory Ltd., Tokyo, Japan). Fasting plasma glucose level was measured using a JCA-BM9030 automated analyzer (Japan Electron Optics Laboratory Ltd.).

Other measurements

Demographic information, medical history of doctor-diagnosed chronic conditions, use of medication, and food intake were obtained using a standardized self-reported questionnaire. Physical activity was assessed using the Global Physical Activity Questionnaire, and metabolic equivalents (METs)-minute per week was computed [23]. Height and weight were measured with the subject wearing light clothing and no shoes using a fixed stadiometer and a digital scale, and used to compute body mass index (BMI).

Statistical Analysis

Differences in subject characteristics between those with and without sarcopenia were examined using Student's t-test or Wilcoxon rank-sum test (for continuous variables) and chi-square test (for categorical variables).

First, we employed logistic regression analysis to evaluate the association of MetS with sarcopenia. Our preliminary analysis suggested that the association of metabolic syndrome with sarcopenia was modified by sex (p<0.01), and therefore the following analyses were stratified by sex.

The model was initially adjusted for age only (model 1). We added height and weight to remove the confounding effect of body size (model 2). We then further adjusted for life-style risk factors for both sarcopenia and MetS, including physical activity and food intake (model 3). In the fully-adjusted model, the interaction between MetS and age was examined to test the hypothesis that the effect of MetS on sarcopenia varies by age.

To test if any MetS component could explain the MetS-sarcopenia association, we initially fitted a fully-adjusted logistic regression model to examine the association between each component of MetS and sarcopenia, followed by other logistic regression models between MetS and sarcopenia adjusted for MetS components.

Second, to examine the association of MetS with each component of sarcopenia (i.e., muscle mass, grip strength and usual gait speed), we employed multiple linear regression models. If the association between MetS and any one of the sarcopenia components was statistically significant, another multiple linear regression model with MetS components as independent variables

Table 1. Characteristics of all subjects and according to sarcopenia status in men and women.

	All	Sarcopenia	No sarcopenia	p
Men	**977**	**139 (14.2%)**	**838 (85.8%)**	
Age (years)	73.1±5.5	78.4±5.5	72.2±5.0	<0.001
Height (cm)	164.2±5.8	160.0±5.6	164.9±5.5	<0.001
Weight (kg)	62.8±8.6	54.1±7.2	64.3±8.0	<0.001
BMI (kg/m²)	23.3±2.8	21.1±2.5	23.6±2.6	<0.001
SMI (kg/m²)	7.28±0.68	6.34±0.48	7.44±0.58	<0.001
Hand grip strength (kg)	34.8±6.0	27.5±4.3	36.0±5.3	<0.001
Usual gait speed (m/s)	1.47±0.26	1.28±0.24	1.51±0.24	<0.001
MetS	43.6%	36.0%	44.9%	0.048
MetS components				
Abdominal obesity	55.5%	36.0%	58.7%	<0.001
High TG	22.7%	21.6%	22.9%	0.73
Low HDL-C	21.4%	20.9%	21.5%	0.87
High BP	90.4%	88.5%	90.7%	0.41
High FPG	51.0%	53.2%	50.6%	0.56
Food intake				
Very large	2.9%	1.4%	3.1%	<0.001
Large	15.3%	5.8%	16.8%	
Normal	65.4%	58.3%	66.6%	
Small	14.4%	30.2%	11.8%	
Very small	2.1%	4.3%	1.7%	
Physical activity (Mets)	3962.9±3981.0	3191.7±3612.2	4090.8±4026.7	0.01
Medical history				
Hypertension	47.2%	51.1%	46.5%	0.32
Diabetes	15.4%	18.0%	14.9%	0.36
Dyslipidemia	29.8%	31.7%	29.5%	0.60
Stroke	7.2%	12.2%	6.4%	0.01
CAD	8.0%	11.5%	7.4%	0.10
Cancer	19.0%	26.6%	17.8%	0.01
Medication use				
Statin	17.6%	18.7%	17.4%	0.71
Women	**994**	**220 (22.1%)**	**774 (77.9%)**	
Age (years)	72.8±5.4	76.2±5.8	71.8±4.9	<0.001
Height (cm)	151.4±5.5	148.2±5.6	152.3±5.1	<0.001
Weight (kg)	51.5±7.7	46.4±5.7	52.9±7.6	<0.001
BMI (kg/m²)	22.5±3.2	21.1±2.6	22.8±3.2	<0.001
SMI (kg/m²)	5.84±0.65	5.25±0.41	6.02±0.60	<0.001
Hand grip strength (kg)	22.4±3.9	18.4±3.2	23.6±3.3	<0.001
Usual gait speed (kg)	1.46±0.26	1.26±0.26	1.51±0.23	<0.001
MetS	28.9%	23.6%	30.4%	0.052
MetS components				
Abdominal obesity	24.0%	14.6%	26.7%	<0.001
High TG	17.9%	16.4%	18.4%	0.50
Low HDL-C	36.6%	33.2%	37.6%	0.23
High BP	84.2%	87.3%	83.3%	0.16
High FPG	33.7%	34.1%	33.6%	0.89
Food intake				
Very large	2.0%	1.4%	2.2%	<0.001

Table 1. Cont.

Men	All	Sarcopenia	No sarcopenia	p
	977	139 (14.2%)	838 (85.8%)	
Large	13.1%	9.6%	14.1%	
Normal	72.4%	64.1%	74.8%	
Small	11.2%	20.9%	8.4%	
Very small	1.3%	4.1%	0.5%	
Physical activity (Mets)	3722.7±3429.5	2748.0±2825.0	4000.0±3535.6	<0.001
Medical history				
Hypertension	39.8%	45.9%	38.1%	0.04
Diabetes	8.8%	8.2%	8.9%	0.73
Dyslipidemia	46.9%	45.5%	47.3%	0.63
Stroke	4.7%	5.9%	4.4%	0.35
CAD	4.9%	5.5%	4.8%	0.68
Cancer	11.2%	11.8%	11.0%	0.73
Medication use				
Statin	30.3%	29.1%	30.6%	0.66

Mean and standard deviation are shown for continuous variables, and proportions as percent for categorical variables. Percentages may not add up to 100 because of rounding.
Abbreviations: BMI, body mass index; SMI, skeletal muscle mass index; MetS, metabolic syndrome; TG, triglycerides; CAD, coronary artery disease; HDL-C, high density lipoprotein cholesterol; BP, blood pressure; FPG, fasting plasma glucose.
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instead of MetS was conducted to evaluate the association between MetS components and the sarcopenia component. Finally, each component of MetS was introduced as a covariate to the multiple linear regression model between MetS and the sarcopenia component to test if the MetS component could explain the association between MetS and the sarcopenia component. Considering that the number of combinations between MetS components and sarcopenia components is quite high, the analyses between MetS components and sarcopenia components were considered supplemental and carried out only when the association between MetS and any of the sarcopenia components was statistically significant, in order to decrease the possibility of finding associations that were significant just by chance alone.

There were no missing values of any variable in the entire analytic sample.

All analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC) and R statistical software version 2.15.2 (R Foundation, Vienna, Austria). Two-sided p<0.05 was considered statistically significant.

Results

Subject characteristics

The prevalence of sarcopenia was 14.2% in men and 22.1% in women, and 43.6% of men and 28.9% of women were classified as having MetS. The characteristics of the study subjects by the sarcopenia status in each sex are shown in Table 1. Those with sarcopenia were older and had smaller body size compared with those without sarcopenia in each sex. Those with sarcopenia were physically less active and had smaller food intake in each sex. The prevalence of MetS was higher in those without sarcopenia, but

Table 2. Adjusted associations of metabolic syndrome with sarcopenia in men and women.

	Men		Women	
	OR (95% CI)	p	OR (95% CI)	p
Model 1	0.58 (0.38, 0.87)	0.008	0.55 (0.38, 0.79)	0.001
Model 2	2.05 (1.21, 3.47)	0.007	1.06 (0.69, 1.65)	0.79
Model 3	2.08 (1.22, 3.54)	0.007	1.03 (0.66, 1.61)	0.89
Model 3a	1.49 (0.80, 2.76)	0.21	1.02 (0.57, 1.85)	0.94
Model 3b	4.99 (1.73, 14.40)	0.003	1.03 (0.52, 2.04)	0.93

Abbreviations: OR, odds ratio; CI, confidence interval.
Model 1: adjusted for age.
Model 2: adjusted for age, height and weight.
Model 3: adjusted for age, height, weight, physical activity and food intake.
Model 3a: Adjusted for the same covariates as in Model 3, restricted to those aged 75 or over.
Model 3b: Adjusted for the same covariates as in Model 3, restricted to those aged 65 to 74.
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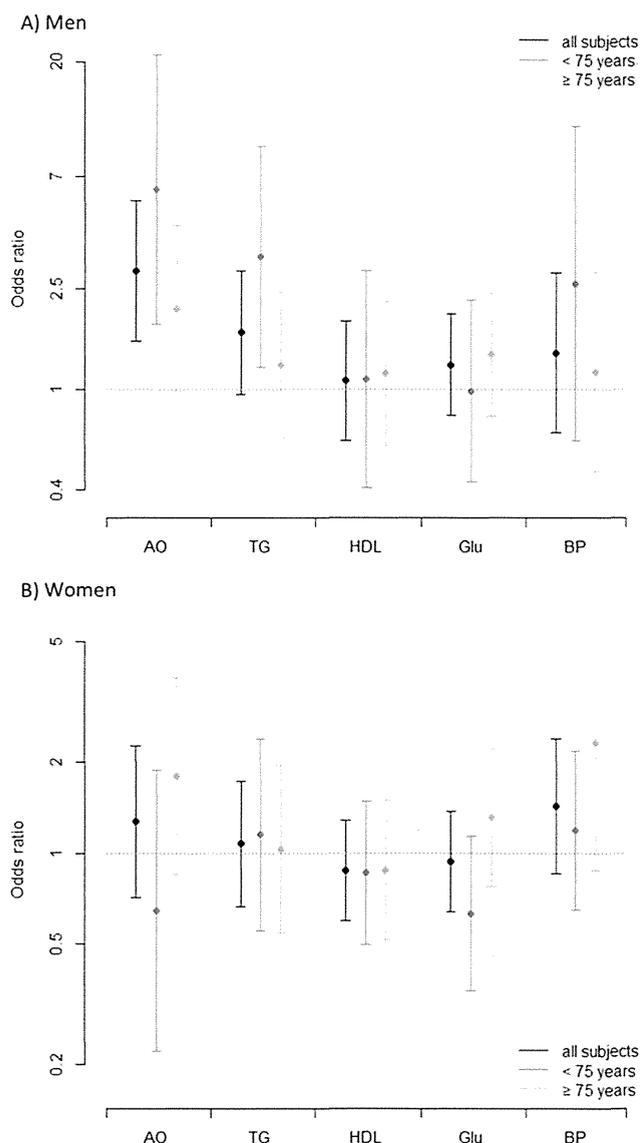
A) Men

B) Women

Figure 1. Fully adjusted odds ratio and 95% confidence interval of sarcopenia by individual metabolic syndrome components in all subjects and according to age group. Black bars: all subjects, dark-gray bars: subjects aged 65 to 74 years, light-gray bars: subjects aged 75 years or over. All models are adjusted for age, height, weight, physical activity and food intake. AO, abdominal obesity; TG, elevated triglycerides; HDL, low high density lipoprotein; Glu, elevated fasting plasma glucose; BP, high blood pressure. A) Men. B) Women.
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the difference was significant only in men (p = 0.048 in men, 0.052 in women). Among the five MetS components, abdominal obesity was significantly more prevalent in those without sarcopenia in each sex.

Association between MetS and sarcopenia

In multiple logistic regression adjusted for age, MetS was significantly associated with *decreased* risk of sarcopenia in each sex (Table 2, Model 1). However, after additional adjustment for body size (i.e., height and weight), MetS was significantly associated with *increased* risk of sarcopenia in men, while the association between MetS and sarcopenia became non-significant

in women (Table 2, Model 2). Further adjustment for life-style risk factors had little effect on the association (Table 2, Model 3). Exclusion of subjects who did not meet the criteria for MetS but had one or two MetS components (i.e., comparing those with MetS and those with *no* MetS component) yielded stronger MetS-sarcopenia association in men (OR 8.25, 95% CI 2.17–31.37, p = 0.002), but the association remained non-significant in women (OR 1.10, 95% CI 0.48–2.94, p = 0.83). In the fully adjusted model, the interaction between MetS and age was statistically significant in men (p = 0.02), suggesting that the effect of MetS on sarcopenia may vary by age. We then divided the subjects into two groups according to age: "young old" (65–74 years) and "old old" (≥75 years). The characteristics of the subjects by the sarcopenia status in each subgroup (young-old and old-old) are shown in Table S1. In the age-stratified analysis, MetS was significantly associated with sarcopenia in "young old" men only (Table 2, Model 3b).

Associations of MetS components with sarcopenia

Multiple logistic regression models demonstrated that, of the five MetS components, only abdominal obesity was significantly associated with increased risk of sarcopenia in men (odds ratio [OR] 2.98, 95% confidence interval 1.55–5.63, p≤0.001) while none of the MetS components was significantly associated with sarcopenia in women (Figure 1). Abdominal obesity was significantly and independently associated with sarcopenia in men in the model including all five MetS components simultaneously (OR 2.89, 95% CI 1.51–5.53, p = 0.001). When abdominal obesity was added as a covariate to the logistic regression model between MetS and sarcopenia, the MetS-sarcopenia association became statistically non-significant (p = 0.12), suggesting that the MetS-sarcopenia association was mainly mediated by abdominal obesity. In the age-stratified analysis, abdominal obesity and elevated TG were significantly associated with sarcopenia (OR 6.22, 95% CI 1.82–21.22, p = 0.004 and OR 3.37, 95% CI 1.23–9.28, p = 0.02, respectively) in young-old men, but no significant associations were observed between MetS components and sarcopenia in old-old men or women. Abdominal obesity and elevated TG remained significantly associated with sarcopenia in young-old men in the model including all five MetS components simultaneously (OR 6.32, 95% CI 1.81–22.06, p = 0.004 and OR 3.30, 95% CI 1.19–9.13, p = 0.02, respectively). Addition of abdominal obesity and elevated TG to the model between MetS and sarcopenia in young-old men made the MetS-sarcopenia association statistically non-significant (p = 0.13).

Associations of MetS with sarcopenia components

In fully-adjusted multiple linear regression models, MetS was associated with lower grip strength in each sex and lower muscle mass in men (Table 3). When analysis was stratified by age, the inverse associations of MetS with muscle mass and grip strength in men remained significant except for the association between MetS and muscle strength in the old-old group, which became statistically non-significant (Table 3). In women, the inverse association between MetS and grip strength was observed in the old-old group only. The association between MetS and muscle mass became significant in old-old women in the age-stratified analysis.

In the subsequent supplementary analysis, abdominal obesity was significantly associated with lower grip strength in each sex and with lower muscle mass in men (Table S2). In addition, low HDL-C was associated with lower grip strength, and high TG was associated with lower muscle mass in men. These associations observed in men were significant in the young-old group only in

Table 3. Adjusted associations of metabolic syndrome with individual sarcopenia components in all subjects and according to age groups in men and women*†.

	Men		Women	
	beta (95% CI)	p	beta (95% CI)	p
Skeletal muscle mass index				
All	−0.14 (−0.20, −0.09)	<0.001	−0.05 (−0.10, 0.007)	0.09
Old-old	−0.13 (−0.24, −0.03)	0.009	−0.10 (−0.19, −0.005)	0.04
Young-old	−0.15 (−0.22, −0.08)	<0.001	−0.02 (−0.09, 0.05)	0.57
Grip strength				
All	−0.98 (−1.68, −0.28)	0.006	−0.61 (−1.11, −0.10)	0.02
Old-old	−0.65 (−1.76, 0.45)	0.25	−0.84 (−1.64, −0.05)	0.04
Young-old	−1.26 (−2.17, −0.34)	0.007	−0.38 (−1.04, 0.27)	0.25
Usual gait speed				
All	−0.02 (−0.06, 0.01)	0.22	−0.01 (−0.05, 0.02)	0.55
Old-old	−0.006 (−0.06, 0.05)	0.83	−0.03 (−0.08, 0.03)	0.36
Young-old	−0.03 (−0.07, 0.009)	0.13	0.004 (−0.04, 0.05)	0.86

Abbreviations; CI, confidence interval.
*All the models were adjusted for age, height, weight, physical activity and food intake.
†The young-old group refers to those aged 65 to 74 and the old-old group to those aged 75 or older.
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the age-stratified analysis. For women, the only significant association observed was between high TG and lower muscle mass in the old-old group.

The association between MetS and grip strength became statistically non-significant after introduction of abdominal obesity into the model in each age group and sex. The introduction of abdominal obesity attenuated the association between MetS and muscle mass (i.e., decreased the magnitude of the regression coefficient) in each age group and sex by more than 10%, more markedly than did any other MetS component, consistent with abdominal obesity dominating the association of MetS with sarcopenia components (data not shown).

Discussion

In this cross-sectional analysis of 1971 functionally-independent, community-dwelling adults older than 65, MetS was associated with *increased* risk of sarcopenia, particularly in "young-old" men (aged 65 to 74), after adjustment for potential confounders including body size. Without adjustment for body size, MetS was associated with *decreased* risk of sarcopenia, suggesting that body size can confound the association between MetS and sarcopenia and should be taken into account when considering the impact of cardiovascular risk factors on muscle.

We demonstrated that MetS was associated with lower muscle mass and lower muscle strength, but the effects varied by sex and age. The adverse effects of MetS on muscle mass and strength were mainly observed in the young-old group for men. In stark contrast, women were mostly insusceptible to adverse effects of MetS on muscle, except for the marginally statistically significant associations of MetS with muscle mass and strength in the old-old group (age 75 or older). The mechanisms underlying the age- and sex-related differences in the associations between MetS and muscle mass/strength need to be explored in future research, but possible explanations may include the effects of sex hormones on

skeletal muscle. MetS is associated with lower testosterone level [24]. Considering that testosterone is positively related to muscle strength [25], it is conceivable that one of the pathways through which MetS exerts its adverse effects on muscle is via testosterone. Since testosterone decreases with age [26] and is lower in women than in men, younger men, with relatively high levels of testosterone, may be especially vulnerable. Another possible explanation is cytokines secreted by adipose tissue, so-called adipokines. Adipose tissue produces and releases adipokines such as adiponectin and leptin as well as pro-inflammatory cytokines such as IL-6 [27]. Skeletal muscle is an important target tissue for these molecules, and circulating levels of such molecules are influenced by the amount of adipose tissue as well as age and sex [28,29].

Several studies have reported an inverse association between MetS and muscle strength in younger men and women [30,31]. One small cross-sectional study of older adults revealed an inverse association between MetS and muscle strength in men, but not in women [19]. This study also demonstrated that the association between MetS and muscle strength was more pronounced in men aged 65–74 compared to men aged 75 or older, consistent with our findings. Low muscle mass, with or without the presence of obesity, is associated with MetS in younger men and women [32–34]. Several studies in older adults showed an inverse association between MetS and muscle mass [35,36], but these studies did not assess men and women separately.

We also demonstrated that the observed associations of MetS with the summary definition of sarcopenia or its individual components were mainly driven by abdominal obesity regardless of sex and age. Neither high BP nor elevated FPG showed a statistically significant association with sarcopenia or its components. Only a few studies have assessed which MetS components are main contributors to the association between MetS and the summary definition of sarcopenia or its components. An inverse