

# Hyperuricemia Associated with Low Skeletal Muscle in the Middle-Aged and Elderly Population in China

## Authors

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## Key words

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## ABSTRACT

**Background** Previous studies have presented inconsistent results on the relationship between serum uric acid and skeletal muscle mass (SMM). We aimed to explore whether a higher serum uric acid level was associated with low SMM in the Chinese population.

**Methods** We performed a cross-sectional analysis of 6595 subjects aged 45 years or older. They were tested for fasting blood glucose, total cholesterol, triglycerides, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, uric acid, blood urea nitrogen, creatinine, and estimated glomerular filtration rate. SMM was assessed by dual-energy x-ray absorptiometry using two approaches: weight-adjusted appendicular skeletal muscle mass (ASM)% and ASM/BMI (body mass index (kg/m<sup>2</sup>)). Low SMM was defined as a cut-off point of ASM/BMI < 0.789 for men and < 0.512 for women.

**Results** Compared with their normal group, patients with hyperuricemia had lower ASM% (29.33 ± 2.33 vs 30.03 ± 2.34 for males and 24.71 ± 1.99 vs 25.19 ± 2.07 for females, P < 0.01) and ASM/BMI (0.83 ± 0.10 vs 0.85 ± 0.10 for male and 0.60 ± 0.07 vs 0.62 ± 0.07 for female), with a higher prevalence of the associated low SMM in both sexes (35.2 vs 26.5% for male and 10.5 vs 5.9% for female, P < 0.01). Pearson analysis showed that ASM% and ASM/BMI were negatively correlated with SUA (male: ASM/BMI, r = -0.097, ASM%, r = -0.146; female: ASM/BMI, r = -0.151, ASM%, r = -0.157; all P < 0.001). Logistic regression analysis showed a positive association of hyperuricemia with adjusted risk of low SMM association.

**Conclusions** In a middle-aged and elderly Chinese population, hyperuricemia is independently and positively associated with low SMM and can vary by age and gender.

## Introduction

The progressive degeneration of skeletal muscle mass (SMM) and muscle strength with aging, a clinical condition referred to as sarcopenia often occurs in older adults. Currently, it is estimated that about 50 million people worldwide suffer from sarcopenia, and by 2050 this number is expected to reach 500 million [1]. Sarcopenia, closely associated with metabolic disorders, disability, fall, and even death, is one of the important causes of physical function decline in the elderly. Additionally, it will seriously affect the quality of life and longevity and increase hospitalization rates and health care costs [2–5]. While the exact mechanism and cause of sarcopenia are complex, the predominant cause was the accumulation of reactive oxygen species (ROS) that leads to oxidative damage in skeletal muscle [6].

Uric acid (UA), once thought to have strong antioxidant properties, is the final product of purine metabolism in humans. There is considerable evidence for a protective effect of urate against oxidative damage of lipids, enzymes, nucleobases, and organ preparations *in vitro* [7, 8]. However, increasing epidemiological evidence suggests that increased serum uric acid (SUA) triggers a risk factor for insulin resistance, hypertension, cardiovascular disease, heart failure, and mortality [9–11]. Within normal levels, UA may have a protective effect against oxidative stress and oxidative injury in cardiac, vascular, and neural cells [12]. Collectively, these findings indicate that UA may be protective at normal levels or may be a risk factor at increased concentrations. To date, only a few studies that have addressed the relationship between SUA levels and muscle function assessments have provided conflicting results and raised concerns. For example, some studies [13–15] showed association between a higher circulating level of UA and better muscle function in older people. In another study, Dong et al. indicated the association between increased SUA levels and greater muscle mass [16]. In contrast, other studies have reported that higher SUA levels may lead to a decrease in muscle mass and strength [17, 18].

In the previous studies, different methods of SMM calculation have been used and have led to varying results for SMM assessment. However, in the diagnosis of metabolic disorders and assessment of their adverse outcomes [19, 20], the appendicular skeletal muscle mass (ASM)/body mass index (BMI) and ASM% methods have been widely used. ASM/BMI, ASM%, and skeletal muscle index (SMI, ASM divided by squared body height) is a widely employed SMM computational method. The SMI is usually calculated using ASM, the total muscle mass in both the arms and legs. Muscle mass, on the other hand, is inversely proportional to body size, implying that persons with larger bodies have more muscle mass. Consequently, after adjusting for the weight (SMM) or body mass index (ASM/BMI), the absolute amount of ASM is used to assess the adequacy of muscle mass in this study [21, 22]. Additionally, previous studies have indicated noticeable effects of the body mass adjusted ASM on the relationship between muscle strength and muscle mass in women [21, 23]. Therefore, in the present study, we used ASM/BMI and ASM% to explore the relationships between hyperuricemia and hyperuricemia associated with low SMM in subjects categorized by gender and age.

## Methods

### Study design and population

The participants in our study were from the Shanghai Changfeng Study, a community-based prospective cohort study of chronic diseases in a middle-aged and elderly Chinese population, conducted from May 2010 to December 2012, and their demographic details have been described earlier [24]. A total of 6595 consecutive participants were enrolled in this study. Inclusion criteria were: 1. the patients of age 45 years and older, and available 2. blood biochemical data, and 3. the dual-energy X-ray absorptiometry (DXA) information. As per exclusion criteria, a total of 405 subjects were excluded: 1. 132 subjects did not have available blood biochemical data, 2. 273 subjects did not have their DXA information to check body composition, and 3. all patients who did not satisfy all the inclusion criteria. Finally, 6190 participants (2627 men and 3563 women; age range 46–93 years) were included in this study.

This study was approved by the Research Ethics Committee of Zhongshan Hospital, affiliated with Fudan University, and all the participants provided written informed consent.

### Anthropometric and biochemical measurements

On the day of the examination, a questionnaire probing lifestyle and medical history, basic anthropometric indicators, and samples for biochemical evaluation was collected by trained investigators. Then, standing height and weight were measured, and the BMI was calculated by dividing weight by height squared ( $\text{kg}/\text{m}^2$ ). Resting blood pressure (BP) was measured three times with an electronic sphygmomanometer (OMRON Model HEM-752 FUZZY, Omron Co., Dalian, China), and the mean value was calculated. The standard protocol followed for all these anthropometric and BMI indexes were estimated as described previously [24, 25].

Blood samples were collected after fasting for at least 10 h. Biochemical indexes including fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), blood urea nitrogen (BUN), creatinine (Cr), and UA were measured with an automated bio-analyzer (HITACHI 7600, Tokyo, Japan). The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) study formula [26] as follows:  $186 \times [\text{serum creatinine (mg/dL)}]^{-1.154} \times (\text{age})^{-0.203} \times [0.742 \text{ (if female)}]$ .

### Definitions

Hyperuricemia was defined as SUA level  $\geq 420 \mu\text{mol}/\text{L}$  in men and  $\geq 360 \mu\text{mol}/\text{L}$  in women or a previous diagnosis. Obesity was defined as BMI  $\geq 28 \text{ kg}/\text{m}^2$  based on Chinese criteria [27]. Diabetes mellitus (DM) was defined as FBG  $\geq 7.0 \text{ mmol}/\text{L}$  or 2 h BG  $\geq 11.1 \text{ mmol}/\text{L}$  based on the oral glucose tolerance test by the World Health Organization 1999 criteria [28] or a previous diagnosis or self-reported current hypoglycemic treatment. Hypertension was defined as systolic blood pressure (SBP)  $\geq 140 \text{ mmHg}$  and/or diastolic blood pressure (DBP)  $\geq 90 \text{ mmHg}$  or a previous diagnosis or self-reported current antihypertensive treatment [29]. Dyslipidemia was defined as elevated levels of TC and/or TG, and/or LDL-C, and/or decreased levels of HDL-C, as reported in our previous study [25]. Low SMM was formally defined by the Foundation for the National Institutes of Health (FNIH)

Sarcopenia Project using a cut-off point of ASM/BMI <0.789 for men and <0.512 for women [30], and further categorized into two age groups (<65 years and ≥65 years).

## Dual-energy X-ray absorptiometry measurements of body composition analysis

Body composition, including appendicular lean mass and fat mass, were measured using dual-energy X-ray absorptiometry (DXA, GE Healthcare). All measurements were carried out by a single, trained technician at a single clinical center. The DXA scans were analyzed using manual DXA analysis software. SMM was calculated by the following two methods.

First, body weight adjusted for ASM was calculated as follows:  $ASM\% = ASM\ (kg)/body\ weight\ (kg) \times 100\%$  [19]. The second formula was ASM/BMI:  $ASM\ (kg)/body\ mass\ index\ (kg/m^2)$ .

## Subgroups

The information obtained from the subjects was further analyzed, univariate and multivariate, using the three models based on age (<65 years and ≥65 years), gender, and SUA levels. There were four SUA quartiles for males (Q1: <299 μmol/L; Q2: 299–346 μmol/L; Q3: 347–400 μmol/L; Q4: ≥401 μmol/L) and female (Q1: <243 μmol/L; Q2: 243–282 μmol/L; Q3: 283–332 μmol/L; Q4: ≥333 μmol/L). Model 1 was age-adjusted; model 2 was model 1 + adjusted by eGFR; model 3 was model 2 + adjusted by DM, HT, and dyslipidemia.

## Statistical Analysis

All statistical analyses were performed using SPSS software version 19.0 (SPSS, Chicago, IL, USA). Continuous variables were presented as the means ± standard deviation. To evaluate a potential relationship

between SUA associated with low SMM and SUA, the subjects were stratified according to the SUA quartiles. ANOVA followed by the Bonferroni test was used for intergroup comparisons, whereas the Chi-squared test was used for the comparisons of categorical variables. Pearson correlation analysis was performed to assess the relationship between SUA associated with low SMM and SUA. The univariate and multivariate logistic regression were applied to investigate the risk factors related to low SMM association for the three models of SUA quartiles. P-value <0.05 was considered to be statistically significant.

## Results

### Subjects' Characteristics

Among 6190 participants, the mean SUA was  $318.49 \pm 81.81\ \mu\text{mol/L}$  (male:  $354.41 \pm 82.24\ \mu\text{mol/L}$  vs female:  $292.00 \pm 70.65\ \mu\text{mol/L}$ ) and the prevalence rate of hyperuricemia was 18.6% (male: 21.2% vs female: 16.6%). The prevalence rate of the associated low SMM was 15.9% (male: 28.4% vs female: 6.7%). Regardless of gender, patients with hyperuricemia had a lower ASM% and ASM/BMI and a higher prevalence of low SMM association compared to the normal group. Compared to the normal group, patients with hyperuricemia were older and showed poor metabolic and renal function, as evidenced by greater BMI, higher blood pressure, and lower eGFR. Also, patients with hyperuricemia had higher TG and TC and lower HDL-C. FBG and LDL-C were higher in female hyperuricemia subjects but not in males. The prevalence of chronic metabolic diseases such as obesity, HT, and dyslipidemia was higher in the hyperuricemia group in both genders, and the prevalence of DM was higher in the female hyperuricemia group (► **Table 1**).

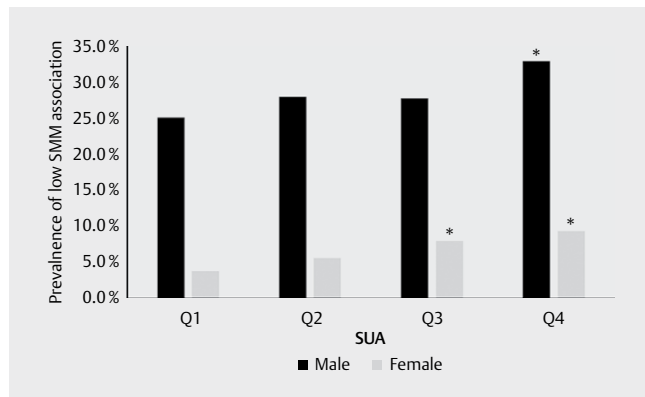
► **Table 1** Analysis of variance-Bonferroni test for the clinical characteristics of participants.

	Total	Male		Female	
	(n=6190)	Normal (n=2070)	Hyperuricemia (n=557)	Normal (n=2970)	Hyperuricemia (n=593)
Age (yrs)	63.62 ± 9.62	64.24 ± 9.53	66.16 ± 10.25*	62.32 ± 9.30	65.60 ± 9.91*
BMI (kg/m <sup>2</sup> )	24.26 ± 3.32	24.24 ± 3.13	25.25 ± 2.86*	23.84 ± 3.40	25.52 ± 3.44*
WC (cm)	84.02 ± 9.66	86.25 ± 9.13	89.44 ± 8.77*	81.07 ± 9.33	85.90 ± 9.18*
SBP (mmHg)	135.75 ± 19.26	136.50 ± 17.96	140.72 ± 18.76*	133.12 ± 19.45	141.66 ± 20.71*
DBP (mmHg)	76.36 ± 10.14	78.12 ± 10.13	79.78 ± 10.78*	74.46 ± 9.62	76.49 ± 10.15*
FBG (mmol/L)	5.60 ± 1.55	5.77 ± 1.74	5.63 ± 1.32	5.49 ± 1.40	5.75 ± 1.40*
TC (mmol/L)	5.07 ± 0.94	4.74 ± 0.88	4.86 ± 0.84*	5.27 ± 0.90	5.44 ± 1.03*
TG (mmol/L)	1.71 ± 1.23	1.63 ± 1.14	2.06 ± 0.54*	1.61 ± 1.11	2.21 ± 1.56*
HDL-C (mmol/L)	1.43 ± 0.37	1.31 ± 0.32	1.24 ± 0.32*	1.56 ± 0.38	1.40 ± 0.33*
LDL-C (mmol/L)	2.89 ± 0.80	2.72 ± 0.76	2.74 ± 0.75	3.00 ± 0.80	3.09 ± 0.89*
BUN (mmol/L)	5.42 ± 1.43	5.45 ± 1.30	6.02 ± 1.81*	5.17 ± 1.24	5.98 ± 1.94*
Cr (μmol/L)	70.30 ± 20.79	79.51 ± 14.48	91.88 ± 29.34*	59.75 ± 10.81	70.72 ± 33.14*
eGFR (mL/min * m <sup>3</sup> )	93.62 ± 20.32	93.91 ± 18.72	81.54 ± 18.97*	97.50 ± 19.79	84.51 ± 22.25*
ASM/BMI	0.71 ± 0.14	0.85 ± 0.10	0.83 ± 0.10*	0.62 ± 0.07	0.60 ± 0.07*
ASM%	27.13 ± 3.22	30.03 ± 2.34	29.33 ± 2.33*	25.19 ± 2.07	24.71 ± 1.99*
Obesity (n, %)	762, 12.4%	215, 10.4%	94, 16.9%*	330, 11.2%	123, 20.9%*
DM (n, %)	1353, 22.0%	529, 25.8%	133, 24.0%	506, 17.2%	185, 31.4%*
HT (n, %)	3425, 55.5%	1179, 57.1%	406, 73.0%*	1416, 47.7%	424, 71.6%*
Dyslipidemia (n, %)	2062, 33.3%	665, 32.2%	261, 46.9%*	855, 28.8%	281, 47.5%*
Low SMM (n, %)	983, 15.9%	549, 26.5%	196, 35.2%*	176, 5.9%	62, 10.5%*

\*: P<0.05; \*\*: P<0.001.

## Correlation of serum uric acid and SMM in subjects by gender

Pearson analysis showed that SUA was negatively associated with SMM in both genders (male: ASM/BMI,  $r = -0.097$ , ASM%,  $r = -0.146$ ; female: ASM/BMI,  $r = -0.151$ , ASM%,  $r = -0.157$ ; all  $P < 0.001$ ). To further investigate the association between SMM and SUA, we stratified subjects according to the SUA quartiles for men and women separately



► **Fig. 1** The prevalence of low skeletal muscle mass (SMM) according to quartiles of serum uric acid (SUA). The results showed that the prevalence of low SMM association increased in all quartiles of SUA, with statistically significant differences (Chi-squared test) between the male and female groups (\* male:  $P = 0.019$ , female:  $P < 0.001$  when compared to Q1).

because cutoff points for hyperuricemia and low SMM association differed by gender. As shown in ► **Fig. 1**, the prevalence of the associated low SMM increased significantly across the quartiles of SUA in both genders (male: 25.1%, 27.9%, 27.7%, 32.8%,  $P = 0.019$ ; female: 3.8%, 5.6%, 8.0%, 9.4%,  $P < 0.001$ ), whereas ASM% and ASM/BMI decreased in the SUA quartiles in both genders ( $P < 0.001$ ). After adjustment for potential confounding factors, including age, renal function, and common metabolic diseases (DM, HT, dyslipidemia), the association between SMM and SUA remains unchanged in both genders (► **Table 2**). In particular, when compared to the first quartile, SMM was significantly lower from the third quartile (men: 347–400  $\mu\text{mol/l}$ ; women: 283–332  $\mu\text{mol/l}$ ) for both genders.

## Logistic regression model testing of the relationship between hyperuricemia and low skeletal muscle mass in subjects categorized by gender

To further explore whether hyperuricemia can explain low SMM association independent of other confounding factors, logistic regression analysis was performed in subjects categorized by gender, using low SMM association as an independent variable and various confounding factors as explanatory variables (► **Table 3**). Unadjusted analysis showed a positive correlation between hyperuricemia and low SMM association (male: OR = 1.504, 95% CI 1.232–1.836,  $P < 0.001$ ; female: OR = 1.854, 95% CI 1.368–2.512,  $P < 0.001$ ). This association persisted in both genders after consecutive adjustment for age, eGFR, DM, HT, dyslipidemia (model 3), the association remained in both genders (model 3, male: OR = 1.459, 95% CI 1.158–1.839,  $P = 0.001$ ; female: OR = 1.458, 95% CI 1.040–2.042,  $P = 0.028$ ).

► **Table 2** Univariate and multivariate adjusted mean values of skeletal muscle mass (SMM) in both genders according to serum uric acid (SUA) quartiles.

Male	Q1 (n=646)	Q2 (n=667)	Q3 (n=651)	Q4 (n=663)	P-value
<b>ASM/BMI</b>					
Unadjusted	0.857 ± 0.003	0.847 ± 0.003*	0.843 ± 0.003*	0.836 ± 0.003*	<0.001
Model 1	0.857 ± 0.003	0.848 ± 0.003	0.843 ± 0.003*	0.836 ± 0.003*	<0.001
Model 2	0.862 ± 0.003	0.849 ± 0.003*	0.841 ± 0.003*	0.832 ± 0.003*	<0.001
Model 3	0.864 ± 0.004	0.849 ± 0.003*	0.844 ± 0.003*	0.839 ± 0.004*	<0.001
<b>ASM %</b>					
Unadjusted	30.323 ± 0.089	30.024 ± 0.087	29.774 ± 0.088*	29.882 ± 0.088*	<0.001
Model 1	30.311 ± 0.089	29.995 ± 0.087*	29.746 ± 0.088*	29.473 ± 0.088*	<0.001
Model 2	30.547 ± 0.090	30.085 ± 0.087*	29.762 ± 0.088*	29.492 ± 0.089*	<0.001
Model 3	30.454 ± 0.092	30.010 ± 0.085*	29.765 ± 0.087*	29.586 ± 0.095*	<0.001
<b>Female</b>	<b>Q1 (n=873)</b>	<b>Q2 (n=894);</b>	<b>Q3 (n=902)</b>	<b>Q4 (n=894)</b>	<b>P-value</b>
<b>ASM/BMI</b>					
Unadjusted	0.627 ± 0.002	0.623 ± 0.002*	0.611 ± 0.002*	0.611 ± 0.002*	<0.001
Model 1	0.627 ± 0.002	0.624 ± 0.002	0.611 ± 0.002*	0.612 ± 0.002*	<0.001
Model 2	0.631 ± 0.002	0.625 ± 0.002	0.610 ± 0.002*	0.606 ± 0.002*	<0.001
Model 3	0.631 ± 0.002	0.626 ± 0.002	0.612 ± 0.002*	0.611 ± 0.002*	<0.001
<b>ASM %</b>					
Unadjusted	25.504 ± 0.069	25.269 ± 0.068*	24.864 ± 0.067*	24.808 ± 0.068*	<0.001
Model 1	25.531 ± 0.070	25.278 ± 0.068*	24.870 ± 0.067*	24.829 ± 0.069*	<0.001
Model 2	25.662 ± 0.071	25.345 ± 0.067*	24.877 ± 0.067*	24.803 ± 0.074*	<0.001
Model 3	25.609 ± 0.071	25.313 ± 0.068*	24.881 ± 0.067*	24.803 ± 0.074*	<0.001

Male: Q1: <299  $\mu\text{mol/L}$ ; Q2: 299–346  $\mu\text{mol/L}$ ; Q3: 347–400  $\mu\text{mol/L}$ ; Q4:  $\geq 401$   $\mu\text{mol/L}$ ; Female: Q1: <243  $\mu\text{mol/L}$ ; Q2: 243–282  $\mu\text{mol/L}$ ; Q3: 283–332  $\mu\text{mol/L}$ ; Q4:  $\geq 333$   $\mu\text{mol/L}$ ; \*: compared to Q1,  $P < 0.05$ ; \*\*: compared Q1,  $P < 0.001$ ; Model 1: adjusted by age; Model 2: model 1 + adjusted by eGFR; Model 3: model 2 + adjusted by DM, HT, and dyslipidemia.

► **Table 3** Logistic regression analysis between hyperuricemia (independent variable) and low skeletal muscle mass (SMM, dependent variable).

	Male OR (95 %CI, P-value)	Female OR (95 %CI, P-value)
<b>Unadjusted</b>	1.504 (1.232–1.836, <0.001)	1.854 (1.368–2.512, <0.001)
<b>Model 1</b>	1.327 (1.070–1.646, 0.01)	1.427 (1.041–1.957, 0.027)
<b>Model 2</b>	1.588 (1.267–1.991, <0.001)	1.600 (1.156–2.215, 0.005)
<b>Model 3</b>	1.459 (1.158–1.839, 0.001)	1.458 (1.040–2.042, 0.028)

Model 1: adjusted by age; Model 2: model 1 + adjusted by eGFR; Model 3: model 2 + adjusted by DM, HT, and dyslipidemia.

► **Table 4** Logistic regression analysis between hyperuricemia (independent variable) and low skeletal muscle mass (SMM, dependent variable) categorized by age.

	Male OR (95 %CI, P-value)	Female OR (95 %CI, P-value)
<b>&lt;65 years</b>		
<b>Unadjusted</b>	1.326 (0.937–1.875, 0.111)	1.238 (0.643–2.386, 0.523)
<b>Model 1</b>	1.345 (0.949–1.904, 0.096)	1.199 (0.622–2.314, 0.588)
<b>Model 2</b>	1.550 (1.080–2.224, 0.018)	1.291 (0.657–2.536, 0.459)
<b>Model 3</b>	1.462 (1.012–2.113, 0.043)	1.075 (0.523–2.209, 0.843)
<b>≥65 years</b>		
<b>Unadjusted</b>	1.385 (1.062–1.806, 0.016)	1.612 (1.128–2.305, 0.009)
<b>Model 1</b>	1.287 (0.977–1.695, 0.073)	1.521 (1.058–2.188, 0.024)
<b>Model 2</b>	1.471 (1.096–1.974, 0.010)	1.661 (1.134–2.433, 0.009)
<b>Model 3</b>	1.355 (1.002–1.833, 0.048)	1.541 (1.041–2.281, 0.031)

Model 1: adjusted by age; Model 2: model 1 + adjusted by eGFR; Model 3: model 2 + adjusted by DM, HT, and dyslipidemia.

### Subgroup analysis of the relationship between hyperuricemia and hyperuricemia associated low skeletal muscle mass stratified by age

About two-thirds of 983 patients associated with low SMM were 65 years of age or older (8.1 % in <65 years; 27.3 % in ≥65 years). Since both hyperuricemia and low SMM association were observed to be closely correlated with aging, we initially explored the difference in the relationship between low SMM and hyperuricemia at different ages by performing logistic regression analysis on subjects categorized by age. The results suggested a positive association of hyperuricemia with low SMM after consecutive adjustment for age, eGFR, DM, HT, and dyslipidemia (model 3) in a male population under 65 years but was not significant in females (male: OR = 1.474, 95 % CI 1.012–2.113, P = 0.043; female: OR = 1.075, 95 % CI 0.523–2.206, P = 0.843). On the other hand, in the population over 65 years of age, the unadjusted analysis showed a positive correlation between hyperuricemia and low SMM association (models 1–3); this relationship remained unchanged in both genders after further adjustment (► **Table 4**).

### Discussion

Our results demonstrated decreased SMM with increasing SUA and that the prevalence of the associated low SMM increased in both genders. Pearson analysis showed that SUA was negatively correlated with SMM. Since both hyperuricemia and sarcopenia were closely associated with age, renal function, and metabolic disorders, we further examined the effect of these confounders on the relationship between SUA and muscle mass. After adjustment, hy-

peruricemia was still an independent risk factor for low SMM association, suggesting that increased SUA may contribute to muscle loss and that this association was independent of age, renal function, and common metabolic disorders. Physical activity plays an important role in both SUA and muscle mass. In the elderly, a low SMM is linked to weak or decreased physical performance [31], and weaker grip strength, slower gait speed, and poor mobility degrade the physical performance and increase the risk of falling [32]. In addition, a low SMM is linked to metabolic syndrome [33], chronic kidney disease (CKD) [34], osteoporosis [35], and liver fibrosis [36]. Several endocrine illnesses, such as CKD, can hasten the loss of muscle mass and strength, resulting in physical impairment [37]. The impact of reduced SMM on medical service and healthcare expenses can be mitigated by a diverse diet and increased physical activity [38]. However, we could not get this data with the present study. A limited number of population studies have shown an inconsistent relationship between SUA and SMM or function [17, 18, 39–41]. Similar to our study, Tanaka et al. [41] reported that higher SUA was a risk factor of muscle mass reduction in Japanese men with type 2 DM. In a study from Korea, Beavers et al. [39] supported the theory that elevations in SUA may lead to low SMM association. A negative impact of hyperuricemia on skeletal muscle function was also reported in other studies [17, 18]. In contrast, others revealed a positive correlation of SUA with SMM or function, especially in the elderly population [14–16, 40, 42]. The discrepancy in results might be due to differences in demographic background characteristics, muscle assessment methods, and various SMM calculation methods. The Chinese researchers, Dong et al. [16] reported a positive association of SUA with SMM, which was

accessed by SMI. Earlier published studies accessed only the muscle function and did not measure muscle mass; besides, most of the subjects were elderly or had different characteristics of other populations [14, 15, 42].

The diagnosis of low SMM defined by the FNIH criterion was based on the population aged above 65 years [30]; we further analyzed the variation in the relationship between hyperuricemia and low SMM association in different age groups. Interestingly, hyperuricemia was independently positively associated with low SMM, which remained unchanged in subjects more than 65 years old. However, a similar phenomenon was observed only in male subjects under 65 years. Although the reason for this gender difference in subjects less than 65 years of age is still unknown, it is likely that circulating UA levels show a significant variation by gender. Men have a higher SUA concentration than age-matched women and may induce a stronger effect of hyperuricemia on muscle mass. Degeneration of renal function with age leads to increased circulating levels of UA in both sexes. One study showed a more significant increase in the UA levels with age in females than in males [43]. Thus, the gap in SUA between genders narrowed, which may neutralize the difference in the relationship of hyperuricemia and low SMM association between genders. In addition, adipose accumulation increases the burden of insulin resistance and inflammation and can lead to skeletal muscle loss [44]; it is evident that women have a higher percentage of body fat than age-matched men.

In our study, the percentage of body fat was 37.6% in women vs 28.3% in men. Thus, the role of hyperuricemia on muscle mass might be concealed by adiposity in the female population. With increasing age, visceral fat accumulation is more prominent in Asian men than women [45]; thus, the difference caused by adipose accumulation was gradually eliminated. Besides, in subjects under 65 years of age, the association between hyperuricemia and low SMM association was significant after adjusting by eGFR. Previous studies have confirmed a significant influence of renal function on skeletal muscle reduction and increased circulating level of UA [46, 47]. Our results indicated a remarkable effect of renal function on the relationship between SUA and muscle mass, and the association between hyperuricemia and muscle loss could be covered up by abnormal renal function. Furthermore, statistical analysis revealed a significant decrease in SMM at different levels of circulating UA by gender (men: 347–400  $\mu\text{mol/L}$ ; women: 283–332  $\mu\text{mol/L}$ ). Our study attributed this differential influence of circulating UA levels in mediating SMM to gender for the first time. Similar effects were previously reported in other clinical events such as gout, metabolic syndrome, and cardiovascular diseases [48, 49]. These results remind us that we should also be cautious against SMM loss at different SUA levels stratified by gender.

There are several limitations to our study. First, its cross-sectional nature made it difficult to obtain a causal relationship between hyperuricemia and low SMM association, and a prospective study is necessary to confirm it further. Second, the definition of sarcopenia includes a decrease in muscle mass as well as a decrease in muscle function. In this study, there are no data to indicate muscle function, such as grip strength; hence, a direct diagnosis of sarcopenia may not be appropriate and therefore may compromise the exploration of the relationship between SUA and sarcopenia.

Third, we did not measure oxidative stress and systemic inflammation which may contribute to a confounding effect. Fourth, this study only included middle-aged and elderly Chinese subjects; therefore, the conclusion might not be generalized to other ethnic populations. Finally, as the SMM was calculated by ASM/height, the inconsistency in the definition of SMM loss makes it difficult to directly compare the results. In addition, the gender difference was not accounted for when evaluating the renal function, which is associated with sarcopenia and hyperuricemia. Based on different population characteristics and muscle assessment methods, so far, it has been difficult to determine the relationship between SUA and SMM and needs further exploration in more studies.

However, despite these limitations, this study has some strengths. First, we obtained precise muscle mass using DXA, which is recommended as the standard technique for muscle mass measurement. Second, we yielded two SMM assessment methods to validate our results. The method of ASM/BMI is recommended by the FNIH guideline, which is widely accepted and recognized. The second, ASM% method, can describe muscle mass more intuitively for clinicians. Most importantly, we first proposed that the relationship between SUA and SMM varies by gender and age and suggested that the different levels of circulating UA between genders have a significant clinical correlation when SMM declines among subjects.

## Conclusions

Hyperuricemia is independently positively associated with low SMM in the Chinese middle-aged and elderly community population, and this relationship can vary by age and gender. Hyperuricemia associated with low SMM has been noted in both sexes. Further analysis reveals that this association persists in men and women older than 65 years and men younger than 65 years, but not in women younger than 65 years. SUA-based stratification may be considered as an individualized intervention for sarcopenia. Further studies are needed to confirm this relationship and to explore possible mechanisms.

## Availability of data and material

The datasets generated and/or analyzed in the current study are available upon reasonable request to the corresponding author.

## Authors' contributions

Conception and design of the experiments: Xin Gao; execution of the experiments: Huandong Lin, Lingyan Chen, Li Wu, Qian Li, Hui Ma, Yu Hu; data collection and analysis: Lingyan Chen and Huandong Lin; manuscript drafting: Lingyan Chen; laboratory experiments: Lingyan Chen, Li Wu, Qian Li. All authors approved the final version of this article. Huandong Lin and Xin Gao are the guarantors of this work and have full access to all data, are responsible for the integrity of the data, and all authors have agreed to publish this study.

## Ethics approval

The study was approved by the Ethics Committee of Zhongshan Hospital of Fudan University (No. 2008–119).

## Consent to participate

All subjects have given their written informed consent at the time of participation.

## Consent for publication

Both the authors and the participants agreed with the publication.

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## Conflicts of Interest

The authors declare that they have no conflict of interest.

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