Original Article

Cross-sectional analysis of the association between serum uric acid levels and handgrip strength among Chinese adults over 45 years of age

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Background: Sarcopenia is the decline in muscle strength and mass attributed to aging. The pathogenesis of sarcopenia may be triggered by oxidative stress; uric acid (UA) has strong antioxidant properties. This study aimed to examine if the serum UA level is associated with handgrip strength (HGS), which is a useful indicator of sarcopenia among Chinese participants aged over 45.

Methods: Our study included 992 eligible participants (583 males and 409 females). Based on serum UA quartiles and gender, the participants were divided into 8 groups. HGS was measured in kilograms using an electronic dynamometer. Face-to-face visits and fasting blood analyses were performed to determine the serum UA levels and various covariates. Univariate analysis of variance (ANOVA) and covariance (ANCOVA) was conducted to analyze the linear or quadratic trend between the UA levels and grip strength.

Results: Participants were grouped according to UA quartiles by gender. In both genders, ANOVA showed an inverted J-shaped association between serum UA levels and HGS (P for quadratic trend =0.004 in men, P for quadratic trend =0.003 in women). After adjusting for potential confounders, the association between the UA quartiles and HGS was unchanged, irrespective of gender.

Conclusions: The results suggest that a specific range of serum UA levels may be associated with better HGS among Chinese adults aged over 45.

Keywords: Uric acid (UA); handgrip strength (HGS); sarcopenia

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Introduction

As the final product of purine metabolism, uric acid (UA) is generated in the xanthine/hypoxanthine reactions catalyzed by xanthine oxidoreductase (XOR). High levels of potentially deleterious prooxidant molecules [e.g., hydrogen peroxide (H_2O_2) and superoxide (O^{2-})] are produced as a by-product of this reaction. Therefore, UA has been proposed as a reliable marker of oxidative stress (1).

Multiple studies have shown that hyperuricemia is a crucial risk factor for hypertension (2), cardiovascular disease (CVD) (3), cerebrovascular disorder (4), Parkinson's disease (PD) (5), chronic heart failure (6), and all-cause mortality risk (7,8); all of these disorders are related to increased oxidative stress. However, somewhat contrarily, UA is an important endogenous antioxidant, which can eliminate reactive oxygen species (ROS) and, thus preventing oxidative stress. Experimental UA therapy protects the heart, blood vessels, and nerve cells from oxidative stress (9). Serum UA has been demonstrated to play an essential role as a neuroprotective agent in animal models of stroke and PD. Additionally, high levels of UA in humans have been associated with neuroprotective effects in several neurodegenerative and neuroinflammatory diseases, which has been demonstrated to be due to the strong antioxidant activity of UA. The URICO-ICTUS trial, a phase 3 study of combined treatment with UA and alteplase administered intravenously in acute ischaemic stroke patients (10) showed that UA therapy as an antioxidant significantly reduced the incidence of early ischemic worsening, and enhanced alteplase-mediated thrombolysis, potentially by preventing oxidative stress, which inhibits fibrinolysis by alteplase in thrombi (10-12).

Sarcopenia is defined as a gradual decrease in skeletal muscle mass and strength related to aging (13). It has become an increasingly severe public health problem, which places a substantial economic burden on the health system, families, and individuals. Increasing evidence has demonstrated that low muscle strength is a consistent and robust predictor of mortality in middle-aged and older adults (14). However, the molecular pathogenesis of sarcopenia is not entirely understood. One crucial contributing factor to the development of sarcopenia is postulated to be the accumulation of ROS, which may cause oxidative damage to skeletal muscle proteins and DNA (15).

More recent research has studied the relationship between serum UA levels with skeletal muscle mass and/or strength, but the conclusions were varied and ambiguous. For example, Huang *et al.* (16) reported that hyperuricemia was associated with reduced muscle strength among 586 Japanese men aged over 30, and serum UA levels (quartiles) showed an inverted J-shaped curve with handgrip strength (HGS). Contrastingly, the findings of Beavers *et al.* (17), from a sample of 7,544 US men and women aged 40 and above, showed that increased serum UA was significantly related to sarcopenia status after adjustment for the potential confounders. These conflicting findings may result from differences in research demographics, including country, population, participant profiles, and also data collection methods. Unfortunately, there are few studies on the association of serum UA levels and sarcopenia in Chinese populations. We speculated that serum UA was related to sarcopenia, particularly in adults. To explore this hypothesis, we performed a cross-sectional study to clarify the relationship between serum UA level with HGS (a useful indicator of sarcopenia) (18) among middle-aged and elderly Chinese people.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-2813a).

Methods

Participants

Participants aged ≥45 years were selected from the Department of Geriatrics in The First Affiliated Hospital of the College of Medicine at Zhejiang University located in Hangzhou, Zhejiang province, China, between January 2016 and December 2018. Information regarding age, gender, height, body weight, smoking, alcohol consumption, history of past illnesses (e.g., hypertension, diabetes, gout, tumors, and chronic kidney disease), and medications (e.g., diuretics and UA lowering medication) was gathered in face-to-face visits. Height and body weight were measured using a digital scale, and body mass index (BMI) was defined as the body weight (kg) divided by the square of the height (m^2). Blood samples were drawn from the antecubital vein in the morning after a minimum of 8 h of fasting. Tests on the samples included the following: hemoglobin (Hb) concentration in the whole blood was detected by Sysmex xn-1000 automatic blood analyzer. The biochemical blood indicators [including albumin, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine, UA, hypersensitive c-reactive protein (hs-CRP)] was detected by Roche Cobas 8000 automatic biochemical analyzer, glycated hemoglobin (HbA1c) was detected by Toshiba TBA-40FR automatic biochemical analyzer. Serum thyroid-stimulating hormone (TSH) and free triiodothyronine (FT3) levels were detected by SIEMENS Advia Centaur CP full-automatic chemiluminescence immune analyzer. The estimated glomerular filtration rate (eGFR) was calculated based on the Modification of Diet

in Renal Disease study equation (19). To help minimize confounding factors, participants with gout, an unbalanced diet, diuretics, UA-lowering medications, and renal failure (eGFR <30 mL/min per 1.73 m^2) were excluded. Signed informed consent was given by all participants before data collection. All research procedures were conducted following the tenets of the Declaration of Helsinki (as revised in 2013) and were approved by the ethics committee of the First Affiliated Hospital, College of Medicine, Zhejiang University. The ethics approval number was No. 2016 (2-1).

Measurements of HGS

To minimize interference, HGS measurements and blood collection were taken on different days. HGS was measured in kilograms by using an electronic dynamometer (Jamar Plus, Shanghai, China). The Jamar grip was set at position 3 (5.1 cm) for all patients according to the stipulations of Richards *et al.* (20). The participants were asked to squeeze the handle as hard as possible while in a standing position with the arm straight down. The grip strength was measured 4 times, twice for each hand alternately, and the average value of the greatest strength of the two hands was recorded as the grip strength.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 23.0 software (IBM SPSS Inc., Chicago, IL, USA). The continuous variables in this study are expressed in the form of the mean ± standard deviation, and the categorical variables are expressed in percentages. The data for Hb, LDL-C, TSH, and hs-CRP were log-transformed because of their markedly skewed distribution. Based on the quartiles of the serum UA level, the participants were divided into four groups according to gender. The association between UA and participants' characteristics was first tested independent of the confounding effect of age using linear regression models for the continuous variables or binary logistic for the categorical variables. Univariate analysis of variance (ANOVA) and covariance (ANCOVA) was conducted to analyze the linear trend or quadratic trend between the UA level and HGS. In the univariate covariance analysis, model 1 was adjusted for age and BMI; model 2 was adjusted for variables in model 1 and eGFR; model 3 was adjusted for lifestyle-related variables including smoking and alcohol consumption in addition to the variables in model 2; model 4 was adjusted for variables in model 3 and medical history, including cancer, diabetes, and hypertension; model 5 was adjusted for variables in model 4 and blood examination except for hs-CRP. Finally, adjustment for variables in model 5 and hs-CRP, a circulating inflammatory marker, was made in model 6. The significance level for the statistical analysis was $P<0.05$.

Results

Participant characteristics

In total, 992 participants (583 males and 409 females) qualified for the analysis. The UA quartiles in males were 1.26–4.20 mg/dL (Q1), 4.21–5.34 mg/dL (Q2), 5.35–6.41 mg/dL (Q3), and 6.42–11.24 mg/dL (Q4). The UA quartiles in females were 1.02–3.39 mg/dL (Q1), 3.40–4.42 mg/dL (Q2), 4.43–5.21 mg/dL (Q3), and 5.22–10.28 mg/dL (Q4). The age-adjusted associations between serum UA and participant characteristics, according to gender, are presented in *Tables 1,2*. For men, the mean weight, BMI, Hb, albumin, TG, TC, LDL-C, and FT3 increased significantly with the quartiles of serum UA ($P<0.01$ for all); whereas the mean eGFR, hs-CRP, and mean proportion of participants with cancer decreased significantly with the quartiles of serum UA ($P<0.01$ for all). Also, the prevalence of hypertension and the mean TSH were higher across the quartiles of serum UA ($P=0.040$, 0.024, respectively) (*Table 1*). For women, the mean weight, BMI, Hb, albumin, TG, TC, and the prevalence of hypertension increased significantly with the quartiles of serum UA ($P<0.01$ for all), and the mean LDL-C were higher across the quartiles of serum UA ($P=0.032$); while the eGFR decreased with the quartiles of serum UA ($P<0.01$) (*Table 2*).

Serum UA level and muscle strength

Scatter plots for UA against HGS by gender were made, respectively. As shown in *Figure 1*, the curve fitting equation between serum UA level and HGS is $y = 17.13 + 4.31*x - 0.29*x*x$ for men, and curve fitting equation between serum UA level, and HGS is $y = 15.53 + 2.45*x - 0.23*x*x$ for women. Thus, it can be seen that there is an inverted J-shaped relationship between UA with grip strength in Chinese adults, regardless of gender.

We assessed the relationship between the quartiles of the serum UA level with HGS using ANOVA. As shown

Table 1 Age-adjusted participant characteristics of male subjects categorized by quartiles of serum uric acid

Characteristics (N=583)	Serum uric acid (mg/dL)				P[1]
	Q1 (1.26–4.20) (N=146)	Q2 (4.21–5.34) (N=145)	Q3 (5.35–6.41) (N=149)	Q4 (6.42–11.24) (N=143)	
Age (years)	68.93±12.31	68.68±12.51	67.03±12.78	67.40±12.93	0.038
Weight (kg)	61.64±10.05	64.79±10.60	67.87±9.44	69.11±9.73	0.000
Height (cm)	166.79±6.15	166.99±6.09	167.65±6.36	167.58±5.78	0.543
BMI (kg/m^2)	22.13±3.20	23.20±3.30	24.13±3.04	24.58±2.99	0.000
Smoking status (%)	50.7	48.3	55.4	55.2	0.540
Drinking status (%)	31.5	29	38.1	38.5	0.223
Diabetes (%)	19.9	11	18.9	19.6	0.143
Hypertension (%)	37.7	40	48	52.4	0.040
Cancer (%)	50	33.1	31.8	30.8	0.001
Hb (g/L)*	121.51±21.71	129.75±26.98	136.93±19.18	137.25±23.53	0.000
Albumin (g/L)	37.46±5.07	40.62±6.35	42.04±4.86	42.77±5.65	0.000
TG (mmol/L)	1.08±0.72	1.31±0.82	1.59±0.62	1.57±1.17	0.000
TC (mmol/L)	3.60±1.09	4.09±1.25	4.18±1.06	4.25±1.06	0.000
LDL-C (mmol/L)*	1.98±0.78	2.28±0.92	2.36±0.84	2.45±0.83	0.000
HDL-C (mmol/L)	1.11±0.44	1.20±0.39	1.16±0.32	1.15±0.41	0.254
HbA1C (%)	6.15±1.45	6.11±1.19	6.00±1.02	5.97±1.04	0.566
FT3 (pmol/L)	4.21±0.85	4.29±0.69	4.60±0.77	4.42±0.66	0.000
TSH (mIU/L)*	1.95±1.39	1.93±1.19	2.26±1.58	2.36±1.61	0.024
eGFR (mL/min/1.73 m^2)	87.30±15.16	85.21±17.71	83.89±16.09	78.44±17.08	0.000
hs-CRP (mg/L)*	8.96±2.18	7.43±2.33	7.74±1.16	7.33±1.33	0.000

*, the data were log-transformed. [1], linear regression for the continuous variables or binary logistic for the categorical variables. BMI, body mass index; Hb, hemoglobin; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; HbA1c, glycated hemoglobin; FT3, free triiodothyronine; TSH, thyroid-stimulating hormone; eGFR, estimated glomerular filtration rate; hs-CRP, hypersensitive c-reactive protein.

in *Figure 2A*, the serum UA levels showed an inverted J-shaped with HGS in men (mean ± SD: Q1, 26.26±8.06 kg; Q2, 29.54±8.69 kg; Q3, 35.63±10.42 kg; and Q4, 30.52± 12.56 kg; P for quadratic trend =0.004). In women, the serum UA levels also showed an inverted J-shaped relationship with HGS (mean ± SD: Q1, 18.59±5.46 kg; Q2, 23.10±5.60 kg; Q3, 22.23±5.14 kg; and Q4, 19.92±4.67 kg; P for quadratic trend =0.003), as shown in *Figure 2B*.

Furthermore, we analyzed the association between muscle strength and serum UA quartiles with ANCOVA after adjusting for potential confounding factors (including age, BMI, eGFR, smoking and alcohol consumption, medical history, laboratory parameters, and hs-CRP). The results showed that in men, even after adjusting for the potential confounding factors, the inverted J-shaped relationship between the UA quartiles with HGS was unchanged (P for quadratic trend: model 1 =0.005, model 2 =0.005, model 3 =0.008, model 4 =0.009, model 5 =0.003, model 6 =0.002). Among the quartiles, HGS of the Q3 group (5.35–6.41 mg/dL) was higher than that of the other three groups (*Table 3*). Similar to men, after adjusting for the potential confounding factors, the relationship between HGS with UA quartiles remained an inverted-J-shaped in women (P for quadratic trend: model 1 =0.034, model 2 =0.028, model 3 =0.027, model 4 =0.013, model 5 =0.012, model 6 =0.013). Among the quartiles, the HGS of the Q2

Table 2 Age-adjusted participant characteristics of female subjects categorized by quartiles of serum uric acid

Characteristics (N=409)	Serum uric acid (mg/dL)				P[1]
	Q1 (1.02–3.39) (N=103)	Q2 (3.40–4.42) (N=102)	Q3 (4.43–5.21) (N=105)	Q4 (5.22–10.28) (N=99)	
Age (years)	62.53±10.97	62.45±11.10	64.06±11.14	64.32±10.78	0.165
Weight (kg)	55.84±8.44	56.72±8.09	58.05±9.03	58.94±9.32	0.008
Height (cm)	156.96±5.72	156.43±5.32	157.31±5.69	155.31±5.47	0.100
BMI (kg/m^2)	22.65±3.09	23.15±2.91	23.44±3.32	24.40±3.83	0.002
Smoking status (%)	1.0	1.0	1.0	1.0	0.561
Drinking status (%)	1.9	1.0	0	4.0	0.356
Diabetes (%)	11.7	10.8	19.0	19.2	0.053
Hypertension (%)	29.1	41.2	49.5	60.6	0.000
Cancer (%)	35.0	35.3	28.6	33.3	0.581
Hb (g/L)*	114.87±16.77	122.67±21.01	123.35±17.45	123.59±18.51	0.001
Albumin (g/L)	38.37±5.11	42.55±4.72	42.88±5.11	43.07±4.98	0.000
TG (mmol/L)	1.20±0.92	1.41±0.67	1.71±1.98	1.89±1.13	0.001
TC (mmol/L)	4.02±1.05	4.59±11.03	4.51±1.00	4.56±1.13	0.000
LDL-C (mmol/L)*	2.27±0.77	2.60±0.86	2.46±0.83	2.59±0.92	0.032
HDL-C (mmol/L)	1.23±0.50	1.38±0.40	1.34±0.50	1.23±0.39	0.801
HbA1C (%)	6.00±1.38	5.74±0.74	5.95±0.74	5.99±0.92	0.756
FT3 (pmol/L)	4.25±0.77	4.36±0.66	4.38±0.59	4.31±0.86	0.534
TSH (mIU/L)*	2.49±1.79	2.28±1.58	2.71±1.70	2.36±1.60	0.953
eGFR (mL/min/1.73 m^2)	92.89±13.80	92.87±12.37	87.21±12.14	81.25±13.06	0.000
hs-CRP (mg/L)*	7.05±2.57	7.81±2.49	7.32±2.23	7.75±2.53	0.234

*, the data were log-transformed. [1], linear regression for the continuous variables or binary logistic for the categorical variables. BMI, body mass index; Hb, hemoglobin; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; HbA1c, glycated hemoglobin; FT3, free triiodothyronine; TSH, thyroid-stimulating hormone; eGFR, estimated glomerular filtration rate; hs-CRP, hypersensitive c-reactive protein.

group (3.40–4.42 mg/dL) was higher than that of the other three groups (*Table 3*).

Discussion

Our cross-sectional population study showed that serum UA levels shared a significant inverted J-shaped curve relationship with HGS after adjustment for potential confounding factors in an adult population aged 45 years and older. The observed inverted J-shaped relationship between muscle strength with serum UA quartiles was consistent with two other cross-sectional population studies conducted by Ruggiero *et al.* (21) and Huang *et al.* (16). Ruggiero *et al.* showed that participants in the middle serum UA quintiles (4.8–5.3 mg/dL) showed less disability in instrumental activities of daily living and better lower extremity function than those with higher or lower UA levels in 966 elderly participants aged over 65 years. The population-based cross-sectional study conducted by Huang *et al.* showed that muscle strength was much lower for people with hyperuricemia than in those without hyperuricemia, and showed an inverted J-shaped association between the serum UA quartiles and muscle strength in 630 male Japanese employees aged over 30 years old. These studies support that maintaining optimal levels of serum UA may help to maintain the quality and strength of skeletal

muscle. To the best of our knowledge, our study is the first to show that men and women have different optimal levels of serum UA, correlating with a positive impact on HGS. For men, the third quartile (Q3) UA (5.35–6.41 mg/dL) had the highest HGS, while for women, the Q2 UA (3.40–4.42 mg/dL) had the highest HGS. In our study, the precise mechanism behind the gender-specific difference in trends between muscle strength and serum UA was not completely clear. Sex hormones may partly explain the differences between genders because they strongly influence serum UA levels. In a study of 160 patients with female to male gender dysphoria, Kurahashi *et al.* (22) highlighted that testosterone hormone therapy raises UA levels in a dose-dependent manner; the incidence of hyperuricemia was more prevalent in participants who received higher doses of testosterone. They also demonstrated that elevated serum UA levels were positively correlated with serum creatinine levels. Serum creatinine level correlates to the individual's muscle mass, which is a significant source of purines and can induce the upregulation of UA; thus, the elevated serum UA observed during testosterone replacement therapy was attributable to increased muscle mass. Other causes of elevated serum UA may include alcohol consumption (which may be higher in men), the use of antihypertensive drugs and diuretics, age distribution, amount of daily exercise, and antioxidant containing food intake (which is known to affect serum UA levels). In our study, the analysis was performed after adjusting for alcohol consumption and medications. The effects of sex hormones, the amount of daily exercise, and antioxidant containing food intake require further investigation in the future.

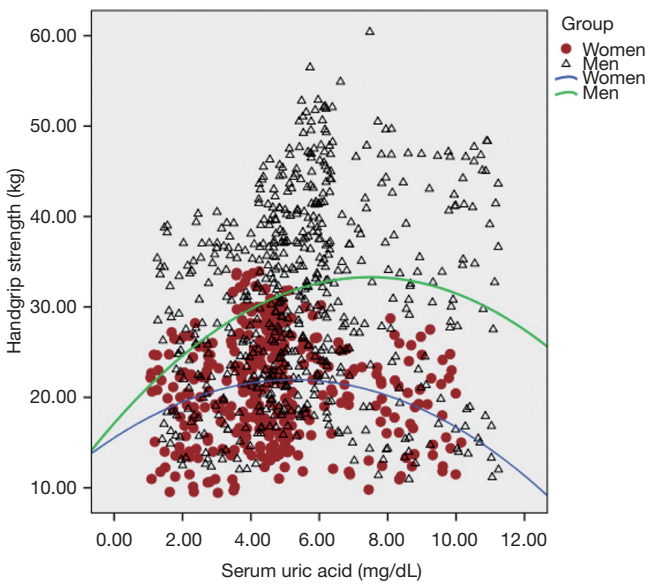

Figure 1 Scatter plots for UA against handgrip strength by gender. UA, uric acid.

On the other hand, several recent studies have reported a linear association of serum UA levels with HGS or/and leg extension. A prospective study by Macchi *et al.* (23) reported a linear relationship between the baseline UA level and increased HGS and/or leg extension over a 3-year follow-up period in 497 people aged 65 and above. Molino-Lova *et al.* (24) showed that higher serum UA levels were associated with better muscle function in older adults, and delayed the progression of sarcopenia in a sample of 73 men and 166 women with a mean age of 92.8. Among Chinese individuals aged 50–74, Wu *et al.* (25) reported that a higher UA level was independently related to better HGS. A cross-

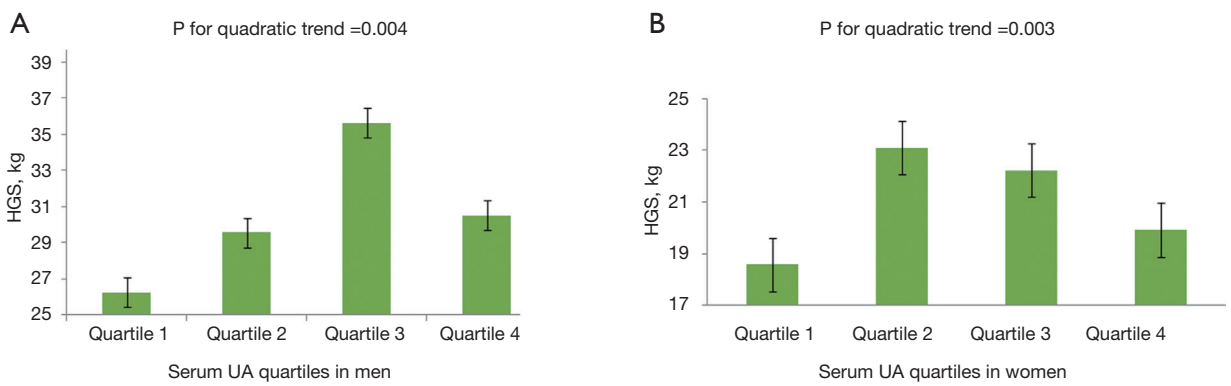

Figure 2 Univariate analysis of variance for the association between the quartiles of UA and HGS (A: men; B: women). UA, uric acid; HGS, handgrip strength.

Table 3 Univariate adjusted mean values (mean ± SD) of grip strength by serum UA quartiles

Serum uric acid (mg/dL)	Grip strength (kg)											
	Men, participants N=583						Women, participants N=409					
	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]	Model 5[e]	Model 6[f]	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]	Model 5[e]	Model 6[f]
Men												
Q1 (1.26–4.20) (N=146)	28.12±1.20	28.19±1.23	28.34±1.25	28.30±1.27	27.88±1.66	26.90±1.70	–	–	–	–	–	–
Q2 (4.21–5.34) (N=145)	31.46±1.11	31.47±1.12	31.48±1.12	31.48±1.14	31.23±1.30	31.09±1.30	–	–	–	–	–	–
Q3 (5.35–6.41) (N=149)	33.12±1.16	33.11±1.16	32.96±1.18	32.98±1.20	33.69±1.26	33.33±1.31	–	–	–	–	–	–
Q4 (6.42–11.24) (N=143)	29.91±1.17	29.83±1.20	29.83±1.20	29.85±1.23	28.80±1.30	28.89±1.32	–	–	–	–	–	–
P[1]	0.198	0.249	0.299	0.3	0.47	0.272	–	–	–	–	–	–
P[2]	0.005	0.005	0.008	0.009	0.003	0.002	–	–	–	–	–	–
Women												
Q1 (1.02–3.39) (N=103)	–	–	–	–	–	–	19.65±0.95	20.04±0.97	19.91±0.98	19.76±0.99	19.54±1.02	19.35±1.04
Q2 (3.40–4.42) (N=102)	–	–	–	–	–	–	22.20±0.88	22.27±0.87	22.20±0.88	22.16±0.88	22.73±0.87	22.61±0.93
Q3 (4.43–5.21) (N=105)	–	–	–	–	–	–	21.55±0.91	21.52±0.90	21.66±0.93	22.01±0.94	22.60±0.98	22.53±1.03
Q4 (5.22–10.28) (N=99)	–	–	–	–	–	–	20.04±0.97	19.56±1.00	19.64±1.03	19.47±1.06	20.57±1.02	20.49±1.04
P[1]	–	–	–	–	–	–	0.900	0.625	0.773	0.829	0.535	0.496
P[2]	–	–	–	–	–	–	0.034	0.028	0.027	0.013	0.012	0.013

[1], P for linear trend; [2], P for quadratic trend. [a], adjusted for age and BMI; [b], same as model 1 + eGFR; [c], same as model 2 + smoking and drinking status; [d], same as model 3 + the disease status, including diabetes (%), hypertension (%), and cancer (%); [e], same as model 4 + blood characteristics; [f], same as model 5 + hs-CRP. BMI, body mass index; eGFR, estimated glomerular filtration rate; hs-CRP, hypersensitive c-reactive protein.

sectional survey based on 4,230 people (aged ≥20) conducted in South Korea by Lee *et al.* (26) showed that there was no association between UA and HGS in participants aged 20–59 after adjusting for confounding factors. However, in individuals over 60, a high serum UA level was related to an increase in HGS. The four studies mentioned above all suggested that the antioxidant properties of UA could enhance muscle strength, especially in the elderly. However, in contrast to our results and the abovementioned cross-sectional results, Beavers *et al.* (17) and Veronese *et al.* (27) revealed contradictory findings. Beavers *et al.* found that increased serum UA was significantly related to sarcopenia status in 7,544 people aged 40 and older, and the participants in the group with the highest serum UA level (>8 mg/dL) were 2.0 times more likely to manifest sarcopenia than those in the group with the lowest serum UA level (<6 mg/dL), after having adjusted for the potential confounders. Veronese *et al.* reported that hyperuricemia seemed to be significantly associated with poor physical performance in the elderly, especially men in a 4.4-year follow-up of 1,904 Italian residents over 65 years old (27). We speculated that the reason the findings of these two studies differed from previous studies was related to the grouping of UA levels and participant characteristics. Hyperuricemia was defined as serum UA concentrations >8 mg/dL regardless of gender in the study by Beavers *et al.*, and ≥6 and ≥7 mg/dL for women and men, respectively, in the study conducted by Veronese *et al.* Our study demonstrated that a certain range of UA levels had a protective effect on HGS. However, in Q4 of serum UA quartiles of both men and women, HGS showed a downward trend when compared with the Q3 quartile. Higher serum UA levels may be related to poor HGS and/or leg extension through the following possible mechanisms: (I) the increase of UA concentration is positively correlated with CRP, tumor necrosis factor-alpha (TNF-α), and cytokine interleukin-6 (IL-6) in both men and women, suggesting that UA may have a role in systemic inflammation and subsequent inflammatory diseases (28). Elevated hs-CRP and IL-6, which can promote CRP synthesis, are related to reduced muscle strength (29-31). In this study, however, additional adjustment for hs-CRP did not alter the results showing the association between the serum UA level and HGS; this suggests that inflammation is not the primary mechanism for this association among Chinese adults older than 45. (II) there are more specific metabolic risk factors such as insulin resistance (IR), nonalcoholic fatty liver disease (NAFLD), CVD, and metabolic syndrome with the increase of serum UA that the effect of UA on muscle strength was negligible. (III) UA, previously an antioxidant, paradoxically switches to being a prooxidant in response to serum levels elevating the surrounding oxidant milieu, acidity, or the depletion of other local antioxidants (32). It is worth noting that serum UA levels were associated with a U-shaped curve with CVD events and all-cause mortality (7,8), suggesting that higher risk is linked to both low and high serum UA levels.

This study had several limitations: first, because of the cross-sectional nature of this study, the association between serum UA level and HGS is temporary, and prospective studies are needed to confirm a causal relationship further. Second, our analysis was based on the serum levels of UA and did not directly measure the antioxidant capacity and total antioxidant capacity of UA in the collected samples. Third, despite including nearly 1,000 people in the study, age bias cannot be ruled out. Also, despite making many adjustments to the covariates, we cannot exclude the residual confounding of unmeasured factors (including sex hormones, daily activity and differences in nutritional status), and comorbid metabolic diseases (including IR, NAFLD). The final limitation of this study is that muscle mass volume was not considered.

Conclusions

In conclusion, our data show that an optimal level of serum UA has a protective effect on skeletal muscle strength, as indicated by HGS. Also, the association between serum UA quartiles and muscle strength shows an inverted J-shaped curve both in men and women. The exact mechanisms responsible for this enhancement in muscle strength remain to be clearly defined. UA itself is a well-known antioxidant, and in some disease states, increasing UA levels is considered a possible drug therapy (33,34). Future prospective population-based studies are needed to investigate whether an intervention, such as effective lifestyle modifications and medications that control serum UA in adults, will improve muscle function.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All research procedures were conducted following the tenets of the Declaration of Helsinki (as revised in 2013) and were approved by the ethics committee of the First Affiliated Hospital, College of Medicine, Zhejiang University. The ethics approval number was No. 2016 (2-1). Signed informed consent was given by all participants before data collection.

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