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Association between serum uric acid levels and cardiovascular disease in middle-aged and elderly Chinese individuals

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Abstract

Background: A link between uric acid (UA) levels and cardiovascular diseases has been previously reported. However, its importance as a risk factor is still controversial. This study sought to determine whether elevated serum uric acid levels are associated with cardiovascular disease (CVD) in middle-aged and elderly Chinese individuals.

Methods: We conducted a population-based cross-sectional study in Shanghai, with a total of 8510 participants aged ≥ 40 years. The CVD included diagnosed coronary heart disease (CHD) and stroke. MetS was defined according to the updated National Cholesterol Education Program Adult Treatment Panel III criteria for Asian Americans.

Results: Uric acid levels were positively associated with BMI, waist circumference, triglycerides, systolic blood pressure, diastolic blood pressure, glycohemoglobin, fasting plasma glucose, postprandial 2-hour plasma glucose (all $P < 0.05$), and negatively associated with HDL-cholesterol ($P < 0.001$). The prevalence of CVD significantly increased with increasing quartiles of UA in those without MetS group (p trend < 0.001), but not necessarily increased in those with MetS. After adjustment for metabolic syndrome and other cardiovascular risk factors, multivariate logistic regression analysis showed that odds ratios (OR) for CHD, stroke, and CVD in those in the fourth quartiles were 2.34 (95% confidence interval [CI] 1.73 to 3.45), 2.18 (95% CI 1.86 to 3.28), and 2.16 (95% CI 1.80 to 3.29), respectively, compared with those in the first quartile of UA.

Conclusions: Elevated serum uric acid level was associated with CVD, independent of conventional cardiovascular disease risk factors and metabolic syndrome.

Keywords: Uric acid, Cardiovascular disease, Metabolic syndrome, Stroke, Coronary heart disease

Background

During the past two decades, China has experienced rapid economic growth and the ageing of its population. Resulting changes in lifestyle and longer life expectancy have led to an increased burden of cardiovascular and other chronic diseases [1-3]. The metabolic syndrome (MetS) is characterized by a clustering of cardiovascular risk factors. Previous studies have demonstrated an association of metabolic syndrome with the development of cardiovascular disease (CVD) [3-5] and increased risk of mortality from CVD [6,7].

Uric acid is the metabolic end product of purine metabolism in humans, excess accumulation can lead to various diseases [8]. Recently, a series of controversial and conflicting findings from epidemiological studies were reported [9-21]. Previous studies have demonstrated a strong relationship between serum uric acid levels and coronary heart disease (CHD) and some studies suggested that uric acid may be an independent risk factor for cardiovascular disease [9-17]. Moreover, recently a meta-analysis showed that hyperuricemia may increase the risk of CHD events, independently of traditional CHD risk factors [18]. However, the nature of the relationship between uric acid and cardiovascular disease remains a subject of debate [19-21].

Furthermore, although previous studies have analyzed the relationship between uric acid and CVD, thus far,

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evidence from large sample populations about the relationship between uric acid and CVD in Chinese people is scarce. In the present study, we undertook in large-scale Chinese populations. We first investigated the association between uric acid levels and confounding factors including metabolic syndrome. In addition, we also assessed whether there is an independent association of uric acid with cardiovascular disease in individuals subdivided according to metabolic syndrome status.

Methods

Study population and design

From May 2011 and November 2011, a population-based cross-sectional survey (Chongming Health Investigation) was conducted in Chongming District, Shanghai, China. A two-stage stratified sampling method was used. First, 12 residential communities or streets were randomly selected from the Chongming District. Of these, 8 urban communities and 4 rural communities were chosen to represent people with high to low socioeconomic status. Secondly, Within each community/street, all eligible individuals were sampled, with the exception that in households with more than one eligible individual, one individual was randomly selected. During the recruiting phase, inhabitants aged ≥ 40 years in these 12 communities were invited by telephone or door-to-door visit to participate in this study. A total of 9,930 subjects completed the survey, yielding a response rate of 92.4%. Each participant signed an informed consent form before completing the questionnaire. The protocol was approved by the Institutional Review Board of Xinhua Hospital affiliated with Shanghai Jiao-Tong University School of Medicine.

After excluding subjects with missing data regarding serum uric acid ($n = 1194$) or coronary heart disease ($n = 129$) or stroke ($n = 97$), 8510 participants were included in the final analysis (Figure 1).

Data collection

A standardized questionnaire was used by trained physicians to collect information such as age, sex, medications, education level (6, 7–9, or ≥ 10 years in school). The history of chronic diseases and current use of medications were recorded. The smoking or alcohol consumption habit was defined as never, current (smoking or consuming alcohol regularly in the past 6 months), or ever (cessation of smoking or alcohol consumption for more than 6 months). The type, amount, and frequency of alcohol consumption were collected. Based on the alcohol content of the beverages reported, mean daily alcohol consumption was calculated and expressed in grams per day. Physical activity at leisure time was estimated using the short form of the International Physical Activity Questionnaire by adding questions on frequency

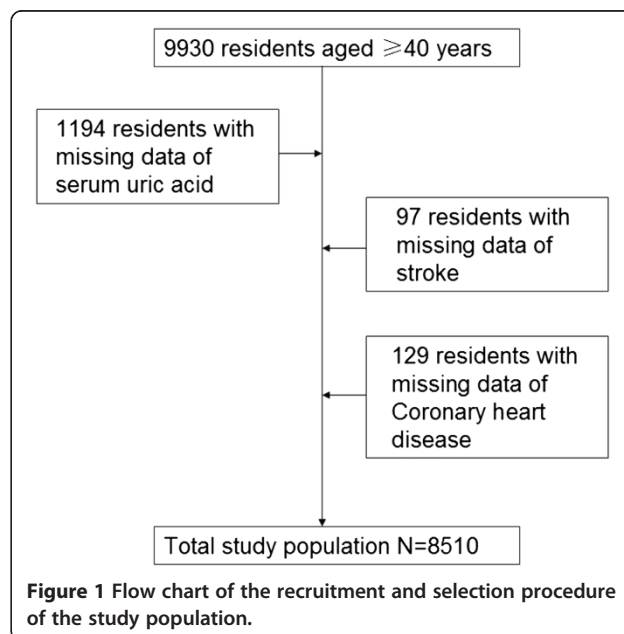


Figure 1 Flow chart of the recruitment and selection procedure of the study population.

and duration of moderate and vigorous activities and walking [22].

Anthropometric measurements were performed by the trained personnel using a standardized protocol. Height was measured to the nearest 0.1 cm, and weight was recorded to the nearest 0.1 kg while participants were wearing lightweight clothing and no shoes. Body mass index (BMI) was defined as body weight in kilograms divided by height squared in meters. Waist circumference (WC) was measured to the nearest 0.1 cm at the umbilical level with the participant in a standing position. Hip circumference was measured over the widest part of the gluteal region, and the waist-to-hip ratio was calculated as a measure of central obesity. Three blood pressure recordings were obtained from the right arm of patients in a sitting position after 30 min of rest; measurements were taken in 5-min intervals, and mean values were calculated.

Biochemical measurements

Peripheral venous blood samples were collected after an overnight fast. The fasting glucose, glucose 2 h after oral glucose tolerance test were measured with the use of the glucose oxidase method on an autoanalyzer (Modular P800; Roche, Basel, Switzerland). Triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and serum uric acid were measured using chemiluminescence methods on the autoanalyzer (Modular E170; Roche). Glycated hemoglobin (HbA1c) was measured with the use of the Chromatography method on an autoanalyzer (D10; Bio-Rad, USA).

Diagnosis of CVD

Hypertension was defined as diastolic blood pressure ≥ 90 mm Hg, systolic blood pressure of ≥ 140 mm Hg, or current medication for hypertension (as defined by WHO 1999) [16]. Coronary heart disease (CHD) and stroke were defined using the WHO MONICA criteria [23]. Myocardial infarction was diagnosed by a representative set of electrocardiogram, cardiac enzyme values, and typical symptoms. Angina was defined as use of nitroglycerine, experience of typical chest pain, and electrocardiogram changes compatible with ischemic heart disease. Strokes were defined as events requiring hospitalization; this information was verified from local hospital records, and 82% of the cases were confirmed using computed tomography and magnetic resonance imaging. Cardiovascular disease in the present study was defined by the presence of one or more of these two outcomes: CHD and stroke. Subjects with a fasting plasma glucose level of 7.0 mmol/l and/or a 2-h plasma glucose level of 11.1 mmol/l during an oral glucose tolerance test and/or who were receiving antidiabetic medications were diagnosed with diabetes mellitus. The diagnosis of cardiovascular events was based on self-reports, confirmed by hospital medical records and further clinical examinations carried out at the time of the survey (including electrocardiogram and ankle-arm systolic blood pressure index).

Definition of MetS

The MetS was defined based upon the updated NCEP-ATPIII for Asian Americans [24] as presenting 3 or more of the following components: 1) waist circumference ≥ 90 cm for men or ≥ 80 cm for women; 2) triglycerides ≥ 1.7 mmol/l; 3) HDL cholesterol < 1.03 mmol/l for men or < 1.30 mmol/l for women; 4) blood pressure $\geq 130/85$ mm Hg or current use of anti-hypertensive medications; and 5) fasting glucose ≥ 5.6 mmol/l or previously diagnosed type 2 diabetes or on oral antidiabetic agents or insulin.

Statistical analysis

Normally distributed data were expressed as means \pm SD, whereas variables with a skewed distribution were reported as median (interquartile range) and log transformed to approximate normality before analysis. Categorical variables were represented by frequency and percentage. The association of demographic, medical, metabolic and clinical characteristics with serum uric acid quartiles was assessed using multivariate linear or logistic regression analyses, adjusting for age and gender, for continuous and dichotomous variables, respectively. The correlations among serum uric acid, anthropometric indices and metabolic features adjusting for age and gender were obtained using Spearman partial correlation analysis. Sampling weights were used when estimating

prevalence of CVD. The trend for age- and sex-adjusted prevalence of CVD according to quartile of uric acid and the presence of metabolic syndrome were analysed using linear regression model. Multivariate logistic regression models were used to estimate the odds ratios (ORs) for CHD, stroke and CVD. Potential confounding variables including age, gender, smoking, alcohol drinking, physical activity, educational level, education, BMI, and metabolic syndrome were controlled in the regression models. All statistical analysis were performed with the SPSS Statistical Package (version 15.0; SPSS Inc., Chicago, IL). $P < 0.05$ was considered statistically significant.

Results

Characteristics of participants according to serum uric acid quartiles

Included were 8510 individuals who had both uric acid and CVD assessments (Figure 1). The mean age of this cohort was 55.90 ± 7.89 years, and approximately 32% were men. Baseline demographic and medical characteristics for both genders combined and divided by uric acid quartiles are presented in Table 1. Higher uric acid levels were associated with higher proportion of metabolic syndrome, proportion of men, age, smoking, alcohol consumption, systolic blood pressure, diastolic blood pressure, BMI, waist circumference, hip circumference, waist to hip ratio, fasting plasma glucose, postprandial 2-hour plasma glucose, glycohemoglobin, triglycerides, total cholesterol, LDL-cholesterol, presence of stroke, presence of CHD, hypertension, diabetes (all $P < 0.05$). In contrast, the patients with higher uric acid levels displayed lower levels of HDL cholesterol ($P < 0.001$) (Table 1).

Association between serum uric acid and CHD, stroke and CVD

Partial Spearman correlation analysis demonstrated the strongest correlation between uric acid and triglycerides among various metabolic features (Table 2). Moreover there was strong partial correlation between uric acid and BMI, TC, Waist circumference (WC), systolic blood pressure (SBP) and diastolic blood pressure (DBP), adjusting for age and gender, (all $P < 0.001$) (Table 2). As presented in Table 3, the ORs for CHD, stroke and CVD were higher with increasing uric acid quartiles (all $p < 0.001$ for linear trend). In the highest uric acid quartile, the adjusted ORs of CHD, stroke and CVD were 2.34 (95% confidence interval [CI] 1.73 to 3.45), 2.18 (95% CI 1.86 to 3.27), and 2.16 (95% CI 1.80 to 3.29), respectively, compared with those in the first quartile of UA (Table 3).

We further analyzed the prevalence of CVD according to quartile of uric acid and the presence of metabolic syndrome. After adjustments for age, gender, alcohol

Table 1 Characteristics of study participants according to uric acid quartiles

Characteristics	Q1 (n = 2428) ≤0.2	Q2 (n = 2114) 0.21-0.24	Q3 (n = 1986) 0.25-0.29	Q4 (n = 1982) ≥0.30	P value
MetS (%)	927 (38.2)	1112 (52.6)	1210 (60.9)	1410 (71.1)	<0.001
Uric acid (mmol/L)	0.18 (0.16-0.19)	0.22 (0.22-0.24)	0.27 (0.26-0.28)	0.34 (0.31-0.37)	<0.001
Male n (%)	316 (13.02)	500 (23.65)	705 (35.52)	1205 (60.80)	<0.001
Age (yrs) ^b	53.29 ± 7.97	55.72 ± 7.75	57.25 ± 7.45	57.93 ± 7.46	<0.001
Smoking (yes)	413 (17.02)	411 (19.44)	501 (25.23)	680 (34.31)	<0.001
Alcohol (yes)	524 (21.59)	514 (24.31)	579 (29.15)	852 (42.99)	<0.001
SBP (mmHg)	125 ± 20	129 ± 21	132 ± 20	135 ± 19	<0.001
DBP (mmHg)	78 ± 10	80 ± 10	81 ± 11	83 ± 10	<0.001
BMI (kg/m ²)	23.41 ± 3.19	24.76 ± 8.45	25.53 ± 11.29	25.79 ± 4.49	<0.001
Waist circumference (cm)	80 ± 10	84 ± 12	86 ± 10	89 ± 9	<0.001
Hip circumference (cm)	94.07 ± 7.40	95.85 ± 7.00	96.85 ± 6.78	98.09 ± 6.89	<0.001
Fasting plasma glucose (mmol/L)	6.05 ± 1.50	6.39 ± 1.89	6.50 ± 1.80	6.53 ± 1.61	<0.001
P2hPG (mmol/L)	7.95 ± 3.49	8.88 ± 4.16	9.26 ± 4.04	9.36 ± 3.91	<0.001
HbA1C	5.84 ± 0.97	6.01 ± 1.10	6.05 ± 1.07	6.02 ± 0.94	0.021
Triglycerides (mmol/L) ^c	1.09 (0.82-1.52)	1.36 (0.98-1.93)	1.49 (1.06-2.24)	1.86 (1.29-2.67)	<0.001
Total cholesterol (mmol/L)	4.59 ± 0.99	4.79 ± 0.99	4.81 ± 1.01	4.88 ± 1.05	<0.001
LDL cholesterol (mmol/L)	2.56 ± 0.75	2.66 ± 0.76	2.72 ± 0.79	2.72 ± 0.78	<0.001
HDL cholesterol (mmol/L)	1.33 ± 0.33	1.27 ± 0.31	1.22 ± 0.31	1.17 ± 0.30	<0.001
Physical activity					0.191
Low	1795 (73.96)	1538 (72.75)	1453 (73.16)	1395 (70.38)	
Moderate	487 (20.07)	435 (20.58)	397 (19.99)	438 (22.10)	
High	145 (5.97)	141 (6.67)	136 (6.85)	149 (7.52)	
Education					0.061
0-6	520 (21.43)	516 (24.41)	497 (25.03)	464 (23.41)	
7-9	1217 (50.14)	1048 (49.57)	989 (47.80)	988 (49.85)	
≥10	690 (28.43)	550 (26.02)	500 (27.17)	530 (26.74)	
Stroke	69 (2.84)	84 (3.97)	99 (4.98)	168 (8.48)	<0.001
Coronary heart disease	149 (6.14)	171 (8.09)	233 (11.73)	379 (19.12)	<0.001
Hypertension	1029 (42.40)	1109 (52.46)	1213 (61.08)	1386 (69.93)	<0.001
Diabetes mellitus	319 (13.14)	453 (21.43)	574 (28.90)	622 (31.38)	<0.001
Anti-hypertension medications	342 (14.09)	351 (16.60)	394 (19.84)	448 (22.60)	<0.001
Anti-diabetic medications	110 (4.53)	111 (5.25)	140 (7.05)	119 (6.00)	0.003
Lipid-lowering medications	65 (2.68)	71 (3.36)	62 (3.12)	57 (2.88)	0.571

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; P2hPG, postprandial 2-hour plasma glucose; HbA1C, Glycated hemoglobin; LDL, Low-density lipoprotein; HDL, high-density lipoprotein.

^aData are presented as mean ± SD, median (interquartile range), or number (percent); P value was calculated after adjustment for age, gender.

^bNot adjusted for itself.

^cThis variables was log transformed before analysis.

drinking, smoking, education, physical activity, TC, LDL, the prevalence of CVD in subjects with metabolic syndrome increased with uric acid quartile ($p < 0.001$ for linear trend) (Figure 2). No trend was observed in subject without metabolic syndrome ($p = 0.217$ for linear trend).

Discussion

In the present study, we found that serum uric acid levels showed association with the risk of CVD from the cross-sectional data in middle-aged and elderly Chinese individuals, independent of conventional cardiovascular risk factors including components of metabolic syndrome.

Table 2 Partial Spearman correlation coefficients among uric acid, anthropometric indicators, and metabolic features

	Uric acid	BMI	WC	HC	WHR	SBP	DBP	FPG	P2hPG	HbA1c	TC	TG	HDL-c
BMI	0.11 ^b												
WC	0.21 ^b	0.33 ^b											
HC	0.11 ^b	0.34 ^b	0.67 ^b										
WHR	0.08 ^b	0.11 ^b	0.47 ^b	-0.11 ^b									
SBP	0.10 ^b	0.11 ^b	0.23 ^b	0.17 ^b	0.12 ^b								
DBP	0.14 ^b	0.11 ^b	0.23 ^b	0.19 ^b	0.09 ^b	0.62 ^b							
FPG	0.04 ^b	0.02 ^c	0.09 ^b	0.03 ^c	0.07 ^b	0.14 ^b	0.10 ^b						
P2hPG	0.09 ^b	0.05 ^b	0.12 ^b	0.07 ^b	0.08 ^b	0.15 ^b	0.11 ^b	0.76 ^b					
HbA1c	0.02 ^c	0.02 ^c	0.07 ^b	0.03 ^c	0.05 ^b	0.05 ^b	0.03 ^c	0.82 ^b	0.71 ^b				
TC	0.12 ^b	0.02	0.08 ^b	0.05 ^b	0.04 ^b	0.12 ^b	0.13 ^b	0.12 ^b	0.10 ^b	0.08 ^b			
TG	0.27 ^b	0.09 ^b	0.21 ^b	0.13 ^b	0.11 ^b	0.11 ^b	0.15 ^b	0.18 ^b	0.21 ^b	0.14 ^b	0.23 ^b		
HDL-c	-0.18 ^b	-0.09 ^b	-0.17 ^b	-0.12 ^b	-0.07 ^b	0.02 ^c	0.00	-0.04 ^b	-0.09 ^b	-0.10 ^b	0.49 ^b	-0.29 ^b	
LDL-c	0.08 ^b	0.02	0.06 ^b	0.07 ^b	0.02 ^c	0.07 ^b	0.08 ^b	0.08 ^b	0.05 ^b	0.08 ^b	0.86 ^b	-0.04 ^c	0.33 ^b

BMI, body mass index; WC, Waist circumference; HC, Hip circumference; WHR, Waist-hip-ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; P2hPG, postprandial 2-hour plasma glucose; HbA1C, Glycated hemoglobin; TC, Triglycerides; Total cholesterol; TG, LDL, Low-density lipoprotein; HDL, high-density lipoprotein.

^aAll correlation coefficients were calculated after adjustment for age, gender.

^bP < 0.001.

^cP < 0.05.

Several previous studies in literature have documented the relationship between serum uric acid levels and cardiovascular diseases [9-17,25]. Increased serum uric acid was found to be associated with important risk factors for atherosclerosis like hypertension [26-29], abdominal obesity [28], diabetes mellitus [29,30], the metabolic syndrome [17], hypertriglyceridemia [31], endothelial dysfunction

[32] and renal failure [33]. However, whether uric acid is an independent risk factor for cardiovascular mortality is still a controversy. Difficulties in determining whether uric acid should be considered a cardiovascular risk factor may be explained by its frequent association with other cardiovascular risk factors [34] for which uric acid is considered as a risk marker or epiphenomenon or even an adaptive

Table 3 Odds ratios and 95% confidence interval for cardiovascular disease according to quartile of serum uric acid

	Q1	Q2	Q3	Q4	P value for trend
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	
CHD					
Model 1*	1	1.73 (1.36-2.19)	1.95 (1.70-2.45)	2.56 (1.95-3.89)	<0.001
Model 2 [†]	1	1.71 (1.35-2.17)	1.90 (1.63-2.42)	2.45 (1.82-3.56)	<0.001
Model 3 [‡]	1	1.65 (1.28-2.14)	1.82 (1.63-2.35)	2.34 (1.73-3.45)	<0.001
Stroke					
Model 1*	1	1.40 (1.02-1.96)	1.74 (1.29-2.43)	2.41 (2.02-3.65)	<0.001
Model 2 [†]	1	1.36 (1.03-1.93)	1.67 (1.27-2.41)	2.27 (1.92-3.39)	<0.001
Model 3 [‡]	1	1.30 (1.02-1.81)	1.60 (1.23-2.29)	2.18 (1.86-3.28)	<0.001
CVD					
Model 1*	1	1.39 (1.14-1.68)	1.87 (1.54-2.44)	2.50 (2.09-3.47)	<0.001
Model 2 [†]	1	1.31 (1.11-1.62)	1.77 (1.49-2.48)	2.40 (2.06-3.40)	<0.001
Model 3 [‡]	1	1.28 (1.09-1.56)	1.64 (1.35-2.38)	2.16 (1.80-3.29)	<0.001

*Model 1 adjusted for age and gender.

[†]Model 2 further adjusted for alcohol drinking, smoking, education, physical activity, TC, LDL and treatments (including antihypertensive therapy, antihyperlipidemic therapy and antihyperglycemic therapy).

[‡]Model 3 further adjusted for metabolic syndrome and BMI.

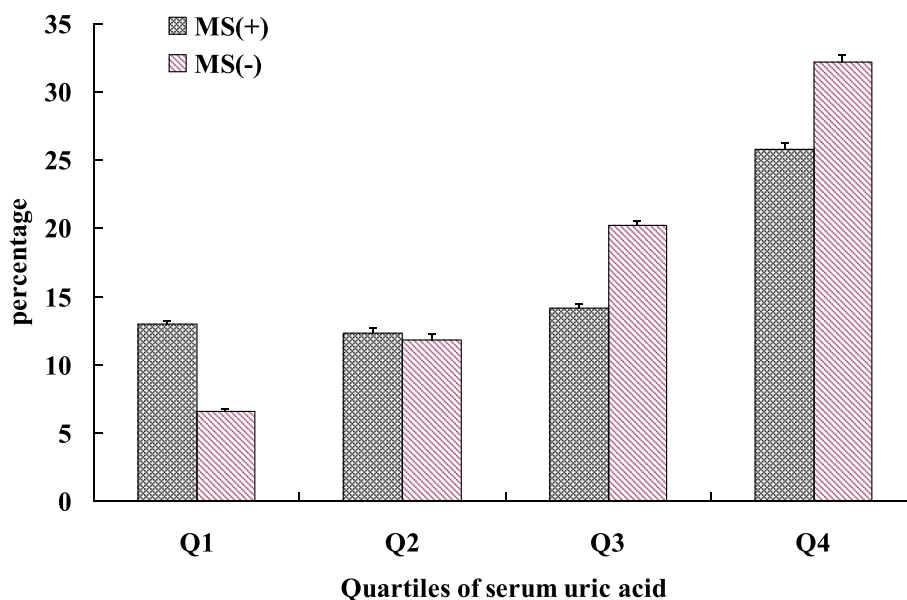


Figure 2 Prevalence of CVD according to quartiles of uric acid and the presence of metabolic syndrome (adjusted for age, gender, alcohol drinking, smoking, education, physical activity, TC, LDL). Data are expressed as percentages \pm SE. $P < 0.001$ for trend in MS(-) group, and $p = 0.217$ for trend in MS(+) group.

change to protect from atherosclerosis due to its antioxidant properties [35] and the controversial and conflicting findings from epidemiological studies [36].

The metabolic syndrome is characterized by a clustering of cardiovascular risk factors, including abdominal obesity, high blood pressure, increased glucose concentration, and dyslipidemia, is a common basis for the development of atherosclerosis, especially CVD [37-39]. Moreover, previous studies claimed that hyperuricemia was a new component of metabolic syndrome. Furthermore, in our study, the proportion of metabolic syndrome is in parallel with increasing serum uric acid quartiles. Thus, in order to explore whether elevated serum uric acid levels are associated with CVD independent of metabolic syndrome, we further analyzed the prevalence of CVD according to quartile of uric acid and the presence of metabolic syndrome. We found that prevalence of CVD is significantly increased with increasing quartiles of uric acid in without MetS group (p trend < 0.001), but not necessarily increased in those with metabolic syndrome. Additional factors besides metabolic syndrome may also play a key role in the development of CVD in hyperuricemia subjects, which requires further research.

The present study may have some implications. In particular, this study may strengthen the need for interventional studies with uric acid-lowering therapies to maintain UA levels in the lower safe range. Moreover, allopurinol – a xanthine oxidase inhibitor – has been shown recently to significantly improve endothelial

function and abolish vascular oxidative stress [40], has a clinically relevant antiischemic effect and has been well tolerated in patients with angina [41]. In analogy with homocysteine-lowering therapy interventional studies with UA-lowering agents, apart from exploring clinical benefits of these agents, may provide valuable additional information regarding causality in the uric acid–cardiovascular disease relationship.

The major strength of our present study was that the large sample size and representative sample with a relatively high response rate. Several limitations of our study have also to be addressed. First, due to the cross-sectional nature of the present study, no causal relationships can be established. Large prospective studies are in urgent need to confirm the relationship between serum uric acid levels and CVD. Second, although most potential confounders were carefully controlled, since some of the study subjects may had several chronic disease, we could not eliminate the possible effect of underlying diseases and medications used for these diseases on the present findings.

Conclusion

In conclusion, the present study showed that elevated serum uric acid level was associated with CVD, independent of conventional CVD risk factors and the presence of metabolic syndrome. The study added more evidence to the notion that the risk of CVD increased in subjects with hyperuricemia.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Conceived and designed the experiments: QS. Analyzed the data: LQ, ZY. Contributed reagents/materials/analysis tools: LQ, ZY, HG, SL, QS, YX, XL, RL, GN. Wrote the paper: LQ, ZY. All authors read and approved the final manuscript.

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