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Associations of serum uric acid with cardiovascular disease risk factors: a retrospective cohort study in southeastern China

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ABSTRACT

Objective To evaluate the associations between serum uric acid (SUA) levels and cardiovascular disease (CVD) risk factors, focusing on potential sex-specific differences.

Design A retrospective cohort study.

Setting A large community-based survey was conducted every two years from 2010 to 2018 in Hangzhou, Zhejiang Province, outheastern China.

Participants 6119 participants aged 40 years and above who underwent at least three times of physical examinations were enrolled.

Methods Participants were categorised into four groups (Q1–Q4) based on baseline SUA quartiles within the normal range, with hyperuricaemia (HUA) as the fifth group. The Q1 was the reference. By stratifying participants by gender, the relationships between SUA levels and systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (FBG) and total cholesterol (TC) were investigated using linear regression models in the generalised estimating equation. Additionally, the associations of elevated SUA levels and HUA with hypertension, hyperglycaemia and dyslipidaemia were correspondingly examined using multivariate logistic regression models.

Results After adjusting for confounding variables, we found positive associations between SUA levels and SBP, DBP, FBG and TC in women, and with TC in men ($p<0.01$). Likewise, elevated SUA quartiles and HUA were linked to increased dyslipidaemia risk in both sexes, and increased hyperglycaemia risk only in women, with HRs (95% CI) of 1.64 (1.05 to 2.55) and 2.37 (1.47 to 3.81) in the Q4 and HUA group, respectively. Women with HUA had higher hypertension risk (HR=1.45, 95% CI 1.21 to 1.73), while no such association was observed in men. Stratified analyses revealed significant associations between elevated SUA levels and CVD risk factors in postmenopausal and non-obese women.

Conclusions Elevated SUA levels increase the risk of dyslipidaemia in both sexes. SUA levels within normal range and HUA are positively associated with hyperglycaemia and hypertension in postmenopausal women, but not in men.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The strength of this study was the utilisation of a large-scale dynamic retrospective cohort in the southeastern community of China.
⇒ The menopausal status in women was considered when we investigated the effect of elevated serum uric acid on cardiovascular disease risk factors.
⇒ Data collected in this retrospective survey did not include sufficient information on possible confounding factors, such as alcoholic consumption, physical activity and dietary habits.

INTRODUCTION

Cardiovascular diseases (CVDs) have a high incidence and disability rate that have worsened the quality of life for middle-aged and elderly individuals.[1] Given the increasing disease burden of CVDs,[2] early monitoring and intervention for the CVD-associated risk factors are imperative in preventing the onset of CVDs.

Uric acid is the end-product of purine metabolism. Hyperuricaemia (HUA) caused by high levels of uric acids increases the risk of developing gout.[3] Numerous epidemiological studies have suggested strong associations between serum uric acid (SUA) and CVD risk factors,[4–7] including hypertension, obesity, diabetes and dyslipidaemia.[8–11] In animal-based studies, elevated SUA levels have been found to affect cardiovascular and metabolic functions via multiple pathways, such as oxidative stress and endothelial dysfunction, and insulin resistance.[6 12–15] However, ambiguity remains regarding the associations between SUA and CVD risk factors. First, conflicting results from previous studies have made it unclear whether SUA levels were associated with systolic blood pressure (SBP), diastolic blood pressure (DBP) or both.[16–21] Second, gender disparities were reported in

the relationship between SUA and fasting blood glucose (FBG), with some studies suggesting a stronger association between SUA and FBG in women than in men,[22–24] while other studies found no correlation between SUA and diabetes in men.[25 26] Third, the investigation into the relationship between SUA within normal range and blood lipids has been relatively limited, most of them focused on studying the association between disease outcomes (HUA or gout) and dyslipidaemia. Therefore, it is necessary to explore the connections between elevated SUA within the normal range and dyslipidaemia. Examining the potential associations can enhance our understanding of the pathophysiology underlying dyslipidaemia.[27–29]

In this study, using a retrospective cohort study conducted in southeastern China, we aimed to investigate the associations of SUA levels and HUA with blood pressure (BP), hyperglycaemia and dyslipidaemia in adults over 40 years old.

METHODS

Study design

A dynamic retrospective cohort study was conducted, based on the 'Public Basic Health Services Project' of China, which aims to understand the health status of residents, monitor and manage patients with chronic disease, and improve overall health awareness and disease prevention. In this national project, participants with local household registration and who live in the community for more than 6 months were eligible for a free health check-up every 2 years. The primary study participants included 12 498 adults aged 40 years or older who finished physical examinations in the Zhanongkou community health service centre, Hangzhou, Zhejiang Province from May 2010 to December 2018. In this current study, participants who had undergone fewer than three physical examinations (n=2618), and those with incomplete SUA data (n=252), missing BP, FBG and total cholesterol (TC) information (n=384), and having a history of hypertension, hyperglycaemia, or dyslipidaemia at baseline (n=3125) were excluded. Ultimately, a total of 6119 eligible participants (2041 men and 4078 women) were included in this study (figure 1).

Data measurement

Each participant was required to complete an in-person interview by a trained nurse using a standardised questionnaire, which included information related to demographic characteristics (age and sex) and the medical history (disease and drug history of hypertension, diabetes, dyslipidaemia). Values of weight and height were measured using a calibrated scale and a stadiometer. BP was measured using a calibrated mercury sphygmomanometer. Two consecutive measurements were taken and recorded, with a 2-minute break across the two measurements. The final value was calculated as the average of the two readings.

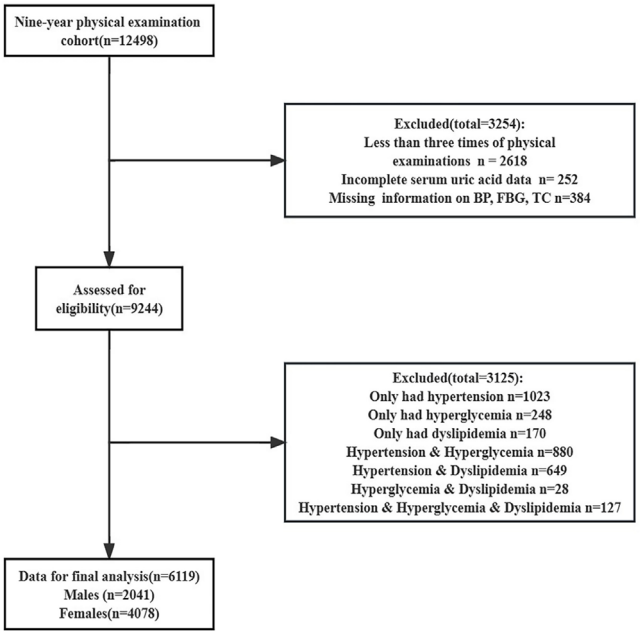

Figure 1 Flow chart of the participant inclusion. BP, blood pressure; FBG, fasting blood glucose; TC, total cholesterol.

Prior to venous blood sample collection, all participants were required to fast for at least 8 hours. Serum creatinine, SUA, FBG and TC for each participant were measured using standard clinical laboratory methods.

Diagnostic criteria

The primary endpoints in this study included hypertension, hyperglycaemia and dyslipidaemia. Hypertension was defined as either SBP ≥140 mm Hg or DBP ≥90 mm Hg, or having been previously diagnosed with hypertension and currently receiving anti-hypertensive treatment. Hyperglycaemia was defined as FBG ≥7.0 mmol/L or self-reported diabetes. Dyslipidaemia was defined as TC ≥6.22 mmol/L.[30] HUA was defined as SUA ≥416 µmol/L (70 mg/L) in men and SUA ≥357 µmol/L (60 mg/L) in women. According to Chinese body mass index (BMI) classification criteria,[31] obesity was defined as BMI ≥28 kg/m^2.

Patient and public involvement

There was no patient and/or public involvement in the design of this study.

Statistical analysis

The normality of continuous variables' distribution was assessed using the Shapiro-Wilk tests. Continuous variables with normal distribution are presented as the mean±SD, and with non-normal distribution are presented as the median (IQR). Categorical variables are expressed as numbers (percentages). The group differences for continuous variables were compared using analysis of variance and the Kruskal-Wallis test. The X^2 test was used for categorical variables. Given the gender differences in SUA levels, all analyses were stratified by gender. SUA levels within the normal range were divided into four

groups based on their SUA levels (Q1–Q4). The HUA was grouped as the fifth group. For women, the detailed grouping information was: Q1 (SUA <227 µmol/L), Q2 (227≤SUA<262 µmol/L), Q3 (262≤SUA<300 µmol/L), Q4 (300≤SUA<357 µmol/L) and HUA (SUA ≥357 µmol/L). For men, the detailed grouping information was: Q1 (SUA <284 µmol/L), Q2 (284≤SUA<327 µmol/L), Q3 (327≤SUA<367 µmol/L), Q4 (367≤SUA<416 µmol/L) and HUA (SUA ≥416 µmol/L). The first quartile (Q1) was used as the reference group. Linear models of generalised estimating equations (GEE) were used to calculate the HRs of SUA levels on SBP, DBP, FBG and TC. The model investigating the relationship between SUA levels and SBP/DBP was adjusted for age, BMI, FBG, TC, serum creatinine and estimated glomerular filtration rate (eGFR). Similarly, the model examining the association between SUA levels and FBG was adjusted for age, BMI, SBP, DBP, TC, serum creatinine and eGFR. Additionally, the model exploring the relationship between SUA levels and TC was adjusted for age, BMI, SBP, DBP, FBG, serum creatinine and eGFR. Multivariate logistic regression models were used to evaluate the risk of hypertension, hyperglycaemia and dyslipidaemia for different SUA levels or HUA, adjusting for the same confounding factors as above. Furthermore, stratified analyses were conducted by women's menopausal status, age and obesity status.

All analyses were performed using SPSS V.26.0 and R software V.4.2.1. We applied the Bonferroni correction method to account for multiple comparisons. Therefore, only two-sided p values of <0.05/3 (0.0167) were considered to be statistically significant.

RESULTS

The baseline characteristics of the study participants by sexes are presented in online supplemental table 1. A total of 6119 participants (2041 men and 4078 women) were included, with an average age of 65.4±9.3 years. The prevalence of HUA was significantly higher in men than in women (20.0% vs 13.4%, respectively, p<0.001). Moreover, men had significantly higher values of age, BMI, SBP, DBP, FBG, creatinine and SUA than women (p<0.001). Conversely, women had significantly higher eGFR and TC levels than men (p<0.001). From May 2010 to December 2018, with a median follow-up time of 6.18 years, 2561 participants were newly diagnosed with hypertension, 605 with hyperglycaemia and 1081 with dyslipidaemia.

The baseline clinical characteristics of participants with different SUA levels are presented in tables 1 and 2. As the SUA levels increased, DBP in women and SBP, FBG, TC and creatinine in both sexes increased, while eGFR decreased in both sexes. Moreover, in both sexes, those with higher SUA levels or HUA were more likely to be older and obese.

Linear regression models with GEE were used to evaluate the association between SUA and CVD risk factors (table 3). After adjustment of the confounding factors, we found that men in the Q3 group displayed a positive association with SBP (beta=1.63 (95% CI 0.31 to 2.94)). Among women, participants in Q4 and the HUA groups had positive associations with SBP (beta=2.02 (95% CI 1.06 to 2.97) for Q4; beta=2.31 (95% CI 1.22 to 3.39) for HUA) and DBP (beta=1.17 (95% CI 0.47 to 1.86) for Q4; beta=1.27 (95% CI 0.49 to 2.06) for HUA). Furthermore, we found a positive association between SUA and FBG in women with beta of 0.11 (95% CI 0.05 to 0.17) in Q3 group, 0.13 (95% CI 0.07 to 0.19) in Q4 group and 0.28 (95% CI 0.19 to 0.36) in HUA group, respectively. However, no significant associations were observed between SUA and SBP, DBP or FBG in men. Notably, there was a linear increase in TC with increasing quartiles

Table 1 Baseline characteristics of the male participants according to different SUA levels

Characteristics	SUA level					P value
	Q1 (n=409)	Q2 (n=414)	Q3 (n=401)	Q4 (n=408)	HUA (n=409)	
Age (years)	67.32±8.52	68.90±8.84	69.73±8.21	70.24±8.83	71.22±9.18	<0.001
Body mass index (%)						<0.001
<18.5 (kg/m^2)	29 (7.1)	20 (4.8)	20 (4.9)	18 (4.4)	9 (2.2)	
18.5~24 (kg/m^2)	248 (61.1)	236 (56.9)	235 (58.2)	181 (44.5)	174 (42.5)	
24~28 (kg/m^2)	107 (26.4)	141 (34.0)	126 (31.2)	170 (41.8)	183 (44.8)	
≥28 (kg/m^2)	22 (5.4)	18 (4.3)	23 (5.7)	38 (9.3)	43 (10.5)	
SBP (mm Hg)	123.25±10.76	124.24±9.76	125.88±9.77	126.22±8.97	126.82±9.11	<0.001
DBP (mm Hg)	76.63±7.16	77.20±6.80	76.86±6.67	77.45±6.39	77.13±6.70	0.464
FBG (mmol/L)	5.33±0.63	5.36±0.61	5.41±0.61	5.45±0.64	5.52±0.62	<0.001
TC (mmol/L)	4.43±0.72	4.51±0.75	4.53±0.75	4.56±0.74	4.67±0.74	<0.001
Creatine (µmol/L)	89.00±19.86	89.08±17.86	90.66±18.67	92.14±19.28	101.78±24.76	<0.001
eGFR (mL/min/1.73 m^2)	87.78±24.92	86.57±24.14	84.70±23.68	83.00±23.17	74.21±23.40	<0.001

DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HUA, hyperuricaemia group; SBP, systolic blood pressure; SUA, serum uric acid; TC, total cholesterol.

Table 2 Baseline characteristics of the female participants according to different SUA levels

Characteristics	SUA level					P value
	Q1 (n=891)	Q2 (n=878)	Q3 (n=901)	Q4 (n=863)	HUA (n=545)	
Age (years)	59.73±8.68	62.41±8.00	63.73±8.43	65.09±8.50	67.81±9.26	<0.001
Body mass index (%)						<0.001
<18.5 (kg/m^2)	61 (6.9)	45 (5.1)	45 (5.0)	29 (3.4)	9 (1.6)	
18.5~24 (kg/m^2)	617 (69.4)	603 (68.6)	539 (59.7)	460 (53.4)	244 (44.7)	
24~28 (kg/m^2)	185 (20.8)	195 (22.2)	267 (29.6)	303 (35.2)	227 (41.6)	
≥28 (kg/m^2)	26 (2.9)	36 (4.1)	52 (5.7)	69 (8.0)	66 (12.1)	
SBP (mm Hg)	120.05±11.42	121.89±10.56	122.66±11.01	125.21±9.82	127.06±9.23	<0.001
DBP (mm Hg)	73.72±7.47	74.23±6.91	74.28±7.29	74.99±7.12	75.27±6.82	<0.001
FBG (mmol/L)	5.16±0.55	5.18±0.54	5.29±0.57	5.32±0.56	5.50±0.62	<0.001
TC (mmol/L)	4.62±0.73	4.75±0.74	4.86±0.72	4.92±0.71	4.96±0.75	<0.001
Creatine (μmol/L)	69.26±15.17	71.06±15.38	73.04±17.06	75.52±17.24	81.15±19.48	<0.001
eGFR (mL/min/1.73 m^2)	96.91±29.01	92.95±27.30	90.31±27.75	86.43±27.38	78.73±25.04	<0.001

DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HUA, hyperuricaemia group; SBP, systolic blood pressure; SUA, serum uric acid; TC, total cholesterol.

of SUA in both sexes. The beta (95% CI) in the HUA group of SUA was 0.16 (95% CI 0.06 to 0.25) in men and 0.15 (95% CI 0.06 to 0.24) in women.

The HRs of hypertension, hyperglycaemia and dyslipidaemia were calculated using multiple logistic regression analyses in the GEE across different SUA levels. After adjustment of the covariates, we found that elevated SUA levels were significantly associated with an increased incidence of hypertension, hyperglycaemia and dyslipidaemia in women. Compared with the lowest SUA quartile, women in the HUA group showed a significantly higher risk of hypertension (HR: 1.45, 95% CI: 1.21 to 1.73, p<0.001). For hyperglycaemia, the HRs were 2.37 (1.47 to 3.81) in HUA group. Similarly, for dyslipidaemia, the HRs were 1.55 (1.16 to 2.06) in HUA group. In men, elevated SUA levels were associated with a higher incidence of dyslipidaemia with HRs of 1.65 (1.28 to 2.12) in HUA; however, no significant associations were observed between SUA levels and hypertension or hyperglycaemia (figure 2).

We stratified participants by age using 65 years as a cut-off point. Among men, elevated SUA levels were significantly

Table 3 Linear regression analysis of baseline SUA levels and BP, FBG and TC

SUA (μmol/L)	Characteristics, beta (95% CI)			
	SBP	DBP	FBG	TC
Men				
Q1	Ref	Ref	Ref	Ref
Q2	0.50 (–0.78, 1.77)	0.74 (–0.12, 1.60)	0.04 (–0.14, 0.06)	0.08 (–0.01, 0.17)
Q3	1.63 (0.31, 2.94)**	0.73 (–0.16, 1.63)	0.01 (–0.12, 0.11)	0.11 (0.01, 0.20)*
Q4	1.00 (–0.26, 2.26)	1.01 (0.16, 1.87)*	0.02 (–0.09, 0.12)	0.10 (0.01, 0.20)*
HUA	1.30 (0.04, 2.56)*	0.89 (–0.02, 1.80)	0.03 (–0.08, 0.14)	0.16 (0.06, 0.25)**
Women				
Q1	Ref	Ref	Ref	Ref
Q2	0.54 (–0.40, 1.48)	0.64 (–0.03, 1.32)	0.01 (–0.05, 0.07)	0.07 (0.01, 0.14)
Q3	0.27 (–0.68, 1.23)	0.42 (–0.26, 1.10)	0.11 (0.05, 0.17)**	0.12 (0.05, 0.19)**
Q4	2.02 (1.06, 2.97)**	1.17 (0.47, 1.86)**	0.13 (0.07, 0.19)**	0.13 (0.06, 0.20)**
HUA	2.31 (1.22, 3.39)**	1.27 (0.49, 2.06)**	0.28 (0.19, 0.36)**	0.15 (0.06, 0.24)**

Model on SBP or DBP was adjusted for age, BMI, FBG, TC, creatine and eGFR. Model on FBG was adjusted for age, BMI, SBP, DBP, TC, creatine and eGFR. Model on TC was adjusted for age, BMI, SBP, DBP, FBG, creatine and eGFR.
*0.0167≤p<0.05, **p<0.0167.
BMI, body mass index; BP, blood pressure; DBP, diastolic BP; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HUA, hyperuricaemia group; SBP, systolic BP; SUA, serum uric acid; TC, total cholesterol.

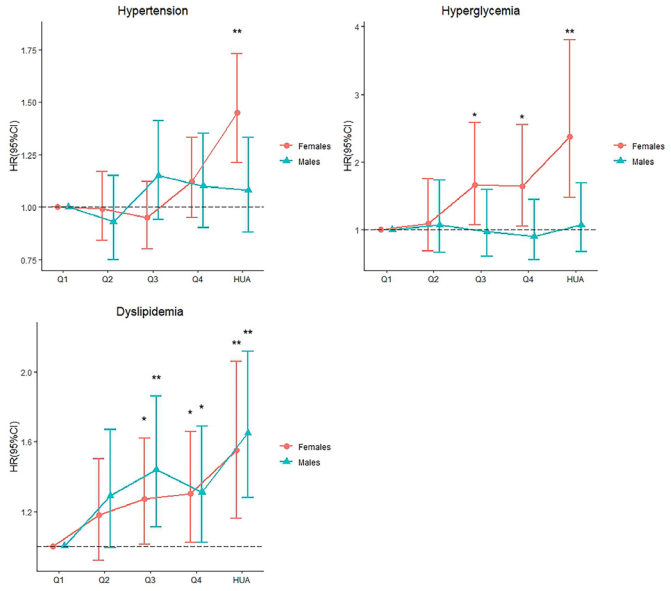

Figure 2 HRs of hypertension, hyperglycaemia and dyslipidaemia according to the SUA levels. Model on hypertension was adjusted for age, BMI, FBG, TC, creatine and eGFR. Model on hyperglycaemia was adjusted for age, BMI, SBP, DBP, TC, creatine and eGFR. Model on dyslipidaemia was adjusted for age, BMI, SBP, DBP, FBG, creatine and eGFR. Q1–Q4 were quartiles of normal SUA. *0.0167≤p<0.05, **p<0.0167. BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HUA, hyperuricaemia group; SBP, systolic blood pressure; SUA, serum uric acid; TC, total cholesterol.

associated with dyslipidaemia. In women aged 40–65 years, elevated SUA levels were linked to hyperglycaemia and dyslipidaemia; women aged ≥65 years showed significant associations between elevated SUA levels and hypertension. Furthermore, women were stratified by menopausal status, using 51 years as the cut-off point. Participants younger than 51 years had no significant association between SUA and hypertension or hyperglycaemia, but a significant association was observed between SUA and dyslipidaemia. For participants aged 51 years and above, we observed a significant association between SUA levels and hypertension, hyperglycaemia and dyslipidaemia. In the obesity-stratified analysis, we found similar associations of SUA with hypertension, hyperglycaemia and dyslipidaemia in the non-obese group. However, none of these associations were statistically significant in the obese population (see online supplemental tables 2–6).

DISCUSSION

Our study investigated the associations between SUA levels, HUA and CVD risk factors, including hypertension, hyperglycaemia and dyslipidaemia, and revealed the gender-specific relationships between SUA levels and these outcomes on continuous and categorical scales. Higher SUA levels increased the risk of dyslipidaemia in both sexes and increased the risk of hypertension and hyperglycaemia in women on a categorical scale.

Previous studies have reported inconsistent relationships between SBP or DBP and SUA.[16–21 32] Our study showed a positive correlation between SUA levels and elevated SBP and DBP, which is in line with the majority of previous research.[8 33] Additionally, numerous earlier studies and meta-analyses have highlighted that HUA and elevated SUA levels are associated with a higher risk of developing hypertension.[34 35] This may be explained by the effect of elevated SUA levels on the renin–angiotensin system, which is closely related to BP regulation.[36] Furthermore, elevated SUA levels may trigger oxidative stress and inflammatory responses, leading to vascular endothelial cell damage and the formation of atherosclerotic plaque, which is one of the leading causes of CVDs. Elevated SUA levels could also inhibit the release of nitric oxide, resulting in endothelial dysfunction. This dysfunction increases BP and promotes cardiovascular pathological damage. In conclusion, the mechanisms of SUA on the development of CVDs are complex and interactive; future studies are required to explain the role of high uric acid in CVDs and its factors.[37]

Higher SUA levels and HUA prevalence are observed in men than in women, possibly due to differences in body metabolism and sex hormone secretion in middle-aged and older women. Oestrogen facilitates SUA excretion, resulting in lower average SUA levels in women than in men.[38] Our study found a significant association between HUA and hypertension in women but not in men, consistent with a cross-sectional study of over 11 000 participants investigating the association between SUA and cardiovascular risk factors.[8] Gender differences were also observed in the association between SUA and hyperglycaemia, with significant association only found in women but not in men. A study in a rural population in northeastern China consistently found that HUA was associated with hyperglycaemia only in women.[39] Furthermore, HUA and diabetes have been demonstrated to have shared common genetic predispositions, and several genes have been shown to be strongly associated with the development and progression of both diseases.[40 41] A genome-wide association study in India revealed that single nucleotide polymorphisms (SNPs) in genes such as SLC2A9, SLC22A11 and ABCG2 were involved in the interaction between HUA and type 2 diabetes.[42] Similarly, several studies in Chinese populations have indicated that SNPs in SLC2A9 are associated with an increased risk of type 2 diabetes, as well as with glucose metabolism and insulin secretion.[43] These genetic correlations between uric acid and diabetes indirectly support our findings.

Dyslipidaemia is a significant risk factor for CVD. In a meta-analysis involving 17 studies, the combined OR for the highest SUA level compared with the lowest SUA level was 1.84 (1.49 to 2.28) for the risk of dyslipidaemia.[27] Our study found a significant positive correlation between SUA and TC, as well as an elevated risk of dyslipidaemia with both HUA and higher SUA levels within the normal

range, which was consistent with earlier studies.[44–47] Notably, previous studies did not find a connection between SUA and dyslipidaemia in females.[48] However, our study found significant associations between both men and women, with a stronger trend observed in men when the analysis was stratified by gender. These findings were also consistent with those of a cross-sectional study conducted in Korea.[29] Furthermore, given the high incidence of HUA among middle-aged women,[49] we stratified women by menopausal status. Our study confirmed a significant association between SUA levels and hypertension, hyperglycaemia and dyslipidaemia for women after menopause, suggesting that SUA is an independent risk factor for CVD in postmenopausal women. These findings are consistent with previous reports.[50] Importantly, our study underlines the necessity of considering the impact of menopausal status on the association between SUA and CVD.

There are several limitations in our study. First, data in relation to potential confounding factors had not been collected, such as smoking, alcohol consumption, physical activity and dietary habits, which may cause overestimations on the associations between uric acid and cardiovascular risk factors in this study. Second, our study was based on a single-centre investigation and included only adults aged 40 years and older residing in the community, which should be cautious when extrapolating our findings to other populations. Third, because of the retrospective study design, our results may be subject to self-reporting bias, such as the disease and drug histories. However, most of the information in this study was based on blood measurements, which suggested that the self-reporting bias might be small. Our study has several strengths, such as a large sample size, a long follow-up period and a prospective design. Analyses using both continuous and categorical scales of the endpoints can provide more reliable and robust findings. Our study provides valuable insights into the association between SUA levels and CVD risk factors in a specific population. Further investigation in this area could improve our understanding of the pathogenesis of CVD and inform the development of preventive and therapeutic interventions.

CONCLUSION

This study highlights the detrimental impact of elevated SUA levels on dyslipidaemia risk in both sexes. Furthermore, it reveals that SUA levels within the normal range and HUA status are positively associated with hyperglycaemia and hypertension in postmenopausal women, but no such associations were observed in men.

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Contributors YL and HM conducted the conception and design of the research protocol. YL, CJ, MH and YW acquired and analysed the data, YL and QW were responsible for writing and revising the article, and FL and RM provided guidance on the research methodology. HM is the guarantor responsible for the overall content. All authors reviewed the manuscript and agreed to submit the paper.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Obtained.

Ethics approval This study involves human participants and was approved by the Ethics Committee of Hangzhou Normal University School of Public Health (20220009). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available.

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