

BMJ Open Relation of serum uric acid to asymptomatic proximal extracranial artery stenosis in a middle-aged Chinese population: a community-based cross-sectional study

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To cite: Yang X, Lv H, Hidru TH, *et al.* Relation of serum uric acid to asymptomatic proximal extracranial artery stenosis in a middle-aged Chinese population: a community-based cross-sectional study. *BMJ Open* 2018;**8**:e020681. doi:10.1136/bmjopen-2017-020681

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2017-020681>).

Received 17 November 2017
Revised 23 May 2018
Accepted 20 June 2018



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ABSTRACT

Objective Serum uric acid (SUA) has been associated with cardiovascular diseases, including atherosclerosis and carotid artery stenosis. However, data on the relationship between SUA level and proximal extracranial artery stenosis (PEAS) are limited. Therefore, this study investigates the association between SUA levels and the risk of PEAS in asymptomatic Chinese population.

Setting This community-based cross-sectional study was conducted in Jidong Community Hospital, Tangshan, Hebei, China between July 2013 and August 2014.

Participants The study examined 3325 asymptomatic participants (40–60 years) to evaluate the risk of PEAS.

Results For the participants stratified into quartiles based on gender-specific SUA levels, the prevalence of PEAS increased from Q1 to Q4 from 12.3% to 29.8% in the vertebral artery (VA), and from 2.8% to 5.8% in the common carotid artery. The proportion of PEAS relative to the detected number of arterial stenosis was lower in Q1 than in Q2–Q4. The multivariable ORs and 95% CI of PEAS in the second through fourth compared with the lowest quartiles for arterial stenosis were 1.278 (0.980 to 1.665), 1.117 (0.851 to 1.468) and 1.375 (1.033 to 1.830) ($p_{\text{trend}}=0.0399$); and for VA stenosis, 1.285 (0.966 to 1.709), 1.085 (0.808 to 1.457) and 1.439 (1.061 to 1.952) ($p_{\text{trend}}=0.0235$).

Conclusion Elevated SUA concentration is significantly associated with PEAS in an asymptomatic middle-aged Chinese population, and vertebral arteries appeared to be the most vulnerable vessels.

INTRODUCTION

Arterial stenosis (AS) is considered to be associated with increased cardiovascular disease (CVD) events and mortality, likely due to a combination of traditional and non-traditional cardiovascular risk factors.^{1 2} Hyperuricaemia is one of the non-traditional cardiovascular risk factors. AS is commonly regarded as an intermediate stage in the pathogenesis of stroke.^{3 4} Early detection of asymptomatic AS could contribute to

Strengths and limitations of this study

- To our knowledge, this is the first community-based study that explores the relationship between serum uric acid (SUA) levels and proximal extracranial artery stenosis (PEAS) in a middle-aged Chinese population.
- The study obtained adequate and representative sample size.
- To our knowledge, this is the first study to evaluate the risk of PEAS using bilateral duplex ultrasound in an asymptomatic middle-aged Chinese population.
- The cause-and-effect association between SUA and PEAS could not be addressed due to the limitation of the cross-sectional design.
- This study did not control the potential confounding effect of dyslipidaemia and may influence the predictive power of SUA as a predictor of PEAS.

improved global risk stratification and identify emerging high-risk populations.⁵ An updated diagnostic clinical evaluation needs to be sensitive enough to detect subclinical AS affecting the systemic vasculature, including arterial stiffness, carotid atherosclerosis, vertebral artery stenosis (VAS).^{6–8} These updated diagnostic clinical evaluation for asymptomatic AS also improved the reliability of scientific research, aid in monitoring treatment and prevent CVDs associated complications.^{3 9}

The serum uric acid (SUA), as the end product of purine metabolism, has been associated with metabolic syndrome¹⁰ and several CVDs such as hypertension (HTN),¹¹ coronary artery disease,¹² myocardial infarction¹³ and stroke,¹⁴ even after adjustment for other traditional risk factors for CVD. Also, a close linkage between SUA and cardiac dysfunction in patients with ischaemic heart disease

was reported previously.¹⁵ Despite these findings in the previous studies, other epidemiological reports have failed to confirm a causal relationship between high SUA level and cardiovascular events.^{16–18} Thus, many in the field have been disinclined to recognise the pathogenetic role of SUA on the progress of HTN, stroke and atherosclerosis.^{19–22} Notwithstanding, the association between AS and SUA has been consistently under surveillance for over decades.^{23–25} However, the precise relationship between proximal extracranial artery stenosis (PEAS) and SUA has not been fully examined. Regardless of the lack of consensus, SUA may have a pivotal role in the development of PEAS according to several mechanisms. Plausible mechanisms include stimulation of inflammatory responses,^{26 27} increased platelet activity,^{12 28} endothelial dysfunction²⁹ and vascular smooth muscle cell proliferation.³⁰ Therefore, this study evaluates whether an SUA elevation can impact PEAS among the Chinese population.

METHODS

Study design and population

A vascular ultrasound (US)-based study of asymptomatic PEAS was conducted between July 2013 and August 2014 with the aim to explore the association between SUA and asymptomatic PEAS in a middle-aged Chinese population. The study was a single-centre, cross-sectional study and comprised Jidong Oilfield, petrochemical employees aged between 40 and 60 years. This study is part of an ongoing prospective study, a Population-based Cohort Study in Outcome of Phased Progression of

Atherosclerosis (PERSUADE) in China. A total of 5635 participants were recruited in Jidong Community Hospital, Tangshan, Hebei, China. Participants who were refused physical examinations (n=965), had coronary disease, stroke and transient ischaemic attack at baseline (n=181), had missing data of SUA (n=51) and vascular US (n=1113) were excluded from the study. Finally, a total of 3325 eligible individuals were included in the analyses (figure 1).

The study was conducted according to the Guidelines of the Declaration of Helsinki. All protocols described here were performed in accordance with the approved guidelines.

Demographic and clinical measurements

A self-administered questionnaire was distributed during US examination to collect data on health-related lifestyle, medical history, alcohol use and risk factors for AS. A fasting blood sample was obtained from the brachial vein. SUA levels were measured using the Uricase-Peroxidase method with an autoanalyser (BECKMAN COULTER AU680 Chemistry Analyzer, USA). All the biochemical measurements, including fasting glucose level, serum concentrations of total cholesterol (TC), triglycerides, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol, were performed at the central laboratory of the Jidong Hospital) using the standard protocols. Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dL or ongoing treatment with insulin, or oral hypoglycaemic medications⁵; whereas arterial HTN was defined as systolic blood pressure (SBP) ≥ 140 mm Hg and diastolic blood pressure (DBP) ≥ 90 mm

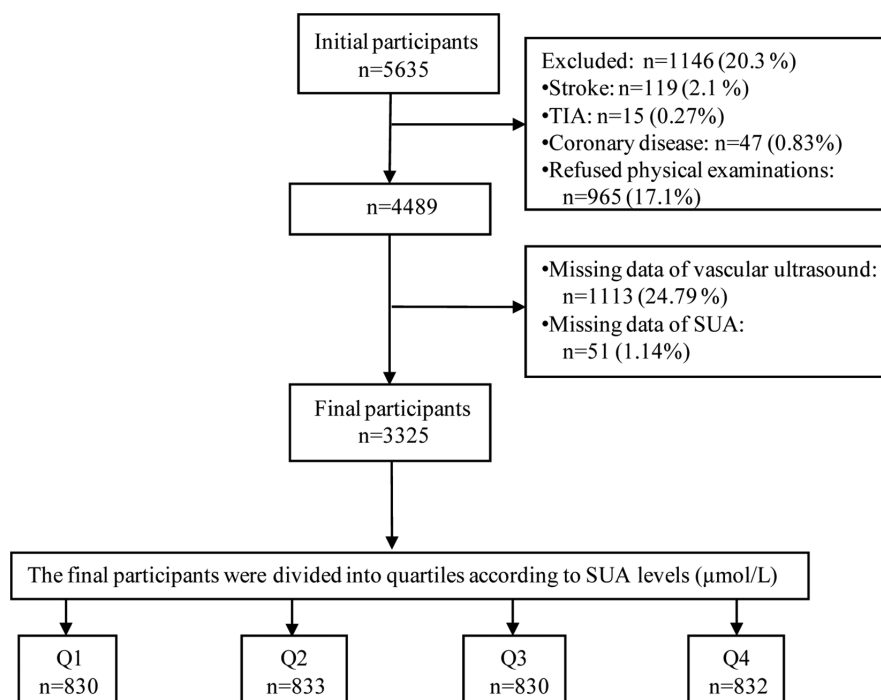


Figure 1 Participant flow chart. The quartiles of SUA concentration were calculated by gender, respectively. In male, the cut-off of SUA levels was ≤ 282.5 , 282.7–332.9, 333–387.6 and ≥ 387.9 $\mu\text{mol/L}$; in female, the cut-off of SUA levels was ≤ 210.9 , 211–248.2, 248.3–292.8 and ≥ 292.9 $\mu\text{mol/L}$. SUA, serum uric acid; TIA, transient ischaemic attack.

Hg, and/or use of antihypertensive medications.⁵ BP was measured in an upright sitting position after waiting 5 min. Dyslipidaemia was defined as TC \geq 240 mg/dL or LDL cholesterol \geq 160 mg/dL or HDL cholesterol $<$ 40 mg/dL, and/or use of lipid-lowering medications.³¹ Participants were considered current smokers if they reported smoking at least 100 cigarettes during their life and were currently smoking.^{32 33} Body mass index (BMI) was calculated as the weight (kg) divided by height squared (m^2). Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation.³⁴

US protocol

Bilateral duplex US (Philips iU-22 Ultrasound System, Philips Medical Systems, Bothell, Washington, USA) determined PEAS. The presence of PEAS was examined from the common carotid artery (CCA), innominate and subclavian arteries (I/SA) and proximal vertebral artery (VA). The diameter measurements was obtained based on the North American Symptomatic Carotid Endarterectomy Trial method, a widely used criteria to evaluate AS.^{35–37} We used a previously validated CT angiography-derived duplex US velocity criteria to grade the 50% CCA and VA stenosis. The CCA stenosis was defined as a focal increase of Doppler peak systolic velocity (PSV) $>$ 182 cm/s.³⁸ The angle-corrected ultrasonographic PSV were obtained at the VAo (vertebral artery origin), V1 (VAo–C6 transverse foramen) and V2 (C6–C1 transverse foramen) segments with a 2.0–3.5 MHz probe and an 8–12 MHz probe, separately. Criteria used for grading \geq 50% vertebral stenosis were focal increase blood flow velocity with a PSV cut-off point of 114 cm/s at the VAo,⁷ 140 cm/s at the V1 and 125 cm/s at the V2 segment of the VA.³⁹ Two experienced radiologists who were blinded to the clinical data reviewed the US results. If there was any disagreement between the two radiologists, images were reviewed and adjudicated by a senior radiologist to reach a consensus.

Patient and public involvement

We neither involved the study participants in the design nor in the recruitment to and conduct of the study. The present study included Jidong Community Hospital in the identification of the participants. The Jidong Oilfield contributed with information about the recruitment criteria and the examination schedule to the study participants. Individual physical examination results were reported to the study participants following their participation in this study. Also, the overall results of this study will be disseminated by the Jidong Oilfield to their employees.

Statistical analysis

Data management and statistical analyses were performed using the Ruichi Precision Medical Record System (RPMRS, Beijing, China) and SAS software V.9.3 (SAS Institute). The study population was stratified into

quartiles based on gender-specific SUA levels. The respective cut-off of SUA levels for Q1, Q2, Q3 and Q4 were \leq 282.5, 282.7–332.9, 333–387.6 and \geq 387.9 $\mu\text{mol/L}$ in men, and \leq 210.9, 211–248.2, 248.3–292.8 and \geq 292.9 $\mu\text{mol/L}$ in women. Test variables were summarised using mean \pm SD for continuous variables, and percentiles for categorical variables. Analysis of variance was employed to compare three or more groups. The χ^2 test was used to compare categorical variables. Trends were evaluated with linear or logistic regression using the median value of SUA for each quartile as an ordinal variable adjusted for age and sex. A logistic regression model was used to estimate the risk association of SUA levels in artery stenosis, SUA levels were entered in the models as quartiles (with the first sex-specific quartile as the baseline reference) to determine the OR and 95% CI. The logistic regression analyses were performed with different adjustments in three models. Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, eGFR, smoking, alcohol use and diuretic use. Model 3 adjusted for age, sex, eGFR, smoking, alcohol use, diuretic use, statins use, BMI, HTN and dyslipidaemia. All statistical tests were two sided, and a p value of less than 0.05 was considered significant.

RESULTS

Baseline characteristics

This community-based population study included 3325 participants (1597 male and 1728 female). Baseline characteristics of participants by SUA quartile are presented in [table 1](#). The values of the mean age, SBP, DBP, BMI, triglyceride, HDL, LDL, creatinine and eGFR were significantly lower in Q1 than in Q2–Q4. The proportion of participants, who were in diuretic use and diagnosed with HTN or dyslipidaemia were higher in the highest quartile (Q4) compared with Q1–Q3. Also, there were a higher proportion of alcohol drinkers in Q4 than in Q1–Q3.

The prevalence of PEAS

[Table 2](#) shows the overall prevalence of PEAS. In this study, the prevalence of PEAS was 24.2%. This study showed that an increase in SUA level significantly increases the prevalence of PEAS ($p < 0.0001$). The prevalence of PEAS increased from Q1 to Q4 from 12.3% to 29.8% in VA and from 2.8% to 5.8% in CCA, respectively. The proportion of PEAS relative to the detected number of AS was lower in Q1 than in Q2–Q4 ([figure 2](#)).

SUA increases the risk of PEAS

We used the logistic regression model to analyse the risk of prevalent PEAS. The OR for PEAS was analysed in each SUA quartile, with the first quartile serving as the reference group. The association between SUA levels and the prevalence of PEAS is presented in [table 3](#). Participants in the highest SUA quartile had a significantly increased risk of PEAS. This association persisted even after adjusting for potential confounding factors, including age, sex, eGFR, smoking, alcohol use and diuretic use. Compared

Table 1 Baseline characteristics of participants by SUA quartiles

	Total	SUA				P for trend
		Q1	Q2	Q3	Q4	
SUA, $\mu\text{mol/L}$	293.7 \pm 83.3	206.9 \pm 44.0	267.6 \pm 40.9	312 \pm 46.8	387.5 \pm 67.7	<0.0001
Number of subjects	3325	830	833	830	832	
Male, N (%)	1597 (48.0)	399 (48.07)	399 (47.90)	399 (48.07)	400 (48.08)	0.9807
Age, years	53.3 \pm 8.5	52.59 \pm 8.73	53.18 \pm 8.50	53.26 \pm 8.40	54.01 \pm 8.40	0.0086
Smoking, N (%)	783 (23.5)	204 (24.58)	195 (23.41)	198 (23.86)	186 (22.36)	0.3445
Moderate-to-heavy alcohol use, N (%)	989 (29.7)	228 (27.47)	237 (28.45)	260 (31.33)	264 (31.73)	0.0273
SBP, mm Hg	131.3 \pm 19.8	127.08 \pm 19.71	129.69 \pm 18.75	132.33 \pm 19.39	136.28 \pm 20.18	<0.0001
DBP, mm Hg	83.7 \pm 13.3	80.85 \pm 13.15	82.35 \pm 12.68	84.74 \pm 12.91	86.85 \pm 13.48	<0.0001
Hypertension, N (%)	1461 (43.9)	276 (33.25)	319 (38.30)	401 (48.31)	465 (55.89)	<0.0001
Diabetes, N (%)	377 (11.3)	107 (12.89)	82 (9.84)	91 (10.96)	97 (11.66)	0.6016
Dyslipidaemia, N (%)	2252 (67.7)	494 (59.52)	517 (62.06)	586 (70.60)	655 (78.73)	<0.0001
Diuretics use, N (%)	32 (1.0)	4 (0.48)	8 (0.96)	5 (0.60)	15 (1.80)	0.0173
Statins use, N (%)	71 (2.1)	13 (1.57)	16 (1.92)	20 (2.41)	22 (2.64)	0.0969
BMI, kg/m^2	24.9 \pm 3.3	23.95 \pm 3.09	24.39 \pm 2.99	25.27 \pm 3.37	26.13 \pm 3.20	<0.0001
TG, mmol/L	1.7 \pm 1.4	1.33 \pm 0.87	1.55 \pm 1.28	1.78 \pm 1.35	2.19 \pm 1.84	<0.0001
HDL-c, mmol/L	1.2 \pm 0.3	1.25 \pm 0.28	1.22 \pm 0.28	1.21 \pm 0.28	1.17 \pm 0.25	<0.0001
LDL-c, mmol/L	2.6 \pm 0.6	2.53 \pm 0.57	2.57 \pm 0.59	2.68 \pm 0.63	2.77 \pm 0.59	<0.0001
Creatinine, $\mu\text{mol/L}$	77.1 \pm 19.5	74.56 \pm 12.64	75.41 \pm 12.53	77.00 \pm 24.55	81.36 \pm 24.04	<0.0001
eGFR (mL/min/1.73 m^2)	89.4 \pm 14.2	92.53 \pm 13.35	90.95 \pm 13.45	89.87 \pm 14.09	84.42 \pm 14.57	<0.0001

Data were presented as mean \pm SD for continuous variable and number (percentage) for category variables.

P for trend tested with linear regression for continuous variables or logistic regression using the median uric acid value for each quartile.

The quartiles of SUA concentration were calculated by gender respectively. In male, the cut-off of SUA levels was ≤ 282.5 , 282.7–332.9, 333–387.6 and ≥ 387.9 $\mu\text{mol/L}$; in female, the cut-off of SUA levels was ≤ 210.9 , 211–248.2, 248.3–292.8 and ≥ 292.9 $\mu\text{mol/L}$.

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SUA, serum uric acid; TG, triglyceride.

with participants in the first quartile, the OR (95% CI) for the subjects in Q2, Q3 and Q4 were 1.369 (1.058 to 1.772), 1.393 (1.070 to 1.813) and 1.878 (1.430 to 2.465),

respectively (p for trend <0.0001). The same relationship between the SUA and PEAS remained, even after adjusting for statin use, BMI, HTN and dyslipidaemia.

Table 2 Distribution of proximal extracranial artery stenosis according to quartiles of SUA levels

	Total	SUA				P for trend
		Q1	Q2	Q3	Q4	
SUA, $\mu\text{mol/L}$	293.7 \pm 83.3	206.9 \pm 44.0	267.6 \pm 40.9	312 \pm 46.8	387.5 \pm 67.7	<0.0001
Number of arterial stenosis						
0, N (%)	2522 (75.8)	706 (85.1)	648 (77.8)	616 (74.2)	552 (66.3)	<0.0001
1, N (%)	748 (22.5)	118 (14.2)	169 (20.3)	204 (24.6)	257 (30.9)	
≥ 2 , N (%)	55 (1.6)	6 (0.7)	15 (1.8)	12 (1.4)	22 (2.6)	
Distribution of arterial stenosis						
CCA, N (%)	153 (4.6)	23 (2.8)	37 (4.4)	45 (5.4)	48 (5.8)	0.0167
VA, N (%)	676 (20.3)	102 (12.3)	152 (18.2)	174 (21.0)	248 (29.8)	<0.0001
I/SA, N (%)	30 (0.9)	5 (0.6)	11 (1.3)	9 (1.1)	5 (0.6)	0.3062

Data were presented as mean \pm SD for continuous variable and number (percentage) for category variables.

P for trend tested with logistic regression using the median uric acid value for each quartile.

The quartiles of SUA concentration were calculated by gender respectively. In male, the cut-off of SUA levels was ≤ 282.5 , 282.7–332.9, 333–387.6 and ≥ 387.9 $\mu\text{mol/L}$; in female, the cut-off of SUA levels was ≤ 210.9 , 211–248.2, 248.3–292.8 and ≥ 292.9 $\mu\text{mol/L}$.

CCA, common carotid artery; I/SA, innominate and subclavian arteries; SUA, serum uric acid; VA, proximal vertebral artery.

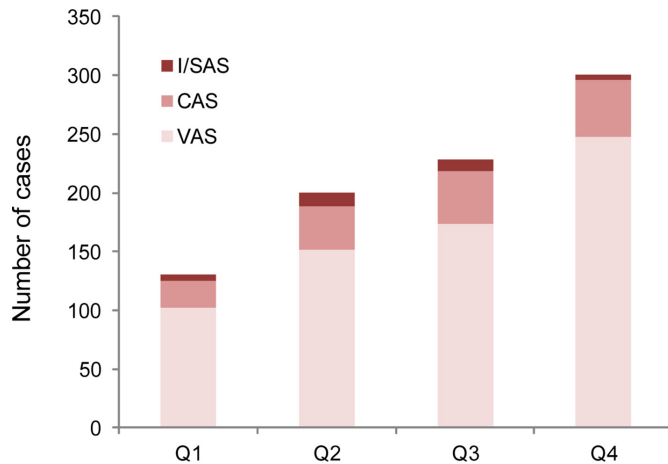


Figure 2 Prevalence of proximal extracranial artery stenosis increased gradually across all SUA quartiles. CAS, carotid artery stenosis; I/SAS, innominate and subclavian artery stenosis; VAS, vertebral artery stenosis.

The OR in model 3 was slightly decreased compared with model 2. We also observed a similar dose–response association between SUA levels and the prevalence of VAS after adjusting for potential confounders.

Sensitivity analysis

When we ran models using age, sex, eGFR, smoking, alcohol use and diuretics use (model 2 in table 3), we found almost identical associations of SUA levels and incident PEAS risk. When we further adjusted for age, sex, eGFR, smoking, alcohol use, diuretics use, statins use, BMI, HTN and dyslipidaemia, the significant relationship between incremental SUA and PEAS remained constant but the relevance attenuated (model 3 in table 3).

DISCUSSION

Several previous studies suggested that SUA was associated with AS,^{8 12 40} but no study investigated the association between SUA and PEAS. The findings of this community-based study consolidated the association between the SUA and the risk of PEAS. Those participants with a high SUA concentration had a greater likelihood of having PEAS. The logistic regression analysis shows that those subjects with SUA concentrations in the fourth quartile were significantly associated with a higher risk of PEAS after adjusting for the confounders.

In the past, VAS has been considered as an uncommon condition with a benign prognosis³⁷; however, VA was the most frequently affected artery in our study (20.3%). In a study that includes autopsies of 339 patients who suffered from fatal strokes, proximal extracranial atherosclerosis occurred more frequently in the proximal VA (12.7%) compared with the CCA (5.3%).⁹ According to the Oxford Vascular Study, stenosis of the proximal VA was more prevalent than CCA (26.2% vs 11.5%).¹⁴ Moreover, a retrospective study about the prevalence of VAO stenosis and occlusion in outpatient cases (includes 2490 extracranial duplexes) reported that the prevalence of

lesions located in the origin of VA was 8%, which they stated as higher than the expected prevalence of VAS.²⁹ In our study, the high prevalence of VAS in relation to SUA can be explained based on the following two reasons. First, is that the AS definition considered a wide range of stenosis proportion. The previous studies defined stenosis as $\geq 75\%$, while the current study defined stenosis as $\geq 50\%$. Second, VAS may be affected by the clinical characteristics of the participants (oilfield population who had a large proportion of HTN (43.9%) and dyslipidaemia (61.4%)). The differences between extracranial artery stenosis locations could be related to differences in vascular risk factors and vascular sensitivity.⁴¹ Previous studies indicated that SUA levels and parameters of inflammation were higher in patients with slow coronary flow than controls.⁴² Moreover, VA is much smaller (diameter: 3–4 mm)⁴³ and more twisted⁴⁴ than CA (diameter: 6–8 mm)⁴⁵ and I/SA (diameter: 6–10 mm).⁴⁶ This predominance of VA stenosis may be related to specific patterns of shear stress and disturbed flow caused by the vessel diameter and curvature.⁴⁷

SUA is implicated for the development of several diseases, such as chronic kidney disease,⁴⁸ diabetes mellitus⁴⁹ and stroke.¹⁴ In our study, the multivariable risk ratios of PEAS in the second through fourth quartiles compared with the lowest quartiles of SUA were continuously increased in model 2. This association marginally decreased, but remained statistically significant in the highest quartile of SUA when BMI, HTN and hyperlipidaemia were brought into multiple regression models. Inter-relationships between these variables can have a substantial impact on regression model results, hence, it is difficult to separate out the independent contribution of SUA for the risk of PEAS. Considering that SUA is closely associated with many aspects of metabolic syndrome including hyperlipidaemia, obesity and insulin resistance,⁴⁹ a nested case–control study is required to confirm the independent association of elevated SUA with the risk of PEAS. According to the Asymptomatic Polyvascular Abnormalities Community longitudinal study⁴⁰ and the Brisighella Heart Study population survey,⁸ high SUA levels were strongly associated with the risk of atherosclerosis. These studies confirmed that SUA elevation predicts the subsequent occurrence of atherosclerosis in a positive and dose-dependent manner, even after adjustment for the confounding variables. In the present study, 67.7% of the population had dyslipidaemia, but only 2.1% were on statin use. Also, the participants in the higher quartiles of SUA tended to be more obese, had lower eGFR and higher prevalence of HTN. Those findings can be major confounding factors of the results in the multivariate model. Nonetheless, the present study confirmed that participants in the highest quartile of SUA level had increased risk of PEAS, even after adjustment for the traditional risk factors for CVD, including BMI, HTN and dyslipidaemia. These findings suggest that reducing the SUA concentration may be beneficial for the treatment and prevention of PEAS.

Table 3 Risk of PEAS according to baseline serum uric acid quartiles in adjusted models

Serum uric acid						
	Q1	Q2	Q3	Q4	Continuous Scale	P for trend
Arterial stenosis, N (%)						
Model 1	1.000 (ref.)	1.368 (1.058–1.771)*	1.384 (1.064–1.799)*	1.841 (1.409–2.405)*	1.002 (1.001–1.004)	<0.0001
Model 2	1.000 (ref.)	1.369 (1.058–1.772)*	1.393 (1.070–1.813)*	1.878 (1.430–2.465)*	1.003 (1.001–1.004)	<0.0001
Model 3	1.000 (ref.)	1.278 (0.980–1.665)	1.117 (0.851–1.468)	1.375 (1.033–1.830)*	1.001 (1.000–1.002)	0.0399
CCA stenosis, N (%)						
Model 1	1.000 (ref.)	1.275 (0.740–2.196)	1.216 (0.708–2.088)	1.311 (0.753–2.281)	1.001 (0.998–1.003)	0.5789
Model 2	1.000 (ref.)	1.277 (0.740–2.203)	1.240 (0.720–2.135)	1.401 (0.799–2.456)	1.001 (0.999–1.003)	0.3604
Model 3	1.000 (ref.)	1.209 (0.698–2.094)	1.140 (0.656–1.979)	1.282 (0.721–2.281)	1.001 (0.998–1.003)	0.6138
VA stenosis, N (%)						
Model 1	1.000 (ref.)	1.391 (1.055–1.835)*	1.391 (1.048–1.846)*	2.027 (1.525–2.695)*	1.003 (1.002–1.004)	<0.0001
Model 2	1.000 (ref.)	1.394 (1.057–1.839)*	1.402 (1.055–1.862)*	2.071 (1.550–2.766)*	1.003 (1.002–1.004)	<0.0001
Model 3	1.000 (ref.)	1.285 (0.966–1.709)	1.085 (0.808–1.457)	1.439 (1.061–1.952)*	1.001 (1.000–1.003)	0.0235
I/SA stenosis, N (%)						
Model 1	1.000 (ref.)	1.958 (0.668–5.736)	1.402 (0.444–4.428)	0.783 (0.207–2.967)	0.999 (0.994–1.004)	0.5839
Model 2	1.000 (ref.)	1.908 (0.650–5.600)	1.350 (0.426–4.274)	0.728 (0.188–2.814)	0.998 (0.993–1.003)	0.5182
Model 3	1.000 (ref.)	2.058 (0.696–6.082)	1.608 (0.495–5.225)	0.946 (0.233–3.837)	0.999 (0.994–1.005)	0.8478

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, eGFR, smoking, alcohol use and diuretics use.

Model 3: adjusted for age, sex, eGFR, smoking, alcohol use, diuretics use, statins use, BMI, hypertension and dyslipidaemia.

The quartiles of serum uric acid concentration were calculated by gender, respectively. In male, the cut-off of serum uric acid levels was ≤ 282.5 , 282.7–332.9, 333–387.6 and ≥ 387.9 $\mu\text{mol/L}$; in female, the cut-off of serum uric acid levels was ≤ 210.9 , 211–248.2, 248.3–292.8 and ≥ 292.9 $\mu\text{mol/L}$.

* $P < 0.05$.

BMI, body mass index; CCA, common carotid artery; eGFR, estimated glomerular filtration rate; I/SA: innominate and subclavian arteries; PEAS, proximal extracranial artery stenosis; VA, proximal vertebral artery.

Hyperuricaemia, defined as SUA levels greater than 360 $\mu\text{mol/L}$ in women and 420 $\mu\text{mol/L}$ in men,⁵⁰ has also been proposed as an independent risk factor for atherosclerosis.^{14 51 52} According to our study, SUA values greater than 292.9 $\mu\text{mol/L}$ in women and 387.9 $\mu\text{mol/L}$ in men have been closely associated with the incidence of PEAS. Earlier studies have established that increased SUA levels^{13 53 54} and PEAS are essential risk factors for stroke.^{55–57} Therefore, the present study suggests that the likelihood of PEAS risk may still exist below the standard definition of hyperuricaemia. Thus, an increase of SUA in the asymptomatic individuals may require a thorough risk assessment for PEAS. Community health strategies aimed at PEAS prevention among asymptomatic individuals, whose SUA levels increased greater than the aforementioned cut-off point (292.9 $\mu\text{mol/L}$ in women and 387.9 $\mu\text{mol/L}$ in men), should be accompanied by US evaluations to improve the treatment outcomes and avoid serious complications of PEAS.

The present study linked elevated SUA and asymptomatic PEAS. This relationship provides novel insights into the pathophysiology of overall AS. Future studies are warranted to examine whether modulating SUA could delay and even prevent PEAS.

To our knowledge, this is the first community-based study that explores the relationship between SUA levels and PEAS in a middle-aged Chinese population. This study has several limitations. First, the cause-and-effect association between SUA and PEAS could not be addressed due to the limitations of cross-sectional design. Second, the present study does not provide data on the underlying cause of the stenosis, which makes it difficult to categorise the origin of AS. Third, the study participants were individuals from an oil field in Northern China, so the results of this study may not be generalised to other populations. Fourth, this study did not control for the potential confounding effect of dyslipidaemia, which may influence the predictive power of SUA as a predictor of PEAS. Therefore, we recommend an additional longitudinal study to provide epidemiological evidence for the association between elevated SUA and incident PEAS among the middle-aged population in China.

CONCLUSION

Elevated SUA concentration is significantly associated with PEAS in an asymptomatic middle-aged Chinese population, and vertebral arteries appeared to be the most vulnerable vessels. Therefore, SUA may help for risk stratification for PEAS prevention among the Chinese population.

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Funding This study was supported by grants from the National Natural Science Foundation of China (No. 81570391), Capital Special Clinical Application Grants (Z141107002514103) and the Recovery Medical Science Foundation.

Competing interests None declared.

Patient consent Obtained.

Ethics approval Ethical approval for the research protocol was approved by the Ethics Committee of Jidong Community Hospital and PERSUADE study prior to study initiation.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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