Clinical Rheumatology (2019) 38:2373–2381
https://doi.org/10.1007/s10067-019-04541-1

ORIGINAL ARTICLE

Neck circumference is associated with hyperuricemia: a cross-sectional study

Xiuhua Shen[1,2] · Shouling Wu[3] · Renying Xu[4,5] · Yuntao Wu[3] · Junjuan Li[6] · Liufu Cui[7] · Rong Shu[7] · Xiang Gao[8]

Received: 31 December 2018 / Revised: 27 February 2019 / Accepted: 1 April 2019 / Published online: 24 April 2019
© International League of Associations for Rheumatology (ILAR) 2019

Abstract

Background/objective Neck circumference (NC) is associated with metabolic abnormalities, independent of other obesity indices. However, data are limited regarding the potential relation between NC and serum uric acid (UA) concentrations. Therefore, we evaluated the cross-sectional association between NC and UA concentration, and odds of having hyperuricemia in a community-based cohort.

Subjects and methods The current study included 87,782 participants (16,317 women and 71,465 men, 52.2 ± 14.1 y) of the Kailuan Study. NC and UA concentration were measured in 2014. We used generalized linear model to investigate the association between NC and serum UA concentration and logistic regression model to investigate the association between NC and likelihood of having hyperuricemia (≥ 7 mg/dl in men and ≥ 6 mg/dl in women), adjusting for demographic factor, anthropometric indices, plasma lipid profiles, blood glucose, blood pressure, physical exercise, snoring, smoking, diet quality, and alcohol consumption.

Results Higher NC was associated with higher serum UA concentration, and higher odds of hyperuricemia in both men and women after adjusting for potential confounders (both $p < 0.001$). Each additional 5-cm increase in NC was associated with 6% higher likelihood of having hyperuricemia (adjusted OR = 1.06; 95% CI 1.02, 1.1) in men and 17% in women (adjusted OR = 1.17; 95% CI 1.06, 1.28) (p interaction = 0.01). Similar pattern was observed after excluding participants who reported use of anti-hypertensive drugs, participants with obesity or higher waist circumference, and participants with history of gout and chronic kidney diseases.

Conclusions Higher NC was associated with higher serum UA concentration and higher risk of hyperuricemia in Chinese adult population.

Clinical trial number Kailuan Study (ChiCTR-TNRC-11001489)

Keywords Hyperuricemia · Neck circumference · Serum uric acid

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10067-019-04541-1) contains supplementary material, which is available to authorized users.

✉ Shouling Wu
drwusl@163.com

✉ Xiang Gao
xxg14@psu.edu

1 Department of Clinical Nutrition, Shanghai Xin Hua Hospital, Shanghai, China

2 Department of Nutrition, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

3 Department of Cardiology, Kailuan General Hospital, No. 57 Xinhua Road (East), Tangshan 063000, China

4 Department of Clinical Nutrition, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

5 Shanghai Key Laboratory of Pediatric Gastroenterology and Nutrition, Shanghai, China

6 Department of Nephrology, Kailuan General Hospital, Tangshan, China

7 Department of Rheumatology, Kailuan General Hospital, Tangshan, China

8 Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA 16802, USA

Introduction

A national-wide study reported that the prevalence of hyperuricemia was 13.7% in urban and 12.3% in rural areas in China [1]. Although most of hyperuricemia is asymptomatic, it is associated with multiple health outcomes, such as gout, kidney stone, and chronic kidney diseases [2]. It is thus important to understand potential risk factors for hyperuricemia, which could help to subsequently lower the risk of these hyperuricemia-related chronic diseases.

Neck circumference (NC) is a simple, convenient anthropometric parameter, which was associated with risk of insulin resistance, type 2 diabetes [3], obstructive sleep apnea [4], non-fatal cardiovascular events [5], and metabolic syndrome [6], independent of conventional obesity indices such as body mass index (BMI) and waist circumference. The association between NC and metabolic components could be explained by the increase of upper body adiposity tissues and its related oxidative stress and insulin resistance [7]. The increase of airway pressure and hypoxia caused by fat deposition in the neck exacerbated oxidative status and insulin resistance [8]. NC is accepted by US army to evaluate soldiers' health; however, it is rarely measured in both clinical practice and epidemiology studies. Further, data are limited regarding the association between NC and hyperuricemia, which strongly relates to metabolic disorder. Recently, two cross-sectional studies reported that individuals with greater NC were more likely to have hyperuricemia [9, 10]. However, these studies were limited by failure to adjust for important confounders such as body mass index (BMI) and waist circumference [10], or small sample size ($n = 177$) [9].

Therefore, we aimed to evaluate the association between NC and serum UA concentration, and the likelihood of having hyperuricemia in a cross-sectional study including approximately 82,000 Chinese adults. Potential confounders such as demographic factors, BMI, waist circumference, dietary intake, alcohol consumption, blood pressure, physical exercise, snoring, smoking, kidney function, lipid profiles, chronic inflammation status, presence of major chronic diseases, and use of anti-hypertensive drugs were adjusted.

Materials and methods

Study population

The Kailuan Study I and II were two ongoing prospective cohort studies of cardiovascular, cerebrovascular, and related disease risk factors based on the Kailuan community population living in Tangshan city [11]. There are 11 hospitals responsible for the health care of the Kailuan community. Standard protocols for all the measurements were designed in advance. All the evaluators were physicians and nurses who worked in these hospitals and they were trained for 3 days before they participated in the measurement. Both studies were followed with the same questionnaires and clinical and laboratory examinations. All the participants signed informed consent (including publishing the research materials).

In the current study, we included 87,782 participants (16,317 women and 71,465 men, mean age 52.2 ± 14.1 y who actively participated in the 2014 survey and had completed the data on NC and UA concentration which were collected in 2014. The flow chart is presented in Fig. 1. The study was approved by the Ethics Committee of the Kailuan General Hospital (No. ChiCTR-TNRC-11001489).

NC measurement

In the 2014 survey, NC was measured at the upper margin of the laryngeal prominence and recorded to the nearest 0.1 cm, using an inelastic tape with the subject standing upright, the face directed forward, and shoulders relaxed [12]. NC was measured twice and the average was used for the current study. The value of skewness and kurtosis for neck circumference was − 1.207 and 6.573, respectively.

Serum UA concentration assessment

Blood samples were collected from the antecubital vein in the morning after an overnight fast (≥ 8 h). Serum UA concentrations were measured using an oxidase method by the Hitachi 7600 automatic biochemical analyzer at the central laboratory in the Kailuan General Hospital, as described previously [3, 13]. The coefficient of variations of serum UA assessment was ≤ 6.0% for both within and between groups. Hyperuricemia was defined as ≥ 7 mg/dl (416 μmol/L) in men and ≥ 6 mg/dl (357 μmol/L) in women [14].

Assessment of potential confounders

Height and body weight were measured during the interview and BMI was calculated as weight in kilograms divided by squared height in meters. Waist circumference was measured at the horizontal position of the ribs and the anterior superior iliac spine edge of the midpoint with the smallest circumference at the end of respiration at the standing position. Blood pressure was measured twice or more after participants were seated quietly for at least 5 min. The average of two determinations was used for further analysis. Hypertension was defined as systolic blood pressure of ≥ 140 mmHg, or diastolic blood pressure of ≥ 90 mmHg, or a history of physician-diagnosed hypertension, or use of anti-hypertensive drugs [15]. Biochemical parameters, including fasting blood glucose, triglyceride, high-sensitivity C-reactive protein, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol, were measured using an auto-analyzer (Hitachi

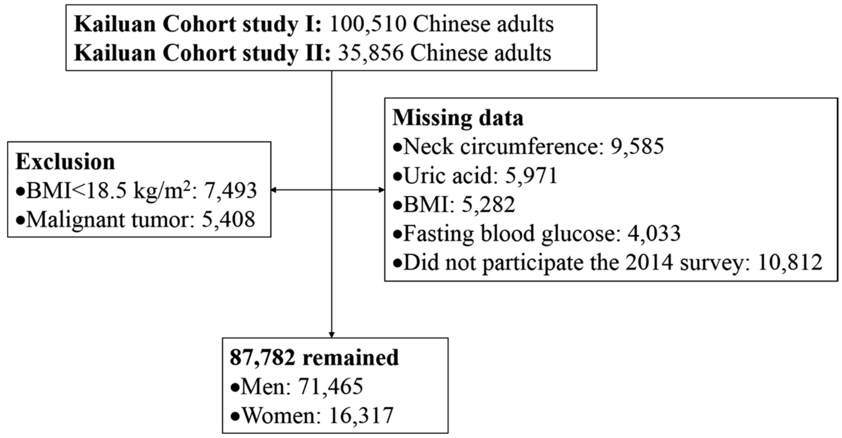

Fig. 1 Sample recruitment

747; Hitachi, Tokyo, Japan), as described elsewhere [16–18]. Diabetes was diagnosed as fasting blood glucose of ≥ 126 mg/dl, history of physician-diagnosed diabetes or taking glucose-lowering medication, impaired fasting glucose as fasting blood glucose of 100–125 mg/dl, and normal as fasting blood glucose of < 100 mg/dl [19]. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration 2-level race equation [20].

Data on demographic variables (e.g., age, sex, and education level), smoking, snoring, and physical exercise were collected via questionnaires, as described previously [21]. The history of myocardial infarction and stroke was confirmed via review of medical records [17, 22]. Self-report gout was collected via a questionnaire.

Dietary intake data were collected with a semi-quantitative validated food frequency questionnaire [23]. A diet quality score was calculated based on the consumption of fruits/vegetables, fish, sodium, sweets/sugar-sweetened beverages, and whole grains [24]. Alcohol consumption was calculated in grams per day by multiplying the average frequency (times per day) by the usual consumption amount of each beverage and its average ethanol content, as described previously [16].

Statistical analyses

We preformed all statistical analyses by using SAS version 9.4 (SAS Institute, Inc., Cary, NC). Formal hypothesis testing was two-sided with a significant level of 0.05. Because there were dramatic differences in NC and uric acid (UA) concentration between men and women [12, 25] and significant interaction between sex and NC, in relation to uric acid concentration (p interaction = 0.01), sex-specific results were present in this report.

We used generalized linear model to investigate the association between NC and serum UA concentration and logistic regression model to investigate the association between NC and risk of hyperuricemia. Potential confounders were adjusted in the final model, which included age (y), education level (≤ middle school or ≥ high school), current smoking ("yes" or "no"), alcohol consumption (g/day), dietary quality score, BMI (kg/m^2), waist circumference (cm), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), high-sensitivity C-reactive protein (mg/dl), fasting blood glucose (mmol/L), total cholesterol (mmol/L), triglyceride (mmol/L), high-density lipoprotein cholesterol (mmol/L), low-density lipoprotein cholesterol (mmol/L), eGFR (ml/min/1.73m^2), regular physical exercise ("yes" or "no"), snoring (never, < 1 time/week, 1–5 times/week, ≥ 6 times/week, or unknown), and history of myocardial infarction and stroke ("yes" or "no" for each).

To test the robustness of the results obtained from the main analysis, we conducted several sensitivity analyses by excluding participants who reported use of anti-hypertensive drugs because they could have effects on serum UA concentration [26], or participants with self-report snoring, obesity (BMI ≥ 28 kg/m^2), central obesity (waist circumference ≥ 85 cm in men and ≥ 80 cm in women), gout, or eGFR< 60 ml/min/1.73 m^2.

Results

Mean age was 52.0 ± 14.4 y and mean NC was 38.8 ± 3.5 cm in men, and 53.4 ± 12.6 y and 36.4 ± 3.6 cm, respectively, in women. Sex-specified basic characteristics, according to NC status, were shown in Table 1.

Higher NC was associated with higher serum UA concentration in both men and women after adjusting potential confounders including demographic factors, diet, physical exercise, snoring, smoking, alcohol consumption, BMI, waist circumference, blood pressure, and blood biochemical factors (Table 2). Each additional 5-cm increase in NC was associated with an increase of 1.5 ± 0.6 μmol/L in serum UA concentration in men and 3.7 ± 0.9 μmol/L in women (both $p < 0.001$, Table 2).

Table 1 Baseline characteristics of 87,782 Chinese adults, according to quartiles of neck circumference

Variables	Groups	Quartiles of neck circumference in men				p trend	Quartiles of neck circumference in women				p trend
		Q1 (< 37 cm)	Q2 (37–39 cm)	Q3 (39–41 cm)	Q4 (≥ 41 cm)		Q1 (< 35 cm)	Q2 (35–37 cm)	Q3 (37–38.2 cm)	Q4 (≥ 38.2 cm)	
Sample number	–	19,338	19,320	14,536	18,271	–	4859	2924	4979	3555	–
Age, y	–	51.9 ± 15.5	52.3 ± 14.4	52.9 ± 14.1	50.9 ± 13.4	< 0.01	52.6 ± 12.9	53.2 ± 13.0	53.0 ± 12.5	54.9 ± 11.8	< 0.01
BMI, kg/m^2	–	23.9 ± 2.8	24.8 ± 2.8	25.4 ± 3.1	26.2 ± 3.4	< 0.01	23.8 ± 3.1	24.3 ± 3.2	24.9 ± 3.3	26.3 ± 3.7	< 0.01
WC, cm	–	84.7 ± 7.7	88.0 ± 8.0	89.5 ± 8.4	91.2 ± 9.2	< 0.01	80.0 ± 7.7	82.2 ± 7.9	83.6 ± 9.0	86.1 ± 10.1	< 0.01
hsCRP, mg/dl	–	2.1 ± 4.1	2.2 ± 4.6	2.0 ± 5.6	2.0 ± 3.7	< 0.01	1.4 ± 4.8	1.9 ± 3.1	2.1 ± 4.2	2.1 ± 3.7	< 0.01
SBP, mmHg	–	135 ± 19.7	137 ± 19.4	138 ± 19.3	137 ± 18.3	< 0.01	128 ± 20.9	128 ± 20.7	130 ± 20.5	136 ± 21.2	< 0.01
DBP, mmHg	–	81.1 ± 10.8	82.9 ± 10.7	83.7 ± 10.5	84.3 ± 10.5	< 0.01	76.4 ± 10.2	77.2 ± 10.3	78.7 ± 10.6	80.4 ± 11.1	< 0.01
FBG, mmol/L	–	5.7 ± 1.7	5.9 ± 1.8	5.9 ± 1.8	5.9 ± 1.8	< 0.01	5.76 ± 1.6	5.7 ± 1.7	5.8 ± 1.8	6.0 ± 1.9	< 0.01
TG, mmol/L	–	1.6 ± 2.0	1.7 ± 1.9	1.9 ± 2.6	1.9 ± 1.9	< 0.01	1.5 ± 1.5	1.5 ± 1.7	1.6 ± 2.4	1.6 ± 1.2	< 0.01
TC, mmol/L	–	5.1 ± 1.5	5.2 ± 1.6	5.2 ± 1.5	5.2 ± 1.4	< 0.01	5.3 ± 1.5	5.3 ± 1.1	5.4 ± 1.1	5.5 ± 1.2	< 0.01
HDL-C, mmol/L	–	1.3 ± 0.7	1.3 ± 0.6	1.3 ± 0.7	1.2 ± 0.7	< 0.01	1.4 ± 0.5	1.3 ± 0.6	1.4 ± 0.7	1.3 ± 0.6	< 0.01
LDL-C, mmol/L	–	2.9 ± 1.2	2.9 ± 1.1	2.9 ± 1.2	2.9 ± 1.2	< 0.01	2.9 ± 0.9	2.8 ± 2.0	3.0 ± 1.7	3.1 ± 1.0	< 0.01
Dietary quality score	–	1.2 ± 0.9	1.2 ± 1.0	1.2 ± 0.9	1.3 ± 0.8	< 0.01	1.2 ± 0.9	1.0 ± 0.9	1.1 ± 0.9	1.2 ± 1.0	< 0.01
Serum uric acid, μmol/L	–	335.2 ± 93.9	345.1 ± 92.1	355.2 ± 92.4	357.5 ± 89.5	< 0.01	258.7 ± 71.5	271.1 ± 70.7	272.8 ± 69.4	283.8 ± 68.2	< 0.01
Hyperuricemia, %	–	17.1	19.6	22.8	23.4	< 0.01	7.9	10.3	11.0	14.0	< 0.01
EGFR, ml/min/1.73m^2	–	93.8 ± 24.7	94.9 ± 20.4	96.2 ± 20.6	97.8 ± 20.2	0.44	95.1 ± 21.1	96.3 ± 20.9	95.4 ± 20.4	96.1 ± 18.4	0.02
Smoking	No	49.6	47.4	47.6	45.4	< 0.01	98.2	98.5	97.8	97.6	0.05
	Yes	50.4	52.6	52.4	54.6		1.8	1.5	2.2	2.4	
Alcohol consumption, g/day*	–	5.8 ± 19.7	7.6 ± 23.9	5.5 ± 19.6	5.0 ± 17.3	< 0.01	0.6 ± 6.2	1.0 ± 9.6	0.7 ± 6.2	0.5 ± 5.1	0.04
Physical exercise	No	24.2	28.6	23.8	19.5	< 0.01	20.9	37.9	32.3	23.6	< 0.01
	Yes	75.8	71.4	76.2	80.5		79.1	62.1	67.7	76.4	
Snoring	Never	82.6	76.1	81.7	79.7	< 0.01	88.8	86.1	83.6	88.2	< 0.01
	< 1/week	2.7	3.1	3.3	3.7		3.2	2.2	2.7	2.2	
	1–5/week	2.9	5.0	3.7	3.7		2.1	3.1	2.7	1.9	
	≥ 6/week	7.2	9.6	7.6	9.0		3.3	5.3	5.6	5.7	
	Unknown	4.7	6.2	3.7	3.9		2.7	3.4	5.4	2.1	
Myocardial infarction	No	99.3	99.2	99.1	99.3	0.1	99.8	99.7	99.6	99.6	0.66
	Yes	0.7	0.8	0.9	0.7		0.2	0.3	0.4	0.4	
Stroke	No	99.1	99.0	99.2	99.3	< 0.01	99.5	99.3	99.2	98.8	0.01
	Yes	0.9	1.0	0.8	0.7		0.5	0.7	0.8	1.2	
Education level	≤middle school	80.7	76.8	80.2	79.9	< 0.01	71.8	74.5	74.2	80.6	< 0.01
	≥high school	19.3	23.2	19.8	20.1		28.2	25.5	25.8	19.4	

BMI body mass index, *WC* waist circumference, *hsCRP* high-sensitivity C-reactive protein, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FBG* fasting blood glucose, *TG* triglyceride, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *EGFR* estimated glomerular filtration rate. – means not applicable. * means abnormal distribution

Table 2 Adjusted means and standard deviation of serum uric acid across quartiles of neck circumference in 87,782 Chinese adult populations

Sex (p interaction = 0.02)		Quartiles of neck circumference				Each 5-cm increase	p trend
		Q1	Q2	Q3	Q4		
Men	Sample size	19,338	19,320	14,536	18,271	–	–
	Model 1	333 ± 0.7	344 ± 0.7	352 ± 0.8	352 ± 0.7	8.2 ± 0.4	< 0.001
	Model 2	356 ± 3.7	363 ± 3.7	367 ± 3.7	370 ± 3.7	5.0 ± 0.6	< 0.001
	Model 3	358 ± 3.6	363 ± 3.6	364 ± 3.7	363 ± 3.6	1.5 ± 0.6	0.009
Women	Sample size	4859	2924	4979	3555	–	–
	Model 1	262 ± 1.0	273 ± 1.3	276 ± 1.0	285 ± 1.2	8.5 ± 0.7	< 0.001
	Model 2	277 ± 8.0	281 ± 8.1	288 ± 8.0	295 ± 8.0	6.6 ± 0.9	< 0.001
	Model 3	277 ± 8.0	280 ± 8.0	285 ± 7.9	288 ± 7.9	3.7 ± 0.9	< 0.001

Adjusting age (y) in model 1. Adjusting age (y), high-sensitivity C-reactive protein (mg/dl), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), fasting blood glucose (mmol/L), total cholesterol (mmol/L), triglyceride (mmol/L), high-density lipoprotein cholesterol (mmol/L), low-density lipoprotein cholesterol (mmol/L), dietary quality score, EGFR (ml/min/1.73m^2), smoking ("yes" or "no"), alcohol consumption (g/day), physical exercise ("yes" or "no"), snoring (never, < 1 time/week, 1–5 times/week, ≥ 6 times/week, unknown), myocardial infarction ("yes" or "no"), stroke ("yes" or "no"), education (≤middle school or ≥ high school) in model 2. Adjusting variables in model 2 and BMI (kg/m^2) and waist circumference (cm) in model 3. – means not applicable

Higher NC was also associated with higher risk of hyperuricemia in fully adjusted model in both men and women (Table 3). Each additional 5-cm increase in NC was associated with 6% higher likelihood of having hyperuricemia (OR = 1.06; 95% CI 1.02, 1.1) in men and 17% in women (OR = 1.17; 95% CI 1.06, 1.28) (Table 3).

Sensitivity analyses showed similar pattern with the main analysis after excluding participants who reported use of anti-hypertensive drugs; participants with snoring, hypertension, diabetes, obesity, and higher waist circumference; and participants with history of gout or eGFR < 60 ml/min/1.73 m^2 (Supplementary Tables 1–2).

The association between NC and UA was more pronounced in younger participants and participants with higher alcohol consumption, relative to their counter parts (p interaction < 0.01 for both) (Tables 4 and 5) in both men and women.

Discussions

In this large-scale community-based study, we observed that higher NC was associated with higher serum UA concentration, and higher odds of having hyperuricemia in both men and women, after adjusting potential confounders including demographic factors, diet, physical exercise, snoring, smoke, alcohol consumption, BMI, waist circumference, blood pressure, and blood biochemical parameters. Strengths of the current study included larger sample size and adjustment for a wide range of potential confounders.

Overall, data regarding the association between NC and hyperuricemia were limited. Only two cross-sectional studies evaluated the association between NC and uric acid, or odds of having hyperuricemia [9, 10]. In a study including 8971 Chinese adult (5604 women and 3309 men), participants in the highest NC quartile group had higher likelihood of having hyperuricemia (adjusted OR was 2.61 in men and 3.27 in women; $p < 0.001$ for both) compared with participants in the lowest NC quartile group [9]. Similar significant results were observed in a small hospital–based study ($n = 177$) [10]. However, in these two studies, residual confounding was of concern. They did not adjust for BMI and waist circumference, which are well-established risk factors for hyperuricemia and are strongly associated with NC status. Of note, these two studies and the current study are all conducted among Chinese adults. Further studies are warranted to replicate our findings in different ethnicity groups.

Our results showed that the association between NC and hyperuricemia remained significant even after adjusting for BMI (for total body fat) and waist circumference (for abdominal visceral fat), suggesting that upper body fat, as estimated by NC, may have a unique role in the pathology of hyperuricemia. Higher neck circumference was associated with insulin resistance [27] and high risk of T2 diabetes [28] after adjusting for both visceral adiposity tissue and BMI. Insulin resistance was strongly correlated with serum uric acid concentration, independent of age, sex, overall obesity, and abdominal obesity ($r = 0.57$; $P < 0.01$) [29]. Insulin resistance could subsequently decrease the excretion of uric acid through increase of proximal tubular sodium reabsorption [30]. Other pathways could be also involved. For example, the impact of larger NC on UA status could also be due

Table 3 Adjusted odd ratios and 95% confidence interval for risk of hyperuricemia, across quartiles of neck circumference in 81,567 Chinese adult population

Sex (*p* interaction = 0.02)		Quartiles of neck circumference				Each 5-cm increase	*p* trend
		Q1	Q2	Q3	Q4		
Men	Case number	3133	3641	3092	4014	–	–
	Model 1	1 (Ref)	1.21 (1.14, 1.27)	1.43 (1.35, 1.52)	1.42 (1.35, 1.5)	1.21 (1.18, 1.24)	< 0.001
	Model 2	1 (Ref)	1.12 (1.04, 1.21)	1.29 (1.19, 1.4)	1.38 (1.28, 1.48)	1.15 (1.11, 1.2)	< 0.001
	Model 3	1 (Ref)	1.05 (0.97, 1.13)	1.14(1.05, 1.24)	1.12 (1.04, 1.21)	1.06 (1.02, 1.1)	0.004
Women	Case number	416	318	592	531	–	–
	Model 1	1 (Ref)	1.29 (1.1, 1.5)	1.45 (1.27, 1.65)	1.8 (1.57, 2.07)	1.33 (1.24, 1.42)	< 0.001
	Model 2	1 (Ref)	1.1 (0.88, 1.38)	1.37 (1.14, 1.64)	1.73 (1.43, 2.09)	1.3 (1.19, 1.43)	< 0.001
	Model 3	1 (Ref)	1.04 (0.83, 1.31)	1.23 (1.02, 1.48)	1.34 (1.1, 1.64)	1.17 (1.06, 1.28)	0.002

Adjusting age (y) in model 1. Adjusting age (y), high-sensitivity C-reactive protein (mg/dl), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), fasting blood glucose (mmol/L), total cholesterol (mmol/L), triglyceride (mmol/L), high-density lipoprotein cholesterol (mmol/L), low-density lipoprotein cholesterol (mmol/L), dietary quality score, EGFR (ml/min/1.73m^2), smoking ("yes" or "no"), alcohol consumption (g/day), physical exercise ("yes" or "no"), snoring (never, < 1 time/week, 1–5 times/week, ≥ 6 times/week, unknown), myocardial infarction ("yes" or "no"), stroke ("yes" or "no"), education (≤middle school or ≥ high school) in model 2. Adjusting variables in model 2 and BMI (kg/m^2) and waist circumference (cm) in model 3. – means not applicable

to the release of free fatty acids from upper body adiposity tissue [31]. High levels of plasma free fatty acids are associated with oxidative stress and insulin resistance [32]. Another pathway might lie in excess neck subcutaneous fat deposition, which could press the airway and leading to hypoxia. Hypoxia, in turn, is associated with oxidative stress and insulin resistance [33].

Alternately, greater NC could be a marker for presence of obstructive sleep apnea (OSA). A retrospective study found that larger NC (≥ 43.2 cm for men and ≥ 36.8 cm for women) associated 2.52-fold of OSA in men and 3.13-fold in women [34]. NC was reported to be the only marker associated with all cardiometabolic risk markers, including homeostasis assessment model and apnea-hypopnea index in 305 women with an average BMI of 44.2 kg/m^2 [35], and including NC in the predictive model was better than BMI to explain apnea-hypopnea index variability in 115 women with morbidity obesity [36]. OSA has been reported to be associated with high UA concentrations. For example, in a cross-sectional study including 1021 adults (mean age 42.5 ± 0.5 y), UA is associated with not only OSA itself, but with related risk factors for OSA, such as triglycerides, systolic blood pressure, and BMI [37]. The potential mechanism may lie in that hypoxia, caused by OSA, leads to activation of xanthine oxidase, an enzyme that plays a mechanistic role in both oxidative stress and production of UA. However, in the current study, significant NC-UA relationship persisted after we excluded participants with snoring (a surrogate of OSA), indicating that higher NC could

Table 4 Adjusted means and standard deviation of serum uric acid concentration across quartiles of neck circumference in 71,465 Chinese men, stratified by age and alcohol consumption

Variables	Group	Quartiles of neck circumference				Each 5-cm increase	*p* trend	*p* interaction
		Q1 (<37 cm)	Q2 (37–39 cm)	Q3 (39–41 cm)	Q4 (≥ 41 cm)			
Age	< 60 y	368 ± 6.4	374 ± 6.3	375 ± 6.4	374 ± 6.4	2.1 ± 0.8	0.006	< 0.001
	≥ 60 y	341 ± 4.5	341 ± 4.5	342 ± 4.5	333 ± 4.5	− 1.1 ± 0.9	0.22	
Alcohol consumption	No	358 ± 3.8	359 ± 3.9	361 ± 3.9	359 ± 3.9	− 0.4 ± 0.6	0.6	< 0.001
	Yes	352 ± 10.3	365 ± 10.2	371 ± 10.3	370 ± 10.2	8.0 ± 1.2	< 0.001	

Adjusting age (y), high-sensitivity C-reactive protein (mg/dl), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), fasting blood glucose (mmol/L), total cholesterol (mmol/L), triglyceride (mmol/L), high-density lipoprotein cholesterol (mmol/L), low-density lipoprotein cholesterol (mmol/L), dietary quality score, EGFR (ml/min/1.73m^2), smoking ("yes" or "no"), alcohol consumption (g/day), physical exercise ("yes" or "no"), snoring (never, < 1 time/week, 1–5 times/week, ≥ 6 times/week, unknown), myocardial infarction ("yes" or "no"), stroke ("yes" or "no"), education (≤middle school or ≥ high school), BMI (kg/m^2), and waist circumference (cm). Overall, the results were based on model 3

Table 5 Adjusted means and standard deviation of serum uric acid concentration across quartiles of neck circumference in 16,317 Chinese women, stratified by age and alcohol consumption

Variables	Group	Quartiles of neck circumference				Each 5-cm increase	*p* trend	*p* interaction
		Q1 (< 35 cm)	Q2 (35–37 cm)	Q3 (37–38.2 cm)	Q4 (≥ 38.2 cm)			
Age	< 60 y	260 ± 12.2	266 ± 12.1	268 ± 12.1	274 ± 12.1	4.3 ± 1.2	< 0.001	< 0.001
	≥ 60 y	294 ± 11.5	284 ± 11.7	296 ± 11.5	294 ± 11.5	0.0 ± 1.5	0.9	
Alcohol consumption	No	279 ± 7.9	281 ± 8.0	286 ± 7.9	288 ± 7.9	2.8 ± 0.9	0.002	0.002
	Yes	246 ± 39.6	244 ± 40.1	260 ± 39.6	271 ± 39.2	19.7 ± 5.8	< 0.001	

Adjusting age (y), high-sensitivity C-reactive protein (mg/dl), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), fasting blood glucose (mmol/L), total cholesterol (mmol/L), triglyceride (mmol/L), high-density lipoprotein cholesterol (mmol/L), low-density lipoprotein cholesterol (mmol/L), dietary quality score, EGFR (ml/min/1.73m^2), smoke (“yes” or “no”), alcohol consumption (g/day), physical exercise (“yes” or “no”), snoring (never, < 1 time/week, 1–5 times/week, ≥ 6 times/week, unknown), myocardial infarction (“yes” or “no”), stroke (“yes” or “no”), education (≤middle school or ≥ high school), BMI (kg/m^2), and waist circumference (cm). Overall, the results were based on model 3

be a risk factor for hyperuricemia, independent of OSA status. It is worth noting that we are aware that snoring is not a perfect measure for OSA status, and we cannot exclude the possibility of misclassification.

We also observed significant interactions between sex, age, and alcohol consumption with NC in relation to UA concentrations in both men and women (all $p \leq 0.01$). Similar gender difference was observed in previous studies regarding NC and UA [12, 25]. Consistently, the association between UA and metabolic diseases appeared to be stronger in women than that in men. For example, in a cross-sectional study including 696 men and 521 women, the presence of hyperuricemia was significantly associated with high cardio-ankle vascular index in women but not in men [38]. In another cohort study based on NHANES I epidemiologic follow-up study, the association between higher UA concentrations and higher cardiovascular mortality was more pronounced in women, relative to men [39]. Interestingly, we also found that younger adults (< 60 y) had a greater association between NC and UA relative to older counterparts (≥ 60 y). In a cross-sectional study in 45,098 Korea adults, significant association between UA and blood pressure and hyperuricemia was only evident in younger participants (< 60 y vs. > 60 y) [40]. However, the exact mechanism remains unknown to data. Alcohol consumption is a well-established risk factor for hyperuricemia and gout [41–43]. Whether the observed significant interaction between NC and alcohol, in relation to UA status, is due to chance or reflects certain underlying mechanisms needs be investigated in future studies.

Our study had some limitations. Because of its cross-sectional study design, we could not detect the temporal relationship between NC and UA. Further, information on gout, a chronic condition strongly associated with UA status, was collected via self-report, which would introduce misclassification. We did not collect information on use of allopurinol and other medicines which are used to reduce UA concentration. However, after excluding participants with gout or chronic kidney disease, or those used antihypertensives, which could also impact UA status, we observed similar results. Finally, we did not do an intra-and inter-rater reliability study of the evaluators for assessment of neck circumference and other related factors, thus might cause variance of the data. Longitudinal studies are warranted to examine which higher NC is a risk factor for developing hyperuricemia and relevant diseases, such as gout.

Conclusions

Higher NC was associated with higher serum UA concentration and higher risk of hyperuricemia in Chinese adults. Integration of NC with traditional anthropometrical parameters such as BMI and waist circumference in obesity management could helpful to identify those who are in high risk of excess fat deposition, OSA, metabolic syndrome, and insulin resistance [12, 44, 45].

Funding The study was supported by National Natural Science Foundation of China (No. 81773407); Natural Science Foundation of Shanghai (No. 17ZR1415700).

Compliance with ethical standards

The study was approved by the Ethics Committee of the Kailuan General Hospital (No. ChiCTR-TNRC-11001489).

Disclosures None.

References

1. Liu R, Han C, Wu D, Xia X, Gu J, Guan H, Shan Z, Teng W (2015) Prevalence of hyperuricemia and gout in mainland China from 2000 to 2014: a systematic review and meta-analysis. Biomed Res Int 2015:762820. https://doi.org/10.1155/2015/762820
2. Chen YY, Kao TW, Yang HF, Chou CW, Wu CJ, Lai CH, Sun YS, Wang CC, Chen WL (2017) The association of uric acid with the risk of metabolic syndrome, arterial hypertension or diabetes in young subjects- an observational study. Clin Chim Acta 478:68–73. https://doi.org/10.1016/j.cca.2017.12.038
3. Li Z, Meng L, Huang Z, Cui L, Li W, Gao J, Wang Z, Zhang R, Zhou J, Zhang G, Chen S, Zheng X, Cong H, Gao X, Wu S (2016) Ideal cardiovascular health metrics and incident hyperuricemia. Arthritis Care Res 68(5):660–666. https://doi.org/10.1002/acr.22830
4. Onat A, Hergenc G, Yuksel H, Can G, Ayhan E, Kaya Z, Dursunoglu D (2009) Neck circumference as a measure of central obesity: associations with metabolic syndrome and obstructive sleep apnea syndrome beyond waist circumference. Clin Nutr 28(1):46–51. https://doi.org/10.1016/j.clnu.2008.10.006
5. Dai Y, Wan X, Li X, Jin E, Li X (2016) Neck circumference and future cardiovascular events in a high-risk population–a prospective cohort study. Lipids Health Dis 15:46. https://doi.org/10.1186/s12944-016-0218-3
6. Zhou JY, Ge H, Zhu MF, Wang LJ, Chen L, Tan YZ, Chen YM, Zhu HL (2013) Neck circumference as an independent predictive contributor to cardio-metabolic syndrome. Cardiovasc Diabetol 12:76. https://doi.org/10.1186/1475-2840-12-76
7. Lee MJ, Wu Y, Fried SK (2013) Adipose tissue heterogeneity: implication of depot differences in adipose tissue for obesity complications. Mol Asp Med 34(1):1–11. https://doi.org/10.1016/j.mam.2012.10.001
8. Sico JJ, Yaggi HK, Ofner S, Concato J, Austin C, Ferguson J, Qin L, Tobias L, Taylor S, Vaz Fragoso CA, McLain V, Williams LS, Bravata DM (2017) Development, validation, and assessment of an ischemic stroke or transient ischemic attack-specific prediction tool for obstructive sleep apnea. J Stroke Cerebrovasc Dis 26(8):1745–1754. https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.03.042
9. Jiang J, Cui J, Yang X, Wang A, Mu Y, Dong L, Wang S, Gaisano H, Dou J, He Y (2017) Neck circumference, a novel indicator for hyperuricemia. Front Physiol 8:965. https://doi.org/10.3389/fphys.2017.00965
10. Liu YF, Chang ST, Lin WS, Hsu JT, Chung CM, Chang JJ, Hung KC, Chen KH, Chang CW, Chen FC, Shih YW, Chu CM (2015) Neck circumference as a predictive indicator of CKD for high cardiovascular risk patients. Biomed Res Int 2015:745410. https://doi.org/10.1155/2015/745410
11. Wu S, Jin C, Li S, Zheng X, Zhang X, Cui L, Gao X (2019) Aging, Arterial Stiffness, and Blood Pressure Association in Chinese Adults. Hypertension. https://doi.org/10.1161/HYPERTENSIONAHA.118.12396
12. Yang GR, Yuan SY, Fu HJ, Wan G, Zhu LX, Bu XL, Zhang JD, Du XP LYL, Ji Y, Gu XN, Li Y, Beijing Community Diabetes Study G (2010) Neck circumference positively related with central obesity, overweight, and metabolic syndrome in Chinese subjects with type 2 diabetes: Beijing Community Diabetes Study 4. Diabetes Care 33(11):2465–2467. https://doi.org/10.2337/dc10-0798
13. Ji C, Li Y, Cui L, Cai J, Shi J, Cheng FW, Li Y, Curhan GC, Wu S, Gao X (2017) Prenatal earthquake exposure and midlife uric acid levels among Chinese adults. Arthritis Care Res 69(5):703–708. https://doi.org/10.1002/acr.22973
14. Bardin T, Richette P (2014) Definition of hyperuricemia and gouty conditions. Curr Opin Rheumatol 26(2):186–191. https://doi.org/10.1097/BOR.0000000000000028
15. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, National Heart L, Blood Institute Joint National Committee on Prevention DE, Treatment of High Blood P, National High Blood Pressure Education Program Coordinating C (2003) The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 289(19):2560–2572. https://doi.org/10.1001/jama.289.19.2560
16. Huang S, Li J, Shearer GC, Lichtenstein AH, Zheng X, Wu Y, Jin C, Wu S, Gao X (2017) Longitudinal study of alcohol consumption and HDL concentrations: a community-based study. Am J Clin Nutr 105(4):905–912. https://doi.org/10.3945/ajcn.116.144832
17. Jin C, Chen S, Vaidya A, Wu Y, Wu Z, Hu FB, Kris-Etherton P, Wu S, Gao X (2017) Longitudinal change in fasting blood glucose and myocardial infarction risk in a population without diabetes. Diabetes Care 40(11):1565–1572. https://doi.org/10.2337/dc17-0610
18. Wu Z, Huang Z, Jin W, Rimm EB, Lichtenstein AH, Kris-Etherton PM, Wu S, Gao X (2017) Peripheral inflammatory biomarkers for myocardial infarction risk: a prospective community-based study. Clin Chem 63(3):663–672. https://doi.org/10.1373/clinchem.2016.260828
19. Clinical Practice Recommendations 2005 (2005) Diabetes Care 28(Suppl 1):S1–S9
20. Kong X, Ma Y, Chen J, Luo Q, Yu X, Li Y, Xu J, Huang S, Wang L, Huang W, Wang M, Xu G, Zhang L, Zuo L, Wang H, Chinese e GFRIC (2013) Evaluation of the Chronic Kidney Disease Epidemiology Collaboration equation for estimating glomerular filtration rate in the Chinese population. Nephrol Dial Transplant 28(3):641–651. https://doi.org/10.1093/ndt/gfs491
21. Huang Z, Huang S, Cong H, Li Z, Li J, Keller KL, Shearer GC, Kris-Etherton PM, Wu S, Gao X (2017) Smell and taste dysfunction is associated with higher serum total cholesterol concentrations in Chinese adults. J Nutr 147(8):1546–1551. https://doi.org/10.3945/jn.117.250480
22. Wu Z, Jin C, Vaidya A, Jin W, Huang Z, Wu S, Gao X (2016) Longitudinal patterns of blood pressure, incident cardiovascular events, and all-cause mortality in normotensive diabetic people. Hypertension 68(1):71–77. https://doi.org/10.1161/HYPERTENSIONAHA.116.07381
23. Li YSJ, Pan H, Yao M, Hu X, Ma G (2006) Validity of food frequency questionnaire to investigate the dietary energy and nutrients intake. Acta Nutrimenta Sinica 28:143–147
24. Huffman MD, Capewell S, Ning H, Shay CM, Ford ES, Lloyd-Jones DM (2012) Cardiovascular health behavior and health factor changes (1988-2008) and projections to 2020: results from the National Health and Nutrition Examination Surveys. Circulation 125(21):2595–2602. https://doi.org/10.1161/CIRCULATIONAHA.111.070722
25. Cui T, Yan BH, Liu Z, Yang H, Gyan M, Ma YX (2017) Neck circumference: a valuable anthropometric measurement to detect metabolic syndrome among different age groups in China. Diabetes Metab Res Rev 34. https://doi.org/10.1002/dmrr.2966
26. Gibson TJ (2013) Hypertension, its treatment, hyperuricaemia and gout. Curr Opin Rheumatol 25(2):217–222. https://doi.org/10.1097/BOR.0b013e32835cedd4
27. Preis SR, Massaro JM, Hoffmann U, D'Agostino RB Sr, Levy D, Robins SJ, Meigs JB, Vasan RS, O'Donnell CJ, Fox CS (2010) Neck circumference as a novel measure of cardiometabolic risk: the Framingham Heart study. J Clin Endocrinol Metab 95(8):3701–3710. https://doi.org/10.1210/jc.2009-1779
28. Preis SR, Pencina MJ, D'Agostino RB Sr, Meigs JB, Vasan RS, Fox CS (2013) Neck circumference and the development of cardiovascular disease risk factors in the Framingham Heart Study. Diabetes Care 36(1):e3. https://doi.org/10.2337/dc12-0738

29. Facchini F, Chen YD, Hollenbeck CB, Reaven GM (1991) Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. JAMA 266(21):3008–3011
30. Cappuccio FP, Strazzullo P, Farinaro E, Trevisan M (1993) Uric acid metabolism and tubular sodium handling. Results from a population-based study. JAMA 270(3):354–359
31. Nielsen S, Guo Z, Johnson CM, Hensrud DD, Jensen MD (2004) Splanchnic lipolysis in human obesity. J Clin Invest 113(11):1582–1588. https://doi.org/10.1172/JCI21047
32. Joshipura K, Munoz-Torres F, Vergara J, Palacios C, Perez CM (2016) Neck circumference may be a better alternative to standard anthropometric measures. J Diabetes Res 2016:6058916. https://doi.org/10.1155/2016/6058916
33. Ryan S (2017) Adipose tissue inflammation by intermittent hypoxia: mechanistic link between obstructive sleep apnoea and metabolic dysfunction. J Physiol 595(8):2423–2430. https://doi.org/10.1113/JP273312
34. Earl DE, Lakhani SS, Loriaux DB, Spector AR (2019) Predictors of moderate to severe obstructive sleep apnea: identification of sex differences. Sleep Breath. https://doi.org/10.1007/s11325-019-01790-x
35. Borel AL, Coumes S, Reche F, Ruckly S, Pepin JL, Tamisier R, Wion N, Arvieux C (2018) Waist, neck circumferences, waist-to-hip ratio: which is the best cardiometabolic risk marker in women with severe obesity? The SOON cohort. PLoS One 13(11): e0206617. https://doi.org/10.1371/journal.pone.0206617
36. Gasa M, Lopez-Padros C, Monasterio C, Salord N, Mayos M, Vilarrasa N, Fernandez-Aranda F, Montserrat JM, Dorca J (2019) Anthropometrical phenotypes are important when explaining obstructive sleep apnea in female bariatric cohorts. J Sleep Res: e12830. https://doi.org/10.1111/jsr.12830
37. Hirotsu C, Tufik S, Guindalini C, Mazzotti DR, Bittencourt LR, Andersen ML (2013) Association between uric acid levels and obstructive sleep apnea syndrome in a large epidemiological sample. PLoS One 8(6):e66891. https://doi.org/10.1371/journal.pone.0066891
38. Zheng X, Wei Q, Long J, Gong L, Chen H, Luo R, Ren W, Wang Y (2018) Gender-specific association of serum uric acid levels and cardio-ankle vascular index in Chinese adults. Lipids Health Dis 17(1):80. https://doi.org/10.1186/s12944-018-0712-x
39. Fang J, Alderman MH (2000) Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey. JAMA 283(18):2404–2410
40. Lee JJ, Ahn J, Hwang J, Han SW, Lee KN, Kim JB, Lee S, Na JO, Lim HE, Kim JW, Rha SW, Park CG, Seo HS, Oh DJ, Kim EJ (2015) Relationship between uric acid and blood pressure in different age groups. Clin Hypertens 21:14. https://doi.org/10.1186/s40885-015-0022-9
41. Makinouchi T, Sakata K, Oishi M, Tanaka K, Nogawa K, Watanabe M, Suwazono Y (2016) Benchmark dose of alcohol consumption for development of hyperuricemia in Japanese male workers: an 8-year cohort study. Alcohol 56:9–14. https://doi.org/10.1016/j.alcohol.2016.08.002
42. Villegas R, Xiang YB, Cai Q, Fazio S, Linton M, Li H, Elasy T, Zheng W, Shu XO (2010) Prevalence and determinants of hyperuricemia in middle-aged, urban Chinese men. Metab Syndr Relat Disord 8(3):263–270. https://doi.org/10.1089/met.2009.0084
43. Neogi T, Chen C, Niu J, Chaisson C, Hunter DJ, Zhang Y (2014) Alcohol quantity and type on risk of recurrent gout attacks: an internet-based case-crossover study. Am J Med 127(4):311–318. https://doi.org/10.1016/j.amjmed.2013.12.019
44. Xu H, Zhao X, Shi Y, Li X, Qian Y, Zou J, Yi H, Huang H, Guan J, Yin S (2019) Development and validation of a simple-to-use clinical nomogram for predicting obstructive sleep apnea. BMC Pulm Med 19(1):18. https://doi.org/10.1186/s12890-019-0782-1
45. Stabe C, Vasques AC, Lima MM, Tambascia MA, Pareja JC, Yamanaka A, Geloneze B (2013) Neck circumference as a simple tool for identifying the metabolic syndrome and insulin resistance: results from the Brazilian Metabolic Syndrome Study. Clin Endocrinol 78(6):874–881. https://doi.org/10.1111/j.1365-2265.2012.04487.x

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.