Clin Rheumatol (2017) 36:1103–1110
DOI 10.1007/s10067-017-3548-2

ORIGINAL ARTICLE

# Association of serum uric acid and risk of hypertension in adults: a prospective study of Kailuan Corporation cohort

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Received: 8 April 2016 / Revised: 1 December 2016 / Accepted: 15 January 2017 / Published online: 7 February 2017
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**Abstract** Whether hyperuricemia is an independent risk factor for hypertension in adults is still under debate. To determine the association between serum uric acid and risk of hypertension in the Chinese population, we conducted a prospective study using the "Kailuan Corporation cohort." A total of 39,233 adult subjects with available data on serum uric acid were enrolled from 2006 to 2007. Subjects with established hypertension were excluded and were then grouped based on the gender and baseline quartile serum uric acid into F1–4 for women and M1–4 for men with F1 and M1 being the lowest quartiles. Incidence of newly described primary hypertension was reevaluated in 2010–2011. The median (interquantile range) baseline uric acid (UA) was 290 (243–344) μmol/L in men and 230 (194–274) μmol/L in women. During a 4-year follow-up period, 12,844 subjects (31.31 %) were newly diagnosed with hypertension. The incidence of hypertension was 14.36, 16.57, 19.06, and 22.35 % in F1 to F4 and 33.64, 33.97, 36.54, and 40.74 % in M1 to M4, respectively. Multiple logistic regression analysis showed that the odds ratios (ORs) of incident hypertension were 1.17 [95 % confidence interval (CI) 1.00–1.37, $P = 0.055$], 1.24 (95 % CI 1.06–1.45, $P = 0.009$), and 1.20 (95 % CI 1.02–1.41, $P = 0.027$) in F2 to F4 compared to the F1 and 0.98 (95 % CI 0.91–1.05, $P = 0.534$), 1.05 (95 % CI 0.98–1.13, $P = 0.190$), and 1.13 (95 % CI 1.05–1.22, $P = 0.002$) in M2 to M4 compared to the M1. Elevated level of serum uric acid is associated with an increased risk of hypertension in adults.

**Keywords** Cohort study · Hypertension · Prospective study · Serum uric acid

Liu-fu Cui and Hui-jing Shi contributed equally to this study.

**Electronic supplementary material** The online version of this article (doi:10.1007/s10067-017-3548-2) contains supplementary material, which is available to authorized users.

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**Abbreviations**

| | |
|---|---|
| BMI | Body mass index |
| BP | Blood pressure |
| CRP | C-reactive protein |
| DBP | Diastolic blood pressure |
| eGRF | Estimated glomerular filtration rate |
| FBG | Fasting blood glucose |
| HDL | High-density lipoprotein |
| MI | Myocardial infarction |
| LDL | Low-density lipoprotein |
| SBP | Systolic blood pressure |
| SUA | Serum uric acid |
| TC | Total cholesterol |
| TG | Triglyceride |

## Introduction

The incidence of primary hypertension in China has increased rapidly in the past 50 years [1]. Although the precise etiology

remains unclear, environmental factors play a crucial role in the pathogenesis of hypertension. Over the past decade, emerging epidemiologic data that indicated the correlation between hyperuricemia and hypertension led to a resurgence of interest in this area [2–9]. With the rapid development of Chinese economy, dietary intake of alcohol and meat has increased considerably, resulting in the increase of serum uric acid (SUA) level [10, 11].

The association between hyperuricemia and hypertension has been indicated by several previous studies. In an animal model, hyperuricemia was shown to increase blood pressure (BP) [12]. In Framingham Heart Study, which included 3329 subjects without hypertension, myocardial infarction, heart failure, renal failure, or gout from 1972 to 1976, 458 (13.8 %) subjects developed hypertension and 1201 (36.1 %) experienced higher BP after 4 years of follow-up. Multivariate analysis showed that elevation of SUA by each standard deviation (SD) was associated with an odds ratio (OR) of 1.17 [95 % confidence interval (CI), 1.02 to 1.33] for developing hypertension and an OR of 1.11 (95 % CI, 1.01 to 1.23) for progression in BP [8]. In another study, after following 2062 healthy men aged 41.7 ± 9.2 years over a mean of 21.5 years, Perlstein et al. found that higher level of SUA was an independent risk factor for hypertension after standardized adjustment for age [9]. Further, treatment with allopurinol in 30 adolescents with newly diagnosed hypertension resulted in BP reduction [13]. These data suggest that hyperuricemia is an independent risk factor for hypertension, and it may be more pronounced in adolescents.

However, other studies have shown variable results in the relationship between SUA and hypertension, especially in older patients, partly because of differences in study design. Most of these studies had small sample sizes, and the presence of confounding factors could not be excluded. Therefore, due to possible shared environmental and genetic factors of hyperuricemia and hypertension, whether hyperuricemia is an independent risk factor for primary hypertension in adult patients is still under debate [6]. In addition, the relationship between SUA and primary hypertension has not been specifically studied in the Chinese population.

Kailuan is a large community located in Tangshan City, the central part of the circulating Bohai Sea Gulf region in China. This community originally consists of workers and families of the Kailuan Group, a major coal mining company in China, which includes 101,510 people (79.9 % men). Although the community is located in the Bohai Bay Area, it was mainly formed by immigrants from inland areas during the Ming Dynasty (1368–1644), making the Tangshan cuisine an inland style. No specific diet habitat has been found, and seafood is not consumed as commonly as in typical coastal cities.

The Kailuan Medical Group includes 11 hospitals (Kailuan General Hospital, Kailuan Linxi Hospital, Kailuan Zhaogezhuang Hospital, Kailuan Tangjiazhuang Hospital, Kailuan Fangezhuang Hospital, Kailuan Jinggezhuang Hospital, Kailuan Lvjiatuo Hospital, Kailuan Linnancang Hospital, Kailuan Qianjiaying Hospital, Kailuan Majiagou Hospital, and Kailuan Hospital) and is responsible for the healthcare of the community. From July 2006 to October 2007, the Kailuan Medical Group had built the health record for all people living in the community [14]. Using this cohort, a prospective study was conducted to examine the effect of baseline level of SUA on the incidence of hypertension (registration number: ChiCTR TNC-11001489).

## Subjects and methods

### Subjects

The Kailuan community cohort includes 101,510 individuals who were mainly Han Chinese that underwent health screening at the 11 hospitals of the Kailuan Medical Group between July 1, 2006 and October 31, 2007.

Subjects were followed up every 2 years. Subsequent medical inspections were conducted between July 1, 2008 and June 30, 2009 and between July 1, 2010 and June 30, 2011, respectively. Subjects with established hypertension (including normotensive subjects receiving antihypertensive medication) or without available data on SUA were excluded. This study was approved by the Ethics Committee of Kailuan Hospital, Hebei United University, and all subjects provided informed consent.

### Data collection

#### *General data collection*

Demographic characteristics, smoking status, salt and alcohol consumption, family and personal medical history, and treatment for hypertension of the subjects were collected. Height and weight were measured during the interview using a calibrated stadiometer and platform scale, respectively. Body mass index (BMI) was defined as weight in kilograms divided by the square of the height in meters ($kg/m^2$). Family history of hypertension was defined as a history of hypertension in one or both of the parents. Salt intake was collected using a questionnaire and was classified as "high" or "not high," based on the responses to questions related to salt preferences. High salt intake was defined as consumption of ≥12 g salt daily. Drinking was defined as >50 g average daily consumption of alcohol for >1 year. Smoking was defined as daily consumption of at least one cigarette for at least 1 year.

#### *Measurement of BP*

The right brachial artery BP was taken after being seated for at least 5 min using a calibrated mercury sphygmomanometer. The

first phase of Korotkoff sound was defined as systolic BP (SBP), and the fifth phase of Korotkoff sound was defined as diastolic BP (DBP). The BP was measured three times continuously with a break of 1–2 min. The mean value of the three measurements was considered as the value of BP. Subjects were instructed to avoid smoking, tea, and coffee for 30 min prior to BP measured [1].

*Laboratory measurements*

The concentration of SUA was examined with a commercial kit (Ke Hua Biological Engineering Corporation, Shanghai, China) using an automatic biochemical analyzer (Hitachi 7600, Tokyo, Japan) according to the manufacturer's instructions. The concentration of SUA, fasting blood glucose (FBG), serum creatinine (enzymatic method), total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and C-reactive protein (CRP) were also measured at the central laboratory of Kailuan General Hospital using the same autoanalyzer.

*Definition of disease and diagnostic criteria*

Hypertension was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg according to the 2010 Chinese guidelines for the management of hypertension [1]. Diagnoses of cerebral stroke and myocardial infarction (MI) were confirmed by specialists. Malignant tumor history was confirmed in subjects with pathological diagnosis.

### Statistical analysis

Data were entered using EipData (EipData, London, UK) and uploaded to the Oracle 10g database (Oracle, CA, USA) in the Kailuan General Hospital. Data analysis was performed using SPSS 13.0 (SPSS, Chicago, IL, USA). Numeric data were expressed as mean ± SD, while categorical data were expressed as percentages. The chi-squared test was used to evaluate the differences in the frequency of characteristics. Variables of C-reactive protein were not normally distributed and were then log transformed for statistical analyses. Baseline characteristics were compared using univariate logistic regression analysis, and data with $P$ values <0.20 in single factor analysis were further compared using multiple logistic regression analysis to assess the relationship with incident hypertension. $P$ values <0.05 were considered statistically significant.

## Results

### Selection of population

Of the 101,510 subjects of the Kailuan Community cohort, 62,276 were excluded from the study, including 47,101 subjects with established hypertension, 392 with no data of baseline SUA, and 14,783 subjects who opted out or were lost to follow-up. The final study population included 39,233 subjects (10,593 women and 28,640 men) aged 18 to 98 years (women 44.72 ± 10.54 years, men 47.31 ± 11.94 years). The selection procedure of the study population is presented in Fig. 1.

### Baseline characteristics of included subjects

The median (interquantile range [IQR]) baseline uric acid (UA) was 290 (243–344) μmol/L in men and 230 (194–274) μmol/L in women. Subjects were divided into eight groups based on the quartiles of the baseline levels of SUA. For women, subjects with UA ≤ 194, 194 < UA ≤ 230, 230 < UA ≤ 274, and UA > 274 μmol/L were classified as groups F1, F2, F3, and F4, respectively. The medians of baseline serum UA in female group

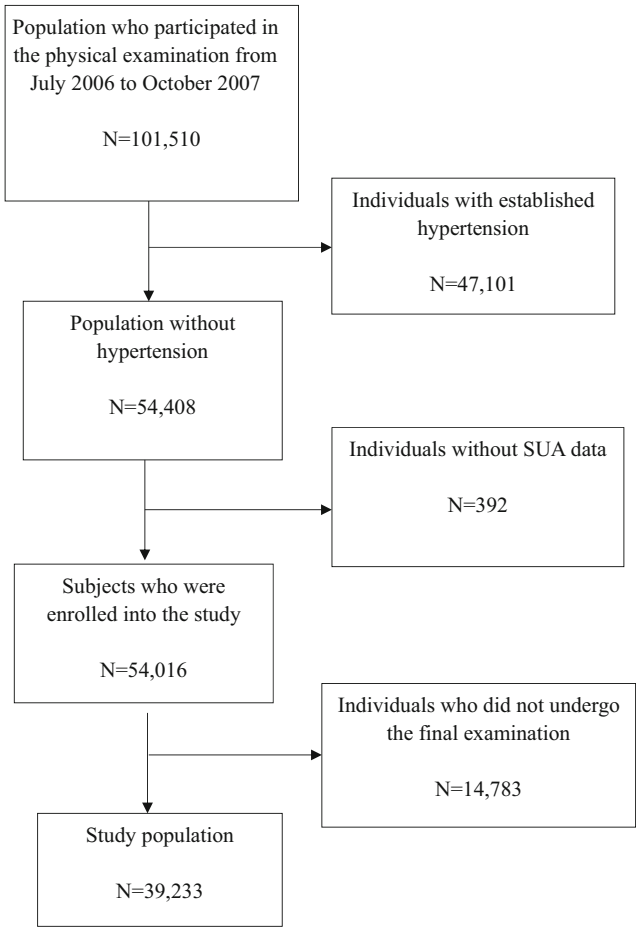


**Fig. 1** Flowchart of population selection in this study. *SUA* serum uric acid. A total of 101,510 individuals from "Kailuan Corporation" underwent health screening from July 1, 2006 to October 31, 2007. In these individuals, 47,101 subjects with established hypertension and 392 individuals without available data of SUA were excluded. Fourteen thousand seven hundred eighty-three individuals did not undergo the final examination and were excluded in the analysis model. A total of 39,233 subjects were enrolled in the prospective cohort study

were 168, 212, 251, and 308 μmol/L. For men, subjects with UA ≤ 243, 243 < UA ≤ 290, 290 < UA ≤ 344, and UA > 344 μmol/L were classified as groups M1, M2, M3, and M4, respectively. The medians of baseline serum UA in male group were 213, 268, 315, and 387 μmol/L. Tables 1 and 2 show the baseline characteristics of the study population.

BP, TG, TC, HDL, LDL, Cr, BMI, frequency of smoking, and family history of hypertension all increased in both women and men with increasing levels of SUA. Interestingly, log CRP was also positively correlated with SUA. Estimated glomerular filtration rate (eGFR) decreased in both women and men with increasing SUA. These characteristics were significantly different among quartiles ($P < 0.05$).

Age was significantly associated with the increasing levels of SUA in women but not men, while FBG, drinking, high salt intake, incidences of MI, and cerebral stroke were significant in men but not women.

### Incidence of hypertension in each quartile

After a follow-up of 4 years, 12,844 (31.31 %) subjects had newly diagnosed primary hypertension, including 1913 (18.06 %) women and 10,371 (36.21 %) men. Female and male subjects with hypertension in each quartile are presented in Table 3. Significant difference was found among the four quartiles ($P < 0.05$).

### Logistic regression analysis for hypertension

Taking hypertension as the dependent variable and SUA quartile as the independent variable, logistic regression analysis was used to evaluate the association between the level of SUA and hypertension. Univariate logistic analysis showed that high salt intake, smoking, drinking, hypercholesterolemia, hyperglycemia, obesity, and history of cerebral stroke were statistically significantly associated with increased risk of incident hypertension. Factors with $P$ values <0.20 in univariate analysis were included in the multiple logistic regression analysis to evaluate the association between the level of SUA and hypertension.

In the unadjusted model (model 1, Tables 4 and 5), using quartile 1 as reference, the risk of hypertension increased with higher quartiles of SUA. The odds ratios (ORs) (95 % CI) were 1.19 (1.02–1.38), 1.41 (1.22–1.62), and 1.72 (1.49–

**Table 1** Baseline characteristics of included female subjects

| Quartiles of SUA | F1 | F2 | F3 | F4 | Total | $F/X^2$ | $P$ |
|---|---|---|---|---|---|---|---|
| (μmol/L) | UA ≤ 194 | 194 < UA ≤ 230 | 230 < UA ≤ 274 | UA > 274 | | | |
| Number | 2675 | 2649 | 2670 | 2599 | 10,593 | | |
| UA (μmol/L) | 162.4 ± 25.79 | 212.23 ± 10.16 | 250.97 ± 12.84 | 322.17 ± 46.46 | 236.39 ± 64.44 | 15,634.42 | 0.000* |
| Age (years) | 44.09 ± 9.58 | 43.79 ± 9.77 | 44.44 ± 10.26 | 46.6 ± 12.16 | 44.72 ± 10.54 | 38.71 | 0.000* |
| SBP (mmHg) | 112.29 ± 11.59 | 113.01 ± 11.31 | 113.37 ± 11.84 | 114.69 ± 11.73 | 113.33 ± 11.65 | 19.43 | 0.000* |
| DBP (mmHg) | 73.82 ± 7.31 | 74.13 ± 7.1 | 74.15 ± 7.18 | 74.8 ± 7.07 | 74.22 ± 7.17 | 8.61 | 0.000* |
| TG (mmol/L) | 1.12 ± 0.85 | 1.23 ± 1 | 1.31 ± 0.95 | 1.56 ± 1.19 | 1.3 ± 1.02 | 93.35 | 0.000* |
| TC (mmol/L) | 4.75 ± 1 | 4.79 ± 0.97 | 4.83 ± 0.99 | 5.02 ± 1.06 | 4.85 ± 1.01 | 37.54 | 0.000* |
| LDL (mmol/L) | 2.05 ± 0.93 | 2.14 ± 0.81 | 2.19 ± 0.73 | 2.24 ± 0.72 | 2.16 ± 0.81 | 27.17 | 0.000* |
| HDL (mmol/L) | 1.54 ± 0.37 | 1.57 ± 0.35 | 1.58 ± 0.36 | 1.6 ± 0.39 | 1.57 ± 0.37 | 12.02 | 0.000* |
| FBG (mmol/L) | 5.11 ± 1.4 | 5.08 ± 1.14 | 5.09 ± 1.12 | 5.15 ± 1.27 | 5.1 ± 1.24 | 1.58 | 0.193 |
| Cr (mmol/L) | 74.8 ± 17.18 | 78.08 ± 21.53 | 79.57 ± 23.39 | 80.45 ± 19.15 | 78.21 ± 20.56 | 39.06 | 0.000* |
| BMI ($kg/m^2$) | 23.1 ± 3.34 | 23.53 ± 3.3 | 23.98 ± 3.39 | 24.65 ± 3.62 | 23.81 ± 3.46 | 98.18 | 0.000* |
| eGRF ($mL/min \cdot 1.73\ m^2$) | 87.28 ± 22.18 | 84.16 ± 22.87 | 82.43 ± 21.46 | 79.5 ± 19.07 | 83.37 ± 21.64 | 60.48 | 0.000* |
| Log CRP | -0.3 ± 0.69 | -0.28 ± 0.65 | -0.17 ± 0.64 | 0 ± 0.63 | -0.19 ± 0.66 | 112.14 | 0.000* |
| Smoking (*N*, %) | 18 (0.67) | 19 (0.72) | 19 (0.71) | 36 (1.39) | 92 (0.87) | 10.71 | 0.013 * |
| High salt intake (*N*, %) | 180 (6.76) | 161 (6.08) | 157 (5.88) | 183 (7.05) | 681 (6.44) | 3.98 | 0.264 |
| Drinking (*N*, %) | 12 (0.45) | 9 (0.34) | 16 (0.6) | 20 (0.77) | 57 (0.54) | 5.14 | 0.162 |
| Family history of hypertension (*N*, %) | 472 (17.64) | 416 (15.7) | 488 (18.28) | 517 (19.89) | 1893 (17.87) | 16.10 | 0.001* |
| MI (*N*, %) | 2 (0.07) | 6 (0.23) | 6 (0.22) | 9 (0.35) | 23 (0.22) | 4.52 | 0.210 |
| Cerebral stroke (*N*, %) | 5 (0.19) | 6 (0.23) | 7 (0.26) | 14 (0.54) | 32 (0.3) | 6.66 | 0.084 |
| Malignant tumor history (*N*, %) | 9 (0.34) | 7 (0.26) | 15 (0.56) | 13 (0.5) | 44 (0.42) | 3.70 | 0.296 |

*BMI* body mass index, *Cr* creatinine, *DBP* diastolic blood pressure, *eGRF* estimated glomerular filtration rate, *FBG* fasting blood glucose, *HDL* high-density lipoprotein, *Log CRP* log transformed C-reactive protein, *LDL* low-density lipoprotein, *MI* myocardial infarction, *SBP* systolic blood pressure, *SUA* serum uric acid, *TC* total cholesterol, *TG* triglyceride, *UA* uric acid

*$P < 0.05$

**Table 2** Baseline characteristics of included male subjects

| Quartiles of SUA | M1 | M2 | M3 | M4 | Total | $F/X^2$ | *P* |
|---|---|---|---|---|---|---|---|
| (μmol/L) | UA ≤ 243 | 243 < UA ≤ 290 | 290 < UA ≤ 344 | UA > 344 | | | |
| Number | 7169 | 7174 | 7200 | 7097 | 28,640 | | |
| UA (μmol/L) | 205.81 ± 30.85 | 267.64 ± 13.29 | 315.92 ± 15.4 | 400.63 ± 53.59 | 297.26 ± 78.12 | 45,746.77 | 0.000* |
| Age (years) | 47.54 ± 11.5 | 47.37 ± 11.5 | 47.16 ± 12.04 | 47.14 ± 12.69 | 47.31 ± 11.94 | 1.83 | 0.139 |
| SBP (mmHg) | 117.94 ± 10.46 | 118.08 ± 10.64 | 118.18 ± 10.75 | 118.84 ± 10.39 | 118.26 ± 10.57 | 10.15 | 0.000* |
| DBP (mmHg) | 76.7 ± 6.57 | 76.9 ± 6.68 | 77.06 ± 6.71 | 77.62 ± 6.34 | 77.07 ± 6.59 | 25.40 | 0.000* |
| TG (mmol/L) | 1.44 ± 1.19 | 1.47 ± 1.21 | 1.59 ± 1.27 | 1.92 ± 1.56 | 1.6 ± 1.33 | 202.83 | 0.000* |
| TC (mmol/L) | 4.71 ± 1.16 | 4.84 ± 1.12 | 4.91 ± 1.07 | 5.01 ± 1.06 | 4.87 ± 1.11 | 95.18 | 0.000* |
| LDL (mmol/L) | 2.28 ± 0.85 | 2.32 ± 0.8 | 2.33 ± 0.79 | 2.34 ± 0.81 | 2.32 ± 0.81 | 5.78 | 0.001* |
| HDL (mmol/L) | 1.53 ± 0.39 | 1.53 ± 0.38 | 1.52 ± 0.38 | 1.49 ± 0.38 | 1.52 ± 0.38 | 16.47 | 0.000* |
| FBG (mmol/L) | 5.48 ± 1.8 | 5.34 ± 1.47 | 5.26 ± 1.23 | 5.21 ± 1.08 | 5.32 ± 1.43 | 49.73 | 0.000* |
| Cr (mmol/L) | 89.74 ± 26.56 | 91.58 ± 24.58 | 92.11 ± 20.42 | 94.69 ± 28.29 | 92.02 ± 25.18 | 47.06 | 0.000* |
| BMI ($kg/m^2$) | 23.92 ± 3.11 | 24.2 ± 3.11 | 24.68 ± 3.21 | 25.47 ± 3.25 | 24.57 ± 3.22 | 325.18 | 0.000* |
| eGRF($mL/min \cdot 1.73\ m^2$) | 90.19 ± 25.89 | 88.45 ± 26.83 | 87.59 ± 25 | 85.87 ± 23.5 | 88.03 ± 25.39 | 35.91 | 0.000* |
| Log CRP | −0.25 ± 0.72 | −0.26 ± 0.66 | −0.2 ± 0.64 | −0.09 ± 0.62 | −0.2 ± 0.67 | 90.80 | 0.000* |
| Smoking (*N*, %) | 2672 (37.27) | 2966 (41.34) | 3150 (43.75) | 3325 (46.85) | 12,113 (42.29) | 143.38 | 0.000* |
| High salt intake (*N*, %) | 779 (10.9) | 757 (10.57) | 857 (11.91) | 932 (13.14) | 3325 (11.63) | 27.86 | 0.000* |
| Drinking (*N*, %) | 1267 (17.67) | 1463 (20.39) | 1616 (22.44) | 1919 (27.04) | 6265 (21.88) | 195.41 | 0.000* |
| Family history of hypertension (*N*, %) | 820 (11.44) | 972 (13.55) | 1075 (14.93) | 1243 (17.51) | 4110 (14.35) | 112.99 | 0.000* |
| MI (*N*, %) | 43 (0.6) | 40 (0.56) | 65 (0.9) | 70 (0.99) | 218 (0.76) | 13.08 | 0.004* |
| Cerebral stroke (*N*, %) | 48 (0.67) | 56 (0.78) | 74 (1.03) | 92 (1.3) | 270 (0.94) | 17.83 | 0.000* |
| Malignant tumor history (*N*, %) | 15 (0.21) | 13 (0.18) | 8 (0.11) | 24 (0.34) | 60 (0.21) | 9.23 | 0.026* |

*BMI* body mass index, *Cr* creatinine, *DBP* diastolic blood pressure, *eGRF* estimated glomerular filtration rate, *FBG* fasting blood glucose, *HDL* high-density lipoprotein, *Log CRP* log transformed C-reactive protein, *LDL* low-density lipoprotein, *MI* myocardial infarction, *SBP* systolic blood pressure, *SUA* serum uric acid, *TC* total cholesterol, *TG* triglyceride, *UA* uric acid

*$P < 0.05$

1.98), respectively, in groups F2 to F4 compared to F1 and 1.01 (0.95–1.09), 1.14 (1.06–1.22), and 1.36 (1.27–1.45), respectively, in groups M2 to M4 compared to M1.

The first adjusted model (model 2, Tables 4 and 5) adjusted for baseline age, SBP, DBP, FBG, TG, TC, HDL, LDL, BMI, and log CRP on the basis of model 1. The ORs (95 % CI) were 1.17 (1.00–1.37), 1.25 (1.07–1.46), and 1.21 (1.03–1.42), respectively, in F2 to F4 compared to F1 and 0.99 (0.92–1.07), 1.08 (1.00–1.16), and 1.18 (1.09–1.27), respectively, in M2 to M4 compared to M1.

The second adjusted model (model 3, Tables 4 and 5) further adjusted for high salt intake, smoking, drinking, history of MI, history of cerebral stroke, and family history of hypertension. This model showed the same results as model 2 in women, whereas only M4 remained statistically significant in men when compared to M1 ($P < 0.05$, Tables 4 and 5).

## Discussion

We found that the incidence of hypertension after 4 years of follow-up was statistically significantly higher with the increasing baseline levels of SUA in adults, even after adjusting for potential confounding factors, suggesting that higher baseline SUA is an independent risk factor for hypertension.

**Table 3** Incidence of hypertension by gender, SUA quartiles

| | | Q1 | Q2 | Q3 | Q4 | Total | $X^2$ | *P* |
|---|---|---|---|---|---|---|---|---|
| Women | Number of subjects | 384 | 439 | 509 | 581 | 1913 | 62.99 | 0.000* |
| | Cumulative incidence (%) | 14.36 | 16.57 | 19.06 | 22.35 | 18.06 | | |
| Men | Number of subjects | 2412 | 2437 | 2631 | 2891 | 10,371 | 99.27 | 0.000* |
| | Cumulative incidence (%) | 33.64 | 33.97 | 36.54 | 40.74 | 36.21 | | |

*SUA* serum uric acid, *Q* quartile

*$P < 0.05$

**Table 4** Logistic regression analysis of hypertension (women)

| | | *B* | SE | Wald | *P* | OR (95 % CI) |
|---|---|---|---|---|---|---|
| Model 1 | F1 | | | 62.38 | 0.000* | |
| | F2 | 0.17 | 0.08 | 5.00 | 0.025* | 1.19 (1.02–1.38) |
| | F3 | 0.34 | 0.07 | 21.17 | 0.000* | 1.41 (1.22–1.62) |
| | F4 | 0.54 | 0.07 | 55.67 | 0.000* | 1.72 (1.49–1.98) |
| Model 2 | F1 | | | 8.52 | 0.036* | |
| | F2 | 0.16 | 0.08 | 3.69 | 0.055 | 1.17 (1.00–1.37) |
| | F3 | 0.22 | 0.08 | 7.55 | 0.006* | 1.25 (1.07–1.46) |
| | F4 | 0.19 | 0.08 | 5.49 | 0.019* | 1.21 (1.03–1.42) |
| Model 3 | F1 | | | 7.80 | 0.050 | |
| | F2 | 0.16 | 0.08 | 3.69 | 0.055 | 1.17 (1.00–1.37) |
| | F3 | 0.21 | 0.08 | 6.92 | 0.009* | 1.24 (1.06–1.45) |
| | F4 | 0.18 | 0.08 | 4.91 | 0.027* | 1.20 (1.02–1.41) |

Model 1: univariate logistic analysis. Model 2: adjusted for baseline age (years), SBP, DBP, FBG, TG, TC, HDL, LDL, BMI, and log CRP. Model 3: adjusted for baseline age (years), SBP, DBP, FBG, TG, TC, HDL, LDL, BMI, log CRP, high salt intake, smoking, drinking, history of MI, history of cerebral stroke, and family history of hypertension

*BMI* body mass index, *CI* confidence interval, *Log CRP* log transformed C-reactive protein, *DBP* diastolic blood pressure, *FBG* fasting blood glucose, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *MI* myocardial infarction, *OR* odds ratio, *SBP* systolic blood pressure, *SE* standard error, *TC* total cholesterol, *TG* triglyceride

*$P < 0.05$

**Table 5** Logistic regression analysis of hypertension (men)

| | | *B* | SE | Wald | *P* | OR (95 % CI) |
|---|---|---|---|---|---|---|
| Model 1 | M1 | | | 99.03 | 0.000* | |
| | M2 | 0.01 | 0.04 | 0.17 | 0.681 | 1.01 (0.95–1.09) |
| | M3 | 0.13 | 0.03 | 13.23 | 0.000* | 1.14 (1.06–1.22) |
| | M4 | 0.30 | 0.03 | 76.60 | 0.000* | 1.36 (1.27–1.45) |
| Model 2 | M1 | | | 26.61 | 0.000* | |
| | M2 | -0.01 | 0.04 | 0.04 | 0.851 | 0.99 (0.92–1.07) |
| | M3 | 0.07 | 0.04 | 3.74 | 0.053 | 1.08 (1.00–1.16) |
| | M4 | 0.17 | 0.04 | 18.77 | 0.000* | 1.18 (1.09–1.27) |
| Model 3 | M1 | | | 16.82 | 0.001* | |
| | M2 | -0.02 | 0.04 | 0.39 | 0.534 | 0.98 (0.91–1.05) |
| | M3 | 0.05 | 0.04 | 1.72 | 0.190 | 1.05 (0.98–1.13) |
| | M4 | 0.12 | 0.04 | 9.98 | 0.002* | 1.13 (1.05–1.22) |

Model 1: univariate logistic analysis. Model 2: adjusted for baseline age (years), SBP, DBP, FBG, TG, TC, HDL, LDL, BMI, and log CRP. Model 3: adjusted for baseline age (years), SBP, DBP, FBG, TG, TC, HDL, LDL, BMI, log CRP, high salt intake, smoking, drinking, history of MI, history of cerebral stroke, and family history of hypertension

*BMI* body mass index, *CI* confidence interval, *log CRP* log transformed C-reactive protein, *DBP* diastolic blood pressure, *FBG* fasting blood glucose, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *MI* myocardial infarction, *OR* odds ratio, *SBP* systolic blood pressure, *SE* standard error, *TC* total cholesterol, *TG* triglyceride

*$P < 0.05$

It should be noted that our cohort is relatively "older" compared to other studies with mean ages of 44.72 ± 10.54 years for women and 47.31 ± 11.94 years for men. Previous studies suggest that the relationship between SUA and hypertension is stronger in younger subjects; however, our results suggested that SUA was also a risk factor in adults, independent of other risk factors. A review including the past 20 years' related studies supported a role for uric acid as a "true" cardiovascular risk factor, particularly for the development of hypertension [15]. A meta-analysis of 18 prospective studies with a total of 55,607 subjects concluded that high level of SUA was an independent risk factor for hypertension with an RR value of 1.41 (1.23–1.58) compared to the normal level of SUA [16]. The RR for incident hypertension after adjusting for potential confounding factors was 1.13 (1.06–1.20) with each increase of 1 mg/dL in SUA level, which was comparable to our study. The impact of UA should be taken into consideration in the treatment of hypertension.

In the present study, 32.7 % of the normotensive subjects at baseline developed hypertension after 2 years of follow-up, and this rate is higher than previously reported in the Framingham Heart study and other studies [8]. This may be due to several factors. First, Framingham Heart study and the other studies were conducted earlier than our study. The incidence of hypertension has increased dramatically during the last decades. In 2002, the prevalence of hypertension was 20 % among men and 17 % among women based on the China National Nutrition and Health Survey [17]. In 2009–2010, that has increased to 29.6 % (95 % CI 28.9–30.4 %) based on a representative sampling study [18]. These estimates may still underrepresent the true prevalence of hypertension, especially for men and those living in rural areas without health insurance. Second, we included different study participants. Our study included a higher proportion of men, and prevalence of hypertension is higher in men compared to women. As this cohort included current and retired employees of the Kailuan Group and their families, the ratio of male to female participants was 2.7, compared to 0.8 in the Framingham Heart Study. In addition, our study sample was taken from the northern China, which has a higher prevalence of hypertension compared to southern China.

The elaborate mechanisms for the effect of SUA on hypertension are yet to be fully understood. Several hypotheses partly explain the phenomenon. One possible mechanism is that the UA deposition on the walls of blood vessels activates the renin-angiotensin system, inhibits the release of carbon monoxide, promotes inflammation, and later on leads to vasoconstriction, which subsequently leads to vascular smooth muscle hyperplasia and hypertension [2, 9, 19, 20]. This hypothesis is consistent with the finding of the present study that higher level of CRP was observed in subjects with higher level of SUA. Hyperuricemia could also induce hypertension by increasing renal tubular reabsorption of sodium [21].

The present study and other studies also confirm the association between high level of SUA and other comorbidities [22–24].

Hyperuricemia is known to coexist with hyperglycemia, dyslipidemia and obesity [25], which could induce microangiopathy and histanoxia related to hypertension. The risk of hypertension was slightly increased with FBG, TG, TC, and BMI, indicating that hyperglycemia, hypercholesterolemia, hypertriglyceridemia, and obesity were also co-risk factors for hypertension. Our study also showed that the prevalence of traditional cardiovascular risk factors increased with the rise in SUA level. However, after adjusting for traditional risk factors (age, SBP, DBP, FBG, TG, TC, HDL, LDL, BMI, log CRP, high salt intake, smoking, drinking, history of MI, history of cerebral stroke, and family history of hypertension), the increase in ORs of hypertension in groups F3, F4, and M4 remained statistically significant at 1.24, 1.20, and 1.13, respectively. These findings support the importance of multiple intervention strategies in the prevention and treatment of hypertension.

Another interesting finding is the greater relationship between uric acid and hypertension in females. Several studies have suggested a similar difference between genders in the correlation of SUA and artery diseases. Silent brain infarction and renal resistive index were associated with SUA only in women [26, 27]. It has also been reported that serum uric acid correlated with internal carotid artery resistive index and pulse wave velocity in women but not in men [28–30]. A systematic review and meta-analysis published in 2011 also indicated that women with the elevated level of uric acid were more vulnerable to hypertension than men [16]. Although data indicated that the sex difference was associated with increased uric acid level in men [31], further studies of the role of sex hormones are required to understanding the underline mechanisms of the sex differences. Effective strategies preventing complications of hyperuricemia should also focus on the sex difference.

There are limitations in the present study. First, 14,783 subjects in the study cohort did not undergo final examination during 2010 to 2011 and were excluded from the analysis. This population may have potential influence on the final results. However, sensitivity analysis including this population did not show any difference. Supplemental Tables 1 and 2 show the baseline characteristics of the study population and the excluded population. Second, female subjects were less than male subjects in the present study due to the nature of the Kailuan Community cohort. Third, the sample subjects in this study were limited to current and retired employees and their families of the Kailuan Group, so this was not a randomly selected sample necessarily representative of the general population in the area. However, the large sample size of present study could produce adequate power and is worthy of reference.

In conclusion, the present study shows that elevated level of SUA is associated with an increased risk of hypertension in adults, especially in women.

## Perspectives

The association between hyperuricemia and hypertension has drawn resurgent attention over the past decade. The present study demonstrated that elevated level of SUA was an independent risk factor for hypertension in Chinese adults. Further experimental researches focusing on the potential pathological role of SUA on hypertension and clinical trials concerning the effect of urate-lowering therapy on the incidence of hypertension are worthy of being explored.

**Acknowledgements** We are very grateful to all participants for their cooperation and for giving consent to participate in this study. We thank all the staff for their dedication.

**Compliance with ethical standards**

**Disclosures** None.

**Funding** This study was supported by the National High Technology Research and Development Program of China (973 Program, No. 2012CB517700) and National Natural Science Foundation of China (No. 31170840 and No. 81471536).

## References

1. Liu LS, Writing Group of 2010 Chinese Guidelines for the Management of Hypertension (2010) 2010 Chinese guidelines for the management of hypertension. Zhonghua Xin Xue Guan Bing Za Zhi 39:579–616
2. Feig DI (2014) Serum uric acid and the risk of hypertension and chronic kidney disease. Curr Opin Rheumatol 26:176–185
3. Mellen PB, Bleyer AJ, Erlinger TP, Evans GW, Nieto FJ, Wagenknecht LE et al (2006) Serum uric acid predicts incident hypertension in a biethnic cohort: the atherosclerosis risk in communities study. Hypertension 48:1037–1042
4. Syamala S, Li J, Shankar A (2007) Association between serum uric acid and prehypertension among US adults. J Hypertens 25:1583–1589
5. Yoo TW, Sung KC, Shin HS, Kim BJ, Kim BS, Kang JH et al (2005) Relationship between serum uric acid concentration and insulin resistance and metabolic syndrome. Circ J 69:928–933
6. Kansui Y, Ohtsubo T, Goto K, Sakata S, Ichishima K, Fukuhara M et al (2011) Association of serum uric acid with blood pressure in Japanese men. Cross-sectional study in work-site quartile. Circ J 75:2827–2832
7. Taniguchi Y, Hayashi T, Tsumura K, Endo G, Fujii S, Okada K (2001) Serum uric acid and the risk for hypertension and type 2 diabetes in Japanese men: the Osaka Health Survey. J Hypertens 19:1209–1215
8. Sundstrom J, Sullivan L, D'Agostino RB, Levy D, Kannel WB, Vasan RS (2005) Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence. Hypertension 45:28–33
9. Perlstein TS, Gumieniak O, Williams GH, Sparrow D, Vokonas PS, Gaziano M et al (2006) Uric acid and the development of hypertension: the normative aging study. Hypertension 48:1031–1036
10. Xiong Z, Zhu C, Qian X, Zhu J, Wu Z, Chen L (2013) Serum uric acid is associated with dietary and lifestyle factors in elderly women in suburban Guangzhou in Guangdong province of South China. J Nutr Health Aging 17:30–34
11. Villegas R, Xiang YB, Cai Q, Fazio S, Linton M, Li H et al (2010) Prevalence and determinants of hyperuricemia in middle-aged, urban Chinese men. Metab Syndr Relat Disord 8:263–270

12. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL et al (2001) Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension 38:1101–1106
13. Feig D, Soletsky B, Johnson R (2008) Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension. JAMA 300:924–932
14. Wu S, Li Y, Jin C, Yang P, Li D, Li H, Shen C (2012) Intra-individual variability of high-sensitivity C-reactive protein in Chinese general population. Int J Cardiol 157:75–79
15. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S et al (2003) Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension 41:1183–1190
16. Grayson PC, Kim SY, LaValley M, Choi HK (2011) Hyperuricemia and incident hypertension: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 63:102–110
17. Wu Y, Huxley R, Li L, Anna V, Xie G, Yao C, Woodward M, Li X, Chalmers J, Gao R, Kong L, Yang X, For the China NNHS Steering Committee (2008) Prevalence, awareness, treatment, and control of hypertension in China: data from the China National Nutrition and Health Survey 2002. Circulation 118:2679–2686
18. Wang J, Zhang L, Wang F, Liu L, Wang H, China National Survey of Chronic Kidney Disease Working Group (2014) Prevalence, awareness, treatment, and control of hypertension in China: results from a national survey. Am J Hypertens 27:1355–1361
19. Kang DH, Park SK, Lee IK, Johnson RJ (2005) Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. J Am Soc Nephrol 16:3553–3562
20. Perlstein TS, Gumieniak O, Hopkins PN, Murphey LJ, Brown NJ, Williams GH et al (2004) Uric acid and the state of the intrarenal renin-angiotensin system in humans. Kidney Int 66:1465–1470
21. Cappuccio FP, Strazzullo P, Farinaro E, Trevisan M (1993) Uric acid metabolism and tubular sodium handling. Results from a population-based study. JAMA 270:354–359
22. Bombelli M, Ronchi I, Volpe M, Facchetti R, Carugo S, Dell'oro R et al (2014) Prognostic value of serum uric acid: new-onset in and out-of-office hypertension and long-term mortality. J Hypertens 32:1237–1244
23. Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA (2009) Hyperuricemia and risk of stroke: a systematic review and meta-analysis. Arthritis Rheum 61:885–892
24. Liu Y, Jin C, Xing A, Liu X, Chen S, Li D et al (2013) Serum uric acid levels and the risk of impaired fasting glucose: a prospective study in adults of North China. PLoS One 8:e84712
25. Pogodina AV, Dolgikh VV, Rychkova LV (2014) Uric acid and factors of cardiometabolic risk in adolescents with arterial hypertension. Kardiologiia 54:36–42
26. Heo SH, Lee SH (2010) High levels of serum uric acid are associated with silent brain infarction. J Neurol Sci 297:6–10
27. Viazzi F, Leoncini G, Ratto E, Falqui V, Parodi A, Conti N et al (2007) Mild hyperuricemia and subclinical renal damage in untreated primary hypertension. Am J Hypertens 20:1276–1282
28. Cipolli JA, Ferreira-Sae MC, Martins RP, Pio-Magalhães JA, Bellinazzi VR, Matos-Souza JR, Junior WN (2012) Relationship between serum uric acid and internal carotid resistive index in hypertensive women: a cross-sectional study. BMC Cardiovasc Disord 12:52
29. Gómez-Marcos MA, Recio-Rodríguez JI, Patino-Alonso MC, Agudo-Conde C, Rodríguez-Sánchez E, Gómez-Sánchez L et al (2013) Relationship between uric acid and vascular structure and function in hypertensive patients and sex-related differences. Am J Hypertens 26:599–607
30. Fang JI, Wu JS, Yang YC, Wang RH, Lu FH, Chang CJ (2014) High uric acid level associated with increased arterial stiffness in apparently healthy women. Atherosclerosis 236:389–393
31. Samimi A, Ramesh S, Turin TC, MacRae JM, Sarna MA, Reimer RA et al (2014) Serum uric acid level, blood pressure, and vascular angiotensin II responsiveness in healthy men and women. Physiol Rep 2(12):e12235