

## ARTICLE



# Mediating effects of insulin resistance on the development of hypertension associated with elevated serum uric acid: a prospective cohort study

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Many studies have demonstrated that elevated serum uric acid independently increases the risk of developing hypertension. However, the role of insulin resistance in the relationship between serum uric acid and hypertension is still unelucidated. Based on a prospective cohort study, we aimed to examine the longitudinal link between serum uric acid and hypertension and whether this relationship was mediated by insulin resistance. Overall, 21,999 participants without hypertension or gout at baseline with a mean age of  $46 \pm 13$  years in the Jinchang Cohort were included in our study. Adjusted Cox-regression analyses and mediation analyses were performed to assess the risk of hypertension by serum uric acid quartile distribution and whether insulin resistance mediated the association between serum uric acid and hypertension. During the first follow-up period, 3080 participants developed hypertension. After controlling for covariates, compared with the lowest quartile of serum uric acid, the risk of hypertension in the highest quartile was 1.21 (1.06, 1.38) in the overall population. The risks for males and females were 1.14 (1.00–1.29) and 1.30 (1.08–1.56), respectively. The correlation between serum uric acid and hypertension was especially observed in younger people (<30 years). The mediating effects of insulin resistance were 0.058 (0.051, 0.065), 0.030 (0.025, 0.036) and 0.056 (0.047, 0.065), and the proportions mediated were 39.73, 36.59 and 38.62% in the overall, male and female populations, respectively. Elevated serum uric acid levels are associated with an increased risk of incident hypertension, and insulin resistance may play a mediating role in the relationship between serum uric acid and hypertension.

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## INTRODUCTION

As one of the important secondary metabolites of purine nucleotides, serum uric acid (SUA) has been shown to be adversely associated with metabolic syndrome, diabetes, kidney disease, cardiovascular diseases (CVDs), etc. [1–3]. SUA has long been considered a powerful risk factor for future hypertension [4]. Numerous observational studies have demonstrated that exposure to high SUA levels was independently associated with the risk of incident hypertension [5–7]. A meta-analysis revealed that the RR for hypertension was 1.13 (95% confidence interval (CI): 1.06–1.20) for each 1 mg/dL increase in SUA, and this relationship was more pronounced in females and young individuals [8]. However, as lifestyle-related disorders, hyperuricaemia usually coexists with metabolic abnormalities such as dyslipidaemia, obesity, hyperglycaemia and insulin resistance. It is unclear what roles metabolic abnormalities play in the development of hypertension associated with elevated SUA.

Animal experiments have indicated that elevated SUA probably induces insulin resistance by inhibiting the IRS1 and Akt insulin signalling pathways [9]. Insulin resistance could significantly increase the risk of hypertension [10]. SUA and an insulin resistance marker (HOMA-IR) above the median synergistically

promoted arterial stiffness [11], which is considered to be a crucial physiological mechanism in the development of hypertension [12]. A previous study employed a cross-lagged panel model and mediation analysis to conclude that hyperuricaemia preceded insulin resistance, and that insulin resistance played a mediating role in the relationship between hyperuricaemia and hypertension [13]. The link between SUA, insulin resistance and hypertension remains to be elucidated.

Based on a prospective cohort study, our research aimed to evaluate the relationship between SUA and incident hypertension, by sex and age. Moreover, mediation analyses were applied to further explore whether insulin resistance played mediating effects on the SUA-correlated incidence of hypertension.

## MATERIALS AND METHODS

### Study population

As previously described elsewhere, the Jinchang Cohort study is an ongoing prospective cohort study in Gansu province, China [14]. Briefly, the baseline data of the Jinchang Cohort were collected during a cross-sectional biannual medical exam conducted in 2011–2013. A total of 48,001 workers completed all four components of the health examinations:

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in-person interviews, physical exams, laboratory tests and donation of blood and urine samples. The mean age of the participants was  $46 \pm 13$  years. The follow-up was initiated after the baseline data collection at an average interval of 2 years. A total of 37,040 participants finished the first follow-up survey in 2015, and the most recent follow-up survey was completed in September 2020. A total of 33,355 follow-up participants were 100% matched with baseline data by employee ID and health insurance ID. To eliminate the potential bias caused by participants with hypertension at baseline, 9595 and 113 patients with hypertension and gout at baseline were excluded from the initial study population. In addition, 1646 individuals without SUA, total cholesterol (TC) or FPG results were further excluded from our study population. Eventually, a total of 21,999 subjects who were hypertension-free and gout-free were selected as our study population for final analysis. All participants signed an informed consent agreement. Our research was approved by the Ethics Committee of Jinchang Industrial Workers Hospital and the Ethics Committee of Public Health School of Lanzhou University. The specific inclusion and exclusion criteria are shown in Supplementary Fig. 1.

### Data collection

After receiving informed consent, an in-person epidemiological survey was conducted by uniformly trained investigators with a standardised questionnaire that included basic demographic characteristics, lifestyle behaviours such as smoking, alcohol consumption status and physical exercise, past medical history and occupational history. At least two measurements of brachial BP were automatically measured by well-trained staffs both for baseline and follow-up surveys. The mean value of the two measurements for each participant was recorded as the final value. Three 6 mL of fasting blood samples were taken from each participant for laboratory testing. Blood biochemical indicators including SUA, TC, triglycerides (TGs), FPG, etc. were automatically tested by biochemical analysers (7 600-020, Kyoto, Japan) produced by Hitachi.

### Outcomes and study variables

Participants with systolic blood pressure above 140 mmHg, diastolic blood pressure above 90 mmHg, self-reported hypertension or definite clinical records of hypertension were defined as hypertensive patients [15]. Diabetes mellitus was defined according to FPG  $\geq 7.0$  mmol/L, self-reported diabetes or definite clinical records of diabetes [16]. At least one of the following criteria needed to be met for a participant to be diagnosed with dyslipidaemia: (1) TC  $\geq 6.22$  mmol/L; (2) total TGs  $\geq 2.26$  mmol/L; (3) low-density lipoprotein  $\geq 4.14$  mmol/L and (4) low-density lipoprotein  $< 1.04$  mmol/L [17].

The smoking index (pack-year) and alcohol index (kilogram-year) were used to quantitatively assess the participants' lifetime consumption of tobacco and alcohol. The smoking index (pack-year) was calculated as smoking packs per day  $\times$  years of smoking. The alcohol index (kilogram-year) was calculated as kilograms of alcoholic beverage per day  $\times$  years of drinking  $\times$  alcohol content. In detail, alcohol content was defined by the quantity of pure ethyl alcohol intake that was determined according to alcohol coefficients of each type of alcoholic beverage. The detailed alcohol coefficients were defined as follows: white wine was 54%, red wine was 12% and beer was 4%. The TG glucose product (TyG) index was calculated as  $\ln[\text{TG} (\text{mg/dL}) \times \text{FPG} (\text{mg/dL})/2]$ , which was an indicator of insulin resistance used in economically underdeveloped areas [18].

### Statistical analysis

All continuous variables are described as the median (interquartile range), and categorical variables are presented as group counts (percentages). Comparisons of baseline characteristics between hypertensive subjects and nonhypertensive subjects were performed by the  $\chi^2$  test or rank sum test.

When analysing the association between SUA and the risk of hypertension, SUA concentration was stratified in quartiles according to the SUA distribution of the nonhypertensive population. The Cox proportional hazards model was employed to evaluate hazard ratios (HRs) of the incidence of hypertension with 95% CIs. The median of each quartile group included as a continuous variable in the regression model for the linear trend test. Subgroup analyses were conducted to determine whether differences existed in the risk of hypertension, and subgroup analyses were conducted for sex (male, female) and age group ( $< 30$  years

**Table 1.** Baseline characteristics of Jinchang Cohort study population, stratified by hypertension incidence.

| Characteristics                | Hypertension<br>(n = 3080) | Nonhypertension<br>(n = 18919) | P value |
|--------------------------------|----------------------------|--------------------------------|---------|
| Sex                            |                            |                                |         |
| Male                           | 2093 (67.95)               | 10819 (57.19)                  | <0.05   |
| Female                         | 987 (32.05)                | 8100 (42.81)                   |         |
| Age (years)                    |                            |                                |         |
| <30                            | 219 (7.11)                 | 2420 (12.79)                   | <0.05   |
| 30–39                          | 410 (13.31)                | 4504 (23.81)                   |         |
| 40–49                          | 1136 (36.88)               | 8196 (43.32)                   |         |
| 50–59                          | 474 (15.39)                | 2038 (10.77)                   |         |
| 60–69                          | 596 (19.35)                | 1329 (7.02)                    |         |
| $\geq 70$                      | 245 (7.95)                 | 432 (2.28)                     |         |
| Education level                |                            |                                |         |
| Primary school or illiterate   | 587 (19.06)                | 1284 (6.79)                    | <0.05   |
| Middle school                  | 1622 (52.66)               | 9940 (52.54)                   |         |
| Junior college                 | 549 (17.82)                | 4524 (23.91)                   |         |
| Bachelor's degree or above     | 322 (10.45)                | 3161 (16.71)                   |         |
| Smoking index (pack-year)      |                            |                                |         |
| 0                              | 1558 (50.58)               | 10950 (57.88)                  | <0.05   |
| 0–7.00                         | 307 (9.97)                 | 2311 (12.22)                   |         |
| 7.01–15.30                     | 357 (11.59)                | 1927 (10.19)                   |         |
| 15.31–26.00                    | 363 (11.79)                | 1979 (10.46)                   |         |
| $\geq 26.01$                   | 495 (16.07)                | 1752 (9.26)                    |         |
| Alcohol index (kilogram-year)  |                            |                                |         |
| 0                              | 2229 (72.37)               | 15177 (80.22)                  | <0.05   |
| 0–56.31                        | 162 (5.26)                 | 1006 (5.24)                    |         |
| 56.32–140.79                   | 192 (6.23)                 | 955 (5.05)                     |         |
| 140.80–312.54                  | 231 (7.50)                 | 917 (4.88)                     |         |
| $\geq 312.55$                  | 266 (8.64)                 | 864 (4.60)                     |         |
| Family history of hypertension |                            |                                |         |
| Yes                            | 1176 (38.18)               | 7067 (37.35)                   | 0.39    |
| No                             | 1904 (61.82)               | 11852 (62.65)                  |         |
| BMI (kg/m <sup>2</sup> )       |                            |                                |         |
| <18.5                          | 56 (1.82)                  | 1237 (6.54)                    | <0.05   |
| 18.5–23.9                      | 1450 (47.08)               | 12029 (63.58)                  |         |
| 24.0–27.9                      | 1250 (40.58)               | 4843 (25.60)                   |         |
| $\geq 28.0$                    | 324 (10.52)                | 810 (4.28)                     |         |
| SUA ( $\mu\text{mol/L}$ )      | 330.00 (106.75)            | 309.00 (108.00)                | <0.05   |
| SBP (mmHg)                     | 126.00 (14.00)             | 114.00 (18.00)                 | <0.05   |
| DBP (mmHg)                     | 80.00 (10.00)              | 73.00 (12.00)                  | <0.05   |
| TC (mmol/L)                    | 4.70 (1.10)                | 4.50 (1.10)                    | <0.05   |
| TGs (mmol/L)                   | 1.70 (1.30)                | 1.40 (1.10)                    | <0.05   |
| FPG (mmol/L)                   | 5.20 (0.90)                | 4.90 (0.70)                    | <0.05   |
| TyG                            | 6.56 (0.80)                | 6.32 (0.79)                    | <0.05   |
| Diabetes                       | 274 (8.90)                 | 641 (3.39)                     | <0.05   |
| Dyslipidemia                   | 1339 (43.47)               | 5905 (31.21)                   | <0.05   |

All numeric variables did not satisfy the normal distribution, presented as median (Interquartile ranges). Smoking index (pack-year) and alcohol index (kilogram-year) distribution were stratified based on the nonhypertension group. All categorical variables were presented as numbers (percentages). P Values were calculated using  $\chi^2$  tests and Wilcoxon test.

BMI body mass index, SUA serum uric acid, SBP systolic blood pressure, DBP diastolic blood pressure, TC total cholesterol, TGs total triglycerides, FPG fasting plasma glucose, TyG triglyceride glucose product.

**Table 2.** Hazard ratios (HRs) of hypertension incidence in Jinchang Cohort population stratified by SUA quartiles distribution.

| SUA ( $\mu\text{mol/L}$ ) <sup>a</sup> | Hypertension, <i>n</i> (%) | Nonhypertension, <i>n</i> (%) | HR (95% CI) <sup>b</sup> | HR (95% CI) <sup>c</sup> |
|--|----------------------------|-------------------------------|--------------------------|--------------------------|
| Q1 (<256)                              | 505 (16.40)                | 4752 (25.12)                  | 1.00 (Ref)               | 1.00 (Ref)               |
| Q2 (256–308)                           | 712 (23.12)                | 4785 (25.29)                  | 1.25 (1.12, 1.41)        | 1.07 (0.95, 1.21)        |
| Q3 (309–363)                           | 840 (27.27)                | 4656 (24.61)                  | 1.57 (1.40, 1.75)        | 1.17 (1.04, 1.33)        |
| Q4 ( $\geq 364$ )                      | 1023 (33.21)               | 4726 (24.98)                  | 1.78 (1.60, 1.98)        | 1.21 (1.06, 1.38)        |
| <i>P</i> for trend                     |                            |                               | <0.05                    | <0.05                    |

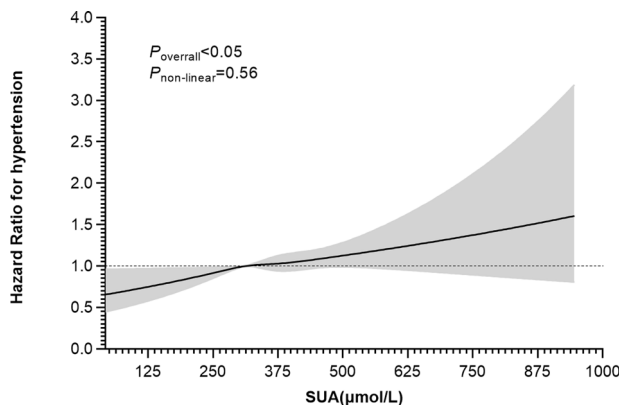
*P* for trend: The median of each group of SUA was treated as continuous variable into the model for trend test.

SUA serum uric acid, HR hazard ratio, CI confidence interval.

<sup>a</sup>Quartile distribution was stratified based on the SUA distribution on the nonhypertension population.

<sup>b</sup>Crude HRs without adjustment for confounding.

<sup>c</sup>Adjusted for age (<30, 30–59,  $\geq 60$ ), sex (male, female), education level (primary school or illiterate, middle school, junior college, bachelor's degree or above), smoking index (0, 0–6.60, 6.61–15.00, 15.01–25.00,  $\geq 25.01$ ), alcohol index (0, 0–53.50, 53.51–129.52, 129.53–295.65,  $\geq 295.66$ ), TC (<4.00, 4.01–4.50, 4.51–5.10,  $\geq 5.11$ ), TGs (<1.00, 1.00–1.40, 1.41–2.10,  $\geq 2.11$ ), exercise (no, yes), family history of hypertension (no, yes) and diabetes (no, yes).



**Fig. 1** Adjusted HRs for incident hypertension according serum uric acid concentration by restricted cubic spline model in Jinchang Cohort population. SUA serum uric acid. Adjusted for age (<30, 30–59,  $\geq 60$ ), sex (male, female), education level (primary school or illiterate, middle school, junior college, bachelor's degree or above), smoking index (0, 0–6.60, 6.61–15.00, 15.01–25.00,  $\geq 25.01$ ), alcohol index (0, 0–53.50, 53.51–129.52, 129.53–295.65,  $\geq 295.66$ ), TC (<4.00, 4.01–4.50, 4.51–5.10,  $\geq 5.11$ ), TGs (<1.00, 1.00–1.40, 1.41–2.10,  $\geq 2.11$ ), exercise (no, yes), family history of hypertension (no, yes) and diabetes (no, yes). The median of SUA was used as the reference value. Four knots of the restricted cubic spline model were 5th, 25th, 75th and 95th.

old, 30–59 years old,  $\geq 60$  years old). In addition, all confounding factors were included in the regression model in the form of categorical variables. Stepwise regression methods were further employed to exclude confounding factors that affected the HR value by less than 10%. Eventually, the following confounders were included in the regression models for final adjustment: age (<30, 30–59,  $\geq 60$ ), sex (male, female), education level (primary school or illiterate, middle school, junior college, bachelor's degree or above), smoking index (0, 0–6.60, 6.61–15.00, 15.01–25.00,  $\geq 25.01$ ), alcohol index (0, 0–53.50, 53.51–129.52, 129.53–295.65,  $\geq 295.66$ ), TC (<4.00, 4.01–4.50, 4.51–5.10,  $\geq 5.11$ ), TGs (<1.00, 1.00–1.40, 1.41–2.10,  $\geq 2.11$ ), exercise (no, yes), family history of hypertension (no, yes) and diabetes (no, yes). The restricted cubic spline model was used to fit the dose–response relationship between SUA and the risk of hypertension.

Bootstrapping approach-based mediation effect analysis was further employed to investigate mediation effects between SUA and hypertension [19]. Necessary confounding factors including exposure–outcome, mediator–outcome and exposure–mediator pathways were strictly controlled during the whole process of analysis. Furthermore, we reported mediation effects, direct effects and proportion mediated. All statistical analyses were carried out using SAS (Version 9.4; SAS Institute Inc., Cary, NC), R statistical environment (Version 3.6.1) and Mplus Editor (Version 8.0).  $P < 0.05$  was regarded as the significance level for all statistical tests, and all of the statistical tests were performed as two-sided tests.

## RESULTS

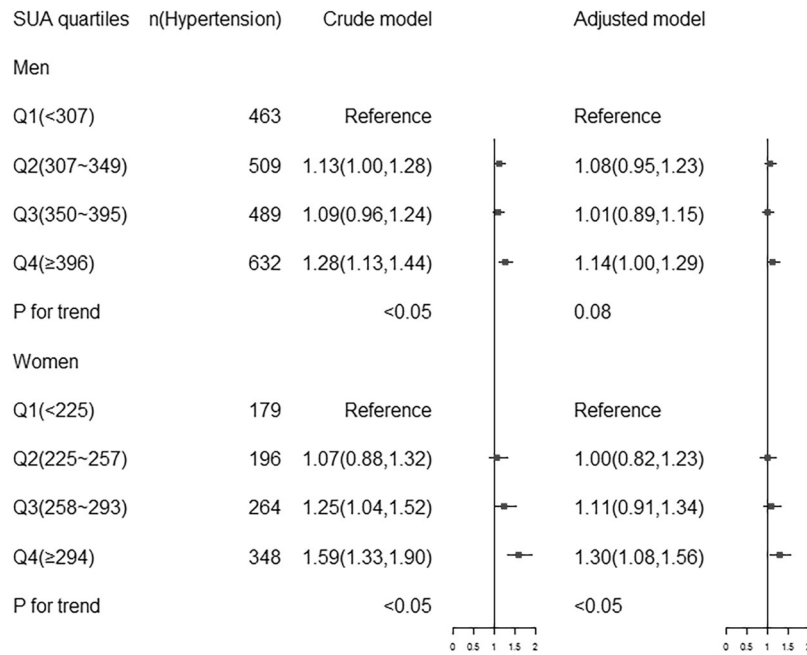
The selected characteristics of baseline participants stratified by incident hypertension are presented in Table 1. All of the selected demographic variables were significantly different between the incident hypertension group and the nonhypertension group, except for the family history of hypertension ( $P$  value < 0.05). The mean levels of SUA, SBP, DBP, TC, TGs, FPG and TyG were all significantly higher in the hypertensive group than in the nonhypertensive group. The prevalence of diabetes and dyslipidaemia was also higher in the hypertensive group than in the nonhypertensive group.

Table 2 demonstrates the HRs of hypertension incidence stratified by SUA quartile distribution. A total of 3080 participants developed hypertension after the first follow-up. In the total population, after adjusting for potential confounding factors, the multivariable-adjusted HRs and 95% CIs of the third and highest quartiles were 1.17 (1.04, 1.33) and 1.21 (1.06, 1.38), respectively, when compared with the lowest quartile of SUA. An increasing trend between the risk of hypertension and SUA quartile ( $P$  for trend < 0.05) was observed in both crude and multivariable-adjusted models. Figure 1 indicates a linear dose–response relationship between SUA and the risk of hypertension in the total population ( $P_{\text{overall}} < 0.05$ ,  $P_{\text{non-linear}} = 0.56$ ).

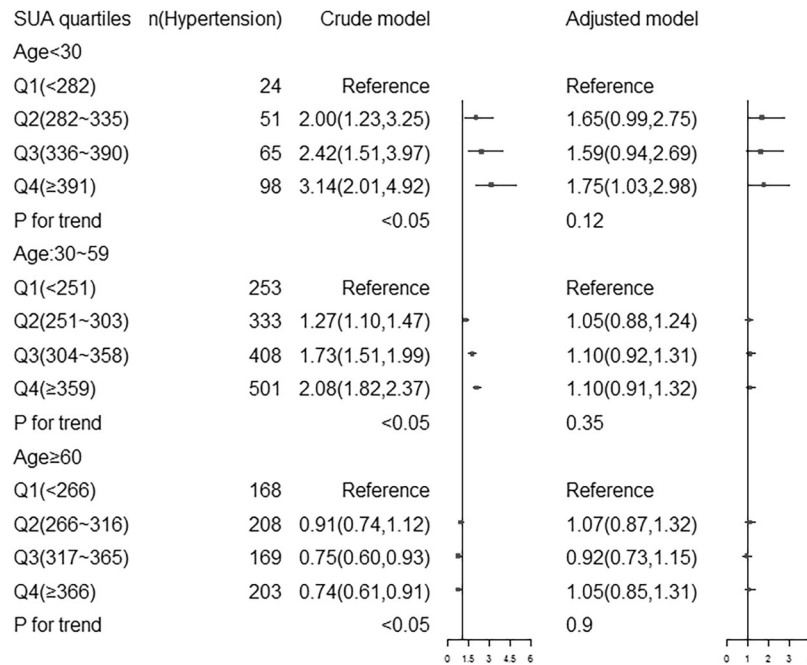
Sex subgroup analyses of SUA exposure levels and the risk of hypertension were further performed due to the SUA distribution difference between the male and female populations (Fig. 2). Both male and female populations demonstrated a positive association between SUA exposure and an increased risk of hypertension incidence in the fourth quartile of SUA compared with the first quartile of SUA (male: 1.14 (1.00–1.29), female: 1.30 (1.08–1.56)).

In the crude model, elevated SUA levels in the three age subgroups were associated with the risk of hypertension. After adjusting for potential confounders, SUA was only associated with hypertension in people under 30 years of age and was not associated with hypertension in people between 30 and 59 years or over 60 years. Taking the lowest quartile of SUA as a reference, the risk of hypertension morbidity in the highest quartile was 75% higher (HR = 1.75, 95% CI: 1.03–2.98) (Fig. 3).

Table 3 shows the mediating effect of the insulin resistance marker TyG on the association between baseline SUA and follow-up hypertension. After controlling for possible confounding factors, the association between SUA and hypertension was partially mediated by TyG. In the total population, the mediation effect was 0.058 (0.051, 0.065), and the proportion of the mediation effect by insulin resistance was 39.73%. The corresponding mediation effects among the male and female populations were 0.030 (0.025, 0.036) and 0.056 (0.047, 0.065), and the proportional mediation effects were 36.59% and 38.62%, respectively (Fig. 4).



**Fig. 2 Sex subgroups analysis of SUA quartiles distribution and hazard ratios (HRs) of hypertension incidence in Jinchang Cohort population.** SUA serum uric acid. Quartile distribution was stratified based on the SUA distribution on the nonhypertension population; crude HRs without adjustment for confounding; adjusted for age (<30, 30–59, ≥60), education level (primary school or illiterate, middle school, junior college, bachelor’s degree or above), exercise (no, yes), TGs (<1.00, 1.00–1.40, 1.41–2.10, ≥2.11), family history of hypertension (no, yes) and diabetes (no, yes) in adjusted model; *P* for trend: The median of each group of SUA was treated as continuous variable into the model for trend test.



**Fig. 3 Age subgroups analysis of SUA quartiles distribution and hazard ratios (HRs) of hypertension incidence in Jinchang Cohort population.** SUA serum uric acid. Quartile distribution was stratified based on the SUA distribution on the nonhypertension population. Crude HRs without adjustment for confounding. Adjusted for sex (male, female), smoking index (0, 0–6.60, 6.61–15.00, 15.01–25.00, ≥25.01), TGs (<1.00, 1.00–1.40, 1.41–2.10, ≥2.11), exercise (no, yes), family history of hypertension (no, yes) in adjusted model. *P* for trend: The median of each group of SUA was treated as continuous variable into the model for trend test.

**DISCUSSION**

Based on this prospective cohort study population, our study found that elevated SUA was an independent risk predictor of incident hypertension. The relationship between elevated SUA and incident

hypertension was not sex-specific, but a significantly increased risk of hypertension was only observed in people under 30 years of age. Mediation analysis further revealed that insulin resistance mediated the relationship between SUA and the development of hypertension.



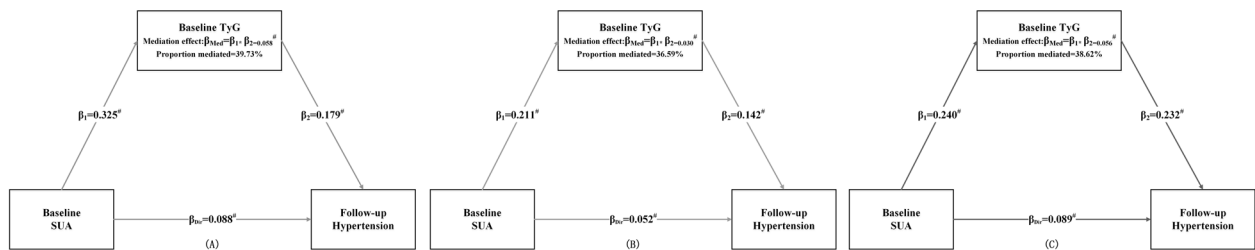
**Table 3.** Mediating effect between SUA and hypertension mediated by insulin resistance in Jinchang Cohort population.

| Metabolism factors | Direct effect          |         | Mediation effect       |         | Proportion mediated (%) <sup>a</sup> |
|--------------------|------------------------|---------|------------------------|---------|--------------------------------------|
|                    | $\beta_{Dir}$ (95% CI) | P value | $\beta_{Med}$ (95% CI) | P value |                                      |
| Total              |                        |         |                        |         |                                      |
| TyG                | 0.088 (0.067, 0.109)   | <0.05   | 0.058 (0.051, 0.065)   | <0.05   | 39.73                                |
| Men                |                        |         |                        |         |                                      |
| TyG                | 0.052 (0.026, 0.079)   | <0.05   | 0.030 (0.025, 0.036)   | <0.05   | 36.59                                |
| Women              |                        |         |                        |         |                                      |
| TyG                | 0.089 (0.054, 0.123)   | <0.05   | 0.056 (0.047, 0.065)   | <0.05   | 38.62                                |

Age (<30, 30–59, ≥60), sex (male, female), smoking index (0, 0–6.60, 6.61–15.00, 15.01–25.00, ≥25.01), alcohol drinking index (0, 0–53.50, 53.51–129.52, 129.53–295.65, ≥295.66) and exercise (no, yes) were controlled in all three pathways in total people. Age (<30, 30–59, ≥60), smoking index (0, 0–6.60, 6.61–15.00, 15.01–25.00, ≥25.01), alcohol drinking index (0, 0–53.50, 53.51–129.52, 129.53–295.65, ≥295.66) and exercise (no, yes) were controlled in all three pathways in men. Age (<30, 30–59, ≥60) and exercise (no, yes) were controlled for in all three pathways in women.

TyG triglyceride glucose product,  $\beta_{Dir}$   $\beta_{direction}$ ,  $\beta_{Med}$   $\beta_{mediation}$ , CI confidence interval.

<sup>a</sup>The ratio of mediating effect to total effect.



**Fig. 4** Mediation effects of baseline insulin resistance (TyG) on the association between baseline SUA and follow-up hypertension in Jinchang Cohort population. SUA serum uric acid, TyG triglyceride glucose product index,  $\beta_{Med}$   $\beta_{mediation}$ . **A** Total population. **B** Male population. **C** Female population. <sup>#</sup> $P < 0.05$ .

Both observational and experimental studies indicated that SUA was an independent risk factor for hypertension [20–22]. However, this adverse effect of SUA on hypertension incidence showed an obvious sex difference. Women with hyperuricaemia were more susceptible to developing CVD than men. A meta-analysis by Grayson et al. also revealed that although higher SUA exposure level could significantly increase the risk of incident hypertension, the female population demonstrated a higher risk (RR: 1.76, 95% CI: 1.46–2.05) of developing hypertension than the male population (RR: 1.38, 95% CI: 1.20–1.57) (coefficient 0.25,  $P = 0.059$ ) [8]. A related study also indicated that the SUA exposure level showed a linear relationship with the severity of coronary artery disease in women ( $P = 0.034$ ), but not in men [23]. This evidence may indicate the increased importance of SUA control for hypertension and CVD prevention in the female population. However, our research did not reflect sex specificity in the relationship between elevated SUA and hypertension. Our study found that high level of SUA exposure was related to an increase in hypertension risk in both sexes after adjusting for all of the potential confounding factors, which was supported by subsequent studies. Yang et al. found that the risk of incident hypertension was positively correlated with increasing SUA concentrations in both sexes [24]. Higher SUA levels were associated with hypertension in Japanese males and females who did not receive anti-hyperuricaemia or hypertension treatment [25].

Another important finding in our study was that the relationship between SUA and the risk of hypertension was marked in the population aged under 30 years. In a cohort of children with cardiovascular risk for long-term healthy lifestyle interventions, elevated baseline uric acid levels were still closely associated with increased blood pressure [26]. A large cohort study in the USA also found a positive association in which elevated SUA was more

correlated with increased blood pressure in adolescents [27]. Hyperuricaemia-related early stage hypertension is reversible and induced by activating the renin–angiotensin–aldosterone system and reducing the production of NO to reduce vasodilator capacity [28]. This result may emphasise the importance of controlling SUA exposure in young individuals. However, Yokoi et al. found inconsistent results that the risk of SUA exposure-related hypertension was stronger among populations ≥ 40 years old than among those younger than 40 years in a Japanese population [29]. Future studies are still strongly warranted to replicate our study results.

There was an independent positive correlation between high SUA concentration and insulin resistance in the Korean population [30]. In children, the effect of insulin resistance on hypertension was independent of obesity, fat distribution and other factors [31]. TyG was associated with hypertension incidence independent of covariates during a 9-year follow-up in the Chinese population [32]. Higher SUA and insulin resistance were associated with increased risks of hypertension incidence.

To the best of our knowledge, Cassano et al. found that insulin resistance might have a positive synergistic effect on the relationship between SUA and vascular damage, however, their study could not fully reveal the causality between SUA, insulin resistance and hypertension due to the cross-sectional design [33]. After establishing the longitudinal link between SUA and hypertension, our research reconfirmed the mediating effect of insulin resistance between SUA and hypertension among the Chinese population, which is consistent with a previous longitudinal cohort study [13]. At a physiological concentration, SUA inhibited insulin-induced eNOS phosphorylation and NO production in endothelial cells, causing vascular endothelial disorders through vascular insulin resistance [34]. Endothelial dysfunction leads to imbalanced vasodilation and contraction causing hypertension [35].

The strength of our study was that we tested the relationship between SUA and hypertension in a prospective cohort platform. We established epidemiological evidence of the mediating roles of insulin resistance in the development of hypertension associated with elevated SUA. At present, several mechanistic studies have speculated that insulin resistance is one of the important mechanisms linking SUA and hypertension. In particular, we found that insulin resistance played a strong mediating role in the relationship between SUA and hypertension, which was of great significance for the study of the mechanism of SUA in the development of hypertension. Our research also had the following limitations. First, we did not test the level of fasting insulin due to restrictions associated with the testing conditions, or the insulin resistance index (HOMA-IR), so TyG was used to assess insulin resistance, and TyG has already been proven to be an effective predictor. Second, our study was an observational study and could not fully infer causality. It is necessary to design well-controlled randomised trials and biological mechanism studies to study the intricate relationships between SUA, insulin resistance and hypertension.

In conclusion, elevated SUA levels can independently predict the incidence of hypertension in a Chinese population in both females and males, especially in people younger than 30 years. Further exploration indicated that insulin resistance mediates the relationship between SUA and hypertension. These findings suggested that attention should be given to the monitoring and control of SUA and insulin resistance to identify high-risk groups for the prevention and control of hypertension.

## Summary

What is known about this topic?

- SUA independently increased the risk of developing hypertension among Chinese population without gender specificity.
- The positive correlation between SUA and hypertension was particularly found in people younger than 30 years.
- Insulin resistance may play mediating effects on the association between SUA and hypertension.

What this study adds?

- The study provided epidemiological association between SUA and hypertension in younger people (<30 years old).
- This cohort study demonstrated again that insulin resistance may mediate the longitudinal link between SUA and hypertension in the Chinese population.

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### COMPETING INTERESTS

The authors declare no competing interests.

### ADDITIONAL INFORMATION

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