Hyperuricemia is Related to the Risk of Cardiovascular Diseases in Ethnic Chinese Elderly Women

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ABSTRACT

Background: The association between hyperuricemia (HUA) and cardiovascular diseases (CVDs) is not fully elucidated.

Objective: To assess the relationship according to factors of sex and age in the Chinese ethnic groups.

Methods: We performed a population-based cross-sectional study in a multi-ethnic population from southwestern China. HUA patients were identified by serum uric acid ≥7 mg/dL in men and 6 mg/dL in women. The outcome was composite prevalent CVDs, including coronary heart disease (CHD), stroke, and arrhythmia. Multivariate logistic regression analysis, estimating odds ratio (ORs) and 95% confidence intervals (CIs), were applied to evaluate the HUA–CVDs relationship.

Results: We included 16,618 people (37.48% Dong, 30.00% Miao, and 32.52% Bouyei) aged 30–79 years without a reduced estimated glomerular filtration rate <60 mL/min/1.73 m². CVDs developed in 250 Dong, 196 Miao, and 205 Bouyei adults. Among women, HUA was positively associated with the risk of stroke in Dong ethnicity and CVDs in Bouyei ethnicity (ORs (95% CIs) 2.02 (1.07–3.81) and 1.66 (1.06–2.59)) compared with non-HUA. In the age-specific analysis, HUA was related to the risk of CVDs (OR 2.32, 95% CI 1.00–5.38) and CHD (5.37, 1.61–17.89) among Miao people aged < median age, CVDs (1.52, 1.11–2.08) and stroke (1.67, 1.02–2.72) among Dong adults aged ≥ median age, and CVDs (1.67, 1.16–2.40) and CHD (1.77, 1.13–2.77) among Bouyei ethnicity aged ≥ median age. After stratification by sex and the median age, for women aged > 50 years, a 55% (1.55, 1.00–2.39) and 65% (1.65, 1.02–2.66) increased risk for CVDs was observed in Dong and Bouyei ethnicities.

Conclusions: HUA may be related to an increased risk of CVDs among women in the Dong and Bouyei ethnic groups in China, especially women aged > 50 years.
1. INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death in the world [1], and more than half of CVD deaths occur in Asia [2], especially China [3, 4]. Global deaths from CVDs may increase approximately 1.4-fold from 2012 to 2030 [5]. A less than 25% reduced burden of CVDs was found in southwestern China over the past 30 years [6]. Therefore, the prevention of CVDs has become a major public health concern.

The association of hyperuricemia (HUA) with the risk of CVDs has been paid considerable attention in recent years [7–11]. However, studies to date have focused primarily on total populations, and the results were inconsistent [8, 11–15]. Also, the sex-specific association between HUA and CVDs risk has rarely been examined and the conclusion remained controversial [7, 9, 10, 16–18]. Additionally, the age-specific analysis in this area is limited [9]. Moreover, to our knowledge, other general population–based data stratified by sex and age on the relationship between HUA and the risk of CVDs are still lacking, except for a cross-sectional study that included 8,285 adults limited to a northeastern Chinese general population [9]. Furthermore, information on whether the association varies by ethnicity is not available.

To fill this evidence gap, we aimed to explore the potential effect of sex and age on the relationship between HUA and the risk of CVDs and its subtypes in the ethnic groups in Guizhou province, southwestern China, based on a cross-sectional design using data from the China Multi-Ethnic Cohort Study [19–23], an ongoing cohort study.

2. METHODS

2.1. STUDY DESIGN AND PARTICIPANTS

Between July of 2018 and August of 2019, 18,790 participants aged 30–79 years were recruited by questionnaire interview, anthropometric and laboratory measurements from Guizhou Province of southwestern China using a multistage, stratified cluster sampling procedure based on the China Multi-Ethnic Cohort Study [19–23]. The three ethnic groups, including Dong, Miao, and Bouyei, were enrolled in this study.

We excluded data for individuals missing data of serum uric acid (SUA) or serum creatinine (Scr) levels (n = 1,726) or with a fasting time of less than eight hours (n = 95). We excluded participants with a reduced estimated glomerular filtration rate (eGFR) [24] <60 mL/min/1.73 m² (n = 351). As a result, there was a 16,618 final analytic sample of participants (6,228 Dong, 4,986 Miao, and 5,404 Bouyei ethnic groups).

Ethics approval was obtained from the Sichuan University Medical Ethical Review Board (K2016038) and the Research Ethics Committee of The Affiliated Hospital of Guizhou Medical University (2018 [094]). All participants gave written informed consent before taking part in this study.

We defined this study as follows according to the PICOS principle: P (population): general population, I (intervention/exposure): HUA, C (comparison): non-HUA, O (outcome): CVDs, S (study design): cross-sectional study.

2.2. DATA COLLECTION

Self-reported data on general sociodemographic information (sex, age, ethnicity, and residence), health-related behaviours (tobacco smoking, alcohol drinking weekly, total physical activity, and dietary intake frequency), and personal and family medical history of CVDs were collected by an interviewer-administered laptop-based questionnaire for each participant. Smokers were defined as people ever smoking at least 100 cigarettes during their lifetime and they were classified as never/ever/current smokers [25]. In detail, current smokers were defined as having smoked 100 or more cigarettes during their lifetime, participants who met the above criteria before the half year and did not smoke during the past half year were classified as former smokers, and the others were never smokers. Participants reporting their frequency of alcohol consumption at least once per week during the past year were defined as alcohol drinking weekly [26]. We converted the total physical activity level to metabolic equivalent tasks hours/day based on job-related physical activity, transportation physical activity, leisure-time physical activity, and housework [27]. We estimated total energy intake (kcal/week)
by summing the number of servings per week of all foods (rice, cooked wheat-based food, vegetables, fruits, meat, etc.), alcohol, tea, oil, and beverages: firstly, we calculated the unit energy of each type of food based on the China Food Composition Tables (2018) and the foods consumption of Guizhou Province; secondly, we further obtained the consumption per week of each type of food based on the data from the food frequency questionnaire; finally, we performed matrix multiplication based on the above two steps. A family history of CVDs was defined as a parent, sibling, or natural child of the participant had a CVDs (coronary heart disease (CHD), stroke, or arrhythmia).

Well-trained examiners took anthropometric and laboratory measurements. We guided all participants to wear light clothing and no shoes and measure twice when measuring body weight and height and the means were used for analysis. We calculated body mass index (BMI) as weight (kg) divided by height (m) squared. Blood pressure was measured three times with a 30-second interval using an electronic sphygmomanometer, with participants in a seated position after five minutes of rest, and they were prohibited to smoke and drink alcohol before measuring their blood pressure. Overnight fasting blood samples after at least eight hours were obtained to assess levels of total cholesterol, triglycerides (TG), high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, fasting plasma glucose (FPG), SUA, and Scr. eGFR was calculated using ‘the Xiangya equation’ based on sex, age, and Scr, an estimating equation applied to a multi-ethnic Chinese population [24].

2.3. DEFINITION OF EXPOSURES AND OUTCOMES

HUA status was defined by SUA ≥ 7 mg/dL (420 µmol/L) in men and ≥6 mg/dL (360 µmol/L) in women [28]. The primary outcome was composite prevalent CVDs, including CHD, stroke, and arrhythmia, which were identified based on self-reported questionnaire data asking if people had ever been diagnosed by a doctor from second-level and above hospitals with CHD, stroke, or arrhythmia. CVDs could be diagnosed by participants if they had one or more of the conditions. The validity of the self-reported data for CVDs has been verified with an accuracy of approximately 97% and this approach has been used in many population–based studies [29–31].

2.4. STATISTICAL ANALYSES

Baseline characteristics of participants were reported as frequency and percent, or median and interquartile range. We assessed the significance of differences between CVDs patients and non-CVDs individuals by the Mann-Whitney U test for continuous variables and χ² test for categorical variables. The age- and sex-standardized prevalence of CVDs and its subtypes were according to the 2010 China Census data [32].

We used multivariate logistic regression models to explore the potential positive associations of HUA with the risk of CVDs and its subtypes, and multi-adjusted odd ratios (ORs) and 95% confidence intervals (CIs) were reported. We investigated potential sex and age interactions by fitting a multiplicative interaction term into the models between HUA in all three ethnicities, and we found significant interactions for the effect of HUA on CVDs and its subtypes by all of these variables (P < 0.05). We conducted stratified analyses by categories of sex (men and women) and age (<median age and ≥ median age) in the Dong, Miao, and Bouyei ethnic groups. All multivariate models were adjusted for the following potential confounders except for the stratified variables: sex, age, residence, tobacco smoking status, alcohol drinking status, total physical activity, total energy intake, family history of CVDs, BMI, and systolic blood pressure, FPG, and TG levels.

All figures were plotted by using STATA version 16 (STATA Corp, College Station, TX) and the other data were analysed with SAS version 9.1 (SAS Inst. Inc., Cary, NC). Statistical significance was set at P < 0.05 based on two-sided probability.

3. RESULTS

3.1. BASELINE CHARACTERISTICS

In total, 16,618 participants (651 CVDs patients) were included in this study (Table 1). The age- and sex-standardized prevalence of CVDs was 3.29% and 4.33%, 3.17% and 4.03%, and 3.27% and 4.22% in the Dong, Miao, and Bouyei ethnic groups, respectively (Figure 1). Compared with
Table 1: Baseline characteristics of 6,228 Dong, 4,986 Miao, and 5,404 Bouyei ethnic groups by cardiovascular diseases status.

Abbreviations: BMI, body mass index; CVDs, cardiovascular diseases; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HUA, hyperuricemia; LDL-C, low-density lipoprotein cholesterol; METs h/d, metabolic equivalent tasks hours/day; SBP, systolic blood pressure; Scr, serum creatinine; SUA, serum uric acid; TC, total cholesterol; TG, triglycerides.

Data are number (percentage) or median (interquartile range).

P comparing non-CVDs and CVDs.

| VARIABLES                    | DONG ETHNIC GROUP | MIAO ETHNIC GROUP | BOUYEI ETHNIC GROUP |
|------------------------------|-------------------|-------------------|---------------------|
|                              | NON-CVDs          | CVDS              | NON-CVDs            | CVDS              | NON-CVDs          | CVDS              |
| No. of participants          | 5,978 (96.00)     | 250 (4.00)        | 4,790 (96.07)       | 196 (3.93)        | 5,199 (96.21)     | 205 (3.79)        |
| Age (years)                  | 51.96 (44.99–60.13) | 61.11 (54.12–67.00) | <0.001              | 50.45 (42.51–59.18) | 62.08 (53.68–68.63) | <0.001            |
| Men                          | 2,052 (34.33)     | 112 (44.80)       | 1,740 (36.33)       | 79 (40.31)        | 1,540 (29.62)     | 85 (41.46)        |
| Rural                        | 4,636 (77.84)     | 188 (75.20)       | 3,421 (71.57)       | 119 (60.71)       | 4,554 (87.59)     | 169 (82.44)       |
| Tobacco smoking status       | 0.118             | 0.571             | 0.001               | 0.257             | 0.001             | 0.29              |
| Never                        | 4,761 (79.66)     | 180 (72.00)       | 3,748 (78.25)       | 154 (78.57)       | 4,301 (82.73)     | 164 (80.00)       |
| Former                       | 210 (3.51)        | 28 (11.20)        | 171 (3.57)          | 12 (6.12)         | 161 (3.10)        | 21 (10.24)        |
| Current                      | 1,006 (16.83)     | 42 (16.80)        | 871 (18.18)         | 30 (15.31)        | 737 (14.18)       | 20 (9.76)         |
| Alcohol drinking weekly      | 188 (3.14)        | 1 (4.26)          | 204 (4.62)          | 9 (4.59)          | 155 (2.98)        | 8 (3.90)          |
| Total physical activity (METs h/d) | 24.96 (14.00–37.16) | 17.55 (8.30–30.65) | <0.001              | 25.18 (13.40–38.80) | 12.12 (5.60–27.03) | <0.001            |
| Total energy intake (kcal/week) | 10.22 (8.20–12.97) | 9.24 (7.35–12.08) | <0.001              | 10.61 (8.16–13.67) | 9.71 (7.84–12.23) | <0.001            |
| BMI (kg/m²)                  | 23.74 (21.46–26.15) | 24.38 (21.81–26.15) | 0.224               | 24.79 (22.51–27.10) | 25.50 (22.97–27.80) | 0.038             |
| SBP (mmHg)                   | 121.60 (110.33–135.67) | 129.50 (115.00–144.00) | <0.001              | 122.30 (111.00–136.67) | 134.30 (118.33–147.67) | <0.001            |
| DBP (mmHg)                   | 79.00 (72.67–87.00) | 81.00 (74.67–90.67) | 0.003               | 80.33 (73.33–88.33) | 83.33 (75.67–92.00) | 0.001             |
| FPG (mmol/L)                 | 5.29 (4.96–5.68)  | 5.30 (4.94–5.75)  | 0.643               | 5.20 (4.90–5.60)  | 5.45 (5.06–5.92)  | <0.001            |
| TC (mmol/L)                  | 4.87 (4.29–5.51)  | 4.84 (4.10–5.52)  | 0.267               | 4.96 (4.35–5.60)  | 5.04 (4.41–5.98)  | 0.162             |
| TG (mmol/L)                  | 1.51 (1.08–2.22)  | 1.58 (1.18–2.39)  | 0.116               | 1.43 (1.02–2.12)  | 1.61 (1.22–2.30)  | 0.002             |
| HDL-C (mmol/L)               | 1.46 (1.22–1.73)  | 1.37 (1.15–1.62)  | <0.001              | 1.43 (1.02–2.12)  | 1.43 (1.25–1.60)  | 0.206             |
| LDL-C (mmol/L)               | 2.94 (2.38–3.50)  | 2.96 (2.26–3.60)  | 0.824               | 2.81 (2.30–3.40)  | 2.90 (2.35–3.61)  | 0.042             |
| SUA (mg/dL)                  | 5.36 (4.45–6.52)  | 5.85 (4.87–7.24)  | <0.001              | 5.39 (4.49–6.45)  | 5.69 (4.86–7.08)  | <0.001            |
| Scr (µmol/L)                 | 65.00 (56.00–77.00) | 71.00 (59.00–85.00) | <0.001              | 62.00 (54.00–74.00) | 68.00 (59.00–79.50) | <0.001            |
| eGFR (mL/min/1.73 m²)        | 81.00 (75.00–87.00) | 76.00 (70.00–82.00) | <0.001              | 84.00 (77.00–90.00) | 76.00 (71.00–82.00) | <0.001            |
| HUA                          | 1,545 (25.84)     | 92 (36.80)        | 1,189 (24.82)       | 66 (33.67)        | 969 (18.64)       | 66 (32.20)        |
people without CVDs, CVDs patients were more frequently older, had HUA, and had a lower level of total physical activity and total energy intake but high levels of systolic blood pressure, diastolic blood pressure, SUA, Scr, and eGFR in all three ethnicities; had higher frequency of women and alcohol drinking weekly but a lower high-density lipoprotein-cholesterol level in the Dong ethnic group; and had a higher proportion of rural residence and higher levels of BMI, FPG, TG, and low-density lipoprotein-cholesterol in the Miao and Bouyei ethnic groups (all \( P < 0.05 \) (Table 1).

### 3.2. THE RISK OF CVDS, CHD, AND STROKE STRATIFIED BY SEX

In the sex-specific analysis, multivariate logistic regression analysis after adjustment for potential risk factors revealed that HUA was positively associated with the risk of CVDs in women in the Bouyei ethnic group, and adjusted OR (95% CI) was 1.66 (1.06–2.59). Additionally, a 2.02-fold increased risk for stroke in women in the Dong ethnic group was found. However, we did not observe a significant association in men in the three ethnic groups (Figure 2).

#### 3.3. THE RISK OF CVDS, CHD, AND STROKE STRATIFIED BY THE MEDIAN OF AGE

After adjusting for potential confounders, among people aged less than the median of age, a 2.32-fold (OR 2.32, 95% CI 1.00–5.38) and 5.37-fold (5.37, 1.61–17.89) increase in the risk of CVDs and CHD related to HUA was observed in the Miao ethnic group (Figure 3). Among people aged greater than or equal to the median of age, we found a 52% (1.52, 1.11–2.08) and 67% (1.67, 1.16–2.40) increased risk for CVDs and stroke in the Dong ethnic group; moreover, a 67% (1.67, 1.16–2.40) and 77% (1.77, 1.13–2.77) increased risk for CVDs and CHD in the Bouyei ethnic group was detected (Figure 3).
3.4. THE RISK CVDS, CHD, AND STROKE STRATIFIED BY SEX AND THE MEDIAN OF AGE

The risk of CVDs was associated with HUA among women aged greater than or equal to the median of age in the Dong and Bouyei ethnic groups but not the Miao ethnic group considering possible confounding factors, multi-adjusted OR (95% CI) 1.55 (1.00–2.39) and 1.65 (1.02–2.66), respectively. Additionally, the risk of stroke increased with HUA, OR (95% CI) 2.11 (1.09–4.09) (Figure 4).

4. DISCUSSION

Among 16,618 participants (6,228 Dong, 4,986 Miao, and 5,404 Bouyei), which included 651 CVDs patients (250 Dong, 196 Miao, and 205 Bouyei) with a normal level of eGFR in the ethnic Chinese groups aged 30–79 years, we found ethnic differences in the relationship between HUA and the risk of CVDs. HUA was positively associated with 55% and 65% risk increases in CVDs among women ≥ median age in the Dong and Bouyei ethnic groups but not among men or the Miao ethnic group. Sex differences in the relationship could be related to intrinsic biologic differences or differences in risk factor management. Sex hormones, visceral adiposity, and muscle mass have sex-specific changes, which have been reported to regulate SUA metabolism. Additionally, there may be differences in gene expression patterns among the three ethnic groups.

In addition, it is still unclear whether the changes of SUA with age will affect the relationship [9, 10, 15–17]. In our study population, those ≥ median age with HUA had an increased risk of CVDs in the Dong and Bouyei ethnic groups; however, a higher risk of CVDs was found in people aged < median age in the Miao ethnic group. Using SUA-lowering drugs in HUA patients at earlier stages of the disease could contribute to the risk reduction in CVDs. The Miao ethnic group may put more emphasis on the control of SUA level in young or middle age than the
As people age, the HUA-related risk of cardiometabolic diseases might be increased. Those with HUA could have extensive vascular damage and need to maintain adequate organ perfusion. HUA may result in reduced nitric oxide availability, increased oxidative stress, endothelial dysfunction, inflammation promotion, or insulin resistance [33, 34]. The proliferation of vascular smooth cells, vascular inflammation, or atherosclerosis may be induced or accelerated by lipid peroxidation and platelet adhesion related to HUA [35, 36]. Atherosclerosis may be caused by renal impairment related to HUA and could induce homocysteinemia [37]. The above-mentioned possible mechanisms are more serious in elderly people, which could be why older participants are at higher risk of CVDs related to HUA compared with middle-aged people. Notably, possible ethnic differences in their living and diet habits may be influential in the HUA–CVDs relationship.

Stratified analyses combined by sex and age have rarely been performed [9]. Only one observational study that included 8,285 adults from northeastern China was performed to assess the association of HUA with the risk of CHD, and it found a positive relationship in women aged ≥ 80 years [9]. The present study suggested that HUA was related to the risk of CVDs in women aged ≥ median age in the Dong and Bouyei ethnic groups. Considering the above-mentioned potential explanations, a combined effect of intrinsic biologic differences, consumption of high purine foods, low metabolic capacity, and SUA-lowering drugs on the HUA–CVDs relationship could be observed in elderly women. Further investigation of the underlying mechanisms is necessary.

The observed relationship between HUA and the risk of CVDs was considerable. If causal, a moderately weak or strong association may be relevant to ‘Health China 2030.’ For example, if good primary prevention and control of HUA were achieved, it could be expected that the CVDs risk might consequently be reduced by at least 55% based on the present findings. CVDs are the leading cause of death, especially women [38], and a small percentage reduction in HUA-related CVDs risk will have a significant public health impact.

5. STRENGTHS AND LIMITATIONS

The primary strength of this study was the multi-ethnic Chinese population. Moreover, we performed stratified analysis by sex and age and considered the effect of kidney function on the association. Additionally, we calculated the eGFR level based on an estimating equation applied to a multi-ethnic Chinese population.

Some limitations warrant consideration when interpreting the findings of this study. First, this study was conducted on participants from the three ethnic groups in one area. We could not evaluate the HUA–CVDs relationship in other ethnicities or the included ethnicities in the present study from other areas. Second, it is difficult to assess the causal association of HUA and the risk of CVDs in consideration of the cross-sectional design. Third, the levels of SUA and Scr were only measured once, and intra-individual variability was not taken into account. Fourth, the average age of the participants was older, and larger samples are needed. Fifth, detailed categories of age, the subtypes of CHD and stroke, and arrhythmia were not analysed because of the limited number of cases. Finally, there is the possibility of residual confounding factors in this observational study because of some unmeasured or unknown covariates.

6. CONCLUSIONS

In conclusion, elderly women in the Dong and Bouyei ethnic groups in China had an increased risk of CVDs associated with HUA. Given the suggestive findings observed in the present study, future multi-ethnic, sex-specific, and age-specific studies are warranted to perform detailed and causal assessments to determine the potential mechanisms. Until the evidence is externally validated, however, most patients with HUA, especially elderly women, will still require control of their SUA level to reduce their potential risk of CVDs.
DATA ACCESSIBILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS AND CONSENT

Ethics approval was obtained from the Sichuan University Medical Ethical Review Board (K2016038) and the Research Ethics Committee of The Affiliated Hospital of Guizhou Medical University (2018 [094]). All participants gave written informed consent before taking part in the study.

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COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS

Feng Hong and Tao Zhang designed and directed the project. Leilei Liu analysed data and wrote the manuscript. Xiao Zhang, Lian Peng, Nana Ma, Tingting Yang, Chan Nie, Linyuan Zhang, Zixuan Xu, Jun Yang, Xuejie Tang, Liubo Zheng, Tao Zhang, and Feng Hong critically revised for important intellectual content. All authors participated in the data acquisition of this cross-sectional survey and approval the final version of the manuscript.

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