Mediation effect of body mass index on the association between spicy food intake and hyperuricemia in rural Chinese adults: the Henan Rural Cohort Study

Xiaokang Dong
Zhengzhou University
Yuqian Li
Zhengzhou University
Kaili Yang
Zhengzhou University
Lulu Zhang
Zhengzhou University
Yuan Xue
Zhengzhou University
Songcheng Yu
Zhengzhou University
Xiaotian Liu
Zhengzhou University
Runqi Tu
Zhengzhou University
Dou Qiao
Zhengzhou University
Zhicheng Luo
Zhengzhou University
Xue Liu
Zhengzhou University
Yan Wang
Zhengzhou University
Wenjie Li
Zhengzhou University
Zhaohui Zheng
Zhengzhou University First Affiliated Hospital
Chongjian Wang (✉ tjwcj2005@126.com)
Zhengzhou University https://orcid.org/0000-0001-5091-6621

Research article

Keywords: Spicy food intake, BMI, Hyperuricemia, Mediation effect

DOI: https://doi.org/10.21203/rs.3.rs-20896/v2

License: © This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Background: The relationship of spicy food intake with hyperuricemia remains unknown. The objective of this study was to examine the association between spicy food intake and hyperuricemia, and whether this association was mediated by body mass index (BMI) in Chinese rural population.

Methods: 38,027 adults aged 18–79 years were recruited from the Henan Rural Cohort Study. Information on spicy food intake was obtained using a validated questionnaire survey. Multivariable logistic regression model was used to estimate the association between spicy food intake and hyperuricemia, multiple linear regression model was performed to estimate the relationships between spicy food intake, BMI and serum urate level. BMI was used as a mediator to evaluate the mediation effect.

Results: After adjusting for potential confounders, compared with no spicy food flavor, the odds ratio (OR) and 95% confidence interval (CI) of mild, middle, and heavy flavor for hyperuricemia were 1.09 (1.00-1.19), 1.10 (0.97-1.24), and 1.21 (1.10-1.46), respectively ($P_{\text{trend}}=0.017$). Similarly, compared with those without intake in spicy food, the multivariable adjusted $OR$ (95% CI) of 1-2 days/week, 3-5 days/week, and 6-7 days/week were 1.15 (1.01-1.31), 1.14 (1.01-1.30) and 1.15 (1.05-1.26), respectively ($P_{\text{trend}}=0.007$). However, when we further controlling for BMI, the associations were substantially attenuated. Furthermore, mediation analysis showed that BMI play a full mediating role in the relationship of spicy food intake with hyperuricemia.

Conclusion: Spicy food flavor and intake frequency are positively related with hyperuricemia in Chinese rural population. BMI may play a full mediating role in the relationship.

Clinical Trial Registration

The Henan Rural Cohort Study registered at Chinese Clinical Trial Register (Registration number: ChiCTR-OOC-15006699). Date of registration: 2015-07-06 http://www.chictr.org.cn/showproj.aspx?proj=11375

Background

In recent decades, epidemiologic studies show that hyperuricemia has caused many severe public health and social problems all over the world [1, 2]. Hyperuricemia is generally detected in people with abnormal purine metabolism, including overproduction of uric acid (UA) and insufficient UA excretion from the kidneys. According to the Meta-Analysis conducted in China, the prevalence of hyperuricemia between 2000 and 2014 was 13.3% [3]. Recent studies found hyperuricemia was not only associated with an increased risk of developing gout, but also caused chronic kidney disease, cardiovascular diseases and metabolic syndrome [4-6]. In many developed countries, the high incidence of hyperuricemia was correlated with the overweight and obesity, hypertension, hypertriglyceridemia, type 2 diabetes mellitus, hypercholesterolemia, as well as the Western diet rich in purine, alcohol, meat consumption, and soft drinks [7, 8], dietary patterns also play an important role in the development of hyperuricemia.

Spices have been an integral part of culinary cultures around the world and have a long history of use for flavoring, coloring and preserving food, as well as for medicinal purposes [9, 10]. Spiciness or pungency was considered as one of the primary tastes in ancient India and China [11, 12]. There is a large geographic and culture difference in terms of spicy food intake. For example, spicy food intake is higher in Asian than European countries [13]. In China, almost more than 30 percent of adults consume spicy food daily [14]. Over the past several decades, many studies have explored the effects of spicy food and capsaicin, which is considered as a major bioactive ingredient. Although some previous studies have found the good effects of spicy food intake on obesity and other metabolic diseases [11, 14-16], there are inconsistent findings of the association between spicy food intake and obesity, which were reported in animal and human intervention studies [17, 18]. The China Kadoorie Biobank (CKB) study found that spicy food consumption was associated with elevated body mass index (BMI) and other adiposity measures among a large Chinese population [19]. Our previous study also found spicy flavor, spicy food intake frequency was associated with increased risk of general obesity [20]. Many epidemiologic studies found that obesity was a major risk factor for hyperuricemia [21, 22]. However, the direct association between spicy food intake and hyperuricemia remain unclear and its potential mechanism has not been fully elucidated. Therefore, the current study aimed to investigate the association between spicy food flavor, intake frequency and prevalence of hyperuricemia in the Henan Rural Cohort Study, and to test whether there was a mediating effect on this association by BMI, which is an important obesity index.

Materials And Methods

Study population

The baseline survey of the Henan Rural Cohort Study was conducted in 5 rural regions of Henan province in China from July 2015 to September 2017. Detailed description on study design and eligibility criteria has been published elsewhere [23, 24]. 39,259 participants aged 18-79 years old were enrolled to complete the questionnaire and physical measurements. The study has been registered in Chinese Clinical Trial Register. To explore the relationship between spicy food intake and hyperuricemia, a total of 1232 subjects were excluded because of no data about SUA levels (n=54); incomplete information of spicy food intake (n=29); cancer and renal disease (n=348); hepatitis and tuberculosis (n=801). Ultimately, the study enrolled 38,027 subjects for the current analysis. Before starting the survey, all participants provided written informed consent, and the protocol was approved by the Zhengzhou University Life Science Ethics Review Committee.

Assessment of spicy food intake

The validated Food Frequency Questionnaire (FFQ) was used to collected dietary information from individuals [25]. The detailed spicy food information has been described [20]. The average daily spicy food intake including spicy food flavor and intake frequency was estimated using a validated dietary habit
questionnaire. Following question was asked: “How much do you like the spicy flavor in your food?” The participants could answer a flavor from four spicy flavors: No, Mild, Middle or Heavy. The participants were also asked “How frequently did you consume spicy foods during a week?” One of following four options could be selected: Never, 1-2 days/week, 3-5 days/ week or 6-7 days/week.

Ascertainment of hyperuricemia

Venous blood samples were drawn from the subjects who had been fasting overnight. The serum was separated at a rate of 2000 revolutions per minute for 10 minutes, 4 times, and stored at -20°C. Serum urate level was measured by ROCHE Cobas C501 automatic biochemical analyzer using enzymatic colorimetric method. In the present study, hyperuricemia was defined as serum urate level $>7.0$ mg/dL (417 μmol/L) in men and serum urate level $>6.0$ mg/dL (357 μmol/L) in women as the standard definition for some studies [26]. Serum creatinine concentration was measured by the ROCHE Cobas C501 automatic biochemical analyzer.

Assessment and definitions of covariates

The detailed information regarding sociodemographic characteristics (name, sex, age, marital status, educational level), lifestyle factors (smoking status, drinking status, physical activity, dietary habits) and personal histories of chronic diseases (such as type 2 diabetes mellitus, dyslipidemia, and hypertension) were collected by the trained public health investigators using a standardized questionnaire [27]. Education levels was divided into three groups: illiterate or elementary, middle school, and high school or above. Both smoking and drinking status were classified into current, former and never groups. According to the international physical activity questionnaire (IPAQ 2001), physical activity included three categories: low, moderate and high [28]. Data on individual dietary intake were collected by a validated FFQ [25]. The FFQ consisted of 13 main food groups. For everyone, the mean daily total energy intake (including protein, fat and carbohydrate energy intake) was calculated from dietary information according to the Chinese Food Composition Table 2004. The standard principal component analysis method was applied to obtain a four-cluster dietary patterns, dietary pattern I: red meat, white meat and fish; pattern II: vegetables, staple food, and fruits; pattern III: grains, nuts, beans, pickles and animal oils; and pattern IV with milk and eggs [29]. Height and weight were measured by trained physicians, to the nearest 0.1 kg and 0.1 cm separately. Before measurement the subjects need remove their shoes, hats, jackets, overcoats. BMI was calculated as weight divided by height squared (kg/m²).

Statistical analysis

Continuous variables were expressed using means and standard deviations, while percentages were used for categorical variables. Continuous and categorical variables were compared by Analysis of Variance (ANOVA) and chi square tests to determine whether there were differences in covariates among different groups of spicy food intake. To evaluate the linear trend with increasing spicy strength and spicy food frequency, Spearman correlation and Cochran-Mantel-Haenszel tests were used for continuous variables and categorical variables, respectively. Age-standardized prevalence of hyperuricemia was also estimated based on the Population Census 2010 across different groups of spicy food intake.

Multivariable-adjusted logistic regression models were employed to evaluate the association between spicy food flavor, intake frequency and hyperuricemia, and the values of odd ratios (ORs) and 95% confidence intervals (CIs) were calculated. A set of models were performed to minimize the effect of confounders on this association. Model 1 was crude model, and model 2 adjusted for age, gender, education level, marital status, smoking and drinking status, physical activity, individual dietary pattern, total energy, serum creatinine and model 3 additionally adjusted for type 2 diabetes mellitus (T2DM), hypertension and dyslipidemia status, and model 4 further adjusted for BMI. Multiple linear regression analyses were further performed to explore the relationships between spicy food intake, BMI and serum urate level, with three models.

In order to further explore whether BMI played a mediate role in the association of spicy food intake with hyperuricemia, a mediation analysis was applied. The mediator needed to be continuous variable as previously described elsewhere [30, 31]. Same confounders in model 3 were also adjusted in the mediation analysis. Several main paths were included in the mediation analysis. Path a: the association between spicy food intake and BMI (the mediator); Path b: the association of BMI with hyperuricemia (outcome); Path c and Path c’: the total and direct effects of spicy food intake on hyperuricemia, respectively. Full mediation effect exists when the indirect effect is significant but not for the direct effect. All statistical analyses were conducted by using SPSS version 21.0 and STATA version 13.1. All tests were two sided and $P$ values<0.05 indicated statistical significance.

Results

General characteristics

The median age of 38,027 subjects was 55.53 ± 12.21 years in the total population. Table 1 presents the general characteristics of the participants by categories of the spicy food flavor and the spicy food intake frequency. Participants with heavier spicy flavor were more likely to be younger in age, be male with married or cohabiting, have more total energy intake, less likely to be drinker and smoker, more physical activity, higher BMI and serum urate level, and less T2DM and hypertension status (all $P_{trend} < 0.001$). Similar differences of distribution in these selected variables were also found among four groups of intake frequency (all $P_{trend} < 0.001$).

Table 1. Sociodemographic characteristics of participants grouped by spicy food flavor and intake frequency
| Variable                                      | No. participants | Spicy food flavor | Trend | Spicy food intake |
|----------------------------------------------|------------------|------------------|-------|-------------------|
|                                              | Mean  | SD   | Mean  | SD   | Mean  | SD   | Mean  | SD   |
| Age (years)                                  | 16282 | 14889| 5326  | 5320 | 1530  | 5326 | 12361 | 3268 |
| Male (%)                                     | 37.8  | 11.4 | 41.5  | 11.7 | 41.9  | 12.3 | 46.4  | 11.5 |
| Educational level (%)                        | <0.001 | 38.4 | 44.1  | 39.1 | 46.4  | 38.1 |
| Illiterate and Elementary                    | 49.0  | 11.4 | 41.0  | 12.3 | 43.5  | 12.4 | 43.5  | 13.7 |
| Middle school                                | 37.1  | 11.4 | 41.9  | 12.3 | 43.5  | 12.4 | 43.5  | 13.7 |
| High school and above                        | 13.9  | 11.4 | 17.2  | 12.3 | 13.7  | 12.4 | 13.7  | 12.4 |
| Marital status (%)                           | <0.001 | 90.7 | 91.9  | 92.0 | 91.4  | 9.3  | 8.1   | 8.0  |
| Widowed/single/divorced/separation           | 12.1  | 11.4 | 8.1   | 11.4 | 8.0   | 11.5 | 8.6   | 11.5 |
| Smoking status (%)                           | <0.001 | 72.4 | 66.5  | 61.1 | 74.6  | 6.5  | 6.5   | 6.5  |
| Ex-smoker                                    | 8.6   | 11.4 | 7.1   | 12.3 | 6.8   | 12.4 | 8.4   | 12.4 |
| Nonsmoker                                    | 76.6  | 11.4 | 66.5  | 12.3 | 61.1  | 12.4 | 75.6  | 12.4 |
| Drinking status (%)                          | <0.001 | 19.9 | 26.4  | 32.1 | 18.8  | 16.0 | 18.8  | 16.0 |
| Non drinker                                  | 82.7  | 11.4 | 68.1  | 12.3 | 68.9  | 12.4 | 83.2  | 12.4 |
| Ex-drinker                                   | 5.3   | 11.4 | 4.1   | 12.3 | 4.4   | 12.4 | 5.3   | 12.4 |
| Smoker                                       | 14.9  | 11.4 | 32.1  | 12.4 | 31.1  | 12.4 | 11.5  | 12.4 |
| Physical activity (%)                        | <0.001 | 30.8 | 28.7  | 31.4 | 34.4  | 35.4 | 32.3  | 35.8 |
| Low                                          | 34.8  | 11.4 | 34.0  | 12.3 | 32.7  | 12.4 | 28.8  | 12.4 |
| Middle                                       | 37.2  | 11.4 | 37.2  | 12.3 | 35.9  | 12.4 | 35.4  | 12.4 |
| High                                         | 28.0  | 11.4 | 30.3  | 12.3 | 32.7  | 12.4 | 28.8  | 12.4 |
| Dietary pattern                              | <0.001 | 20.9 | 23.2  | 27.5 | 20.9  | 18.7 | 29.1  | 18.7 |
| Pattern I                                    | 18.6  | 11.4 | 20.9  | 12.3 | 23.2  | 12.4 | 27.5  | 12.4 |
| Pattern II                                   | 30.7  | 11.4 | 35.3  | 12.3 | 33.9  | 12.4 | 38.8  | 12.4 |
| Pattern III                                  | 22.4  | 11.4 | 19.2  | 12.3 | 20.1  | 12.4 | 16.4  | 12.4 |
| Total energy intake (kcal/d)                 | 2387  | 11.4 | 663.9 | 12.3 | 691.2 | 12.4 | 2700  | 12.4 |
| BMI (kg/m²)                                  | 24.63 | 11.4 | 35.1  | 12.3 | 25.20 | 12.4 | 25.13 | 12.4 |
| Serum creatinine (umol/L)                    | 62.58 | 11.4 | 10.5  | 12.3 | 61.45 | 12.4 | 62.68 | 12.4 |
| Serum urate level (umol/L)                   | 282.43| 11.4 | 77.0  | 12.3 | 287.7 | 12.4 | 80.5  | 12.4 |
| Total hemoglobin level (%)                   | 10.6  | 11.4 | 8.5   | 12.3 | 8.88  | 12.4 | 8.6   | 12.4 |
| T2DM (%)                                     | <0.001 | 30.8 | 29.5  | 22.7 | 31.7  | 0.004| 38.7  | 38.8 |
| Hypertension (%)                              | 36.5  | 11.4 | 30.88 | 12.3 | 29.5  | 12.4 | 36.2  | 12.4 |
| Dyslipidemia (%)                              | 37.8  | 11.4 | 38.4  | 12.3 | 39.5  | 12.4 | 37.8  | 12.4 |

SD, standard deviation. T2DM, type 2 diabetes mellitus

**Prevalence of hyperuricemia**

The prevalence of hyperuricemia across different categories of spicy food flavor and intake frequency is displayed in Figure 1. In all participants, the crude prevalence of hyperuricemia with No, Mild, Middle, and Heavy spicy flavors were 9.03%, 10.02%, 10.21% and 11.90%, respectively; and the corresponding age-standardized hyperuricemia prevalence were 10.30%, 12.47%, 13.76% and 15.67%, respectively (Fig. 1A). Similarly, the crude prevalence of hyperuricemia with intake frequency of Never, 1-2 d/week, 3-5 d/week and 6-7 d/week were 9.94%, 12.61%, 13.15%, and 11.65%, respectively; and the corresponding age-standardized...
standardized hyperuricemia prevalence were 11.66%, 14.50%, 15.44%, and 15.91%, respectively (Fig. 1B). In addition, increased trends in the prevalence of hyperuricemia were observed with the increasing level of spicy flavor and intake frequency (all $P_{\text{trend}} < 0.001$).

**Association of spicy food intake with hyperuricemia**

As shown in Table 2, the findings revealed a positive relationship between spicy food intake and hyperuricemia. After controlling for multiple variables in model 3, the ORs (95% CIs) of Mild, Middle, and Heavy flavors compared with no spicy food flavor were 1.09 (1.00-1.19), 1.10 (0.97-1.24) and 1.21 (1.10-1.46), respectively ($P_{\text{trend}} = 0.017$). The adjusted OR (95% CI) for each level increment in spicy flavor strength was 1.06 (1.01-1.10). Compared with those without intake in spicy food, participants in intake frequency of 1-2 days/week, 3-5 days/week, and 6-7 days/week were 1.15, 1.14 and 1.15 times more likely to have hyperuricemia ($P_{\text{trend}} = 0.007$). The adjusted OR (95% CI) for each level increment in spicy food intake frequency was 1.02 (1.01-1.03). But the association of spicy food flavor or intake frequency with hyperuricemia was significantly attenuated after additional adjustment for BMI in model 4 (all $P_{\text{trend}} > 0.05$).

**Table 2. OR (95%CI) of hyperuricemia grouped by spicy food flavor and intake frequency**

| Events/N | Model 1 | Model 2 | Model 3 | Model 4 |
|----------|---------|---------|---------|---------|
| Spicy food flavor | OR (95%CI) | OR (95%CI) | OR (95%CI) | OR (95%CI) |
| No | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Mild | 1.12 (1.04, 1.21) | 1.10 (1.00, 1.20) | 1.09 (1.00, 1.19) | 1.05 (0.96, 1.15) |
| Middle | 1.15 (1.03, 1.27) | 1.11 (0.99, 1.26) | 1.10 (0.97, 1.24) | 1.02 (0.91, 1.16) |
| Heavy | 1.42 (1.21, 1.67) | 1.21 (1.01, 1.45) | 1.21(1.10, 1.46) | 1.13 (0.93, 1.36) |
| Each level increment | 1.10 (1.06, 1.14) | 1.06 (1.01, 1.11) | 1.06 (1.01, 1.10) | 1.03 (0.98, 1.08) |
| Spicy food intake frequency | | | | |
| Never | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| 1-2d/week | 1.31 (1.16, 1.47) | 1.18 (1.04, 1.34) | 1.15 (1.01, 1.31) | 1.10 (0.97, 1.25) |
| 3-5d/week | 1.37 (1.22, 1.54) | 1.16 (1.03, 1.32) | 1.14 (1.01, 1.30) | 1.10 (0.97, 1.26) |
| 6-7d/week | 1.19 (1.10, 1.30) | 1.15 (1.05, 1.26) | 1.15 (1.05, 1.26) | 1.10 (0.99, 1.21) |
| Each level increment | 1.02 (1.01, 1.04) | 1.02 (1.01, 1.03) | 1.02 (1.01, 1.03) | 1.01 (0.99, 1.02) |

Model 1: unadjusted.
Model 2: adjusted for age, gender, education level, marital status, smoking and drinking status, physical activity, dietary pattern, serum creatinine, total energy intake.
Model 3: adjusted for model 2 plus T2DM, hypertension and dyslipidemia status.
Model 4: adjusted for model 2 plus BMI.

**Association of spicy food intake with BMI and serum urate level**

The associations of spicy food flavor, intake frequency with BMI and serum urate level are presented in Table 3. After adjusting for potential confounders in model 2, compared with no spicy food flavor, the $\beta$ Coefficients and 95% CI of Mild, Middle, and Heavy with BMI were 0.29 (0.20, 0.38), 0.50 (0.37, 0.63) and 0.49 (0.28, 0.70), respectively ($P_{\text{trend}} < 0.001$). Compared with those without intake in spicy food, the adjusted ORs (95% CIs) for 1-2 days/week, 3-5 days/week, and 6-7 days/week were 0.39 (0.26, 0.53), 0.26 (0.12, 0.40) and 0.27 (0.17, 0.36), respectively. Similarly, in model 3, the Mild, Middle, and Heavy flavor were associated with a 5.27μmol/L (95% CI: 3.47, 7.08), 4.62μmol/L (2.08, 7.17) and 10.78μmol/L (6.70, 14.86) higher serum urate levels; the 1-2 days/week, 3-5 days/week, and 6-7 days/week intake frequency were associated with 5.29μmol/L (95% CI: 2.59, 7.12), 4.40μmol/L (1.69, 7.12) and 5.80μmol/L (3.91, 7.68) higher serum urate levels.

**Table 3 The association ($\beta$ coefficients and 95% CI) of spicy food flavor or intake frequency with BMI and serum urate level.**
The current study is the first study to explore the relationship between spicy food intake and hyperuricemia among rural Chinese adults. We found that both spicy food flavor and intake frequency were positively associated with the prevalence of hyperuricemia. Furthermore, a higher level of spicy food flavor or intake frequency tended to be associated with a higher BMI and serum urate level. In addition, the relationship of spicy food intake with hyperuricemia was mediated by BMI.

The current study revealed that both spicy food flavor and spicy food intake frequency were positively associated with BMI, serum urate level and risk of hyperuricemia. Although it is the first time using cross-sectional study to find the relationship of spicy food intake with hyperuricemia, there are many previous studies which can support the current results. Firstly, a large amount of studies had proved that obesity is an independent influencing factor for hyperuricemia in US [32], China [33], Japan [34], and Korean patients [35] despite the difference in race, cross-sectional, case-control, or cohort study design. In addition, some large sample studies had found the association of spicy food consumption with obesity, as our previous study have found that spicy flavor and intake...
frequency were associated with increased risk of general or abdominal obesity [20], it is consistent with the findings of CKB, which reported that the spicy food intake frequency might associate with elevated BMI and other obesity measures [19]. Moreover, a recent cross-sectional study also showed that spicy food intake may increase the risk of overweight/obesity [36]. Secondly, some studies found the association between spicy food consumption and abnormal lipid metabolism in adults [37] and older people in China [38], respectively. Abnormal lipid metabolism can cause dyslipidemia, as an important risk factor for hyperuricemia was observed in series cross-sectional studies and longitudinal studies [32, 33, 35]. In addition, a study in Korean found that a strong preference for spicy food may be a risk factor for alcohol dependence [39]. Alcohol intake can promote the synthesis of uric acid and subsequently hinder the excretion of uric acid, which finally lead to hyperuricemia [34, 40]. Therefore, the indirect association between spicy food intake and hyperuricemia from both cross-sectional and longitudinal analyses largely conclude the possibility of this positive causation.

In the present study, the association between spicy food intake and hyperuricemia still remained robust after controlling for multiple potential confounding factors in model 3 including drinking status, dyslipidemia status, dietary pattern, total energy intake and so on. But when we further controlled for BMI, the association became nonsignificant. Furthermore, in the mediation analysis BMI played a full mediation with spicy food flavor or intake frequency and hyperuricemia. These findings supported our hypothesis, it seems plausible that spicy food intake predisposes to high BMI and general obesity [19, 20], and in turn to high serum uric acid and hyperuricemia [33].

Although the exact mechanisms of the adverse effects of spicy food intake on hyperuricemia are yet to be elucidated, several potential hypotheses have been proposed. Firstly, a underlying reason for the association may be explained by the meat-based diet with chili intake in Chinese cuisines [41]. In Chinese cuisines, spicy food is inclined to be more meat-based rather than vegetable-based, excessive fat meat intake with spicy foods may increase the risk of obesity [19], general obesity is an independent risk factor for hyperuricemia. Spicy food intake also may increase carbohydrates intake to relieve the burning sensation [20], which might lead to weight increase and a high BMI. Fat accumulation may cause excessive uric acid production, which in turn result in an elevated influx of plasma free fatty acid into the portal vein and liver, stimulation of neutral fat synthesis, and a consequent attendant surge in uric acid production in the activated uric acid synthesis pathway [34]. Moreover, compared with other foods, meat contains more purines. In China, spicy flavor is often used for flavor of mutton, fish, particularly hotpot that contains plenty of purine [19, 42]. The excessive purines intake with spicy foods can directly cause high serum uric acid.

As a consequence, it could further develop into hyperuricemia [42]. Secondly, in China diet, chili sauce and chili oil are widely used for flavoring [24], which may increase fat intake, and further elevate serum lipid levels. The increase of lipid levels especially the triglycerides (TG) will induce more free fatty acid production, accelerate the decomposition of adenosine triphosphate, and increase the production of uric acid [43]. In our study, although many possible confounders such as demographics, lifestyle, dietary pattern, total energy intake and personal disease status have been adjusted, the positive association between spicy food intake and hyperuricemia remained virtually unchanged. In addition, some unmeasured factors like accurate chilli and purine intake could not be fully controlled. Thus further clinical research and prospective studies in general population are essential to elucidate the mechanisms of the relationship spicy food intake with hyperuricemia.

This study was the first observational study to explore whether the BMI as mediation role on spicy food intake and hyperuricemia. The current study also includes a large sample rural population and adjustment for many established and potential risk factors for hyperuricemia, which provide sufficient statistical power. However, several limitations of the study should be acknowledged. Firstly, the study was conducted based on design of cross-sectional study, which may not be able to accurately determine the cause-effect association. Secondly, because the assessment of spicy food intake and other dietary information of participants were collected through FFQ, the recall bias cannot be neglected. However, a validation study had been conducted with the 3-day 24 hours recall to confirm that the FFQ is a representative tool to obtain reliable dietary data on a rural population [25]. Thirdly, although wide range risk factors for hyperuricemia were controlled, the lack of some other unmeasured and unselected covariates (such as the actual data of chili and purine intake) were not considered, which may be limited our ability to explore the mechanism of spicy food on hyperuricemia. Finally, our participants are from Henan rural areas in China, which may be limited to expand these findings to other countries and areas. Further validation of the current results in other countries and areas is necessary in the later study. On all accounts, the findings based on the large sample population study can provide us with some prospective about the association of spicy food intake with hyperuricemia in Chinese rural population.

**Conclusion**

The current analysis showed significant positive association of spicy food flavor, spicy food intake frequency with hyperuricemia prevalence. Furthermore, BMI may play a mediator effect in this association. The positive associations of spicy food intake with BMI and prevalence of hyperuricemia suggest that we not only need to care about the food we intake, but also pay attention to the spicy itself. Reducing spicy food intake (both spicy flavor and intake frequency) may be a beneficial way to improve metabolic health.

**Abbreviations**

BMI: Body mass index; T2DM: Type 2 diabetes mellitus. OR: Odds ratio; CI: Confidence interval; CVD: Cardiovascular diseases; ANOVA: Analysis of Variance; FFQ: Food Frequency Questionnaire CKB: China Kadoorie Biobank; SD: Standard deviation; TG: Triglycerides.

**Declarations**

**Ethics approval and consent to participate**

All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its ethical standards. Ethics approval was obtained from the “Zhengzhou University Life Science Ethics Committee”. Ethic approval code: [2015] MEC (S128). Written informed consent was obtained for all participants recruited in the study.
Consent for publication

Not applicable.

Availability of data and materials

The data used in this study are available. It will be shared on reasonable request to the corresponding author.

Competing interests

No competing interests exist.

Authors' Contributions

WCJ designed and conceptualized the study. DXK, LYQ, YKL, ZLL, XY, YSC, WY, LX, QD, LZC, ZZH and LWJ collected data. DXK, LYQ, LXT, and TRQ analyzed data. DXK and LYQ wrote the manuscript. All authors have read and approved the final version of manuscript.

Funding

This research was supported by the Foundation of National Key Program of Research and Development of China (Grant NO: 2016YFC0900803), National Natural Science Foundation of China (Grant NO: 81573243, 81602925, U1304821), Science and Technology Foundation for Innovation Talent of Henan Province (Grant NO: 164100510021, 154200510010), Science and Technology Innovation Talents Support Plan of Henan Province Colleges and Universities (Grant NO: 14HASTIT035), High-level Personnel Special Support Project of Zhengzhou University (Grant NO: ZGDG13001). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements

The authors thank the Henan Rural Cohort participants, staff, and investigators for their contributions to the study. In addition, the authors thank Tanko Abdulai for his writing assistance.

Authors' Information

Email addresses:

Xiaokang Dong⁴: dong4568529173@163.com
Yuqian Li²: liyuqian@zzu.edu.cn
Kaili Yang¹: kelly1992abc@163.com
Lulu Zhang¹: lulzhang@126.com
Yuan Xue³: xueyuan@163.com
Songcheng Yu³: scyu@zzu.edu.cn
Xiaotian Liu¹: xtLIU2008@126.com
Runqi Tu¹: 15093296877@163.com
Dou Qiao¹: xiaojiaozhi@126.com
Zhicheng Luo¹: luozhicheng@zzu.edu.cn
Xue Liu¹: liuxue_hyun@163.com
Yan Wang¹: wy1833717@163.com
Wenjie Li³: lwj@zzu.edu.cn
Zhaohui Zheng⁴: fcczhengzh@zzu.edu.cn
Chongjian Wang¹*: tjwcj2005@126.com

Authors affiliations:

¹ Department of Epidemiology and Biostatistics, College of Public Health, Zhengzhou University, Zhengzhou, Henan, PR. China.
² Department of Clinical Pharmacology, School of Pharmaceutical Science, Zhengzhou University, Zhengzhou, Henan, PR. China.
References

1. Liu H, Zhang XM, Wang YL, Liu BC. Prevalence of hyperuricemia among Chinese adults: a national cross-sectional survey using multistage, stratified sampling. Journal of nephrology. 2014;27, 653-658. doi:10.1007/s40620-014-0082-z

2. B L, T W, Hn Z, Ww Y, Hp Y, Cx L, et al. The prevalence of hyperuricemia in China: a meta-analysis. BMC public health. 2011;11, 832. doi:10.1186/1471-2458-11-832

3. Liu R, Han C, Wu D, Xia X, Gu J, Guan H, et al. Prevalence of Hyperuricemia and Gout in Mainland China from 2000 to 2014: A Systematic Review and Meta-Analysis. BioMed research international 2015, 762820. doi:10.1155/2015/762820

4. Zhang Q, Lou S, Meng Z, Ren X. Gender and age impacts on the correlations between hyperuricemia and metabolic syndrome in Chinese. Clinical rheumatology. 2011;30, 777-787. doi:10.1007/s10067-010-1660-7

5. Zhang H, Li Y, Mao Z, Liu X, Zhang X, Yang K, et al. Sex-specific associations of serum uric acid with metabolic syndrome in Chinese rural population: The RuralDiab study. Clinica chimica acta; international journal of clinical chemistry. 2018,480, 119-125. doi:10.1016/j.cca.2018.02.003

6. Yadav D, Lee ES, Kim HM, Choi E, Lee EY, Lim JS, et al. Prospective study of serum uric acid levels and incident metabolic syndrome in a Korean rural cohort. Atherosclerosis. 2015;241, 271-277. doi:10.1016/j.atherosclerosis.2015.04.797

7. Zgaga L, Theodoratou E, Kyle J, Farrington SM, Agakof F, Tenesa A, et al. The association of dietary intake of purine-rich vegetables, sugar-sweetened beverages and dairy with plasma urate, in a cross-sectional study. PloS one. 2012;7, e38123. doi:10.1371/journal.pone.0038123

8. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. The New England journal of medicine. 2004;350, 1093-1103. doi:10.1056/NEJMoa035700

9. Nilius B, Appendino G. Spices: the savory and beneficial science of pungency. Reviews of physiology. Rev Physiol Biochem Pharmacol. 2013;164:1–76. doi:10.1007/112_2013_11 12.

10. Szolcsanyi J. Forty years in capsaicin research for sensory pharmacology and physiology. Neuropeptides. 2004;38, 377-384. doi:10.1016/j.npep.2004.07.005

11. Astrup A, Kristensen M, Gregersen NT, Belza A, Lorenzen JK, Due A, et al. Can bioactive foods affect obesity? Annals of the New York Academy of Sciences. 2010;1190, 25-41. doi:10.1111/j.1749-6632.2009.05272.x

12. Lv J, Qi L, Yu C, Yang L, Guo Y, Chen Y, et al. Consumption of spicy foods and total and cause specific mortality: population based cohort study. BMJ (Clinical research ed). 2015;351, h3942. doi:10.1136/bmj.h3942

13. Shi Z, Riley M, Taylor AW, Page A. Chilli consumption and the incidence of overweight and obesity in a Chinese adult population. International journal of obesity. 2005;41,1074-1079. doi:10.1038/sj.ijo.0803670

14. Whiting S, Derbyshire EJ, Tiwari B. Could capsaicinoids help to support weight management? A systematic review and meta-analysis of energy intake data. Appetite. 2014;73, 183-188. doi:10.1016/j.appet.2013.11.005

15. Yoneshiro T, Alta S, Kawai Y, Iwanaga T, Saito M. Nonpungent capsaicin analogs (capsinoids) increase energy expenditure through the activation of brown adipose tissue in humans. The American journal of clinical nutrition. 2012,95, 845-850. doi:10.1093/ajcn/njs1206

16. Shu Z, Riley M, Taylor AW, Page A. The role of herbs and spices in cancer prevention. The Journal of nutritional biochemistry. 2008;19, 347-361. doi:10.1016/j.jnutbio.2007.11.015

17. Ludy MJ, Mattes RD. Comparison of sensory, physiological, personality, and cultural attributes in regular spicy food users and non-users. Appetite. 2014;73, 183-188. doi:10.1016/j.appet.2013.11.005

18. Sun D, Lv J, Chen W, Li S, Guo Y, Bian Z, et al. Spicy food consumption is associated with adiposity measures among half a million Chinese people: the China Kadoorie Biobank study. BMC public health. 2014;14, 1293. doi:10.1186/1471-2458-14-1293

19. Yang K, Li Y, Mao Z, Liu X, Zhang H, Liu R, et al. Relationship between spicy flavor, spicy food intake frequency, and general obesity in a rural adult Chinese population: The RuralDiab study. Nutrition, metabolism, and cardiovascular diseases : NMCD. 2018;28, 252-261. doi:10.1016/j.numecd.2017.10.021

20. Fu S, Luo L, Ye P, Xiao W. Epidemiological associations between hyperuricemia and cardiometabolic risk factors: a comprehensive study from Chinese community. BMC cardiovascular disorders. 2015;15, 129. doi:10.1186/s12872-015-0116-z

21. Liu X, Mao Z, Li Y, Wu W, Zhang X, Hoo W, et al. Cohort Profile: The Henan Rural Cohort: a prospective study of chronic non-communicable diseases. Int J Epidemiol. 2019;48(6):1756–1756. doi:10.1093/ije/dyz039

22. Hou J, Liu X, Tu R, Dong X, Zhai Z, Mao Z, et al. Long-term exposure to ambient air pollution attenuated the association of physical activity with metabolic syndrome in rural Chinese adults: A cross-sectional study. Environ Int. 2020;136:105459. doi:10.1016/j.envint.2020.105459

23. Xue Y, Yang K, Wang B, Liu C, Mao Z, Yu S, et al. Reproducibility and validity of an FFQ in the Henan Rural Cohort Study. Public Health Nutr. 2020;23(1):34–40. doi:10.1017/S1368980019002416
26. Dong X, Zhang H, Wang F, Liu X, Yang K, Tu R, et al. Epidemiology and prevalence of hyperuricemia among men and women in Chinese rural population: The Henan Rural Cohort Study [published online ahead of print, 2019 Sep 16]. Mod Rheumatol. 2019; 1–11. doi:10.1080/14397595.2019.1660048

27. Wang Y, Li Y, Liu X, Tu R, Zhang H, Qian X, et al. The prevalence and related factors of familial hypercholesterolemia in rural population of China using Chinese modified Dutch Lipid Clinic Network definition. BMC Public Health. 2019; 19(1):837. doi: 10.1186/s12889-019-7212-4.

28. Ekelund U, Sepp H, Brage S, Becker W, Jakes R, Hennings M, et al. Criterion-related validity of the last 7-day, short form of the International Physical Activity Questionnaire in Swedish adults. Public health nutrition. 2006;9, 258-265. doi:10.1079/phn2005840

29. Wang B, Liu L, Qiao D, Xue Y, Liu X, Zhang D, et al. The association between frequency of away-from home meals and type 2 diabetes mellitus in rural Chinese adults: the Henan Rural Cohort Study. Eur J Nutr. 2020; 10.1007/s00394-020-02212-5. doi:10.1007/s00394-020-02212-5.

30. Vanderweele TJ, Vansteelandt S. Odds ratios for mediation analysis for a dichotomous outcome. Am J Epidemiol. 2010;172(12):1339–1348. doi:10.1093/aje/kwq332

31. Zhang L, Li Y, Wang C, Mao Z, Zhou W, Tian Z, et al. Early menarche is associated with an increased risk of type 2 diabetes in rural Chinese women and is partially mediated by BMI: the Henan Rural Cohort Study. Menopause. 2019; 26(11):1265–1271. doi:10.1097/GME.0000000000001385

32. Fu S, Luo L, Ye P, Xiao W. Epidemiological associations between hyperuricemia and cardiometabolic risk factors: a comprehensive study from Chinese community. BMC cardiovascular disorders. 2015;15, 129. doi:10.1186/s12872-015-0116-z

33. Chen Y, Zhang N, Sun G, Guo X, Yu S, Yang H, et al. Metabolically healthy obesity also has risk for hyperuricemia among Chinese general population: A cross-sectional study. Obesity research & clinical practice. 2016;10 Suppl 1, S84-s95. doi:10.1016/j.orcp.2016.03.008

34. Shiraishi H, Une H. The effect of the interaction between obesity and drinking on hyperuricemia in Japanese male office workers. Journal of epidemiology. 2009;19, 12-16. doi:10.2188/jea.je20080016

35. McAdams-DeMarco MA, Law A, Maynard JW, Coresh J, Baer AN. Risk factors for incident hyperuricemia during mid-adulthood in African American and white men and women enrolled in the ARIC cohort study. BMC musculoskeletal disorders. 2013;14, 347. doi:10.1186/1471-2474-14-347

36. Xu Q, Yan S, Wang C, Yu B, Zhou X, Luan Q, et al. Spicy Food Intake Increases the Risk of Overweight and Obesity. Wei Sheng Yan Jiu. 2019;48(3):374–379.

37. Xue Y, He T, Yu K, Zhao A, Zheng W, Zhang Y, et al. Association between spicy food consumption and lipid profiles in adults: a nationwide population-based study. The British journal of nutrition. 2011;118, 144-153. doi:10.1017/S000711451100157X

38. Yu K, Xue Y, He T, Guan L, Zhao A, Zhang Y. Association of Spicy Food Consumption Frequency with Serum Lipid Profiles in Older People in China. The journal of nutrition, health & aging. 2017;22, 311-320. doi:10.1007/s12603-018-1002-z

39. Park JH, Kim SG, Kim JH, Lee JS, Jung WY, Kim HK, et al. Spicy Food Preference and Risk for Alcohol Dependence in Korean. Psychiatry investigation. 2017;14, 825-829. doi:10.4306/pi.2017.14.6.825

40. Makinouchi T, Sakata K, Oishi M, Tanaka K, Mogawa K, Watanabe M, et al. Benchmark dose of alcohol consumption for development of hyperuricemia in Japanese male workers: An 8-year cohort study. Alcohol (Fayetteville, NY). 2016;56, 9-14. doi:10.1016/j.alcohol.2016.08.002

41. Sherman PW, Hash GA. Why vegetable recipes are not very spicy. Evol Hum Behav. 2001;22(3):147–163. doi:10.1016/s1090-5138(00)00068-4

42. Nan H, Qiao Q, Dong Y, Gao W, Tang B, Qian R, et al. The prevalence of hyperuricemia in a population of the coastal city of Qingdao, China. J Rheumatol. 2006;33(7):1346–1350.

43. Peng TC, Wang CC, Kao TW, Chan JY, Yang YH, Chang YW, et al. Relationship between hyperuricemia and lipid profiles in US adults. BioMed research international. 2015, 127596. doi:10.1155/2015/1275