The Association Between Dietary Calcium Intake and Hyperuricemia Among Chinese Adults

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Abstract

Background

Previous studies demonstrated that dietary nutrients intake is associated with the risk of hyperuricemia. Calcium, acting as an essential nutrient in human body, therefore, may be associated with hyperuricemia. However, until now, no studies have independently assessed the association between dietary calcium intake.

Methods

7,606 participants aged 18–94 years from the China Health and Nutrition Survey (CHNS) in 2009 were extracted. Three consecutive 24 dietary recalls were used to assess all dietary intake. Multivariable logistic regression and restricted cubic spline (RCS) was performed to evaluate the relationship between dietary calcium intake and hyperuricemia after adjustment for confounders.

Results

The crude prevalence of hyperuricemia was 15.67% (20.51% for male, 11.66% for female). A positive association between dietary calcium intake and risk of hyperuricemia even in the fully adjusted model. Compared with the lowest quintile, the odds rations for hyperuricemia were 1.130 [95% confidence interval (CI): 0.885–1.441], 1.257 (95% CI: 0.987–1.600), 1.309 (95% CI: 1.020–1.680), and 1.552 (95% CI: 1.180–2.041) for the second to highest quintiles of dietary calcium intake, respectively (*P* for trend = 0.015), and a positive dose-response relationship was observed.

Conclusions

Higher dietary calcium intake is associated with an increased risk of hyperuricemia independent of some major confounding factors.

1. Introduction

hyperuricemia (HUA) is a common metabolic disease caused by an increase in uric acid production or a decrease in uric acid elimination due to the disorder of purine metabolism. Previous studies have proved that hyperuricemia is not only closely related to the occurrence and development of gout, chronic kidney disease, hypertension, diabetes etc., but also an evaluation indicator of all-cause death and a prognosis indicator of heart failure (1–12). According to epidemiological data, although the prevalence of hyperuricemia has mildly decreased in the United States from 2007 to 2016 (13). The prevalence of hyperuricemia varies from 9.8 to 26.8% in worldwide, a high number (13–16). Hyperuricemia is still a serious threat to public health, which not only affects the quality of patients' life but also increases the social and economic burden.

In recent years, more and more studies have demonstrated that increasing the intake of dietary nutrients such as vitamin B, vitamin C, zinc and magnesium may help to reduce serum uric acid in human and animal experiments and probably be a protective factor for hyperuricemia (17–22). As an important component of dietary nutrients, calcium plays an important role in maintaining normal physiological functions of the body, such as maintaining bones, regulating hormone secretion, transmitting nerve impulses and vascular activity. Recent epidemiological studies and clinical randomized controlled trials have found that calcium appears to be positively associated with hyperuricemia (15, 23, 24). There are also studies with inconsistent results. For example, a randomized controlled clinical trial showed that dietary calcium intake was independent of urate concentration (25), studies in South Korea and the United Kingdom found that people with higher dietary calcium intake had lower uric acid levels (26, 27). Current research on relationship between calcium and hyperuricemia is controversial and limited, especially literatures on the association between dietary calcium intake and hyperuricemia. Until now, no research has independently assessed the relationship between dietary calcium intake and hyperuricemia. Therefore, it is necessary to explore the association between dietary calcium intake and hyperuricemia to fill this literature gap.

2. Methods

2.1 Study Population

Data for this study came from the China Health and Nutrition Survey (CHNS), an ongoing prospective study conducted by the National Institute for Nutrition and Health (NINH, former National Institute of Nutrition and Food Safety) at the Chinese Center for Disease Control and Prevention (CCDC) and the Carolina Population Center at the University of North Carolina at Chapel Hill. This survey has finished ten rounds from 1989 to 2015 by using a multistage, random cluster process to draw samples in 15 provinces and municipal cities that substantially vary in geography, economic development, public resources and health indicators. As a diagnostic indicator of HUA, serum uric acid was only detected in the published CHNS data in 2009. Therefore, a cross-sectional data of CHNS in 2009 were used in this study. Data sources are available on the official website https://www.cpc.unc.edu/projects/china. In 2009, blood samples were collected from 9,549 respondents who completed a structured questionnaire under the guidance of a professional person, asking about socioeconomic characteristics, lifestyle exposure, general health and medical history, and

completing physical measurements. People who have complete sociodemographic data and serum uric acid values and three-day 24-hour dietary recall were considered valid subjects. The exclusion criteria include: (1) Age < 18 or currently pregnant; (2) Lack of blood samples or diet or other information; (3) Exceeding the energy intake limit (Male: > 6000 kcal or < 800 kcal; Female: > 4000 or < 600 kcal), systolic blood pressure (SBP) < 40 mmHg or > 300 mmHg, diastolic blood pressure (DBP) < 30 mmHg or > 200 mmHg, body mass index (BMI) < 14 kg/ m^2 or > 45kg/ m^2 or other unreliable observations. The final analysis sample included 7,634 adults (Fig. 1). All individuals had signed a written informed consent prior to participating in the study, which was in accordance with the Declaration of Helsinki and approved by the Institutional Review Boards of the National Institute of Nutrition and Food Safety of China (Beijing) and the University of North Carolina (Chapel Hill, NC, USA) (28).

2.2 Study Variables

2.2.1 Definition of disease

hyperuricemia was defined as serum uric acid ≥ 420 umol/L for men and ≥ 360 umol/L for women (29). Hypertension (HT) was defined by SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, currently undertaking antihypertensive medication or hypertension (self-reported doctor diagnosed). Diabetes (DM) was defined by fasting blood glucose (FPG) ≥ 7.0 mmol/l, HbA1C ≥ 6.5%, currently undergoing drug treatment, injecting insulin for blood glucose control or diabetes (self-reported doctor diagnosed). Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate(eGFR) < 60 mL/min/1.73 m^2. Cardiovascular disease (CVD) was determined by self-reported physician-diagnosed myocardial infarction or stroke as in the questionnaire.

2.2.2 Assessment of dietary calcium and energy intake

We collected diet data at the household level and individual level using weighing methods in combination with 3 consecutive 24-h dietary recalls (30). Firstly, household food consumption was assessed based on the sum of food stocks at the start of the survey, food produced at home and purchased at market during the survey period minus the amount wasted. Then, with the help of food models and pictures, each family member was asked to report the amount and location of each type of food they had eaten in the previous day, so that, trained field interviewers can more accurately record each person's consumption of each food item through a combination of personal meal reporting and home weight techniques (31). Finally, according to the nutrient content of each food in the 2002 and 2004 edition of the Chinese Food Composition Table, the individual nutrient intake was calculated.

2.2.3 Detection of serum biomarkers and anthropometry

Participants were required to fast for more than 8 hours without strenuous exercise in 30 minutes before drawing blood. Trained and qualified blood collector will collect 12ml of blood from participants' veins in the morning, meanwhile, experienced professionals will carry out on-site quality control. The blood samples were tested in the field, at provincial and national laboratories. The blood transportation process strictly complies with the guidelines of blood related standards. Please refer to the 2009 Blood Specimen Collection Manual for sample collection, treatment, storage and related analysis and testing https://www.cpc.unc.edu/projects/china/data/datasets/Blood%20Collection%20Protocol_English.pdf. The biomarker test results used in this study provided by Beijing National Central Laboratory (Medical Laboratory Accreditation Certificate: ISO 15189:2007). The detection of FPG, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), serum uric acid (SUA) was measured by automatic biochemical analyzer (Hitachi 7600). The detection, reagent manufacturers and equipment of other serum biomarkers, please refer to the follow list https://www.cpc.unc.edu/projects/china/data/datasets/Biomarker_Methods.pdf. eGFR was calculated from the Chronic Kidney Disease Epidemiology Collaboration equation.

Following standard procedures, anthropometric measurements were administrated by well-trained researchers in private and comfortable room. All participants were requested to remove bulky clothing and shoes before measurement. Standing height was measured to the nearest 0.1 cm using a SECA 206 wall-mounted metal tape, and weight was measured to the nearest 0.1 kg using a calibrated beam balance. BMI (kg/m^2) was calculated as weight in kilograms divided by height in meters square. Three blood pressure measurements were taken with a mercury sphygmomanometer at least 10 minutes apart after sitting for 5 minutes, and the average of the three blood pressure measurements was used for the final analysis (32).

2.2.4 Definitions of other Covariates

Age, gender, nationality, marital status, education level, sleep duration, activity level, smoking status, drinking status, tea status and other information were obtained based on a self-reported questionnaire. The selection of covariables is recognized in the literature or related to hyperuricemia, the intake and demand of dietary calcium.

2.3 Statistical Analyses

All statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, North Carolina, USA) and R version 4.0.5. continuous variables were expressed as mean ± standard deviation, while categorical values were expressed as numbers (percentage). Differences between groups were evaluated using *t* test or Kruskal-Wallis H test when appropriate for the continuous variables, and the chi-square test for the categorical variables. Multivariable logistic regression analysis was used to estimate the odds ratio (OR) and 95% confidence interval (CI) of HUA among different quintile of dietary calcium intake, with the lowest quintile being considered as the references. Model 1 was adjusted for age, gender and nationality. Model 2 was additionally adjusted for, marital status, education and activity level, smoking status, drinking status, tea status, sleep duration and body mass

index based on model 1. Model 3 was further adjusted for triglyceride, total cholesterol, high-density lipoprotein cholesterol, hypertension, diabetes, chronic kidney disease and cardiovascular disease based on model 2. Model 4 was further adjusted for daily energy, protein, fat, cholesterol, diet-fiber intake based on model 3. All *P*-values were two-sided, and $P < 0.05$ was considered to statistical significance.

3. Results

A total of 7606 subjects aged (50.57 ± 14.87) years were included in the study, including 1192 patients with hyperuricemia, with a crude prevalence of 15.67%. Among 3567 males, 721 were patients, with a crude prevalence of 20.21%. There were 4039 females, including 471 patients, with a crude prevalence of 11.66%. When the population was divided into hyperuricemia and non-hyperuricemia, excepting for nationality ($P = 0.3634$), sleep duration ($P = 0.1223$), diet fiber intake ($P = 0.4359$), other characteristics were statistically significant. When people were grouped by quintile of dietary calcium intake, characteristics were statistically significant differences in age, gender, nationality, residence, marital status, education level, activity level, smoking status, drinking status, tea status, hypertension, chronic kidney disease, energy, protein, fat, cholesterol, dietary fiber (Table 1).

Table 1 Baseline characteristics of participants according to whether had hyperuricemia and quintiles of dietary calcium

intakes

	Hyperuricemia			Calcium intake					
Characteristics	No	Yes	P [a]	Q1	Q2	Q3	Q4	Q5	P[b]
No. of subjects (n)	6414	1192		1521	1522	1521	1522	1520	
Male [n (%)]	2846(44.37)	721(60.49)	**< 0.0001**	541(35.57)	668(43.89)	760(49.97)	770(50.59)	828(54.47)	**< 0.0001**
Han nationality [n (%)]	5687(88.67)	1046(87.75)	0.3634	1322(86.92)	1352(88.83)	1346(88.49)	1328(87.25)	1385(91.12)	**0.0024**
Urban [n (%)]	1950(30.40)	455(38.17)	**< 0.0001**	354(23.27)	410(26.94)	477(31.36)	538(35.35)	626(41.18)	**< 0.0001**
Marital status [n (%)]									
Never married	373(5.82)	62(5.20)	**0.0039**	83(5.46)	86(5.65)	102(6.71)	78(5.12)	86(5.66)	**< 0.0001**
Married	5475(85.36)	989(82.97)		1229(80.80)	1291(84.82)	1282(84.29)	1338(87.91)	1324(87.11)	
Divorced, widowed or separated	566(8.82)	141(11.83)		209(13.74)	145(9.53)	137(9.01)	106(6.96)	110(7.24)	
Education level [n (%)]									
Primary school	2707(42.20)	493(41.36)	**0.0037**	750(49.31)	678(44.55)	630(41.42)	607(39.88)	535(35.20)	**< 0.0001**
Middle school	2241(34.94)	376(31.54)		493(32.41)	518(34.03)	515(33.86)	542(35.61)	549(36.12)	
High school	1466(22.86)	323(27.10)		278(18.28)	326(21.42)	376(24.72)	373(24.51)	436(28.68)	
Activity level [n (%)]									
Light	3256(50.76)	737(61.83)	**< 0.0001**	854(56.15)	792(52.04)	796(52.33)	740(48.62)	811(53.36)	**< 0.0001**
Moderate	862(13.44)	159(13.34)		165(10.85)	185(12.16)	201(13.21)	217(14.26)	253(16.64)	
Heavy	2296(35.80)	296(24.83)		502(33.00)	545(35.81)	524(34.45)	565(37.12)	456(30.00)	
Smoking status[n (%)]									
Never	4490(70.00)	737(61.83)	**< 0.0001**	1147(75.41)	1062(69.78)	1023(67.26)	1019(66.95)	976(64.21)	**< 0.0001**
Former	204(3.18)	50(4.19)		39(2.56)	45(2.96)	56(3.68)	59(3.88)	55(3.62)	
Current	1720(26.82)	405(33.98)		335(22.02)	415(27.27)	442(29.06)	444(29.17)	489(32.17)	
Drink alcohol [n (%)]	1955(30.48)	508(42.62)	**< 0.0001**	334(21.96)	423(27.79)	513(33.73)	581(38.17)	612(40.26)	**< 0.0001**
Drink tea [n (%)]	2133(33.26)	468(39.26)	**< 0.0001**	466(30.64)	452(29.70)	547(35.96)	570(37.45)	566(37.24)	**< 0.0001**
Hypertension [n (%)]	1798(28.03)	535(44.88)	**< 0.0001**	498(32.74)	426(27.99)	461(30.31)	443(29.11)	505(33.22)	**0.0053**
Diabetes [n (%)]	572(8.92)	222(18.62)	**< 0.0001**	155(10.19)	162(10.64)	155(10.19)	173(11.37)	149(9.80)	0.6756
CKD [n (%)]	569(8.87)	312(26.17)	**< 0.0001**	219(14.40)	154(10.12)	176(11.57)	165(10.84)	167(10.99)	**0.0026**
CVD [n (%)]	131 (2.04)	43 (3.61)	**0.0009**	45 (2.96)	37 (2.43)	24 (1.58)	32 (2.1)	36 (2.37)	0.1498

[a] *P*-value of *t* test, [b] *P*-value of Kruskal-Wallis H test.

BMI, body mass index; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; CKD, chronic kidney disease; CVD, cardiovascular disease

	Hyperuricemia			Calcium intake					
Age ($x \pm s$, years)	50.06 ± 14.76	53.27 ± 15.14	**< 0.0001**	52.5 ± 16.08	50.01 ± 14.63	50.09 ± 15.01	49.76 ± 14.26	50.48 ± 14.13	**< 0.0001**
Sleep duration ($x \pm s$, h)	7.94 ± 1.23	7.87 ± 1.28	0.0684	7.98 ± 1.29	7.91 ± 1.21	7.96 ± 1.24	7.91 ± 1.23	7.89 ± 1.24	0.1902
BMI ($x \pm s$, kg/m^2)	23.1 ± 3.37	24.79 ± 3.63	**< 0.0001**	23.3 ± 3.6	23.31 ± 3.41	23.41 ± 3.42	23.42 ± 3.51	23.41 ± 3.41	0.7466
Energy ($x \pm s$, kcal)	1864.1 ± 630.08	1928.88 ± 643.92	**0.0012**	1453.8 ± 476.72	1721.72 ± 487.48	1867.82 ± 527.52	2017.8 ± 585.87	2310.42 ± 710.66	**< 0.0001**
protein ($x \pm s$, g)	69.96 ± 26.98	75.3 ± 28.94	**< 0.0001**	49.49 ± 17.05	60.96 ± 17.82	69.03 ± 19.16	77.21 ± 21.83	97.3 ± 31.55	**< 0.0001**
fat ($x \pm s$, g)	39.97 ± 26.3	44.47 ± 27.55	**< 0.0001**	28.06 ± 21.63	34.41 ± 21.47	40.39 ± 24.66	44.81 ± 25.68	55.7 ± 29.81	**< 0.0001**
cholesterol ($x \pm s$, mg)	301.06 ± 255.55	331.48 ± 249.15	**0.0002**	218.51 ± 180.87	259.07 ± 209.92	301.64 ± 224.05	328.03 ± 251.73	421.97 ± 332.6	**< 0.0001**
Diet fiber ($x \pm s$, g)	12.49 ± 8.45	12.33 ± 7.88	0.5408	8.71 ± 4.81	11.31 ± 7.47	11.64 ± 5.84	13.12 ± 7.05	17.55 ± 12.02	**< 0.0001**
TG ($x \pm s$, mmol/L)	1.43 ± 1	3 ± 2.59	**< 0.0001**	1.65 ± 1.37	1.64 ± 1.37	1.65 ± 1.34	1.7 ± 1.67	1.74 ± 1.67	0.6655
TC ($x \pm s$, mmol/L)	4.79 ± 0.97	5.26 ± 1.09	**< 0.0001**	4.89 ± 1.04	4.85 ± 1.03	4.83 ± 0.99	4.85 ± 0.95	4.88 ± 1.01	0.7039
HDL_C ($x \pm s$, mmol/L)	1.46 ± 0.46	1.28 ± 0.61	**< 0.0001**	1.44 ± 0.47	1.44 ± 0.65	1.42 ± 0.38	1.44 ± 0.44	1.43 ± 0.46	0.4718

[a] *P*-value of *t* test, [b] *P*-value of Kruskal-Wallis H test.

BMI, body mass index; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; CKD, chronic kidney disease; CVD, cardiovascular disease

A positive relationship between calcium intake and the prevalence of hyperuricemia was observed in all the 4 multivariable models, as shown in (Table 2). As shown in model 1, the ORs (95% CIs) for hyperuricemia, with adjustment for age, gender and nation, were 1.059 (95% CI: 0.854–1.314), 1.247 (95% CI: 1.012–1.536), 1.371 (95% CI: 1.116–1.685), 1.655 (95% CI: 1.354–2.024) from the second to the highest calcium intake quintile, respectively (*P* for trend < 0.001), compared with the lowest quintile. With further adjustment for residence, marital status, education level, activity level, smoking, drinking status, tea status, sleep duration and body mass index (model 2), the multivariable-adjusted ORs (95% CIs) for hyperuricemia were higher than that for the lowest quintile in the second (1.062, 95%CI: 0.852–1.323), third (1.223, 95%CI: 0.987–1.515), fourth (1.351, 95%CI: 1.092–1.671), and fifth (1.591, 95%CI: 1.291–1.960) quintiles of calcium intake (*P* for trend < 0.001). On the basis of model 2, an additional model including triglyceride, total cholesterol, high-density lipoprotein cholesterol, hypertension, diabetes, chronic kidney disease, cardiovascular disease (model 3), the ORs (95% CIs) for hyperuricemia were 1.153 (95% CI: 0.906–1.468), 1.321 (95% CI: 1.045–1.671), 1.410 (95% CI: 1.115–1.784), 1.750 (95% CI: 1.391–2.202) from the second to the highest calcium intake quintile, respectively (*P* for trend was < 0.001), compared with the lowest quintile. On the basis of model 3, an additional model including daily energy, protein, fat cholesterol, diet-fiber intake (model 4) did not materially alter the results (*P* for trend was 0.0015). In addition, we further explored the dose-response relationship between dietary calcium intake and the risk of hyperuricemia. (Fig. 2)

Table 2
Odds ratios (95% confidence intervals) of hyperuricemia according to quintiles of dietary calcium intake

	Dietary calcium intake					P [1] for trend
	Q1	Q2	Q3	Q4	Q5	
Median intake (mg/d)	194.25	277.98	352.90	456.75 ± 40.43	682.00	
Case/ Total	190/1521	201/1522	238/1521	257/1522	306/1520	
Model 1	Ref	1.059 (0.854, 1.314)	**1.247 (1.012, 1.536)**	**1.371 (1.116, 1.685)**	**1.655 (1.354, 2.024)**	**< 0.0001**
Model 2	Ref	1.062 (0.852, 1.323)	1.223 (0.987, 1.515)	**1.351 (1.092, 1.671)**	**1.591 (1.291, 1.960)**	**< 0.0001**
Model 3	Ref	1.153 (0.906, 1.468)	**1.321 (1.045, 1.671)**	**1.410 (1.115, 1.784)**	**1.750 (1.391, 2.202)**	**< 0.0001**
Model 4	Ref	1.130 (0.885, 1.441)	1.257 (0.987, 1.6)	**1.309 (1.020, 1.680)**	**1.552 (1.180, 2.041)**	**0.0015**
Model 1, adjusted for age, gender, nation.						
Model 2, further adjusted for marital status, education and activity level, smoking status, drinking status, tea status, sleep duration and body mass index based on model 1.						
Model 3, further adjusted for triglyceride, total cholesterol, high-density lipoprotein cholesterol, hypertension, diabetes, chronic kidney disease and cardiovascular disease based on model 2.						
Model 4, further adjusted for daily energy, protein, fat, cholesterol, diet-fiber intake based on model 3.						
[1] Tests for trend were conducted by modeling the median of each quintile-defined category as a continuous variable in Logistic regression models.						

Age, gender and BMI are recognized risk factors for hyperuricemia. The prevalence of hyperuricemia was significantly different between hypertensive and non-hypertensive patients, diabetic and non-diabetic patients, and patients with chronic kidney disease and non-chronic kidney disease, so we conducted a stratified analysis of age, gender, BMI, hypertension, diabetes, chronic kidney disease and the positive association of dietary calcium intake with the risk of hyperuricemia was unchanged among participants with various risk profiles (all P for interaction > 0.10). The trend of associations between dietary calcium intake and hyperuricemia remained similar in most subgroups Table 3.

Table 3

Stratified odds ratios (95% confidence intervals) [1] of hyperuricemia according to quintiles of dietary calcium intake by various characteristics of participants

	Dietary calcium intake					P [2] for trend	P [3] for interaction
	Q1	Q2	Q3	Q4	Q5		
Age (years)							
<50	Ref	1.169 (0.773, 1.767)	1.424 (0.96, 2.112)	1.328 (0.882, 2.000)	1.481 (0.953, 2.302)	0.1171	0.9325
≥ 50	Ref	1.133 (0.834, 1.538)	1.196 (0.878, 1.628)	1.245 (0.904, 1.714)	**1.694 (1.189, 2.415)**	**0.0025**	
Gender							
Male	Ref	1.298 (0.944, 1.784)	1.372 (0.995, 1.891)	**1.453 (1.044, 2.022)**	**1.976 (1.375, 2.839)**	**0.0004**	0.8311
Female	Ref	0.922 (0.635, 1.338)	1.099 (0.766, 1.578)	1.054 (0.721, 1.541)	1.177 (0.778, 1.781)	0.3335	
BMI (kg/m^2)							
< 24	Ref	1.274 (0.894, 1.815)	1.336 (0.941, 1.898)	1.224 (0.847, 1.768)	**1.755 (1.187, 2.597)**	**0.0104**	0.8483
≥ 24	Ref	1.069 (0.762, 1.5)	1.244 (0.888, 1.743)	**1.445 (1.021, 2.046)**	**1.545 (1.049, 2.276)**	**0.0153**	
Hypertension							
No	Ref	1.081 (0.782, 1.495)	1.161 (0.842, 1.602)	1.377 (0.991, 1.912)	**1.708 (1.199, 2.435)**	**0.0009**	0.5983
Yes	Ref	1.028 (0.708, 1.493)	1.366 (0.946, 1.972)	1.123 (0.765, 1.649)	1.259 (0.815, 1.945)	0.3699	
Diabetes							
No	Ref	1.009 (0.772, 1.318)	1.195 (0.921, 1.551)	1.269 (0.97, 1.659)	**1.532 (1.142, 2.054)**	**0.0012**	0.1311
Yes	Ref	1.846 (0.976, 3.493)	1.731 (0.884, 3.391)	1.61 (0.806, 3.214)	1.69 (0.769, 3.713)	0.5076	
CKD							
No	Ref	1.073 (0.809, 1.424)	1.239 (0.939, 1.635)	1.293 (0.971, 1.721)	**1.465 (1.07, 2.005)**	**0.0118**	0.9305
Yes	Ref	1.283 (0.777, 2.118)	1.507 (0.901, 2.521)	1.356 (0.792, 2.32)	**1.952 (1.077, 3.539)**	**0.0459**	

[1] Covariates: age (continuous), gender (men/woman), nation (Han/other), residence (urban/rural), marital status (never married/married/divorced, widowed or separated), education level (primary school/middle school/high school), activity level (light, moderate, heavy), smoking status (yes/no), drinking status (yes/no), tea status (yes/no), sleep duration (continuous), BMI (continuous),TG (continuous), TC (continuous), HDL_C (continuous), hypertension (yes/no), diabetes (yes/no), CKD (yes/no), CVD (yes/no), energy, protein, fat, cholesterol, diet fiber intakes (continuous), except for the stratifying variables per se.

[2] P for trend values were calculated by modeling the median of each quintile-defined category as a continuous variable in the model.

[3] P for interaction values were calculated using the likelihood-ratio test.

Two sensitivity analyses were conducted to assess the robustness of the associations. Individuals who might be taking medications which may affect serum uric acid concentration, such as hypertension, cardiovascular disease and chronic kidney disease were excluded, and the results were consistent in the primary analysis. The cumulative mean dietary calcium intake between 2004 and 2009 was used to replace average calcium intake (2009) as it better reflects a long-term diet and may reduce dietary measurement error, the associations remained consistent with before results (Table 4).

Table 4
Sensitivity analysis

	Dietary calcium intake					P [1] for trend
	Q1	Q2	Q3	Q4	Q5	
Exclude individuals who might be taking medications which may affect serum uric acid concentration						
Model 1	Ref	1.061 (0.765, 1.47)	1.271 (0.929, 1.739)	**1.399 (1.028, 1.903)**	**1.755 (1.302, 2.366)**	**< 0.0001**
Model 2	Ref	1.079 (0.774, 1.504)	1.264 (0.919, 1.74)	**1.386 (1.01, 1.901)**	**1.669 (1.228, 2.269)**	**0.0002**
Model 3	Ref	1.243 (0.865, 1.786)	**1.438 (1.013, 2.043)**	**1.553 (1.094, 2.205)**	**1.88 (1.339, 2.638)**	**0.0002**
Model 4	Ref	1.228 (0.852, 1.77)	1.373 (0.959, 1.967)	**1.462 (1.01, 2.114)**	**1.738 (1.168, 2.586)**	**0.0075**
Cumulative mean dietary calcium intake						
Model 1	Ref	1.108 (0.851, 1.444)	1.167 (0.898, 1.517)	1.25 (0.963, 1.622)	**1.466 (1.137, 1.89)**	**0.0016**
Model 2	Ref	1.102 (0.841, 1.445)	1.162 (0.887, 1.524)	1.226 (0.934, 1.608)	**1.397 (1.07, 1.824)**	**0.0097**
Model 3	Ref	1.186 (0.881, 1.595)	1.16 (0.859, 1.566)	1.236 (0.918, 1.666)	**1.543 (1.153, 2.064)**	**0.0034**
Model 4	Ref	1.17 (0.868, 1.576)	1.116 (0.823, 1.512)	1.175 (0.865, 1.596)	**1.419 (1.036, 1.944)**	**0.0355**
Model 1, adjusted for age, gender, nation.						
Model 2, further adjusted for marital status, education and activity level, smoking status, drinking status, tea status, sleep duration and body mass index based on model 1.						
Model 3, further adjusted for triglyceride, total cholesterol, high-density lipoprotein cholesterol, hypertension, diabetes, chronic kidney disease and cardiovascular disease based on model 2.						
Model 4, further adjusted for daily energy, protein, fat, cholesterol, diet-fiber intake based on model 3.						
[1] Tests for trend were conducted by modeling the median of each quintile-defined category as a continuous variable in Logistic regression models.						

4. Discussion

In this large cross-sectional study, we found that dietary calcium intake related to the increment of the risk of hyperuricemia even after adjusting for age, gender, nationality, residence, marriage status, educational level, activity level, smoking status, drinking status, tea status, sleep duration, BMI, triglyceride, total cholesterol, high-density lipoprotein cholesterol, hypertension, diabetes, chronic kidney disease, cardiovascular disease, daily energy, protein, fat, cholesterol, diet fiber intake. Therefore, calcium is an independent risk factor for hyperuricemia. Due to different age, gender, BMI status, whether with hypertension, diabetes or chronic kidney disease, the prevalence of hyperuricemia is very different. Therefore, we conducted a stratified analysis of the above factors, and found similar results in most stratified factors. In addition, sensitivity analysis support above results. All these results indicated that an increased risk of hyperuricemia with increased dietary calcium intake

To the best of our knowledge, this is the first study independently revealing the relationship between dietary calcium intake and hyperuricemia. A multicenter, randomized, double-blind, placebo-controlled study found that the group who received calcium + vitamin D had significantly elevated concentrations of serum uric acid compared with those who received placebo (52.3% vs 37.2%; P = 0.046) which is similar to our study (24). Another study based on the Chinese population seemed also support our research and this study concluded that the concentration of serum calcium was positively with hyperuricemia in both man and women (23). The failure of the current study to find significant result in women may be due to the fact that the previous study was conducted participants aged > 65 years and 40 years old or above respectively, while participant was ≥ 18 years old in our study. Besides, the adjusted OR of hyperuricemia increased with rising serum calcium concentrations in Irish (15). This relationship was also found in kidney transplant recipients with intact graft function and Coates V and Raiment PC had found elevated blood calcium concentrations in gout patients as early as 1924 (33, 34). However, to our knowledge, no study has independently assessed the relationship between hyperuricemia and dietary calcium intake. Additional studies may be required to assess the relationships of hyperuricemia and dietary calcium intake.

However, a study from Korean found that hyperuricemia subjects had significantly a lower intake of calcium (268.7mg vs 300.3mg, p < 0.001) (26). This study adjusted age, gender and BMI merely, whereas, our study adjusted for living habits and dietary nutrient intake besides age, gender, BMI. Lina Zgaga et al. found a significant weak association between calcium intake and urate among 2,037 healthy individuals from the UK (27). Several factors may account for the difference. Firstly, dietary calcium in westerners were mainly derived from dairy products which might be helpful in protection against hyperuricemia (35). Whereas, dietary calcium consumed by the Chinese mainly sourced from soy food, sea food and meat. Secondly, the amount of dietary calcium intake and requirement varies from region to region, which may cause differences in results. The average dietary calcium intake (412.63 mg/day, 437.07 mg/day for men and 391.05 mg/day for women) in our study was much lower than that of westerners. Although calcium intake of Chinese is low, calcium concentration in the body has reached a state of equilibrium and some scholars believe that the

demand for calcium of Chinese people may only be half of Western countries (36). Finally, clinical treatment of alkalization of urine is commonly used to promote uric acid excretion and calcium supplements such as calcium carbonate and calcium citrate are also weakly alkaline. We hypothesized that calcium supplements may promote uric acid excretion. Nevertheless, the proportion of Chinese individuals using dietary supplements was quite low compared to the use of calcium supplements in the Western population (37, 38).

The biological mechanism underlying the association between dietary calcium intake and the prevalence of hyperuricemia was not completely understood, but may be related to the inflammatory mechanism. It has been suggested that high levels of serum uric acid may contribute to inflammatory arthritis (39). Some important inflammatory cytokines, such as IL-6, TNF-A and high-sensitivity C-reactive protein, are positively correlated with serum uric acid (40, 41). serum calcium concentration is also positively correlated with inflammation, and hypercalcemia has been recognized to be associated with many inflammatory diseases (42, 43). Thus, the relationship between calcium and hyperuricemia may be mediated by inflammatory mechanisms. In addition, our previous studies have shown that dietary zinc intake is inversely associated with hyperuricemia (21). Whereas, R J Wood and J J Zheng suggested that consumption of a high calcium diet can significantly reduce net zinc absorption and zinc balance and increase the risk of developing negative zinc balance (44). This may be another reason for the relationship between calcium and hyperuricemia.

In addition, a large number of studies have proved that hyperuricemia is an independent risk factor for metabolic diseases, cardiovascular disease and some scholars call hyperuricemia the second largest metabolic disease after diabetes. Calcium may mediate the relationship between uric acid and metabolic syndrome. M K Kim et al showed that excessive dietary calcium may increase the prevalence of metabolic syndrome in men, but for postmenopausal women, calcium intake does not increase the risk of metabolic syndrome (45). A meta-analysis concluded that calcium supplements with or without vitamin D modestly increase the risk of cardiovascular events, especially myocardial infarction (46).

The main strengths of our study are as follows. firstly, to our knowledge, this is the first study to independently assess the relationship between dietary calcium and hyperuricemia. In addition, our study adjusted for a wide range of potential confounding variables. Several limitations also need to be acknowledged. First, the 24-h dietary recall method was utilized to obtain dietary intake and may not reflect long-term calcium intake status. To compensate for this, sensitivity analysis was performed using cumulative mean calcium intake, the conclusions were not altered. Second, there is a lack of information on calcium supplementation in this survey, although the proportion of Chinese individuals using dietary supplements was quite low. Third, we considered the effects of hormone therapy (postmenopausal women) on hyperuricemia. Although in the CHNS survey, the questionnaire did not provide information about hormone therapy in postmenopausal women. Analyses were repeated performed among women under the age of 50 and women 50 or older respectively (Table S1 in supplementary material). Fourth, the potential confounders were adjusted to the extent possible, the residual confounding could not be completely ruled out. Five, our study was restricted to persons of Chinese whose average dietary calcium only about 400 mg/d, and it is unknown whether our results can be generalized to other ethnic groups. Finally, due to the limitations of cross-sectional studies, the causal relationship between dietary calcium and hyperuricemia cannot be determined, and even causal inversion may occur. Therefore, further prospective studies are necessary.

5. Conclusions

In conclusion, our findings indicated that higher dietary calcium intake was positively related to the risk of hyperuricemia independent of some major confounding factors.

Declarations

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Authors' Contributions: Y Z, H Q, and H Z contributed to the design and conduct of the research. H Z and X G carried out data analysis and the initial draft of the paper. S W, and X S conducted the data collection and advised on statistical analysis. All authors reviewed and edited the draft, and approved the final version of the manuscript. Yiying Zhang, Hongbin Qiu, and Huanxiang Zhang contributed to the design and conduct of the research. Huanxiang Zhang and Xia Gu carried out data analysis and the initial draft of the paper. Shanjie Wang, and Xiaofang Sui conducted the data collection and advised on statistical analysis. All authors reviewed and edited the draft, and approved the final version of the manuscript..

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Data availability statement: The dataset presented in this study can be found in online repositories. The name of the repository/repositories and accession number(s) can be found here: https://www.cpc.unc.edu/projects/china.

Ethics approval and consent to participate: All individuals had signed a written informed consent prior to participating in the study, which was in accordance with the Declaration of Helsinki and approved by the Institutional Review Boards of the National Institute of Nutrition and Food Safety of China (Beijing) and the University of North Carolina (Chapel Hill, NC, USA)

Consent for publication: Not applicable.

Competing interests: The authors declare that they have no competing interests.

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Figures

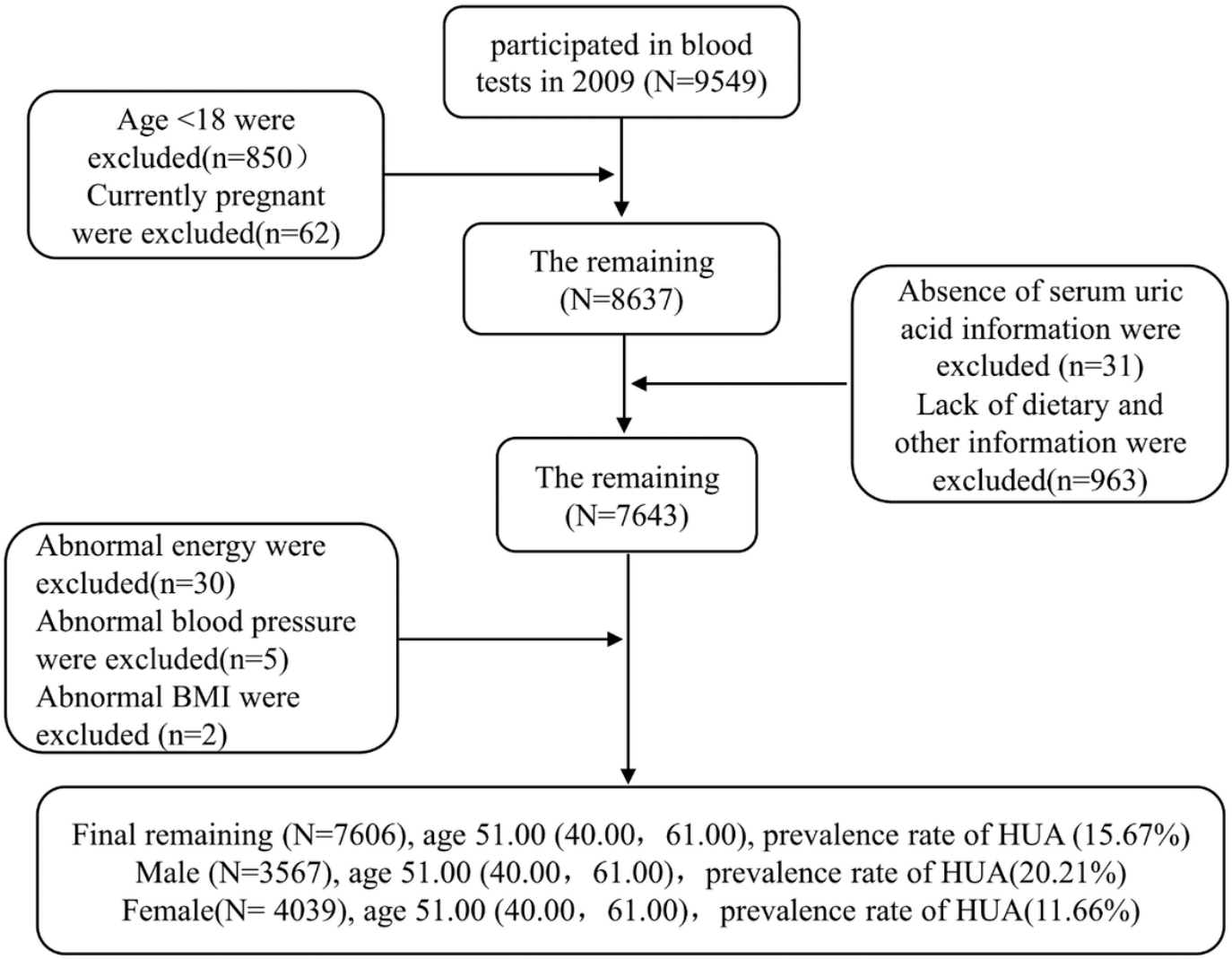

Figure 1

Data extraction process

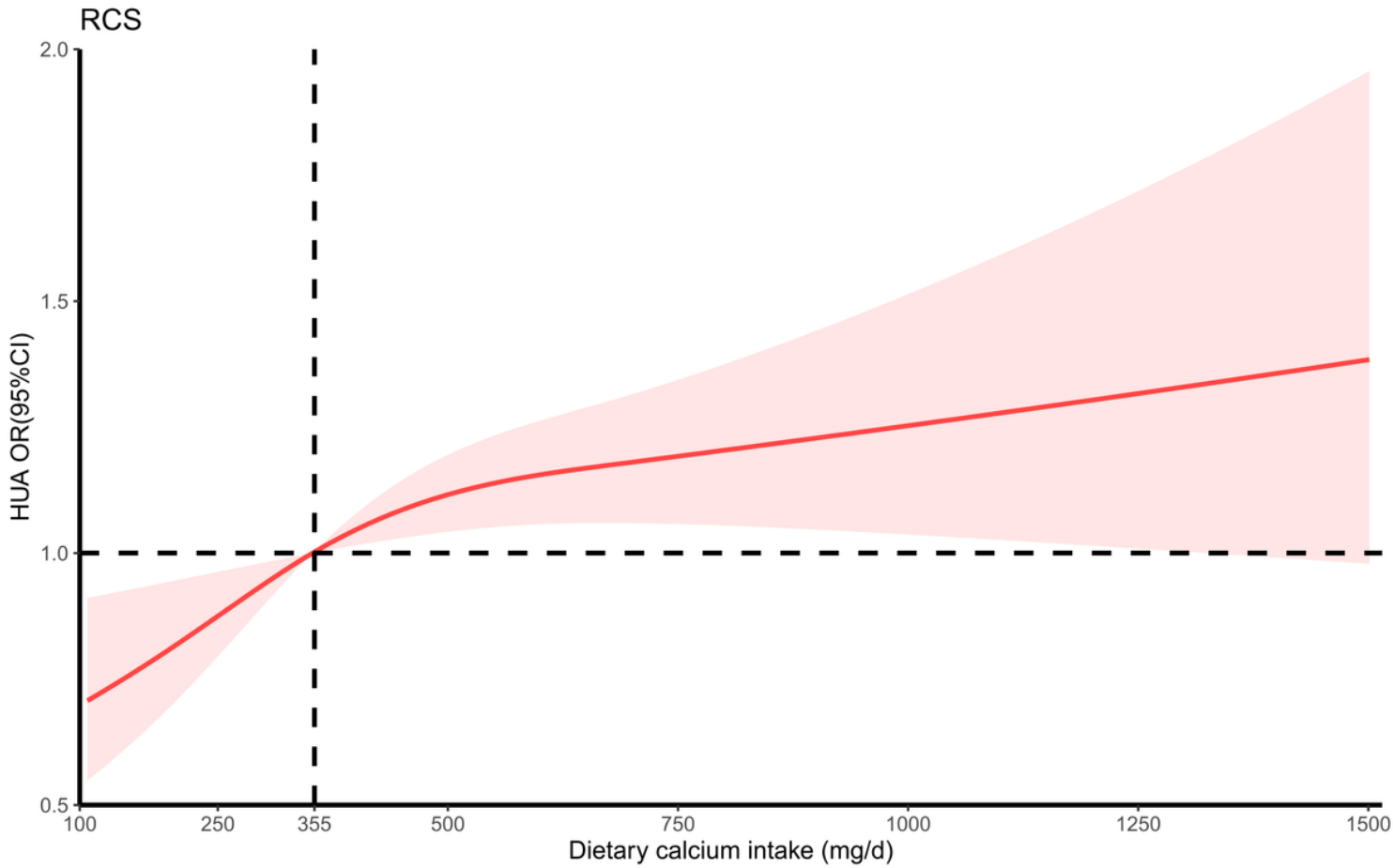

Figure 2

Dose-response relationship between dietary calcium intake and the odds ratio for HUA in total population (n=7606). CI=confidence interval, HUA=hyperuricemia, OR=odds ratio.

Supplementary Files

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