



Hyperuricemia prevalence and its association with metabolic disorders: a multicenter retrospective real-world study in China

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Background: The prevalence of hyperuricemia (HUA) and gout continues to increase in China. Research suggests that HUA may be related to many diseases other than gout. However, further population research is required to investigate the association between HUA and metabolic syndromes. This study sought to investigate the prevalence of HUA in an average population in China, and the association between serum uric acid (UA) levels and related metabolic disorders.

Methods: This multicenter retrospective real-world study examined the hospital information system data of 4 tertiary hospitals in 3 provinces in China. The data of patients aged between 18 and 80 years, who had attended at least 1 medical appointment at which their UA level was recorded, were analyzed to evaluate associations between UA levels and metabolic disorders.

Results: Among the 374,506 enrolled subjects (49.7% male; mean age 51.5 years old), the overall prevalence of HUA and gout were 14.8% and 0.5%, respectively. The prevalence was higher among males than females (17.6% vs. 12.0%, 0.8% vs. 0.1%; both $P < 0.001$). Groups exhibiting higher UA levels had increased adjusted odds ratios for dyslipidemia and chronic kidney disease (CKD) in both sexes. Changes in UA levels from the baseline were negatively correlated with changes in the estimated glomerular filtration rate and hemoglobin A1c among both sexes (all $P < 0.001$), and were positively correlated with changes in total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) (all $P < 0.05$) among males, and changes in TC, TG, LDL-C and glucose (all $P < 0.001$) among females.

Conclusions: HUA is associated with dyslipidemia and CKD both cross-sectionally and longitudinally. Similar phenomena were observed in both sexes.

Keywords: Hyperuricemia (HUA); serum uric acid level; metabolic disorder; sex difference

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Introduction

Hyperuricemia (HUA) is considered the main cause of gout owing to the accumulation of uric acid crystals (1). According to epidemiological studies, HUA may be related to obesity caused by a diet rich in purine, alcohol, meat,

and soft drinks (2,3). In recent decades, HUA has become a common metabolic disorder worldwide (4). A meta-analysis indicates that the pooled prevalence of HUA was 13.3% in mainland China from 2000 to 2014 (5). Another survey showed that the prevalence of HUA was higher in southern

(19.9% for men and 9.3% for women) and rural (20.1% for men and 9.0% for women) areas than northern (17.0% for men and 6.7% for women) and urban (16.4% for men and 6.6% for women) areas (6).

Serum uric acid (UA) is known to be associated with cardiovascular, kidney and metabolic diseases and its components such as hyperglycaemia, hypertriglyceridaemia and obesity (7). Lipid has been found to have a stronger association with UA than any other metabolic syndrome components, but the role of a single lipid species associated with UA levels was found to vary in different populations (8-10). According to previous research, in both sexes, serum triglyceride (TG) has the strongest association with HUA in the Chinese population (11). Individuals with higher levels of UA are at a higher future risk of type 2 diabetes independent of other known risk factors (12,13). Previous studies have confirmed that insulin resistance exists in gout patients (14). However, UA is negatively correlated with hemoglobin A1c (HbA1c) in type 2 diabetes patients, and positively correlated with HbA1c in normal glucose serum (15). HUA is also associated with hypertension in a certain Chinese population (16).

Additionally, UA is an important biomarker and a potentially treatable risk factor for cardiovascular diseases (CVDs) (7). Increased uric acid levels appear to be associated with an increased incidence of acute myocardial infarction, stroke and, chronic heart failure in middle-aged subjects with prior CVD (17,18). It will assist readers if this is stated. U-shaped association between uric acid levels and cardiovascular mortality exists in both women and men (19), which may be due to the protective role of uric acid as an antioxidant (20).

Data on the association between HUA and metabolic syndromes in the Chinese population is limited (6,21,22). This study sought to investigate associations among UA and related diseases using Chinese hospital data from urban areas in 3 provinces and to explore the sex-specific association of serum uric acid dynamics with the incidence of metabolism-related diseases and biochemical measurements.

We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/atm-21-5052>).

Methods

Study design

A multicenter, retrospective, cross-sectional, real-world

study was conducted. The prevalence of HUA and gout overall and in male and female populations was analyzed. The factors affecting differences in prevalence between males and females were also investigated. In addition, associations among UA and metabolism-related diseases and metabolism-related biochemical measurements were assessed. Associations between changes in UA levels from the baseline and changes in metabolism-related biochemical measurements from the baseline were also examined.

The enrolled subjects were categorized using prespecified sex-specific cut-off values for UA levels (male cut-off: 7, 8, and 9 mg/dL; female cut-off: 6, 7, and 8 mg/dL). The lowest cut-off values were set as the top values of the normal range for UA in both sexes, and the higher cut-off represented every 1 mg/dL increase of UA level (23). The index medical appointment at which the UA measurement of each patient was taken was set as the baseline for the cross-sectional analysis. Using the index visit and the follow-up visit data of the participants, a retrospective cohort was established.

Setting

This study was based on de-identified hospital information system (HIS) data collected from 4 tertiary hospitals in 3 provinces of China from July 2012 to January 2018.

Participants

A total of 432,002 patients, who had attended at least 1 medical appointment at which their UA level was recorded, were screened. After excluding those with missing date of birth or sex data (N=85), those aged <18 years (N=35,392), and those aged >80 years (N=22,019), 374,506 adult participants were identified and enrolled in this study (see *Figure 1*). Of these, there were data of at least 1 follow-up UA level (after the baseline level) for 114,054 participants. These data were studied to examine correlations among UA changes and metabolism-related biomarker changes. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by committee ethics board of Jinan Central Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China (No. 2020-026-01). Individual consent for this retrospective analysis was waived.

Variable

In this study, prevalence was defined as the proportion of

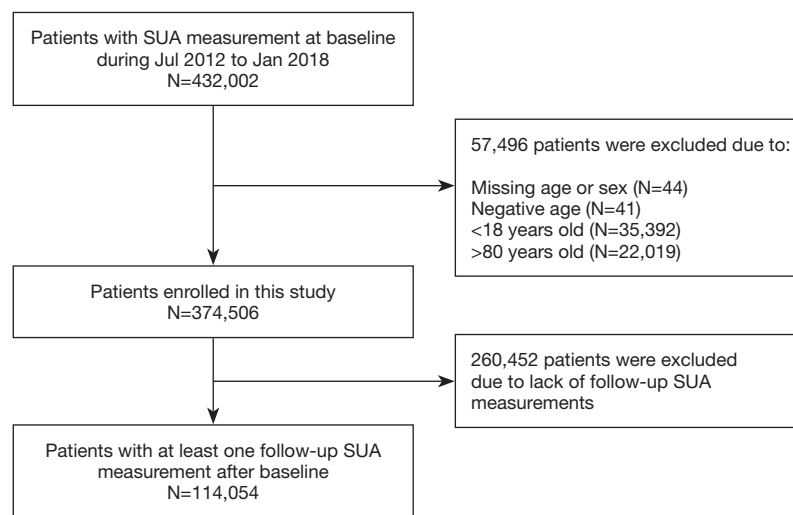


Figure 1 Population screening scheme.

patients with a specific disease and the whole population enrolled in the study. Subgroup population was defined as the denominator for the subgroup analysis. Odds ratios (ORs) were calculated for the association analysis between UA levels and related diseases. The definitions of diseases are as follows:

- ❖ Dyslipidemia: patients with diagnoses of dyslipidemia, or those prescribed lipid-lowering medication, or those with a total cholesterol (TC) level ≥ 5.72 mmol/L, or a TG level > 1.70 mmol/L, or a high-density lipoprotein (HDL-C) level < 0.91 mmol/L;
- ❖ Type 2 diabetes mellitus (T2DM): patients with a prescribed intake of hypoglycemic agents or insulin, or serum with a Hb1Ac level $\geq 6.5\%$, or a fasting blood glucose level ≥ 7 mmol/L, or a 2-hour postprandial glucose level ≥ 11.1 mmol/L (24), excluding those with type 1 diabetes mellitus;
- ❖ Hypertension: Patients with diagnoses of stroke, coronary arterial disease or heart failure (who were subsumed under the cardio-cerebrovascular cases category), hypertension, or with a systolic blood pressure (SBP) ≥ 140 mmHg, or a diastolic blood pressure (DBP) ≥ 90 mmHg (25);
- ❖ Chronic kidney disease (CKD): patients with diagnoses of CKD, or a kidney disease as diagnosed at the index visit and at an earlier visit at least 90 days before the index visit;
- ❖ Kidney and ureter calculus: patients with diagnoses of calculus of the kidney and ureter.

Data sources

The data used in this study are from the HISs of 4 tertiary hospitals.

Bias

We included the related factors (age, center, hypertension, glucose TG, HDL-C, and LDL-C) into the model to adjust for the potential bias.

Study size

The sample size in this study was determined by applying screening criteria in real-world settings.

Outliers

For the data of measurements, including Hb1Ac level, glucose level, TC, TG, HDL-C, SBP, DBP, and UA level, no outliers were found.

Statistical methods

The data are reported as mean \pm standard deviation for the normally distributed continuous variables, median and interquartile range for the non-normally distributed continuous variables, and proportions for the categorical variables. Differences between any 2 groups were compared

using a *t*-test for the normally distributed continuous variables, a Wilcoxon test for the non-normally distributed continuous variables, and a Chi-squared test or Fisher test for the categorical variables. The Chi-squared test was also used to examine trends in proportions across groups with different UA levels. A Pearson or Spearman correlation analysis was used to examine the correlations among the continuous variables and uric acid levels. A multivariate binary logistic regression analysis was used to analyze associations among UA levels and dyslipidemia, T2DM, cardio-cerebral vascular disease, and CKD adjusting for demographic and clinical features. ORs and 95% confidence intervals were calculated. A multivariate linear regression analysis was conducted to assess the linear associations among UA and biochemical parameters both as continuous variables.

Results

Of the 374,506 patients, 49.7% were male, and 50.3% were female. The mean age at the time at which the investigation was conducted of the overall test group, male population, and female population was 51.53, 51.62 and 51.43 years, respectively. The overall prevalence of HUA and gout were 14.8% and 0.5%, respectively, and there were no significant differences within different provinces. Notably, Significant differences were observed between the sexes. The prevalence was higher in males than in females (17.6% *vs.* 12.0%, 0.8% *vs.* 0.1%; both $P < 0.001$). Male patients with elevated UA levels had a decreased mean age, HDL-C level, and estimated glomerular filtration rate (eGFR), but increased prevalence rates for gout and CKD (see *Table 1*). Females with elevated UA levels had a decreased mean HDL-C level and eGFR, but an increased mean C-reactive protein (CRP) level, and prevalence rates for diseases, including gout, composite and individual cardio-cerebrovascular diseases, and CKD (see *Table 2*).

Associations among UA levels and metabolism-related diseases

In relation to the lowest (normal) UA level male group, higher UA level groups had significantly increased adjusted ORs (aORs) for dyslipidemia and CKD, and a decreased aOR for T2DM. Male patients with a UA level ≥ 9.0 mg/dL were more likely to have cardio-cerebrovascular events than those with normal UA levels (see *Table 3*). The associations between UA levels and diseases were similar among females,

except that female in higher UA level groups did not have a significantly different aOR for T2DM than those in the lowest UA level group (see *Table 4*).

Associations among UA levels and metabolism-related biochemical measurements

Among the male subjects, UA was found to be negatively associated with HDL-C, CRP, glucose, HbA1c, eGFR and SBP, but positively associated with TG, and low-density lipoprotein cholesterol (LDL-C) (see *Table 5*).

Among the female subjects, UA was found to be negatively associated with HDL-C, glucose, and eGFR, but positively associated with TC, TG, and LDL-C (see *Table 5*).

Associations among UA level changes from the baseline and changes in metabolism-related biochemical measurements from the baseline

We established a retrospective cohort comprising 114,054 participants with follow-up UA data. The median interval from the baseline assessment to the latest follow-up UA level assessment of patients in the cohort was 98.9 days. Changes in UA from the baseline were negatively correlated with changes in eGFR and HbA1c from the baseline ($r = -0.319$ and -0.074 ; both $P < 0.001$) and positively correlated with changes in blood glucose, TC, TG, LDL-C, ($r = 0.110$, 0.144 , 0.082 , and 0.012 respectively; all $P < 0.05$), however, no correlation was found with HDL-C among males. After adjusting the covariates, changes in UA levels were found to be negatively correlated with changes in eGFR and HbA1c, and positively correlated with changes in TC, TG, LDL-C, and glucose (see *Table 6* and *Figures 2-8*).

Among females, changes in UA from the baseline measurement were negatively correlated with changes in eGFR, HDL-C, and HbA1c from the baseline measurements ($r = -0.317$, -0.025 , and -0.052 ; all $P < 0.001$) and positively correlated with changes in TC, TG, and LDL-C ($r = 0.094$, 0.147 , 0.073 respectively; all $P < 0.001$). After adjusting the covariates, changes in UA were found to be significantly negatively associated with changes in eGFR, HDL-C, and HbA1c, but positively correlated with changes in TC, TG, LDL-C, and glucose (see *Table 6* and *Figures 9-15*).

Discussion

This research examined the prevalence of HUA in

Table 1 Baseline characteristics of adult males by uric acid levels

Characteristics	UA <7.0 mg/dL	7.0 mg/dL ≤ UA <8.0 mg/dL	8.0 mg/dL ≤ UA < 9.0 mg/dL	UA ≥9.0 mg/dL	P
N (% of all males)	154,074 (82.7%)	16,681 (9%)	7,635 (4.1%)	7,917 (4.2%)	
Demographics					
Age (years)	52.72±15.43	47.69±15.85	46.3±15.83	43.77±16.77	<0.001
Lab examination					
TG (mmol/L)	1.15 (0.84)	1.54 (1.16)	1.64 (1.3)	1.57 (1.36)	<0.001
TC (mmol/L)	4.48±1.04	4.75±1.09	4.76±1.12	4.61±1.22	<0.001
HDL-C (mmol/L)	1.12±0.31	1.07±0.28	1.05±0.28	1±0.31	<0.001
LDL-C (mmol/L)	2.69±0.81	2.84±0.85	2.82±0.86	2.71±0.91	<0.001
CRP (mg/L)	7.82±38.01	5.35±20.3	6.19±21.8	8.23±24.78	<0.001
Glucose (mmol/L)	5.4±1.4	5.4±1.19	5.41±1.22	5.4±1.2	<0.001
HbA1c (%)	6±1.9	6±1.2	5.9±1.2	6.0±1.3	<0.001
eGFR (mL/min/1.73 m ²)	100.61±19.43	94.95±25.85	92.44±29.34	90.82±35.19	<0.001
SBP (mmHg)	130.97±18.43	132.21±19.05	132.72±21.34	130.31±21.89	0.09
DBP (mmHg)	78.85±11.7	80.64±12.37	80.92±12.74	79.72±13.52	<0.001
Comorbidities (%)					
Hyperuricemia	0.4	100	100	100	<0.001
Gout	0.5	3.2	7.7	12.2	<0.001
Dyslipidemia	48.7	57.7	57.6	51	<0.001
Type 2 diabetes mellitus	13.3	9.3	8.5	8.5	<0.001
Hypertension	30.8	31.4	31.3	29.6	0.654
Cardio-cerebrovascular disease	27.5	22.7	21.8	22.8	<0.001
Stroke	12.7	8.5	8.2	7.4	<0.001
Coronary arterial disease	17.5	15.7	15	15.3	<0.001
Heart failure	7.7	7.3	8.4	10.9	<0.001
Chronic kidney disease	2.2	4.8	6.9	9.5	<0.001
Calculus of kidney and ureter	1.6	1.9	2.4	1.8	<0.001

CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

populations from 3 provinces. In light of the different characteristics between the sexes found in previous studies (26,27), male and female subjects were analyzed separately. HUA was defined as UA ≥7.0 mg/dL in males or ≥6.0 mg/dL in females. Using this criterion, the enrolled HUA subjects were subsequently subdivided into 3 groups based on the prescribed cut-off values, and a statistical analysis was carried out. Under the newly published guidelines for the

diagnosis and management of HUA and gout in China (28), the UA cut-off value used to diagnose HUA has been redefined as ≥420 μmol/L (7 mg/dL) in both sexes. However, in this retrospective study, we continued to use the former standard to ensure conformity with real-world clinical practice in China during the study period. As *Table 1* shows, the percentages of cardio-cerebrovascular disease in the reference group were higher than those in other groups;

Table 2 Baseline characteristics of adult females by uric acid levels

Characteristics	UA <6.0 mg/dL	6.0 mg/dL ≤ UA <7.0 mg/dL	7.0 mg/dL ≤ UA <8.0 mg/dL	UA ≥8.0 mg/dL	P
N (% of all females)	165,678 (88%)	12,512 (6.6%)	5,028 (2.7%)	4,981 (2.6%)	
Demographics					
Age (years)	51.3±15.89	53.7±17.18	52.29±18.3	49.22±19.36	0.359
Lab examination					
TG (mmol/L)	1.14 (0.81)	1.54 (1.06)	1.64 (1.2)	1.51 (1.19)	<0.001
TC (mmol/L)	4.83±1.07	5.07±1.16	5.02±1.22	4.76±1.33	<0.001
HDL-C (mmol/L)	1.29±0.33	1.2±0.32	1.16±0.32	1.09±0.39	<0.001
LDL-C (mmol/L)	2.83±0.85	3±0.9	2.96±0.95	2.79±1.00	<0.001
CRP (mg/L)	4.1 (17.4)	4.35 (12.96)	4.43 (15.03)	4.99 (16.54)	0.078
Glucose (mmol/L)	5.24 (1.18)	5.43 (1.46)	5.42 (1.49)	5.3 (1.4)	<0.001
HbA1c (%)	6.0 (1.6)	6.3 (1.6)	6.3 (1.5)	6.4 (1.7)	<0.001
eGFR (mL/min/1.73 m ²)	103.57±19.73	90.37±28.32	86.04±33.37	83.47±38.28	<0.001
SBP (mmHg)	127.68±18.86	129.96±19.47	130.39±21.4	129.68±23.67	<0.001
DBP (mmHg)	76.43±11.16	77.83±11.86	78.54±13.22	76.57±13.94	<0.001
Comorbidities (%)					
Hyperuricemia	0.1	100	100	100	<0.001
Gout	0.1	0.3	0.6	1.6	<0.001
Dyslipidemia	42.3	57.8	58.9	51	<0.001
Type 2 diabetes mellitus	10.8	13.7	14.1	13.1	<0.001
Hypertension	25.5	33.6	36.6	36.5	<0.001
Cardio-cerebrovascular disease	23.1	28.9	30.1	33.2	<0.001
Stroke	7.8	8	8.4	9.8	<0.001
Coronary arterial disease	17.5	23.6	24	25.8	<0.001
Heart failure	7.5	11.3	13.4	17.4	<0.001
Chronic kidney disease	1.6	5.2	10	12.7	<0.001
Calculus of kidney and ureter	0.8	0.8	0.6	1.1	0.618

CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

however, as the aOR was >1 (see *Table 3*) there might be reasons for this. First, the aOR for cardio-cerebrovascular disease in *Table 3* was adjusted for age, center, hypertension, and glucose. Second, due to missing data, the population used for the multivariate logistic regression was a subset of the population for *Table 1*.

Nationwide epidemiological data for HUA in China remains limited. Previous studies from different periods

and regions have indicated that the prevalence of HUA continues to increase (5). Research has shown that the prevalence of HUA was 6.9–27.30% in men and 3.65–15.33% in women (22,29–31). In this study, the severity of HUA was assessed using UA levels. Consistent with the results of previous regional epidemiological studies, we found that the total prevalence of HUA was 17.6% in men and 12.0% in women. More than half of the patients

Table 3 Associations between uric acid levels and metabolism-related diseases among adult males

UA levels	aOR	95% CI	P value
Dyslipidemia^a			
UA level 1 (<7.0 mg/dL)	Ref	–	–
UA level 2 (7.0 to <8.0 mg/dL)	1.66	1.58–1.74	<0.001
UA level 3 (8.0 to <9.0 mg/dL)	1.88	1.76–2.02	<0.001
UA level 4 (≥9.0 mg/dL)	1.89	1.75–2.05	<0.001
Type 2 diabetes mellitus^b			
UA level 1 (<7.0 mg/dL)	Ref	–	–
UA level 2 (7.0 to <8.0 mg/dL)	0.65	0.60–0.70	<0.001
UA level 3 (8.0 to <9.0 mg/dL)	0.59	0.53–0.67	<0.001
UA level 4 (≥9.0 mg/dL)	0.74	0.65–0.84	<0.001
Chronic kidney disease^c			
UA level 1 (<7.0 mg/dL)	Ref	–	–
UA level 2 (7.0 to <8.0 mg/dL)	2.27	2–2.59	<0.001
UA level 3 (8.0 to <9.0 mg/dL)	3.69	3.15–4.32	<0.001
UA level 4 (≥9.0 mg/dL)	5.37	4.59–6.3	<0.001
Cardio-cerebrovascular disease^d			
UA level 1 (<7.0 mg/dL)	Ref	–	–
UA level 2 (7.0 to <8.0 mg/dL)	1.02	0.96–1.09	0.523
UA level 3 (8.0 to <9.0 mg/dL)	1.07	0.97–1.18	0.207
UA level 4 (≥9.0 mg/dL)	1.21	1.08–1.36	<0.001

Among adult males, the number of dyslipidemia, type 2 diabetes mellitus, chronic kidney disease, cardio-cerebrovascular disease is 93,094, 23,365, 5,469, 49,626, respectively. ^a, adjusted for age, center, hypertension, and glucose; ^b, adjusted for age, center, hypertension, TG, HDL-C, and LDL-C; ^c, adjusted for age, center, hypertension, TG, HDL-C, LDL-C and glucose; ^d, adjusted for age, center, hypertension, TG, HDL-C, LDL-C and glucose. CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

with HUA were categorized into the mild group (men: 7.0–8.0 mg/dL, women: 6.0–7.0 mg/dL). Female patients with HUA were more likely to be older than males and to be post-menopausal. The reason for this may be related to the change in estradiol (32), which is considered to play a protective role in regulating UA. Similar to our findings, a meta-analysis showed that the pooled prevalence of gout in the Chinese population was 1.1%, and is remarkably higher in men (1.5%) than women (0.9%) (5).

HUA is often accompanied by hyperlipidemia. This may be because lipid metabolism disorders and uric acid metabolism share mutual influence mechanisms. Increased serum lipid, especially TG, is positively correlated with

UA (33), and elevated TG is an independent risk factor of HUA (34). Serum LDL, TC, and the ratio of TG to HDL are positively correlated with UA level, while HDL level is negatively correlated with UA level (35). In this study, we observed that TG, TC, and LDL increased as UA increased, while HDL was decreased. Consistent with previous studies, TG appeared to be more relevant than the other lipid indexes. Further, adults with HUA showed a higher possibility of concomitant dyslipidemia.

Previously, HUA was thought to be a predictor of insulin resistance and diabetes mellitus. HUA and insulin resistance can be interactive (36). Increased UA levels may be related to abnormal glucose tolerance, which may ultimately

Table 4 Associations between uric acid levels and metabolism-related diseases among adult females

UA levels	aOR	95% CI	P value
Dyslipidemia^a			
UA level 1 (<6.0 mg/dL)	Ref	–	–
UA level 2 (6.0 to <7.0 mg/dL)	1.78	1.69–1.87	<0.001
UA level 3 (7.0 to <8.0 mg/dL)	2.06	1.90–2.24	<0.001
UA level 4 (≥8.0 mg/dL)	1.89	1.71–2.08	<0.001
Type 2 diabetes mellitus^b			
UA level 1 (<6.0 mg/dL)	Ref	–	–
UA level 2 (6.0 to <7.0 mg/dL)	0.99	0.92–1.07	0.826
UA level 3 (7.0 to <8.0 mg/dL)	1.01	0.90–1.14	0.830
UA level 4 (≥8.0 mg/dL)	1.08	0.95–1.23	0.227
Chronic kidney disease^c			
UA level 1 (<6.0 mg/dL)	Ref	–	–
UA level 2 (6.0 to <7.0 mg/dL)	2.92	2.54–3.35	<0.001
UA level 3 (7.0 to <8.0 mg/dL)	5.72	4.84–6.77	<0.001
UA level 4 (≥8.0 mg/dL)	8.69	7.30–10.33	<0.001
Cardio-cerebrovascular disease^d			
UA level 1 (<6.0 mg/dL)	Ref	–	–
UA level 2 (6.0 to <7.0 mg/dL)	1.05	0.98–1.12	0.204
UA level 3 (7.0 to <8.0 mg/dL)	1.02	0.91–1.14	0.785
UA level 4 (≥8.0 mg/dL)	1.18	1.03–1.35	0.014

Among adult females, the number of dyslipidemia, type 2 diabetes mellitus, chronic kidney disease, cardio-cerebrovascular disease is 82,816, 20,969, 4,437, 45,055, respectively. ^a, adjusted for age, center, hypertension, and glucose; ^b, adjusted for age, center, hypertension, TG, HDL-C, and LDL-C; ^c, adjusted for age, center, hypertension, TG, HDL-C, LDL-C and glucose; ^d, adjusted for age, center, hypertension, TG, HDL-C, LDL-C and glucose. CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

develop into diabetes mellitus (37). HUA with diabetes or abnormal glucose tolerance accounted for 31% to 55% (38). Similar to previous studies (27,39), we found that UA levels were negatively correlated with blood glucose levels in both sexes at the baseline. This might be due to hyperfiltration caused by hyperglycemia, which can enhance the excretion of UA.

Emerging evidence suggests that HUA is associated with an increased risk of incidence and the progression of CKD (40). The results of previous studies on the association between UA with CKD in different sexes have been mixed (41-44). Despite lower concentrations of UA in females, the association between HUA and CKD in

females was significantly stronger than that in males (23), demonstrated by eGFR measurement and CKD prevalence. The association between UA and CKD is consistent with our conclusion. Further, in our study, the prevalence of calculus of the kidney and ureter was associated with HUA in males, but this association was statistically non-significant in females.

Similar to our findings, epidemiological evidence supports an association between UA and the incidence of hypertension. Many observational studies have suggested that an increased risk of hypertension incidence may be independently caused by elevated UA levels (45-48). A previous study suggested that the risk of high blood

Table 5 Correlation and coefficient between SUA levels' change and metabolism-related biochemical measurements' change among adult males and females (correlation analysis, Δ SUA as independent variable)

Δ SUA	Male			Female		
	β	95% CI	P value	β	95% CI	P value
Δ TC ^a	0.001	-0.001-0.002	0.273	0.003	0.001-0.005	<0.001
Δ TG ^b	0.065	0.063-0.067	<0.001	0.064	0.061-0.067	<0.001
Δ HDL-C ^c	-0.007	-0.008 to -0.006	<0.001	-0.013	-0.014 to -0.012	<0.001
Δ LDL-C ^d	0.005	0.004-0.006	<0.001	0.003	0.002-0.005	<0.001
Δ CRP ^a	-1.593	-1.983 to -1.202	<0.001	0.171	-0.292-0.635	0.468
Δ Glucose ^e	-0.111	-0.119 to -0.103	<0.001	-0.045	-0.054 to -0.036	<0.001
Δ HbA1c ^f	-0.036	-0.044 to -0.028	<0.001	-0.009	-0.019 to -0.001	0.078
Δ eGFR ^a	-4.202	-4.276 to -4.128	<0.001	-4.81	-4.894 to -4.727	<0.001
Δ SBP ^a	-0.007	-0.008 to -0.006	<0.001	-0.008	-0.118-0.103	0.893
Δ DBP ^a	0.015	-0.038-0.068	0.572	-0.054	-0.12-0.012	0.108

^a, adjusted for age, center, hypertension, TG, HDL-C, LDL-C, glucose; ^b, adjusted for age, center, hypertension, TC, HDL-C, LDL-C, glucose; ^c, adjusted for age, center, hypertension, TC, TG, LDL-C, glucose; ^d, adjusted for age, center, hypertension, TC, TG, HDL-C, glucose; ^e, adjusted for age, center, hypertension, TG, HDL-C, LDL-C and DM treatment; ^f, adjusted for age, center, hypertension, TG, HDL-C, LDL-C, glucose, and DM treatment. SUA, serum uric acid; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Table 6 Multivariate linear regression analysis of the association between change of serum uric acid from baseline and change of metabolism-related biochemical measurements from baseline among males and females

Variables	Male			Female		
	β	95% CI	P value	β	95% CI	P value
eGFR ^a	-4.199	-4.315 to -4.082	<0.001	-4.464	-4.599 to -4.329	<0.001
TC ^a	0.053	0.046-0.061	<0.001	0.067	0.058-0.076	<0.001
TG ^b	0.065	0.059-0.071	<0.001	0.078	0.071-0.085	<0.001
LDL-C ^c	0.038	0.032-0.044	<0.001	0.042	0.037-0.047	<0.001
HDL-C ^d	0.001	-0.002-0.003	0.607	-0.005	-0.008 to -0.002	<0.001
Glucose ^e	0.040	0.023-0.058	<0.001	0.037	0.017-0.056	<0.001
HbA1c ^e	-0.035	-0.052 to -0.018	<0.001	-0.030	-0.048 to -0.011	0.002

^a, adjusted for sex, age, center, hypertension, TG, HDL-C, LDL-C, and glucose; ^b, adjusted for sex, age, center, hypertension, TC, HDL-C, LDL-C, and glucose; ^c, adjusted for sex, age, center, hypertension, TC, TG, HDL-C, and glucose; ^d, adjusted for sex, age, center, hypertension, TC, TG, LDL-C, and glucose; ^e, adjusted for sex, age, center, hypertension, TG, HDL-C, and LDL-C. CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

pressure in men with a UA level >7.0 mg/dL was 80% higher than the risk at norm uricemia (49). Sex differences also exist. Notably, the prevalence of hypertension in HUA patients increased by 1.7 times in men and 3.4 times in

women (50). We found a positive correlation between UA and hypertension both in SBP and DBP. Further, we found that this association was stronger in women than in men. This is probably because the average age of patients with

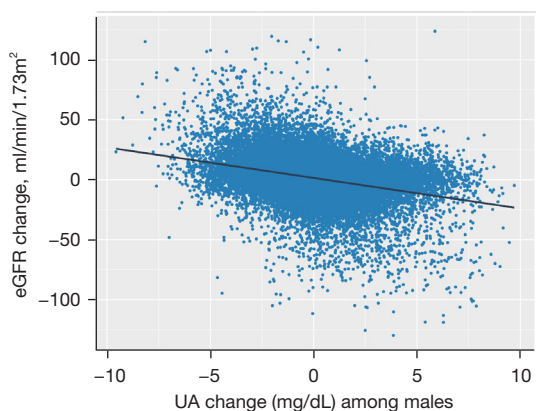


Figure 2 Correlation between changes in serum uric acid (UA) and changes in estimated glomerular filtration rate (eGFR) among males.

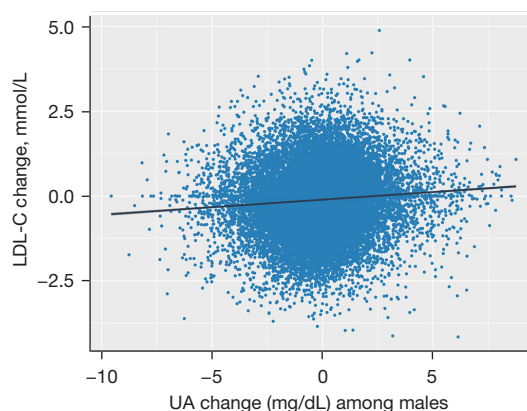


Figure 5 Correlation between changes in serum uric acid (UA) and changes in low-density lipoprotein cholesterol (LDL-C) among males.

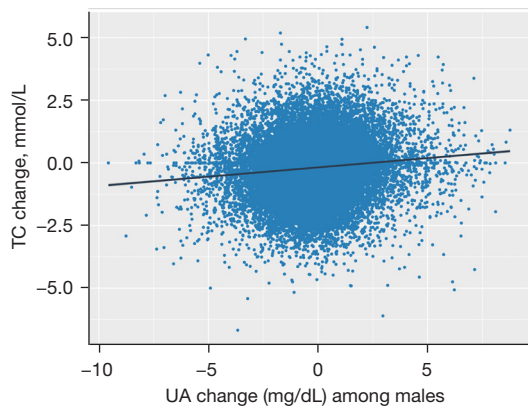


Figure 3 Correlation between changes in serum uric acid (UA) and changes in total cholesterol (TC) among males.

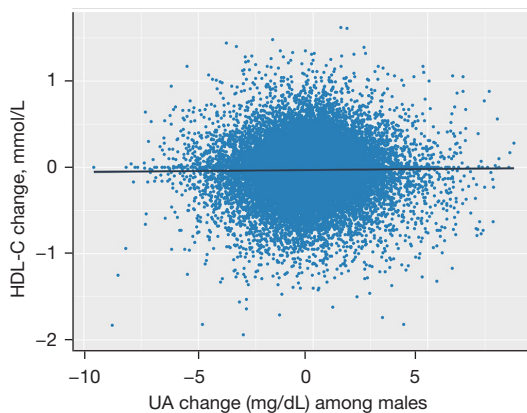


Figure 6 Correlation between changes in serum uric acid (UA) and changes in high-density lipoprotein cholesterol (HDL-C) among males.

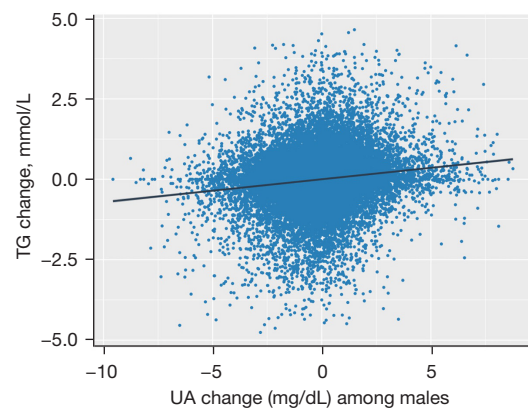


Figure 4 Correlation between changes in serum uric acid (UA) and changes in triglyceride (TG) among males.

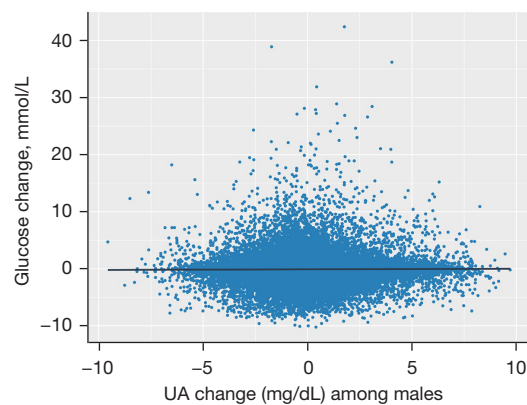


Figure 7 Correlation between changes in serum uric acid (UA) and changes in blood glucose among males.

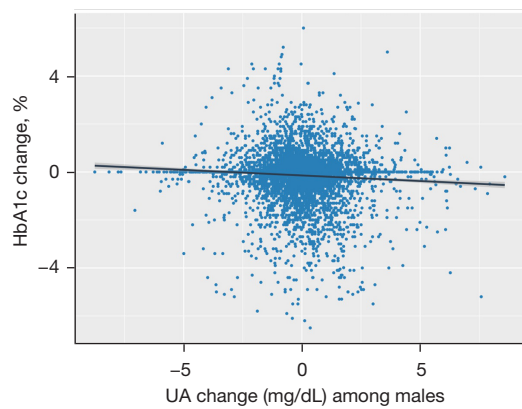


Figure 8 Correlation between changes in serum uric acid (UA) and changes in hemoglobin A1c (HbA1c) among males.

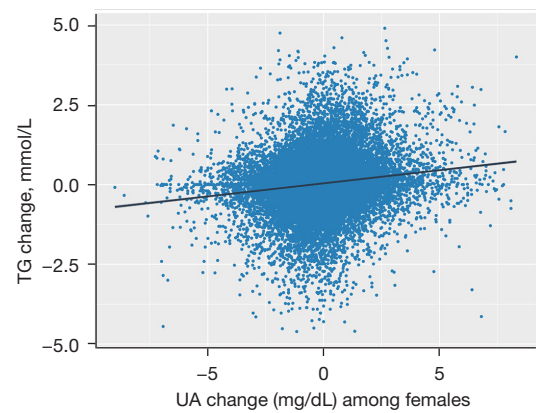


Figure 11 Correlation between changes in serum uric acid (UA) and changes in triglyceride (TG) among females.

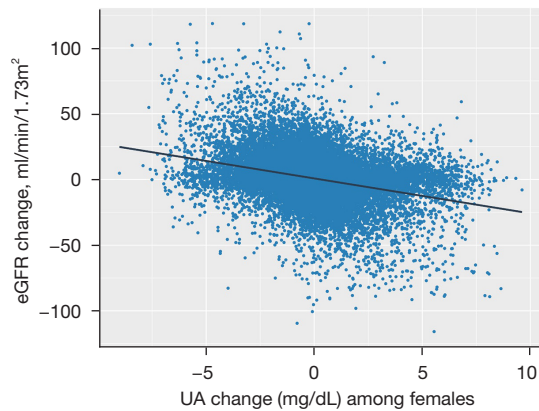


Figure 9 Correlation between changes in serum uric acid (UA) and changes in the estimated glomerular filtration rate (eGFR) among females.



Figure 12 Correlation between changes in serum uric acid (UA) and changes in low-density lipoprotein cholesterol (LDL-C) among females.

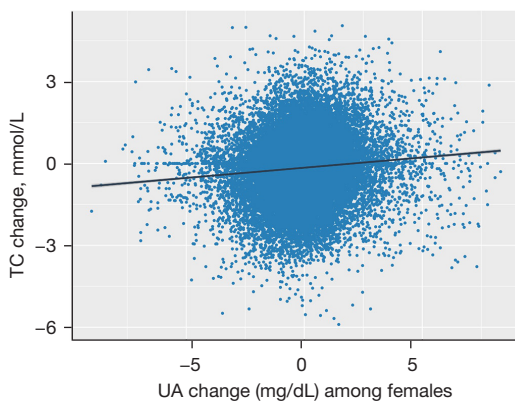


Figure 10 Correlation between changes in serum uric acid (UA) and changes in total cholesterol (TC) among females.

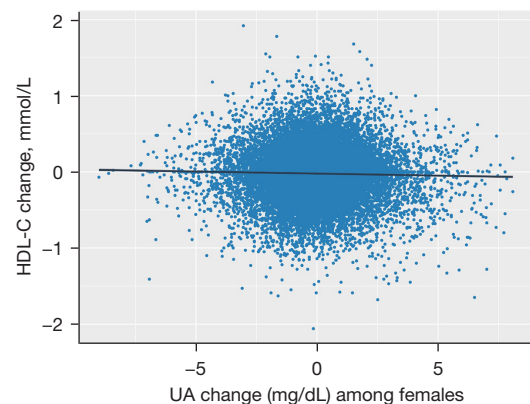


Figure 13 Correlation between changes in serum uric acid (UA) and changes in high-density lipoprotein cholesterol (HDL-C) among females.

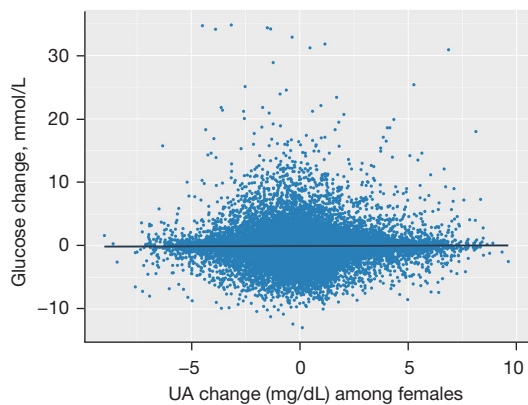


Figure 14 Correlation between changes in serum uric acid (UA) and changes in blood glucose among females.

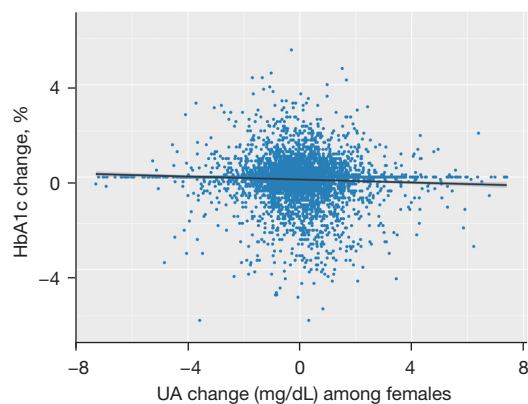


Figure 15 Correlation between changes in serum uric acid (UA) and changes in hemoglobin A1c (HbA1c) among females.

HUA is higher in women than man, and older people are at higher risk of hypertension.

HUA is a risk factor for cardiovascular events, development, and death (51). Our study showed that HUA is associated with a clustering of major CVD risk factors in the Chinese population. Further, we observed the prevalence of cardio-cerebrovascular diseases, including stroke, heart failure, and coronary arterial disease. As stated above, women with a higher age showed a stronger prevalence than men.

This study had several limitations. First, the relationship between UA and metabolism-related diseases was examined using cross-sectional data, and causality was not considered due to the lack of retrospective real-world data. Second, the retrospective real-world data were fully based on HIS and digital platforms, and the population enrolled were all

subjects who sought healthcare services; thus, the overall population was not totally represented in the test group. Third, while we conducted an exploration of longitudinal data based on the retrospective cohort, the rate of loss in the follow-up data was high in the real-world setting. Finally, some potential confounders were not included in this study due to the data accessibility in the databases consulted, such as body weight, body mass index, insulin level and smoking and drinking history, resulted in the lack of subsequent analysis.

The prevention and treatment of uncertainties in real world study concludes a more principled approach to design and analysis in the presence of missing data. A careful design and conduct to limit the amount and impact of missing data.

In conclusion, we used large-scale retrospective HIS data to examine the sex-specific relationship among UA levels and metabolism-related diseases in Chinese patients. The sex-specific prevalence of HUA was observed in the Chinese population. The elevated prevalence of some metabolism-related diseases might be associated with elevated UA levels in both male and female Chinese patients in real-world settings. Notably, both our cross-sectional and longitudinal results revealed that HUA was associated with dyslipidemia and CKD in both sexes.

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Footnote

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YZ, and JL reported that they are from Jiangsu Hengrui Pharmaceuticals Co., Ltd. XY and TC reported that they are from Shanghai Palan DataRx Co., Ltd. FZ reported that he is from Shandong Health Medical Big Data Co., Ltd. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by committee ethics board of Jinan Central Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China (No. 2020-026-01). Individual consent for this retrospective analysis was waived.

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