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Elevated triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio increased risk of hyperuricemia: a 4-year cohort study in China

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Abstract
Purpose Previous studies revealed that high serum uric acid (SUA) levels correlated with increased triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio. However, evidence is lacking regarding whether TG/HDL-C is an independent risk factor or just a simple marker of hyperuricemia. We aimed to investigate the relationship between TG/HDL-C and the risk of hyperuricemia in Chinese population.
Methods This retrospective cohort study involved 15,198 subjects (43.14 ± 13.13 years, 54.9% men) who were free of hyperuricemia at baseline. The association between TG/HDL-C and the risk of hyperuricemia, in the total sample and stratified by subgroups, was examined by multiple logistic regression analyses.
Results During 4 years follow-up, hyperuricemia occurred in 2365 (15.6%) participants. The cumulative incidence of hyperuricemia was significantly elevated with increasing TG/HDL-C quartiles (5.9, 10.8, 18.4, and 27.5%, respectively). After multivariate adjustment, the odds ratio for hyperuricemia in the highest compared with the lowest quartile of TG/HDL-C was 1.80 (95% confidence interval [CI] 1.49, 2.18), and each SD increment of TG/HDL-C ratio caused a 10% additional risk for hyperuricemia. Moreover, subgroup analyses showed that the association between TG/HDL-C and the risk of hyperuricemia was more pronounced in women and normal-weight adults. The results were consistent when analyses were restricted to participants without metabolic syndrome.
Conclusions TG/HDL-C ratio was positively related to the risk of hyperuricemia in Chinese population, particularly in women and normal-weight individuals. These findings suggested the potential of TG/HDL-C ratio to serve as an independent risk indicator in the prevention of hyperuricemia.

Keywords Hyperuricemia · Triglyceride · High-density lipoprotein cholesterol · Insulin resistance

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Introduction

Hyperuricemia is a condition characterized by abnormally elevated levels of serum uric acid (SUA) and it has become a great challenge to public health concerns worldwide [1]. Hyperuricemia is a common metabolic disease in Europe and the United States, affecting more than 20% of the general population [2, 3]. In China, the prevalence of hyperuricemia ranged from 13% to 25%, and it will continue to increase because of the alteration in diet, lifestyle and population age structure [4, 5]. Hyperuricemia has long been recognized as the major etiologic factor in gout, an excruciatingly painful inflammatory arthritis [6]. Moreover, accumulating evidence suggests that hyperuricemia is closely related to the presence and severity of multiple

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comorbidities that affect longevity and well-being, such as cardiovascular disease, type 2 diabetes mellitus (T2DM), chronic kidney disease, non-alcoholic fatty liver disease and cancer [7–10]. Accordingly, identifying and managing the risk factors of hyperuricemia may be a promising strategy to prevent and delay adverse outcomes of hyperuricemia.

It is well established that lipid abnormalities, especially increased triglycerides (TG) levels together with decreased high-density lipoprotein cholesterol (HDL-C) levels, are commonly presented in hyperuricemia patients [11–14]. On the other hand, compelling evidence indicated that hyperuricemia is closely linked to insulin resistance [15, 16]. Since the ratio of triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) not only contained pivotal components of hyperlipidemia, but also formulated as a proxy for insulin resistance [17, 18], we hypothesized that TG/HDL-C ratio may potentially associate with the development of hyperuricemia. However, it has yet to be elucidated whether the TG/HDL-C ratio could serve as a risk indicator to optimize the prevention of hyperuricemia. In addition, multiple related risk factors, such as gender, drinking, and body mass index (BMI), could affect the ratio of TG/HDL-C as well as the risk of hyperuricemia [5, 19]. Therefore, we conducted a retrospective cohort study to investigate the relationship between TG/HDL-C and hyperuricemia, and to evaluate whether this association was modified by other related factors.

Methods

Study design and study subjects

This single-center, retrospective cohort study was conducted based on the population who participated in their physical examination in the Health Management Center of the Third Xiangya Hospital (Changsha, China). All of the data were obtained from the database of the Third Xiangya Hospital, and we have previously published studies using this database [20–22]. In the present study, we included 19,795 subjects between 20 and 85 years old whose data were available at 2012 and 2016. If the subjects in this study had more than one annual exam, we only used the first record of that year to avoid double counts. Subjects who met the following criteria were excluded: (1) no available data on key variables, including SUA, TG and HDL-C ($n =$ 277); (2) with hyperuricemia at baseline ($n = 2094$); (3) taking lipid-lowering drugs ($n = 125$); (4) with chronic kidney disease ($n = 2101$). Finally, a total of 15,198 subjects were included in the present study (Fig. 1).

Ethics approval for the study protocol and analysis of the data was obtained from the Medical Ethics Committee of Third Xiangya Hospital. All of the work has been carried
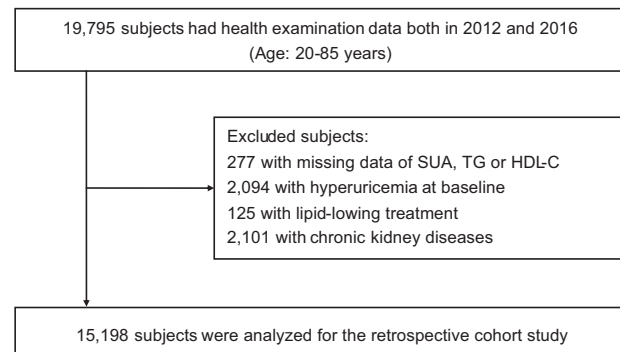

Fig. 1 Flow diagram of study subjects selection

out in accordance with the Declaration of Helsinki, and informed written consent was obtained from all subjects.

Data collection and measurements

All subjects were interviewed by trained interviewers using questionnaires to collect information on age, sex, education level, cigarette smoking, drinking habits and medical history. Smoking status was classified as a current smoker (smoking in the past 6 months) and non-smoker (cessation of smoking for more than 6 months or never smoking). The same rules were implemented to define drinking status. Anthropometric measurements were performed with the subjects wearing light clothing. Waist circumference (WC) was measured at umbilical level in a standing position with light expiration. Body weight and height were measured in a standing position using calibrated weighing scales, and BMI was calculated as weight (kg) divided by height (m) squared. Blood pressure (BP) was measured twice on the right arm with a mercury sphygmomanometer while the subjects were in a seated position after at least 10 min of rest. The final BP value was obtained by averaging the values of the measurements. Blood samples were collected from the antecubital vein after an overnight fasting and stored at $-20\,°C$ until analyzed. Fasting blood glucose (FBG), total cholesterol (TC), TG, low-density lipoprotein cholesterol (LDL-C), HDL-C, SUA, albumin (ALB), creatinine (SCr) and alanine aminotransferase (ALT) were determined using standard laboratory methods and tested using an auto-analyzer (Hitachi 7600-110; Hitachi, Tokyo, Japan). Renal function was estimated by calculated glomerular filtration rate (eGFR) using a modified Chinese equation based on inulin clearance as follows: eGFR $(mL/min/1.73\,m^2) = 175 \times$ (Scr in enzymatic method)$^{-1.234} \times$ age$^{-0.287}$ ($\times 0.79$, if female) [23].

Definitions of obesity, hypertension, diabetes, metabolic syndrome, and hyperuricemia

Participants with a BMI $\geq 25.0\,kg/m^2$ were defined as overweight/obesity according to the World Health

Organization (WHO) criteria [24]. Hypertension was defined on the basis of the Joint National Committee 7 report as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg, or individuals who were on antihypertensive medications or a prior diagnosis of hypertension [25]. T2DM was diagnosed according to the American Diabetes Association diagnostic criteria in subjects with FBG ≥7.0 mmol/L, or using hypoglycemic drugs or a previous diagnosis of diabetes [26]. Modified NCEP-ATPIII guideline that specifically applied for Asians was used for classification of metabolic syndrome [27]. Participants with three or more of these criteria were considered to have metabolic syndrome: (1) TG ≥ 1.7 mmol/L or lipid-lowering drugs; (2) SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or antihypertensive drugs; (3) FBG ≥ 5.6 mmol/L or medications for diabetes; (4) HDL-C < 1.04 mmol/L for men or <1.29 mmol/L for women; and (5) WC ≥ 90 cm in men or ≥80 cm in women. Hyperuricemia was defined as SUA ≥ 420 mmol/L in men or ≥360 mmol/L in women, or any treatment for hyperuricemia [4]. Subjects who were free of hyperuricemia in 2012 but received a diagnosis of hyperuricemia in 2016 were defined as incident hyperuricemia cases.

Statistical analysis

The entire study population was divided into four groups according to their quartiles of baseline TG/HDL-C ratio (Q1: < 0.459, Q2: 0.459~0.753, Q3: 0.754~1.296, Q4: > 1.296), and the parameters were compared between these four groups. The data were presented as numbers with percentages for categorical variables, and as means ± standard deviation or as medians (25th and 75th percentile) values for continuous variables. The analysis of one-way analysis of variance (ANOVA) or a post hoc analysis of the least significant difference (LSD) was used to compare the means of the normally distributed continuous variables, otherwise, the Kruskal–Wallis test was used. The Chi-square test was used for categorical variables. The odds ratios (ORs) and 95% confidence intervals (CIs) for hyperuricemia were calculated using the logistic regression model after adjustment for multiple confounders. Model 1 was adjusted for age and sex. In Model 2, the analysis was adjusted for age, sex, education status, smoking, drinking, overweight/obesity, hypertension, and diabetes. In addition to the confounders analyzed in Model 2, Model 3 included admission of TC, LDL-C, eGFR, ALB, and ALT. Model 4 added baseline SUA based on Model 3. We also estimated the risk of hyperuricemia associated with TG/HDL-C as continuous variables in all models. In addition, sensitivity analyses were conducted to assess the robustness of the results by rerunning all the models in participants without metabolic syndrome at baseline ($N = 12,813$). Further

stratification analyses were conducted to obtain ORs and 95% CIs for incident hyperuricemia in various subgroups. All analyses were performed using IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA) and two-tailed P values of <0.05 were considered statistically significant.

Results

Demographic data and clinical characteristics

The baseline demographic and clinical characteristics of the study participants are summarized in Table 1. The mean age of 15,198 subjects was 43.14 ± 13.13 years and 54.9% of participants were men. The median TG/HDL-C ratio was 0.75 (0.46–1.28). Compared with lower TG/HDL-C levels, subjects who had higher TG/HDL-C levels were more likely to be older and males. Subjects with higher TG/HDL-C levels also had a tendency to have higher BMI, WC, BP, FBG, TG, TC, LDL-C, SUA, SCr, ALT, and ALB. Besides, the frequencies of overweight/obesity, hypertension, diabetes, current smoking or drinking habit also increased with TG/HDL-C levels. On the other hand, there was an inverse association between HDL-C, eGFR as well as levels of education and TG/HDL-C ratio.

Association between TG/HDL-C and the risk of hyperuricemia

During 4 years follow-up, hyperuricemia occurred in 2365 (15.6%) participants. Figure 2 A depicts that the incidence of hyperuricemia increased from 5.9% to 27.5% from the lowest TG/HDL-C quartile to the highest in all subjects. Table 2 illustrates the multiple adjusted associations between TG/HDL-C and incident hyperuricemia. In all four models of the statistical analysis, the ORs for hyperuricemia increased across the TG/HDL-C quartiles. After adjusting for age and sex (Model 1), the OR for hyperuricemia in the comparison between the highest and lowest quartiles of TG/HDL-C was 4.37 (95% CI 3.71–5.16). After further adjusting for all confounders (Model 4), the association between TG/HDL-C and incident hyperuricemia was also significant. Compared with the first quartile, the ORs for hyperuricemia in the second, third and fourth TG/HDL-C quartiles were 1.25 (95% CI 1.04–1.50), 1.60 (95% CI 1.33–1.92), and 1.80 (95% CI 1.49–2.18), respectively. Moreover, the OR of hyperuricemia per 1-SD increase in the TG/HDL-C was 1.10 (95% CI, 1.05–1.16). In addition, we tried a broader diagnostic criterion (SUA levels ≥360 mmol/L) [28, 29] to reevaluate the association between TG/HDL-C ratio and incident hyperuricemia, and our results indicated that TG/HDL-C ratio was also positively related to the risk of hyperuricemia (Supplemental Fig. 1 and Table S1).

Table 1 Baseline characteristics of subjects by TG/HDL-C quartiles

Variables	Total (N = 15,198)	TG/HDL-C ratio				P value
		Quartile 1 (N = 3829)	Quartile 2 (N = 3832)	Quartile 3 (N = 3806)	Quartile 4 (N = 3731)	
Age (years)	43.14 ± 13.13	39.50 ± 13.15	43.07 ± 13.43[a]	45.41 ± 13.26[a,b]	44.64 ± 11.80[a,b]	<0.001
Male (n, %)	8351 (54.9)	897 (23.4)	1767 (46.1)[a]	2537 (66.7)[a,b]	3150 (84.4)[a,b,c]	<0.001
BMI (kg/m^2)	23.40 ± 3.06	21.36 ± 2.41	22.73 ± 2.74[a]	24.17 ± 2.76[a,b]	25.4 ± 2.74[a,b,c]	<0.001
WC (cm)	80.25 ± 9.50	72.95 ± 7.52	78.15 ± 8.38[a]	83.05 ± 7.96[a,b]	87.05 ± 7.73[a,b,c]	<0.001
SBP (mmHg)	120.35 ± 15.63	113.56 ± 14.11	118.62 ± 15.13[a]	123.20 ± 15.37[a,b]	126.18 ± 14.92[a,b,c]	<0.001
DBP (mmHg)	74.26 ± 10.80	69.56 ± 9.53	72.68 ± 9.90[a]	75.84 ± 10.49[a,b]	79.11 ± 10.84[a,b,c]	<0.001
TC (mmol/L)	4.76 (4.20–5.37)	4.46 (3.97–5.03)	4.65 (4.13–5.20)[a]	4.89 (4.32–5.48)[a,b]	5.07 (4.47–5.69)[a,b,c]	<0.001
TG (mmol/L)	1.18 (0.82–1.75)	0.67 (0.57–0.77)	0.99 (0.87–1.12)[a]	1.42 (1.25–1.62)[a,b]	2.43 (1.98–3.17)[a,b,c]	<0.001
HDL-C (mmol/L)	1.57 (1.31–1.87)	1.99 (1.79–2.23)	1.68 (1.50–1.88)[a]	1.45 (1.30–1.62)[a,b]	1.21 (1.08–1.36)[a,b,c]	<0.001
LDL-C (mmol/L)	2.48 (1.99–3.02)	2.14 (1.75–2.58)	2.49 (2.04–3.00)[a]	2.77 (2.27–3.26)[a]	2.57 (2.03–3.13)[a,c]	<0.001
TG/HDL-C	0.75 (0.46–1.28)	0.34 (0.28–0.40)	0.59 (0.52–0.66)[a]	0.97 (0.85–1.11)[a,b]	1.94 (1.54–2.72)[a,b,c]	<0.001
FBG (mmol/L)	5.33 ± 1.13	5.05 ± 0.69	5.19 ± 0.82[a]	5.38 ± 1.06[a,b]	5.73 ± 1.62[a,b,c]	<0.001
SUA (mmol/L)	272.27 ± 72.14	224.41 ± 61.37	258.17 ± 65.97[a]	289.16 ± 65.03[a,b]	318.62 ± 59.62[a,b,c]	<0.001
ALB (g/L)	46.00 ± 2.60	45.84 ± 2.55	45.71 ± 2.60	45.99 ± 2.59[a,b]	46.45 ± 2.59[a,b,c]	<0.001
ALT (U/L)	20.0 (14.0–30.0)	15.0 (12.0–19.0)	18.0 (13.0–25.0)[a]	22.0 (16.0-31.0)[a,b]	29.0 (20.0–43.0)[a,b,c]	<0.001
SCr (μmol/L)	63.31 ± 12.72	56.90 ± 11.06	61.84 ± 12.78[a]	65.67 ± 12.39[a,b]	68.99 ± 11.28[a,b,c]	<0.001
eGFR (ml/min/1.73 m^2)	85.71 ± 18.72	93.04 ± 20.50	86.58 ± 18.89[a]	82.51 ± 17.06[a,b]	80.54 ± 15.48[a,b,c]	<0.001
College and above (n, %)	13245 (87.1)	3467 (90.5)	3346 (87.3)[a]	3236 (85.0)[a,b]	3196 (85.7)[a]	<0.001
Smoking (n, %)	4858 (32.0)	445 (11.6)	952 (24.8)[a]	1412 (37.1)[a,b]	2049 (54.9)[a,b,c]	<0.001
Drinking (n, %)	7811 (51.4)	1465 (38.3)	1768 (46.1)[a]	2126 (55.9)[a,b]	2452 (65.7)[a,b,c]	<0.001
Overweight/Obesity (n, %)	4290 (28.2)	263 (6.9)	720 (18.8)[a]	1340 (35.2)[a,b]	1967 (52.7)[a,b,c]	<0.001
Hypertension (n, %)	2659 (17.5)	272 (7.1)	570 (14.9)[a]	785 (20.6)[a,b]	1032 (27.7)[a,b,c]	<0.001
Diabetes (n, %)	828 (5.4)	87 (2.3)	123 (3.2)	211 (5.5)[a,b]	407 (10.9)[a,b,c]	<0.001

Data are presented as mean ± standard deviation or median (interquartile range) for continuous variables, and number (percentage) for categorical variables

BMI body mass index, *WC* waist circumstance, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglyceride, *TC* total cholesterol, *FBG* fasting blood glucose, *SUA* serum uric acid, *ALT* alanine aminotransferase, *ALB* albumin, *SCr* serum creatinine, *eGFR* estimated glomerular filtration rate

[a] $p < 0.05$ compared with Quartile 1

[b] $p < 0.05$ compared with Quartile 2

[c] $p < 0.05$ compared with Quartile 3

To completely rule out the impact of metabolic syndrome on the relationship between TG/HDL-C and hyperuricemia, we reevaluate the relationship between TG/HDL-C and hyperuricemia in participants without metabolic syndrome (N = 12,813). Figure 2b displays that the cumulative incidence of hyperuricemia was significantly elevated with increasing TG/HDL-C quartiles (5.6, 9.4, 15.5, and 24.0%, respectively). Table 3 manifests the OR for hyperuricemia in the highest compared with the lowest quartile of TG/HDL-C was 1.70 (95% CI 1.38–2.10), and each SD increment of TG/HDL-C ratio caused a 18% additional risk for hyperuricemia in people without metabolic syndrome after adjusting for all confounders (Model 4).

Subgroup analyses

The associations between quartiles of TG/HDL-C and hyperuricemia were further investigated among subgroups. We found that the association differed significantly according to gender (P = 0.001) and BMI categories (P = 0.006) in all participates. However, no heterogeneity was observed with age (P = 0.186), smoking (P = 0.110), drinking (P = 0.747), diabetes (P = 0.701) and hypertension (P = 0.612). The subgroup analyses to assess the relationship between TG/HDL-C quartiles and hyperuricemia according to sex and BMI categories in all subjects were presented in Fig. 3a. After multivariate adjustment (Model 4), a stronger association was observed among
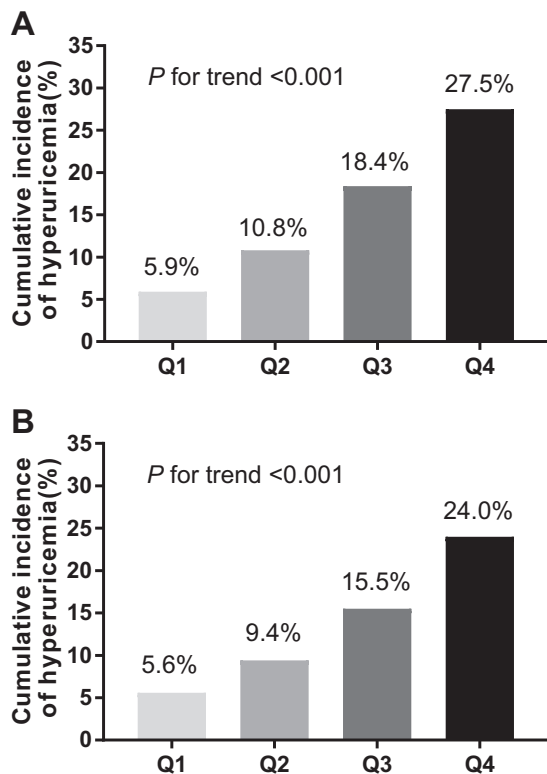
Fig. 2 Cumulative incidence of hyperuricemia according to TG/HDL-C quartiles in **a** all subjects ($N = 15,198$) and **b** subjects without metabolic syndrome ($N = 12,813$)

women and normal-weight individuals than in men and overweight/obesity subjects.

Similarly, no heterogeneity was observed with age ($P = 0.459$), smoking ($P = 0.277$), drinking ($P = 0.444$), diabetes ($P = 0.805$) and hypertension ($P = 0.520$) in subjects without metabolic syndrome ($N = 12,813$). After excluded subjects with metabolic syndrome, Fig. 3b depicts that TG/HDL-C ratio is also more strongly associated with incident hyperuricemia in women and in normal-weight individuals.

Discussion

The primary findings supported our hypothesis that people with high TG/HDL-C ratio are at an increased risk of developing hyperuricemia among Chinese adults. After adjusted for all the potential confounding factors, subjects in the highest quartile of TG/HDL-C were nearly 1.8-fold more likely to develop hyperuricemia compared with those in the lowest quartile, and each SD increment of TG/HDL-C ratio caused a 10% additional risk for hyperuricemia. In addition, the association between TG/HDL-C ratio and the risk of hyperuricemia was more pronounced in women and normal-weight subjects. To the best of our knowledge, this is the first population-based cohort study that evaluated

whether TG/HDL-C ratio was an independent risk factor of hyperuricemia.

Hyperuricemia has emerged as a major public health concern because of its increasing prevalence and significant impact on various clinical disorders [1–3, 7]. In this 4-year follow-up study of 15,198 subjects (43.14 ± 13.13 years, 54.9% men), we observed that 15.6% of Chinese adults developed hyperuricemia. Cao et al. conducted a large prospective cohort study of 58,542 Chinese people (44.0 ± 13.36 years for men and 42.0 ± 12.26 years for women, 59.75% men), the incidence of hyperuricemia was 12.1% with a median of 2.5 years of follow-up. In another prospective cohort study in China, Zhang et al. found that hyperuricemia occurred in 25.9% of participants after 6 years [30]. Strikingly, in the Atherosclerosis Risk in Communities Study of 9451 American who usually consumption of high-fructose corn syrup such as sugar-sweetened soda, 34.8% of them developed hyperuricemia during 6-year follow-up [31]. Since Chinese people have experienced drastic changes in dietary habits with the rapid westernization of lifestyle, the prevalence of hyperuricemia will continue increase in China, leading to serious adverse health outcomes. Thus, exploring of the risk factors that identify those who are prone to develop hyperuricemia is beneficial to early prevention and treatment of the cardiovascular diseases and subsequent gouty arthritis.

The ratio of TG/HDL-C has been recognized as a simple and convenient marker of atherogenic dyslipidemia and insulin resistance [17, 18]. Although the TG/HDL-C ratio has been suggested as a potential tool to identify patients at increased risk of cardiovascular diseases, T2DM, fatty liver and chronic kidney disease [32–35], limited data were available regarding the association between TG/HDL-C and hyperuricemia. Peng et al. utilized the data of the Third National Health and Nutrition Examination Survey (NHANES III), which demonstrated that TG/HDL-C ratio was significantly associated with increased SUA level [11]. Similarly, in a cross-sectional study of 3518 individuals, Tanya et al. observed that high SUA levels were associated with increased TG/HDL-C ratio even after controlling for traditional cardiovascular disease risk factors and confounders including obesity and metabolic syndrome [12]. Besides, SUA levels were also found to be positively related to TG/HDL-C ratio in children [36]. Nevertheless, it is remains unclear whether TG/HDL-C ratio is a causative risk factor or merely a simple marker of hyperuricemia, because the cross-sectional design limited the interpretation of causality between TG/HDL-C and hyperuricemia. In this cohort study, we found that TG/HDL-C ratio was positively correlated with increased risk of hyperuricemia, which extended previous studies by confirming the causative effect of TG/HDL-C on the development of hyperuricemia. These findings were also confirmed when using a more extensive

Table 2 Odds ratios and 95% confidence intervals of TG/HDL-C ratio and incident hyperuricemia in all subjects ($N = 15,198$)

Baseline TG/HDL-C	Model 1	P value	Model 2	P value	Model 3	P value	Model 4	P value
Q1 (<0.459)	1 (References)		1 (References)		1 (References)		1 (References)	
Q2 (0.459~0.753)	1.69 (1.43–2.01)	<0.001	1.62 (1.36–1.92)	<0.001	1.60 (1.34–1.90)	<0.001	1.25 (1.04–1.50)	0.020
Q3 (0.754~1.296)	2.87 (2.43–3.39)	<0.001	2.59 (2.19–3.07)	<0.001	2.55 (2.15–3.03)	<0.001	1.60 (1.33–1.92)	<0.001
Q4 (>1.296)	4.37 (3.71–5.16)	<0.001	3.73 (3.15–4.43)	<0.001	3.45 (2.90–4.12)	<0.001	1.80 (1.49–2.18)	<0.001
P for trend	<0.001		<0.001		<0.001		<0.001	
Per SD increment	1.21 (1.17–1.24)	<0.001	1.17 (1.14–1.21)	<0.001	1.24 (1.19–1.30)	<0.001	1.10 (1.05–1.16)	<0.001

Model 1: adjusted for sex and age

Model 2: adjusted for sex, age, education status, smoking, drinking, overweight/obesity, hypertension and diabetes

Model 3: Model 2 and further adjusted for total cholesterol, low-density lipoprotein cholesterol, albumin, estimated glomerular filtration rate and alanine aminotransferase

Model 4: Model 3 and further adjusted for serum uric acid

Table 3 Odds ratios and 95% confidence intervals of TG/HDL-C ratio and incident hyperuricemia in subjects without metabolic syndrome ($N = 12,813$)

Baseline TG/HDL-C	Model 1	P value	Model 2	P value	Model 3	P value	Model 4	P value
Q1 (<0.423)	1 (References)		1 (References)		1 (References)		1 (References)	
Q2 (0.424~0.654)	1.65 (1.38–1.96)	<0.001	1.57 (1.31–1.87)	<0.001	1.52 (1.27–1.82)	<0.001	1.21 (1.00–1.47)	0.048
Q3 (0.655~1.048)	2.65 (2.23–3.15)	<0.001	2.40 (2.01–2.86)	<0.001	2.31 (1.93–2.77)	<0.001	1.51 (1.24–1.83)	<0.001
Q4 (>1.049)	3.77 (3.14–4.52)	<0.001	3.42 (2.83–4.13)	<0.001	3.19 (2.63–3.87)	<0.001	1.70 (1.38–2.10)	<0.001
P for trend	<0.001		<0.001		<0.001		<0.001	
Per SD increment	1.30 (1.23–1.36)	<0.001	1.27 (1.21–1.34)	<0.001	1.40 (1.30–1.50)	<0.001	1.18 (1.09–1.27)	<0.001

Model 1: adjusted for sex and age

Model 2: adjusted for sex, age, education status, smoking, drinking, overweight/obesity, hypertension and diabetes

Model 3: Model 2 and further adjusted for total cholesterol, low-density lipoprotein cholesterol, albumin, estimated glomerular filtration rate and alanine aminotransferase

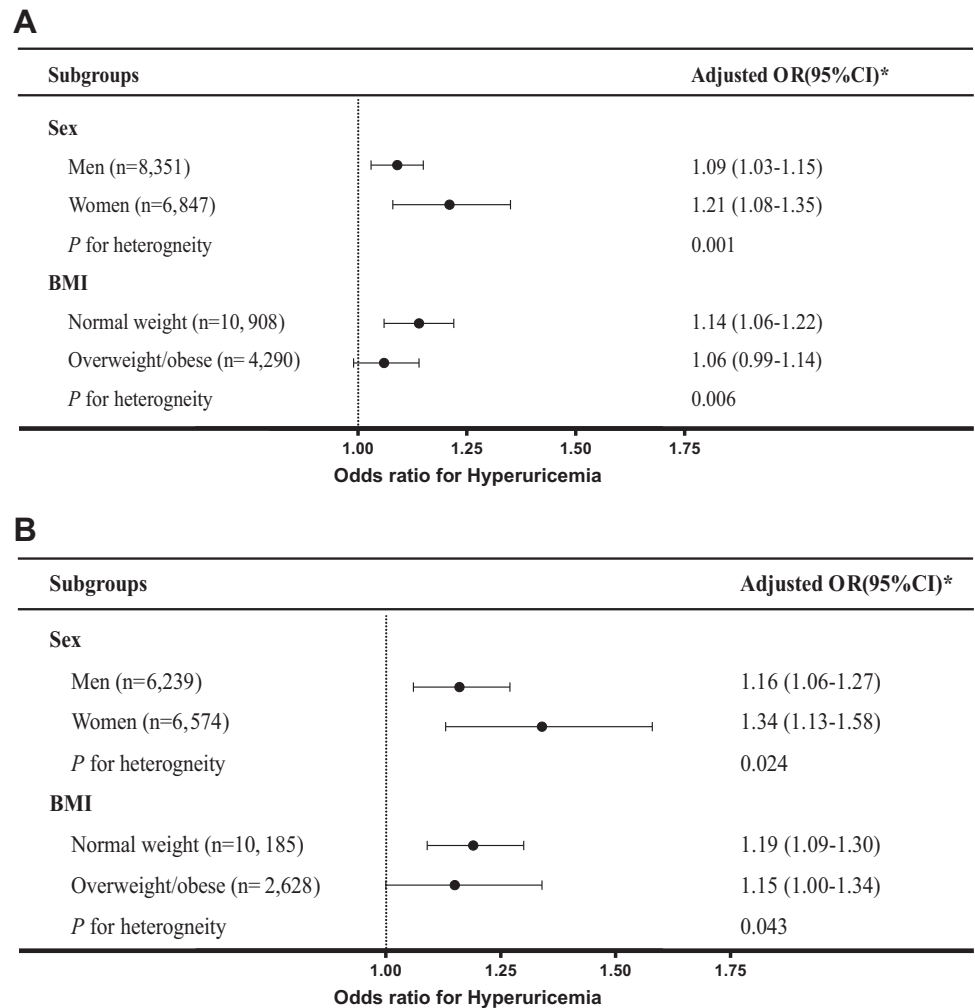Model 4: Model 3 and further adjusted for serum uric acid

criterion to identify hyperuricemia [28, 29]. Moreover, it is well established that metabolic syndrome is a major contributor to the development of hyperuricemia [37, 38], which may cause a spurious association between TG/HDL-C and hyperuricemia. In this case, we reevaluated whether elevated TG/HDL-C ratio is still related to the increased risk of hyperuricemia in subjects without metabolic syndrome, and our data showed that the relationship between TG/HDL-C and incident hyperuricemia was still robust regardless of the presence of metabolic syndrome. Furthermore, the association between TG/HDL-C and the risk of hyperuricemia remained significant even after adjusted for multiple confounders included baseline SUA, suggesting the potential of TG/HDL-C ratio to serve as an independently risk indicator of hyperuricemia in clinical practice.

Several potential mechanisms could be proposed to explain TG/HDL-C as a risk factor for the development of hyperuricemia. First, elevated TG level may contribute to the overproduction of uric acid through free fatty acids metabolic pathways. More specifically, hypertriglyceridemia

caused more free fatty acid production and utilization, and the synthesis of fatty acids in the liver is associated with the de novo synthesis of purines, thereby accelerating uric acid production [39, 40]. Second, low HDL-C level was independently associated with a decreased eGFR and increased risk of renal impairment, which may result in decreased excretion of uric acid [41–43] Third, TG/HDL-C is a surrogate marker of insulin resistance [18], which also involved in the development of hyperuricemia. Insulin resistance is able to enhance renal urate reabsorption via stimulation of the uric acid transporter 1 (URAT1) [44] and/or the Na-dependent anion co-transporter in brush border membranes of the renal proximal tubule [45, 46]. Moreover, insulin resistance could lead to accelerated rate of lipolysis and decreased adipose tissue lipoprotein lipase activity [47], in turn, caused hyperlipemia and the subsequent overproduction of uric acid.

Interestingly, accumulating evidence suggested that hyperuricemia, hyperlipidemia and insulin resistance reflect the common lifestyles and dietary habits such as lack of physical activity, alcohol consumption and high-fructose

Fig. 3 Subgroup Analyses for TG/HDL-C and incident hyperuricemia in **a** all subjects (N = 15,198) and **b** subjects without metabolic syndrome (N = 12,813). *adjusted for sex, age, education status, smoking, drinking, overweight/obesity, diabetes, hypertension, total cholesterol, low-density lipoprotein cholesterol, albumin, alanine aminotransferase, estimated glomerular filtration rate and serum uric acid

A

Subgroups	Adjusted OR(95%CI)*
Sex	
Men (n=8,351)	1.09 (1.03-1.15)
Women (n=6,847)	1.21 (1.08-1.35)
P for heterogneity	0.001
BMI	
Normal weight (n=10, 908)	1.14 (1.06-1.22)
Overweight/obese (n= 4,290)	1.06 (0.99-1.14)
P for heterogneity	0.006

Odds ratio for Hyperuricemia

B

Subgroups	Adjusted OR(95%CI)*
Sex	
Men (n=6,239)	1.16 (1.06-1.27)
Women (n=6,574)	1.34 (1.13-1.58)
P for heterogneity	0.024
BMI	
Normal weight (n=10, 185)	1.19 (1.09-1.30)
Overweight/obese (n= 2,628)	1.15 (1.00-1.34)
P for heterogneity	0.043

Odds ratio for Hyperuricemia

diet [48, 49]. In addition, some lipid-lowering drugs such as fenofibrate, atorvastatin and simvastatin could play a possible role in decreasing the concentration of SUA via an enhanced urinary excretion of uric acid [50, 51]. Similarly, drug treatments for improving insulin sensitivity were also demonstrated to reduce SUA levels [52, 53]. Hence, appropriate management of high TG/HDL-C levels, through dietary, exercise or pharmacological interventions, may be helpful in preventing progression of hyperuricemia.

We also conducted stratified analyses to explore whether the association between TG/HDL-C and hyperuricemia was affected by several established risk factors. Our study showed significant gender differences in the relation of TG/HDL-C ratio with hyperuricemia risk, and this association was significantly higher in women than in men. Intriguingly, similar pattern has been observed for the association between TG/HDL-C and risk of diabetes, chronic kidney disease and non-alcoholic fatty liver disease [33–35]. Although the underlying mechanism of such gender-specific differences remains unknown, one possible explanation might be due to sex hormones. Current literature

supported a robust role of estrogen signaling through Estrogen Receptor alpha (ERα) to impact glucose and TG metabolism [19]. Thus, decline in estrogen levels after menopause may lead to dysregulation of lipid metabolism, which put women under greater risk of developing hyperuricemia. In addition, the association between TG/HDL-C levels and the presence of hyperuricemia was more pronounced in normal-weight individuals. It is possible that some additional mechanisms linked overweight/obesity to hyperuricemia may attenuate the association between TG/HDL-C and risk of hyperuricemia. A genome-wide association study found that hyperuricemia and genes mediating uric acid homeostasis are significantly associated with the overweight/obese state [54]. In addition, Bedir et al. proposed that leptin, secreted from adipose tissue, could be a pathogenic factor responsible for hyperuricemia in obese subjects [55]. Thus, it is important to identify women and normal-weight people with high TG/HDL-C levels as high-risk population of hyperuricemia, and further studies are required to validate and explicate these findings in our study.

The main strength of the current study was the retrospective cohort design with a relatively large sample size, which provided sufficient statistical power to reflect the authentic relationship between TG/HDL-C ratio and the risk of hyperuricemia. Nevertheless, several limitations also required consideration. As a retrospective, single-center study, selection bias is inevitable in our study. In fact, there were 62,748 subjects who underwent annual health checkup at our hospital in 2012. In this study we enrolled 19,795 subjects who came to the health management center both in 2012 and in 2016, however, the background demographics were almost same. The demographic data and clinical characteristics of all the subjects in 2012 and this cohort study subjects after using the same exclusion criteria showed no significant differences (Supplemental Table S2). Moreover, our study cannot rule out the possibility that both high TG/HDL and elevated SUA might be the result of the collinearity with other conditions instead of the consequence of a direct interaction, which has a limitation to reveal the causal relationship between TG/HDL-C and hyperuricemia. Furthermore, we did not get the data of insulin sensitivity of participants, because insulin sensitivity test is not a routine item for health examination population. However, a large body of evidence demonstrated that the TG/HDL-C ratio is a good marker of insulin resistance in Chinese people [56, 57]. In addition, some other factors that may influence SUA levels were not collected in our study, such as physical activity, diets rich in purine or fructose, menopausal status, and concomitant medication treatment. Finally, the study population is comprised of only Chinese. Thus, extrapolating the results to other ethnic population should be interpreted cautiously, especially for African descent with "TG paradox" [58]. Further prospective studies with multiethnic and more detailed information collection are needed to assess the value of TG/HDL-C ratio in prevention of hyperuricemia.

Conclusions

The present study indicated that elevated TG/HDL-C ratio increased future risk of hyperuricemia in Chinese population, especially in female and normal-weight individuals. From a clinical and public health perspective, clinicians should pay attention to the risk of hyperuricemia in individuals with high TG/HDL-C ratio and develop proper management to decrease the risk of hyperuricemia by improving TG/HDL-C levels.

Compliance with ethical standards

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