Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Association Between Serum Uric Acid Levels and Metabolic-Associated Fatty Liver Disease in Southeast China: A Cross-Sectional Study

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Objective: This study aimed to explore the association between serum uric acid (sUA) levels and metabolic-associated fatty liver disease (MAFLD) in Southeast China.

Methods: We performed a cross-sectional study of 2605 subjects who underwent physical examination between 2015 and 2017 in Southeast China. To explore the association between sUA levels and the risk of MAFLD, we employed logistic regression, restricted cubic spline (RCS), subgroups and multiplicative interaction analysis.

Results: Logistic regression analysis showed a positive association between sUA and MAFLD [$aOR_{\text{total population}}$ (95% *CI*)= 1.90 (1.49 ~ 2.42)], [aOR_{male} (95% *CI*)= 2.01 (1.54 ~ 2.62)], [aOR_{female} (95% *CI*)= 1.15 (0.62 ~ 2.11)], respectively. The RCS plot presented a significant nonlinear dose–response relationship between sUA levels and MAFLD risk, and the risk of MAFLD increased significantly when sUA> 5.56 mg/dL ($P_{\text{nonlinear}}$< 0.001). Subgroups analysis revealed that the positive association between sUA and MAFLD was consistent across strata of gender, age, BMI, drinking status, smoking status and tea drinking status. Significant associations between sUA and MAFLD were not only found in males but also existed in subjects whose age ≤60, BMI ≥24 kg/m^2, drinkers, smokers and tea-drinkers. Adjusted *OR*s were estimated to be 2.01, 1.95, 2.11, 2.29, 2.64 and 2.20, respectively. Multiplicative interactions were not observed between gender, age, drinking status, smoking status, tea drinking status and sUA (all $P_{\text{interaction}}$> 0.05).

Conclusion: According to our study, sUA was positively associated with the risk of MAFLD. Additionally, the risk of MAFLD increased significantly when sUA levels exceeded 5.56 mg/dL. Our study may help clarify whether sUA plays a diagnostic role in MAFLD.

Keywords: metabolic-associated fatty liver disease, serum uric acid, risk, cross-sectional study

Background

Non-alcoholic fatty liver disease (NAFLD) refers to the excessive deposition of fat in hepatocytes, which is diagnosed after excluding excessive alcohol consumption and other definite factors that lead to liver damage.[1] However, with the increasing prevalence of hepatic steatosis, the diagnostic criteria for NAFLD are gradually unable to meet the needs of clinical work. In 2020, the International Panel of Liver Experts renamed NAFLD to metabolic-associated fatty liver disease (MAFLD),[2] which is a more appropriate disease designation for liver diseases associated with metabolic dysfunction.[3] MAFLD is one of the most prevalent chronic liver diseases worldwide, affecting at least 25% of the world's adult population and 29–46% of the Chinese population.[4–6] MAFLD not only cause cirrhosis and hepatocellular

Received: 27 June 2024
Accepted: 22 August 2024
Published: 7 September 2024

carcinoma, but also increases the risk of type 2 diabetes, cardiovascular disease (CVD), chronic kidney disease, and metabolic syndrome.[7–9] Therefore, early detection and intervention of risk factors for MAFLD is extremely important.

Uric Acid (UA), the end product of purine metabolism, is continuously produced, excreted, and maintained at a certain concentration in the blood. Overproduction or reduced UA excretion increases serum Uric Acid (sUA) levels. Several studies have shown that sUA was a risk factor of CVD, type 2 diabetes mellitus, and metabolic syndrome.[10,11] Worldwide, high level of sUA is also associated with an increased prevalence of metabolic syndrome.[12–14] Many studies have demonstrated that sUA is a risk factor for NAFLD, a study in US found that sUA was independently associated with NAFLD, increasing sUA was associated with increasing severity of NAFLD.[15] A cross-sectional study also showed serum uric acid/creatinine ratio was significantly higher in subjects with NAFLD than those without NAFLD.[16] Meta-analysis showed positive correlations between sUA and the risk of NAFLD.[17–19] But the different definitions of NAFLD and MAFLD inevitably lead to differences between the affected populations. The association between sUA levels and MAFLD remained unclear. The participants included in our study were permanent residents of Nanping City, where the prevalence of NAFLD was 32.8%, which was higher than other cities in Fujian province.[20] This cross-sectional study aimed to explore the association between sUA and the risk of MAFLD in Southeast China.

Materials and Methods

Study Design and Subjects

This cross-sectional study, involving 2605 subjects who underwent physical examination and completed abdominal ultrasonography between April 2015 and August 2017 at the Physical Examination Center of Nanping First Hospital Affiliated to Fujian Medical University. All participants provided informed consent before the start of the study.

The inclusion criterion for participants was permanent residents of Nanping, aged between 18–74 years old. The exclusion criteria were as follows: (A) presence of acute and chronic infections; (B) participants with missing information on abdominal ultrasound, blood tests, and physical measurements; (C) participants with chronic hepatitis and cirrhosis, coronary heart disease, stroke, and cancer; and (D) pregnant or lactating mothers.

Diagnostic Criteria for MAFLD

The diagnosis of MAFLD is based on ultrasound showing hepatic steatosis using one of the following three criteria: (A) overweight or obesity (BMI≥ 23.0 kg/m^2), (B) type 2 Diabetes Mellitus, and (C) metabolic dysfunction among non-overweight individuals (BMI< 23.0 kg/m^2). Metabolic dysfunction is defined as meeting two of the following indicators: (a) Waist circumference: Asian male/female≥ 90/80 cm; (b) Blood pressure≥ 130/85 mmHg or receiving specific medication; (c) Plasma triglycerides≥ 150 mg/dL (≥ 1.7 mmol/L) or on specific drug treatment; (d) HDL-c< 40 mg/dL (1.0 mmol/L) for men and < 50 mg/dL (1.3 mmol/L) for women or on specific drug treatment; (e) Pre-diabetes; (f) HOMA-IR≥ 2.5; (g) C-reactive protein> 2 mg/L.

Data Collection and Measurement

Information on MAFLD risk factors was obtained from face-to-face interviews with trained investigators. Risk factors included gender, age, smoking status, drinking status, tea drinking status, lifestyle, dietary habits, disease history and treatment status. Clinical variables were collected after overnight fasting, including height (m), weight (kg), body mass index (BMI, kg/m^2), hip circumference (HC, cm), waist circumference (WC, cm), Waist-hip Ratio (WHR), diastolic blood pressure (DBP, mmHg), systolic blood pressure (SBP, mmHg), serum triglyceride (TG, mmol/L), total cholesterol (TC, mmol/L), low-density lipoprotein (LDL, mmol/L), high-density lipoprotein (HDL, mmol/L), fasting plasma glucose (FPG, mmol/L), gamma-glutamyl transferase (GGT, U/L), blood urea nitrogen (BUN, mmol/L), creatinine (CR, umol/L) and serum Uric Acid (sUA, mg/dL). Hypertension was defined as SBP≥ 140 mmHg and/or DBP≥ 90 mmHg or current use of antihypertensive medication. Diabetes was defined as FPG≥ 7.0 mmol/L or current use of hypoglycaemic agents.

Statistical Analysis

The baseline characteristics of the subjects were analyzed using the Nonparametric Kruskal–Wallis test for non-normal continuous variables and the chi-square test for nominal variables. Continuous variables were expressed as median (interquartile range, IQR). Nominal variables are expressed as frequencies (n) and constitutive ratios (%).

Univariate and multivariate logistic regression analysis were performed to analyze the association between sUA and MAFLD risk. A RCS plot was used to present the dose–response relationship between sUA and MAFLD risk. Subgroups analysis and multiplicative interaction analysis were used to examine the relationship of sUA with MAFLD risk by the following subgroups: gender (male or female), age (≤ 60 years or> 60 years), BMI (<24 kg/m^2 or≥24 kg/m^2), drinking status (yes or no), smoking status (yes or no), tea drinking status (yes or no). I^2 and Q tests were used to assess heterogeneity. A P value < 0.05 for the Q statistic or I^2 more than 50% suggests notable heterogeneity. Multiplicative interaction analysis was performed based on the heterogeneity. Statistical analysis were performed in SPSS version 26.0, Stata version 17.0, and R version 4.3.0. P significance was set at P< 0.05.

Results

Baseline Characteristics

The demographics, lifestyle habits, and clinical characteristics of subjects are shown in Tables 1 and 2. Of the 2605 participants, 726 had MAFLD, with a prevalence of 27.9%. Compared with subjects without MAFLD, subjects with MAFLD were more likely to be male, smokers, drinkers, tea drinkers, have higher BMI, prefer salty foods, eat fast, and have diabetes or hypertension (all P< 0.001). Additionally, there were significant differences in clinical detection indicators (WC, HC, WHR, SBP, DBP, HDL, LDL, GGT, TC, FPG, TG, sUA, BUN, and CR) between the two groups (all P < 0.001).

Table 1 Comparison of Demographic and Lifestyle Habits Characteristics

Variables	Overall (n = 2605)	Non-MAFLD (n = 1879)	MAFLD (n = 726)	P
Age (years), n (%)				0.255
≤60	2431 (93.32)	1760 (93.67)	671 (92.42)	
>60	174 (6.68)	119 (6.33)	55 (7.58)	
Gender, n (%)				<0.001
Male	1471 (56.47)	887 (47.21)	584 (80.44)	
Female	1134 (43.53)	992 (52.79)	142 (19.56)	
BMI (kg/m^2), n (%)				<0.001
<24	1636 (62.80)	1441 (76.69)	195 (26.86)	
≥24	969 (37.20)	438 (23.31)	531 (73.14)	
Smoking status, n (%)				<0.001
No	2026 (77.77)	1534 (81.64)	492 (67.77)	
Yes	579 (22.23)	345 (18.36)	234 (32.23)	
Drinking status, n (%)				<0.001
No	1669 (64.07)	1264 (67.27)	405 (55.79)	
Yes	936 (35.93)	615 (32.73)	321 (44.21)	
Tea Drinking Status, n (%)				<0.001
No	1060 (40.69)	852 (45.34)	208 (28.65)	
Yes	1545 (59.31)	1027 (54.66)	518 (71.35)	
Taste, n (%)				<0.001
Light	613 (23.53)	514 (27.35)	99 (13.64)	
Normal	1546 (59.35)	1061 (56.47)	485 (66.80)	
Salty	446 (17.12)	304 (16.18)	142 (19.56)	

(*Continued*)

Table 1 (Continued).

Variables	Overall (n = 2605)	Non-MAFLD (n = 1879)	MAFLD (n = 726)	*P*
Eating speed (min), n (%)				<0.001
<10	658 (25.26)	449 (23.90)	209 (28.79)	
10–30	1831 (70.29)	1326 (70.57)	505 (69.56)	
≥30	116 (4.45)	104 (5.53)	12 (1.65)	
Hypertension, n (%)				<0.001
No	1669 (64.07)	1373 (73.07)	296 (40.77)	
Yes	936 (35.93)	506 (26.93)	430 (59.23)	
Hypertension treatment status, n (%)				<0.001
No	2513 (96.47)	1833 (97.55)	680 (93.66)	
Yes	92 (3.53)	46 (2.45)	46 (6.34)	
Diabetes, n (%)				<0.001
No	2459 (94.40)	1809 (96.27)	650 (89.53)	
Yes	146 (5.60)	70 (3.73)	76 (10.47)	
Diabetes treatment status, n (%)				0.012
No	2571 (98.69)	1861 (99.04)	710 (97.80)	
Yes	34 (1.31)	18 (0.96)	16 (2.20)	

Abbreviation: BMI, body mass index.

Table 2 Comparison of Biochemical Indices

Variables	Overall (n = 2605)	Non-MAFLD (n = 1879)	MAFLD (n = 726)	*P*
WC (cm), M (IQR)	82.00 (75.00–89.00)	78.00 (73.00–85.00)	90.00 (85.00–95.00)	<0.001
HC (cm), M (IQR)	95.00 (91.00–99.00)	93.00 (90.00–97.00)	99.00 (96.00–103.00)	<0.001
WHR, M (IQR)	0.86 (0.81–0.91)	0.84 (0.80–0.88)	0.91 (0.87–0.94)	<0.001
SBP (mmHg), M (IQR)	118.00 (110.00–128.00)	115.00 (107.00–123.00)	125.00 (118.00–136.00)	<0.001
DBP (mmHg), M (IQR)	80.00 (72.00–86.00)	78.00 (70.00–82.00)	85.00 (80.00–90.00)	<0.001
HDL (mmol/L), M (IQR)	1.32 (1.14–1.46)	1.38 (1.19–1.48)	1.17 (1.02–1.33)	<0.001
LDL (mmol/L), M (IQR)	3.11 (2.62–3.60)	3.07 (2.62–3.54)	3.22 (2.63–3.78)	<0.001
GGT (U/L), M (IQR)	23.00 (16.00–36.00)	20.00 (15.00–29.00)	34.00 (24.00–52.00)	<0.001
TC (mmol/L), M (IQR)	4.99 (4.48–5.58)	4.95 (4.43–5.45)	5.17 (4.65–5.87)	<0.001
FPG (mmol/L), M (IQR)	5.17 (4.91–5.54)	5.12 (4.87–5.40)	5.37 (5.06–5.91)	<0.001
TG (mmol/L), M (IQR)	1.25 (0.90–1.84)	1.07 (0.83–1.49)	1.91 (1.34–2.75)	<0.001
SUA (mg/dL), M (IQR)	5.56 (4.59–6.69)	5.21 (4.41–6.26)	6.60 (5.47–7.46)	<0.001
BUN (mmol/L), M (IQR)	4.44 (3.56–5.36)	4.29 (3.44–5.26)	4.74 (3.94–5.57)	<0.001
CR (umol/L), M (IQR)	80.47 (67.77– 91.32)	77.18 (65.70–88.83)	86.41 (76.87– 96.90)	<0.001

Notes: M (IQR), Data are presented as medians with interquartile ranges (M (P25, P75)).
Abbreviations: WC, waist circumference; HC, hip circumference; WHR, Waist-hip Ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GGT, gamma-glutamyl transferase; TC, total cholesterol; FPG, fasting plasma glucose; TG, serum triglyceride; SUA, serum uric acid; BUN, blood urea nitrogen; CR, creatinine.

Association of sUA with MAFLD

sUA levels were categorized into two groups according to the normal reference range of sUA (2.5–7.0 mg/dL for males; 1.5–6 mg/dL for females). A logistic regression model was used to analyze the association between sUA and MAFLD. As shown in Table 3, in the crude model, sUA was positively correlated with MAFLD in total population, males and females. After adjusting for age, BMI, smoking status, drinking status, tea drinking status, taste, eating speed, hypertension, hypertension treatment status, diabetes, diabetes treatment status, HDL, LDL, TC, BUN and CR, the positive association between sUA and MAFLD remained unchanged in total population and males.

Table 3 Univariate and Multivariate Logistic Analysis of sUA and MAFLD

Variables	Crude model		Adjusted model*	
	OR (95% *CI*)	*P* value	*OR* (95% *CI*)	*P* value
sUA levels in total population				
Normal	1.00		1.00	
High	3.48 (2.87–4.22)	<0.001	1.90 (1.49–2.42)	<0.001
sUA levels in males				
Normal (≤ 416 μmol/L)	1.00		1.00	
High (> 416 μmol/L)	2.36 (1.89–2.96)	<0.001	2.01 (1.54–2.62)	<0.001
sUA level in females				
Normal (≤ 357 μmol/L)	1.00		1.00	
High (> 357 μmol/L)	3.54 (2.26–5.54)	<0.001	1.15 (0.62–2.11)	0.659

Notes: *Adjusted for age, BMI, smoking status, drinking status, tea drinking status, taste, eating speed, hypertension, hypertension treatment status, diabetes, diabetes treatment status, HDL, LDL, TC, BUN and CR.

The dose-response relationship between sUA and MAFLD risk was interpreted by RCS analysis. There was a significant nonlinear correlation between sUA and MAFLD risk ($P_{\text{nonlinear}} < 0.001$), and the risk of MAFLD increased significantly when sUA> 5.56 mg/dL (Figure 1).

Subgroups Analysis

Subgroup analysis was performed to investigate the robustness of relationship between sUA and MAFLD risk. The positive association between sUA and MAFLD risk was consistent across strata of gender, age, BMI, drinking status, smoking status and tea drinking status. Significant associations between sUA and MAFLD risk were not only found in males but also existed in subjects whose age≤ 60, BMI≥ 24 kg/m^2, drinkers, smokers and tea-drinkers. Adjusted *OR*s were estimated to be 2.01, 1.95, 2.11, 2.29, 2.64 and 2.20, respectively (Figure 2).

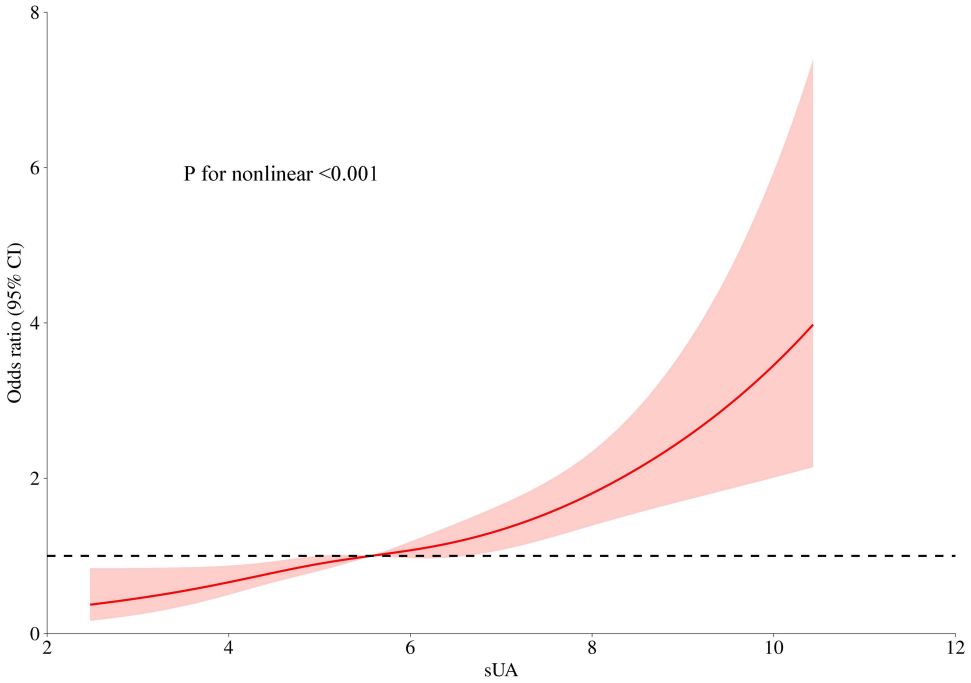

Figure 1 Restrictive cubic spline modelling of the association between sUA levels and MAFLD risk.
Notes: Red area, 95% *CI*. The RCS model was adjusted for age, gender, BMI, smoking status, drinking status, tea drinking status, taste, eating speed, hypertension, hypertension treatment status, diabetes, diabetes treatment status, HDL, LDL, TC, BUN and CR.

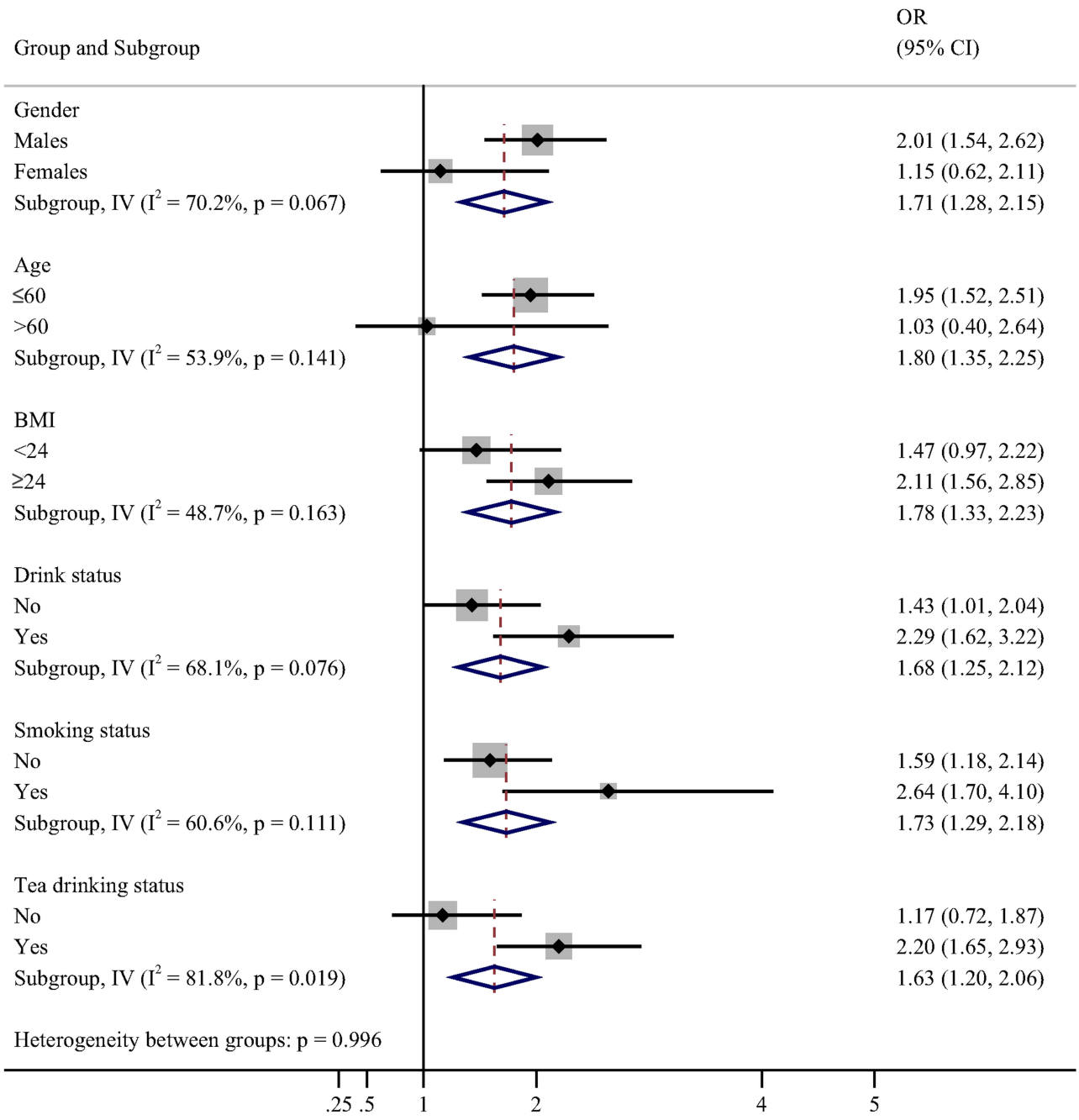

Figure 2 Forest plot of subgroups analysis of the relationship between sUA and MAFLD risk.
Notes: Adjusted for gender, age, BMI, smoking status, drinking status, tea drinking status, taste, eating speed, hypertension, hypertension treatment status, diabetes, diabetes treatment status, HDL, LDL, TC, BUN and CR.

Interaction Analysis

According to the subgroups analysis, a large heterogeneity was observed in the subgroup of gender, age, drinking status, smoking status and tea drinking status (I^2_{gender}=70.2%, I^2_{age}=53.9%, $I^2_{drinking\ status}$=68.1%, $I^2_{smoking\ status}$=60.6% and $I^2_{tea\ drinking\ status}$=81.8%), indicating possible interactions between gender, age, drinking status, smoking status, tea drinking status and sUA. Multiplicative interactions analysis were performed to further explore the robustness of association between sUA and MALFD risk. The results showed multiplicative interactions were not observed ($P_{interaction}$ all > 0.05) (Tables 4–8).

Table 4 Multiplicative Interaction Analysis Between Gender and sUA

Variables		MAFLD n(%)	Non-MAFLD n(%)	*aOR* (95% *CI*)	$P_{interaction}$
Gender*	sUA				
Males	Normal	329 (45.3)	668 (35.6)	1.00	
Females	Normal	108 (14.9)	911 (48.4)	0.41 (0.30–0.55)	< 0.001
Males	High	255 (35.1)	219 (11.7)	2.08 (1.60–2.72)	< 0.001
Females	High	34 (4.7)	81 (4.3)	0.68 (0.42–1.13)	0.138
Gender × sUA				0.80 (0.45–1.42)	0.451

Notes: *Adjusted for age, BMI, smoking status, drinking status, tea drinking status, taste, eating speed, hypertension, hypertension treatment status, diabetes, diabetes treatment status, HDL, LDL, TC, BUN and CR.

Table 5 Multiplicative Interaction Analysis Between Age and sUA

Variables		MAFLD n(%)	Non-MAFLD n(%)	*aOR* (95% *CI*)	$P_{interaction}$
Age*	sUA				
≤60	Normal	399 (55.0)	1484 (79.0)	1.00	
>60	Normal	38 (5.2)	95 (5.0)	0.99 (0.61–1.60)	0.969
≤60	High	272 (37.5)	276 (14.7)	2.10 (1.64–2.68)	<0.001
>60	High	17 (2.3)	24 (1.3)	0.99 (0.48–2.06)	0.991
Age × sUA				0.48 (0.20–1.14)	0.097

Notes: *Adjusted for gender, BMI, smoking status, drinking status, tea drinking status, taste, eating speed, hypertension, hypertension treatment status, diabetes, diabetes treatment status, HDL, LDL, TC, BUN and CR.

Table 6 Multiplicative Interaction Analysis Between Drinking Status and sUA

Variables		MAFLD n(%)	Non-MAFLD n(%)	*aOR* (95% *CI*)	$P_{interaction}$
Drinking status*	sUA				
No	Normal	270 (37.2)	1106 (58.9)	1.00	
Yes	Normal	167 (23.0)	473 (25.2)	0.65 (0.49–0.86)	0.003
No	High	135 (18.6)	158 (8.4)	1.90 (1.38–2.62)	<0.001
Yes	High	154 (21.2)	142 (7.5)	1.35 (0.97–1.90)	0.079
Drinking status × sUA				1.10 (0.69–1.75)	0.681

Notes: *Adjusted for gender, age, BMI, smoking status, tea drinking status, taste, eating speed, hypertension, hypertension treatment status, diabetes, diabetes treatment status, HDL, LDL, TC, BUN and CR.

Table 7 Multiplicative Interaction Analysis Between Smoking Status and sUA

Variables		MAFLD n(%)	Non-MAFLD n(%)	*aOR* (95% *CI*)	$P_{interaction}$
Smoking status*	sUA				
No	Normal	313 (43.1)	1312 (69.8)	1.00	
Yes	Normal	124 (17.1)	267 (14.2)	0.82 (0.60–1.13)	0.232
No	High	179 (24.7)	222 (11.8)	1.77 (1.33–2.34)	<0.001
Yes	High	110 (15.1)	78 (4.2)	2.14 (1.44–3.17)	<0.001
Smoking status × sUA				1.46 (0.89–2.42)	0.135

Notes: *Adjusted for gender, age, BMI, drinking status, tea drinking status, taste, eating speed, hypertension, hypertension treatment status, diabetes, diabetes treatment status, HDL, LDL, TC, BUN and CR.

Table 8 Multiplicative Interaction Analysis Between Tea Drinking Status and sUA

Variables		MAFLD n(%)	Non-MAFLD n(%)	*aOR* (95% *CI*)	$P_{interaction}$
Tea drinking status*	sUA				
No	Normal	140 (19.2)	739 (39.3)	1.00	
Yes	Normal	297 (41.0)	840 (44.7)	1.22 (0.93–1.62)	0.149
No	High	68 (9.4)	113 (6.0)	1.68 (1.10–2.54)	0.015
Yes	High	221 (30.4)	187 (10.0)	2.62 (1.88–3.66)	< 0.001
Tea drinking status × sUA				1.28 (0.78–2.10)	0.332

Notes: *Adjusted for gender, age, BMI, drinking status, smoking status, taste, eating speed, hypertension, hypertension treatment status, diabetes, diabetes treatment status, HDL, LDL, TC, BUN and CR.

Discussion

In this cross-sectional study, we explore the association between sUA levels and MALFD risk in Southeast China. Our results highlighted that sUA was positively associated with the risk of MAFLD. This association persisted after adjustment for potential confounding factors. The RCS plot demonstrated that there was a significant nonlinear correlation between sUA and MAFLD risk, and the risk of MAFLD increased significantly when sUA> 5.56 mg/dL. Subgroup and multiplicative interaction analysis were performed to investigate the robustness of association between sUA and MAFLD risk. The results revealed that the positive association between sUA and MAFLD risk persisted in all subgroups, indicating strong robustness.

Previous studies have investigated the association between sUA and NAFLD, and the results showed that high sUA levels may be associated with NAFLD.[21–24] However, there are differences in diagnostic criteria and epidemiological characteristics between NAFLD and MAFLD.[25] Evidence on association between sUA and MAFLD are limited. Several studies revealed that serum uric acid to serum creatinine ratio was positively associated with the risk of MAFLD. But the diagnosis of MAFLD in these studies was based on abdominal computed tomography rather than ultrasound,[26,27] and these studies did not explore the dose-response relationship between sUA and MAFLD risk. In our study, univariate logistic regression analysis revealed a strong association between sUA and MAFLD risk, *OR* (95% *CI*) =3.48 (2.87–4.22). SUA is also associated with hypertension,[28] obesity,[29] metabolic syndrome,[30] type 2 diabetes mellitus,[31] chronic kidney disease,[32] dyslipidemia,[33] and CVD.[34] The treatment received by patients with diabetes and hypertension, particularly those involving diuretics,[35] has also been identified as an important factor influencing sUA levels. Therefore, we further included relevant variables in the multivariate model. After adjusting for potential confounders, the positive association between sUA and MAFLD risk remained unchanged, *OR* (95% *CI*)= 1.90 (1.49 ~ 2.42).

Despite the lack of consensus on the optimal range of sUA levels, a widely accepted therapeutic goal for patients with hyperuricemia is to maintain sUA levels of< 6.0 mg/dL for females and< 7.0 mg/dL for males.[36] In our study, the RCS plot demonstrated that there was a significant nonlinear correlation between sUA and MAFLD risk, and the risk of MAFLD increased significantly when sUA> 5.56 mg/dL, a threshold lower than the aforementioned therapeutic goal. Similar findings have also been observed in the relationship between sUA and CVD.[37] A large-scale cohort study conducted in Italy has revealed a significant association elevated sUA levels and the risk of fatal myocardial infarction, with a clear cutoff value established at SUA levels exceeding 5.70 mg/dL.[38] Another study demonstrated U-shaped curve relationship between sUA levels and CVD. Specifically, sUA levels> 370.5 μmol/L (6.2mg/dL) in males and 327.65 μmol/L (5.5mg/dL) in females were associated with increased CVD mortality.[39] The similarity between the sUA cut-off values in MAFLD patients and the sUA levels predictive of cardiovascular (CV) events could be attributed to the similar pathophysiological roles that sUA plays in both MAFLD and CVD, serving as a promoter of oxidative stress, inflammatory response, and endothelial dysfunction.[40] Furthermore, hypouricemic agents have already shown to reduce CV outcomes in people with metabolic syndrome.[41–43] Hence, controlling sUA levels in patients with MAFLD may help identify those at higher risk of CV events, enabling earlier intervention and potentially improving outcomes.

Subgroups analysis revealed that the positive association between sUA and MAFLD persisted significantly in males but not in females, aOR_{male} (95% *CI*)= 2.01 (1.54 ~ 2.62), aOR_{female} (95% *CI)*= 1.15 (0.62 ~ 2.11), respectively. Our

findings are consistent with previous studies. He and Ye found sUA levels were positively associated with the severity of steatosis in male MAFLD patients. However, these associations were not found for females.[44] Similar gender differences have been found in other related studies involving sUA and NAFLD.[45,46] We also found the prevalence of MAFLD was higher in males (39.7%) than females (12.5%), which was consistent with previous studies.[25,47,48] In general, males have higher sUA levels than females because the estrogen in females can promote UA excretion.[49] In addition, gender-specific differences in genetic factors and gene expression may also lead to differential associations between sUA and MAFLD.[50,51]

However, the specific mechanism of the association between sUA and MAFLD has not been confirmed. Studies have shown that there exists a bidirectional relationship between sUA and metabolic syndrome. Metabolic syndrome is characterized by a cluster of metabolic abnormalities, including hypertension, dyslipidemia, and abdominal obesity, all of which can contribute to increased sUA production and decreased excretion.[52] On the other hand, sUA has emerged as a definitive role for metabolic syndrome. High level of sUA is associated with hypertension, NAFLD, chronic kidney disease, and CVD.[40] MAFLD is generally considered to be the hepatic manifestation of metabolic syndrome. Studies have shown that multiple components of metabolic syndrome, such as dyslipidemia, and central obesity, are potential pathophysiologic mechanisms and risk factors for the development of MAFLD.[53–55] These risk factors shared by MAFLD and metabolic syndrome contribute to increased sUA production and decreased excretion, and increased the risk of developing NAFLD.[56] Our findings are consistent with this argument. In our study, compared to subjects without MAFLD, subjects with MAFLD had higher BMI, SBP, DBP, LDL, TG, TC levels and lower HDL levels. Furthermore, after adjustment for components of metabolic syndrome and other potential confounders, elevated sUA is independently associated with increased risk of MAFLD, with the adjusted OR of 1.90 (1.49 ~ 2.42) ($P < 0.01$). Insulin resistance (IR) is the basis of the occurrence and development of metabolic dysfunction and MAFLD.[57] Both IR and the triglyceride–glucose (TyG) index were positively associated with sUA.[58] It has been well documented that high concentration of UA can induce oxidative stress and promote the generation of reactive oxygen species, which cause IR and lead to the occurrence of MAFLD.[59,60] Our previous findings are in favor of this argument. We found the TyG index can be used as an alternative maker for IR and effectively identify MAFLD, and the AUC of the TyG index for predicting MAFLD was up to 0.793.[61] The energy metabolism of hepatocytes is mainly mediated by mitochondria. UA can induce mitochondrial morphological changes and oxidative stress, which promote the development of MAFLD.[62,63] Basic studies have shown that sUA may induce hepatic fat accumulation through ROS/JNK/AP-1 signaling pathway, thus promoting MAFLD progression.[64] High levels of sUA activates the NLRP3 inflammasome, which may be positively correlated with the progression of MAFLD.[65–67] The effect of UA on lipid accumulation in hepatocytes may be related to microRNA,[68] and the abnormal expression of microRNA is involved in the pathogenesis of MAFLD.[69] Overall, sUA may affect the progression and development of MAFLD through several mechanisms, but the exact mechanism remains to be further investigated.

Compared to NAFLD, MAFLD is a more appropriate disease definition for liver diseases associated with metabolic dysfunction. Our study demonstrates a significant positive association between sUA levels and MAFLD risk. Notably, we also found the risk of MAFLD increased significantly when sUA levels exceed 5.56 mg/dL, a threshold lower than the traditional used cut-off value for the diagnosis of hyperuricemia. It is meaningful that our findings may promote the further consideration of the underestimated diagnostic role of sUA in MAFLD. However, our study has several limitations. First, this was a cross-sectional study, and cause-effect inferences could not be made. Second, due to the limitations of the research region and population, the representativeness of the results is limited, and multi-region and multi-center research should be performed to confirm the results. Third, as an observational study, the presence of unmeasured confounders is possible. For example, as diuretics were reported to be associated with increased sUA levels,[33] related data were lack in our study. Hence, the possible interference of diuretics may exist. However, we have collected the information on whether subjects with hypertension and diabetes have received treatment. After further adjustment for hypertension, hypertension treatment status, diabetes, and diabetes treatment status, the positive association between sUA and MAFLD remained statistically significant in the total population and in males. Moreover, we have performed subgroups and multiplicative interactions analysis to examine the relationship of sUA levels and MAFLD risk. This suggests that the variable of not having a diuretic did not have a large impact on our results. Last, in our study, MAFLD was diagnosed by ultrasonic examination, which is not sufficiently sensitive to detect the severity of hepatic steatosis. However, this non-invasive method has a specificity of 84% and is still widely used in population-based studies.[70]

Conclusion

According to our study, sUA was positively associated with the risk of MAFLD. Additionally, the risk of MAFLD increased significantly when sUA levels exceeded 5.56 mg/dL. Our study may help clarify whether sUA plays a diagnostic role in MAFLD.

Data Sharing Statement

Data are available upon reasonable request. Data are stored in the Department of Epidemiology and Health Statistics, Fujian Provincial Key Laboratory of Environment Factors and Cancer, School of Public Health, Fujian Medical University, Fujian, China. Data are available upon request from Xian-E Peng; Email address: fmuxe@163.com.

Ethics Approval and Consent to Participate

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) and was approved by Ethics Committee of Fujian Medical University (ethics number 2014096). Participants gave informed consent to participate in the study before taking part.

Acknowledgments

The authors express their gratitude to all the participants for their cooperation.

Funding

This work was supported by the National Natural Science Foundation of China (No. 81473047), the Natural Science Foundation of Fujian Province (No. 2019J01316), and the Natural Science Foundation of Fujian Province (No. 2023J01628).

Disclosure

The authors report no conflicts of interest in this work.

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