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Combined effect of fasting blood glucose and serum uric acid on nonalcoholic fatty liver disease

Yifan Hao[1†], Xuerui Li[1†], Yiting Zhang[1], Jun Zheng[1], Yuyang Miao[1], Jin Tan[1] and Qiang Zhang[1,2*]

Abstract

Background This study sought to investigate the independent and synergistic impacts of fasting blood glucose (FBG) and serum uric acid (SUA) levels on non-alcoholic fatty liver disease (NAFLD) in participants with and without type 2 diabetes mellitus (T2DM).

Method A total of 12,430 participants (mean age: 54.34 ± 15.23, 34.34% female) were enrolled through the Health Screening Center of Tianjin Medical University General Hospital. FBG was classified as < 6 mmol/L, 6–7 mmol/L, and ≥ 7 mmol/L. SUA was classified into two categories: normal SUA and hyperuricemia (SUA level ≥ 420 μmol/L for men, ≥ 360 μmol/L for women). T2DM was ascertained through self-reported data. The diagnosis of NAFLD is established via abdominal ultrasound imaging. Logistic regression models and interaction effect models are used for data analysis.

Result Of the 12,430 participants, 4846 (38.99%) were diagnosed with NAFLD. In comparison to individuals with FBG < 6 mmol/L and no self-reported T2DM, those with FBG ≥ 7 mmol/L and no self-reported T2DM exhibited the highest prevalence of NAFLD (odds ratio [OR] 2.91, 95% CI 2.16–3.93) following multi-adjusted analysis. In the joint effect analysis of FBG and SUA, FBG ≥ 7 mmol/L and hyperuricemia were linked to a greater prevalence of NAFLD compared to FBG < 6 mmol/L and normal SUA, both in individuals with self-reported T2DM (OR 2.92, 95% CI 1.68–5.05) and those without self-reported T2DM (OR 7.87, 95% CI 3.57–17.34). An additive interaction existed between FBG and SUA regarding NAFLD in individuals without self-reported T2DM (AP 0.488, 95% CI: 0.068–0.909, $P = 0.02$).

Conclusion Elevated FBG levels are associated with NAFLD irrespective of self-reported T2DM status. The concomitant elevation of FBG and SUA levels exhibits a significant correlation with NAFLD, particularly in individuals lacking self-reported T2DM.

Keywords Non-alcoholic fatty liver disease, Cross-sectional study, Type 2 diabetes mellitus, Serum uric acid, Fasting blood glucose

†Yifan Hao and Xuerui Li contributed equally as first authors to this work.

*Correspondence:
Qiang Zhang
zhangqiangyulv@163.com
[1]Department of Geriatrics, Tianjin Medical University General Hospital, Key Laboratory of Post-Neuroinjury Neuro-Repair and Regeneration in the Central Nervous System, State Key Laboratory of Experimental Hematology, Tianjin Key Laboratory of Elderly Health, Ministry of Education, Tianjin Geriatrics Institute, Tianjin, China
[2]Department of Geriatrics, Tianjin Medical University General Hospital, Tianjin Key Laboratory of Elderly Health, Tianjin Geriatrics Institute, Anshan Road NO.154, Tianjin 300052, China

Introduction

Non-alcoholic fatty liver disease (NAFLD) is acknowledged as the most widespread liver disease globally and represents a significant aspect of chronic liver conditions. The global prevalence is roughly 30%, though this statistic differs by country and is on the rise [1, 2]. In China, the incidence of NAFLD attained 29.2% from 2008 to 2018 [3]. Forecasts suggest that by 2030, NAFLD could emerge as the primary reason for liver transplantation [4], resulting in significant health and economic challenges.

NAFLD is widely acknowledged as a hepatic manifestation of metabolic syndrome, with its progression influenced by a complex interaction of multiple metabolic factors [5]. Recent evidence indicates that type 2 diabetes mellitus (T2DM) is an independent risk factor for NAFLD [6]. Increased fasting blood glucose (FBG) levels are recognized to enhance hepatic de novo lipogenesis and induce steatosis, thus facilitating the onset of NAFLD [7]. A prospective cohort study indicated that individuals with FBG levels ≥ 5.54 mmol/L exhibited a 50% heightened risk of developing NAFLD in comparison to those with FBG levels < 5.54 mmol/L [8]. However, the relationship between pre-diabetes (i.e., elevated fasting blood glucose without a diagnosis of T2DM) and the risk of NAFLD remains ambiguous.

Serum uric acid (SUA), the final metabolite in purine metabolism pathways and a weak acid, has been associated with an increased risk of NAFLD [9–11]. A dose-response analysis indicated that each 1 mg/dL increase in SUA levels correlated with a 21% heightened risk of NAFLD [12]. Additionally, lowering SUA levels may constitute a viable therapeutic approach for NAFLD [13, 14]. Furthermore, studies have shown that SUA correlates with NAFLD in individuals with T2DM [15, 16]. However, scant research has examined the synergistic effects of FBG and SUA on NAFLD risk in both diabetic and non-diabetic groups.

Current research has primarily concentrated on the individual impacts of FBG or SUA on NAFLD. This study sought to examine their synergistic effects, thereby offering preliminary evidence for investigating the "multi-target additive effects" of metabolic disorders instead of single-factor linear effects. This study aims to enhance the metabolic network theory of NAFLD, promote precision intervention strategies, and stimulate the creation of innovative biomarkers for this increasingly common disease.

Methods

Participants

The study participants were sourced from Tianjin Medical University General Hospital and received health evaluations from July 2022 to November 2023. Of the 12,448 individuals who received liver ultrasonography and reported negligible alcohol intake (categorized as < 10 g/day for women, < 20 g/day for men), 18 participants were excluded due to absent data on FBG and SUA. Finally, a total of 12,430 participants were incorporated into the final analysis. All participants granted informed consent and willingly engaged in the study. The Ethics Committee of Tianjin Medical University General Hospital reviewed and approved the study protocol.

Data collection

A standardized questionnaire, conducted by a trained researcher, was utilized to gather data on sex, age, clinical history, smoking and alcohol consumption status, educational attainment, and physical activity levels. Educational attainment was quantified by the number of years of formal education completed. Smoking and alcohol consumption were classified as either "never" or "current/former." Physical activity was categorized as "active" or "inactive" according to the World Health Organization (WHO) guidelines. Individuals who participated in moderate-intensity physical activity (e.g., dancing, brisk walking, bowling, table tennis, badminton) for a minimum of 150 min weekly, or high-intensity physical activity (e.g., swimming, aerobic exercise, running, fast cycling, soccer, basketball) for at least 75 min weekly, were designated as "active"; those who did not meet these criteria were classified as "inactive" [17].

A qualified physician assessed participants' height, weight, systolic blood pressure/ diastolic blood pressure (SBP/ DBP). Body mass index (BMI) was calculated as the weight divided by height squared (kg/m2). Hypertension was characterized by any of the subsequent criteria: (1) self-reported hypertension history, (2) current antihypertensive medication usage, or (3) measured SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg. T2DM was identified through (1) self-reported history of T2DM or (2) current utilization of insulin or oral hypoglycemic medications. Total cholesterol (TC) levels were derived from fasting blood specimens.

Assessment of FBG and SUA

Venous blood specimens were drawn in the morning by proficient nurses following an overnight fasting interval. The hospital laboratory examined the blood samples employing the enzymatic method with an automated analyzer, in accordance with established protocols. FBG levels were classified into three categories: <6 mmol/L, 6–7 mmol/L, and ≥ 7 mmol/L. Furthermore, participants were categorized into six groups based on self-reported T2DM status:1) < 6 mmol/L and no-T2DM, 6–7 mmol/L and no-T2DM, ≥ 7 mmol/L and no-T2DM, < 6 mmol/L and T2DM, 6–7 mmol/L and T2DM, ≥ 7 mmol/L and T2DM. SUA levels were categorized as normal SUA and

hyperuricemia, with hyperuricemia defined as uric acid levels ≥ 420 μmol/L in men and ≥ 360 μmol/L in women.

Ascertainment of NAFLD

After an overnight fast of at least 8 h, an experienced physician performed abdominal ultrasound examinations on the participants, using a Toshiba Nemio 20 ultrasound machine (Toshiba, Tokyo, Japan) equipped with a 3.5-MHz probe by well-trained staff. Participants were categorized into the NAFLD or non-NAFLD group based on the findings of the hepatic ultrasound and alcohol consumption levels (≤ 10 g/day for women, ≤ 20 g/day for men).

Statistical analyses

Baseline data stratified by NAFLD diagnostic status were analyzed using independent-samples t-tests or Mann–Whitney U tests for continuous variables, reported as mean ± standard deviation (SD) or median (interquartile range). Categorical variables were examined utilizing Chi-square tests and reported as frequencies (percentages).

To evaluate the correlation between NAFLD and FBG, along with self-reported T2DM, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated utilizing logistic regression models. Subsequent analyses categorized participants based on T2DM status to assess the distinct impacts of FBG and SUA on NAFLD. The combined effect of FBG and SUA on NAFLD, in individuals with and without T2DM, was evaluated by generating dummy variables reflecting concurrent exposure to both factors. The existence of an additive interaction was assessed by calculating the relative excess risk due to interaction (RERI), the attributable proportion (AP), and the synergy index (S). Additive interaction was deemed statistically significant if the 95% CI for RERI or AP excluded 0, or if the 95% CI for S excluded 1. All models were initially controlled for sex and age, subsequently adjusted for educational attainment, BMI, smoking and alcohol consumption status, physical activity, hypertension, and TC. In sensitivity analyses, logistic regression and additive interaction analyses were reiterated following: (1) Imputing absent values for covariates, comprising education ($n = 1$), BMI ($n = 1{,}074$), physical activity ($n = 223$), smoking status ($n = 4$), alcohol consumption ($n = 12$), TC ($n = 1$), and hypertension ($n = 13$), employing Rubin's rule for the aggregation of estimates; (2) Incorporating dietary habits as an additional covariate. $P \leq 0.05$ was deemed statistically significant. Stata SE 15.0 for Windows (StataCorp, College Station, Texas) was employed for all data analyses.

Results

Baseline characteristics of participants

Of the total subjects ($n = 12{,}430$, mean age: 54.34 ± 15.23), 4,846 participants (38.99%) received a diagnosis of NAFLD. Individuals with NAFLD were typically older, predominantly male, and more frequently current or former smokers and alcohol consumers. They exhibited lower levels of physical activity, elevated BMI, TC, FBG, and SUA levels, along with a higher prevalence of T2DM and hypertension compared to those without NAFLD. No substantial statistical differences were observed regarding educational attainment (Table 1).

Association of FBG and self-reported T2DM with NAFLD

In the logistic regression models, adjusted for age, sex, drinking, smoking, education, physical exercise, BMI, hypertension, TC, the 95% CI for NAFLD compared to FBG < 6 mmol/L without self-reported T2DM were as follows: 2.00 (1.65–2.44) for FBG 6–7 mmol/L without self-reported T2DM, 2.91 (2.16–3.93) for FBG ≥ 7 mmol/L without self-reported T2DM, 1.15 (0.87–1.51) for FBG < 6 mmol/L with self-reported T2DM, 1.76 (1.36–2.28) for FBG 6–7 mmol/L with self-reported T2DM, and 1.90 (1.54–2.34) for FBG ≥ 7 mmol/L with self-reported T2DM. The findings of this study indicated that individuals with FBG ≥ 7 mmol/L and without self-reported T2DM exhibited the highest OR for NAFLD (Table 2; Fig. 1).

Separate and joint effects of FBG and SUA level on NAFLD in individuals with self-reported T2DM

In individuals with self-reported T2DM, the OR for NAFLD was 1.12 (95% CI:1.04–1.20) per 1 mmol/L increase in FBG, following multivariable adjustment in logistic regression analyses. In comparison to participants with FBG < 6 mmol/L, the OR (95% CI) after multivariable adjustment for NAFLD was 1.69 (1.17–2.43) for those with FBG 6–7 mmol/L, and 1.79 (1.28–2.51) for individuals with FBG ≥ 7 mmol/L. Similarly, the OR (95% CI) for NAFLD with multi-adjustment of SUA (continuous) in individuals with T2DM was 1.17 (1.06–1.29). In contrast, the odds ratio (95% CI) for NAFLD in individuals with hyperuricemia was 1.46 (95% CI 1.06–2.02) compared to those with normal SUA.

In the joint effect analysis of self-reported T2DM group, compared to participants with FBG < 6 mmol/L and normal SUA, the multi-adjusted ORs (95% CI) for NAFLD were 1.63 (1.07–2.49) for those with FBG 6–7 mmol/L and normal SUA, 1.66 (1.13–2.44) for individuals with FBG ≥ 7 mmol/L and normal SUA, 1.20 (0.64–2.24) for individuals with FBG < 6 mmol/L and hyperuricemia, 2.38 (1.29–4.40) for individuals with FBG 6–7 mmol/L and hyperuricemia, and 2.92 (1.68–5.05) for individuals with FBG ≥ 7 mmol/L and hyperuricemia. While the

Table 1 Characteristic of the study population ($n = 12430$)

	Nonalcoholic fatty liver disease ($n = 4846$)	Non-nonalcoholic fatty liver disease ($n = 7584$)	*P*
Age, year	55.59 ± 13.85	53.55 ± 16.00	< 0.001
Sex			< 0.001
men	3596 (74.21)	4565 (60.19)	
women	1250 (25.79)	3019 (39.81)	
Education, year	17.73 ± 3.39	17.81 ± 3.28	0.206
Smoking			< 0.001
Never	3326 (68.63)	5942 (78.39)	
Current/Ever	1520 (31.37)	1638 (21.61)	
Drinking			< 0.001
Never	3732 (77.06)	6402 (84.51)	
Current/Ever	1111 (22.94)	1173 (15.49)	
Physical exercise			< 0.001
Unactive	3893 (81.73)	5758 (77.35)	
Active	870 (18.27)	1686 (22.65)	
BMI, kg/m2	26.73 ± 3.01	23.31 ± 2.83	< 0.001
Total cholesterol, mmol/L	5.15 ± 1.02	5.04 ± 1.17	< 0.001
Fasting, mmol/L	5.65 ± 1.46	5.14 ± 1.05	< 0.001
Uric Acid, mg/dl	6.50 ± 1.50	5.58 ± 1.41	< 0.001
Hypertension	2760 (57.05)	2613 (34.48)	< 0.001
T2DM	639 (13.27)	628 (8.34)	< 0.001

Data are presented as mean ± standard deviations, or number (proportion %)

Missing data: education = 1; smoking = 4; drinking = 12; physical exercise = 223; BMI = 1074; total cholesterol = 1; hypertension = 13; T2DM = 83

Table 2 NAFLD ORs (95% CIs) in relation to FBG

Fasting, mmol/L	Self-reported T2DM	No. of subjects	No. of Cases	Basic-adjusted OR (95%CI) [a]	Multi-adjusted OR (95%CI) [b]
< 6	No	10,058	3523	Reference	Reference
6–7	No	696	424	2.77 (2.36–3.26)	2.00 (1.65–2.44)
≥ 7	No	326	228	3.97 (3.12–5.07)	2.91 (2.16–3.93)
< 6	Yes	335	136	1.15 (0.91–1.44)	1.15 (0.87–1.51)
6–7	Yes	363	195	1.87 (1.51–2.32)	1.76 (1.36–2.28)
≥ 7	Yes	569	308	1.96 (1.65–2.34)	1.90 (1.54–2.34)

[a] Adjusted age and sex

[b] Adjusted age, sex, education, smoking, drinking, physical exercise, body mass index, hypertension, and total cholesterol

additive interaction between FBG and SUA on NAFLD in participants with self-reported T2DM was not statistically significant (*P* for RERI, AP, and S > 0.05) (Table 3).

Separate and joint effects of FBG and SUA level on NAFLD in individuals without self-reported T2DM

In individuals without self-reported T2DM, the OR (95% CI) for NAFLD after multivariable adjustment of FBG (continuous) was 1.49 (1.39–1.60). In comparison to individuals with FBG < 6 mmol/L, the OR (95% CI) after multivariable adjustment for NAFLD was 1.97 (1.62–2.41) for participants with FBG 6–7 mmol/L, and 2.86 (2.12–3.86) for those with FBG ≥ 7 mmol/L. The multivariate-adjusted OR (95% CI) of SUA (continuous) for NAFLD was 1.38 (1.33–1.44). In comparison to individuals with normal uric acid levels, the OR (95% CI) for NAFLD was 2.04 (95% CI 1.83–2.27) for those with hyperuricemia.

In the joint effect analysis among participants without self-reported T2DM, relative to individuals with FBG < 6 mmol/L and normal SUA, the multi-adjusted OR (95% CI) for NAFLD were 2.02 (1.60–2.55) for those with FBG 6–7 mmol/L and normal SUA, 2.99 (2.61–5.43) for those with FBG ≥ 7 mmol/L and normal SUA, 2.08 (1.85–2.32) for those with FBG < 6 mmol/L and hyperuricemia, 3.77 (2.61–5.43) for those with FBG 6–7 mmol/L and hyperuricemia, and 7.87 (3.57–17.34) for those with FBG ≥ 7 mmol/L and hyperuricemia. The additive interaction between FBG and SUA levels on NAFLD in participants without self-reported T2DM was statistically significant (AP 0.488, 95% CI: 0.068–0.909, $P = 0.02$), indicating the necessity of monitoring glycemic and uric acid levels in NAFLD, particularly in individuals without self-reported T2DM (Table 4).

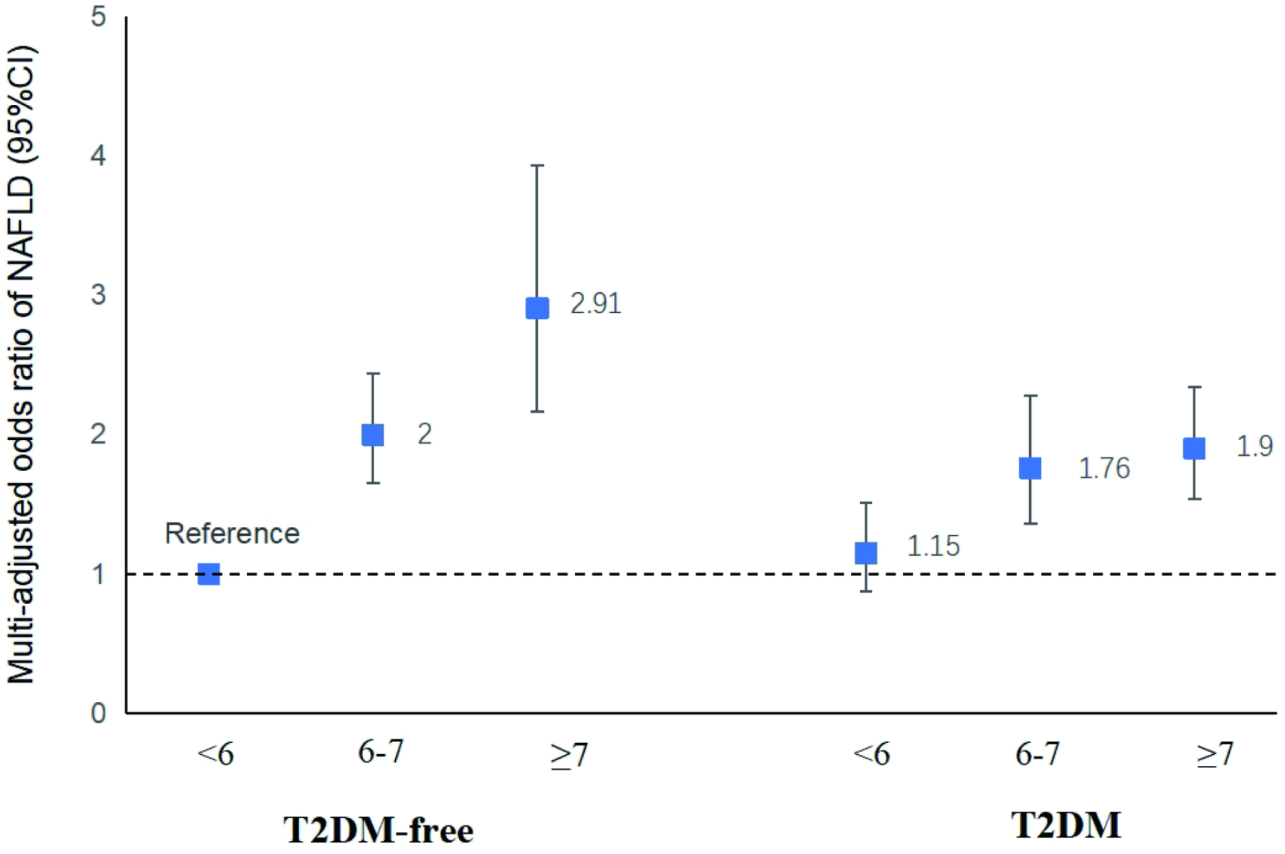

Fig. 1 Odds ratios (ORs) and 95% confidence intervals (CIs) of nonalcoholic fatty liver disease (NAFLD) in relation to fasting glucose
Model was adjusted for age, sex, education, smoking, drinking, physical exercise, body mass index, hypertension, and total cholesterol

Supplementary analysis

The results remained largely unchanged relative to the initial analysis when conducted the subsequent analyses by (1) executing multiple imputations for missing covariate values (Supplementary Tables 1, 2, 3); (2) including dietary habits as a covariate (Supplementary Tables 4, 5, 6).

Discussion

This cross-sectional study of Chinese adults from a population-based cohort showed a significant relationship between increased FBG levels and NAFLD, regardless of self-reported T2DM status. Elevated FBG and SUA levels were independently and collectively associated with NAFLD in participants, regardless of self-reported T2DM status. A notable interaction between increased FBG and SUA levels concerning NAFLD was observed in participants without self-reported T2DM.

The correlation between elevated FBG levels and NAFLD has been firmly established. A cross-sectional study in Japan, comprising 8,352 participants, demonstrated that the prevalence of NAFLD was link to glycemic status, revealing rates of 25.6% in individuals with normal fasting glucose, 56.2% in those with impaired fasting glucose, and 68% in individuals with FBG levels surpassing 126 mg/dL [18]. Likewise, a prospective cohort study involving Black and White adults indicated that fluctuations in FBG levels may serve as a marker for identifying high-risk NAFLD populations [19]. A study by Pang et al., involving 512,891 adults, revealed that diabetes and elevated glucose levels in individuals without a established T2DM diagnosis were linked to a heightened risk of NAFLD [20]. The current study revealed a significant correlation between elevated FBG levels and NAFLD. The analysis indicated that the cohort with FBG ≥ 7 mmol/L, lacking self-reported T2DM, demonstrated the highest OR for NAFLD. The correlation between FBG and NAFLD was more pronounced in individuals without self-reported T2DM than in those with self-reported T2DM. This discrepancy may stem from individuals who are unaware of their diabetic status being less inclined to monitor or regulate their blood glucose levels, a factor closely linked to the development of NAFLD. Conversely, individuals diagnosed with diabetes frequently engage in glucose-lowering strategies, including pharmacological treatments (e.g., metformin, sodium-glucose cotransporter-2 inhibitors) or lifestyle changes, which may mitigate the direct correlation

Table 3 NAFLD ORs (95% CIs) in relation to FBG and SUA in participants with self-reported T2DM

T2DM participants		No. of subjects	No. of Cases	Basic-adjusted OR (95%CI) [a]	Multi-adjusted OR (95%CI) [b]
Fasting				1.11 (1.05–1.18)	1.12 (1.04–1.20)
< 6		335	136	Reference	Reference
6–7		363	195	1.86 (1.37–2.53)	1.69 (1.17–2.43)
≥ 7		569	308	1.85 (1.40–2.44)	1.79 (1.28–2.51)
Uric Acid				1.24 (1.15–1.35)	1.17 (1.06–1.29)
Normal		984	470	Reference	Reference
Hyperuricemia		279	166	1.69 (1.28–2.22)	1.46 (1.06–2.02)
Fasting	Uric Acid				
< 6	Normal	257	98	Reference	Reference
6–7	Normal	280	146	1.92 (1.35–2.73)	1.63 (1.07–2.49) *
≥ 7	Normal	447	226	1.78 (1.29–2.46)	1.66 (1.13–2.44) **
< 6	Hyperuricemia	78	38	1.60 (0.95–2.69)	1.20 (0.64–2.24)
6–7	Hyperuricemia	82	49	2.89 (1.72–4.87)	2.38 (1.29–4.40) *
≥ 7	Hyperuricemia	119	79	3.56 (2.23–5.68)	2.92 (1.68–5.05) **

[a] Adjusted age and sex

[b] Adjusted age, sex, education, smoking, drinking, physical exercise, body mass index, hypertension, and total cholesterol

* Measures of additive interaction for nonalcoholic fatty liver disease:

Relative excess risk due to interaction: 0.487, 95%CI: -0.903-1.878, $P > 0.05$;

Attributable proportion: 0.220, 95%CI: -0.329-0.770, $P > 0.05$;

Synergy index: 1.672, 95%CI: 0.362–7.733, $P > 0.05$

** Measures of additive interaction for nonalcoholic fatty liver disease:

Relative excess risk due to interaction: 1.034, 95%CI: -0.362-2.430, $P > 0.05$;

Attributable proportion: 0.369, 95%CI: -0.007-0.746, $P > 0.05$;

Synergy index: 2.350, 95%CI: 0.671–8.226, $P > 0.05$

Table 4 NAFLD ORs (95% CIs) in relation to FBG and SUA in participants without self-reported T2DM

T2DM-free participants		No. of subjects	No. of Cases	Basic-adjusted OR (95%CI) [a]	Multi-adjusted OR (95%CI) [b]
Fasting				1.89 (1.78–2.02)	1.49 (1.39–1.60)
< 6		10,058	3523	Reference	Reference
6–7		696	424	2.72 (2.31–3.20)	1.97 (1.62–2.41)
≥ 7		326	228	3.88 (3.04–4.95)	2.86 (2.12–3.86)
Uric Acid				1.62 (1.56–1.67)	1.38 (1.33–1.44)
Normal		8153	2479	Reference	Reference
Hyperuricemia		2917	1692	2.94 (2.68–3.21)	2.04 (1.83–2.27)
Fasting	Uric Acid				
< 6	Normal	7435	2063	Reference	Reference
6–7	Normal	477	260	2.81 (2.32–3.40)	2.02 (1.60–2.55) *
≥ 7	Normal	241	156	4.06 (3.09–5.33)	2.99 (2.61–5.43) **
< 6	Hyperuricemia	2615	1458	3.00 (2.73–3.29)	2.08 (1.85–2.32)
6–7	Hyperuricemia	217	162	6.88 (5.04–9.41)	3.77 (2.61–5.43) *
≥ 7	Hyperuricemia	85	72	13.67 (7.54–24.80)	7.87 (3.57–17.34) **

[a] Adjusted age and sex

[b] Adjusted age, sex, education, smoking, drinking, physical exercise, body mass index, hypertension, and total cholesterol

* Measures of additive interaction for nonalcoholic fatty liver disease:

Relative excess risk due to interaction: 0.687, 95%CI: -0.753-2.317, $P > 0.05$;

Attributable proportion: 0.182, 95%CI: -0.139-0.604, $P > 0.05$;

Synergy index: 1.330, 95%CI: 0.772–2.290, $P > 0.05$

** Measures of additive interaction for nonalcoholic fatty liver disease:

Relative excess risk due to interaction: 3.820, 95%CI: -2.405-10.045, $P > 0.05$;

Attributable proportion: 0.488, 95%CI: 0.068–0.909, $P = 0.02$;

Synergy index: 2.272, 95%CI: 0.873–5.911, $P > 0.05$

between FBG and NAFLD, suggesting the importance of blood glucose monitor, control, and early detection for NAFLD. However, further well-designed prospective studies are needed to validate this hypothesis. Therefore, timely diagnosis of T2DM and effective blood glucose control require attention, as they may help reduce the prevalence of NAFLD.

The findings of this study demonstrated that increased SUA levels were independently linked to NAFLD in Chinese adults, irrespective of self-reported T2DM status. These results correspond with earlier cross-sectional and prospective research conducted in diverse populations throughout the United States and Asia [21]. A meta-analysis of 2,079,710 participants, comprising 719,013 NAFLD cases, revealed a positive association between increased SUA levels and NAFLD, indicating that lowering SUA levels may be an effective strategy for NAFLD prevention [22]. A study by Zheng et al. indicated that the prevalence of NAFLD escalated with increasing SUA levels in non-obese Chinese adults, irrespective of other metabolic risk factors [23]. The results of this study support previous research, suggesting that keeping SUA within a normal range may aid in the prevention of NAFLD. Previous studies in hypertensive populations have indicated a possible association between plasma aldosterone and elevated SUA levels, as well as an increased prevalence of NAFLD [24–26]. This indicates that hypertension may act as a confounding variable affecting the observed correlation. Hypertension was accounted for in this study to reduce potential bias and enhance the precision of the results.

In addition, this study demonstrated that the simultaneous presence of elevated FBG and SUA levels significantly intensified the risk of NAFLD. Hu et al. previously indicated that, in patients with T2DM, increased SUA levels remained an independent risk factor for NAFLD prevalence, even when controlled for other metabolic parameters [27]. Cui et al. additionally indicated that SUA may function as a reliable predictor for categorizing non-obese T2DM patients at increased risk for NAFLD [28]. The findings align with the current study, which revealed that elevated FBG and SUA levels were concurrently linked to a greater prevalence of NAFLD. Furthermore, the analysis demonstrated that the additive interaction effect of FBG and SUA levels on NAFLD was statistically significant in individuals without self-reported T2DM. This observation may be ascribed to the diminished probability of blood glucose monitoring and regulation among individuals lacking a confirmed T2DM diagnosis, while those with self-reported T2DM may implement more efficacious glucose management techniques. The results indicate that simultaneous increases in FBG and SUA levels may act as a significant predictor of heightened NAFLD risk. The cumulative impact of these metabolic factors on NAFLD is still not fully comprehended. Consequently, the dynamic correlation between FBG levels and SUA on NAFLD progression requires more comprehensive investigation.

The mechanisms underlying the association between increased FBG and SUA levels concerning NAFLD are not well understood. The pathophysiological progression of NAFLD may be mediated through insulin resistance, serving as a critical metabolic determinant. Elevated FBG and SUA levels have been demonstrated to enhance insulin resistance [29, 30], thereby impairing hepatic lipid metabolism, promoting hepatic fat accumulation, and contributing to the development of NAFLD [31]. Additionally, inflammation has been identified as a significant mechanism in the initiation and development of NAFLD. A published study established that SUA activates the NLRP3 inflammasome, leading to lipid accumulation in hepatocytes and insulin resistance, both in vivo and vitro [30], thereby advancing the progression of NAFLD. Finally, elevated SUA levels have been demonstrated to induce mitochondrial oxidative stress, enhance reactive oxygen species production, and facilitate hepatic steatosis, thereby expediting the progression of NAFLD [32]. Recent genetic research has identified the transmembrane 6 superfamily 2 (TM6SF2) E167K polymorphism functions as a non-confounded NAFLD risk determinant [33]. Research on animals has shown that TM6SF2 plays a role in the function of the smooth endoplasmic reticulum, and its deficiency hinders the lipidation of very-low-density lipoproteins in hepatocytes, thus facilitating the development of NAFLD [34]. Moreover, TM6SF2 mutations are linked to heightened insulin resistance, compromised pancreatic β-cell functionality, and diminished incretin effect [35], which may partially elucidate the observed correlation between elevated FBG, SUA levels, and NAFLD at the genetic level.

Study strengths and limitations

While this study provides novel insights, several strengths and limitations warrant careful consideration. The primary strength of this investigation is primarily attributed to its substantial sample size and the application of standardized diagnostic protocols by qualified sonographers and physicians. Nonetheless, various limitations must be recognized. First, causal interpretations between elevated FBG and SUA on NAFLD were constrained by the cross-sectional study design. Additional extensive, rigorously executed prospective studies are essential to corroborate the findings. Second, the diagnosis of NAFLD in this study was determined through abdominal ultrasonography. This method, while widely accessible, well-established, noninvasive, and convenient, exhibits sensitivity and specificity that are significantly influenced by the operator's proficiency and the imaging

equipment's performance. Therefore, NAFLD identified through ultrasonography may possess specific intrinsic limitations [36]. Third, due to the lack of a standardized approach for quantifying NAFLD severity via hepatic ultrasound, the association between FBG/SUA concentrations and hepatic steatosis severity could not be reliably assessed. Furthermore, data regarding other hepatic diseases and metabolic disorders were not gathered in this study. Therefore, the possible impact of these factors on the observed correlations cannot be dismissed, requiring caution in the applicability of the findings. Fourth, the study population was selected from a particular group of Chinese adults. Due to possible ethnic variations in metabolic profiles, population-specific applicability warrants judicious evaluation prior to cross-regional implementation. Fifth, certain covariates, such as smoking, drinking and medication use, and exercise habits, relied on self-reported data, were derived from self-reported data. Therefore, potential measurement inaccuracies stemming from recall bias or social desirability bias may have compromised the precision of these variables. These limitations may jeopardize the accuracy of the findings, requiring careful interpretation of the observed correlations. Finally, the genetic factors, including the TM6SF2 variant, are recognized to contribute to the pathogenesis of NAFLD. Unfortunately, genetic data were unavailable in this study, hindering the evaluation of genetic predisposition's impact on NAFLD risk. Future research should integrate genetic analyses to further clarify the gene-NAFLD relationship.

Conclusion

Elevated FBG demonstrated a significant association with NAFLD incidence, irrespective of the presence or absence of self-reported T2DM. The concurrent increase of FBG and SUA levels was significantly linked to NAFLD, particularly in individuals without self-reported T2DM. This research underscores the significance of early diabetes diagnosis and the regulation of FBG and SUA levels in the prevention of NAFLD. This discovery could establish a foundation for early screening and risk stratification of NAFLD, assisting clinicians in prioritizing interventions for high-risk patients and facilitating the development of personalized treatment strategies. Simultaneous monitoring of fluctuations in FBG and SUA during treatment can evaluate the efficacy of metabolic interventions and inform treatment modifications. Future studies should concentrate on in-depth mechanistic investigations to clarify the relationships between phenotypic observations and molecular mechanisms, as well as on clinical translation via intervention-focused clinical trial designs to assess the effectiveness of combined glucose-lowering and uric acid-reducing therapies in reversing liver fibrosis in patients with NAFLD. In areas with a high incidence of metabolic disorders, it is advisable to integrate combined FBG and SUA testing into standard non-alcoholic fatty liver disease screening programs and to develop regional screening-intervention networks.

Abbreviations

AP	Attributable proportion
BMI	Body mass index
CIs	Confidence intervals
DBP	Diastolic blood pressure
FBG	Fasting blood glucose
ORs	Odds ratios
RERI	Relative excess risk due to interaction
SBP	Systolic blood pressure
S	Synergy Index
SD	Standard deviation
TC	Total cholesterol
TM6SF2	Transmembrane 6 superfamily 2
T2DM	Type 2 diabetes mellitus
NAFLD	Non-alcoholic fatty liver disease
SUA	Serum uric acid

Supplementary information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions

QZ designed the study. YFH was responsible for collection of data, data interpretation, manuscript writing and coordination of research. XRL were responsible for data analysis and manuscript writing. YTZ and JZ were responsible for manuscript writing. YYM and TJ helped collect the data. All authors have read and approved the final version of the manuscript.

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Data availability

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by the Ethics Committee of Tianjin Medical University General Hospital (Ethical No. IRB2022-YX-135-01). All participants signed written informed consent.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

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