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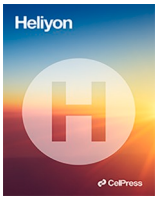

Research article

Effect of uric acid on lipid metabolism assessed via restricted cubic splines: A new insight

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ABSTRACT

Background: Hyperuricemia can promote both blood lipids and non-alcoholic fatty liver disease (NAFLD). However, the role of the entire uric acid (UA) span, especially low concentrations below hyperuricemia, on lipid metabolism remains unclear.
Methods: A cross-sectional study was designed. Data on the age, sex, UA, triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) of 1977 participants, who underwent physical examination, were collected. NAFLD and non-alcoholic fatty pancreas disease (NAFPD) were diagnosed using abdominal ultrasound. Restricted cubic splines (RCS) linear regression model was used to evaluate the effect of the UA span on TG, TC, HDL, and LDL, respectively. RCS logistic regression model was employed to evaluate the effect of the UA span on NAFLD and NAFPD.
Results: RCS linear regression model showed that TG was negatively correlated with UA at first, then exhibiting a positive correlation. Meanwhile, HDL was positively correlated with UA at first, then negatively correlated. There was a positive linear correlation between TC and UA (P for nonlinear = 0.578) and a positive nonlinear correlation between LDL and UA (P for nonlinear = 0.021). RCS logistic regression model showed that NAFLD and NAFPD were negatively correlated with UA at first and then positively correlated with UA.
Conclusion: our study showed that the entire UA span has a J-shaped effect on some lipids, NAFLD, and NAFPD. Besides, TG and HDL, compared with TC or LDL, may better reflect the status of NAFLD and NAFPD.

1. Introduction

Over the past decade, noncommunicable diseases have gradually surpassed communicable diseases to become the most common cause of death worldwide [1]. Overweight and obesity are the main causes of noncommunicable diseases, and the prevalence of both conditions is on the rise [2]. Body fat is preferentially stored in the adipose tissue. When fat content continues to increase beyond the upper storage limit of adipose tissue, it is deposited ectopically in non-adipose tissues, such as the liver, pancreas, and muscle [3,4].

Nonalcoholic fatty liver disease (NAFLD) is the major consequence of ectopic fat deposition in the liver [5]. It affects approximately 25 % of the global population and the number of children with NAFLD is increasing annually, resulting in a younger patient population [6]. Clinically, NAFLD is often regarded as an important indicator of abnormal fat metabolism. Under normal circumstances, triglycerides synthesized by the liver together with other lipids and apolipoproteins form very-low-density lipoproteins that are secreted

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into the blood. If apolipoprotein synthesis is impaired or the amount of triglyceride synthesis exceeds the ability to synthesize apolipoproteins, triglyceride transport is affected, and excessive triglyceride accumulation in the liver occurs, causing NAFLD. Therefore, the blood lipids of patients with NAFLD are usually elevated [7].

The pancreas is a major endocrine and metabolic organ in humans. The concept of nonalcoholic fatty pancreas disease (NAFPD) was first described in 1933 [8] and is now often used to describe non-alcohol-induced pancreatic steatosis. The relationship between NAFPD and NAFLD is complex. Some studies have shown that the former is a predictor of the latter [9], whereas others have shown that the latter is a risk factor for the former [10]. However, all studies agree that overweight and obesity are key factors that lead to ectopic fat deposition. There is substantial evidence that NAFPD is associated with diabetes, pancreatitis, and pancreatic cancer [11–14]. The presence of intrapancreatic fat has a considerable impact on the severity of acute pancreatitis [15]. Because the fat in chronic pancreatitis is replaced by more fibrous tissue, the latter acts like a compartment, separating fat cells from the pancreatic parenchyma and reducing damage to the pancreas. In contrast, acute pancreatitis does not lead to tissue fibrosis [16]. The prevalence of NAFPD is higher than that of NAFLD, with several studies showing an average prevalence between 30 and 33 % [17,18].

Uric acid (UA) is the end product of purine metabolism and is distributed in the extracellular fluid in the form of urate. Under normal physiological conditions, UA in plasma has a better antioxidant effect than vitamin C, which can scavenge oxygen free radicals and chelate iron [19], directly or indirectly suppressing oxidative stress and thus exerting a protective effect. However, when the serum UA level exceeds a certain threshold, its antioxidant effect shifts to a pro-oxidative effect [20], thus becoming a pathogenic factor. Numerous studies have demonstrated this dual role of UA. A nonlinear correlation between serum uric acid levels and all-cause mortality has been described with <300 μmol/L being negatively correlated, while >300 μmol/L was significantly positively correlated [21]. Small increases in UA levels may improve the short-term functional outcomes of ischemic stroke in patients with type 2 diabetes [22] and may also reduce the risk of death related to prostate cancer [23].

Hyperuricemia can lead to liver lipid accumulation and metabolic disorders by inhibiting the activity of AMP-activated protein kinase (AMPK), which reduces fatty acid oxidation [24]. Additionally, uric acid stimulates the activity of nicotinamide adenine dinucleotide phosphate oxidase, altering oxidative stress and inflammation levels. This affects the activity of key enzymes involved in lipid synthesis and breakdown, thereby impairing lipid metabolism [25]. Oxidative stress and inflammation can also result in insulin resistance, promoting lipid breakdown in adipose tissue and increasing free fatty acid levels in the blood [26]. Furthermore, hyperuricemia is often accompanied by chronic low-grade inflammation, with inflammatory factors such as TNF-α and IL-6 regulating the expression and activity of lipid metabolic enzymes, leading to changes in the lipid profile [27]. Finally, uric acid influences lipid synthesis and breakdown by modulating the expression of peroxisome proliferator-activated receptors (PPARs), particularly PPAR-γ [28].

Previous studies have reported the promoting contribution of hyperuricemia (UA>420 μmol/L) to lipids [29] and NAFLD [30]. However, few studies have investigated the role of the entire UA span, especially low concentrations below hyperuricemia, on lipid metabolism. This study aimed to explore the effect of the entire UA span on blood lipids, as well as the effect of the span on NAFLD and

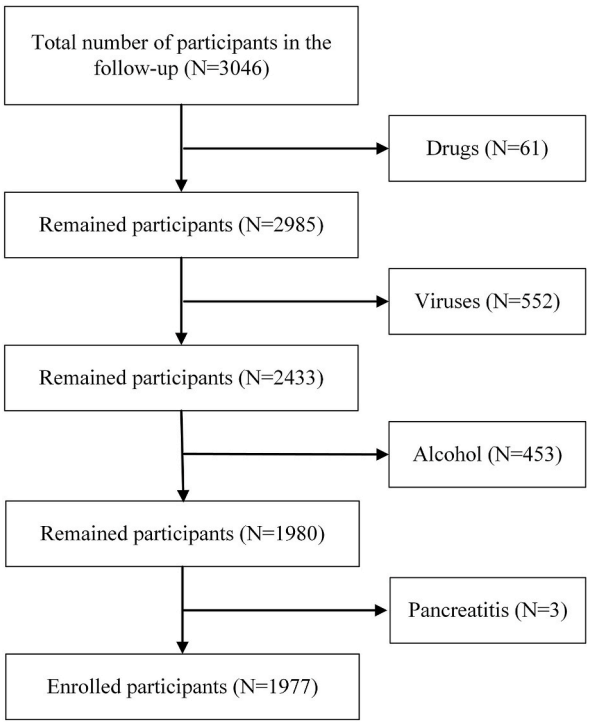

Fig. 1. Flow chart of inclusion and exclusion criteria.

NAFPD using restricted cubic splines. Further, we hopefully provide a theoretical basis for the treatment and prevention of lipid metabolic disease.

2. Materials and methods

2.1. Study population

A cross-sectional study was designed. The sample size is calculated by the formula $n = \frac{u_{\alpha/2}^2 \pi(1-\pi)}{\delta^2}$. n represents estimated sample size; $\alpha = 0.05$; $\pi = 0.5$, δ represents allowable error, we set as $0.01 < \delta < 0.05$. We end up with n in the range of 384.16–9604. We used simple random sampling. A total of 3046 participants, from 1 September 2021 to 1 August 2023, were selected from the Physical Examination Center of the Second Affiliated Hospital of Fujian Medical University.

2.2. Inclusion and exclusion criteria

After excluding liver disorders caused by drugs, viruses, or alcohol, or pancreatic disorders such as pancreatitis and so on, the remained 1977 participants were enrolled (Fig. 1).

2.3. Ethics and informed consent

This study was approved by the Ethics Committee of The Second Affiliated Hospital of Fujian Medical University (protocol code 231; approval date: 2022) and the informed consent, including participation in research and publication of clinical data, was obtained in written from all participants.

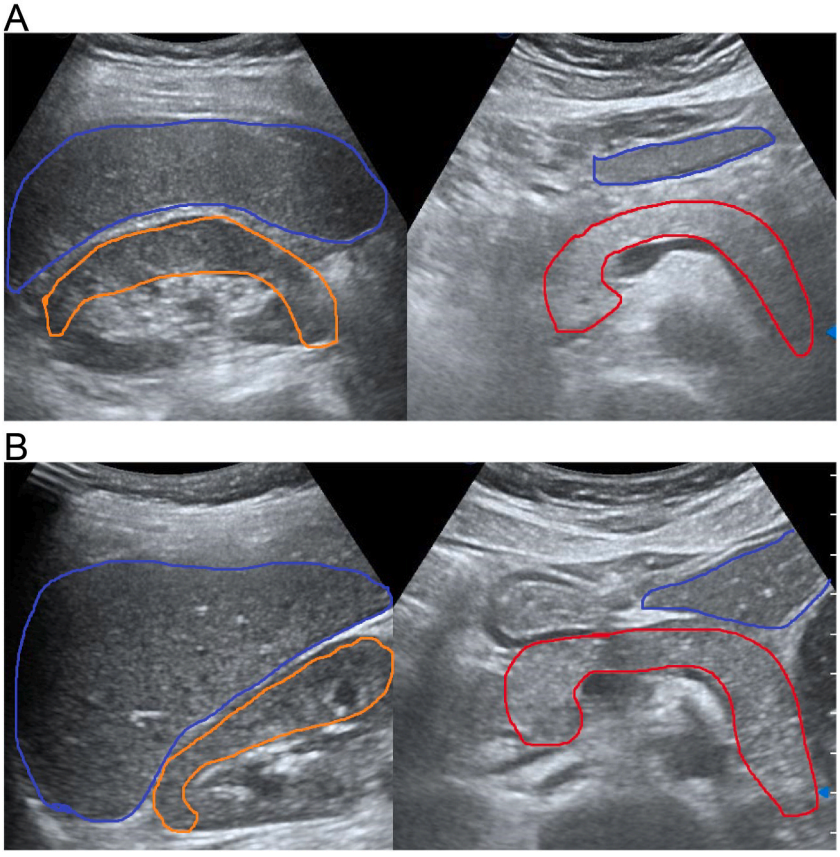

Fig. 2. Schematic diagram of the pancreas under ultrasound. (**A**) The liver (blue circle), pancreas (red circle), and right renal cortex (orange circle) of a patient with NAFPD. The echo intensity in the pancreas was significantly higher than that in the right renal cortex. Liver echo was used as an intermediate bridge to better distinguish between the pancreas and the right renal cortex. (**B**) Liver (blue circle), pancreas (red circle), and right renal cortex (orange circle) of healthy subjects. The echo intensity in the pancreas was comparable to that in the right renal cortex. NAFPD: Nonalcoholic fatty pancreas disease.

2.4. Data collection

We used the hospital system to obtain participants' data by name and clinical number. After a continuous fast of at least 8 h [31], peripheral venous blood samples were obtained on the following morning. The UA, TG, TC, HDL, and LDL levels were measured by enzyme colorimetry. Age and sex were recorded.

2.5. Diagnosis of NAFLD and NAFPD

Liver and pancreatic ultrasound examinations were performed by trained technicians, and experienced physicians evaluated the ultrasound images without knowledge of the clinical information and biochemical results of the participants.

NAFLD was diagnosed based on four ultrasound characteristics: liver echo intensity, liver-kidney echo contrast, vascular blur, and deep attenuation. The diagnosis was established if the characteristic ultrasound findings were ultimately greater than or equal to one [32–34].

NAFPD was diagnosed on the basis of an enhanced pancreatic echo, which was higher than that of the renal cortex (Fig. 2A). The healthy subject was considered similar echo intensity of the pancreas and renal cortex (Fig. 2B). Since the pancreas and kidney are often difficult to display on the same screen, the echo difference between the liver and kidney can be compared first, followed by that between the liver and pancreas [18,35].

2.6. Statistical analysis

Data were analyzed using SPSS 26.0 software and R software (version 4.3.1). For continuous variables, QQ plots and Shapiro-Wilk tests were used to evaluate distribution patterns. Continuous variables with approximately normal distribution are expressed as mean (standard deviation), and continuous variables with skewed distribution are expressed as median (interquartile range) and compared using the Student's t-test or Mann-Whitney *U* test. Categorical variables are expressed as numbers (%) and compared using Pearson's chi-square test. The RCS linear regression model was used to analyze the effect of the entire UA span on blood lipids. The RCS logistic regression model was used to determine the effect of the entire UA span on NAFLD and NAFPD. All P values were two-sided, and statistical significance was set at $P < 0.05$.

3. Results

3.1. Baseline characteristics of the study participants

The baseline characteristics of the study participants are presented in Table 1. It describes the sex, age, and blood biochemical parameters according to whether the study participants were diagnosed with NAFLD or NAFPD. A total of 1977 participants were included in this study. A total of 771 participants (39.00 %) were diagnosed with NAFLD, including 367 males (18.56 %) and 404 females (20.44 %) ($\chi2 = 3.052$, $P = 0.218$). The age ($t = 13.961$, $P < 0.001$), UA ($t = 12.827$, $P < 0.001$), TG ($u = 18.774$, $P < 0.001$), and TC ($t = 4.711$, $P < 0.001$) levels of participants with NAFLD were significantly higher than those of healthy controls. LDL ($t = 8.093$, $P < 0.001$) levels were significantly higher in participants with NAFLD than those in participants without NAFLD. The HDL levels in participants with NAFLD ($t = 13.073$, $P < 0.001$) were significantly lower than those in participants without NAFLD. A total of 939 participants (47.50 %) were diagnosed with NAFPD, including 453 males (22.91 %) and 486 females (24.59 %) ($\chi2 = 5.052$, $P = 0.080$). Age ($t = 11.883$, $P < 0.001$), UA ($t = 9.959$, $P < 0.001$), TG ($u = 14.726$, $P < 0.001$), TC ($t = 7.330$, $P < 0.001$), and LDL ($t = 10.513$, $P < 0.001$) levels were significantly higher in NAFPD participants than in participants without NAFPD. Further, HDL levels in participants with NAFPD ($t = 9.211$, $P < 0.001$) were significantly lower than those in participants without NAFPD.

Table 1
Baseline characteristics of study subjects with and without NAFLD or NAFPD.

	Non-NAFLD	NAFLD	P-value	Non-NAFPD	NAFPD	P-value
No.	1206 (61.00 %)	771 (39.00 %)		1038 (52.50 %)	939 (47.50 %)	
Sex			0.218			0.080
Male	541 (27.36 %)	367 (18.56 %)		455 (23.01 %)	453 (22.91 %)	
Female	665 (33.64 %)	404 (20.44 %)		583 (29.49 %)	486 (24.59 %)	
Age, years	39.65 (13.76)	49.17 (15.43)	<0.001	39.62 (13.69)	47.50 (15.62)	<0.001
UA, μmol/L	308.47 (83.48)	361.77 (94.12)	<0.001	310.10 (83.23)	350.43 (95.58)	<0.001
TG, mmol/L	0.78 (0.62)	1.52 (1.50)	<0.001*	0.77 (0.69)	1.30 (1.35)	<0.001*
TC, mmol/L	4.41 (1.29)	4.73 (1.56)	<0.001	4.31 (1.27)	4.78 (1.52)	<0.001
HDL, mmol/L	1.37 (0.39)	1.15 (0.34)	<0.001	1.37 (0.39)	1.20 (0.36)	<0.001
LDL, mmol/L	2.92 (0.88)	3.25 (0.89)	<0.001	2.85 (0.84)	3.27 (0.91)	<0.001

Values are expressed as mean (SD), median (quartile interval), or n (%).
Abbreviations: NAFLD: Nonalcoholic fatty liver disease; NAFPD: Nonalcoholic fatty pancreas disease; UA: Uric acid; TG: Triglyceride; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.
* These data are presented as median (quartile interval) using the Mann-Whitney *U* test due to non-normally distributed data.

3.2. Effect of entire UA span on blood lipids

The RCS linear regression model was used to perform a piecewise regression of the UA span on TG (Fig. 3A), TC (Fig. 3B), HDL (Fig. 3C), and LDL (Fig. 3D). There was a nonlinear J-shaped effect of the UA span on TG ($P < 0.001$, P for nonlinear <0.001). When UA <200 μmol/L, it was negatively correlated with TG. When UA >200 μmol/L, it was positively correlated with TG. There was a nonlinear inverted J-shaped effect of the UA span on HDL ($P < 0.001$, P for nonlinear <0.001). When UA <230 μmol/L, it was positively correlated with HDL. When UA >230 μmol/L, it was negatively correlated with HDL. There was a linear positive effect of the UA span on TC ($P = 0.002$, P for nonlinear = 0.578) and a nonlinear positive effect of the UA span on LDL ($P < 0.001$, P for nonlinear = 0.021).

3.3. Effect of entire UA span on NAFLD and NAFPD

The RCS logistic regression model used to perform piecewise regression of the UA span on NAFLD (Fig. 4A) and NAFPD (Fig. 4B). There was a J-shaped effect of the UA span on NAFLD ($P < 0.001$, P for nonlinear <0.001). When UA <250 μmol/L, it was negatively correlated with NAFLD. Meanwhile, when UA >250 μmol/L, it was positively correlated with NAFLD. There was a J-shaped effect of the UA span on NAFPD ($P < 0.001$, P for nonlinear <0.001). When UA <250 μmol/L, it was negatively correlated with NAFPD. When UA >250 μmol/L, it was positively correlated with NAFPD.

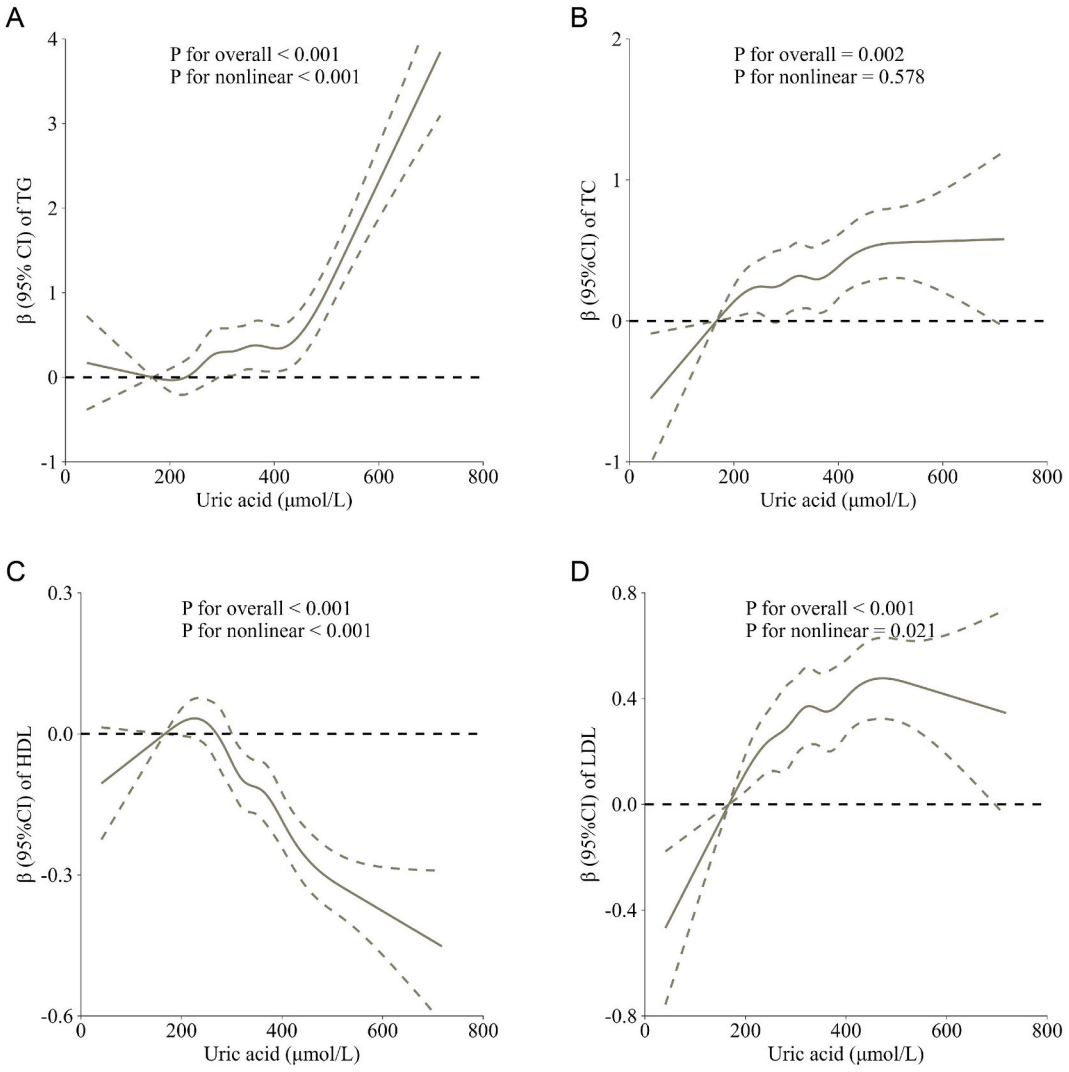

Fig. 3. The effect of the entire UA span on blood lipids ((**A**) TG, (**B**) TC, (**C**) HDL, and (**D**) LDL). UA: Uric acid; TG: Triglyceride; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CI: Confidence interval.

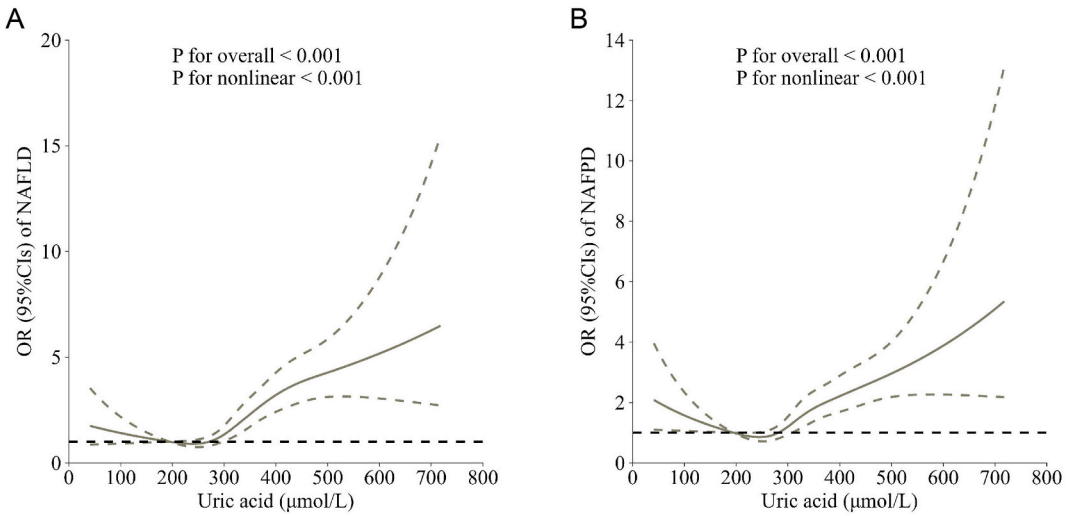

Fig. 4. The effect of the entire UA span on (**A**) NAFLD and (**B**) NAFPD. UA: Uric acid; NAFLD: Nonalcoholic fatty liver disease; NAFPD: Nonalcoholic fatty pancreas disease; OR: Odds ratio; CI: Confidence interval.

4. Discussion

The rate of NAFLD diagnosis in this study was 39 %, which is slightly higher than that reported in the literature [36]. However, since ultrasound has a missed diagnosis rate of approximately 30 % for mild NAFLD [37], and the diagnosis of NAFLD by ultrasound has certain subjective factors. Therefore, a certain error is acceptable. The rate of NAFLD diagnosis in this study can be considered to be within the normal range. The rate of NAFPD diagnosis in this study was 47.5 %, which was still slightly higher than that reported in the literature [17,18]. Previous studies have reported a higher diagnosis rate of NAFPD than that of NAFLD [17,18,36]. The results in this study are consistent with those in previous studies. Therefore, the rate of NAFPD diagnosis reported herein can be considered within the normal range. Combined with the higher diagnosis rates of NAFLD and NAFPD than previous reports, misdiagnosis can be excluded to some extent, and it is speculated that this region may be a high incidence area of NAFLD and NAFPD.

Age as well as UA, TG, TC, and LDL were higher in participants with NAFLD and participants with NAFPD than those in participants without the respective disease. Meanwhile, HDL was lower in both participants with NAFLD and NAFPD. Thus, the biochemical parameters of participants with NAFLD or NAFPD are indeed elevated relative to those of participants without the respective disease, which is consistent with previous reports [7,38]. In addition, disease prevalence was slightly higher in women than in men. However, there was no significant difference.

Previous reports concluded that TG, TC, and LDL were linearly positively correlated with UA, while HDL was linearly negatively correlated with UA [39,40], according to the traditional Pearson linear regression model. This used to be a good method, but it weakened the role of UA in each stage and might lose some key information. We used the RCS linear regression model to evaluate the effect of the UA span on the four major lipid parameters (TG, TC, HDL, and LDL). The RCS linear regression model suggested a J-shaped effect of the UA span on TG. With the increase of UA, TG first decreased and then increased, with a turning point at about 200 μmol/L. Meanwhile, HDL first increased and then decreased, with the turning point at about 230 μmol/L. These observations are consistent with the dual effects of UA [21–23]. However, the effects of the UA span on TC and LDL were consistent with that expressed by the Pearson linear regression model, which showed a positive correlation.

We used the RCS logistic regression model to evaluate the effect of the UA span on NAFLD and NAFPD. J-shaped effects were observed for both conditions. With the increase of UA, the prevalence of both first decreased and then increased, with a turning point of about 250 μmol/L. This provided further evidence that UA has a dual effect on lipid metabolism, which may be related to its dual properties [41]. In particular, we found that the degree of pancreatic steatosis was reduced when UA was elevated at low concentrations below hyperuricemia [42]. There may exist a new target for the treatment of pancreatic steatosis.

Combined with the above lipid analysis (the effect of the UA span on TG and HDL was J-shaped and inverted J-shaped, respectively), TG and HDL may better reflect the effect of the UA span on NAFLD and NAFPD. Therefore, TG and HDL may be of greater relevance than TC or LDL when assessing lipid metabolism in the context of these diseases.

The current study has some limitations. First, the diagnosis of NAFLD and NAFPD is based only on ultrasound examination, which may lead to missed diagnoses. Second, as this was a retrospective study, other data from physical examination patients were missing or omitted, which made it difficult to collect covariates. Future studies should collect more covariates and conduct comprehensive analyses on those. Third, the study population included in this study was exclusively Chinese, meaning that the current findings may not be applicable to other populations.

5. Conclusion

In conclusion, our study showed that the entire UA span has a J-shaped effect on some lipids, NAFLD, and NAFPD. Besides, TG and HDL, compared with TC or LDL, may better reflect the status of NAFLD and NAFPD.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Yang Xiao: Writing – review & editing, Writing – original draft, Visualization, Software, Formal analysis, Conceptualization. **Han Wang:** Writing – review & editing, Visualization, Software, Investigation. **Lina Han:** Writing – review & editing, Visualization, Software, Investigation, Data curation. **Guorong Lyu:** Writing – review & editing, Supervision, Methodology, Formal analysis. **Shilin Li:** Writing – review & editing, Supervision, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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