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Caffeine intake associated with a lower risk of liver fibrosis in different glucose status

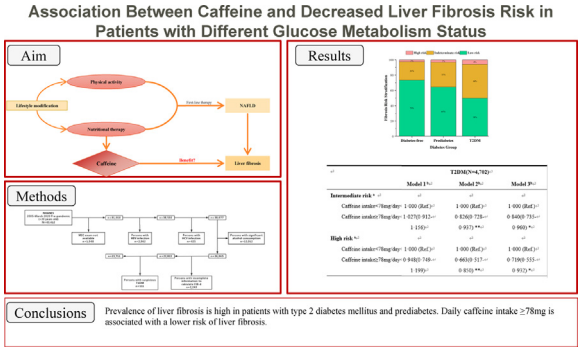
Jiahao Han [a,b,c,1], Chuan Liu [a,b,1], Huanhuan Yang [d,1], Zihe Dong [e], Xiaoguo Li [a,b,e], Ruixia Gao [c], Jie Li [f], Qun Zhang [g], Wai-kit Ming [h], Zhihui Li [d], Jia Li [c,*], Xiaolong Qi [a,b,2,*]

[a] Liver Disease Center of Integrated Traditional Chinese and Western Medicine, Department of Radiology, Zhongda Hospital, Medical School, Southeast University, Nurturing Center of Jiangsu Province for State Laboratory of AI Imaging & Interventional Radiology (Southeast University), Nanjing, China
[b] Basic Medicine Research and Innovation Center of Ministry of Education, Zhongda Hospital, Southeast University, State Key Laboratory of Digital Medical Engineering, Nanjing, China
[c] Department of Ultrasound, Zhongda Hospital, Medical School, Southeast University, Nanjing, China
[d] Vanke School of Public Health, Tsinghua University, Beijing, China
[e] Institute of Portal Hypertension, The First Hospital of Lanzhou University, Lanzhou, China
[f] Department of Infectious Disease, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China
[g] Department of Infectious Disease, Zhongda Hospital, Medical School, Southeast University, Nanjing, China
[h] Department of Infectious Diseases and Public Health, Jockey Club College of Veterinary Medicine and Life Sciences, City University of Hong Kong, Hong Kong, China

HIGHLIGHTS

- Coffee were believed to benefit liver fibrosis in previous articles.
- Caffeine intake ≥ 78 mg per day benefits lower risk of liver fibrosis.
- Caffeine could be considered to prevent liver fibrosis.

GRAPHICAL ABSTRACT



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ABSTRACT

Background and aims: To investigate the prevalence of liver fibrosis, and the association between caffeine intake and fibrosis in populations with different glucose metabolism status.
Methods: This was a cross-sectional study based on the National Health and Nutrition Examination Survey (2005-March 2020). Of the 39,221 adult individuals with no necessary laboratory results missing, a total of 23,711 eligible individuals were included in the study. Individuals were divided into T2DM, pre-diabetes, and diabetes-free groups. Fibrosis-4 index was calculated to evaluate the risk of liver fibrosis. Caffeine intake was obtained through a 24-hour dietary recall.
Results: The mean ± SE age of prediabetes group was 53 ± 0·4 years, and in type 2 diabetes mellitus group, the individuals have a mean ± SE age of 62 ± 0·3 years. The participants with type 2 diabetes

* Corresponding authors at: Liver Disease Center of Integrated Traditional Chinese and Western Medicine, Department of Radiology, Zhongda Hospital, Medical School, Southeast University, Nurturing Center of Jiangsu Province for State Laboratory of AI Imaging & Interventional Radiology (Southeast University), Nanjing, China; Basic Medicine Research and Innovation Center of Ministry of Education, Zhongda Hospital, Southeast University, State Key Laboratory of Digital Medical Engineering, Nanjing, China (Xiaolong Qi). Department of Ultrasound, Zhongda Hospital, Medical School, Southeast University, Nanjing, China (Jia Li).
E-mail addresses: 13951609892@163.com (J. Li), qixiaolong@vip.163.com (X. Qi).
[1] Contributed equally as joint first authors.
[2] Lead contact.

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Prediabetes
Type 2 diabetes mellitus

mellitus had significantly higher risk of liver fibrosis than those with prediabetes or normal glucose tolerance (5·9% vs. 3·2% vs. 2·5%, $P < 0·001$). Compared to individuals with daily caffeine intake < 78 mg, individuals with daily caffeine intake ≥ 78 mg had significantly lower risk of liver fibrosis in all subgroups (odds ratio: diabetes-free group: 0·698[0·577–0·846]; prediabetes group: 0·553[0·397-0·769]; type 2 diabetes mellitus group: 0·720[0·556-0·933]; all $P < 0·05$).

Conclusions: Prevalence of liver fibrosis is high in patients with type 2 diabetes mellitus and prediabetes. It is indicated that individuals with prediabetes should also be screened for fibrosis. Caffeine intake ≥ 78 mg per day is associated with a lower risk of liver fibrosis.

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Introduction

Diabetes is a common metabolic disorder and was the third leading cause of global years lived with disability [1]. Patients with diabetes are more likely to have nonalcoholic fatty liver disease (NAFLD) [2], which had been redefined as metabolic dysfunction associated steatotic liver disease in the recent consensus [3]. Patients with NAFLD have a high risk for liver fibrosis and cirrhosis, leading to poor outcomes such as portal hypertension, ascites, varices, hepatic encephalopathy, hepatocellular carcinoma (HCC), and even mortality [4–6].

To counter the substantial burden of diabetes and NAFLD, prediabetes screening, fibrosis stage monitoring and lifestyle modification are of high significance [1,7]. Multiple studies have found a potentially negative relationship between caffeine intake and liver fibrosis, cirrhosis, together with their adverse clinical outcomes [8,9]. However, there is no evidence that coffee and caffeine work in the same way in patients with different glucose metabolism status to prevent liver fibrosis, which is vital for selecting the appropriate populations who can benefit from caffeine intake.

Therefore, we aimed to investigate the prevalence of liver fibrosis and determine whether caffeine intake influences on liver fibrosis in individuals with different glucose metabolism status by evaluating a large, nationally representative cohort of Americans.

Material and methods

Study design and population

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative cross-sectional study. It enrolls individuals through a stratified multistage probability and oversampling design allowing for a weighted analysis that represents the noninstitutionalized United States (US) civilian population. Demographic, socioeconomic and health information were collected through a general questionnaire. Dietary information was gathered in collaboration with the US Department of Agriculture and the US Department of Health and Human Services through a 24-hour dietary recall. All the foods and beverages consumed within 24 h before the individual attends the Mobile Examination Center (MEC) were recorded. The interviews were conducted by trained dietary interviewers fluent in both Spanish and English. They used a standard set of measuring guides, which helped respondents report the volume and dimensions of the items they consumed.

We retrospectively included adults (≥20 years old) who were both interviewed at home and performed examinations and laboratory tests at the MEC from NHANES 2005 to March 2020. Individuals with significant alcohol consumption, HBV or HCV infection, and suspicious type 1 diabetes mellitus (T1DM) were excluded. Significant alcohol consumption was defined as ≥ 3 standard drinks (1 standard drink = 14 g of pure alcohol) per day for men and ≥ 2 standard drinks per day for women. Suspicious T1DM was defined when the person was ever told having diabetes before the age of 20. The flowchart of sample inclusion is shown in Fig. 1.

The samples were divided into three groups: Type 2 diabetes mellitus (T2DM), prediabetes, and diabetes-free groups. T2DM is diagnosed when any of the following five criteria was met: (1) Fasting plasma glucose (FPG) ≥ 7·0mmol/L; (2) Random plasma glucose ≥ 11·1mmol/L; (3) Glycohemoglobin (HbA_{1c}) ≥ 6·5%; (4) Taking insulin or diabetes pills currently; (5) Ever told having diabetes. Prediabetes is diagnosed when patients are not diagnosed diabetes, and with FPG ≥ 5·6mmol/L, HbA1c ≥ 5·7%, or ever told having prediabetes. The other samples were defined as "diabetes-free".

Variates

Age, gender, race/ethnicity, educational level, marital status, and poverty-income ratio were obtained in the demographics data. Body mass index (BMI) and waist circumference were obtained in the examination data. Vigorous activity was determined when the individual's work or recreational activity caused large increases in breathing or heart rate. Cardiovascular disease (CVD) was determined when coronary heart disease and stroke were ever diagnosed. Heart failure was determined when congestive heart failure was ever diagnosed. Chronic kidney disease (CKD) was determined when weak or failing kidneys was ever diagnosed. Hypertension was determined when high blood pressure was ever found more than two times or reach the diagnose (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) in any three measures of blood pressure at MEC. The levels of aspertate aminotransferase (AST), alanine transaminase (ALT), total protein (TP), albumin, total bilirubin (TB), total cholesterol (TC), triglycerides, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), and platelet count were obtained in the laboratory data.

Caffeine intake from all foods and beverages was calculated according to the first 24-hour dietary recall interview. Consumption of coffee in liquid form was calculated according to the first 24-hour dietary recall interview. The caffeine intake is divided into groups according to the median (78 mg/day) and the quartiles (3 mg/day, and 192 mg/day).

FIB-4 index = age(years) × AST(U/L)/[platelet count (10^9/L) × $ALT^{1/2}$ (U/L)]. As suggested by the American Association for the Study of Liver Diseases (AASLD), FIB-4 index < 1·3 is considered to be low risk of liver fibrosis and > 2·67 to be high risk, the others are considered to be intermediate risk [2,10].

Ethics

The NHANES protocols were approved by the National Center for Health Statistics Ethics Review Board of the U.S. CDC, and written informed consent from all the individuals was provided during the survey.

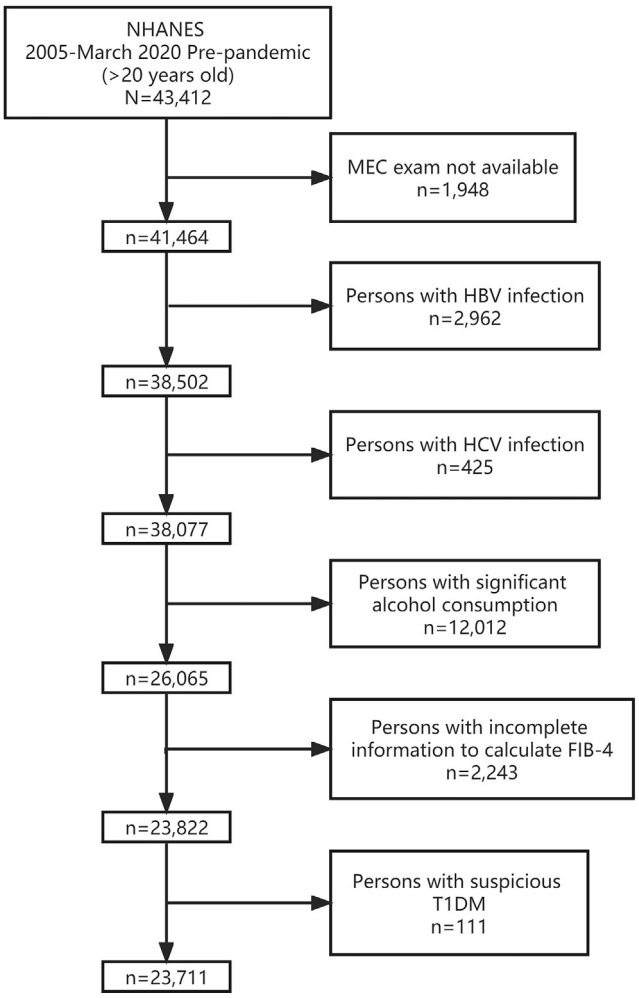


Fig. 1. Flow chart of the study individuals.

Statistical analysis

Description of individuals' characteristics

Appropriate weights were applied in each analysis to confirm the samples are representative of the civilian noninstitutionalized US population. Accounting for the complex survey design of NHANES, data are expressed as numbers and weighted proportions for categorical variables and as weighted means ± SE for continuous variables. To compare the difference of demographics, examination, dietary, laboratory, and questionnaire data between the samples of diabetes, prediabetes and diabetes-free groups, one-way ANOVA was performed for continuous variables and the design-adjusted Rao-Scott Chi-square test was performed for categorical variables.

Outcomes of the study

Disordered multi-classification logistic regression was employed to interrogate the association between caffeine and liver fibrosis for $P < 0.001$ for test of parallel line. Based on prior studies and theoretical considerations [2,4,11], we selected established risk factors for liver fibrosis, which were also known to be associated with caffeine intake. Model 1 did not adjust for any confounders. Model 2 adjusted for gender and race. Model 3 further adjusted for educational level, poverty, vigorous activity, hypertension, levels of HbA1c, HDL-C, LDL-C, TC, triglycerides, albumin, TB and BMI. For all models, the existence of multicollinearity was verified using the variance inflation factor.

Dealing with missing data

As not all participants provided biospecimens or enough volume for all the tests to be performed, triglycerides of 51·5 %, LDL-C of 52·2 %, HDL-C, albumin, ALP, TB, TP, and TC of less than 0·2 % individuals were unavailable. As not all participants responded to all the questionnaires, poverty-income ratio of 10·2 %, educational level, and marital status of less than 0·2 % individuals were unavailable. As unrealistic values were deleted during the review of measures record, weight of 1·3 %, height of 1·4 %, and waist circumference of 6·0 % individuals were unavailable. Hypertension of 5·6 % individuals could not be determined for unresponsive to the questionnaire and deletion of unreasonable blood pressure measurements. So multiple imputation was performed to account for missing data, using predictive mean matching for continuous variables, logistic regression for binary data, and polytomous regression for categorical data. All the characteristics were considered as predictors.

Subgroup comparison

We performed subgroup analysis in individuals of different diabetes conditions. Additionally, we performed sensitivity analysis by excluding those who take in caffeine less than 78 mg/day. We further categorized caffeine intake into two groups according to the lower quartile and assessed its relationship with liver fibrosis. A two-sided $P < 0.05$ was considered statistically significant.

Statistical analysis

All data analyses were conducted using R version 4·2·2 (R Foundation Vienna, Austria) and SPSS version 21.

Results

General description

The comparison of the individuals according to the glucose metabolism status is described in Table 1. Among the 23,711 individuals included in our analysis, the weighted prevalence of T2DM in the studied individuals was 15·4% (95 % confidence interval [CI] 14·7%–16·0%). The individuals in diabetes-free group consisted of 6,543 (46·1%, 95 % CI 45·1%–47·0%) males, and the mean ± SE age was 47 ± 0.3 years. While the mean ± SE age of individuals in prediabetes group is 53 ± 0.4 years, and 55·8% (95 % CI 53·7%–58·0%) of the individuals are male. In T2DM group, the individuals have a mean ± SE age of 62 ± 13 years and a percentage of male of 51·2% (95 % CI 49·3%–53·0%).

The levels of HDL-C, LDL-C, and triglycerides have significant difference between all three groups. The levels of TB and TC are lower in T2DM group compared with the other two groups. The level of albumin is lower in both prediabetes and T2DM group (all $P < 0.001$). The total protein shows no difference between the three groups ($P = 0.306$).

Prevalence of liver fibrosis in different glucose metabolism status

There are 3·2% (95 % CI 2·9%–4·0%) samples with high risk of liver fibrosis and 67·9% (95 % CI 66·5%–69·0%) with low risk. The ratio of individuals at high risk of liver fibrosis in the T2DM group is 5·9% (95 % CI 5·1%–7·0%), significantly higher (all P 0·001) than that in the diabetes-free (2·5%, 95 % CI 2·3%–3·0%) and prediabetes groups (3·2%, 95 % CI 2·5%–4·0%). However, the ratio of high risk of liver fibrosis is not significantly different between prediabetes and diabetes-free group ($P = 0.156$). The ratio of individuals with an intermediate risk of liver fibrosis is significantly different between the three groups (diabetes-free: 24·2%, 95 % CI 23·0%–25·0%; prediabetes: 32·3%, 95 % CI 30·1%–35·0%; T2DM: 44·3%, 95 % CI 42·0%–47·0%, $P < 0.001$) (Fig. 2).

Table 1
Features of the population.

	Categories of Diabetes			
	Diabetes-free (n = 14,519)	Prediabetes (n = 4,490)	T2DM (n = 4,702)	*P*
Male	6,543(46·1)	2,406(55·8)	2,348(51·2)	<0·001
Age(years)	47 ± 0·3	53 ± 0·4	62 ± 0·3	<0·001
<45	6,759(47·4)	1,290(30·3)	448(10·8)	
≥45, <60	3,237(26·6)	1,208(31·2)	1,185(30·4)	
≥60	4,523(25·9)	1,992(38·5)	3,069(58·9)	
Body mass index (kg/m^2)	28·02 ± 0·085	30·39 ± 0·178	33·07 ± 0·153	<0·001
<25	4,889(34·8)	974(19·8)	587(10·6)	
≥25, <30	4,939(34·2)	1,611(36·7)	1,336(26·9)	
≥30	4,691(31·0)	1,905(43·5)	2,779(62·4)	
Waist circumference (cm)	96·5 ± 0·23	103·3 ± 0·37	111·4 ± 0·35	<0·001
Vigorous Activity	5,249(41·8)	1,474(37·2)	900(21·5)	<0·001
Race/Ethnicity				<0·001
Mexican American	1,999(7·4)	615(6·9)	832(9·1)	
Other Hispanic	1,287(5·2)	455(5·6)	477(5·7)	
Non-Hispanic White	6,537(68·8)	2,103(71·5)	1,776(63·9)	
Non-Hispanic Black	3,043(10·8)	774(7·9)	1,155(13·2)	
Other race	1,653(7·8)	543(8·1)	462(8·1)	
Educational level				<0·001
Less than 9th grade	1,364(5·0)	475(5·8)	852(10·4)	
9-11th grade	1,824(9·3)	556(9·1)	732(12·3)	
High school graduate	3,132(21·7)	1,002(23·3)	1,076(25·9)	
Some college or AA degree	4,244(29·6)	1,270(29·6)	1,240(29·6)	
College graduate or above	3,955(34·5)	1,187(32·2)	802(21·8)	
Marital status				<0·001
Married/Living with Partner	8,959(66·5)	2,918(68·7)	2,820(64·4)	
Widowed/Divorced/Separated	2,957(16·6)	1,043(19·9)	1,484(27·5)	
Never married	2,603(16·9)	529(11·3)	398(8·1)	
Poverty-income ratio	3·06 ± 0·035	3·14 ± 0·047	2·77 ± 0·043	<0·001
≤0·99	2,868(13·5)	843(11·9)	1,051(15·6)	
≥1	11,651(86·5)	3,647(88·1)	3,651(84·4)	
Comorbidity				
Cardiovascular disease	81(0·4)	36(0·6)	109(2·3)	<0·001
Heart failure	314(1·6)	165(3·0)	477(9·4)	<0·001
Chronic kidney disease	329(2·1)	149(2·8)	415(7·4)	<0·001
Hypertension	4,412(26·9)	1,964(39·7)	3,079(64·9)	<0·001
Laboratory feature				
Albumin(g/dl)	9·7 ± 0·42	8·8 ± 0·40	8·4 ± 0·35	<0·001
Total bilirubin(umol/L)	11·24 ± 0·094	11·40 ± 0·115	10·59 ± 0·133	<0·001
Total cholesterol(mmol/L)	5·04 ± 0·012	5·07 ± 0·026	4·70 ± 0·027	<0·001
HDL-C(mmol/L)	1·40 ± 0·006	1·34 ± 0·008	1·21 ± 0·007	<0·001
Triglycerides(mmol/L)	1·386 ± 0·0130	1·478 ± 0·0239	1·796 ± 0·0329	<0·001
LDL-C(mmol/L)	3·003 ± 0·0097	3·062 ± 0·0203	2·718 ± 0·0219	<0·001
Total Protein(g/dl)	7·1 ± 0·01	7·1 ± 0·01	7·1 ± 0·01	0·306
FIB-4	1·075 ± 0·011	1·214 ± 0·024	1·451 ± 0·018	<0·001
Caffeine Intake(mg/day)	159 ± 3·5	178 ± 4·9	162 ± 5·4	0·003
None	3,078(17·7)	798(14·3)	962(17·2)	
>0, ≤78	4,357(26·7)	1,319(25·9)	1,413(25·6)	
>78, ≤192	3,636(25·7)	1,102(24·1)	1,164(25·7)	
>192	3,448(29·9)	1,271(35·6)	1,163(31·5)	
Coffee Consumption(cup/day)	1·3 ± 0·03	1·6 ± 0·05	1·4 ± 0·05	<0·001
None	7,745(50·3)	2,129(43·9)	2,158(45·8)	
>0, <3	5,076(34·3)	1,712(38·2)	1,935(37·7)	
≥3, <5	1,218(10·8)	455(12·5)	472(12·3)	
≥5	480(4·6)	194(5·3)	137(4·1)	
Caffeinated coffee Consumption (cup/day)	1·2 ± 0·03	1·4 ± 0·05	1·2 ± 0·05	0·003
None	8,683(56·2)	2,459(50·9)	2,624(54·2)	
>0, <3	4,401(30·6)	1,469(33·8)	1,559(31·7)	
≥3, <5	1,012(9·2)	390(10·7)	402(10·8)	
≥5	423(4·1)	172(4·6)	117(3·3)	

Data are presented as weighted means ± SE for continuous variables, n(weighted proportions) for categorical variables.
HDL-C: high-density lipoprotein-cholesterol, LDL-C: low-density lipoprotein-cholesterol.

Male sex, non-Hispanic whites, and lower educational level are associated with a higher risk of fibrosis (all $P < 0·01$). Individuals with high risk of fibrosis have the lowest income, also are less likely to be involved in vigorous activity. The level of HDL-C is the lowest, the levels of TC, LDL-C, and triglycerides are highest in individuals with low risk of fibrosis. The prevalence of heart failure, CVD, CKD, and hypertension is also the highest in individuals with high risk of fibrosis.

Associations between caffeine intake and the FIB-4 index

Supplementary Table S1 compares cohort characteristics based on caffeine intake. Females, and non-Hispanic Whites are more likely to take in caffeine ≥ 78 mg per day. And individuals who take in caffeine ≥ 78 mg per day have higher age, BMI, waist circumference, educational level, income, levels of TC, triglycerides, LDL-C, lower level of HDL-C, and more likely to be married, and involved

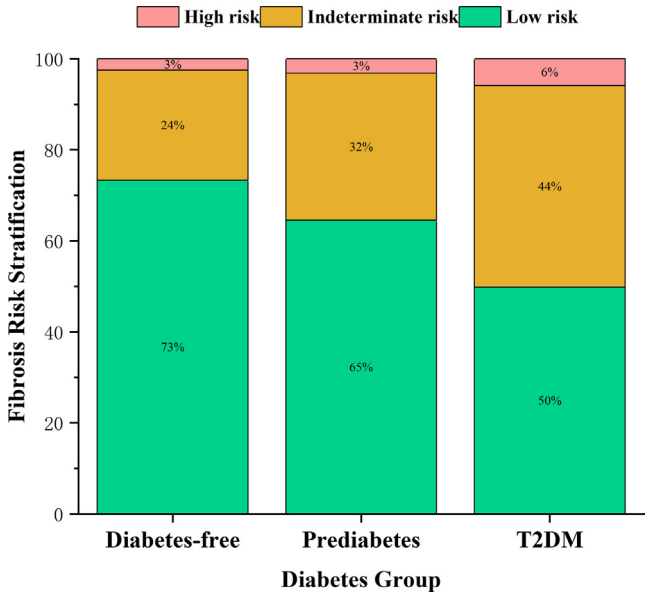


Fig. 2. The fibrosis risk stratification in individuals with different diabetes conditions.

in vigorous activity. Individuals with caffeine intake ≥ 78 mg per day are also less likely to have heart failure, CKD and high risk of liver fibrosis.

We assess the relationship between caffeine intake and the FIB-4 index (Table 2). There shows no multicollinearity in both developed models. According to multi-classification logistic regression analysis, individuals with caffeine intake ≥ 78 mg per day are less likely ($P < 0.05$) to be at high risk of liver fibrosis with a crude odd ratio (OR) of 0·881(0·776-0·999) compared with those with caffeine intake < 78 mg. After adjusting gender and race (Model 2), caffeine intake ≥ 78 mg per day is still significantly associated with risk of fibrosis. In Model 3 in which gender, race, poverty, educational level, vigorous activity, hypertension, HbA1c, HDL-C, LDL-C, TB, TC and BMI were adjusted, individuals who take in caffeine ≥ 78 mg per day have less possibility ($P < 0.001$) of high risk of fibrosis with an OR of 0·707 (0·617-0·812). When investigating the relationship between caffeine intake and risk of liver fibrosis in separate groups, caffeine intake ≥ 78 mg/day is negatively associated with high risk of liver fibrosis in all groups (diabetes-free group: OR 0·698[0·577-0·846]; prediabetes group: OR 0·553[0·397-0·769]; T2DM group: OR 0·720[0·556-0·933]; all $P < 0.05$). However, caffeine intake ≥ 78 mg/day is only negatively associated with intermediate risk of liver fibrosis in the T2DM group (OR 0·840[0·735-0·960]; $P = 0.010$) (Table 3). In dose analysis, the risk of liver fibrosis is not different between individuals with caffeine intake ≥ 3 mg/day and those with caffeine intake < 3 mg/day which is lower quartile of levels of caffeine intake (Supplementary Tables S2 and S3).

Compared to those who do not take in caffeine at all, individuals with caffeine intake ≥ 78 mg per day are still more likely to be at low risk of fibrosis than high risk with an OR of 0·806 (0·670-0·970) (Supplementary Table S4).

Discussion

In this study, we find that: (1) The prevalence of fibrosis in individuals with T2DM or prediabetes is higher than individuals absent of both; (2) Consuming at least 78 mg of caffeine per day is negatively associated with high risk of liver fibrosis in all individuals, independent from sex, race, educational level, poverty, vigorous activity, hypertension, and levels of HbA1c, HDL-C, LDL-C, TC, triglycerides, albumin, TB and BMI; (3) Consuming at least 78 mg of caffeine is also negatively associated with intermediate risk of liver fibrosis in individuals with T2DM.

The relationship between diabetes and NAFLD is considered bidirectional [12], and some also believed that T2DM patients suffer from more severe NAFLD [4,13]. There is insufficient evidence to confirm the role of prediabetes in the progression of NAFLD towards NASH and cirrhosis. Our results show that prediabetes also has an impact on the development of liver fibrosis, indicating that abnormal glycemic metabolism is one of the contributors to fibrosis, even when the condition is not as severe as diabetes.

Lifestyle modification remains the cornerstone of NASH therapy [14]. Coffee, a popular beverage in many societies, has been proven to benefit the outcomes of individuals with, or at risk for CLD [15]. Caffeine and chlorogenic acid are the most abundant bioactive compounds in coffee. In our study, caffeine intake ≥ 78 mg was negatively associated with a high risk of liver fibrosis. Barré et al. confirmed that coffee consumption of no less than three cups per day prevents HBV patients on treatment from clinically significant fibrosis [16]. A cohort study by Kennedy also showed that the maximal protective effect of coffee on CLD arose when consuming approximately three to four cups each day. This protective effect was proven the strongest in those who consumed ground coffee, and less apparent in decaffeinated and instant coffee groups [9]. Niezen's study also found the significant association between decreased liver stiffness measurement (LSM) and consumption of caffeinated coffee [8]. These results are all consistent with our results. We also confirmed the hypothesis that caffeine plays an important role in the mechanism through which coffee affect liver fibrosis. Caffeine has been proven to act as a non-selective antagonist of the A2aA receptor to hinder the stimulation of collagen production [17]. Furthermore, Niezen found no association between

Table 2
The relationship between caffeine intake and fibrosis risk stratification.

	Case (%)	Model 1 †			Model 2 †			Model 3 †		
		β	SE	aOR (95 % CI)	β	SE	aOR (95 % CI)	β	SE	aOR (95 % CI)
Intermediate risk *										
Caffeine intake <78 mg/day	3,563 (47·7)	/	/	1·000 (Ref.)	/	/	1·000 (Ref.)	/	/	1·000 (Ref.)
Caffeine intake ≥78 mg/day	3,905 (52·3)	0·143	0·028	1·154(1·092-1·220) §	−0·019	0·030	0·981 (0·926-1·080)	−0·11	0·032	0·989 (0·929-1·053)
High risk *										
Caffeine intake <78 mg/day	562 (54·5)	/	/	1·000 (Ref.)	/	/	1·000 (Ref.)	/	/	1·000 (Ref.)
Caffeine intake ≥78 mg/day	470 (45·5)	−0·127	0·065	0·881(0·776-0·999) ‡	−0·429	0·067	0·651(0·571-0·743) §	−0·346	0·070	0·707(0·617-0·812) §

SE: standard error; aOR, adjusted odds ratio; CI: confidence interval.
* Low risk of fibrosis was employed as the reference group; † Reference (Ref.); Model 2 adjusted for gender and race; Model 3 adjusted for gender, race, educational level, poverty, vigorous activity, hypertension, levels of HbA1c, HDL-C, LDL-C, TC, triglycerides, albumin, TB and BMI. ‡ $P < 0.05$; § $P < 0.001$.

Table 3
The relationship between caffeine intake and fibrosis risk stratification in different groups.

	Diabetes-free(n = 14,519)									Prediabetes(n = 4,490)								
	Model 1 †			Model 2 †			Model 3 †			Model 1 †			Model 2 †			Model 3 †		
	β	SE	aOR (95 % CI)	β	SE	aOR (95 % CI)	β	SE	aOR (95 % CI)	β	SE	aOR (95 % CI)	β	SE	aOR (95 % CI)	β	SE	aOR (95 % CI)
Intermediate risk ‡																		
Caffeine intake <78 mg/day	/	/	1·000 (Ref.)	/	/	1·000 (Ref.)	/	/	1·000 (Ref.)	/	/	1·000 (Ref.)	/	/	1·000 (Ref.)	/	/	1·000 (Ref.)
Caffeine intake ≥78 mg/day	0·188	0·038	1·207 (1·120-1·300) ‖	0·004	0·040	1·004 (0·929-1·086)	−0·039	0·044	0·961 (0·882-1·048)	0·124	0·064	1·133 (1·000-1·283)	0·001	0·066	1·001 (0·879-1·140)	0·022	0·072	1·023 (0·889-1·177)
High risk ‡																		
Caffeine intake <78 mg/day	/	/	1·000 (Ref.)	/	/	1·000 (Ref.)	/	/	1·000 (Ref.)	/	/	1·000 (Ref.)	/	/	1·000 (Ref.)	/	/	1·000 (Ref.)
Caffeine intake ≥78 mg/day	−0·107	0·090	0·898 (0·754-1·071)	−0·416	0·093	0·660 (0·549-0·792) ‖	−0·359	0·098	0·698 (0·577-0·846) ‖	−0·364	0·152	0·695 (0·515-0·936) ‡	−0·692	0·158	0·500 (0·367-0·682) ‖	−0·593	0.169	0·553 (0·397-0·769) ‖

	T2DM(n=4,702)								
	Model 1 †			Model 2 †			Model 3 †		
	β	SE	aOR (95% CI)	β	SE	aOR (95% CI)	β	SE	aOR (95% CI)
Intermediate risk ‡									
Caffeine intake <78mg/day	/	/	1·000 (Ref.)	/	/	1·000 (Ref.)	/	/	1·000 (Ref.)
Caffeine intake ≥78mg/day	0.027	0·060	1·027 (0·912-1·156)	−0.191	0·064	0·826 (0·728-0·937) §	−0·174	0·068	0·840 (0·735-0·960) ‡
High risk ‡									
Caffeine intake <78mg/day	/	/	1·000 (Ref.)	/	/	1·000 (Ref.)	/	/	1·000 (Ref.)
Caffeine intake ≥78mg/day	−0·054	0·120	0·947 (0·749-1·199)	−0·411	0·127	0·663 (0·517-0·850) §	−0·328	0·132	0·720 (0·556-0·933) ‡

SE: standard error; aOR, adjusted odds ratio; CI: confidence interval.
* Low risk of fibrosis was employed as the reference group; † Reference (Ref.); Model 2 adjusted for gender and race; Model 3 adjusted for gender, race, educational level, poverty, vigorous activity, hypertension, levels of HbA_{1c}, HDL-C, LDL-C, TC, triglycerides, albumin, TB and BMI. ‡ $P < 0·05$; § $P < 0·01$; || $P < 0·001$.

coffee consumption and the controlled attenuation parameter (CAP) [8]. This finding may explain why individuals in low risk and intermediate risk for liver fibrosis didn't have different caffeine intake in our research. In other words, caffeine may only prevent persons from significant hepatic fibrosis but have no impact on liver steatosis and mild liver fibrosis. In Zhang Y's Mendelian randomization study, they concluded no causal relationship between coffee consumption and risk of NAFLD based on a published genome-wide association study [18]. Zheng, et al. concluded that coffee lower the risk for HCC instead of NAFLD [19]. In a randomized clinical trial, caffeine intake also showed no significant impact on non-invasive markers of hepatic steatosis in patients with NAFLD [20].

There is still no research on the relationship between caffeine intake and liver fibrosis in individuals with different glucose metabolism status. Instead, some studies have focused on investigating the influence of caffeine intake on liver fibrosis in population with T2DM. In Margarida's research, total urine caffeine metabolites from 24 h urine samples of 98 T2DM patients were higher in subjects without liver fibrosis than in those with liver fibrosis [21]. Asieh's random control trial on T2DM patients with NAFLD found that compared with the placebo group, the caffeine group have a lower level of TC, and the chlorogenic acid plus caffeine group had a high level of fasting insulin. Our research confirmed that caffeine intake was negatively associated with high risk of liver fibrosis in all persons regardless of whether they have diabetes, prediabetes, or neither. However, only in T2DM group, caffeine intake was also negatively associated with an intermediate risk of fibrosis. This may result from an additional benefit of caffeine on T2DM. Larsson's mendelian randomisation study concluded that caffeine could reduce adiposity, including improving BMI and preventing from T2DM [22]. In our study, the BMI is the highest in T2DM group, so it is reasonable that caffeine has an additional benefit on T2DM individuals and so as to negatively associated with high risk as well as intermediate risk of liver fibrosis only in T2DM group. Therefore, we recommend that NAFLD patients take more than 78 mg of caffeine per day, regardless of the etiology but especially in those with T2DM.

Our study has several strengths. First, the samples from NHANES are nationally representative with no selection bias. We combined data from NHANES 2005–2006 to 2017-March 2020 (pre-pandemic), resulting in a large number of samples. Second, the 24-hour dietary recall is considered the most accurate and complete description of dietary intake. Third, although vibration-controlled transient elastography is superior to other non-invasive indices for measuring the severity of liver fibrosis, LSM may be unavailable in some persons or in some institutions. Instead, the FIB-4 index could be applied in all individuals, avoiding selection bias, and it has been proven to be the most validated diagnostic panel among blood tests to diagnose NAFLD with clinically significant fibrosis to date [23].

The limitations of this study are as follows. Since the NHANES 2019–2020 was not completed as a result of the Coronary Virus Disease-19, the data collected were combined with some data from 2017 to 2018 to form the NHANES 2017-March 2020 pre-pandemic, which in fact cannot reflect the condition in 2019–2020. Therefore, the trend in liver fibrosis from 2018 to 2020 should be applied with caution. What's more, the 24-hour dietary recall may not represent a person's overall diet behavior as it depends significantly on the memory of individuals. However, the 24-hour dietary recall applied in NHANES is still the most efficient and accurate means with low risk of recall bias to collect intakes for large-scale national surveys [24]. Also, as a cross-sectional study, the results of our research only represent an association between caffeine and liver fibrosis, but cannot conclude a protective effect of caffeine on the development of liver fibrosis. Lastly, apart from the variates included in our analysis, post-menopausal status, hepatic inflammation, specific pharmacological drugs are also potential factors affecting liver fibrosis, however inaccessible in NHANES. However, the conclusions drawn according to our research still provide important and valuable information for further well-designed prospective researches to investigate the actual influence of caffeine intake on preventing individuals from developing liver fibrosis.

In summary, we found that people with prediabetes and T2DM are more likely to have a higher risk of liver fibrosis. It is indicated that individuals with prediabetes is also screened for fibrosis. Caffeine intake ≥ 78 mg per day is associated with a lower risk of liver fibrosis.

CRediT authorship contribution statement

Jiahao Han: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. **Chuan Liu:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – review & editing. **Huanhuan Yang:** Investigation, Writing – review & editing. **Zihe Dong:** Validation. **Xiaoguo Li:** Validation. **Ruixia Gao:** Data curation. **Jie Li:** Writing – review & editing. **Qun Zhang:** Writing – review & editing. **Wai-kit Ming:** Writing – review & editing. **Zhihui Li:** Investigation, Writing – review & editing. **Jia Li:** Conceptualization, Supervision, Writing – review & editing. **Xiaolong Qi:** Conceptualization, Investigation, Supervision.

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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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Guarantor statement

X.Q is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing statement

Aggregated data might be made available upon reasonable request via email to the corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jare.2025.02.004.

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