Journal of Clinical and Translational Hepatology **2022**
DOI: 10.14218/JCTH.2021.00490

Original Article

Association between Metabolic Dysfunction-associated Fatty Liver Disease and Cognitive Impairment

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Received: 29 October 2021 | **Revised:** 2 December 2021 | **Accepted:** 27 December 2021 | **Published:** 17 February 2022

Abstract

Background and Aims: Metabolic dysfunction-associated fatty liver disease (MAFLD) is a newly proposed term based on modified criteria. Although nonalcoholic fatty liver disease (NAFLD) has been well-documented as a multisystem disease, research on the correlation of MAFLD and extrahepatic diseases is limited. This study aimed to clarify the association of MAFLD, as well as NAFLD status with cognitive function. ***Methods:*** A total of 5,662 participants 20–59 years of age who underwent cognitive tests and liver ultrasonography in the Third National Health and Nutrition Examination Survey were included in the analysis. Cognitive function was evaluated using three computer-administered tests, the serial digit learning test (SDLT), the simple reaction time test (SRTT) and the symbol digit substitution test (SDST). ***Results:*** Participants with MAFLD had significantly poorer performance on the SRTT [odds ratio (OR) 1.47, 95% confidence interval (CI): 1.14–1.89)]. MAFLD with moderate-severe liver steatosis was associated with higher risks of scoring low in the SDLT (OR 1.37, 95% CI: 1.04–1.82) and SRTT (OR 1.55, 95% CI: 1.19–2.02). NAFLD combined with metabolic dysfunction, instead of NAFLD without metabolic disorders, was associated an increased risk of a low SRTT score (OR 1.44, 95% CI: 1.10–1.82). MAFLD patients had a high probability of fibrosis, prediabetes, and diabetes and were also significantly associated with increased risks based on the SDST or SRTT score. ***Conclusions:*** MAFLD was significantly associated with increased risk of cognitive impairment, especially among MAFLD patients with a high degree of liver fibrosis, moderate-severe steatosis, or hyperglycemia.

Citation of this article: Yu Q, He R, Jiang H, Wu J, Xi Z, He K, *et al*. Association between Metabolic Dysfunction-associated Fatty Liver Disease and Cognitive Impairment. J Clin Transl Hepatol 2022. doi: 10.14218/JCTH.2021.00490.

Keywords: NHANES; Metabolic dysfunction-associated fatty liver disease; Nonalcoholic fatty liver disease; Cognitive dysfunction.

Abbreviations: 2 h PG, 2 h post-load glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; MAFLD, metabolic dysfunction-associated fatty liver disease; MD, metabolic dysfunction; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; NHANES, National Health and Nutrition Examination Survey; Non-MD-NAFLD, non-metabolic dysfunction NAFLD; OR, odds ratio; SBP, systolic blood pressure; SDLT, the serial digit learning test; SDST, the symbol digit substitution test; SRTT, the simple reaction time test; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

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Introduction

Nonalcoholic fatty liver disease (NAFLD), characterized by liver steatosis with exclusion of excess alcohol intake and other secondary causes of liver disease, is one of the most common causes of all kinds of chronic liver diseases worldwide,[1,2] affecting approximately 30% of adults.[3] Accumulating evidence links NAFLD with extrahepatic diseases, such as cardiovascular disease,[4] diabetes,[5,6] and stroke.[7] Based on the definition of NAFLD, an international panel of hepatologists from 22 countries proposed metabolic dysfunction-associated fatty liver disease (MAFLD) as a new term in 2019 to emphasize the indispensable role of metabolic dysfunction in causes, progression, and outcome of fatty liver disease.[8] The pathogenesis of MAFLD involves a multitude of interlinked processes, such as insulin resistance, lipotoxicity, and infiltration of proinflammatory cells,[9] which increase the risk of extrahepatic complications, including chronic kid-

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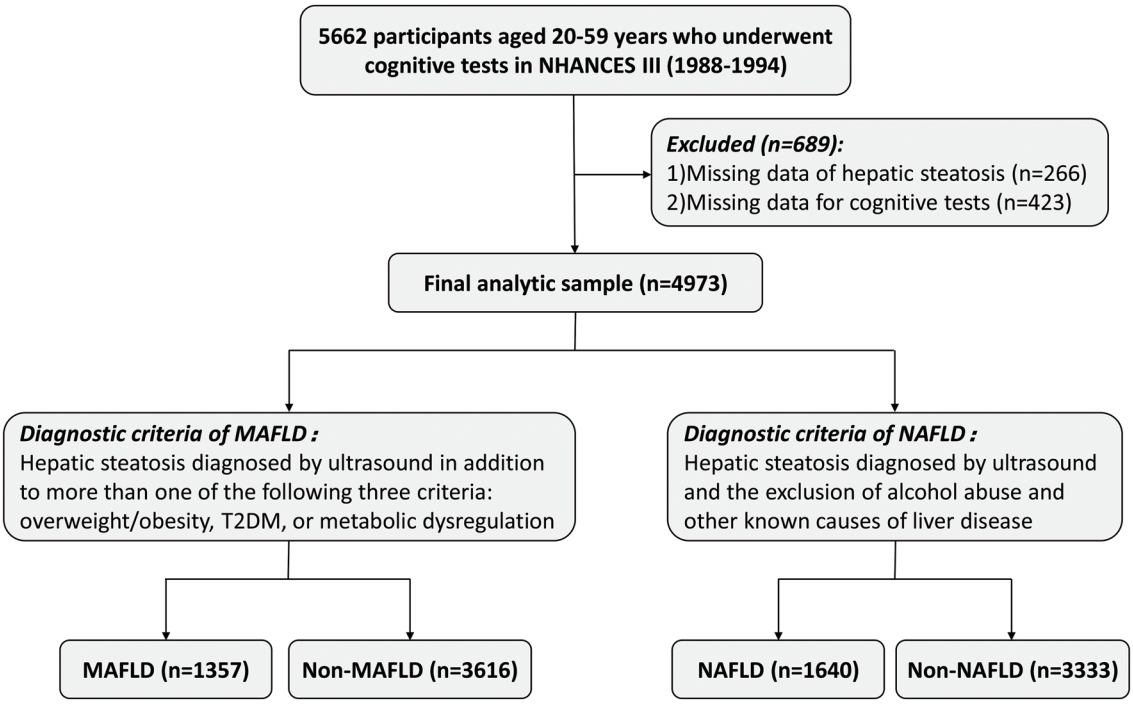

Fig. 1. Flow chart of NHANES III participant selection. MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; NHANES III, third National Health and Nutrition Examination Survey; T2DM, type 2 diabetes mellitus.

ney disease[10] and cardiovascular diseases.[11] Recent studies indicated that the definition of MAFLD was more appropriate than NAFLD for assessment of risks of liver disease progression,[12] but whether MAFLD definition was superior to the old definition with regard to evaluation of extra-hepatic disease risks remains unclear.

The number of people living with dementia worldwide in 2015 was estimated at 47.47 million, and is expected to reach 135.46 million by 2050.[13] Observational studies reported that NAFLD patients exhibited impaired executive function, abstract reasoning, and global cognitive function, especially those with high risks of hepatic fibrosis.[14,15] This might be attributed to systemic inflammation, vascular dysfunction, and impaired urea cycle function related to NAFLD.[14] However, evidence regarding the risks of cognitive impairment in key domains associated with MAFLD status has never been reported. Furthermore, whether the severity of liver steatosis, the probability of fibrosis or glucose metabolic status could modify the associations between MAFLD and cognitive function warrants explorations.

Therefore, taking advantage of the National Health and Nutrition Examination Survey (NHANES), a nationally representative sample of adults in the USA, we investigated the correlations of MAFLD status with cognitive functions in key domains and whether they were driven by the degree of liver fibrosis, liver steatosis, and hyperglycemia.

Methods

Study population

NHANES is an ongoing national cross-sectional survey to assess nutritional and health status of civilians in the USA. The survey is performed by the National Center for Health Statistics (https://www.cdc.gov/nchs/nhanes/index.htm) and has a complex, multistage, stratified sampling design that provides nationally representative data. A group of 5,662 participants 20–59 years of age who underwent cognitive tests in the Third National Health and Nutrition Examination Survey (NHANES-III) were included in this study. The study sample was selected from households in 81 counties across the USA. The survey period was 1988–1994, and consisted of two phases of equal length and sample size. Both Phase 1 (conducted in 1988–1991) and Phase 2 (conducted in 1991–1994) were random samples of a population living in households in the USA.[16] As summarized in Figure 1, participants with missing data of hepatic steatosis assessment (n=266) or cognitive tests (n=423) were excluded. As a consequence, 4,973 samples were included in the final analysis. The National Center for Health Statistics ethics review board reviewed and approved the survey and the NHANES participants gave informed consent prior to enrolment.

Data collection and definition

Demographic statistics and clinical data were collected in the in-home interviews by experienced interviewers. Categorical variables included sex (male and female), ethnicity (non-Hispanic, Mexican-American, other Hispanic), education (less than ninth grade and more than ninth grade), and history of stroke (yes and no).

Plasma glucose, serum low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglycerides (TG) were measured with a Hitachi 704 Analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN, USA). Alanine aminotransferase (ALT), aspartate aminotransferase (AST) were measured with a Hitachi 737 Analyzer (Boehringer Mannheim Diagnostics).[17] In this study, the presence of diabetes was defined as fasting plasma glucose (FPG) ≥ 7.0 mmol/L, 2 h

post-load glucose (2 h PG) ≥11.1 mmol/L, glycated hemoglobin (HbA_{1c}) ≥6.5%, or under oral hypoglycemic agent or insulin treatment.[18] Prediabetes was defined as a FPG of 5.6–6.9 mmol/L, 2 h plasma glucose 7.8–11 mmol/L or HbA_{1c} 5.7–6.4%.[19] The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as fasting glucose (mmol/L) × plasma insulin (μIU/mL)/22.5 and used as surrogate measurement of insulin resistance.[20]

Height, weight, waist circumference (WC), and blood pressure (BP) were measured by trained examiners. BP was tested after resting for more than 5 m. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were tested three consecutive times and the average was used in the analysis. A body mass index (BMI, kg/m^2) of >25 kg/m^2 was considered overweight and >30 kg/m was considered obese.[2,21]

Cognitive function

Three computerized tests from the Neurobehavioral Evaluation System 2 were used to evaluate cognitive function, the serial digit learning test (SDLT), the simple reaction time test (SRTT) and the symbol digit substitution test (SDST).[22,23] All cognitive tests were administered by trained examiners in either English or Spanish. The SDLT is a comprehensive measurement of learning ability, short-term memory, and concentration. Participants were shown sequences of eight Arabic numbers and were asked to type the entire sequence on the keyboard in the order in which it was presented. The test was over when participant completed a total of eight trials or correctly completed two consecutive trials, with the final output scored as the sum of errors.[22–24] The SRTT evaluates visual-motor speed and response time. Participants were asked to press a button as soon as they could when they saw a square in the screen. The test was repeated 50 times, and the average reaction time of the last 40 trials was calculated and reported as the SRTT score. Reaction times of <50 milliseconds or >750 milliseconds and trials repeated <20 times were invalid according to the NHANES III instructions.[24] The SDST assesses processing speed and visual attention. In this test, the digits one to nine were matched to different symbols. Participants were required to match the numbers and the symbols as quickly as possible. Four trials were conducted with different pairings of digits and symbols. The mean seconds per correct digit for each trial was calculated as the SDST result.[22–24] Higher scores indicated worse cognitive performance. Cognitive impairment was defined as the highest quartile of test scores (SDLT ≥6, SRTT ≥247 and SDST ≥13).

MAFLD and NAFLD definitions

Hepatic ultrasonography was performed with a Toshiba SSA-90 A (Tustin, CA) machine using a 3.75 and 5.0 MHz transduces.[25] Degree of hepatic steatosis was determined with a standard algorithm as none, mild, moderate, and severe.[25] NAFLD was defined as hepatic steatosis detected by ultrasound in the absence of alcohol abuse (≥2 drinks per day for men and ≥1 drink per day for women),[26,27] hepatitis B and hepatitis C.[28,29] The diagnostic criteria of MAFLD[30] included hepatic steatosis in addition to more than one of the following three criteria: overweight or obesity, type 2 diabetes mellitus (T2DM), and metabolic dysregulation. Metabolic dysregulation met more than two of (1) waist circumference (WC) ≥102 cm for men or 88 cm for women, (2) SBP ≥130 or DBP ≥85 mmHg or using antihypertensive medications; (3) plasma triglycerides ≥1.7 mmol/L or prescribed antilipemic medications, (4) plasma HDL-C <1 mmol/L or <1.3 mmol/L for men or women or used of prescribed medications, (5) prediabetes, (6) HOMA-IR ≥2.5, or (7) plasma high-sensitivity C-reactive protein level >2 mg/L.

Non-metabolic dysfunction NAFLD (non-MD-NAFLD) referred to participants who were diagnosed with NAFLD but did not meet the MAFLD criteria. NAFLD with metabolic dysfunction (MD) was defined as those participants who meet the criteria of both NAFLD and MAFLD.[12] The presence of liver fibrosis was estimated by the NAFLD fibrosis score (NFS),[31] which was calculated as −1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × impaired fasting glucose/diabetes (yes =1, no =0) + 0.99 × AST/ALT ratio − 0.013 × platelet count (×10^9/L) − 0.66 × albumin (g/dL). A NFS ≤1.455 indicated a low probability of liver fibrosis; as NFS >1.455 indicated a higher probability of liver fibrosis.

Statistical analysis

Statistical analysis was performed using STATA 11.0, R 4.0.3 and took into consideration the complex sampling design in NHANES, including calculation of baseline weight, adjustment for nonresponse and over sampling of target populations. Weighted means with standard deviations of normally distributed variables, medians with 25th–75th percentiles of skewed distributed variables and percentages with 95% confidence intervals (CIs) of categorical data. We performed *t*-tests for continuous data and design-based χ^2 tests for categorical data to determine statistical difference between characteristics of participants with normal and low scores in each cognitive test. ALT, AST, and HOMA-IR were log-transformed before statistical comparisons owing to their nonnormal, positively-skewed distributions. To evaluate the associations of MAFLD or NAFLD status with the risks of cognitive impairment, we conducted multivariate logistic regression analysis. Model 1 was unadjusted, and model 2 was adjusted for sex, age, ethnicity, education level, and history of stroke.

Results

Population characteristics

Table 1 shows the characteristics of the 4,973 participants by MAFLD and NAFLD status. Participants with MAFLD or NAFLD were significantly older. Differences were also observed in constituent ratios of race and educational level between MAFLD participants and non-MAFLD participants, and between NAFLD participants and non-NAFLD participants. As for their physical conditions, participants with MAFLD or NAFLD were more likely to be overweight, have diabetes or prediabetes, hypertension, higher WC, lower HDL-C level, and more severe insulin resistance.

Risk of cognitive impairment according to MAFLD status

As shown in Table 2, significant associations between MAFLD and risk of cognitive impairment based on SDLT (OR 1.55, 95% CI: 1.22–1.98), SRTT (OR 1.55, 95% CI: 1.24–1.94), and SDST (OR 1.71, 95% CI: 1.36–2.15) were observed, and the associations remained robust for SRTT after adjusting for sex, age, ethnicity, education level, and history of stroke (OR 1.47, 95% CI: 1.14–1.89). It is worth mentioning that the odds of cognitive impairment assessed by SDLT (OR 1.37, 95% CI: 1.04–1.82) and SDST (OR 1.55, 95% CI: 1.19–2.02) increased significantly in MAFLD patients

Table 1. Characteristics of the study population by MAFLD and NAFLD status

	MAFLD	Non-MAFLD	*p*	NAFLD	Non-NAFLD	*p*
Patients, *n*	1,357	3,616		1,640	3,333	
Weighted percentage, %	23.4	76.6		29.9	70.1	
Age, years	41.26±10.94	35.86±10.30	<0.001	39.10±11.11	36.28±10.43	<0.001
Male, %	56.3 (51.9–60.8)	47.2 (45.4–49.1)	<0.001	52.1 (47.8–56.3)	47.9 (43.7–52.2)	0.154
Ethnicity						
Non-Hispanic, %	86.2 (83.0–89.4)	91.5 (89.8–93.2)	0.002	87.5 (84.8–90.2)	91.5 (89.8–93.2)	0.009
Mexican-American, %	9.1 (6.7–11.4)	4.8 (3.8–5.9)		8.0 (5.6–10.2)	4.9 (2.5–4.7)	
Other Hispanic, %	4.7 (2.4–7.1)	3.6 (2.5–4.7)		4.5 (25.7–6.5)	3.6 (2.5–4.7)	
Education level						
<9 years, %	14.7	9.8	0.002	12.3	10.1	0.050
History of stroke, %	0.51	0.74	0.58	0.66	0.52	0.72
BMI, kg/m^2	31.33±7.17	25.0±4.63	<0.001	28.96±7.59	25.46±4.75	<0.001
Diabetes, %	13.0 (9.5–16.6)	3.1 (2.3–4.0)	<0.001	9.9 (6.9–12.8)	3.6 (2.6–4.5)	<0.001
Prediabetes, %	44.0 (38.2–49.8)	19.5 (16.7–22.0)	<0.001	34.9 (30.2–39.6)	21.1 (18.4–23.8)	<0.001
Hypertension, %	43.0 (37.5–48.5)	17.9 (15.9–20.0)	<0.001	33.1 (28.1–38.0)	19.8 (17.5–22.1)	<0.001
Hyperlipemia, %	38.1 (31.5–44.8)	14.8 (11.6–17.9)	<0.001	29.7 (24.1–35.2)	16.2 (12.8–19.6)	<0.001
Waist circumference, cm	103.4±16.2	86.8±12.2	<0.001	96.95±18.61	88.06±12.33	<0.001
HDL-C, mmol/L	1.16±0.38	1.35±0.37	<0.001	1.23±0.41	1.34±0.38	<0.001
HOMA-IR	3.15 (2.15–5.08)	1.61 (1.19–2.38)	<0.001	2.79 (1.83–4.78)	1.66 (1.23–2.50)	<0.001
AST, IU/L	21 (17–26)	18 (16–22)	<0.001	20 (17–25)	18 (16–22)	<0.001
ALT, IU/L	20 (14–29)	21 (17–26)	<0.001	18 (12–27)	14 (10–19)	<0.001
Albumin, g/dL	41.69±4.02	42.45±3.60	<0.001	41.99±3.66	42.39±3.66	0.073
Platelet count, ×10^9/L	277.32±76.97	271.60±63.94	0.163	275.13±75.26	272.01±63.52	0.378
NFS >−1.455, %	26.1 (21.7–30.2)	12.4 (10.3–14.5)	<0.001	20.5 (17.2–23.8)	13.5 (11.1–15.9)	<0.001

Data are means ± standard deviation for normally distributed variables, median (25th–75th percentile) for variables with skewed distributions, and weighted percentages for categorical variables. *t*-tests for continuous data and design-based χ^2 tests for categorical data. MAFLD vs. non-MAFLD or NAFLD or non-NAFLD. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-estimated insulin resistance MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; NFS, nonalcoholic fatty liver disease fibrosis score.

with moderate-severe liver steatosis, compared with those without hepatic steatosis even after adjusting for the aforementioned covariables.

Risks of cognitive impairment by NAFLD status

As shown in Table 3, NAFLD with MD was significantly associated with high risk of poor performance in the SDLT (OR 1.59, 95% CI: 1.24–2.03), SRTT (OR 1.49, 95% CI: 1.19–1.87), and SDST (OR 1.68, 95% CI: 1.34–2.10), but the fully adjusted risks models were only significant for SRTT (OR 1.44, 95% CI: 1.10–1.82).It is worth mentioning that, there was no significance difference between participants with NAFLD but without metabolic dysfunction and participants without fatty liver regarding the risks of cognitive impairment.

Risk of cognitive impairment by probability of fibrosis in MAFLD participants

After adjusting for aforementioned covariables, we observed that MAFLD with high probability of fibrosis was associated with significantly higher risks of cognitive impairment as assessed by the SRTT (OR 1.81, 95% CI: 1.19–2.76) and SDST (OR 1.67, 95% CI: 1.17–2.37), compared with MAFLD and a low probability of fibrosis. (Fig. 2)

Risk of cognitive impairment by glucose metabolic status in MAFLD participants

Glucose metabolic status was categorized as normal, prediabetes, and diabetes. Compared with MAFLD patients with normal glycemia, patients with prediabetes had a two-fold risk of developing cognitive impairment based on the SDST score (OR 2.01, 95% CI: 1.37–2.96). Moreover, the ORs of impaired performance in the SDST was nearly tripled in MAFLD with diabetes, compared with MAFLD patients with normal glycemic metabolism (OR 2.87, 95% CI: 1.44–5.74, Fig. 3).

Discussion

To the best of our knowledge, this is the first comprehensive

Table 2. Risk of cognitive impairment by to MAFLD status

	Model 1 (OR and 95% CI)	*p*	Model 2 (OR and 95% CI)	*p*
SDLT ≥ 6 (Q4)				
No fatty liver (*n*=3,153)	Reference		Reference	
MAFLD	1.55 (1.22–1.98)	0.001	1.18	0.193
MAFLD with mild hepatic steatosis (*n*=421)	1.12 (0.81–1.54)	0.485	0.88 (0.62–1.26)	0.487
MAFLD with moderate-to-severe hepatic steatosis(*n*=867)	1.81 (1.38–2.37)	<0.001	1.37 (1.04–1.82)*	0.026
SRTT ≥ 247 (Q4)				
No fatty liver (*n*=3,253)	Reference		Reference	
MAFLD (*n*=1,346)	1.55 (1.24–1.94)	<0.001	1.47 (1.14–1.89)	0.004
MAFLD with mild hepatic steatosis (*n*=439)	1.30 (0.87–1.96)	0.197	1.24 (0.83–1.87)	0.289
MAFLD with moderate-to-severe hepatic steatosis (*n*=907)	1.64 (1.32–2.04)	<0.001	1.55 (1.19–2.02)	0.002
SDST ≥13 (Q4)				
No fatty liver (*n*=3,223)	Reference		Reference	
MAFLD (*n*=1,335)	1.71 (1.36–2.15)	<0.001	1.06 (0.82–1.37)	0.668
MAFLD with mild hepatic steatosis (*n*=437)	1.42 (1.03–1.96)	0.031	1.00 (0.68–1.47)	0.990
MAFLD with moderate-to-severe hepatic steatosis (*n*=898)	1.80 (1.30–2.49)	0.001	1.10 (0.77–1.56)	0.593

Model 1 was univariate; Model 2 adjusted for sex, age, ethnicity, education level, and history of stroke. CI, confidence interval; MAFLD, metabolic dysfunction-associated fatty liver disease; OR, odds ratio; Q4, fourth quartile; SDLT, the serial digit learning test; SDST, the symbol digit substitution test; SRTT, the simple reaction time test.

study to determine the association of MAFLD with domain-specific cognitive function among US adults. MAFLD was associated with an increased risk of impaired visual-motor speed and response time evaluated by the SRTT. MAFLD with moderate-severe liver steatosis was also associated with poorer performance on the SDLT and SRTT tests assessing learning ability, short-term memory, and concentration. Moreover, among MAFLD patients, high probabilities of fibrosis and abnormal glycemic metabolism were associated with worse processing speed and visual attention based on SDST scores. NAFLD without metabolic dysfunction was not associated with cognitive impairment.

Studies addressing associations between NAFLD and cognitive function are limited. One study reported that NAFLD was not independently associated with cognitive function, whereas NAFLD patients with a high risk of liver fibrosis, had worse executive function and abstract reasoning than those with a low risk.[8] Similarly, another cross-sectional

Table 3. Risks of cognitive impairment according to NAFLD status

	Model 1 (OR and 95% CI)	*p*	Model 2 (OR and 95% CI)	*p*
SDLT ≥ 6 (Q4)				
Non-NAFLD (*n*=3,168)	Reference		Reference	
Non-MD-NAFLD (*n*=330)	0.90 (0.61–1.31)	0.566	1.06 (0.71–1.58)	0.756
NAFLD with MD (*n*=1,233)	1.59 (1.24–2.03)	<0.001	1.20 (0.95–1.57)	0.119
SRTT ≥ 247 (Q4)				
Non-NAFLD (*n*=3,270)	Reference		Reference	
Non-MD-NAFLD (*n*=342)	0.78 (0.51–1.21)	0.268	0.79 (0.52–1.21)	0.279
NAFLD with MD (*n*=1,305)	1.49 (1.19–1.87)	0.001	1.44 (1.10–1.82)	0.008
SDST ≥13 (Q4)				
Non-NAFLD (*n*=3,240)	Reference		Reference	
Non-MD-NAFLD (*n*=339)	0.70 (0.44–1.10)	0.120	0.99 (0.58–1.69)	0.98
NAFLD with MD (*n*=1,293)	1.68 (1.34–2.10)	<0.001	1.06 (0.82–1.37)	0.634

Model 1 was univariate; Model 2 adjusted for sex, age, ethnicity, education level, and history of stroke. CI, confidence interval; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD with MD, metabolic dysfunction-associated nonalcoholic fatty liver disease; non-MD-NAFLD, non-metabolic dysfunction-associated nonalcoholic fatty liver disease; OR, odds ratio; Q4, fourth quartile; SDLT, serial digit learning test; SDST, symbol digit substitution test; SRTT, the simple reaction time test.

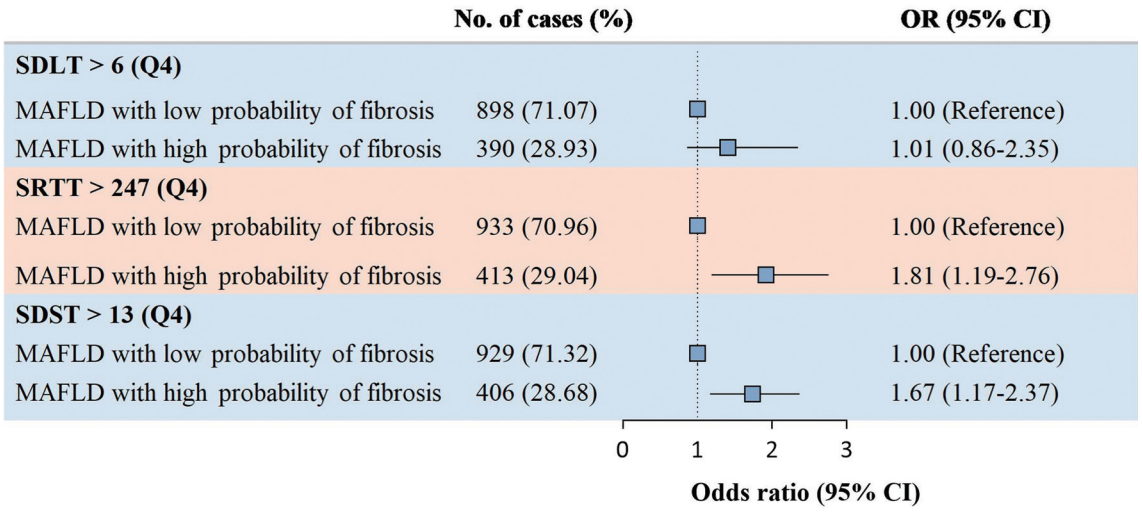

Fig. 2. Risk of cognitive impairment by probability of fibrosis in participants with MAFLD. Logistic regression models were used to generate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) to estimate the risk of cognitive impairment adjusted for sex, age, ethnicity, education level, and history of stroke. MAFLD, metabolic dysfunction-associated fatty liver disease; Q4, fourth quartile; SDLT, the serial digit learning test; SDST, the symbol digit substitution test; SRTT, the simple reaction time test.

study reported that NAFLD alone was not associated with cognition, but NAFLD combined with T2DM was significantly associated with impaired visuospatial function.[32] The results are in line with our findings that only NAFLD with metabolic dysfunction, but non-MD-NAFLD, was significantly associated with cognitive impairment, whereas MAFLD was independently associated with cognitive function, indicating the key role of metabolic dysfunction in the outcomes of fatty liver diseases. Hence, our study supports the emphasis of the new MAFLD definition that metabolic dysfunction is the core element together with accumulation of liver fat.[8]

MAFLD has been shown to be correlated with various extrahepatic diseases, such as CKD[10] and cardiovascular disease.[33] Our study contributes new knowledge that MAFLD is correlated with neurodegenerative diseases, making it a multisystem disease that warrants further exploration and attention. In addition to the comparison between MAFLD and non-MAFLD individuals, current evidence indicates the effect of MAFLD severity on various health outcomes. For example, the severity of MAFLD evaluated by fibrosis scores had a graded association with the risk of CKD.[10] A previous cross-sectional study reported that hepatic fibrosis was independently associated with coronary artery calcification in NAFLD patients.[34] Inflammation was one of the most important process promoting the development of cognitive impairment.[35,36] MAFLD accelerated cognitive decline through

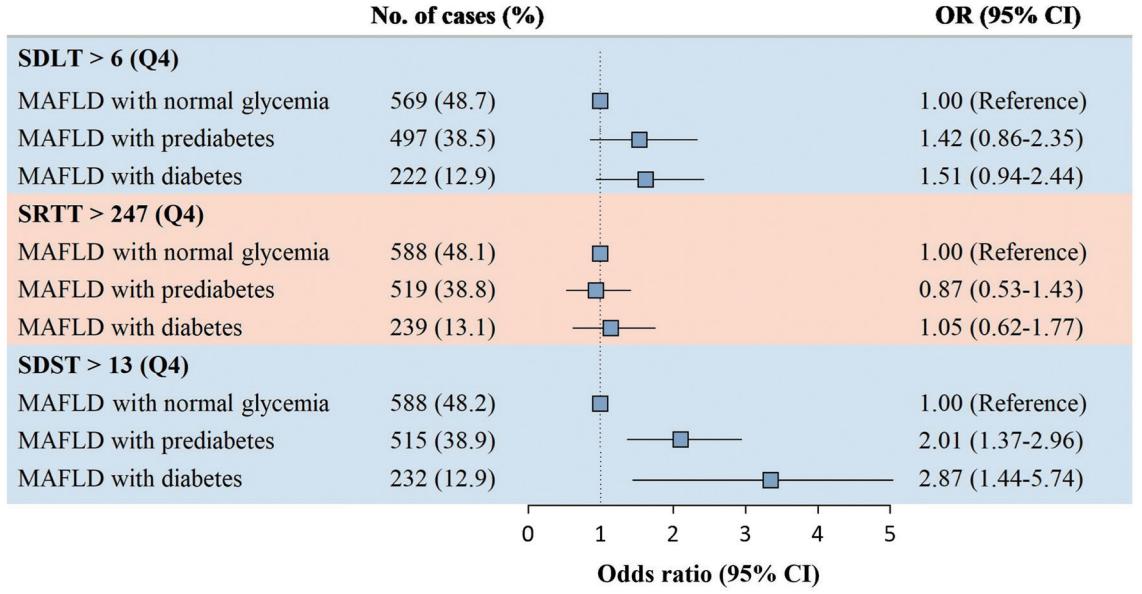

Fig. 3. Risk of cognitive impairment according to glucose metabolic status among MAFLD participants. Logistic regression models were used to generate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) to estimate the risk of cognitive impairment, adjusted for sex, age, ethnicity, education level, and history of stroke; MAFLD, metabolic dysfunction-associated fatty liver disease; Q4, fourth quartile; SDLT, serial digit learning test; SDST, the symbol digit substitution test; SRTT, simple reaction time test.

chronic inflammation caused by imbalance of cytokines and adipokines.[37] Hepatic fibrosis and fat accumulation may have mediating roles.[38,39]

In the context of the previous findings, our study demonstrated that degrees of liver steatosis and probability of liver fibrosis was associated with cognition, stressing the important role of MAFLD severity as a strong risk factor for multiple health conditions. As diabetes is a key element in the pathogenesis of MAFLD,[8] we extended the knowledge by adding glucose metabolic status as the stratified variable. We found that both prediabetes and diabetes were significantly associated with increased risk of impaired processing speed and attention in MAFLD patients. The findings highlighted the importance of monitoring and management of glycemic status, even at a relatively early stage of glucose metabolic abnormalities.

The primary strengths of the study are a nationally representative sample, comprehensive measurements of liver steatosis, liver fibrosis, and cognitive functions in multiple domains. However, the study does have some limitations. Firstly, owing to the cross-sectional design of our data, a causal relation cannot be established between MAFLD and cognitive function. Secondly, the study population was restricted to individuals between 20 and 59 years of age, so the external validity for elder populations is uncertain. Further, ultrasound and NFS scores are widely used noninvasive standard procedure. Nonetheless, liver biopsy (the gold standard technique) is an invasive procedure that is not well suited for large population studies. Moreover, since only participants of NHANES III, rather than other NHANES cycles, received both hepatic ultrasound and cognitive tests, we performed the analysis using data derived from NHANES III. However, NHANES III was conducted in 1988–1994 and the population characteristics may be different from that of current population. Lastly, although our study provided epidemiological evidence supporting the association between MAFLD and cognitive impairment, biomedical studies are needed to further explore the pathological mechanism underlying the association.

In conclusion, our nationwide cross-sectional study showed that MAFLD was associated with cognitive impairment, and the presence of advanced fibrosis and glucose abnormalities were linked with cognitive impairment in MAFLD patients, Awareness of the associations is important for clinicians, as liver-focused treatments may reduce the risk of extrahepatic complications. Moreover, our findings suggest that management of dementia risk factors and screening for cognitive impairment should be added into the routine management of patients with MAFLD.

Funding

This work was supported by National Natural Science Foundation of China (Grant No. 32000525) and Shanghai Municipal Science and Technology Major Project (Grant No. TM202101H011).

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conception and design (QY, RH, HY, QX), data collecting (QY, RH, HJ, JW, ZX, KH, data analysis (QY, RH, HJ, JW), data interpretation (ZX, KH, YL, TZ, MF, PW, QX), manuscript drafting and revising (QY, RH, HJ, JW, ZX, KH, YL, TZ, MF, PW, HY, QX).

Ethical statement

This study was carried out in accordance with the recommendations of the Institutional Review Board of the Center for Disease Control and Prevention. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Data sharing statement

The datasets presented in this study can be found in online repositories (https://wwwn.cdc.gov/nchs/nhanes/Nhanes3/datafiles.aspx#core).

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