Nonalcoholic fatty liver disease is associated with cognitive function in adults

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ABSTRACT

Objective: We hypothesized that nonalcoholic fatty liver disease (NAFLD) is independently associated with cognitive impairment in a representative sample of the general US population regardless of the presence of cardiovascular disease (CVD) or its risk factors.

Methods: This was a cross-sectional study of 4,472 adults aged 20–59 years who participated in the Third National Health and Nutritional Examination Survey. The participants underwent assessment of liver enzyme activity and hepatic steatosis by ultrasound, and underwent cognitive evaluation using the following computer-administered tests: the Simple Reaction Time Test (SRTT), the Symbol-Digit Substitution Test (SDST), and the Serial Digit Learning Test (SDLT). We defined NAFLD as moderate/severe steatosis as determined by ultrasound in the absence of hepatitis B or C or excessive alcohol consumption. We used multiple linear regression models to examine the association between NAFLD and cognitive function while controlling for potential confounders.

Results: Participants with NAFLD showed lower overall performance on the SDLT (β = 0.726, 95% confidence interval [CI] 0.105–1.347), while associations with SRTT and SDST did not reach significance. Increased activity of the liver enzymes alanine aminotransferase (β = 0.018, 95% CI 0.006–0.030) and aspartate aminotransferase (β = 0.021, 95% CI 0.005–0.037) correlated with lower performance on the SDLT, while increased alanine aminotransferase was also correlated with lower performance in the SDST (β = 0.002, 95% CI 0.0001–0.004).

Conclusions: NAFLD was independently associated with lower cognitive performance independent of CVD and its risk factors. Given the scarcity of risk factors associated with age-related cognitive decline, these findings may have significant implications. ***Neurology*® 2016;86:1136–1142**

GLOSSARY

AD = Alzheimer disease; **ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **BMI** = body mass index; **CI** = confidence interval; **CVD** = cardiovascular disease; **MI** = myocardial infarction; **NAFLD** = nonalcoholic fatty liver disease; **NASH** = nonalcoholic steatohepatitis; **NCHS** = National Center for Health Statistics; **NHANES III** = Third National Health and Nutrition Examination Survey; **SDLT** = Serial Digit Learning Test; **SDST** = Symbol Digit Substitution Test; **SRTT** = Simple Reaction Time Test.

In the United States and globally, nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease.[1,2] By definition, NAFLD occurs in the absence of excessive alcohol consumption,[3] and is associated with cardiovascular disease (CVD) and its risk factors including type 2 diabetes, obesity, hyperlipidemia, and hypertension.[4,5] Such risk factors are known to contribute to cognitive impairment with or without the mediation of CVD.[6,7] Furthermore, considering findings from previous studies suggesting that NAFLD could be an independent CVD risk factor,[8] it appears reasonable to hypothesize that NAFLD is independently associated

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with cognitive impairment. To our knowledge, the relationship between NAFLD and cognitive impairment has not been investigated previously.

In the current study, we analyzed data from the Third National Health and Nutrition Examination Survey (NHANES III), covering a representative sample of the general US population. Our aim was to investigate the relationships between NAFLD determined by ultrasonography and cognitive impairment as assessed by 3 computerized tests. As a secondary objective, we investigated the relationships between liver enzyme activity, another common surrogate marker of inflammatory NAFLD, and cognitive impairment.

METHODS

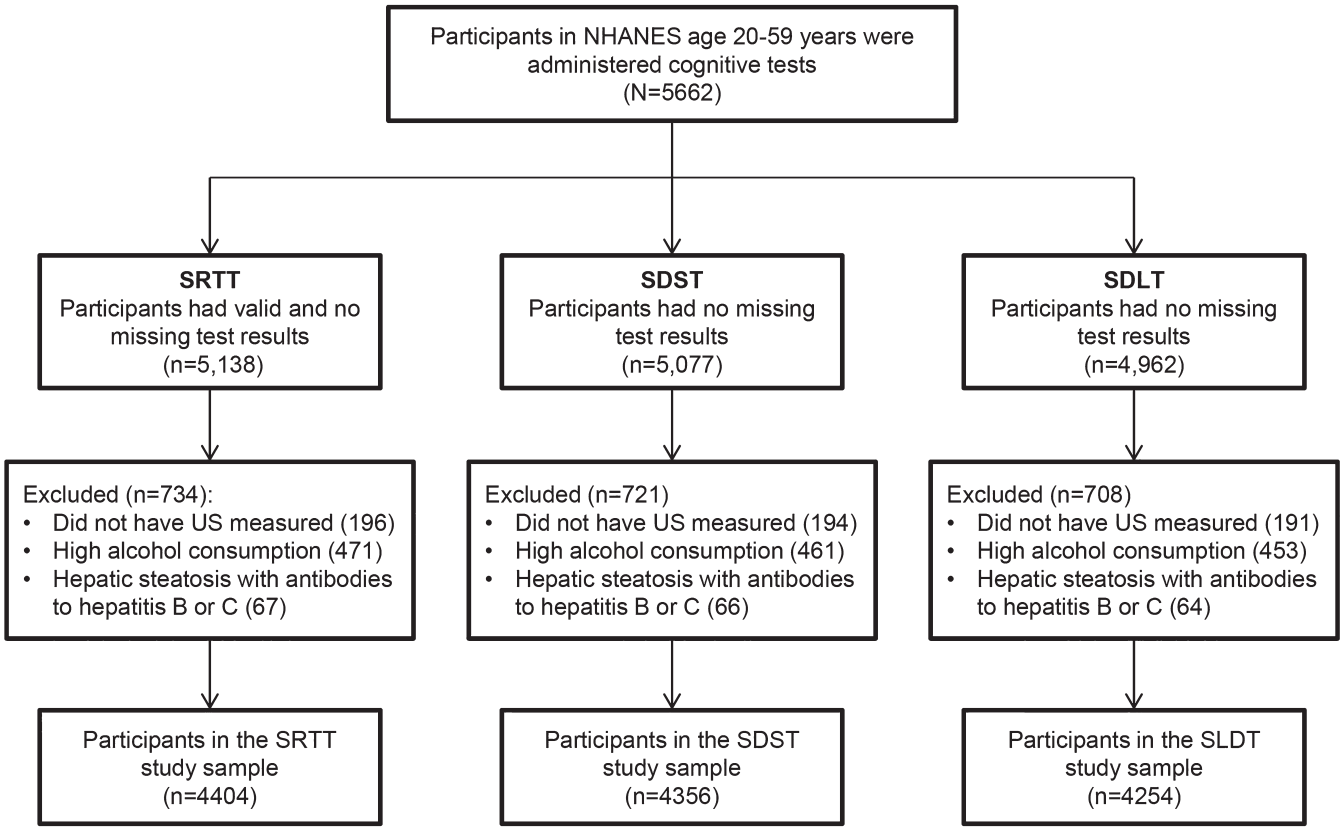
Participants. NHANES III was conducted in the United States between 1988 and 1994 and represents a complex, multistage, clustered, stratified, probability-sampled survey undertaken by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention. NHANES III was designed to obtain a representative sample of the US population living in households.[9,10]

Standard protocol approvals, registrations, and patient consents. All participants were required to provide signed informed consent. The Institutional Review Board of NCHS approved NHANES III.

Cognitive function testing and definition of outcomes. The evaluation of cognitive function was conducted for a random half-sample of NHANES III examinees between 20 and 59 years old who participated in the physical examination conducted at the mobile examination center (n = 5,662; figure). Individuals with survey identification numbers that were odd-numbered received cognitive tests, with the exclusion of those who were unable to speak English or Spanish, as well as those determined to be legally blind.[11]

To evaluate cognitive function, 3 computerized tests were used. The tests used were taken from the Neurobehavioral Evaluation System 2, developed by Baker and Letz,[12,13] and have been used frequently in epidemiologic studies. Further details of the protocol have been published previously.[14] All cognitive tests were conducted with a standardized protocol by trained technicians in either English or Spanish. A practice phase preceded each test. The Simple Reaction Time Test (SRTT) assesses response time, or visual-motor speed, with an output measured in milliseconds. The test involves an "a" appearing in the center of a blank computer monitor, after which the participants are instructed to press a button as fast as possible. The output for the SRTT was the average reaction time, with 50 trials conducted in total and results from the first 10 trials excluded. Reaction times that were ≥750 or ≤50 milliseconds, or individuals who had mean scores involving <20 trials, were determined by NHANES III to be invalid.[11]

Figure Details of the study sample used for cognitive testing



NHANES = Third National Health and Nutrition Examination Survey; SDLT = Serial Digit Learning Test; SDST = Symbol Digit Substitution Test; SRTT = Simple Reaction Time Test; US = ultrasonography.

The Symbol Digit Substitution Test (SDST) involves a set of 9 symbols matched to the digits 1 to 9 and is designed to assess visual attention and coding ability. A series of symbols are shown to the participant, who is required to match the symbol with the correct corresponding digit as fast as possible. Different pairings of digits and symbols were used over 4 trials, with the final output scored as the average total time for overall completion, in seconds.[11–13] The Serial Digit Learning Test (SDLT) displays a digital series on a computer screen, and is designed to test learning, recall, and concentration. Participants were requested to enter the full sequence on a keyboard from memory. With the exception of a practice trial, all tests used the same 8-digit sequence. When each participant responded correctly for 2 consecutive trials or after 8 trials in total were completed, testing ceased, and the sequence of digits entered was recorded. The output of the SDLT is the sum of the errors entered by the participants during the test.[11–13]

Assessment of NAFLD and liver enzymes. NHANES III participants underwent gallbladder examination by ultrasound with a Toshiba SSA-90A (Tustin, CA) machine with a 3.75 and 5.0 MHz transducer.[15] Further details of the protocol have been described previously.[16,17] Data concerning the presence of kidney to liver contrast, echogenic walls within the small intrahepatic vessels and deep beam attenuation, as well as the brightness of the liver parenchyma, and definition of the gallbladder walls was obtained. These data were processed using a standardized algorithm in order to categorize the extent of steatosis initially as a 4-level classification (none, mild, moderate, or severe steatosis) and then as a 2-level classification: none to mild or moderate to severe. The intrarater and interrater κ statistics for the reliability of the 2-level variable have been determined to be 0.77 (95% confidence interval [CI] 0.73–0.82) and 0.70 (0.64–0.76), respectively.[17]

Liver enzymes including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were assayed with a Hitachi 737 automated multichannel chemistry analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). Further details of the assays and quality control procedures have been described previously.[18]

Covariates. Standardized questionnaires were conducted with all participants and included data for age, sex, race/ethnicity, income, education, alcohol consumption, smoking, prevalent medical conditions, drug use, and physical activity.[19] An average daily estimate for alcohol consumption was obtained by multiplying the number of drinks on an average drinking day by the number of drinking days reported over the past 12 months and dividing the result by 365. Never drinkers were those who answered no to the following question: "In your entire life, have you had at least 12 drinks of any kind of alcoholic beverage?" Increased alcohol consumption was categorized as 1 or more drinks per day for women or 2 or more drinks per day for men.[20]

Standardized measurements of weight, waist circumference, height, and systolic/diastolic blood pressure were obtained, with body mass index (BMI) calculated. A history of CVD was self-reported as a history of heart failure, acute myocardial infarction (MI), or stroke. A second-generation enzyme immunoassay (Abbott Laboratories, Chicago, IL) was used to detect the presence of hepatitis C antibodies, and confirmed by MATRIX assay (Abbott Laboratories), while a solid phase competitive immunoassay (Abbott Laboratories) was used to detect antibodies to the hepatitis B core antigen.

NAFLD was defined as moderate/severe steatosis as determined by ultrasound in the absence of elevated alcohol consumption (≥1 drink per day for women and ≥2 drinks per day for men) as previously described[21,22] and in the absence of a positive test for viral hepatitis B or hepatitis C.

Statistical analysis. Statistical analysis was conducted using SAS, version 9.2, PROC SURVEY procedures (SAS Institute, Inc., Cary, NC) and took into consideration the complex sampling design used by NHANES. Specifically, these include strata, cluster, and weight statements, which account for the unequal probability of selection from the survey cluster design, adjustments for nonresponse and oversampling of target populations, and adjustments to independent population controls. The baseline characteristics of the participants by NAFLD status were compared using PROC SURVEYFREQ for categorical variables or PROC SURVEYMEANS for continuous variables. In the PROC SURVEYFREQ, we used the Rao-Scott χ^2 test to test for differences in categorical variables and the Wald F test in the PROC SURVEYREG to test for differences in continuous variables.

In order to evaluate the relationship between NAFLD and cognitive impairment, we performed multivariate linear regression analysis (SAS PROC SURVEYREG). In model 1, we adjusted for sex, age, race, and education, and in model 2, we further adjusted for BMI, waist circumference, hypertension, diabetes mellitus, hypercholesterolemia, history of acute MI, and stroke.

In a secondary analysis to evaluate the relationships between liver enzymes (as additional surrogate markers for NAFLD) and cognitive test scores, we performed multivariate linear regression analysis using liver enzyme data instead of NAFLD.

RESULTS

Demographics. Table 1 summarizes the characteristics of the participants according to NAFLD status. Of the initial study population (4,472 adult participants from NHANES III), 874 individuals fulfilled the ultrasound definition of NAFLD. Participants with NAFLD were older and more likely to have a higher BMI, higher waist circumference, and higher prevalence of diabetes mellitus, hypertension, hypercholesterolemia, acute MI, and stroke than those without NAFLD.

Association between NAFLD and cognitive function. Compared to participants without NAFLD, participants with NAFLD had lower performances on SRTT, SDST, and SDLT after controlling for age, sex, race, and education (table 2). After further controlling for BMI, waist circumference, hypertension, diabetes mellitus, hypercholesterolemia, acute MI, and stroke (table 2), these results were unchanged for SDLT ($\beta = 0.726$, 95% CI 0.105–1.347) but the associations between NAFLD and SRTT and SDST lost statistical significance (SRTT, $\beta = 6.658$, 95% CI −0.496 to 13.812; SDST, $\beta = 0.101$, 95% CI −0.009 to 0.211).

Association between liver enzyme activity and cognitive function. In model 1, increased liver enzyme activity was correlated with lower performance on the SDST and SDLT (table 3). In model 2, increased liver enzyme activity was correlated with lower

Table 1 Characteristics of the study sample by NAFLD status

	Total participants (n = 4,472)	Participants without NAFLD (n = 3,598)	Participants with NAFLD (n = 874)	*p* Value
Age, y	37.3 (0.3)	36.6 (0.3)	40.9 (0.7)	0.002
Male sex	47.5 (1.0)	46.3 (1.1)	53.7 (2.1)	0.001
Black race	12.0 (0.9)	12.2 (0.9)	10.6 (1.5)	0.307
Education >12 y	45.6 (1.5)	47.8 (1.6)	35.0 (2.8)	<0.001
BMI category				<0.001
<18.5	2.4 (0.4)	2.5 (0.4)	1.9 (0.8)	
18.5–24.9	43.4 (1.5)	48.7 (1.5)	17.0 (1.9)	
25–29.9	31.4 (1.2)	31.1 (1.3)	32.9 (2.8)	
30–34.9	14.0 (0.7)	12.1 (0.7)	23.5 (1.7)	
≥35	8.8 (0.9)	5.6 (0.8)	24.7 (2.3)	
High waist circumference[a]	33.7 (1.3)	27.2 (1.3)	66.1 (2.7)	<0.001
Diabetes mellitus[b]	6.6 (0.6)	5.2 (0.6)	13.6 (1.7)	<0.001
Hypertension[c]	20.7 (1.1)	17.5 (1.0)	36.3 (2.7)	<0.001
Hypercholesterolemia[d]	23.6 (1.0)	22.2 (1.2)	30.4 (2.7)	0.004
Acute MI	1.5 (0.3)	1.2 (0.2)	3.3 (1.2)	0.013
Stroke	0.6 (0.2)	0.5 (0.2)	1.5 (0.7)	0.024
ALT, U/L	18.0 (0.4)	16.5 (0.4)	25.7 (0.9)	<0.001
AST, U/L	20.8 (0.2)	20.0 (0.2)	25.0 (0.8)	<0.001

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; MI = myocardial infarction; NAFLD = nonalcoholic fatty liver disease.
Continuous variables expressed as means (standard error) and categorical variables expressed as percentage (standard error). *p* Values based on Wald F test for continuous variables or Rao-Scott χ^2 test for categorical variables, both of which account for National Health and Nutrition Examination Survey complex multisampling design. Values are expressed as mean (SD) or n (%).
[a] >102 cm (men) and >88 cm (women).
[b] Self-reported doctor diagnosis, drug use, fasting plasma glucose concentration ≥7.0 mmol/L, or random plasma glucose concentration ≥11 mmol/L.
[c] Self-reported doctor diagnosis, drug use, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg.
[d] Self-reported doctor diagnosis, drug use, or total cholesterol concentration >6.2 mmol/L.

performance on the SDLT (ALT, β = 0.018, 95% CI 0.006–0.030; and AST, β = 0.021, 95% CI 0.005–0.037). Increased ALT activity was also correlated with lower performance on the SDST (β = 0.002, 95% CI 0.0001–0.004) (table 3).

Because participants with minimal hepatic encephalopathy might be included in these analyses, we investigated the relationships between NAFLD and cognitive impairments only in participants with no advanced NAFLD fibrosis. We calculated liver fibrosis score because this score can accurately predict the absence of advanced fibrosis in NAFLD.[23] The regression formula (risk score) is as follows:

NAFLD fibrosis score = −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 (×10^9/l) − 0.66 × albumin (g/dL).

We performed further analyses in participants with no advanced NAFLD fibrosis (NAFLD fibrosis score <−1.445).[23] The new results were generally similar with previous results (tables e-1 and e-2).

DISCUSSION This cross-sectional study of a large representative sample of the US population identified an independent association between NAFLD and cognitive function. Our major finding was that NAFLD is independently associated with inferior learning, recall, and concentration function. The magnitude of the association with cognition was modest, but persisted even when CVD and its risk factors (known to affect cognition) were included in models. Furthermore, liver enzyme activity, a surrogate marker for NAFLD, was associated predominantly with lower performance on the SDLT and SDST. Considering the lack of modifiable risk factors for age-related cognitive decline, and the very high prevalence of NAFLD, these findings have important implications for public health.

It remains possible that the association between NAFLD and cognitive impairment is an

Table 2 Association between NAFLD and cognitive function in 4,472 adults aged between 20 and 59 years who participated in the US Third National Health and Nutrition Examination Survey (1988–1994)

	β	SE	95% CI
SRTT			
Model 1	7.827	3.496	0.975 to 14.679
Model 2	6.658	3.650	−0.496 to 13.812
SDST			
Model 1	0.110	0.054	0.004 to 0.216
Model 2	0.101	0.056	−0.009 to 0.211
SDLT			
Model 1	0.880	0.287	0.317 to 1.443
Model 2	0.726	0.317	0.105 to 1.347

Abbreviations: β = unstandardized regression coefficient; CI = confidence interval; NAFLD = nonalcoholic fatty liver disease; SDLT = Serial Digit Learning Test; SDST = Symbol Digit Substitution Test; SRTT = Simple Reaction Time Test.
All results were obtained with consideration for National Health and Nutrition Examination Survey sampling design effects. Model 1 adjusted for age (continuous), sex (male, female), race (white, black), education (≤12, >12 years). Model 2: model 1 + further adjusted for body mass index (<18.5, 18.5–24.9, 25–29.9, 30–34.9, ≥35), waist circumference (>102, ≤102 in men, >88, ≤88 in women), hypertension (yes, no), diabetes mellitus (yes, no), hypercholesterolemia (yes, no), acute myocardial infarction (yes, no), and stroke (yes, no).

epiphenomenon, because cardiovascular risk factors and diseases are related to both NAFLD and cognition. However, in our study, the association with cognition still existed after controlling for these possible confounders. The pathobiology of the relationship between NAFLD and cognitive impairments remains unknown. Insulin resistance might explain the association between NAFLD and cognitive impairment, because insulin resistance plays critical roles in the pathogenesis of NAFLD and Alzheimer disease (AD).[4,24] A preclinical study has suggested that increased insulin resistance induced by exposure to nitrosamine leads to nonalcoholic steatohepatitis (NASH) and AD in rats.[25] Alternatively, NAFLD might affect cognitive impairment via inflammatory processes. Previous studies have shown that expanded and inflamed liver fat, especially in patients with NASH, releases inflammatory cytokines and adipokines, possibly accompanied by abnormal levels of lipoproteins, endothelial dysfunction, and oxidative stress, suggesting that NAFLD is a marker of inflammation.[26–28] Other previous studies have suggested that inflammation might be one of the most important causes of degenerative dementia.[29,30] In addition, carotid intimal thickness might provide a link, given that carotid intimal thickness is associated with both NAFLD and cognitive impairment.[31,32]

Interestingly, the association between NAFLD and cognitive impairment varied across the cognitive tests. That is, NAFLD was associated only with SDLT scores, independent of cardiovascular risk factors and diseases, while the association with SRTT and SDST scores disappeared after adjusting for metabolic components and cardiovascular diseases. SRTT, SDST, and SDLT are designed to assess psychomotor speed, visual attention, and learning, recall, and concentration function, respectively. Previous studies suggest that SDLT scores are generally

Table 3 Association between liver enzyme activity and cognitive function in 4,472 adults aged between 20 and 59 years who participated in the US Third National Health and Nutrition Examination Survey (1988–1994)

	Model 1			Model 2		
	β	SE	95% CI	β	SE	95% CI
SRTT						
ALT	0.130	0.083	−0.033 to 0.292	0.108	0.085	−0.059 to 0.275
AST	0.100	0.099	−0.095 to 0.294	0.108	0.102	−0.092 to 0.308
SDST						
ALT	0.002	0.001	<0.001 to 0.004	0.002	0.001	<0.001 to 0.004
AST	0.003	0.002	<0.001 to 0.006	0.003	0.002	−0.001 to 0.007
SDLT						
ALT	0.021	0.006	0.009 to 0.033	0.018	0.006	0.006 to 0.030
AST	0.022	0.009	0.005 to 0.039	0.021	0.008	0.005 to 0.037

Abbreviations: ALT = alanine aminotransferase (U/L); AST = aspartate aminotransferase (U/L); β = unstandardized regression coefficient; CI = confidence interval; SDLT = Serial Digit Learning Test; SDST = Symbol Digit Substitution Test; SRTT = Simple Reaction Time Test.
All results were obtained with consideration for National Health and Nutrition Examination Survey sampling design effects. Model 1 adjusted for age (continuous), sex (male, female), race (white, black), education (>12, ≤12 years). Model 2: model 1 + further adjusted for body mass index (<18.5, 18.5–24.9, 25–29.9, 30–34.9, ≥35), waist circumference (>102, ≤102 in men, >88, ≤88 in women), hypertension (yes, no), diabetes mellitus (yes, no), hypercholesterolemia (yes, no), acute myocardial infarction (yes, no), and stroke (yes, no).

influenced by the presence of medial temporal lesions in the hippocampus, although SDLT performance also requires some frontal related processes. Therefore, our findings suggest that NAFLD might affect brain function through region-specific processes rather than diffuse cortical dysfunction. Further studies are required to examine this hypothesis in detail.

The results from the analyses examining the association between liver enzyme activity and cognition were largely consistent with the determination of NAFLD by ultrasound; namely, that there was an independent association with SDLT. The only difference, however, was that liver enzyme activity, but not the presence of NAFLD, was associated with SDST. Liver enzymes have been used as noninvasive surrogates for NAFLD in the context of no elevated alcohol consumption,[2] although their use involves some degree of limited sensitivity and specificity.[33,34] These markers are thought to reflect inflammatory status, and thus support the hypothesis that inflammation in the liver, more than simply the presence of fat, is the major driver of the observed association. Future studies with detailed assessments of liver fat and inflammation are needed to further distinguish differences within these associations by the level of damage.

Our study assessed a large and nationally representative sample of healthy middle-aged adults, with standardized administration of 3 computerized tests to evaluate cognitive functioning and a thorough medical workup for liver disease, including ultrasound, serologic testing, and standardized questionnaires to define NAFLD; other evaluation of medical conditions also allowed further adjustment of potential demographic, metabolic, and cardiovascular diseases. However, we acknowledge some limitations. First, the cross-sectional nature of the study does not permit us to ascertain causality in the relationship between NAFLD and cognition. It also leaves open the possibility for unmeasured confounding, particularly with regards to dietary and lifestyle risk factors. We also could not determine the relationship between NAFLD and deficits in specific cognitive domains, as participants did not undergo detailed neuropsychological tests across a range of cognitive functions. Liver ultrasound is the most widely used method to assess hepatic steatosis in large population-based studies, with a sensitivity of 84.8% and a specificity of 93.6%.[35] However, some limitations have been reported, including lower sensitivity among people with obesity.[36] Another common limitation of ultrasound is its operator dependency. In the NHANES, data were collected by trained staff following rigorous, standardized protocols to ensure that measurement errors are minimized, and to also minimize operator-dependent variations. Furthermore, liver ultrasound cannot distinguish between progressive NAFLD with advanced hepatic fibrosis/cirrhosis and benign steatosis. As a consequence, our study may have included cirrhotic patients with minimal hepatic encephalopathy. However, given the nature of NHANES, is it highly unlikely that very sick patients such as those with cirrhosis and complications would be participating in the survey. NHANES participants included in the present study were required to undergo a 5-hour examination at a mobile examination unit. Moreover, in further analyses, the results based on participants with no advanced NAFLD fibrosis were similar to those based on total participants. Future studies with liver biopsy data are needed to further demonstrate an association between advanced NAFLD and cognition. Despite these limitations, we are left with the suggestion that NAFLD might be a potential independent risk factor for cognitive impairment. Such an association could provide insight regarding the role of NAFLD in cognitive impairment and assist with more effective management of individuals with NAFLD. This is particularly important given the rising incidence of obesity and metabolic syndrome, which could portend rising rates of NAFLD. Furthermore, the assessment of NAFLD might be a novel and helpful approach for dementia risk stratification.

AUTHOR CONTRIBUTIONS

Dr. Seo: study concept and design; acquisition, analysis, and interpretation of data. Dr. Gottesman: study concept and design, critical revision of the manuscript. Dr. Clark: critical revision of the manuscript. Dr. Hernaez: critical revision of the manuscript. Dr. Chang: critical revision of the manuscript. Dr. Kim: analysis and interpretation. Dr. Ha: analysis and interpretation. Dr. Guallar: study concept and design. Dr. Lazo: study concept and design, critical revision of the manuscript, study supervision.

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DISCLOSURE

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