

Association of Nonalcoholic Fatty Liver Disease and Fibrosis With Incident Dementia and Cognition

The Rotterdam Study

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Abstract

Background and Objectives

Nonalcoholic fatty liver disease (NAFLD) might affect brain health via the so-called liver-brain axis. Whether this results in an increased risk for dementia remains unclear. Therefore, we investigated the association of NAFLD and fibrosis with incident dementia and cognition among the elderly.

Methods

We performed longitudinal and cross-sectional analyses within the Rotterdam Study, an ongoing prospective cohort. Participants visiting between 1997 and 2002 with available fatty liver index (FLI) (set 1) or participants visiting between 2009 and 2014 with abdominal ultrasound (set 2) and liver stiffness (set 3) were included. Exclusion criteria were secondary causes for steatosis, prevalent dementia, and missing alcohol data. NAFLD was defined as FLI ≥ 60 or steatosis on ultrasound and fibrosis as liver stiffness ≥ 8.0 kPa. Dementia was defined according to the *DSM-III-R*. Associations between NAFLD, fibrosis, or liver stiffness and incident dementia were quantified using Cox regression. Finally, the association between NAFLD and cognitive function was assessed cross-sectionally.

Results

Set 1 included 3,975 participants (age 70 years, follow-up 15.5 years), set 2 4,577 participants (age 69.9 years, follow-up 5.7 years), and set 3 3,300 participants (age 67.6 years, follow-up 5.6 years). NAFLD and fibrosis were consistently not associated with an increased risk for dementia (NAFLD based on ultrasound, hazard rate [HR] 0.84, 95% CI 0.61–1.16; NAFLD based on FLI, HR 0.92, 95% CI 0.69–1.22; fibrosis, HR 1.07, 95% CI 0.58–1.99) in fully adjusted models. Of interest, NAFLD was associated with a significantly decreased risk for incident dementia until 5 years after FLI assessment (HR 0.48; 95% CI 0.24–0.94). Moreover, NAFLD was not associated with worse cognitive function, covering several domains.

Conclusions

NAFLD and fibrosis were not associated with an increased risk for incident dementia, nor was NAFLD associated with impaired cognitive function. In contrast, NAFLD was even protective in the first 5 years of follow-up, hinting toward NAFLD regression before dementia onset.

Trial Registration Information

Clinical Trial Number: NTR6831.

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Glossary

BMI = body mass index; **DSM-III** = *Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition*; **FLI** = fatty liver index; **G-factor** = general cognitive factor; **HR** = hazard rate; **ICD-10** = *International Classification of Diseases, 10th Revision*; **LDST** = Letter Digit Substitution Test; **MD** = mean difference; **NAFLD** = nonalcoholic fatty liver disease; **PPB test** = Purdue Pegboard Test; **WFT** = Word Fluency Test.

Nonalcoholic fatty liver disease (NAFLD) is increasingly common and affects >25% of the global population.¹ It has become one of the most prevalent chronic liver diseases, ranging from simple fat accumulation to liver cirrhosis.² In addition, recent studies indicate that NAFLD is associated with kidney dysfunction,^{3,4} cardiovascular disease,⁵ and extrahepatic malignancies such as colon and stomach cancer.^{6,7} However, its link with neurodegenerative conditions, such as dementia or cognition impairment, remains unclear.

As a metabolic disease, NAFLD has several risk factors in common with dementia, for example, insulin resistance, hypertension, obesity, physical inactivity, and dyslipidemia.⁸ Accumulating evidence also suggests a direct association of NAFLD with brain structural changes via the so-called liver-brain axis.⁹⁻¹¹ This might link NAFLD to dementia, driven by the following mechanisms: (1) inflammation due to liver fat may activate microglial cells resulting in elevated expression of inflammatory cytokines in the brain¹²; (2) increased brain insulin resistance in patients with NAFLD may cause oxidative stress, excessive free fatty acids, and brain mitochondrial disorders¹³; and (3) cerebrovascular and hemodynamic disturbances provoked by a prothrombotic state.⁸ Despite this growing evidence for a liver-brain axis, current available studies reported no effects of NAFLD on dementia^{14,15} or only in frail participants with NAFLD with fibrosis.¹⁶ However, some other studies indicated that cognitive impairment was more common in patients with NAFLD¹⁷ or fibrosis,¹⁸ which might indicate a potential association with dementia and NAFLD.

The majority of those studies are, however, cross-sectional, had limited follow-up, or had a small sample size. Moreover, some studies lacked abdominal imaging to determine steatosis, and transient elastography was often not available to assess fibrosis. Given these limitations and the inconsistent results, the effect of NAFLD on dementia remains unclear. Therefore, we aim to study the associations of NAFLD and fibrosis with incident dementia and cognitive function in a well-defined, prospective cohort with available ultrasound and transient elastography data. A defining feature of our study is the use of different measures of NAFLD using various modalities that together provide a comprehensive assessment of liver function.

Methods

Participants

This study was conducted within the Rotterdam Study, a prospective ongoing cohort that started in 1990. All

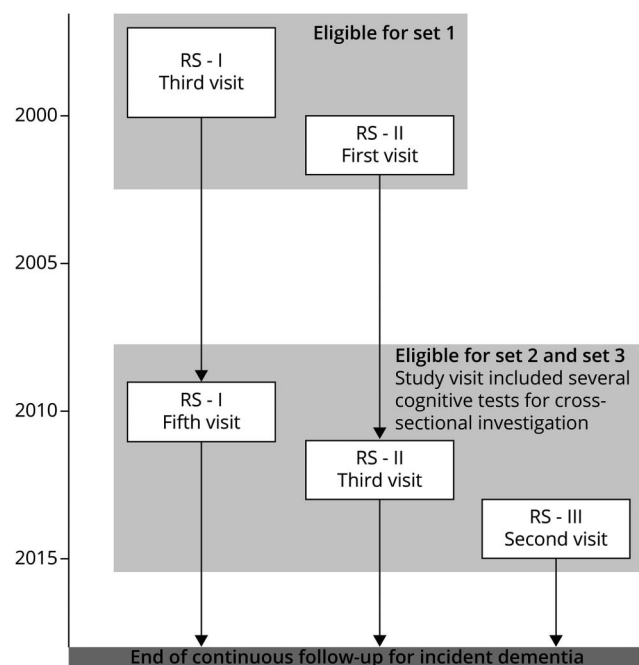
individuals aged ≥ 45 years from a well-defined suburb in Rotterdam (Ommoord) were invited to participate in this longitudinal cohort designed to investigate chronic diseases in the general population. Several extensions to the cohort have been made over the years with an overall response rate of 72.0%.¹⁹ Study visits comprised a home interview and various physical examinations at the research center and were repeated every 4 to 6 years. In this study, we included 3 different sets (Figure 1) in which we assessed the effect of NAFLD or fibrosis on the risk of incident dementia in several ways. Set 1 comprised participants in whom we had available fatty liver index (FLI) to determine NAFLD, measured between 1997 and 2002. Set 2 comprised participants visiting the study center between 2009 and 2014 in whom we had abdominal ultrasound performed to assess NAFLD; this set comprised 40.3% of participants of set 1. Set 3 is a subset of set 2 and comprises participants who also underwent liver stiffness measurement (LSM) to assess fibrosis. Sets 2 and 3 were also used to investigate the association with cognition cross-sectionally.

Exclusion criteria were (1) prevalent dementia; (2) lack of follow-up; (3) missing dementia data; and (4) secondary causes for steatosis or missing alcohol data. These secondary causes were steatosis-inducing drug use, viral hepatitis, or excessive alcohol consumption (>20 g/d for female or >30 gr/d for male) assessed by food frequency questionnaire or alcohol interview.²⁰ In addition, for set 3, participants with invalid LSMs were also excluded.

Steatosis Assessment

NAFLD was defined as the presence of FLI ≥ 60 (set 1) or steatosis based on abdominal ultrasound (set 2) in the absence of secondary causes for steatosis. FLI was calculated with the following algorithm: $FLI = (e^{0.953} \times \log_e(\text{triglycerides}) + 0.139 \times BMI + 0.718 \times \log_e(\text{GGT}) + 0.053 \times \text{waist circumference} - 15.745) / (1 + e^{0.953} \times \log_e(\text{triglycerides}) + 0.139 \times BMI + 0.718 \times \log_e(\text{GGT}) + 0.053 \times \text{waist circumference} - 15.745) \times 100$, where triglycerides were measured in mg/dL, GGT in U/L, waist circumference in cm, and BMI in kg/m². Participants were categorized according to their FLI score as no NAFLD for FLI <30 and NAFLD for FLI ≥ 60 .²¹ Steatosis based on abdominal ultrasound was defined as hyperechoic liver parenchyma compared with the spleen or kidney.²² Abdominal ultrasound was performed by a single certified and experienced sonographer on a Hitachi Hi Vision 900.

Figure 1 Overview of Different Study Sets and Key Characteristics for Investigating the Association Between NAFLD and Fibrosis With Dementia and Cognitive Function



	Liver assessment	Inclusions	Follow-up	Events
Set 1	Fatty liver index	3,975	15.5 year	753
Set 2	Abdominal ultrasound	4,577	5.7 year	262
Set 1	Transient elastography	3,300	5.6 year	127

Set 1 and set 2 were used to study associations between NAFLD with incident dementia. Set 3 was used to study associations between liver stiffness and fibrosis with incident dementia. In addition, the effect of NAFLD and fibrosis on cognitive function was studied cross-sectionally in set 2 and set 3. NAFLD = nonalcoholic fatty liver disease.

Fibrosis Assessment

Liver stiffness was assessed using transient elastography (FibroScan, EchoSens, Paris, France). At least 10 measurements were obtained through either M or XL probe according to the device's instructions. Final measurements >7.1 kPa with an interquartile range $>30\%$ were considered unreliable and discarded.²³ Liver fibrosis was defined as LSM ≥ 8.0 kPa.²⁴

Dementia Assessment

Dementia assessment was performed at baseline and subsequent center visits with the Mini-Mental State Examination and the Geriatric Mental Schedule.²⁵ Those with a Mini-Mental State Examination score <26 or Geriatric Mental Schedule score >0 underwent further investigation including Cambridge Examination for Mental Disorders of the Elderly. Moreover, diagnosis of dementia by other health care professionals was available through electronic linkage of the study database with medical records from general practitioners and the regional institute for outpatient mental health care. An

adjudication panel led by a consultant neurologist established the final diagnosis according to the standard criteria for dementia (*DSM-III-R*) for all sets and throughout the study period. Follow-up was complete until January 1, 2018. Within this period, participants were followed until the date of dementia, death, or January 1, 2018, whichever came first.

Cognitive Testing

Besides the independent assessment of dementia, participants in set 2 and set 3 underwent several neuropsychological tests during the study visit; this includes the Stroop test, the Letter Digit Substitution Test (LDST), the Word Fluency Test (WFT), a 15-Word Learning Test with immediate and delayed recall, and Purdue Pegboard Test, which are described in eTable 1, links.lww.com/WNL/C90. These test results were transformed into a Z score, this reflects the number of SDs the test results were below or above the mean score. To assess the overall cognitive function, a general cognitive factor (G-factor) was calculated using principal component analysis. For this factor, we only included the LDST, WFT, WLTdel tests, and the trial 3 of Stroop test to prevent distortion of the G-factor by highly correlated tasks.²⁶

Covariates

Demographic and physiologic information was collected at baseline and included age, sex, education level (lower education, intermediate education, and higher education), smoking status (never, former, and current), alcohol intake (units/d), body mass index (BMI, kg/m^2), alanine aminotransferase (U/L), and comorbidity (diabetes, hypertension, and stroke).¹⁹ Diabetes was defined as fasting glucose ≥ 7 mmol/L or use of antidiabetic drugs. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg or the use of antihypertensive medication. Presence of stroke was based on linkage with hospital records and verified by 2 experienced vascular neurologists. Depressive symptoms were assessed with a validated version of the Centre for Epidemiologic Studies Depression scale. Depression was defined as at least 16/60 points.²⁷ APOE genotype was determined using a PCR and a biallelic TaqMan assay (rs7412 and rs429358) on labeled DNA samples. APOE $\epsilon 4$ allele represented carrier of 1 or 2 $\epsilon 4$ alleles.

Statistical Analysis

Baseline characteristics are described for the overall population in all 3 sets. Data are expressed as mean \pm SD or as median (with 25th–75th percentile [P25–P75]). For time-to-event analyses, we assessed the associations between NAFLD and liver stiffness with the risk of incident dementia using Cox proportional hazard regression analyses. Baseline was defined as the date of the blood test (for FLI) or abdominal ultrasound and follow-up ended at the diagnosis of dementia, death, or January 1, 2018. Model 1 was adjusted for APOE phenotype, age, sex, and education. Model 2 was in addition adjusted for alcohol, smoking, stroke, hypertension, diabetes, and cholesterol. Model 3 was in addition adjusted for BMI.

Covariates above were selected based on previous literature, clinical relevance, and data availability.^{28,29} Missing genetic data were not imputed as they are innate and not modifiable; the remaining missing data were not imputed due to very low missingness (<2%).

Next, we determined the cross-sectional association of NAFLD or fibrosis with cognitive function using linear regression analyses and Tukey all-pair comparisons method based on analysis of variance models. We calculated the differences of the individual cognitive tests and G-factor for participants with NAFLD compared with those without NAFLD and for fibrosis compared with no fibrosis. Results were adjusted for age, sex, education level, smoking status, BMI, cholesterol, triglycerides, hypertension, stroke, diabetes, depression, and APOE genotypes.

A *p* value of <0.05 was considered statistically significant. All analyses were performed using R version 4.0.4 (Foundation for Statistical Computing, Vienna, Austria).

Standard Protocol Approvals, Registrations, and Patient Consents

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study Personal Registration Data collection is filed with the Erasmus MC Data Protection Officer under registration number EMC1712001. The Rotterdam Study has been entered into the Netherlands National Trial Register (trialregister.nl) and into the WHO International Clinical Trials Registry Platform (who.int/ictrp/network/primary/en/) under shared catalog number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians. All authors had access to the study data and take full responsibility for the data, analyses, and interpretation of results.

Data Availability

Data can be obtained on request. Requests should be directed toward the management team of the Rotterdam Study (secretariat.epi@erasmusmc.nl), which has a protocol for approving data requests. Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository.

Results

Baseline Characteristics

There were 3,975 participants with available NAFLD data based on FLI included in set 1, 4,577 participants with available ultrasound to assess NAFLD in set 2, and 3,300 participants with available LSM to assess fibrosis in set 3; exclusions are described in eTable 2, links.lww.com/WNL/C90. Participants from the different sets had a similar mean

age (around 70 years) and BMI (near 27 kg/m²), and approximately 60% of them were women. In set 1, 1,293 (32.5%) participants had NAFLD (FLI ≥60), and in set 2, 1,586 (34.7%), which was based on abdominal ultrasound. In set 3, the median liver stiffness was 4.8 kPa (P25–P75: 3.8–5.9), and 192 (5.8%) participants had fibrosis (Table 1).

As shown in Figure 1, in set 1, 753 (18.9%) participants developed dementia during a median follow-up of 15.5 years. In set 2, the median follow-up was 5.7 years, and 262 (5.7%) participants had incident dementia. In set 3, only 127 (3.8%) had incident dementia with 5.6 years of median follow-up. Participants' characteristics stratified by NAFLD status for sets 1 and 2 are presented in eTable 3, and the characteristics stratified for fibrosis status (set 3) are available in eTable 4, links.lww.com/WNL/C90.

NAFLD and Fibrosis in Relation to Incident Dementia

The presence of NAFLD (based on FLI ≥60, set 1) did not increase the risk of incident dementia (hazard rate [HR] 0.92; 95% CI 0.69–1.22) in the fully adjusted model. Similarly, no increased risk of dementia could be demonstrated for the presence of NAFLD, based on abdominal ultrasound in set 2. NAFLD was even associated with a significantly decreased risk for incident dementia in model 2 (HR 0.73, 95% CI 0.54–0.98), which was no longer significant after additional adjusting for BMI (HR 0.84; 95% CI 0.61–1.16). Consistent with those results, no association was found for fibrosis (HR 1.07; 95% CI 0.58–1.99) or liver stiffness (HR 1.01 per kPa; 95% CI 0.92–1.10) with incident dementia in fully adjusted models in set 3 (Table 2).

Of interest, for the first 5 years of follow-up, participants with NAFLD (FLI ≥60, set 1) were at a significantly lower risk of incident dementia (HR 0.49; 95% CI 0.25–0.96) in the fully adjusted model, compared with no NAFLD (FLI <30). With the period of follow-up extending, the protective association between NAFLD and risk of incident dementia disappeared (between 5 and 10 years, HR 1.08; 95% CI 0.62–1.87; above 10 years, HR 1.25; 95% CI 0.80–1.96, Table 3).

Weight loss before abdominal ultrasound since the participants' previous visit (mean time between visits 6.1 years) was more evident among participants who had developed dementia during the follow-up, compared with those without incident dementia (mean: –0.37 vs –0.05 kg per year; set 2).

NAFLD and Liver Fibrosis in Relation to Cognitive Performance

Figure 2 presents the association of NAFLD (abdominal ultrasound, set 2) and liver fibrosis (set 3) with cognitive performance. Cross-sectional analyses revealed that NAFLD was not significantly associated with poor performance on global cognition reflected in G-factor (mean difference [MD] of Z score): 0.032 (95% CI –0.029 to 0.092); in fact, better performance of Stroop test 2 was observed in cross-sectional

Table 1 Baseline Characteristics Per Analysis Set

	Set 1, n = 3,975	Set 2, n = 4,577	Set 3, n = 3,300
Demographics			
Age (y)	70.0 (8.0)	69.9 (9.1)	67.6 (8.4)
Female	2,408 (60.6)	2,709 (59.2)	1,892 (57.3)
Alcohol consumption	3,068 (77.2)	3,866 (84.5)	2,830 (85.8)
Former/current smoking	2,495 (63.1)	2,933 (64.2)	2,081 (63.2)
Educational level			
Low	2,357 (59.8)	2,237 (49.4)	1,517 (46.4)
Intermediate	1,129 (28.6)	1,355 (29.9)	972 (29.7)
High	456 (11.6)	934 (20.6)	779 (23.8)
Physical examination			
BMI (kg/m ²)	27.0 (4.1)	27.6 (4.4)	27.1 (3.9)
Enlarged waist circumference ^a	1,799 (45.3)	2,015 (44.1)	1,356 (41.1)
Comorbidity			
Metabolic syndrome	1,983 (50.0)	2,268 (50.4)	1,529 (47.0)
Diabetes	549 (13.8)	715 (15.8)	458 (14.0)
Stroke	71 (1.8)	122 (2.7)	59 (1.8)
Hypertension	2,727 (68.8)	3,374 (73.7)	2,276 (69.0)
Biochemistry/genetics			
ALT (U/L)	20 [16–25]	18 [15–24]	18 [14–24]
GGT (U/L)	23 [17–32]	23 [17–33]	22 [16–33]
Cholesterol (mmol/L)	5.78 (0.97)	5.42 (1.11)	5.48 (1.10)
Triglycerides (mmol/L)	1.34 [1.02–1.83]	1.27 [0.98–1.72]	1.26 [0.97–1.70]
APOE ε4	1,062 (27.8)	1,137 (26.7)	842 (27.5)
Hepatic comorbidity			
NAFLD ^b	1,293 (32.5)	1,586 (34.7)	1,066 (32.3)
Liver stiffness (kPa)	—	4.8 [3.8–5.9]	4.8 [3.8–5.9]

Abbreviations: ALT = alanine transaminase; BMI = body mass index; FLI = fatty liver index; GGT = gamma glutamyl transpeptidase; NAFLD = nonalcoholic fatty liver disease.

Data are presented as mean (SD), median [P25–P75], or n and percentage. Baseline characteristics are presented per set.

^a Waist circumference >102 cm for male and >88 cm for female.

^b Based on FLI ≥60 in set 1 or ultrasound in sets 2 and 3.

analyses. On the contrary, we found that liver fibrosis was associated with lower global cognition scores (MD -0.172 , 95% CI -0.307 to -0.037) and lower scores of LDST and more time to finish Stroop tests 1 and 3 (eTable 5, links.lww.com/WNL/C90).

Discussion

We investigated the effect of NAFLD on dementia and cognitive function in a large prospective ongoing population-

based cohort with up to 15.5 years of median follow-up. NAFLD was not associated with an increased risk of incident dementia or impaired cognitive function. In addition, the presence of NAFLD was not associated with impaired cognitive function.

In contrast to the suggested liver-brain axis in previous studies, NAFLD did not increase the risk of incident dementia in this study, regardless of the modality of diagnosis (FLI or ultrasound). We even found NAFLD to be significantly protective for dementia within the first 5 years after FLI

Table 2 Risk of Incident Dementia for NAFLD and Liver Stiffness

	Cases	FU ^a (y)	Model 1		Model 2		Model 3	
			HR	95% CI	HR	95% CI	HR	95% CI
NAFLD (FLI ≥60)	753/3,975	15.5	0.91	0.76–1.10	0.79	0.65–0.97	0.92	0.69–1.22
NAFLD (ultrasound)	262/4,577	5.7	0.87	0.66–1.15	0.73	0.54–0.98	0.84	0.61–1.16
Fibrosis^b	127/3,300	5.6	1.12	0.61–2.05	1.08	0.58–2.00	1.07	0.58–1.99
Liver stiffness (kPa)	127/3,300	5.6	1.02	0.95–1.10	1.00	0.92–1.09	1.01	0.92–1.10

Abbreviations: BMI = body mass index; FLI = fatty liver index; FU = follow-up; HR = hazard rate; kPa = kilopascals; NAFLD = nonalcoholic fatty liver disease. Results are given as HR and 95% CI for incident dementia as outcome. Model 1: adjusted for *APOE-4*, age, sex, and education; model 2 was in addition adjusted for alcohol, smoking, stroke, hypertension, diabetes, and cholesterol; model 3 was in addition adjusted for BMI. NAFLD was either based on FLI ≥60 or on hepatic steatosis assessed with abdominal ultrasound and was compared with participants with FLI <30 or participants without hepatic steatosis.

^a Median follow-up in years.

^b Defined as LSM ≥8.0 kPa.

assessment. Similar trends were seen for the association between ultrasound-based NAFLD and incident dementia during the 5.7 years of median follow-up. This points us toward one of the challenges regarding NAFLD and dementia research: the reversibility of NAFLD due to weight loss.³⁰ Dementia, albeit unintentionally, is also accompanied by weight loss during its preclinical phase,³¹ which was confirmed by our results. This could induce NAFLD regression, as even minor improvements in body fat have rather large effects on liver fat and hepatic triglycerides.^{32,33} Consequently, weight loss in the years before dementia could thus obscure any relation between NAFLD and incident dementia. In our study, the demonstrated protective effect of NAFLD on dementia disappeared after 5 years. This suggests that if NAFLD is associated with an increased risk for dementia at all, it is a long-term effect, and NAFLD itself might already have disappeared before dementia is diagnosed.

Given the reversibility of NAFLD, exposure duration could be of major importance to comprehend the association between NAFLD and dementia. Individuals with NAFLD can develop permanent liver fibrosis, resulting in higher liver stiffness, based on the duration and severity of NAFLD.³⁴ Therefore,

we assessed the association between fibrosis and liver stiffness with incident dementia longitudinally. In line with our results for NAFLD, fibrosis and liver stiffness were also not associated with incident dementia, indicating that neither NAFLD nor severity of NAFLD is associated with an increased risk for incident dementia. Considering cognitive impairment as a classic prodromal symptom preceding the onset of dementia,³³ we explored the cross-sectional association between NAFLD and cognition independent of dementia. Similarly, we did not find a significant association between NAFLD and impaired cognitive function. However, fibrosis was significantly associated with impaired performance on the Stroop test and Letter Digit Substitution Test resulting in a lower G-factor score. These tests cover attention and concentration, processing speed, and global cognitive function, respectively. Further research is required whether this hints toward an association with dementia as well or is driven by common risk factors (e.g., the presence of diabetes or metabolic syndrome) or accumulation of toxins by impaired liver function.

Given these consistently negative results, we cannot demonstrate an association of NAFLD with dementia or cognitive function within our follow-up duration. This is in line with a recent registry study among over 40,000 participants, which could not link NAFLD and dementia using *ICD-10* codes.¹⁴ Moreover, a study with almost 20 years of follow-up could not identify NAFLD as risk factor for incident dementia.¹⁵ However, they reported that histology-proven fibrosis improved the prediction of dementia. Fibrosis was also linked to dementia among the frail elderly previously.¹⁶ However, these results need to be interpreted with caution because fibrosis was calculated based on age, which itself is undisputedly associated with dementia.

More literature is available on cognitive function, and in these studies, NAFLD has been linked to impaired performance on Serial Digit Learning Test¹⁷ and Symbol Digit Substitution Test,¹⁷ reduced reaction time,¹⁷ lower MoCA scores,^{35,36} brain volume reduction,⁹ and reduced brain activity.³⁶ However, most results were unadjusted or disappeared after

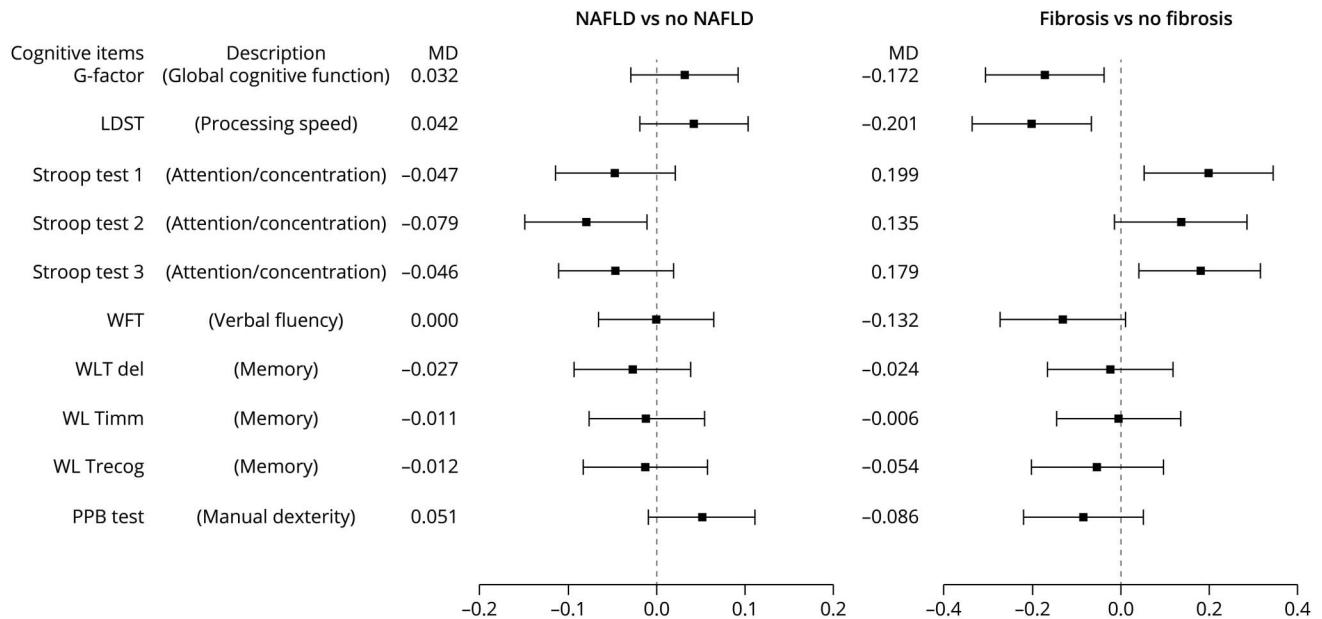
Table 3 Risk of Incident Dementia for NAFLD Based on Fatty Liver Index Per 5 Years of Follow-up

Period	Cases	Model 1		Model 2		Model 3	
		HR	95% CI	HR	95% CI	HR	95% CI
0–5 y	155/3,975	0.59	0.38–0.91	0.50	0.32–0.80	0.48	0.24–0.94
5–10 y	194/3,472	0.85	0.59–1.21	0.78	0.54–1.14	1.10	0.63–1.91
>10 y	404/2,786	1.11	0.87–1.43	0.94	0.71–1.23	1.07	0.72–1.57

Abbreviations: BMI = body mass index; HR = hazard rate; NAFLD = non-alcoholic fatty liver disease.

Model 1 was adjusted for *APOE-4*, age, sex, and education; model 2 was in addition adjusted for alcohol, smoking, hypertension, diabetes, and cholesterol; model 3 was in addition adjusted for BMI. NAFLD was based on FLI ≥60 and compared with FLI <30.

Figure 2 Mean Difference of Performance on Cognitive Tests Between Participants With NAFLD Compared With No NAFLD and Fibrosis Compared With No Fibrosis Expressed in Z-Scores



Presence of NAFLD or fibrosis, in relation to cognition tests in cross-sectional analyses. Higher scores indicate better performance, except for the Stroop tests. Results were obtained from linear regression analyses and Tukey all-pair comparisons method based on ANOVA models. Differences were calculated for the individual cognitive tests and G-factor for participants with NAFLD compared with those without NAFLD and for fibrosis compared with no fibrosis. Results were adjusted for age, sex, education level, smoking status, BMI, cholesterol, triglycerides, hypertension, stroke, diabetes, depression, and *APOE* genotypes. G-factor = general cognitive factor; LDST = Letter Digit Substitution Test; MD = mean difference; PPB test = Purdue Pegboard Test; WFT = Word Fluency Test; WLTdel = Word Learning Test, delayed recall; WLTimm = Word Learning Test, immediate recall; WLTrecog = Word Learning Test, recognition.

adjustment for important confounders such as age and education level. Moreover, most findings were not replicated, and some studies, similar to ours, could not identify any association with NAFLD and cognition.¹⁸ Therefore, the effect of NAFLD on cognitive function and dementia seems to be minor, if existing at all. In fact, in our study, we had 80% power to demonstrate an association between NAFLD and dementia for an HR of 1.25 in set 1 and an HR of 1.44 in set 2.

Although this study had a large sample size and extensive analysis was performed for both incident dementia and cognitive function in relation to NAFLD and fibrosis, the following limitations need mentioning. First, this cohort is almost entirely European, with a mean age of 70 years at baseline. Therefore, our results might not be generalizable to multiethnic and younger populations. Second, NAFLD and fibrosis were not based on liver biopsy because that procedure is invasive and subject to potential complications and therefore unethical to perform in a healthy population on this scale. Alternatively, we used FLI in set 1 and abdominal ultrasound in set 2. The FLI diagnosis correlates strongly with ultrasound diagnosis of NAFLD (AUROC 0.813) in the Rotterdam Study.³⁷ Despite fully adjusted models, residual confounding might not be ruled out, as FLI includes BMI. In line with this limitation, NAFLD was only assessed at baseline, and no data were available for NAFLD exposure duration. Third, because we had only 192 cases of fibrosis, we might not have found an

association with incident dementia. Therefore, the continuous outcome of liver stiffness was also used to explore associations with incident dementia; it should be noted, however, that this might not reflect only liver injury per se. Fourth, the cross-sectional study design for NAFLD and cognition allows not to study causal relationships for NAFLD on cognition. However, it served as indirect evidence for the absence of associations between NAFLD and dementia, in line with the longitudinal analysis. Finally, because NAFLD has clear associations with survival, survivor bias may have occurred. However, among the elderly, these effects are less obvious, and even protective effects of NAFLD on mortality have been observed; therefore, survivor bias is unlikely to have affected our results.³⁸⁻⁴⁰

In conclusion, individuals with NAFLD were not at an increased risk of dementia among this general elderly population, nor could an association with liver stiffness or fibrosis and dementia be demonstrated. Moreover, NAFLD was associated with a reduced risk of dementia for the first 5 years after the assessment, suggesting that NAFLD regression is likely before dementia onset, which could be driven by weight loss before dementia onset. As yet, NAFLD may have no clinical implications for dementia awareness. Further studies should focus on NAFLD exposure duration, NAFLD trajectory, and risk of dementia with longer follow-up durations.

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Appendix Authors

Name	Location	Contribution
Tian Xiao, MD	Department of Epidemiology Erasmus MC University Medical Center, Rotterdam, The Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Laurens A. van Kleef, MD	Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
M. Kamran Ikram, MD, PhD	Department of Neurology, Erasmus MC University Medical Center, Rotterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content

Appendix (continued)

Name	Location	Contribution
Robert J. de Knegt, MD	Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands	Drafting/revision of the manuscript for content, including medical writing for content, and study concept or design
M. Arfan Ikram, MD, PhD	Department of Epidemiology Erasmus MC University Medical Center, Rotterdam, The Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data

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Association of Nonalcoholic Fatty Liver Disease and Fibrosis With Incident Dementia and Cognition: The Rotterdam Study

Tian Xiao, Laurens A. van Kleef, M. Kamran Ikram, et al.

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Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Editor
Aravind Ganesh, MD, DPhil, FRCPC, Deputy Editor
Ariane Lewis, MD, Deputy Editor
James E. Siegler III, MD, Deputy Editor

Editors' Note: Gender Representation Among Physician Authors of Practice Guidelines Developed, Endorsed, or Affirmed by the American Academy of Neurology

In the Research Article entitled “Gender Representation Among Physician Authors of Practice Guidelines Developed, Endorsed, or Affirmed by the American Academy of Neurology,” Ross et al. reported that a review of 68 American Academy of Neurology (AAN)–recommended practice guidelines published from 2015 to 2020 authored by 709 physicians demonstrated low women physician author representation across all benchmarks.

Pringsheim et al., representing prior and current leaders of AAN guideline development, (1) emphasized their commitment to gender equity in the guideline development process and (2) identified 3 concerns with the methodology in the study conducted by Ross et al. First, because the AAN published only 30 guidelines during the study period, the AAN was not involved in authorship selection for more than half of the 68 practice guidelines included in this study. Second, the benchmarks referenced in this study are specific to academic neurologists, but the AAN membership includes nonacademic neurologists too. Third, Ross et al. made a “timing error” because they did not address the fact that authors of AAN guidelines are identified many years before publication, and gender proportions changed during this time frame. Pringsheim et al. performed their own analysis of gender representation among physician authors of AAN practice guidelines published annually from 2015 to 2020, addressing their first 2 concerns, and found that in aggregate, there was no significant gender difference in authors, physician authors, neurologist authors, first authors, or last authors.

Regarding methodology concerns by Pringsheim et al., Ross et al. responded that (1) while the AAN is not responsible for authorship selection for external practice guidelines, authorship gender equity should be considered when the AAN makes a decision whether to endorse or affirm an external practice guideline; (2) all 68 practice guidelines included in this study are presented as a collective on the AAN website under the label “Practice Guidelines,” making it appropriate to include them all in their analysis; (3) while the use of benchmarks based on data from academic neurologists is imperfect because authors may come from other backgrounds, this is the best comparator; and (4) it is inappropriate to describe the use of publication year instead of empanelment year as a “timing error,” given this methodology is consistent with other gender equity literature. Furthermore, even if the proportion of women who were practice guideline authors in 2015 was compared with that of women neurologists in 2007, the number of women authors would still be low. Although appreciative that Pringsheim et al. performed their own analysis using internal AAN data, Ross et al. noted they could not compare the results of this analysis with their own. Data used by Pringsheim et al. were not made available for further review. In addition, it was unclear whether their “aggregate” summary was based on the year-by-year analysis or a separate analysis of the entire 5-year period.

While Ross et al. and Pringsheim et al. disagreed about whether there was gender equity in AAN practice guidelines published from 2015 to 2020, they agreed that there is a need for continued vigilance to prevent gender inequity in guideline authorship.

Ariane Lewis, MD, and Steven Galetta, MD
Neurology® 2023;101:92. doi:10.1212/WNL.0000000000207574

Reader Response: Gender Representation Among Physician Authors of Practice Guidelines Developed, Endorsed, or Affirmed by the American Academy of Neurology

Tamara Pringsheim (Calgary, Canada), Sarah Benish (Minneapolis), Cynthia Harden (Vancouver, Canada), Lyell Jones (Rochester, MN), Pushpa Narayanaswami (Boston), Anup Patel (Columbus, OH), Sonja Potrebic (Oakland, CA), Alex Rae-Grant (Ipswich, MA), Amy Sanders (Plymouth, MN), Adam Webb (Atlanta), and Heidi B. Schwarz (Rochester, MN)
Neurology® 2023;101:93–94. doi:10.1212/WNL.0000000000207575

As prior and current leadership of American Academy of Neurology (AAN) practice guideline development, we were discouraged by the conclusions reported in the article by Dr. Ross and colleagues on gender parity in AAN guideline authorship.¹ We are and have been collectively committed to principles of equity in our guideline development process. Writing now in our individual capacities, we feel it is necessary to address, in our opinion, the shortcomings and flawed methodology in the report from Dr. Ross and colleagues.

As a group, we are and have been steadfastly committed to achieve equity in this work. We know there is always more progress to be made; however, we fear that the errors by Dr. Ross and colleagues will mischaracterize prior efforts and discourage future efforts, to achieve gender equity. There are multiple potential sources of error in their analysis of neurology guideline authorship, with 3 foundational flaws in their report:

1. In their article, revised from its June 2022 ahead-of-print version, Dr. Ross and colleagues report that women are under-represented in authorship of 68 neurology practice guidelines published between 2015 and 2020. The AAN only published 30 guidelines during this span. Most documents in their analysis fall outside AAN's influence over authorship. Many of the documents included in their analysis were, in fact, not practice guidelines. Sixteen of the guidelines analyzed were quality measure sets, which do not include practice guideline recommendations.
2. Dr. Ross and colleagues compare guideline authorship to a benchmark that does not meet the AAN's rigorous standards for inclusion.² Dr. Ross and colleagues selected academic neurologists (from the Association of American Medical Colleges database) as the comparator for author gender proportions. The AAN is intentionally more inclusive in its author empanelment, incorporating panel membership from throughout the field of neurology, including academic neurologists, nonacademic neurologists, and other neurology providers. While we do not believe that the bias of Dr. Ross and colleagues toward academic authors is intentional, it is important to note this major difference from our guideline development policy. The AAN membership database is a better approximation of our eligible guideline author pool.
3. The analysis by Dr. Ross and colleagues fails to consider the long development cycle of rigorous, evidence-based guidelines. Most guideline panels are formed years before publication, and in the setting of growing representation of women in neurology, it is inappropriate to compare gender benchmarks with the publication year rather than the empanelment year. For example, the authors of the 4 AAN guidelines published in 2015 were empaneled between 2006 and 2010, a long interval during which gender proportions in neurology changed considerably.

To perform an analysis that corrects some of these methodologic shortcomings, we undertook an independent review of AAN published guidelines between 2015 and 2020. Data were gathered from (1) publicly available sources on the AAN site and (2) internal membership data and were analyzed to replicate the stated aim by Dr. Ross and colleagues (primary analysis performed by T.P.). Data were analyzed according to the number of authors, number of authors identified as women, whether the first author was a woman, and whether the last author (senior author) was

Author disclosures are available upon request (journal@neurology.org).

a woman. Additional information on author identity as a physician or neurologist was also obtained. For the reasons described above, AAN membership was used as the benchmark comparator. Our results were as follows: For guidelines published in 2015 and 2016, there was no significant gender difference in authors who were guideline panelists, physician panelists, neurologist panelists, first author, or last author.

In 2017, there were only 3 guidelines published, with guideline panelists, physician panelists, and neurologist panelists more likely to be men ($p = 0.017$ – 0.024 , Z test of 2 proportions) but no difference in first or senior authorship according to sex. In 2018, there was no significant difference in percentages of authors who were guideline panelists, physician panelists, neurologist panelists, or first author, according to sex; in 2018, significantly more women were last authors (7 of 8 senior authors, $p < 0.01$). In 2019, there was a larger percentage of guideline panelists, physician panelists, neurologist panelists, and first authors who were women ($p = 0.0002$ – 0.03) with no difference in sex of the last author. For 2020, there were no significant differences in any of these measures compared with AAN membership. In aggregate from 2015 to 2020, there were no differences in any authorship category according to sex. It should be noted that this analysis does not correct for the timing error by Ross and colleagues (i.e., using publication year instead of empanelment year), which given the lower proportion of women in our field in those earlier years would almost certainly strengthen our findings.

As the current and former leaders of AAN guideline development, we know our teams have a long-standing commitment to pursuing gender diversity in our panels. Therefore, we are gratified to know from the analysis presented here that those efforts, years in the making, have resulted in overall gender parity in authorship of AAN guidelines. We fully acknowledge that there are many known and unknown opportunities to improve equity across numerous domains in our specialty and that there is no room for complacency in all goals of equity. In that context, we believe it is important to counter a flawed characterization of our efforts and outcomes in achieving gender equity in guideline authorship.

1. Ross L, Hassett C, Brown P, et al. Gender representation among physician authors of practice guidelines developed, endorsed, or affirmed by the American Academy of Neurology. *Neurology*. 2022;100(5):e465-e472.
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Author Response: Gender Representation Among Physician Authors of Practice Guidelines Developed, Endorsed, or Affirmed by the American Academy of Neurology

Lindsay A. Ross (Cleveland), Catherine Hassett (Cleveland), M. Shazam Hussain (Cleveland), Peter Brown (Cleveland), Elizabeth Spurgeon (Cleveland), Rachael Mathew (Cleveland), Gabriella Bal (Cleveland), Amarilis Martin (Mount Pleasant, MI), Julie K. Silver (Boston), and Mary Rensel (Cleveland)
Neurology® 2023;101:94–96. doi:10.1212/WNL.0000000000207576

We want to thank the group of American Academy of Neurology (AAN) practice guideline (PG) leaders for their attention to our study,¹ but we find their complaints related to our work to be unfounded.

We strongly disagree that any of the PGs analyzed “fall outside the AAN’s influence over authorship.” While it is obvious that the AAN has jurisdiction over the authorship of its developed guidelines, we note that the AAN also decides the standards by which it endorses or affirms guidelines from other organizations. The decision to include (or not include) criteria focused on inclusive authorship is the AAN’s alone. In our discussion, we specifically address

Author disclosures are available upon request (journal@neurology.org).

this choice to include the entire scope of PGs presented on the AAN's PG website to account for interorganizational structural discrimination (ISD).² In addition, for those specifically interested in PGs developed by the AAN, we provided a detailed subanalysis where the results mirrored the overall analysis.

The AAN PG leadership group also takes issue with the documents included in our analysis. As noted in our work, at the time of our analysis, all of these documents were presented as a collective on the AAN website labeled "Practice Guidelines" under the statement: "Access clinical practice guidelines to help make decisions on the diagnosis and treatment of neurologic diseases." As such, we analyzed them as a collective. This definition of PGs also helps to avoid selection bias in our analysis. Moreover, the gender representation among physician authors of all of these documents is important for the same reasons as traditional clinical practice guidelines: effect on patient care and author career advancement.

The AAN PG leadership group suggested that AAN membership data would be better than Association of American Medical Colleges (AAMC) data on full-time academic neurology physicians as a field comparator. However, PG authorship is not restricted to AAN members, especially for those PGs which are affirmed or endorsed by the AAN. In addition, we focused on the physician authorship in PGs, whereas AAN membership is open to a broader group of caregivers. Accordingly, although still imperfect as noted in our discussion, our field benchmark choice was carefully thought out and appropriate for this study.

The AAN PG leadership group states that we made a "timing error" by using publication year instead of empanelment year. While we agree that empanelment year might be another way to conduct this analysis, our methodology using publication year is consistent with other current literature assessing gender representation among PG authors.^{3,4} Thus, stating that we made an error is a serious mischaracterization. Moreover, in our aim to ensure the fairest comparison with available data, we used 3 different time-point benchmarks. Further, we would argue that even if one were to consider empanelment timing (data that were not publicly available) instead of publication year, that for the collective of PGs published between 2015-2020, we would expect at the very least the 2015 and likely the 2018 benchmarks would remain reasonable comparators. Moreover, we found that women represented only 18% of physician first authors, whereas even back as far as 2007 (the earliest AAMC data report we could find), women already represented 23% of the active academic and nonacademic neurology physician field.⁵ It seems clear that the representation of women among physician authors of AAN developed, endorsed, or affirmed PGs is low in important ways.

We appreciate that the AAN PG leadership group is looking closely at these data. However, their self-presented subanalysis lacks details on methodology and rigor in analysis. The group does not state how it identified the gender and terminal degrees of the authors and makes no note of verifications for these crucial assignments. They use the AAN proprietary membership data as their benchmark without providing these values for reference. Thus, we and others are not able to verify their analysis.

Moreover, they pursue an ill-advised year-by-year analysis and base their conclusions only on *p* values without providing any of the raw values or even confidence intervals. In the resultant small sample sizes of PGs for analysis each year, a gender disparity would have to be egregious to reach statistical significance, and a more modest pattern of gender disparity (as we identified) would easily be missed. In fact, it was for this reason that in our subanalysis of AAN-developed PGs we did not perform z-testing as we noted in our work. A year-by-year analysis could also be subject to the Simpson paradox.

Furthermore, the AAN PG leadership group notes that in aggregate they find no difference in gender representation, but they provide no statement of an AAN membership year used for the comparator. Accordingly, one must assume this to be simply a summary statement of their year-

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by-year analysis, and no true aggregate analysis was performed. As such, we are left wholly unclear whether the AAN PG leadership group's self-analysis even truly differs from our own.

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CORRECTION & REPLACEMENTS

Trajectories of Cognitive Decline in Brain Donors With Autopsy-Confirmed Alzheimer Disease and Cerebrovascular Disease

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In the Research Article “Trajectories of Cognitive Decline in Brain Donors With Autopsy-Confirmed Alzheimer Disease and Cerebrovascular Disease” by Frank et al,¹ the fifth author's name should be listed as “Caroline Labriola.” The article has been replaced by a corrected version. The authors regret the error.

Reference

1. Frank B, Ally M, Tripodis Y, et al. Trajectories of cognitive decline in brain donors with autopsy-confirmed Alzheimer disease and cerebrovascular disease. *Neurology*. 2022;98(24):e2454-e2464. doi:10.1212/wnl.0000000000200304.

Association of Nonalcoholic Fatty Liver Disease and Fibrosis With Incident Dementia and Cognition

The Rotterdam Study

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In the Research Article “Association of Nonalcoholic Fatty Liver Disease and Fibrosis With Incident Dementia and Cognition: The Rotterdam Study” by Xiao et al,¹ the second author's name should be listed as “Laurens A. van Kleef,” and the fourth author's name should be listed as “Robert J. de Knegt.” The article has been replaced by a corrected version. The authors regret the errors.

Reference

1. Xiao T, van Kleef LA, Ikram MK, de Knegt RJ, Ikram MA. Association of nonalcoholic fatty liver disease and fibrosis with incident dementia and cognition: the Rotterdam Study. *Neurology*. 2022;99(6):e565-e573. doi:10.1212/WNL.0000000000200770.