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

This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (CC BY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.
Author(s):
Tian Xiao, MD; Laurens van Kleef, MD; M. Kamran Ikram, MD PhD; Robert De Knegt, MD; M. Arfan Ikram, MD PhD

Corresponding Author:
M. Arfan Ikram, m.a.ikram@erasusmc.nl

Affiliation Information for All Authors: 1. Department of Epidemiology Erasmus MC university medical center, Rotterdam, The Netherlands; 2. Department of Gastroenterology and Hepatology, Erasmus MC university medical center, Rotterdam, The Netherlands; 3. Department of Neurology, Erasmus MC university medical center, Rotterdam, The Netherlands

Equal Author Contribution:
T. Xiao and L.A. van Kleef contributed equally to this manuscript.

Contributions:
Tian Xiao: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Laurens van Kleef: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
M. Kamran Ikram: Drafting/revision of the manuscript for content, including medical writing for content
Robert De Knegt: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design
M. Arfan Ikram: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data

Figure Count:
2

Table Count:
3

Search Terms:

Acknowledgment:
We gratefully acknowledge the contribution of the participants of the Rotterdam Study, research assistants (particularly Paulien van Wijngaarden for performing the liver ultrasounds), the general practitioners, hospitals, and pharmacies in
Study Funding:
This study was partly performed as part of the Netherlands Consortium of Dementia Cohorts (NCDC), which receives funding in the context of Deltaplan Dementie from ZonMW Memorabel (projectnr 73305095005) and Alzheimer Nederland. The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), the Research institute for Diseases in the Elderly (Ride), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII) and the Municipality of Rotterdam. Financial support was also provided by the Foundation for Liver and Gastrointestinal Research, Rotterdam, the Netherlands. The funding sources did not influence study design, data collection, analysis and interpretation of the data, nor the writing of the report and decision to submit for publication.

Disclosures:
R. de Knegt is a speaker for Echosens, consultant for AbbVie and received grants from Abbvie, Gilead and Janssen. The remaining authors reported no relevant disclosures.

Preprint DOI:

Received Date:
2021-12-20

Accepted Date:
2022-04-08

Handling Editor Statement:
Submitted and externally peer reviewed. The handling editor was Linda Hershey, MD, PhD, FAAN.

ABSTRACT
Background & Objectives: Non-alcoholic fatty liver disease (NAFLD) might affect brain health, via the so-called liver-brain axis. Whether this results in 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. Last, 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 increased risk for dementia (NAFLD based on ultrasound, 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. Interestingly, NAFLD was associated with a significantly decreased risk for incident dementia until five 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 increased risk for incident dementia, nor was NAFLD associated with impaired cognitive function. In contrast, NAFLD was even protective in the first five years of follow up, hinting towards NAFLD regression before dementia onset.

**Clinical trial number:** NTR6831

**Keywords:** NAFLD; fibrosis; liver stiffness; cognition; dementia; epidemiology; general population; longitudinal analysis

**INTRODUCTION**

Non-alcoholic 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 extra-hepatic
malignancies such as colon and stomach cancer. 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 dyslipidemi. Accumulating evidence also suggests a direct association of NAFLD with brain structural changes via the so-called liver-brain axis. 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 brain; 2) increased brain insulin resistance in patients with NAFLD may cause oxidative stress, excessive free fatty acids and brain mitochondrial disorders; 3) cerebrovascular and hemodynamic disturbances provoked by a prothrombotic state. Despite this growing evidence for a liver-brain axis, current available studies reported no effects of NAFLD on dementia or only in frail NAFLD participants with fibrosis. However, some other studies indicated that cognitive impairment was more common in patients with NAFLD or fibrosis, 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 impact 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%.

Study visits comprised a home interview and various physical examinations at the research center and were repeated every four to six years. In this study, we included three different sets (Figure 1) in which we assessed the impact of NAFLD or fibrosis on the risk of incident dementia several ways. Set 1 comprised of participants in whom we had available fatty liver index (FLI) to determine NAFLD, measured between 1997 and 2002. Set 2 comprised of 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 that also underwent liver stiffness measurement 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; 4) Secondary causes for steatosis or missing alcohol data. These secondary causes were steatosis-inducing drug use, viral hepatitis or excessive alcohol consumption (>20 grams/day for female or >30 grams/day for male) assessed by food frequency questionnaire (FFQ) or alcohol interview. In addition, for set 3, participants with invalid liver stiffness measurements 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*\log_e(\text{triglycerides})} + 0.139*\text{BMI} + 0.718*\log_e(\text{GGT}) + 0.053*\text{waist circumference} - 15.745) / (1 + e^{0.953*\log_e(\text{triglycerides})} + 0.139*\text{BMI} + 0.718*\log_e(\text{GGT}) + 0.053*\text{waist circumference} - 15.745) x 100, where triglycerides were measured in mg/dL, GGT in U/L, waist circumference in cm, and BMI in kg/m^2. Participants were categorized according to their FLI score as no NAFLD for FLI <30 and NAFLD for FLI \geq 60.\textsuperscript{21} Steatosis based on abdominal ultrasound was defined as hyperechoic liver parenchyma compared to the spleen or kidney according to the protocol of Hamaguchi et al.\textsuperscript{22} Abdominal ultrasound was performed by a single certified and experienced sonographer on a Hitachi Hi Vision 900.

**Fibrosis assessment**

Liver stiffness was assessed using transient elastography (FibroScan, EchoSens, Paris, France). At least ten 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.\textsuperscript{23} Liver fibrosis was defined as liver stiffness measurement (LSM) \geq 8.0 kPa.\textsuperscript{24}

**Dementia assessment**

Dementia assessment was performed at baseline and subsequent center visits with the Mini-Mental State Examination and the Geriatric Mental Schedule.\textsuperscript{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 standard criteria for dementia (DSM-III-R) for all sets and throughout the study period. Follow-up was complete
until 1\textsuperscript{st} January 2018. Within this period, participants were followed until the date of dementia, death or 1\textsuperscript{st} of January 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 Task (LDST), the Word Fluency Task (WFT), a 15-Word Learning Test with immediate (WLTimm) and delayed recall (WLTdel), and Purdue Pegboard test (PPB test), which are described in eTable 1, supplement. These test results were transformed into a Z-score, this reflects the number of standard deviations 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.\textsuperscript{26}

**Covariates**

Demographic and physiological information was collected at baseline and included age, sex, education level (lower education, intermediate education, higher education), smoking status (never, former, current), alcohol intake (units/day), body mass index (BMI, kg/m\textsuperscript{2}), alanine aminotransferase (ALT, U/L) and comorbidity (diabetes, hypertension and stroke)\textsuperscript{19}. Diabetes was defined as fasting glucose \(\geq 7\) mmol/L or use of anti-diabetic drugs, hypertension as systolic blood pressure \(\geq 140\) mmHg, diastolic blood pressure \(\geq 90\) mmHg or the use of antihypertensive medication and stroke was based on linkage with hospital records and verified by two experienced vascular neurologists. Depressive symptoms were assessed with a validated version of the Centre for Epidemiologic Studies Depression (CES-D) scale. Depression was defined as at least 16/60 points.\textsuperscript{27} Apolipoprotein E (APOE) genotype was
determined using a PCR and a bi-allelic TaqMan assay (rs7412 and rs429358) on labelled DNA samples. APOE-ε4 allele represented carrier of one or two ε4 alleles.

Statistical analysis
Baseline characteristics are described for the overall population in all three sets. Data are expressed as mean ± standard deviation (SD) or as median (with 25th-75th percentile [P25-P75]). For time-to-event analyses, we assessed the associations between of NAFLD and liver stiffness with the risk of incident dementia using Cox proportional-hazards regression analyses. Baseline was defined as date of blood test (for FLI) or abdominal ultrasound and follow-up ended at the diagnosis of dementia, death, or 1<sup>st</sup> January 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. Missing genetic data was not imputed as they are innate and not modifiable, remaining missing data was 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 ANOVA models. We calculated the differences of the individual cognitive tests and G-factor for participants with NAFLD compared to those without NAFLD and for fibrosis compared to 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 analysis 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 (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue 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 upon request. Requests should be directed towards 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 liver stiffness measurement to assess fibrosis in set 3, exclusions are described in eTable 2, supplement. Participants from the different sets had a similar mean age (around 70 years), 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 set 1 and 2 are presented in eTable 3 and the characteristics stratified for fibrosis status (set 3) are available in eTable 4, supplement.

**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 (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).

Interestingly, for the first five 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 to no NAFLD (FLI <30). With the period of follow-up extending, the protective association between NAFLD and risk of incident dementia disappeared (between 5-10 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 prior to abdominal ultrasound since the participants’ previous visit (mean time between visits 6.1 years) was more evident among participants that had developed dementia during the follow up, compared to 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;0.092); in fact, better performance of Stroop test 2 was observed in cross-sectional analyses. On the contrary, we found that liver fibrosis was associated with lower global cognition scores (MD: –0.172, 95%CI: -0.307;-0.037) and lower scores of LDST and more time to finish Stroop test 1 and 3 (eTable 5, supplement).

**DISCUSSION**

We investigated the impact of NAFLD on dementia and cognitive function in a large prospective ongoing population-based cohort with up to 15.5 years 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 five years after FLI-assessment. Similar trends were seen for the association between ultrasound-based NAFLD and incident dementia during the 5.7 years median follow-up. This
points us towards one of the challenges regarding NAFLD and dementia research: the reversibility of NAFLD due to weight loss. Dementia, albeit unintentionally, is also accompanied by weight loss during its preclinical phase, 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. Consequently, weight loss in the years prior to dementia could thus obscure any relation between NAFLD and incident dementia. In our study, the demonstrated protective effect of NAFLD on dementia disappeared after five 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. 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 increased risk for incident dementia. Considering cognitive impairment as a classic prodromal symptom preceding the onset of dementia, 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, Letter-Digit substitution test resulting in lower G-factor score. These tests cover attention and concentration, processing speed and global cognitive function respectively. Further research is required whether this hints towards 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.\textsuperscript{14} Moreover, a study with almost 20 years of follow-up could not identify NAFLD as risk factor for incident dementia.\textsuperscript{15} However, they reported that histology proven fibrosis improved the prediction of dementia. Fibrosis was also linked to dementia among the frail elderly previously.\textsuperscript{16} However, these results need to be interpreted with caution since 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 test\textsuperscript{17} and symbol digit substitution test,\textsuperscript{17} reduced reaction time,\textsuperscript{17} lower MoCA scores,\textsuperscript{35,36} brain volume reduction,\textsuperscript{9} and reduced brain activity.\textsuperscript{36} However, most results were unadjusted or disappeared after 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.\textsuperscript{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 a HR of 1.25 in set 1 and a HR of 1.44 in set 2.

Although this study had a large sample size and extensive analysis were 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 multi-ethnic and younger populations. Second, NAFLD and fibrosis were not based on liver biopsy since 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 was 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. Last, since 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.\(^{38-40}\)

**CONCLUSION**

In conclusion, individuals with NAFLD were not at 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 five 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.
FIGURE 1 Overview of different study sets and key characteristics for investigating the association between NAFLD and fibrosis with dementia and cognitive function. 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. Additionally, the impact of NAFLD and fibrosis on cognitive function was studied cross-sectionally in set 2 and set 3.

<table>
<thead>
<tr>
<th>Liver assessment</th>
<th>Inclusions</th>
<th>Follow-up</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty liver index</td>
<td>3,975</td>
<td>5.5 year</td>
<td>753</td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td>4,577</td>
<td>5.7 year</td>
<td>262</td>
</tr>
<tr>
<td>Transient elastography</td>
<td>3,300</td>
<td>5.6 year</td>
<td>127</td>
</tr>
</tbody>
</table>
FIGURE 2 Mean difference of performance on cognitive tests between participants with NAFLD compared to no NAFLD and fibrosis compared to 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 to those without NAFLD and for fibrosis compared to no fibrosis. Results were adjusted for age, sex, education level, smoking status, BMI, cholesterol, triglycerides, hypertension, stroke, diabetes, depression and APOE genotypes.

Abbreviations: APOE, apolipoprotein E; G-factor, principle component scores of cognition tests; 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.
REFERENCES


6. Allen AM, Hicks SB, Mara KC, Larson JJ, Therneau TM. The risk of incident extrahepatic cancers is higher in non-alcoholic fatty liver disease than obesity - A longitudinal cohort study. *J Hepatol*. Dec 2019;71(6):1229-1236.


Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.

Table 1: Baseline characteristics per analysis set

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Set 1</th>
<th>n = 3.975</th>
<th>Set 2</th>
<th>n = 4.577</th>
<th>Set 3</th>
<th>n = 3.300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70.0 (8.0)</td>
<td>69.9 (9.1)</td>
<td>67.6 (8.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2408 (60.6)</td>
<td>2709 (59.2)</td>
<td>1892 (57.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>3068 (77.2)</td>
<td>3866 (84.5)</td>
<td>2830 (85.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former/current smoking</td>
<td>2495 (63.1)</td>
<td>2933 (64.2)</td>
<td>2081 (63.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>2357 (59.8)</td>
<td>2237 (49.4)</td>
<td>1517 (46.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>1129 (28.6)</td>
<td>1355 (29.9)</td>
<td>972 (29.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>456 (11.6)</td>
<td>934 (20.6)</td>
<td>779 (23.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.0 (4.1)</td>
<td>27.6 (4.4)</td>
<td>27.1 (3.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enlarged waist circumference*</td>
<td>1799 (45.3)</td>
<td>2015 (44.1)</td>
<td>1356 (41.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>1983 (50.0)</td>
<td>2268 (50.4)</td>
<td>1529 (47.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>549 (13.8)</td>
<td>715 (15.8)</td>
<td>458 (14.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>71 (1.8)</td>
<td>122 (2.7)</td>
<td>59 (1.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2727 (68.8)</td>
<td>3374 (73.7)</td>
<td>2276 (69.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biochemistry / genetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>23 [17, 32]</td>
<td>23 [17, 33]</td>
<td>22 [16, 33]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.78 (0.97)</td>
<td>5.42 (1.11)</td>
<td>5.48 (1.10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.34 [1.02, 1.83]</td>
<td>1.27 [0.98, 1.72]</td>
<td>1.26 [0.97, 1.70]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOE-ɛ4</td>
<td>1062 (27.8)</td>
<td>1137 (26.7)</td>
<td>842 (27.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAFLD†</td>
<td>1293 (32.5)</td>
<td>1586 (34.7)</td>
<td>1066 (32.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver stiffness (kPa)</td>
<td>-</td>
<td>4.8 [3.8, 5.9]</td>
<td>4.8 [3.8, 5.9]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data is presented as mean (SD), median [P25-P75] or n and percentage. Baseline characteristics are presented per set. *Waist circumference > 102 cm for male and > 88 cm for female. †Based on FLI ≥ 60 in set 1 or ultrasound in set 2 and 3.

Abbreviations: APOE, apolipoprotein E; ALT, alanine transaminase; BMI, body mass index; FLI, fatty liver index; GGT, gamma glutamyl transpeptidase; NAFLD, non-alcoholic fatty liver disease.
<table>
<thead>
<tr>
<th></th>
<th>cases</th>
<th>FU* (year)</th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>NAFLD (FLI ≥ 60)</td>
<td>753/3975</td>
<td>15.5</td>
<td>0.91</td>
<td>0.76 - 1.10</td>
<td>0.79</td>
<td>0.65 - 0.97</td>
<td>0.92</td>
<td>0.69 – 1.22</td>
</tr>
<tr>
<td>NAFLD (Ultrasound)</td>
<td>262/4577</td>
<td>5.7</td>
<td>0.87</td>
<td>0.66 – 1.15</td>
<td>0.73</td>
<td>0.54 – 0.98</td>
<td>0.84</td>
<td>0.61 – 1.16</td>
</tr>
<tr>
<td>Fibrosis*</td>
<td>127/3300</td>
<td>5.6</td>
<td>1.12</td>
<td>0.61 – 2.05</td>
<td>1.08</td>
<td>0.58 – 2.00</td>
<td>1.07</td>
<td>0.58 – 1.99</td>
</tr>
<tr>
<td>Liver stiffness (kPa)</td>
<td>127/3300</td>
<td>5.6</td>
<td>1.02</td>
<td>0.95 – 1.10</td>
<td>1.00</td>
<td>0.92 – 1.09</td>
<td>1.01</td>
<td>0.92 – 1.10</td>
</tr>
</tbody>
</table>

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 to participants with FLI < 30 or participants without hepatic steatosis.

*Median follow up in years. †Defined as LSM ≥ 8.0 kPa.

Abbreviations: APOE, apolipoprotein E; BMI, body mass index; CI, confidence interval; FLI, fatty liver index; FU, follow-up; HR, hazard rate; kPa, kilopascals; NAFLD, non-alcoholic fatty liver disease.
Table 3: Risk of incident dementia for NAFLD based on fatty liver index per 5 years of follow up

<table>
<thead>
<tr>
<th>Period</th>
<th>cases</th>
<th>Model 1</th>
<th></th>
<th></th>
<th>Model 2</th>
<th></th>
<th></th>
<th>Model 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>0 – 5 years</td>
<td>155/3975</td>
<td>0.59</td>
<td>0.38 – 0.91</td>
<td>0.50</td>
<td>0.32 – 0.80</td>
<td>0.48</td>
<td>0.24 – 0.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 – 10 years</td>
<td>194/3472</td>
<td>0.85</td>
<td>0.59 – 1.21</td>
<td>0.78</td>
<td>0.54 – 1.14</td>
<td>1.10</td>
<td>0.63 – 1.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>404/2786</td>
<td>1.11</td>
<td>0.87 – 1.43</td>
<td>0.94</td>
<td>0.71 – 1.23</td>
<td>1.07</td>
<td>0.72 – 1.57</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 to FLI < 30.

Abbreviations: APOE, apolipoprotein E; BMI, body mass index; CI, confidence interval; HR, hazard rate; NAFLD, non-alcoholic fatty liver disease.
Association of Nonalcoholic Fatty Liver Disease and Fibrosis With Incident Dementia and Cognition: The Rotterdam Study

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

*Neurology* published online May 26, 2022
DOI 10.1212/WNL.0000000000200770

This information is current as of May 26, 2022