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

The Rotterdam Study

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Study Question
Is there an association between nonalcoholic fatty liver disease (NAFLD) and fibrosis with incident dementia and cognition?

What Is Known and What This Paper Adds
There is increasing evidence for a direct association of NAFLD with brain structural changes through the so-called liver-brain axis. Several studies investigated the association of NAFLD with dementia, but these were hampered by a cross-sectional design, limited follow-up, small sample size, or poor definition of NAFLD and/or dementia (e.g., International Classification of Diseases-10 codes), and so far, inconsistent results have been published. This study’s results did not find an association between NAFLD and fibrosis with an increased risk for incident dementia, nor was NAFLD associated with impaired cognitive function.

Methods
Within the Rotterdam Study, a large, well-defined ongoing prospective cohort, we performed longitudinal and cross-sectional analyses. The analyses include data from 3,975 participants (mean age 70.0 ± 8.0 years, follow-up [FU] 15.5 years, 753 with incident dementia) visiting between 1997 and 2002 with the available fatty liver index (FLI; set 1), 4,577 participants (mean age 69.9 ± 9.1 years, FU 5.7 years, 262 with incident dementia) visiting between 2009 and 2014 with abdominal ultrasound (set 2), and 3,300 participants (mean age 67.6 ± 8.4 years, FU 5.6 years, 127 with incident dementia) visiting between 2009 and 2014 with liver stiffness measurements (set 3). 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. The primary outcome, incident dementia, was defined according to the DSM-III-R. Associations between NAFLD, fibrosis or liver stiffness, and incident dementia were quantified using Cox regression. The association between NAFLD and cognitive function was assessed cross-sectionally.

Results and Study Limitations
Consistently, there was no association between NAFLD and fibrosis with an increased risk for dementia in fully adjusted models (Table). However, NAFLD was associated with a significantly decreased risk for incident dementia until 5 years after FLI assessment (hazard rate: 0.48; 95% CI 0.24–0.94). Moreover, NAFLD was not associated with worse cognitive function in multiple individual domains. This study has limitations, including potentially limited generalizability to non-Caucasians, lack of liver biopsy due to ethical concerns, cross-sectional design of the cognition analysis, and NAFLD being only assessed at baseline.

Study Funding and Competing Interests
This study has been entered into the NTR (trialregister.nl) and the ICTRP (who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. The study received targeted funding from the NCDC; ZonMw; Alzheimer Nederland; Erasmus MC; Erasmus University; RIDE; Ministry of Education, Culture and Science; Ministry of Health, Welfare and Sport; EU; and SLO. The authors report no competing interests. Go to Neurology.org/N for complete disclosures.
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