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The prevalence and risk factors for cognitive impairment in obesity and NAFLD

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Abstract

Background: Severe obesity may be accompanied by cognitive dysfunction and NAFLD, but the associations remain unclear. We describe the prevalence and features of cognitive dysfunction and examine the associations between cognitive dysfunction and the presence and severity of NAFLD, and the associations between cognitive dysfunction and signs of other obesity-related comorbidities and neuronal damage.

Methods: A cross-sectional study of patients with a body mass index of 35 kg/m^2 underwent evaluation for bariatric surgery. They were screened for adiposity-related comorbidity and underwent a liver biopsy and basic cognitive testing with the Continuous Reaction Time test, the Portosystemic Encephalopathy Syndrome test, and the Stroop Test. A representative subgroup also underwent the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The primary study outcome was "cognitive impairment," defined as $\geq$2 abnormal basic cognitive tests and/or an abnormal RBANS. The Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) served as a biomarker for neuronal damage.

Results: We included 180 patients; 72% were women, age 46 $\pm$ 12 years, 78% had NAFLD, and 30% with NASH without cirrhosis. 8% were cognitively impaired by the basic tests and 41% by RBANS results. Most impaired were executive and short-time memory functions. There were no associations between cognitive impairment and BMI, NAFLD presence or severity, or metabolic comorbidities. Male sex (OR: 3.67, 95% CI, 1.32–10.27) and using 2 or more psychoactive medications (5.24, 95% CI, 1.34–20.4) were associated with impairment. TREM2 was not associated with cognitive impairment.

Abbreviations: CRT, The Continuous Reaction Time Test; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; PSE, The Portosystemic Encephalopathy Score; OPEN, Open Patient Data Explorative Network; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RedCap, Research Electronic Data Capture; TREM2, Triggering receptor expressed on myeloid cells 2.

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Conclusions: Nearly half of this severely obese study cohort exhibited measurable multidomain cognitive impairment. This was not dependent on NAFLD or another adiposity comorbidity.

INTRODUCTION

Obesity and its comorbidities may involve cognitive problems, which is of concern because obesity rates are increasing across age groups. Among the obesity-related comorbidities, NAFLD and its manifestation, NASH, have attracted particular interest due to the possible relation to minimal HE. In patients with cirrhosis, HE is a common cause of reduced quality of life and hospital admission, but it remains uncertain if noncirrhotic NAFLD/NASH may cause HE. Furthermore, abundant adipose tissue and NAFLD/NASH may be drivers of neuroinflammation, neurodegeneration, and organic brain disease through low-grade systemic inflammation activation. Also, insulin resistance and vascular dysfunction may contribute. NAFLD/NASH, thus, could increase the risk for cognitive dysfunction based on metabolic and organic brain impairment.

Obesity or NAFLD-related cognitive dysfunction is not systematically well characterized. A recent review states that "mental speed, attention, and psychomotor speed" and "ideas, abstraction, figural creations, and mental flexibility" are significantly affected.[1] However, varying and often single-domain cognitive test strategies are used and reported, and only a few studies (7,8,9,10) use liver biopsy as the diagnostic and grading standard for NAFLD. Studies on the association between NAFLD and organic brain disease are in contradiction: a Swedish study based on the National Patient Registry showed a weak association with dementia,[2] whereas a prospective Dutch cohort study with both longitudinal and cross-sectional data found no association between NAFLD and liver fibrosis biomarkers and dementia, nor was NAFLD associated with cognitive dysfunction.[3] Still, when taken together, the available evidence may suggest that even noncirrhotic NAFLD may be related to cognitive dysfunction, possibly independent of other risk factors.[4,5] To gain more insight, we need studies in larger well-characterized cohorts with liver biopsies and multidomain cognitive evaluation, preferably including a marker of neuroinflammatory damage.

The Triggering Receptor Expressed on Myeloid cells 2 (TREM2) is such a marker that has been reported to be higher in plasma and cerebrospinal fluid from patients with Alzheimer disease, Parkinson disease, traumatic brain injury, and amyotrophic lateral sclerosis.[6–10] TREM2 is expressed in microglia, the brain's resident macrophages. It has been reported to have a neuroprotective role in Alzheimer disease, where TREM2 loss of function results in more severe neuronal damage.[11,12]

It thus remains unsettled to what extent obesity or NAFLD is associated with cognitive dysfunction. Furthermore, it is unclear whether obesity-associated cognitive dysfunction is a presentation of HE. We wanted to determine the prevalence of cognitive dysfunction in severe obesity patients, describe which cognitive domains are dysfunctional, examine the association between cognitive dysfunction and the presence and severity of NAFLD, and examine the associations between cognitive dysfunction and signs of other obesity-related comorbidities, including neuronal damage. We *a priori* expected that cognitive impairment would be more frequent in our patients than reported in the background population, multiple cognitive domains would be impaired, and NAFLD and other obesity-related comorbidities would be associated with impairment. Furthermore, we expected that TREM2, as a biomarker of ongoing neuronal damage, in plasma might be higher in patients with impaired cognition.

METHODS

Patients

We included 180 participants in this cross-sectional study. Inclusion criteria were obesity class II–III (body mass index $\geq$35 kg/m^2), age 18–70 years, ability to cooperate with liver biopsy, and provision of informed written consent. Possible participants were approached about the study during an outpatient visit or after having permitted us to telephone them. If the patients consented to screen for eligibility, data to evaluate inclusion and exclusion criteria were retrieved from the electronic patient file where all prior imagining, biochemical, histological, and chart records were available. Patients were excluded if they had alcohol use above >7/14 units per week for females and males, respectively, prior or current use of fatty-liver–inducing drugs (eg, amiodarone, methotrexate, tamoxifen, glucocorticoids, and valproate), concomitant liver diseases (autoimmune and viral hepatitis B and C), clinical signs or symptoms of cirrhosis (ascites, overt HE, and esophageal varices), dementia, history of stroke, delirium, or amnesia. Participants were recruited at bariatric surgery evaluation visits,

outpatient clinics, and the University Hospital of Southern Denmark emergency waiting room between 2018 and 2022. All data and investigations were collected on the day of inclusion.

Approvals and registrations

All research was conducted in accordance with both the Declarations of Helsinki and Istanbul. All participants gave written informed consent. The study received ethics approval from the Regional Ethics Committee of Southern Denmark (DK S-20160006G) and is registered at ClinicalTrial.gov (NCT03535142). Data from the visit were entered directly into Redcap (Research Electronic Data Capture), a secure database hosted by the Open Patient Data Explorative Network (OPEN) at the University of Southern Denmark.

Cognitive assessment

We used a set of psychometric tools to assess cognition broadly. Minimal HE can only be detected at psychometric testing and is characterized by altered attention, visuospatial perception, visuospatial construction, psychomotor speed, and motor accuracy. The Continuous Reaction Time Test (CRT), the interstudy comparator Portosystemic Encephalopathy Syndrome Test (PSE), and a digitalized Stroop test (EncephalApp) have all separately been validated for diagnosing minimal HE. We included all three tests, here collectively mentioned as basic tests (cf. below). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a generic and comprehensive neuropsychological screening tool. The RBANS includes cognitive functions usually unaffected by HE, such as verbal and visual anterograde memory, working memory, and language. However, RBANS also assess HE-related features, such as cognitive processing speed, language, and visuospatial function. RBANS is often used for the assessment of dementia but is also closely correlated with liver disease severity graded by the model for end-stage liver disease and has been used to grade HE.[13] The test is time-demanding and supervision-demanding, and we included it as many participants as logistically possible, randomly selected.

All participants initially underwent a round of basic cognitive tests. A representative subgroup (n = 63) additionally performed the RBANS. The testing program is outlined in Figure 1, and the psychometric tests are described in Table 1. All tests were done between 8 and 10 AM in a closed room, supervised by 2 experienced research nurses.

The CRT test is a computerized test that determines motor reaction time in response to 150 auditory stimuli presented randomly through headphones.[14] The intraindividual variation in reaction time (50 percentile-/90–10 percentiles) is the CRT index used as the primary test result.[14] In patients with known chronic liver disease, a value below 1.9 indicates minimal HE.

The Portosystemic Encephalopathy Syndrome (PSE) test is the most widely used psychometric test for minimal HE.[15] It comprises the five subtests presented in Table 1. The test is scored using norm values from a German population, and a score of −18 to 6 is assigned. A score of −5 or lower is considered abnormal.

We used a digital version of the Stroop test (StroopEncephalApp).[16] The test has 2 parts. In the first part (Off state), the participant sees hash marks in color and the names of different colors, and they need to tap the matching color name to respond correctly. In the second part (On state), color names appear on the screen written in a nonmatching color (ie, the word "blue" written with letters in green), and one is asked to tap the correct color of the word.[17] Danish Stroop on+off time cutoff for ages below 55 years is >190 seconds and for ages 55 years and older is >240 seconds.

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).[18] We used the reported cutoff <79 to define mild cognitive impairment,[18] where a total index score of 100 is the norm.

Histopathology

A liver biopsy was done with a suction needle. All biopsies were reviewed by a single pathologist specialized in NAFLD (Tina DiCaterino) and blinded to other data. Biopsies were graded by the NAFLD activity score [19] of 0–8, combining grades of steatosis (0–3), lobular inflammation (0–3), and ballooning (0–2). We also used the Kleiner fibrosis score of F0–F4, where F4 is cirrhosis.[20]

Biochemistry and TREM2 measurements

Venous blood samples were collected after a minimum of 10 hours of fasting, and samples were transported to the Department of Molecular Medicine (Odense, DK) on dry ice. The plasma was analyzed for TREM2 by human ELISA kits (ab224881, Abcam). CRP, liver enzymes, HbA1c, blood glucose, and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) were measured in all participants. Venous blood samples for measurement of ammonia were immediately stored on ice and analyzed within 15 minutes.

Covariates

Depressive symptoms were assessed using the Major Depression Inventory.[21] A total score >20 indicates depression, which is graded from mild to severe. The

TABLE 1 Overview of the 4 cognitive tests used

Name	Type and method of test	Main result	Abnormal Cut-off	Cognitive domains evaluated	Adjustment of score
Basic cognitive assessment with 3 tests (n = 180)					
The Continuous Reaction Time test 	Computerized test with headphones and a trigger button. Measures reaction times to 150 auditory stimuli (bitmatic.com)	*The CRT-Index*: 50th reaction time percentile/ (90^{th}–10^{th} percentile)	**< 1.90**	Executive functions, vigilance, and inhibitory control	CRT index is not impacted by age, gender, intelligence, or education.
The Portosystemic Encephalopathy Syndrome test 	Five paper-pencil sub-tests: Number Connection Tests A and B, Digit Symbol Test, Serial Dotting Test, and Line Tracing Test. Instructor necessary	The *PHES Sum score* ranging from -18–6	**< -4**	Attention, visuospatial-perception and -construction, psychomotor speed, and motor accuracy	Normal values are adjusted for age
The Stroop EncephalApp 	An app for an electronic device. Written tasks are given on the device screen. (https://encephalapp.com/)	*Stroop On+Off Time Score* (seconds)	Age 18-54: **>190** Age >55: **>240**	Psychomotor speed and cognitive flexibility, attention	Normal values are adjusted for age
Sub-group additional testing (n = 63)					
Repeatable Battery for the Assessment of Neuropsychological Status 	12 paper-pencil sub-tests: List learning, Story memory, Figure copy, Line orientation, Picture naming, Semantic fluency, Digit span, Coding, List recall, List recognition, Story recall, and Figure recall. Instructor necessary	*Total index sum score,* and 12 sub-test index scores	**< 79**	Immediate memory, visuospatial/construction, language, attention, and delayed memory	Normal values are adjusted for age

Basic tests: Continuous reaction time (CRT) test; the portosystemic encephalopathy syndrome test (PSE); and the stroop encephalApp. A representative subgroup did additional testing with the repeatable battery for the assessment of neuropsychological status (RBANS).

questionnaire was sent out to all participants, and 176 answered it.

We collected registered diagnoses of sleep apnea, hypertension, and diabetes and information on the use of psychoactive medications (antidepressants, antipsychotics, benzodiazepines, and central-acting pain medications) from the patient records.

Statistics

Descriptive statistics for continuous data are presented as means (±SD) or medians (IQR) as appropriate, and categorical variables are expressed as absolute frequencies/percentages unless otherwise noted. For comparison, we used a 2-tailed Student *t* test for normally distributed data and the Wilcox Mann-Whitney test or Kruskal-Wallis as appropriate. We followed the Fisher least significant difference procedure and did not perform Wilcox rank-sum pairwise tests if the initial Kruskal-Wallis test was nonsignificant.

Cognitive impairment was defined as ≥2 abnormal cognitive test results in the basic test round or as an abnormal sum score in the RBANS battery (Table 1 and Figure 1). RBANS was done in 63 randomly chosen participants, and we ensured that this subgroup was representative of, and its results, extrapolatable to the whole cohort (Supplemental Table S1, http://links.lww.com/HC9/A366).

We stratified participants into 3 groups by histopathological severity according to NAS-CRN criteria; no-NAFLD (<5% fat in the liver), NAFLD (≥5% fat in the liver), and NASH, at least 1 point for steatosis, inflammation, and ballooning). We further categorized the participants into low-moderate (F0–2) and severe fibrosis (F3–4) grades.

Univariable and multivariable logistic regression analyses were used to identify predictors associated with cognitive impairment. First, we evaluated variables for univariable analysis: age, years of education, MDI score, HOMA-IR, alanine aminotransferase, aspartate transaminase, triglycerides, LDL and HDL cholesterol, plasma TREM2, CRP, ammonium, liver stiffness (all as continuous variables); sex (M/F), type 2 diabetes (Y/N), obstructive sleep apnea (Y/N), arterial hypertension (Y/N), receiving statins (Y/N), psychoactive medication (Y/N), the severity of NAFLD (no-NASH vs. NASH), and severe fibrosis (F0–2 vs. F3–4) (all as categorical variables with 2 levels). For the multivariable model, we included variables that were *a priori* considered clinically relevant: sex, age, education (years), ammonium ion, sleep apnea, hypertension, severe fibrosis, and psychoactive medication, as well as significant variables from univariable analysis. Second, we applied stepwise-backward elimination to remove terms with $p \geq 0.2$ and add those with $p < 0.1$ to identify a subset of variables as stronger predictors. Postestimation of the Hosmer-Lemeshow goodness-of-fit test showed no evidence that our model did not fit the data. The statistical analysis plan

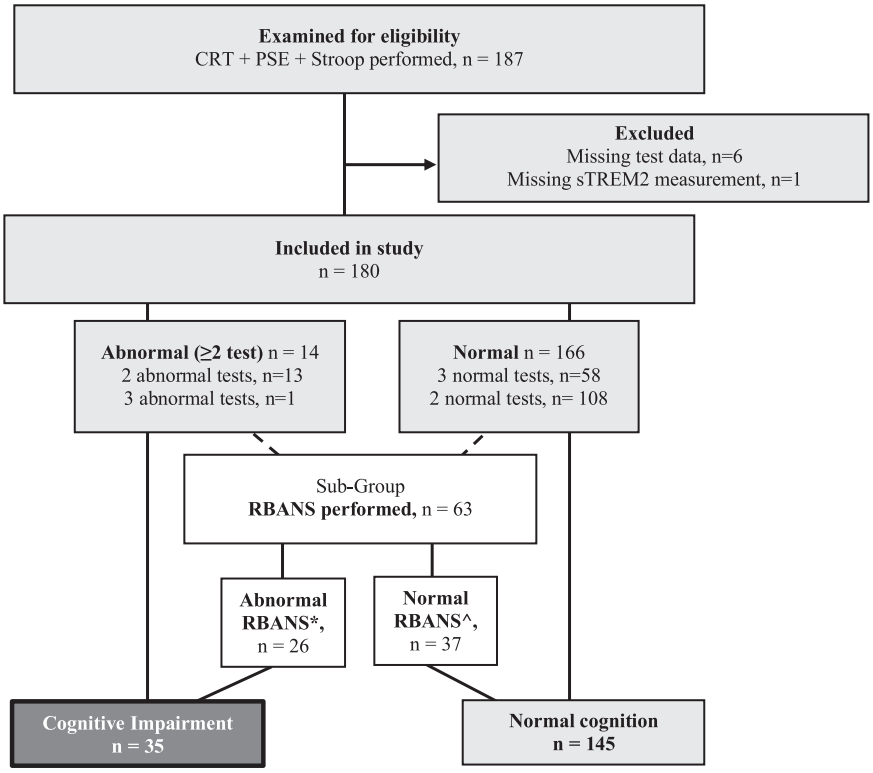

FIGURE 1 Flowchart describing the identification of participants with impaired cognition. Cognitive impairment was defined as ≥2 abnormal tests in the continuous reaction time (CRT), the Portosystemic Encephalopathy Syndrome Test (PSE), and Stroop EncephalApp, that is, the basic tests, or as an abnormal RBANS index score.

did not include a provision for correcting for multiplicity when tests were conducted to evaluate associations, and results are reported as point estimates with 95% CIs.

RESULTS

Of the 180 participants, 71% were women, their mean age was 45 ± 12 years, and their mean BMI was 41.6 ± 7.6 kg/m^2. Baseline characteristics are shown in Table 2. Twenty-two percent (39/180) did not have liver steatosis; 78% (141/180) had NAFLD, and out of these, 30% (43/141) had NASH. Seventy-five percent of those with NAFLD had low grades of fibrosis (F0–1), 19% had moderate fibrosis (F2), and only 6% had severe fibrosis (F3–4) (Table 2).

Prevalence of cognitive impairment

Approximately 30% performed normally in the 3 or 4 tests that they were submitted to, while the rest had at least 1 abnormal test. The prevalence of impaired cognition, as defined by ≥2 abnormal basic cognitive tests, was 7.8% (14/180) (Table 1 and Fig. 1). In the subgroup, the RBANS identified 41% (26/63). These were all impaired by the basic tests, and no one was impaired by the RBANS alone (Figure 1, Table 3). By extrapolation, the cohort prevalence of cognitive impairment, had we used both test strategies in all participants, was, thus, 41%.

Cognitive domains involved

We reviewed performance in each of the four tests to assess the cognitive domains involved. Sixty-five percent had abnormally high reaction time variability (CRTindex), and 50- and 90-percentile reaction times were slower than the norm in 38% and 53%, respectively. In most cases, the CRT was the only abnormal test. In the PSE test, 8% had an abnormal result below −4 points. In the Stroop test, only 3% performed out of the norm. In RBANS, immediate memory was the most affected domain, with 57% in the abnormal range (mean index score 76 ± 21). Visuospatial functions and late memory were below the norm at 30% and 32%, respectively (82 ± 12 and 84 ± 12). The participants who performed well on RBANS had normal test results in the basic cognitive assessment (CRT + PSE + Stroop) (Figure 1).

Association between cognitive dysfunction and NAFLD

There were no differences in performance for any of the cognitive tests across the strata of the cohort,

no-NAFLD versus NAFLD versus NASH (Supplemental Table S2, http://links.lww.com/HC9/A367). Also, dichotomization into a no-NASH group (no-NAFLD and NAFLD together) versus a NASH group did not reveal differences. Patients with severe fibrosis (F3–4) versus those with low/moderate fibrosis (F0–2) did not perform worse by comparison of means. The regression analyses indicated that patients with severe fibrosis have a lower PSE sum score ($p = 0.013$) (Supplemental Table S3B, http://links.lww.com/HC9/A368).

Association between cognitive dysfunction and sociodemographic variables and extrahepatic obesity–related comorbidities

The group with impaired cognition comprised more men (51% vs. 34%, $p = 0.002$) had slightly shorter education (11 vs. 12 years, $p = 0.016$), and their triglycerides and LDL cholesterol were lower but still within the normal range (1.6 vs. 1.4, $p = 0.042$; 3.1 vs. 2.7, $p < 0.001$). The groups did not differ regarding BMI or the prevalence of diabetes or hypertension. Likewise, responder frequency for the Major Depression Inventor was equal between groups (97%), with no difference in the score (median 7 vs. 8, $p = 0.66$), and the prevalence of a score ≥ 20 (indicating depression) was similar (17% vs. 15%) (Table 3). The prevalence of sleep apnea use of psychoactive medication was higher in the cognitively impaired, but the difference did not reach statistical significance (Table 3). When looking solely at the RBANS group, the same clinical characteristics applied regarding male sex and LDL, but education and triglycerides were not associated with cognitive impairment.

In the univariable analysis, impaired cognition was associated with the male sex, lower age, and lower LDL cholesterol (Table 4). The multivariable analysis confirmed that males were more likely to be in the cognitively impaired group (OR: 3.67, 95% CI, 1.32–10.27), as were participants taking a combination of 2 psychoactive medications (5.24, 95% CI, 1.34–20.4). The latter association was only present in women, of whom 40% used these medications. Higher LDL cholesterol lowered the risk of being in the cognitively impaired group (0.59, 95% CI, 0.37–0.96) (Table 4). No association was found for the use of a single psychoactive medication (antidepressants, antipsychotics, or pain medication), age, MDI score, years of education, HOMA-IR, aspartate transaminase, triglycerides, HDL cholesterol, plasma TREM2, CRP, venous ammonium, liver stiffness, type 2 diabetes, sleep apnea, hypertension, or lipid-lowering medications. In the RBANS subgroup (Table 5), the pattern was the same and confirmed that male sex (OR: 32.7 95% CI, 2.5–420) was associated with an abnormal RBANS and LDL cholesterol seemed protective (OR: 0.34, 95% CI, 0.12–0.99). However, the use of 2 or more psychoactive medications was not associated with abnormal RBANS.

Association between cognitive performance and TREM2

TREM2 was not different between participants with normal and impaired cognition based on the basic tests ($p = 0.28$) in the overall cohort. TREM2 was higher in patients with normal RBANS (53.8 vs. 38.1 ng/mL, $p = 0.015$) (Table 3), but TREM2 was not associated with cognitive dysfunction in the multivariable (Table 5).

DISCUSSION

We studied 180 patients with severe obesity, who all underwent liver biopsies and multidomain cognitive tests. We found that the occurrence of two abnormal results of the basic cognitive tests (CRT, PSE, and Stroop) identified 8% as cognitively impaired. By further including the RBANS, this number was expanded to 41%. Three-quarters of the cohort had NAFLD, and one-third of these had NASH. The cognitive impairment was not associated with the presence of NAFLD or NASH. The impairment was associated with male sex, psychoactive polypharmacy in women, and low LDL. TREM2 was not generally associated with cognitive performance, but, in patients with normal RBANS, TREM2 was higher.

The higher male risk of impaired cognition is in accordance with other studies. Among them, 2 large cohort studies indicate that obese men perform worse at cognitive testing in executive functions and memory. Also, higher BMI seems to protect cognition but only in females.[22] These observations could imply that the male brain is somehow more susceptible to metabolic and inflammatory disturbances in obesity, the males in our study were less motivated during the testing, or they a priori, independent of obesity, had a poorer cognitive function. Other studies suggest that differences in diet could explain the discrepancy.[23,24]

The use of psychoactive medications was frequent in our cohort and is a critical confounder as it can both slow cognitive functions and contribute to weight gain. Patients on psychoactive drugs are often excluded from studies on cognition. Still, since a significant fraction of obese patients uses these types of medication, we decided to keep them in the analysis. In our cohort, 23% of men and 40% of women used psychoactive drugs. We found that impaired cognition was indeed associated with the use of more than one type of psychoactive substance (ie, antidepressants, antipsychotics, or pain medications), but the use of a single psychoactive substance did not impact cognition. The association was only present in women, which may be a sex difference or due to less precise estimates in men.

Higher, but within normal range, concentrations of LDL cholesterol seemed to lower the risk of being cognitively impaired, which was not explained by

TABLE 2 Baseline characteristics of 180 participants with obesity stratified according to liver histopathology graded using NAFLD activity score (NAS-CRN), No-NAFLD < 1 grade of steatosis, NAFLD ≥1 grade of steatosis, and NASH have ≥1 grade for all features of steatosis, inflammation, and ballooning

	All n = 180	No-NAFLD n = 39	NAFLD n = 98	NASH n = 43
n (%)	180 (100.0)	39 (21.7)	98 (54.4)	43 (23.9)
Demographics				
Age (y), mean (SD)	45 (12)	42 (11)	46 (13)	47 (12)
Sex (male), n (%)	52 (28.9)	6 (15.4)	37 (37.8)	9 (20.9)
Education (y)[a]	12.0 (5.0)	12.0 (5.0)	12.0 (5.0)	12.0 (5.0)
Metabolic comorbidity				
BMI (kg/m^2)	41.6 (7.6)	41.2 (9.4)	42.1 (7.3)	40.7 (7.8)
Diabetes, n (%)	44 (24.4)	2 (5.1)	24 (24.5)	18 (41.9)
Cholesterol-lowering meds, n (%)	46 (25.6)	5 (12.8)	24 (24.5)	17 (39.5)
Hypertension, n (%)[a]	77 (43.3)	12 (30.8)	44 (45.8)	21 (48.8)
Sleep apnea, n (%) [a]	42 (23.5)	5 (12.8)	25 (25.5)	12 (28.6)
Psychoactive medication, n (%)	64 (35.5)	14 (35.9)	35 (35.7)	15 (34.9)
Major Depression Inventory Score[c]	7.0 (10.0)	7.0 (15.0)	7.0 (9.5)	8.5 (10.0)
Biochemistry				
ALT (U/L)	35.0 (35.8)	23.0 (17.0)	34.0 (30.8)	58.0 (34.0)
AST[c] (U/L)	25.0 (16.3)	22.0 (9.5)	25.0 (15.0)	37.5 (29.0)
GGT[a] (U/L)	34.0 (44.0)	23.0 (38.0)	32.0 (29.5)	65.5 (64.0)
Albumin (g/L)	42.0 (3.0)	42.0 (3.0)	42.0 (3.3)	41.0 (3.0)
Ammonium ion[b] (μmol/L)	29.0 (8.0)	28.0 (6.8)	29.0 (9.0)	30.0 (6.5)
Hemoglobin (mmol/L)	8.7 (0.8)	8.5 (0.6)	8.7 (0.8)	8.9 (0.7)
Bilirubin[a] (μmol/L)	9.0 (5.0)	9.0 (3.0)	9.0 (5.3)	10.0 (5.0)
Triglycerides (mmol/L)	1.5 (1.0)	1.0 (0.6)	1.6 (0.9)	2.0 (1.0)
Total cholesterol (mmol/L)	4.5 (1.3)	4.3 (1.2)	4.5 (1.1)	4.6 (1.5)
LDL cholesterol (mmol/L)	3.0 (1.4)	2.9 (1.1)	3.1 (1.3)	3.0 (1.6)
HbA1c (mmol/mol)	38.0 (9.0)	34.0 (6.0)	39.0 (8.3)	43.0 (18.0)
HOMA-IR[c] (mmol/L)	6.6 (6.5)	4.3 (3.6)	6.7 (5.7)	10.9 (10.2)
CRP[c] (mg/L)	6.0 (8.1)	5.5 (8.1)	5.9 (7.0)	6.7 (8.7)
Liver related				
Liver stiffness (kPa)[a]	7.7 (6.3)	5.5 (6.8)	7.8 (5.9)	8.8 (8.5)
Fibrosis stage 0/1/2/3/4, (%)	23/52/19/4/2	59/33/3/0/5	17/61/19/1/1	5/46/35/14/0
NAFLD activity score: 1-2/3-5/6-8, (%)	56/39/5	100/0/0	63/37/0	0/79/21

Note: Continuous data are presented as medians (±IQR), and categorical variables are expressed as frequencies and percentages. Psychoactive medication (Yes) is one or several prescription drugs of either antidepressants, benzodiazepines, opioids, or antipsychotics.
[a]Missing data for: n = 1–2.
[b]n = 23.
[c]n = 6–10.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; GGT, gamma-glutamyl transferase; HbA1c, hemoglobin A1C; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; no-NAFLD, not meeting the criteria for NAFLD.

differences in the use of lipid-lowering medications (Table 3). The basis for this association is unknown, but the brain is the most cholesterol-rich organ in the body, and its cholesterol metabolism seems independent of the peripheral tissue.[25] Some studies suggest that, although low LDL reduces the risk of strokes, it might be associated with a faster age-dependent cognitive decline.[26,27]

The observed cognitive impairment occurred irrespective of NAFLD and NASH. This infers that these disease entities were not the leading causes of cognitive dysfunction in our patients, and the cognitive alterations are not, in general, minimal HE. Still, in the 6% with advanced hepatic fibrosis, there was a tendency toward poorer performance in all the cognitive tests, and advanced fibrosis was indeed a predictor of a significantly lower PSE test result (Supplemental Table 3, http://links.lww.com/HC9/A368). These findings may be taken to imply that minimal HE first emerges with advancing fibrosis.

TABLE 3 Characteristics of the cognitively unimpaired versus impaired

	All (CRT, PSE, Stroop, and RBANS)			Subgroup (RBANS)		
Variables	**Normal cognition (n = 145)**	**Cognitive impairment (n = 35)**	***p***	**Normal cognition (n = 37)**	**Cognitive impairment (n = 26)**	***p***
Sex (male), n (%)	34 (23.4)	18 (51.4)	**0.002**	6 (16)	14 (54)	**0.002**
Age, years	45 (12)	45 (13)	0.78	48.8 (12)	45.9 (13)	0.446
Education, years	12.0 (5.0)	11.0 (4.0)	**0.016**	12.9 (2.8)	11.3 (2.3)	0.117
BMI (kg/m^2)	41.6 (7.4)	42.0 (8.7)	0.52	41.8 (4.5)	41.7 (4.3)	0.451
Type 2 diabetes, n (%)	34 (23.4)	10 (28.6)	0.76	7 (19)	6 (23)	0.757
Sleep apnoea, n (%)	30 (20.8)	12 (34.3)	0.12	6 (16)	9 (35)	0.137
Major Depression Inventory	7.0 (9.8)	8.0 (13.5)	0.66	10.4 (7.9)	8.8 (6.2)	0.415
Cholesterol-lowering meds, n (%)	37 (25.5)	9 (25.7)	0.89	10 (27)	4 (15)	0.362
Hypertension, n (%)	60 (42.0)	17 (48.6)	0.57	15 (41)	12 (46)	0.798
Psychoactive medication, n (%)	47 (32.4)	17 (48.6)	0.08	—	—	0.483
Antidepressants	22 (15.7)	7 (20.0)	—	6 (16)	5 (19)	—
Antipsychotics	3 (2.1)	1 (2.8)	—	0	1 (4)	—
Pain medication, narcotics	8 (5.5)	4 (11.4)	—	2 (5)	4 (15)	—
More than one of the above	14 (9.6)	5 (14.3)	—	6 (16)	3 (12)	—
HOMA-IR (mmol/mol)	6.5 (6.1)	7.2 (9.7)	0.91	9.8 (6.2)	8.5 (5.6)	0.417
ALT (U/L)	35.0 (35.5)	37.0 (35.0)	0.86	45.2 (28)	40.7 (27)	0.539
AST[a](U/L)	25.5 (15.8)	25.0 (18.3)	0.73	33.0 (22)	28.3 (17)	0.358
Triglycerides (mmol/L)	1.6 (1.0)	1.4 (1.1)	**0.042**	1.9 (0.9)	1.5 (0.9)	0.082
LDL cholesterol (mmol/L)	3.1 (1.4)	2.7 (1.2)	< **0.001**	3.5 (0.95)	2.7 (0.9)	**0.003**
HDL cholesterol (mmol/L)	1.0 (0.3)	1.0 (0.3)	0.96	1.2 (0.3)	1.1 (0.2)	0.606
Plasma TREM2 (ng/mL)	41.1 (38.4)	38.3 (28.3)	0.28	53.8 (28)	38.1 (19.2)	**0.015**
Ammonium[b] (μmol/L)	29.0 (7.0)	30.5 (8.0)	**0.05**	31-0 (8.7)	31.5 (7.8)	0.848
Hemoglobin (mmol/L)	8.7 (0.7)	8.7 (0.8)	0.87	8.8 (0.8)	8.8 (0.9)	0.89
CRP (mg/L)	5.8 (9.1)	6.2 (5.8)	0.70	6.2 (5.1)	7.8 (9)	0.390
Liver stiffness (kPa)	7.7 (5.9)	7.9 (9.0)	0.64	8.3 (5.8)	12.0 (11.8)	0.101
Steatohepatitis (NASH), n (%)	34 (23.4)	9 (25.7)	0.77	11 (29.7)	6 (23.1)	0.774
Advanced fibrosis (F3-F4), n (%)	6 (4.1)	4 (11.4)	0.09	3 (8.1)	2 (7.8)	1.00

Note: We defined cognitive impairment as ≥2 abnormal cognitive tests in the basic test round using CRT, PSE, and Stroop, or an abnormal RBANS index score. An abnormal RBANS was defined as an index score < 79.

Results are presented as means (SD) if not noted otherwise. Fisher exact test and *t* test were used for the comparison of means.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; TREM2, triggering receptor expressed on myeloid cells 2.

[a]Missing data for: n = 10.

[b]n = 23.

Our participants with impaired cognition did not have higher TREM2. Conversely, the patients with abnormal RBANS had lower TREM2 although the difference was not present in the adjusted analyses. The available literature suggests that elevated TREM2 marks ongoing cellular damage, but TREM2 exists in several tissues, including the

TABLE 4 Univariable and stepwise multivariable logistic regression analysis of the association between impaired cognition and other possible predictor variables

	Univariable			Stepwise multivariable		
Variables	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Sex (male)	**3.46**	**1.61–7.44**	**0.002**	**3.67**	**1.32–10.27**	**0.013**
Age (y)	1.00	0.97–1.03	0.93	0.96	0.93–1.00	0.051
Education (y)	**0.84**	**0.72–0.96**	**0.013**	0.86	0.72–1.02	0.077
MDI score	1.01	0.97–1.04	0.67	—	—	—
HOMA-IR (mmol/mol)	1.00	0.96–1.04	0.97	—	—	—
AST (U/L)	1.00	0.70–1.01	0.39	—	—	—
Triglycerides (mmol/L)	0.65	0.38–1.09	0.11	—	—	—
LDL cholesterol (mmol/L)	**0.58**	**0.39–0.86**	**0.007**	**0.59**	**0.37–0.96**	**0.035**
HDL cholesterol (mmol/L)	0.81	0.21–3.15	0.76	—	—	—
Plasma TREM2 (ng/mL)	0.99	0.98–1.00	0.13	—	—	—
CRP (mg/L)	0.98	0.93–1.04	0.55	—	—	—
Ammonia ion (μmol/L)	1.05	1.00–1.11	0.069	—	—	—
Hemoglobin (μmol/L)	1.04	0.64–1.68	0.87	—	—	—
Liver stiffness measure (kPa)	1.03	0.99–1.06	0.100	—	—	—
Type 2 diabetes	1.31	0.57–2.99	0.528	—	—	—
Sleep apnoea	1.98	0.89–4.44	0.096	—	—	—
Hypertension	1.31	0.62–2.74	0.48	—	—	—
Psychoactive medication						
Antidepressants	1.73	0.65–4.65	0.27	1.99	0.55–7.09	0.288
Antipsychotics	1.81	0.18–18.4	0.61	4.90	0.36–65.7	0.230
Pain medication, narcotics	2.72	0.74–10.0	0.13	2.67	0.55–12.9	0.222
More than one of the above	1.94	0.62–6.07	0.25	**5.24**	**1.34–20.4**	**0.017**
Lipid-lowering meds	0.83	0.34–1.99	0.684	—	—	—
Steatohepatitis, NASH	1.13	0.48–2.64	0.778	—	—	—
Severe fibrosis, F3–4	2.99	0.80–11.2	0.100	2.95	0.60–14.3	0.181

Note: The OR indicates the impact of each variable on the odds of being cognitively impaired. We used stepwise multivariable, backward selection, removing terms with $p \geq 0.2$, and adding those with $p < 0.1$, with covariates: sex, age, education (years), ammonium, LDL cholesterol, psychoactive medication, sleep apnea, hypertension, and advanced fibrosis (F3-F4). We used 152 observations after removing participants with missing data.
Psychoactive medication, antidepressants (SSRI; TCA, SNRI, and NARI); antipsychotics (eg, seroquel, quetiapine, and benzodiazepines); pain medication, narcotics (morphine or analogs); treatment with meds from 2 groups (combination of antidepressants, antipsychotics, and/or pain medications). Cholesterol-lowering meds, prescription, and stating these are taken. *p*-values < 0.05 are marked in bold in the table.
Abbreviations: AST, aspartate aminotransferase; CRP, C-reactive protein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; MDI score, Major depression Inventory; plasma TREM2, Triggering receptor expressed on myeloid cells 2.

liver, where TREM2 is a marker of NASH.[28] However, the observed association between abnormal RBANS and lower TREM2 did not seem confounded by NASH as NASH prevalence was similar in the RBANS normal and abnormal groups (Table 3). If the association between abnormal RBANS and lower TREM2 is real, then it is best explained by TREM2's suggested neuroprotective role. This implies that, when TREM2 is lacking or has been depleted, neuronal damage cannot be adequately repaired or controlled, and this could result in abnormal RBANS.[12] Postbariatric surgery follow-up and cohort expansion may inform us, in more detail, about the roles of TREM2.

The most striking finding was the high prevalence of memory impairment. Deficits in immediate and late memory are not considered a dominant feature of minimal HE but frequently occur in neurodegenerative diseases, such as dementia. As mentioned, there is evidence that obesity may lead to neuronal inflammation, neurodegeneration, and premature aging over time. Particularly, western diet-induced obesity might increase blood-brain-barrier permeability and lead to neuroinflammation and hippocampal dysfunction.[29] The hippocampus is responsible for memory and learning. This theory, therefore, fits well with our findings.

It was also striking that two-thirds of participants had reaction time instability and slowing of psychomotor reaction time. This is far beyond what is reported from background population cohorts.[14] It may be a point of debate whether cognitive impairment can be defined only by the CRT, but the test clearly characterizes the patients

TABLE 5 Subgroup RBANS, univariate, and stepwise multivariate logistic regression analysis of the association between impaired cognition, defined by abnormal RBANS, and other possible predictor variables

	Univariable			Stepwise multivariable		
Variables	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Sex (male)	**6.02**	**1.88–19.3**	**0.003**	**32.7**	**2.5–420**	**0.007**
Age (y)	0.98	0.94–1.02	0.344	0.89	0.83–0.97	0.008
Education (y)	**0.78**	**0.63–0.97**	**0.026**	0.69	0.48–1.02	0.065
MDI score	0.97	0.89–1.04	0.411	—	—	—
HOMA-IR (mmol/mol)	0.96	0.88–1.05	0.411	—	—	—
AST (U/L)	0.99	0.95–1.02	0.368	—	—	—
Triglycerides (mmol/L)	0.60	0.29–1.09	0.090	—	—	—
LDL cholesterol (mmol/L)	**0.41**	**0.22–0.78**	**0.006**	**0.34**	**0.12–0.99**	**0.049**
HDL cholesterol (mmol/L)	0.62	0.10–3.78	0.600	—	—	—
Plasma TREM2 (ng/mL)	**0.97**	**0.94–0.99**	**0.022**	—	—	—
CRP (mg/L)	1.03	0.96–1.12	0.400	—	—	—
Ammonia ion (μmol/L)	1.01	0.94–1.08	0.844	0.89	0.79–1.00	0.052
Hemoglobin (μmol/L)	0.96	0.53–1.75	0.897	—	—	—
Liver stiffness measure (kPa)	1.05	0.99–1.13	0.126	—	—	—
Type 2 diabetes	1.29	0.38–4.39	0.688	—	—	—
Sleep Apnea	2.65	0.80–8.72	0.109	—	—	—
Hypertension	1.20	0.43–3.32	0.725			
Psychoactive medication						
Antidepressants	1.47	0.37–5.79	0.578	—	—	—
Antipsychotics	1.00	—	—	—	—	—
Pain medication, narcotics	3.54	0.56–22.0	0.176	—	—	—
More than one of the above	0.88	0.19–4.14	0.876	—	—	—
Cholesterol-lowering meds	0.49	0.14–1.78	0.279	—	—	—
Steatohepatitis, NASH	0.71	0.22-2.25	0.559	—	—	—
Severe fibrosis, F3–4	0.944	0.14–6.09	0.952	0.04	0.001–1.64	0.090

Note: The OR indicates the impact of each variable on the OR of the event being cognitively impaired. Multivariable, adding variables with $p \leq 0.1$ and forcing the presence of age, sex, education, and psychoactive drugs. Stepwise multivariable, backward stepwise selection, removing terms with $p \geq 0.2$, and adding those with $p < 0.1$. We used 46 observations after removing participants with missing data.

Abbreviations: AST, aspartate aminotransferase; CRP, C-reactive protein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; MDI score, Major Depression Inventory; plasma TREM2, Triggering receptor expressed on myeloid cells 2.

Psychoactive medication, antidepressants (SSRI; TCA, SNRI, and NARI); antipsychotics (e.g., seroquel, quetiapine, and benzodiazepines); pain medication, narcotics (morphine or analogs); and treatment with meds from two groups, combination of antidepressants, antipsychotics, and/or pain medications. Cholesterol-lowering meds, prescription, and stating these are taken. *p*-values < 0.05 are marked in bold in the table.

as deviating from normal. The slowing of reaction times supports the previously mentioned review[1] where it is suggested that obesity and obesity-related comorbidities synergistically cause inflammation and oxidation and induce premature cognitive aging, which causes a slowing of reaction times. Reaction time stability, however, is largely unaffected by age, and an alternative explanation for the reaction time instability could be attention deficits, which relatively often coexist with obesity.[30,31]

Taken together, the cognitive deficits that we describe suggest that brain dysfunction in obesity is a frequent, multidomain, multifactorial cognitive impairment, not dependent on fatty liver involvement, and possibly driven by premature neuronal aging and a high prevalence of attention deficit disorders.

A significant strength of our study is the large cohort, where all participants had liver histology and cognitive test results. Another strength is our multidomain testing strategy. It is a limitation that we could not perform RBANS in all participants. However, the RBANS subgroup had a reasonable size, and we ensured that it was representative of the whole cohort, allowing meaningful extrapolation. Moreover, we did not have brain imagining to gauge organic brain disease. We had to rely on the patient files for information on prior strokes and other brain-related health issues. In future studies, hippocampal and thalamic imaging may be of particular interest.[32]

Another limitation of our study is that it is observational, so we must rely on internal associations and cannot speculate on causality. However, we will reinvite

all participants after 2.5 years, at which point half will have undergone bariatric surgery. This hopefully will show whether any of the cognitive deficits are reversible with weight loss and the disappearance of NAFLD, as suggested by a study by Anwar et al.[33]

Another limitation is the low number of participants with severe liver fibrosis. This might make us underestimate the importance of minimal HE. Furthermore, tiering of participants could be an issue, but the CRT was conducted as the first test and had more abnormal performances than RBANS, which was performed last.

In conclusion, we report that multidomain cognitive impairment was present in 40% of our cohort of severely obese individuals, with executive and memory functions being the most affected domains. Cognitive impairment was not restricted to patients with NAFLD or NASH, but male sex, psychoactive polypharmacy, and low LDL cholesterol were associated with increased risk for being cognitively impaired.

AUTHOR CONTRIBUTIONS

Charlotte W. Wernberg: formal analysis and visualization; Charlotte W. Wernberg and Mette M. Lauridsen: conceptualization and writing—original draft; Charlotte W. Wernberg, Mette M. Lauridsen, Lea L. Grønkjær, and Birgitte Gade: investigation and project administration; Charlotte W. Wernberg, Mette M. Lauridsen, Lea L. Grønkjær, Birgitte Gade, Jonas H. Graversen, and Vineesh I. Chandran: data curation; Charlotte W. Wernberg, Aleksander Krag, Jonas H. Graversen, and Mette M. Lauridsen: funding acquisition and Supervision; Mette M. Lauridsen and Charlotte W. Wernberg: methodology; all authors: writing—review and editing.

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CONFLICTS OF INTEREST

Mette Munk Lauridsen has worked as a speaker for Norgine. The remaining authors have no conflicts to report.

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