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Nonalcoholic Fatty Liver Disease and Measures of Early Brain Health in Middle Aged Adults: The CARDIA study

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Abstract

Objective—To assess associations between nonalcoholic fatty liver disease (NAFLD) and measures of brain health in a population-based sample of adults.

Methods—Participants from the CARDIA study (Y25 exam; age 43–55 years) with concurrent CT quantification of liver fat, visceral adipose tissue (VAT) and brain magnetic resonance (MR) images were included (n=505). NAFLD was identified after exclusion of other causes of liver fat.

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Author Contributions: LVW and JGT developed the proposal and analytic plan. LJL designed the brain MR protocol. JJC designed the abdominal CT protocol. JT and HK analyzed data. LVW drafted the manuscript. All authors were involved in interpretation of results, manuscript revision and had final approval of the submitted and published versions.

Total tissue volume (TTV) and gray matter cerebral blood flow (GM-CBF) were estimated using 3T brain MR images.

Results—NAFLD prevalence was 18%. NAFLD was associated with lower TTV and GM-CBF after adjusting for intracranial volume, demographics, and health behaviors ($p<0.04$ for all). In models with additional adjustment for cardiovascular risk factors the association of NAFLD with GM-CBF remained significant ($p=0.04$), but was attenuated after adjustment for VAT ($p=0.06$), and eliminated with BMI ($p=0.20$). NAFLD was not associated with TTV after adjustment for cardiovascular risk factors ($p=0.10$), or additional adjustment for VAT ($p=0.14$) or BMI ($p=0.05$).

Conclusions—NAFLD is negatively associated with early brain health as assessed by MR measures of structure (TTV) and perfusion (GM-CBF). BMI and VAT attenuated this relationship providing insight into the potential metabolic role of liver fat in brain health and disease.

Keywords

NAFLD; magnetic resonance imaging; epidemiology; obesity; subclinical disease

Introduction

Non-alcoholic fatty liver disease (NAFLD) is an obesity-related condition and the most common cause of chronic liver disease in the United States(1). In North America, 24% of the general population is estimated to have NAFLD, and NAFLD prevalence is as high as 90% among those with morbid obesity(2). NAFLD can progress to cirrhosis, liver cancer(3), and need for liver transplantation(4). NAFLD is a systemic disease associated with the metabolic syndrome(5), subclinical(6–8) and incident cardiovascular disease (CVD)(9), and in the presence of liver fibrosis is an independent risk factor for cardiovascular mortality(10, 11). In fact, CVD is the leading cause of death in persons with NAFLD and among those who receive a liver transplantation(12, 13).

Cognitive decline with age is common and may be caused by a variety of conditions, including Alzheimer's disease and vascular dementia. A growing body of literature now recognizes that deterioration in vascular function over time is a major contributor to the process of cognitive aging. Liver disease, particularly NAFLD, may be involved in the process of cognitive aging through several potential mechanisms (Figure 1). First, persons with NAFLD have a high prevalence of individual vascular risk factors (e.g., hypertension) that contribute to the progression of cognitive aging. Additional risk factors that may accelerate vascular aging include microvascular endothelial dysfunction in concert with high levels of liver-derived gamma glutamyltransferase (GGT) and insulin-like growth factor-1 (IGF-1)(14). Second, the concurrent presence of chronic systemic inflammation and the metabolic syndrome, which are highly prevalent in NAFLD, have been shown to contribute to cognitive impairment in older persons(15). Finally, obesity, in particular visceral adiposity, is related to neurodegenerative, vascular, and metabolic processes that affect brain structures underlying cognitive function(16, 17). Despite these associations, there is little evidence for whether presence of NAFLD per se is associated with markers of early brain health independent of visceral adiposity and metabolic risk factors.

Our central hypothesis is that prevalent NAFLD is a marker for underlying pathologic processes that lead to vascular cognitive aging independent of general measures of adiposity and cardiovascular risk factors. Thus, the objective of the current study was to quantify associations between presence of NAFLD and global imaging measures of brain structure and physiology. We further aimed to investigate whether obesity and other components of the metabolic syndrome attenuate this association.

Methods

Study Population

Participants were enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA) Study, a longitudinal study to investigate the determinants and development of CVD in young adults. Details of the recruitment of the study sample have been previously described(18). Of the 5,115 adults enrolled in CARDIA, 3,498 (72% of survivors) were evaluated at the 25-year (Y25) follow-up exam (2010–2011) where a sub-sample participated in the CARDIA Brain Magnetic Resonance Imaging (MRI) sub-study. The sample was enrolled at the time Y25 appointments were made, with the aim of achieving a balance within four strata of ethnicity/race (black, white) and sex from three of the CARDIA field centers: Birmingham, AL, Minneapolis, MN, and Oakland, CA. The CARDIA Brain MRI sub-study was designed to investigate the morphology, pathology, physiology and function of the brain with MRI technology. Exclusion criteria were a contraindication to MRI or a body size that was too large for the MRI scanner. Of those who were eligible for the sub-study, our target was scans in 700 individuals; we obtained brain MRI scans of 719 individuals. The present study includes participants from the CARDIA Brain sub-study who also underwent concurrent computed tomography (CT) scanning of the abdomen as part of the Y25 core examination. Participants were excluded from the CT exam if they were pregnant or were unable to fit within the CT gantry.

Of 679 participants with available brain MRI and abdominal CT images, we further excluded participants with a medically verified history of stroke (n=4), a self-reported history of hepatitis C or cirrhosis (n=21), a risk factor for chronic liver disease or with a potential cause of secondary hepatic steatosis: alcohol consumption ≥ 20 g/day in women and ≥ 30 g/day in men(1) (n=108), self-reported human immunodeficiency virus (n=6), prior intravenous drug use (n=28), and medications known to cause hepatic steatosis (e.g. valproic acid, methotrexate, tamoxifen or amiodarone) (n=7). The remaining 505 participants formed the sample population (Figure 2).

All participants provided written informed consent at each exam, including separate participant consent for the CARDIA Brain sub-study. Institutional review boards (IRB) from each field center, the coordinating center and the Intramural Research at the National Institute on Aging annually approved the CARDIA study.

Measurements

Standardized protocols for data collection and quality control were used across study centers and have been described in detail previously(18). Obesity was defined as body mass index

(BMI) ≥ 30 kg/m^2. The metabolic syndrome was defined according to Adult Treatment Panel III criteria(19). To quantify physical activity (reported as exercise units), the CARDIA physical activity history questionnaire was used, which was an interviewer-based self-report of duration and intensity of participation in 13 categories of exercise over the previous 12 months(20). As a reference, 300 EU approximates 150 minutes of moderate-intensity activity per week(20).

Brain MRI Protocol

Brain MRI were acquired on 3T MR scanners (UCB: Siemens 3T Tim Trio/VB 15 platform; UMN: Siemens 3T Tim Trio/VB 15 platform and UAB: Philips 3T Achieva/2.6.3.6 platform). Details of the training of MRI technologists at the different sites, implementation of study protocols, and quality assurance of scanner stability and performance have been previously published(21). Image processing was performed at a centralized reading center (University of Pennsylvania, Philadelphia, PA). A quality control protocol was employed prior to scan processing through an automated pipeline(21).

Structural MR brain images were processed using previously described methods(22–24). An automated multispectral computer algorithm classified total brain tissue volume (TTV) into gray matter (GM), white matter (WM), and cerebral spinal fluid (CSF). The GM of the brain contains the cell bodies, dendrites, and axon terminals of all the neurons in the brain, whereas the WM contains all the connecting tracts between the various GM regions of the brain. Total, GM and WM tissue volumes were further characterized as normal (NTV) and abnormal (ATV) tissue volumes, and then into specific regions of interest (98 in the normal tissue and 94 in the abnormal tissue). Abnormal WM includes tissue damage due to ischemia, demyelination and inflammation. Abnormal GM includes infarcted cortical tissue. NTV was adjusted for intracranial volume (ICV, total brain volume (TBV) plus CSF).

The imaging protocol also included an axial pseudo-Continuous Arterial Spin Labeling (pCASL), which measures cerebral blood flow (CBF)(25). CBF is the volume of blood traversing a brain region per unit of time (ml/100g/min). The mean perfusion volume from the pCASL was quantified into CBF units using the model and software described in Wang et al.(26) resulting in a CBF map. Due to technical difficulties, the CBF measures from the UAB site were not included in this analysis (n=131). Here we present the estimate for the GM-CBF as it is more reliably obtained than measures in WM. The technical error of measurement, an accuracy index that reflects measurement quality of both acquisition and processing of scans, was estimated from scans of 3 persons measured 3 times in the 3 centers; results were 1.2% for TBV, 27.8% for Abnormal WM, and 7.3% for GM-CBF.

CT Imaging Protocol

The CT protocol included the heart and abdomen using a non-contrast CT scan performed using GE (GE 750HD 64 and GE LightSpeed VCT 64 Birmingham and Oakland Centers, respectively; GE Healthcare, Waukesha, Wisconsin) or Siemens (Sensation 64, Chicago and Minneapolis Centers; Siemens Medical Solutions, Erlangen, Germany) multidetector CT scanners and has been described previously(7). Quality control and image analysis was

performed at a core reading center (Wake Forest University Health Sciences, Winston-Salem, North Carolina).

NAFLD was defined as liver attenuation (LA) < 51 Hounsfield Units (HU, equivalent to a liver/spleen ratio < 1.0) after exclusion of other causes of liver fat (Figure 2)(7, 8). Measurement of LA was performed in the right lobe of the liver using CT slices through the upper abdomen and was reported as the average of nine measurements on three slices using circular regions of interest of 2.6 cm^2. The interclass correlation coefficient between different readers on a random selected sample of 156 participants was 0.975 for LA, indicating high reproducibility of CT measured LA in this study. The methods for assessment of adiposity within the CARDIA study have also been described previously(7).

Statistical Analysis

Participant characteristics were described using means and proportions as appropriate. Tests for differences by NAFLD status included t-test and Wilcoxon rank sum test for continuous variables and chi-square test for categorical variables. Linear regression models were used to quantify cross-sectional associations between the exposure (continuous CT LA or NAFLD), and the outcome variables (brain MRI measures). Covariates in the multivariable model were chosen *a priori* for clinical importance. Potential confounders included age, race, sex, study center, socioeconomic level, cardiovascular risk factors (e.g., smoking status, physical activity score, diabetes status, systolic blood pressure, high sensitivity c-reactive protein (hsCRP), cholesterol and antihypertensive medication use) and additional NAFLD risk factors (e.g., alcohol intake and HDL-cholesterol). Spearman correlation coefficients were computed between obesity measures and LA, and between obesity and brain MRI measures. We verified the model assumptions of linearity, normality of residuals, homoscedasticity, and absence of collinearity. In addition, the variance inflation factors were < 2 for models including LA and VAT or BMI., suggesting that multicollinearity did not interfere with model fit. All models for tissue volumes were adjusted for intracranial volume (ICV), as a measure of head size. Models for CBF were adjusted for TTV, as a measure of total brain tissue perfused. Five models were fitted: Model 1 (base model): ICV (tissue volume models) or TTV (cerebral blood flow models), study center, age, race, sex, education level, alcohol intake (mL/day), smoking status (current versus never/former) and physical activity score; Model 2: Base model + CVD risk factors (systolic blood pressure, diabetes status, HDL-cholesterol, hsCRP and cholesterol and hypertension treatment); Model 3: Model 2 + VAT; Model 4: Model 2 + subcutaneous adipose tissue (SAT); Model 5: Model 2 + BMI. We tested for interactions between NAFLD and age, race, sex, systolic blood pressure or diabetes status and levels of VAT volume or BMI in terms of TTV, total-NTV, total-CBF and GM-CBF. Since no interactions approached significance p>0.2, we did not include these in the final models. A P value < 0.05 was considered statistically significant. Analyses were performed using SAS 9.4 (SAS institute, Cary, NC).

Results

Clinical, Fat Distribution, and Metabolic Characteristics

Table 1 compares the clinical characteristics of NAFLD participants to those without NAFLD. NAFLD prevalence was 18.2%. Mean age across the population was 50.1 ± 3.6 years, 55.8% female and 55.2% white. NAFLD participants had higher BMI (33.6 vs. 28.1 kg/m^2), waist circumference (105.5 vs. 88.9 mm), and obesity prevalence (76.1% vs. 29.1%) than non-NAFLD ($p<0.0001$ for all). NAFLD participants were also more likely to have dyslipidemia (e.g., high triglycerides, low HDL), hypertension and diabetes mellitus and 37.0% met criteria for the metabolic syndrome ($p<0.001$ for all). When compared to participants without NAFLD, participants with NAFLD exhibited higher levels of hsCRP, fasting insulin, glucose, and insulin resistance as defined by the homeostatic model assessment of insulin resistance (HOMA-IR). Notably, there was no significant difference in low density lipoprotein (LDL), total cholesterol, or prevalence of cholesterol treatment use between NAFLD groups. Total physical activity level and median alcohol use were lower among participants with NAFLD. Finally, NAFLD participants had higher volumes of CT-defined abdominal, subcutaneous, and visceral fat, and higher levels of liver fat indicated by lower levels of mean LA ($p<0.0001$).

Association of NAFLD with Brain MRI Measures of Structure and Physiology: Univariate Analyses

No significant differences in normal or abnormal tissue volumes were observed between participants with and without NAFLD (Table 2). Utilizing quartiles of Total-CBF, we assessed differences in the severity of subclinical changes in brain perfusion (Figure 3). NAFLD participants were more likely to have significantly lower levels of total-CBF than those without NAFLD ($p=0.004$).

Multivariable Analyses

In multivariable linear regression analyses lower LA (e.g., higher liver fat) was associated with lower TTV and total-NTV, and decreased total-CBF and GM-CBF after adjustment for ICV or TTV, demographics and health behaviors (Table 3). Lower LA remained associated with decreased total-CBF and GM-CBF after adjustment for CVD risk factors. After additional adjustment for VAT the association between LA and GM-CBF remained significant ($p<0.04$). Additional adjustment for SAT further attenuated associations between LA and measures of brain physiology (e.g., CBF) and when adjusted for BMI, LA was no longer statistically associated with CBF. In contrast, the relationship between LA and several measures of brain structure (e.g., TTV, total-NTV) was attenuated when adjusted for CVD risk factors and VAT, but remained significant when adjusted for CVD risk factors plus BMI or SAT (Table 3, Figure 4). In fully adjusted models for markers of adiposity that included both BMI and VAT, the associations between LA and total-CBF, GM-CBF, and NTV were further weakened ($p=0.13$, $p=0.09$, $p=0.05$, respectively).

Table 4 displays the associations between presence of CT-defined NAFLD and MRI measures of brain structure and physiology. Similar to the findings with continuous LA, CT-defined NAFLD was associated with lower TTV and total-NTV and decreased total-CBF

and GM-CBF when adjusted for ICV, demographics, and health behaviors (Base model, $p<0.04$ for all). Associations of NAFLD with measures of brain physiology were attenuated when adjusted for CVD risk factors. Additional adjustment for VAT had little effect on the associations of NAFLD with CBF, but adjustment for BMI or SAT left the associations non-significant. Associations of NAFLD with measures of brain structure (e.g., TTV, Total-NTV) were non-significant when adjusted for CVD risk factors or VAT, however there was a trend towards statistical significance when adjusted for SAT ($p=0.06$) or BMI ($p=0.05$). Finally, we examined associations between liver fat from any cause (e.g., including participants with heavy alcohol use) and brain MRI measures of structure and physiology. The pattern and magnitude of all observed associations were unchanged (Supplemental Table 1).

Discussion

In a large, population-based, cross-sectional study of black and white middle-aged adults without prevalent cerebrovascular disease, these data indicate that presence of NAFLD is associated with less favorable subclinical MRI measures of brain health even when controlled for traditional CVD risk factors and central adiposity. To the best of our knowledge, this is the first study to consider the effect of VAT, a potential effect modifier of the association between NAFLD and vascular cognitive aging, on these associations.

A growing body of literature demonstrates that asymptomatic patients who have risk factors for CVD, such as hypertension and diabetes, show significant structural and physiologic brain imaging changes(27). Furthermore, the presence of an increasing number of individual vascular risk factors (e.g., the metabolic syndrome) appears to increase the magnitude of these brain imaging changes(28). We now add the observation that degree of liver fat and presence of NAFLD, are associated with unfavorable brain imaging changes even when controlled for recognized vascular risk factors for cognitive aging.

Higher levels of adiposity including BMI, waist circumference, subcutaneous adipose tissue, and VAT have all been associated with lower total brain volume(16, 29). BMI, in particular, has been associated with regional brain GM volume decreases, although the location and magnitude of these decreases has been inconsistent(30–33). Some investigations report lower GM volume only in those with obesity (BMI ≥ 30 kg/m^2)(29), whereas others report significant GM volume reductions in those who are merely overweight (BMI ≥ 25 kg/m^2) (30, 32). There is no consensus on the association of adiposity (particularly BMI) with WM volumetric changes(34). In the current study, there was no significant association between continuous LA or CT-defined NAFLD and GM or WM tissue volumes, nor was there an interaction between NAFLD status and BMI and tissue volumes. In contrast, CT-defined NAFLD was associated with global loss of brain tissue volume. After controlling for BMI, continuous LA remained associated with decreased total tissue volumes and there was a trend toward significance after adjustment for BMI in the models using CT-defined NAFLD. These findings suggest that the relationship between liver fat and decreased total brain tissue volume is not explained by global adiposity alone.

An important aspect of the present study was the inclusion of VAT as a potential effect-modifying variable. Different fat compartments carry differential metabolic risks(35), and

there is evidence that abdominal obesity and visceral fat are more correlated with vascular risk than global body mass(36). In the Framingham Offspring study, the inverse association between VAT and total brain volume was the strongest and most robust compared to associations between total brain volume and BMI, waist circumference or SAT(37). However, the mechanisms underlying the inverse association between VAT with total brain volume are speculative, and have not included the potential role of liver fat. In the current study, the association between NAFLD and MR measures of brain structure was no longer statistically significant after adjustment for VAT. Thus, the association between NAFLD and decreased brain tissue volume is not wholly independent of VAT, and whether NAFLD is a mediator of the relationship between VAT and brain MR volume requires further study. On the other hand, the association of continuous LA with physiologic changes in brain imaging (e.g., total and GM-CBF) remained significant after adjusting for VAT and vascular risk factors, and there was a trend towards significance between NAFLD and GM-CBF when controlled for VAT. The direction of these associations was congruent between continuous LA and GM-CBF, and NAFLD and GM-CBF further strengthening the hypothesis that VAT may only partially explain the relationship between liver fat and measures of brain physiology. Notably, there was also no interaction between NAFLD and VAT in our analysis. In contrast, when vascular risk factor models were adjusted for BMI, NAFLD (and continuous LA) was no longer associated with decreased CBF. These observations provide important insight into the potential pathophysiologic mechanisms of increased adiposity in the development of vascular cognitive aging.

To date, few studies have been published evaluating the effects of adiposity on brain blood flow(38, 39). In one study of 36 adults, authors investigated the effects of high BMI on regional cerebral blood flow using single photon emission computed tomography (SPECT) imaging in healthy subjects(38). They observed that higher BMI is associated with lower CBF in the prefontal cortex, which is the area of the brain responsible for executive function(38). This finding is supported by other studies that report diminished metabolic activity in the prefrontal cortex with high BMI(40). In another study of 25 healthy lean participants and 23 participatns with overweight/obesity, investigators revealed significantly lower CBF in both the prefrontal cortex and the hypothalamus (area of brain that produces hormones that govern body weight hemostasis) after intranasal insulin administration compared with placebo, pointing to selective central insulin resistance(39). In this study, the magnitude of hypothalamic response correlated with the amount of VAT independent of other tissue volumes, though did not account for liver fat volume(39). We have observed an inverse association between NAFLD, a condition highly associated with systemic insulin resistance, and total and GM-CBF in a large population of asymptomatic adults. Our finding raises important questions about the potential role of central insulin resistance in the development of vascular cognitive aging (Figure 1).

This study has several strengths. It provides the first data on a large community-based biracial middle age (50 years) cohort on the relationship between NAFLD and a range of MRI characteristics in relation to key risk factors for cerebrovascular disease. In addition, we provide the modifying effects of total (BMI) and visceral adiposity (VAT) on these observed associations. Such studies on this age cohort are important as they will provide clues of early changes in the brain that may eventually predict who is at risk for vascular

cognitive decline. The main limitation in this study is its cross-sectional study design, for which we cannot infer causal direction and an additional follow-up is planned. We also cannot extrapolate the differential effects of VAT versus liver fat on brain structure and physiology and the distinctions between these relationships warrant further study. NAFLD prevalence in CARDIA is on the lower end of the reported spectrum of disease, which is likely attributable to differences in population-level reporting of NAFLD (e.g., ultrasound vs. CT imaging). In addition, those with morbid obesity in whom NAFLD is highly prevalent were excluded from analysis if they were unable to fit in the CT or MR scanner. Finally, brain physiology was only assessed by cerebral blood flow. The relationship between NAFLD and other markers of early brain dysfunction, such as alterations in default mode networks or functional connectivity, require further study.

Conclusion

In conclusion, presence of NAFLD is negatively associated with measures correlating with brain health in a population-based middle age sample of black and white adults. BMI attenuates the association between NAFLD and physiologic measures of brain health, whereas VAT attenuates the association between NAFLD and brain structure. An important clinical manifestation of vascular risk factor-related structural and physiologic brain imaging changes in otherwise healthy persons is cognitive impairment. The evolving body of literature in this area suggests that in asymptomatic at-risk persons, physiologic brain imaging changes compared with structural changes, specifically, reductions in CBF and glucose metabolism during rest, affect cerebral hemodynamics via impairment in the microcirculation before the occurrence of detectable structural changes, which can then lead to cognitive impairment. Future studies are needed to assess the longitudinal effect of NAFLD on progression of structural and physiologic brain changes and on cognitive function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Importance Questions

1. What is already known about this subject?

- Cardiovascular disease is the leading cause of morbidity and mortality in persons with nonalcoholic fatty liver disease (NAFLD).
- Obesity and the metabolic syndrome are risk factors for accelerated cognitive aging.
- NAFLD is highly associated with obesity and the metabolic syndrome but the association between NAFLD and markers of early vascular cognitive aging independent of overall adiposity is unknown.

2. What does your study add?

- NAFLD is negatively associated with brain health in a population-based middle age sample of black and white adults.
- Level of visceral adiposity attenuates this association providing insight into the potential role of metabolic activity of liver fat in brain health and disease.

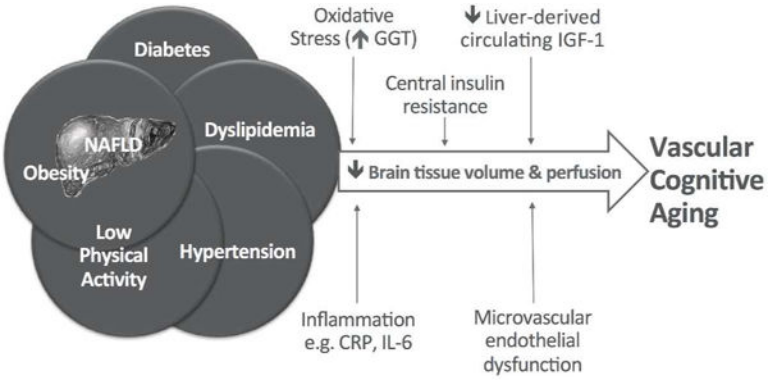

Figure 1.

The Liver and Vascular Cognitive Aging: Proposed Pathophysiology.

There are several explanations on why the liver might be involved in the process of cognitive aging. The presence of an increasing number of individual vascular risk factors including increased liver-derived GGT and IGF-1, ongoing microvascular endothelial dysfunction and central insulin resistance in concert may contribute to the progression of vascular cognitive aging.

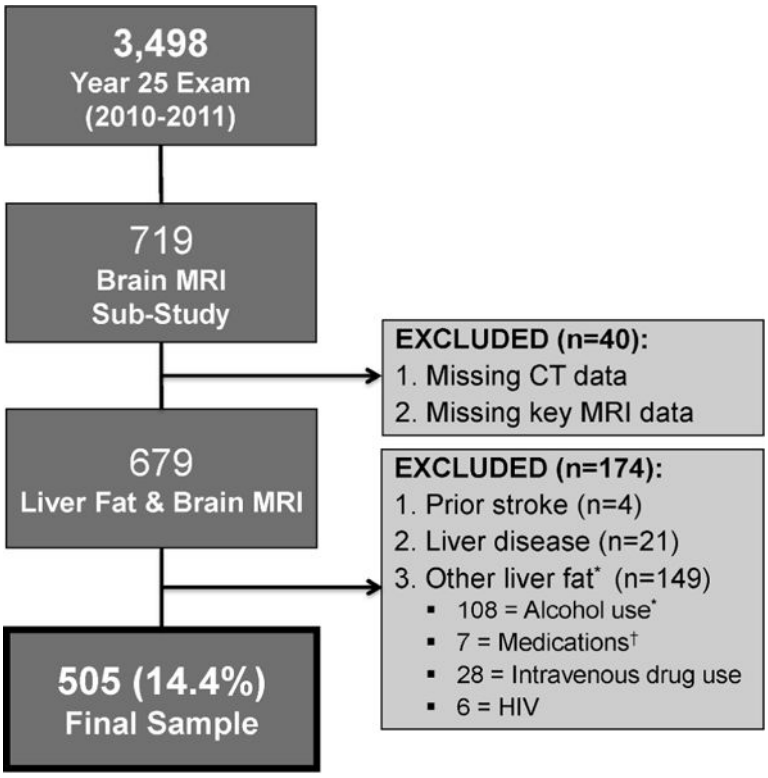

Figure 2.

Study sample—Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; HIV, human immunodeficiency virus

*Alcohol use was defined as ≥ 20 g/day in women, ≥ 30 g/day in men. †Medications = valproic acid, methotrexate, tamoxifen and amiodarone.

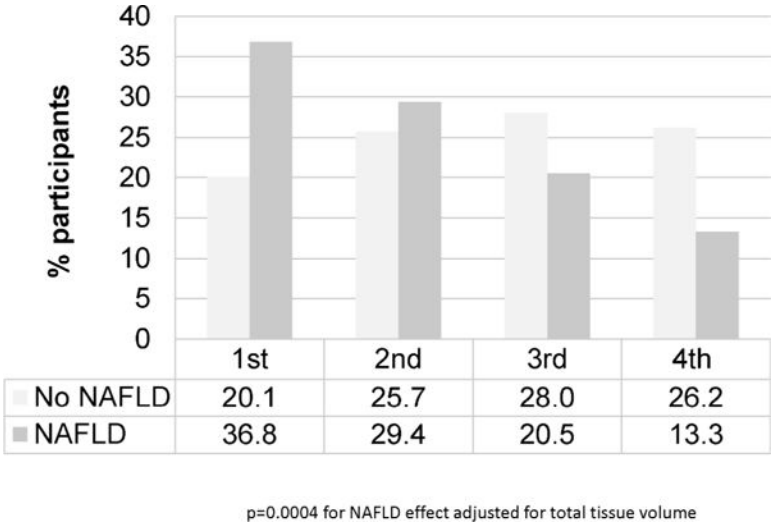

Figure 3.

Proportion of participants with NAFLD across Quartiles of Total-CBF (ml/100g/min). NAFLD participants were more likely to have significant subclinical decreases in total-CBF than those without NAFLD (p=0.0004 for NAFLD effect adjusted for total tissue volume).

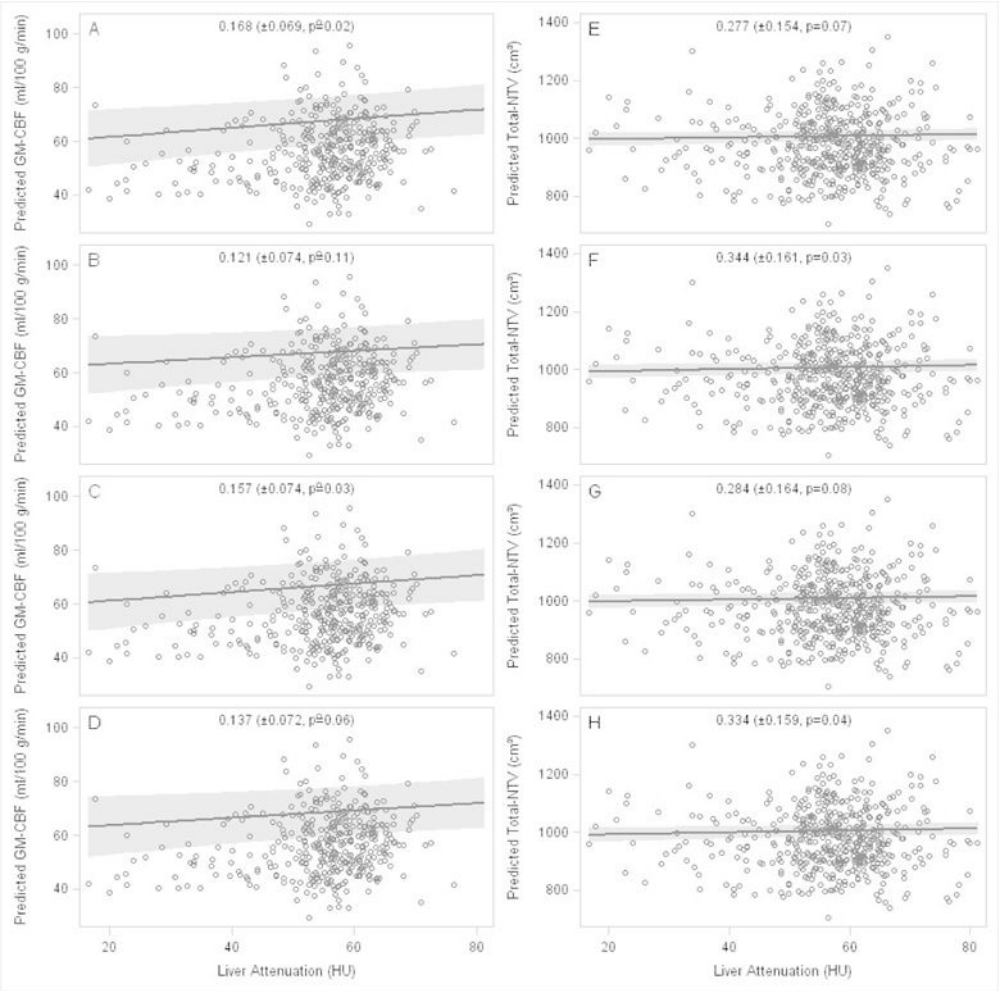

Figure 4.

Multivariable* association between continuous liver attenuation and either GM-CBF (A–D) or total-NTV (E–H) adjusted for A,E) CVD risk factors alone B,F) CVD risk factors + BMI,C,G) CVD risk factors + VAT, and D,F) CVD risk factors + SAT *All models were adjusted for either TTV (GM-CBF models) or intracranial volume (total-NTV models), center, age, race, sex, education, smoking, physical activity, and alcohol (mL/day). CVD risk factors included systolic blood pressure, hypertension treatment, high density lipoprotein (HDL) cholesterol, cholesterol treatment, diabetes, and high sensitivity c-reactive protein (hsCRP).

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; GM-CBF, gray matter cerebral blood flow; NTV, normal tissue volume; TTV, total tissue volume; VAT, visceral adipose tissue

Table 1

Demographic, Behavioral and Clinical Participant Characteristics by NAFLD Status in the CARDIA Brain MRI Sub Study, Year 25 Exam (2010–2011)

	Overall Sample (n=505)	No NAFLD (n=413)	NAFLD (n=92)	P value*
Age, years	50.1(3.6)	50.0 (3.6)	50.7 (3.6)	0.13
Female, %	55.8%	57.9%	46.7%	0.05
White, %	55.2%	55.4%	54.3%	0.85
Education, years	15.5(2.4)	15.5(2.4)	15.5 (2.4)	0.84
Physical Activity, exercise units/week	285 (142.0, 510.0)	297.0 (144.0, 537.5)	237.5 (97.5, 410.5)	0.02
Smoking, %				0.79
Never	64.5%	64.7%	63.3%	
Past	21.9%	21.4%	24.4%	
Current	13.6%	13.9%	12.2%	
Alcohol drinkers, %	74.0%	74.0%	73.9%	0.98
Alcohol Use, mL/day	0 (0,9.2)	2.4 (0,9.7)	0.0 (0,7.4)	0.03
Anthropometric measures				
BMI, kg/m^2	29.1 (5.9)	28.1 (5.4)	33.6 (5.5)	<0.0001
Waist circumference, mm	91.9 (13.6)	88.9 (12.1)	105.5 (11.6)	<0.0001
CT Fat Measures				
Total Abdominal Fat, cm3	458.5 (196.2)	422.1 (182.6)	623.3 (170.3)	<0.0001
Subcutaneous Fat, cm3	319.3 (154.4)	298.8 (150.2)	412.1 (139.0)	<0.0001
Visceral Fat, cm3	122.4 (67.3)	108.2 (58.7)	186.6 (67.0)	<0.0001
Liver Attenuation, HU	56.9 (10.1)	60.4 (6.1)	40.8 (8.9)	<0.0001
Comorbidities, %				
Obesity	37.6%	29.1%	76.1%	<0.0001
Diabetes	9.7%	6.3%	25.0%	<0.0001
Hypertension	28.5%	25.7%	41.3%	0.003
Metabolic Syndrome†	15.2%	10.4%	37.0%	<0.0001
Diastolic BP, mmHg	73.6 (11.0)	72.7 (10.9)	77.6 (10.8)	0.0001
Systolic BP, mmHg	118.0 (14.7)	117.1 (14.2)	121.8 (16.1)	0.01
HTN Treatment, %	23.0%	21.1%	31.5%	0.03
Metabolic Variables				
Total Cholesterol, mg/dl	193.2 (36.5)	194.5 (36.1)	187.4 (37.5)	0.10
Triglycerides, mg/dl	89.0 (65.0, 129.0)	85.0 (62.0,123.0)	117.5 (84.5,166.0)	<0.0001

	Overall Sample (n=505)	No NAFLD (n=413)	NAFLD (n=92)	P value*
LDL Cholesterol, mg/dl	114.0 (32.8)	114.9 (33.2)	110.2 (31.0)	0.21
HDL Cholesterol, mg/dl	57.5 (16.9)	59.4 (17.2)	48.7 (12.4)	<0.0001
High TG/Low HDLC, %	32.1%	27.7%	52.2%	<0.0001
Cholesterol Treatment, %	13.1%	11.9%	18.5%	0.09
Fasting Glucose+, mg/dl	91.3 (8.9)	90.7 (8.7)	94.8 (9.0)	0.005
Fasting Insulin+, mg/dl	9.3 (6.8)	8.1 (5.6)	15.7 (9.1)	<0.0001
HbA1c, %	5.4 (0.4)	5.4 (0.4)	5.5 (0.3)	0.016
HOMA-IR score+, mean	2.2 (1.0, 2.8)	1.9 (1.0, 2.4)	3.8 (2.2, 4.3)	<0.0001
hsCRP, mg/dl	1.2 (0.6,2.7)	1.0 (0.5,2.2)	2.6 (1.3,4.7)	<0.0001

NAFLD = liver attenuation < 51 HU after exclusion for secondary causes of liver fat (alcohol/medications) Abbreviations: NAFLD, nonalcoholic fatty liver disease, LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein.

*Results are expressed as mean (standard deviation), median (25^{th}, 75^{th} percentile) or %; t test or Wilcoxon rank sum for continuous variables, chi-square test for categorical variables for the difference between NAFLD and no NAFLD.

†Defined using the National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) criteria.

+Participants with a diagnosis of diabetes or those on diabetes medications were excluded from analyses for glucose, insulin, HbA1c and HOMA-IR score

Table 2

Brain MRI Measures of Structure and Physiology by NAFLD Status in the CARDIA Brain MRI Sub Study, Year 25 Exam (2010–2011)

	No NAFLD (n=413)	NAFLD (n=92)	P value*
Measures of Brain S tructure			
Total Tissue Volume (TTV), cm^3	979.1(1.4)	973.4(2.9)	0.08
Normal Tissue Volume, cm^3			
Total-NTV	978.4(1.4)	972.9(2.9)	0.09
GM-NTV	514.8(1.1)	513.9(2.3)	0.73
WM-NTV	463.6(1.2)	458.9(2.5)	0.09
Abnormal Tissue Volume, cm^3			
Total-ATV	0.69(0.07)	0.61(0.15)	0.63
GM-ATV	0.17(0.02)	0.13(0.04)	0.30
WM-ATV	0.51(0.06)	0.47(0.13)	0.77
Measures of Brain Physiology			
Cerebral Blood Flow (CBF), ml/100g/min			
Total-CBF	51.0(0.6)	47.3(1.1)	**0.004**
GM-CBF	57.8(0.6)	53.6(1.2)	**0.003**

NAFLD = liver attenuation < 51 HU after exclusion for secondary causes of liver fat (alcohol/medications) Abbreviations: MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NTV, normal tissue volume; ATV, abnormal tissue volume; GM, gray matter; WM, white matter; CBF, cerebral blood flow

*Results are expressed as mean (standard error), linear regression analysis adjusted for intracranial volume (structure models) or TTV (function models), center, age, race and sex.

Table 3

Multivariable Association of Continuous Liver Attenuation* with Brain MRI Measures of Structure and Physiology

	Measures of Brain Structure								Measures of Brain Physiology			
Model	**TTV, cm^3**		**Total-NTV, cm^3**		**GM-NTV, cm^3**		**WM-NTV, cm^3**		**Total-CBF ml/100 g/min**		**GM-CBF ml/100 g/min**	
	β (SE)	**p**	**β (SE)**	**p**	**β (SE)**	**p**	**β (SE)**	**p**	**β (SE)**	**p**	**β (SE)**	**p**
Base model	0.339 (0.139)	**0.02**	0.337 (0.139)	**0.02**	0.156 (0.105)	0.14	0.181 (0.117)	0.12	0.135 (0.056)	**0.02**	0.165 (0.062)	**0.008**
Model Adjusted R^2	0.933		0.933		0.852		0.846		0.200		0.192	
+ CVD factors	0.275 (0.154)	0.07	0.277 (0.154)	0.07	0.154 (0.116)	0.19	0.123 (0.131)	0.35	0.136 (0.062)	**0.03**	0.168 (0.069)	**0.02**
Model Adjusted R^2	0.934		0.934		0.850		0.850		0.202		0.191	
+ CVD + VAT	0.279 (0.164)	0.09	0.284 (0.164)	0.08	0.140 (0.124)	0.26	0.144 (0.139)	0.30	0.130 (0.067)	0.05	0.157 (0.074)	**0.03**
Model Adjusted R^2	0.934		0.934		0.850		0.845		0.195		0.185	
+ CVD +SAT	0.333 (0.159)	**0.04**	0.334 (0.159)	**0.04**	0.180 (0.121)	0.14	0.153 (0.135)	0.26	0.113 (0.065)	0.08	0.137 (0.072)	0.06
Model Adjusted R^2	0.934		0.934		0.850		0.845		0.198		0.189	
+ CVD + BMI	0.342 (0.161)	**0.04**	0.344 (0.161)	**0.03**	0.183 (0.122)	0.13	0.160 (0.137)	0.24	0.097 (0.067)	0.15	0.121 (0.074)	0.11
Model Adjusted R^2	0.934		0.934		0.850		0.844		0.205		0.196	

*NOTE: When interpreting β coefficients, the reader is reminded that LOW liver attenuation is associated with HIGH levels of liver fat. All models are per single Hounsfield Unit (HU) decrease in liver attenuation.

Abbreviations: BMI, body mass index; CBF, cerebral blood flow; CVD, cerebrovascular disease; GM, gray matter; MRI, magnetic resonance imaging; SAT, subcutaneous adipose tissue; TTV, total tissue volume; VAT, visceral adipose tissue; WM, white matter

Base model: Intracranial volume (structure models) or TTV (physiology models), center, age, race, sex, education, smoking, physical activity, and alcohol (mL/day); CVD factors: systolic blood pressure, hypertension treatment, high density lipoprotein (HDL) cholesterol, cholesterol treatment, diabetes, high sensitivity c-reactive protein (hsCRP)

Table 4

Multivariable Association of CT-defined NAFLD with Brain MRI Measures of Structure and Physiology

	Measures of Brain Structure								Measures of Brain Physiology			
Model	**TTV, cm^3**		**Total-NTV, cm^3**		**GM-NTV, cm^3**		**WM-NTV, cm^3**		**Total-CBF ml/100 g/min**		**GM-CBF ml/100 g/min**	
	β (SE)	**p**	**β (SE)**	**p**	**β (SE)**	**p**	**β (SE)**	**p**	**β (SE)**	**p**	**β (SE)**	**p**
Base model	−3.69 (1.69)	**0.03**	−3.65 (1.69)	**0.03**	−1.40 (1.28)	0.27	−2.25 (1.41)	0.11	−1.37 (0.63)	**0.03**	−1.60 (0.70)	**0.02**
Model Adjusted R^2	0.933		0.933		0.848		0.846		0.197		0.187	
+ CVD factors	−2.98 (1.78)	0.10	−2.98 (1.79)	0.10	−1.29 (1.35)	0.34	−1.69 (1.51)	0.27	−1.31 (0.68)	0.05	−1.52 (0.75)	**0.04**
Model Adjusted R^2	0.934		0.934		0.850		0.845		0.199		0.187	
+ CVD + VAT	−2.83 (1.89)	0.14	−2.86 (1.89)	0.13	−1.10 (1.43)	0.44	−1.76 (1.60)	0.27	−1.39 (0.73)	0.06	−1.54 (0.81)	0.06
Model Adjusted R^2	0.934		0.934		0.850		0.845		0.195		0.182	
+ CVD +SAT	−3.50 (1.85)	0.06	−3.50 (1.85)	0.06	−1.59 (1.41)	0.26	−1.90 (1.57)	0.23	−1.22 (0.70)	0.08	−1.34 (0.78)	0.09
Model Adjusted R^2	0.934		0.934		0.850		0.845		0.198		0.188	
+ CVD + BMI	−3.63 (1.86)	0.05	−3.64 (1.86)	0.05	−1.55 (1.41)	0.27	−2.09 (1.58)	0.19	−0.91 (0.71)	0.21	−1.01 (0.79)	0.20
Model Adjusted R^2	0.934		0.934		0.850		0.845		0.204		0.193	

NAFLD = liver attenuation < 51 HU after exclusion for secondary causes of liver fat (alcohol/medications)

Abbreviations: BMI, body mass index; CBF, cerebral blood flow; CVD, cerebrovascular disease; GM, gray matter; MRI, magnetic resonance imaging; TTV, total tissue volume; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; WM, white matter

Base model: Intracranial volume (structure models) or TTV (physiology models), center, age, race, sex, education, smoking, physical activity, and alcohol (mL/day); CVD factors: systolic blood pressure, hypertension treatment, high density lipoprotein (HDL) cholesterol, cholesterol treatment, diabetes, high sensitivity c-reactive protein (hsCRP)