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ORIGINAL RESEARCH

Relations of Metabolic Health and Obesity to Brain Aging in Young to Middle-Aged Adults

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BACKGROUND: We aimed to evaluate the association between metabolic health and obesity and brain health measured via magnetic resonance imaging and neurocognitive testing in community dwelling adults.

METHODS AND RESULTS: Framingham Heart Study Third Generation Cohort members (n=2170, 46±9 years of age, 54% women) without prevalent diabetes, stroke, dementia, or other neurologic conditions were grouped by metabolic unhealthiness (≥2 criteria for metabolic syndrome) and obesity (body mass index ≥30 kg/m^2): metabolically healthy (MH) nonobese, MH obese, metabolically unhealthy (MU) nonobese, and MU obese. We evaluated the relationships of these groups with brain structure (magnetic resonance imaging) and function (neurocognitive tests). In multivariable-adjusted analyses, metabolically unhealthy individuals (MU nonobese and MU obese) had lower total cerebral brain volume compared with the MH nonobese referent group (both $P<0.05$). Additionally, the MU obese group had greater white matter hyperintensity volume ($P=0.004$), whereas no association was noted between white matter hyperintensity volume and either groups of metabolic health or obesity alone. Obese individuals had less favorable cognitive scores: MH obese had lower scores on global cognition, Logical Memory-Delayed Recall and Similarities tests, and MU obese had lower scores on Similarities and Visual Reproductions-Delayed tests (all $P\leq0.04$). MU and obese groups had higher free water content and lower fractional anisotropy in several brain regions, consistent with loss of white matter integrity.

CONCLUSIONS: In this cross-sectional cohort study of younger to middle-aged adults, poor metabolic health and obesity were associated with structural and functional evidence of brain aging. Improvement in metabolic health and obesity may present opportunities to improve long-term brain health.

Key Words: aging ■ cognitive aging ■ magnetic resonance imaging ■ metabolic syndrome ■ obesity

Stroke and cardiovascular disease share common risk factors such as age, hypertension, arterial stiffness, and diabetes.[1,2] The presence and progression of these risk factors over time can result in oxidative stress, abnormal pressure transmission to distal small vessels, hypoperfusion, and cerebral microvascular injury, leading to subclinical cognitive impairment.[3–8] Cardiometabolic dysfunction may be associated with neurocognitive dysfunction through to inflammation, altered hemodynamics, and disruption of the blood–brain barrier, all ultimately manifesting in brain atrophy and small vessel disease on magnetic resonance imaging (MRI) as well as cognitive dysfunction.[1,9,10] Several cross-sectional studies have demonstrated the association of individual risk factors and/or cardiovascular disease equivalents including hypertension, diabetes, and coronary artery disease, with cognitive impairment.[11–13] A recent cross-sectional investigation using data from the UK Biobank further showed that these disease entities appear additive,

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CLINICAL PERSPECTIVE

What Is New?

- In young to middle-aged adults without diabetes, stroke, or dementia, we studied the association of metabolic health and obesity with a comprehensive evaluation of brain structure, including brain volume, white matter hyperintensity volume, free water content, fractional anisotropy, and neurocognitive testing spanning domains of executive function, memory, abstract reasoning, and visual processing.
- In this large community cohort, both poor metabolic health and obesity were associated with subclinical measures of brain aging and poorer cognitive function.

What Are the Clinical Implications?

- Clinicians should be aware of the subclinical connections of poor metabolic health and obesity with poor brain health in younger to middle-aged adults.
- Our results support further investigation of preventative strategies to decrease cardiometabolic disease burden, which may reduce signs and symptoms of brain aging.

Nonstandard Abbreviations and Acronyms

FA	fractional anisotropy
FW	free water
MH	metabolically healthy
MU	metabolically unhealthy
TCBV	total cerebral brain volume
WMHV	white matter hyperintensity volume

with the presence of more diseases associated with greater cognitive dysfunction.[14]

The relations of subclinical cardiometabolic disease with brain health are of particular interest in adults who have not reached advanced ages, whereby longer opportunities to intervene exist. We hypothesized that cardiometabolic risk factors and higher body mass index (BMI) are associated with subclinical brain abnormalities detected by imaging and cognitive testing. Because relatively sparse data on younger individuals exist, the Framingham Heart Study Third Generation cohort provides an opportunity to address these questions in younger and middle-aged adults, at times when preventative measures or intervention may impact cognitive decline later in life. Using the detailed cardiovascular phenotyping and assessment of brain structure and function in these Framingham Heart Study individuals, we sought to determine the cross-sectional associations of metabolic health and obesity with subclinical markers of brain injury.

METHODS

Study Participants and Clinical Covariates

The study participants were members of the Framingham Heart Study Third Generation Exam 2 (2008–2011). The recruitment of these participants has been previously described.[15,16] Briefly, participants in the Third Generation were recruited starting in 2002 and then underwent examinations every 4 years. At each examination, updated medical history and cardiovascular exam-focused physical examination, blood pressure, and phlebotomy were collected. Of the 3411 participants who attended Exam 2, 3409 had data on metabolic dysfunction. Of these participants, 2335 underwent neurocognitive testing. We then excluded individuals with prevalent dementia (n=0), stroke (n=14), and other confounding neurologic conditions (eg, severe head injury, craniectomy, multiple sclerosis, or brain tumor; n=44), and prevalent diabetes (n=107), resulting in a final sample size of 2170 individuals for analyses of the relations of metabolic health and obesity with neurocognition. Of these individuals, 1977 also had brain MRI scans (Figure 1).

Covariates were assessed in the Third Generation at Exam 2 (2008–2011), with serum samples obtained after an overnight fast. Manual blood pressure measurements were obtained, with participants seated, by a physician using a mercury sphygmomanometer twice during each clinic visit, and the average was

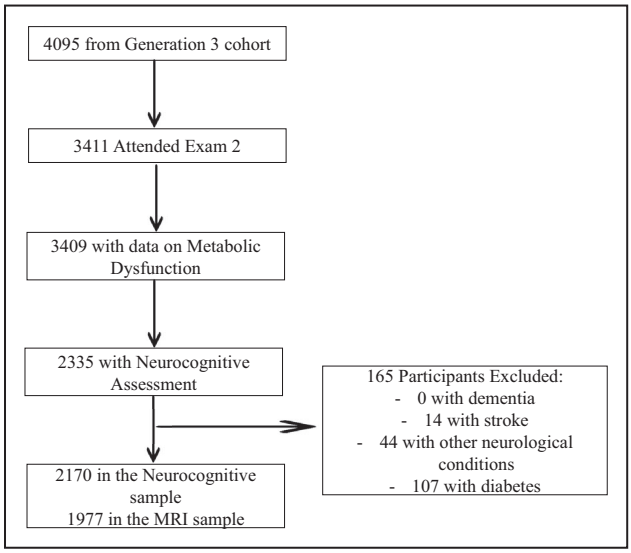

Figure 1. Flowchart of participants illustrating those included/excluded.
MRI indicates magnetic resonance imaging.

recorded as the brachial blood pressure. BMI was calculated as the ratio of weight in kilograms and height in meters squared. Smoking was considered positive if the participant smoked ≥1 cigarette, pipe, or cigar at least once daily in the year before examination. Metabolic health groups were based on the metabolic status as defined by the National Cholesterol Education Program-Adult Treatment Panel [17] in addition to BMI. Poor metabolic health was defined as ≥2 of the following criteria: triglycerides ≥1.69 mmol/L [150 mg/dL]), high-density lipoprotein cholesterol <1.03 mmol/L [40 mg/dL] in men and <1.29 mmol/L [50 mg/dL] in women, use of lipid-lowering medications, elevated systolic blood pressure >130 mm Hg, diastolic blood pressure >85 mm Hg, or use of antihypertensive medications; elevated blood glucose ≥6.1 mmol/L [110 mg/dL] or use of glucose-lowering agents (oral medications or insulin). Each participant was classified as nonobese for a BMI <30 kg/m^2 and obese for a BMI ≥30 kg/m^2.

Participants were divided into 4 groups: metabolically healthy (MH) nonobese (referent), MH obese, metabolically unhealthy (MU) nonobese, and MU obese (Table 1). We omitted the waist circumference criterion because of high correlation with BMI (0.91) and concern for collinearity. We were unable to isolate the effect of waist circumference from obesity given insufficient sample size of individuals with low waist circumference, precluding sensitivity analysis.

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol was approved by the institutional review board at Boston University Medical Center and all participants gave written consent.

Table 1. Description of the 4 Study Groups Defined by Obesity Status and Metabolic Health Status

Metabolic health	BMI	
	Nonobese: BMI <30 kg/m^2	Obese: BMI ≥30 kg/m^2
MH	+ Metabolic health – Obese MH nonobese	+ Metabolic health + Obese MH obese
MU*	– Metabolic health – Obese MU nonobese	– Metabolic health + Obese MU obese

BMI indicates body mass index; MH, metabolically healthy; and MU, metabolically unhealthy.

*Poor metabolic health defined as ≥2 of the following criteria: triglycerides ≥1.69 mmol/L [150 mg/dL]; high-density lipoprotein cholesterol <1.03 mmol/L [40 mg/dL] in men and <1.29 mmol/L [50 mg/dL] in women; use of lipid lowering medications; elevated systolic blood pressure >130 mm Hg and diastolic blood pressure >85 mm Hg, or use of antihypertensive medications; elevated blood glucose ≥6.1 mmol/L [110 mg/dL] or use of medications for diabetes such as insulin or oral glucose-lowering agents.

Volumetric Brain MRI Outcomes

The detailed methods for brain MRI collection and blinded analysis have been described previously.[18,19] We evaluated total cerebral brain volume (TCBV) as an indicator for general brain aging and calculated it as a ratio of the total volume of the head to normalize to head size. Intracranial volume is determined by early brain growth. As the brain shrinks later in life, the ratio of the brain parenchyma to the space within the skull volume reflects a loss of volume associated with age and disease. Lower TCBV is associated with brain aging.[20] Higher white matter hyperintensities are associated with greater age and vascular brain damage to deep brain small vessels.[21] Both white matter hyperintensity volume (WMHV) and hippocampal volume are analyzed as percent of TCBV (correcting for brain size and volume). WMHV was log-transformed to normalize a skewed distribution. Silent cerebral infarction was another marker for vascular brain aging and was defined as size >3 mm, located in a vascular distribution, lacking mass effect, and demonstrating hyperintensity of T2- and proton density–weighted images. We also measured free water (FW) and fractional anisotropy (FA) and measures on diffusion tensor imaging MRI. FA and FW are measures of myelin integrity, with lower FA and higher FW content associated with brain aging. These values were computed from diffusion tensor imaging using previously established methods.[22–24] Interrater reliabilities were between 0.90 and 0.94 for TCBV and WMHV.[19] All measurements were performed on QUANTA 6.2, operating on a Sun Microsystems (Santa Clara, CA) Ultra 5 workstation.

Neurocognitive Outcomes

Interviewers implemented neurocognitive testing based on protocol, and comparisons were made to previously normalized data.[25] Domains that were tested included executive function, memory, abstract reasoning, and visual processing. Trail Making Test Part B minus Part A is measured in minutes to complete the test, with higher values indicating poorer executive function. Trail Making Test B – A is a marker for vascular brain aging. Logical Memory-Delayed Recall is a measure of verbal memory, with higher scores indicating better neurocognitive functioning. Similarities testing evaluates abstract reasoning, with higher values indicating better cognitive functioning. Visual Reproductions-Delayed tests measure visual details and spatial memory, with higher scores indicating better functioning. The Global Cognitive Score has been used in other studies.[26,27] It is derived from a principal component analysis forcing a single score solution. The score combines weighted loadings for Trail-Making Test Part B, Hooper Visual Organization Test, Logical Memory, Visual Reproduction, Paired

Associate Learning, and Similarities (Data S1). In this calculation, Trails B and Hooper Visual Organization Test are log-transformed to convert their skewed distribution to a bivariate normal distribution, and directionality is reversed such that higher scores reflect better performance. The component loadings were derived using the Framingham Offspring examination cycle 7 data, and all measures were standardized. The final score is analyzed as a continuous measure, and higher global cognitive scores indicate superior neurocognitive functioning. The Hooper Visual Organization Test assesses visual perception, with higher values associated with better functioning.

Statistical Analysis

Descriptive statistics for all covariates are presented as either percentage or mean±standard deviation. WMHV, Trails, and Hooper Visual Organization Test were natural logarithmically transformed to normalize the skewed distributions. Volumetric brain MRI measures were expressed as a percentage of total cranial volume. We used linear regression analyses to relate metabolic health groups (referent=MH with normal BMI) to continuous measures of brain MRI abnormalities and neurocognitive function, adjusting for age, age squared, sex, interval between risk factors assessment (Exam 2) and MRI or neurocognitive assessment, and education for neurocognitive outcomes. Blood pressure and medications were not included because these were already incorporated in the definition of metabolic health. We then used logistic regression to evaluate the association of metabolic health groups with binary neurologic outcomes (eg, presence of silent cerebral infarcts), adjusting for age/sex and covariates listed in multivariable models. Then, we examined the contribution of individual components of the metabolic syndrome to the neurocognitive outcomes of interest to determine which risk factors in particular drove the observed associations. Statistical analyses for FA and FW were completed as previously described.[6] Only significant values for the associations of metabolic health and obesity groups with FA and FW are described, and nonsignificant indicates there were no voxels within the tracts with significant associations with the exposures. If a certain number of voxels within the tract were significant after correction for multiple comparisons, then we computed the average of these values within these significant voxels for each participant and reran the analysis using these measures.

We additionally ran models testing for interactions between metabolic health and obesity on the brain MRI and cognitive measures of interest. In secondary analyses, we examined effect modification by sex on brain MRI measures and neurocognitive testing for each metabolic health/obesity group. A P value of ≤0.05 was considered significant. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

Data Availability

Data used in this study are available upon reasonable request.

RESULTS

Baseline Characteristics

The baseline characteristics of the Third Generation sample are listed in Table 2. Compared with those in the MH nonobese and MH obese groups, individuals who were metabolically unhealthy were slightly older, with a higher prevalence of men and treatment for hypertension and dyslipidemia. The study sample had a low prevalence of smoking, and the majority had at least a partial college education, though a larger proportion of the MH groups attained college degrees compared with individuals in the metabolically unhealthy groups.

Associations Among Metabolic Health, Obesity, and Brain Structure by MRI

Table 3 shows the association between metabolic health and obesity groups with brain MRI measures, relative to MH nonobese as the referent group. Both MU groups, MU nonobese and MU obese, had lower TCBV (β±SE=−0.30±0.14, P=0.034 and β=−0.28±0.14, P=0.042, respectively), whereas no association was noted in the MH obese group compared with the MH nonobese group. The MU obese group had greater WMHV (β±SE=0.23±0.08, P=0.004), whereas no association between WMHV and either metabolic health or obesity alone was noted. Metabolic unhealthiness and/or obesity were not associated with changes in hippocampal volumes and silent brain infarcts. We also evaluated for possible interactions between metabolic health and obesity on brain structure. Among all MRI variables, there was only a significant interaction between metabolic health and obesity with WMHV (P=0.039), indicating a negative synergistic effect of poor metabolic health with obesity in development of greater WMHV. There was no effect modification by sex on the association of metabolic health and obesity groups with MRI variables of brain structure.

We observed differences in the patterns of FW and FA in MU obese individuals compared with the MH nonobese referent group (Tables 4 and 5 and Figure 2). Those in the MH obese group had higher FW volume in the regions of the superior corona radiata

Table 2. Baseline Characteristics of Framingham Heart Study Generation 3 Cohort by Metabolic Health and Obesity Group

	+ Metabolic health – Obese MH nonobese N=1385	+ Metabolic health + Obese MH obese N=423	– Metabolic health – Obese MU nonobese N=164	– Metabolic health + Obese MU obese N=198
Age, y	45 (8)	46 (8)	52 (8)	50 (8)
Women	835 (60)	226 (53)	52 (32)	58 (29)
BMI, kg/m^2	24.8 (2.9)	34.0 (4.0)	27.0 (2.0)	34.9 (4.3)
Hypertension medications	58 (4)	46 (11)	87 (53)	112 (57)
Lipid-lowering medications	78 (6)	47 (11)	83 (51)	93 (47)
Smoking	127 (9)	33 (8)	21 (13)	17 (9)
Apoe4	286 (22)	81 (20)	41 (26)	49 (26)
Education				
No high school degree	4 (0)	2 (0)	2 (1)	0 (0)
High school degree	147 (11)	54 (13)	33 (20)	36 (18)
Some college	381 (27)	135 (32)	50 (30)	78 (39)
College degree	853 (62)	232 (55)	79 (48)	84 (42)
MRI variables				
TCBV, %	79.2 (1.7)	79.2 (1.8)	78.2 (2.1)	(2.2)
WMHV, %	0.7 (1.3)	0.7 (0.9)	1.1 (1.9)	(5.9)
HPV, %	6.8 (0.7)	6.9 (0.8)	6.9 (0.7)	7.1 (0.7)
Neurocognitive measures				
PC1	0.7 (0.8)	0.5 (0.8)	0.4 (0.8)	(0.9)
LMd	11.8 (3.8)	11.2 (3.7)	11.2 (3.3)	(3.6)
VRd, raw score	9.1 (2.5)	8.8 (2.5)	8.3 (2.6)	(3.0)
TrB-TrA	0.6 (0.4)	0.6 (0.5)	0.7 (0.6)	(0.5)
Sim, raw score	17.5 (3.0)	17.0 (3.4)	17.5 (3.1)	16.8 (3.1)
HVOT	26.6 (2.1)	26.6 (2.2)	26.3 (2.4)	26.4 (2.5)

Continuous variables are mean (SD) and categorical variables are n (%). BMI indicates body mass index; HPV, hippocampal volume; HVOT, Hooper Visual Organization Test; MRI, magnetic resonance imaging; LMd, Logical Memory–Delayed Recall; MH, metabolically healthy; MU, metabolically unhealthy; PC1, Global Cognitive Score; Sim, similarities; TCBV, total cerebral brain volume; TrB-TrA, Trail Making Test (B–A); VRd, Visual Reproduction–Delayed Recall; and WMHV, white matter hyperintensity volume.

and body of the corpus callosum (3.77 and 2.19 mL, respectively; Table 4). Individuals in the MU nonobese group had the largest number of regions with elevated FW content (Table 5), including the largest volumes of FW in regions of the superior longitudinal fasciculus, superior corona radiata, body of corpus callosum, anterior corona radiata, external capsule, and cingulum (6.75, 4.05, 3.60, 3.46, 2.91, and 2.23 mL, respectively). Participants in the MU obese group had high FW volumes in the body of the corpus collosum, genu of corpus collosum, retrolenticular part of internal capsule and anterior corona radiata (1.60, 0.56, 0.52, and 0.57 mL, respectively).

Participants in the MH obese group had lower FA prominently in the region of anterior corona radiata (4.58 mL higher volume versus MH nonobese; Table 4). Those in the MU nonobese group also had lower FA within the superior corona radiata, external capsule, posterior limb of internal capsule, splenium of corpus callosum, and posterior thalamic radiation (4.53, 3.29, 2.87, 2.11, and 2.16 mL, respectively; Table 5). There were no significant differences in FA content between individuals in the MU obese and the MH nonobese groups.

Associations Among Metabolic Health, Obesity, and Neurocognitive Testing

We next assessed the association between metabolic health obesity groups and cognitive function, relative to the MH nonobese group as referent (Table 3). Individuals in the MH obese group had lower scores on global cognition (β±SE=−0.09±0.04, *P*=0.035) and Logical Memory-Delayed Recall (β±SE=−0.40±0.20, *P*=0.040). Additionally, both obese groups, MH obese and MU obese, showed less favorable Similarities testing scores (β±SE= −0.40±0.17, *P*=0.016 and −0.47±0.23, *P*=0.043, respectively). MU obese individuals also had lower scores on Visual Reproduction-Delayed tests (β±SE=−0.48±0.19, *P*=0.013). There were no interactions observed in the associations between metabolic health and obesity with any cognitive tests.

Table 3. Measures of Brain MRI and Neurocognitive Testing by Metabolic Health and Obesity as Compared With Metabolically Healthy Nonobese

	+ Metabolic health + Obese N=423	– Metabolic health – Obese N=164	– Metabolic health + Obese N=198
Brain MRI			
Total cerebral brain volume	0.06±0.09	−0.30±0.14*	−0.28±0.14*
Hippocampal volume	0.002±0.003	0.006±0.004	0.006±0.004
White matter hyperintensity volume	−0.01±0.05	−0.001±0.08	0.23±0.08*
Silent brain infarct	1.02 [0.55–1.90]	1.10 [0.50–2.44]	0.48 [0.17–1.41]
Neurocognitive testing			
Global Cognitive Score	−0.09±0.04*	0.01±0.06	−0.09±0.06
Logical Memory-Delayed Recall	−0.40±0.20*	0.17±0.30	−0.19±0.28
Visual Reproduction-Delayed Recall	−0.23±0.14	−0.34±0.21	−0.48±0.19*
Trails B-Trails A	−0.01±0.01	0.004±0.01	0.003±0.01
Similarities	−0.40±0.17*	0.18±0.25	−0.47±0.23*
Hooper Visual Organization Test	0.02±0.03	0.02±0.04	0.06±0.04

+ Metabolic health, – Obese (metabolically healthy nonobese)=referent group (N=1385). Data are presented as β±SE except for silent brain infarcts, which are presented as odds ratio [95% CI]. β values are expressed per unit increment in the brain measures. For MRI volumes: percent of total cerebral volume, for neurocognitive testing: correct score (except Trails, time in seconds). White matter hyperintensity volume, Hooper Visual Organization Test, and Trails B-Trails A were log-transformed to normalize their distributions. Directionality was adjusted for Trails B-Trails A so that higher values represent better performance in accordance with the other neurocognitive measures. Silent brain infarct defined as >3 mm, vascular distribution, lack of mass effect, hyperintensity of T2- and proton density-weighted images. Brain MRI models: adjusted for age, age^2, sex, and time between Framingham Heart Study exam and MRI. Neurocognitive testing models: adjusted for age, age^2, sex, time between Framingham Heart Study exam and testing, and education. MRI indicates magnetic resonance imaging; and Trails B-Trails A, Trail Making Test (B–A).

*P<0.05.

†P≤0.01.

DISCUSSION

Table 4. Significant Differences in FW and FA Among Metabolically Healthy Obese as Compared With Metabolically Healthy Nonobese

	+ Metabolic health + Obese N=423			
	FW		FA	
	Volume, mL	β	Volume, mL	β
Body of corpus callosum	2.19	0.24†	1.31	−0.30†
Superior corona radiata	3.77	0.19†	0.77	−0.25†
Genu of corpus callosum	0.71	0.21†	1.31	−0.24†
Posterior limb of internal capsule	1.00	0.16†	0.28	−0.19†
Retrolenticular part of internal capsule	0.68	0.21†	0.36	−0.24†
Anterior corona radiata	0.26	0.16†	4.58	−0.27†
Posterior corona radiata	0.64	0.18†	0.05	−0.21†
External capsule	0.02	0.13	0.53	−0.29†

Metabolically healthy nonobese=referent group (N=1385). Results for both FA and FW for each anatomical segment listed. Regions where only FA significant: cerebral peduncle 0.61 mL, β −0.20; anterior limb of internal capsule 1.92 mL, β −0.28. All results with P<0.05 unless with † indicating P≤0.01. FA indicates fractional anisotropy (no unit), between 0 and 1; and FW, fraction measure of extracellular water (no unit), between 0 and 1.

Volume indicates the volume of voxels where significant associations were found in the respective tract. β indicates the mean FW (or FA) difference (or effect) in these voxels.

In this study of younger to middle-aged adults in the community without existing brain disorders who underwent brain MRI and neurocognitive testing, we observed several indicators that both poor metabolic health and obesity were associated with adverse measures of brain aging on MRI and tests of cognition. We found that poor metabolic health was associated with reduced total cerebral brain volume. Additionally, we observed an interaction between metabolic unhealthiness and obesity on WMHV. Individuals with both poor metabolic health and obesity had greater WMHV than the referent group of MH nonobese individuals. Notably, compared with the referent, metabolic unhealthiness, more than obesity, was associated with greater areas of reduced cerebral white matter integrity by diffusion tensor imaging. We observed that primarily obesity, rather than metabolic health, was associated with poorer neurocognitive function. Our findings overall suggest that both poor cardiometabolic health and obesity are associated with subclinical neurologic dysfunction and hallmarks of brain aging.

The presence of 1 or more cardiovascular risk factors of metabolic unhealthiness is associated with physiologic changes leading to end-organ damage, particularly to the brain. Such factors may have a synergistic effect leading to endothelial damage and maladaptive changes. For example, hypertension is associated with higher pulsatile stress, particularly affecting the small vessels of the brain, and diabetes

Table 5. Significant Differences in FW and FA Among Metabolically Unhealthy Nonobese Versus Metabolically Healthy Nonobese

	– Metabolic Health – Obese N=164			
	FW		FA	
	Volume, mL	β	Volume, mL	β
Body of corpus callosum	3.6	0.35†	0.51	−0.34†
Superior corona radiata	4.05	0.22†	4.53	−0.35†
Posterior limb of internal capsule	1.56	0.23	2.87	−0.29†
Retrolenticular part of internal capsule	1.89	0.27†	1.26	−0.32†
Anterior corona radiata	3.46	0.25†	1.97	−0.34†
Posterior corona radiata	0.45	0.23†	0.82	−0.35†
Sagittal stratum	1.17	0.31†	0.47	−0.38†
External capsule	2.91	0.25†	3.29	−0.39†
Cingulum (cingulate gyrus)	2.23	0.28†	0.3	−0.42†
Superior longitudinal fasciculus	6.75	0.26†	1.96	−0.40†
Splenium of corpus callosum	0.59	0.28†	2.11	−0.31†
Cerebral peduncle	0.72	0.30†	1.53	−0.30†
Anterior limb of internal capsule	1.64	0.25†	1.71	−0.33†
Posterior thalamic radiation	0.61	0.23†	2.16	−0.33†

Metabolically healthy nonobese=referent group (N=1385). Results for both FA and FW for each anatomical segment listed. Regions where only FW significant: genu of corpus collosum 2.66 mL, β 0.30; middle cerebellar peduncle 0.62 mL, β 0.49. All results with $P<0.05$ unless with † indicating $P\leq0.01$. FA indicates fractional anisotropy (no unit), between 0 and 1. FW, fraction measure of extracellular water (no unit), between 0 and 1.

Volume indicates the volume of voxels where significant associations were found in the respective tract. β indicates the mean FW (or FA) difference (or effect) in these voxels.

confers vulnerability of the vasculature to this stress.[28] Additionally, obesity is associated with maladaptive changes of the vasculature.[29] Excess adipose tissue leads to insulin resistance and increased inflammation; those with metabolic syndrome defined as central adiposity along with 2 of 4 elevated triglycerides, reduced high-density lipoprotein, hypertension, or abnormal fasting plasma glucose have been shown to have a higher risk of Alzheimer disease, which in part is thought to be from abnormal insulin signaling and inflammation.[30] Furthermore, biomarkers that are elevated in obesity, such as ghrelin and leptin, have been linked to cognitive dysfunction. In older adults (average age, 74 years) without neurologic dysfunction, higher leptin levels were associated with worse performance on neuropsychological testing of executive function.[31] In a similar population, higher ghrelin was associated with worse performance on neuropsychological testing of verbal memory, working memory, and naming.[32]

Our results suggest that metabolic unhealthiness and obesity have differential effects on brain structure and function. We observed that in multivariable models, TCBV was lower in metabolically unhealthy groups with similar effect sizes regardless of obesity status, suggesting that poor metabolic health was the primary determinant of lower brain volume. Because normal aging results in a decline in brain volume,[33] poor metabolic health is thus associated with effective premature brain aging, which has been demonstrated in metabolic syndrome.[34] Our results provide further support that structural abnormalities of the brain occur in even earlier stages of metabolic dysfunction. We also observed an interaction between metabolic unhealthiness and obesity on WMHV, indicating a synergistic effect of these conditions on WMHV. Compared with the MH nonobese referent group, the combination of poor metabolic health and obesity was associated with greater WMHV. Although we did not study incident dementia as an outcome, WMHV is a marker of small vessel disease seen in Alzheimer disease/dementia.[35] Moreover, higher WMHV has been found to be associated with both incident stroke and dementia, underscoring the risk of such subclinical findings in the MU obese sample.[36,37]

The importance of metabolic dysregulation in brain health is underscored by our observation that metabolic health, more than obesity, was associated with the greatest number of brain regions and volumes with elevated FW and reduced FA, indicating earlier brain injury that may predate permanent damage, or white matter hyperintensities.[6] These earlier markers may result from vascular endothelial dysfunction with breakdown of the blood–brain barrier, demonstrated in hypertension, in particular, and ultimately predict cognitive impairment.[38] Furthermore, FW has been shown to be a more sensitive marker than WMHV of worsening processing speed.[39] Higher FW has also been associated with worsened episodic memory and executive function[40] as well as cognitive impairment and Alzheimer disease.[41] Our findings add to the growing evidence that unfavorable levels of metabolic health parameters and cardiovascular risk factors including elevated BMI, waist hip ratio, blood pressure, hemoglobin A1c, and metabolic syndrome are associated with WMHV and thus subclinical vascular brain damage.[42,43]

Although metabolic unhealthiness was more prominently associated with adverse brain structure than obesity, evidenced by adverse brain MRI measures in both MU groups, obesity was associated with poor scoring on a broad range of administered neurocognitive tests spanning domains of memory, visual processing, and global cognition. Other studies in both adults older than 65 years as well as younger patients with an average age of 41 years, have shown a similar association of higher BMI with poorer performance on neuropsychiatric testing that appears independent of related metabolic conditions including diabetes and

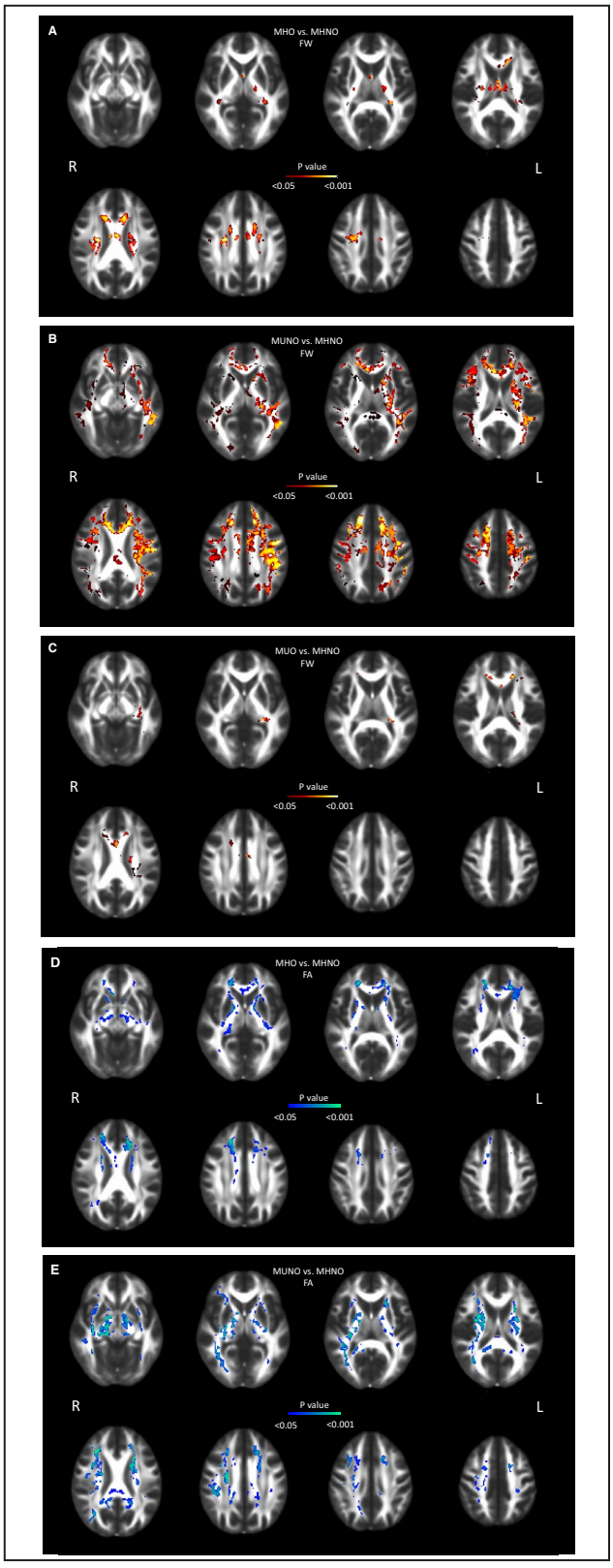

Figure 2. Associations of metabolic group with free water (FW) and fractional anisotropy (FA).
P value strength is indicated by color. **A**, Regions of higher FW content in metabolically healthy (MH) obese compared with MH nonobese (referent). **B**, Regions of higher FW content in metabolically unhealthy (MU) nonobese compared with MH nonobese (referent). **C**, Regions of higher FW content in MU obese compared with MH nonobese (referent). **D**, Regions of lower FA content in MH obese compared with MH nonobese (referent). **E**, Regions of lower FA content in MU nonobese compared with MH nonobese (referent). L indicates left; MHNO indicates metabolically healthy nonobese participants; MHO, metabolically healthy obese; MUNO, metabolically unhealthy nonobese; MUO, metabolically unhealthy obese; and R, right.

hypertension.[44,45] Notably, in our study, the presence of metabolic unhealthiness with obesity conferred worse scoring in Visual Reproductions and Similarities compared with obesity in the presence of metabolic health. Other groups studying individuals of ≈65 years of age without neurologic comorbidities have also demonstrated worse neuropsychologic testing scores in those with metabolic syndrome compared with those without metabolic syndrome.[46] These worsened scores on neuropsychiatric testing have been associated with the development of Alzheimer disease,[47] thus raising the possibility of a similar prognosis in our healthy population sample.

However, in contrast to prior work demonstrating the link between obesity and executive function,[48] we did not find a significant association of obesity with Trail Making Test Part B – A, a measure of executive function. One explanation may be because lower executive functioning as detected by Trails testing may be a later finding in this population. Supporting this possibility, FA was lower in MH obese individuals in the region of anterior corona radiata; white matter disease in the frontal lobes of adults without cognitive dysfunction has been shown to be associated with worse performance on tests of executive function.[49] These regional white matter disease findings may be related to risk for cognitive impairment in those without overt cognitive dysfunction.[50]

Prior research has demonstrated the associations of metabolic disease, white matter tract integrity, and cognitive decline. Compared with healthy controls, individuals with metabolic syndrome have been shown to have worse processing speed with associated white matter changes on diffusion tensor imaging, increased silent brain infarctions, periventricular hyperintensities, and subcortical white matter lesions.[53,51,52] However, the relationships between metabolic factors and obesity and their impact on brain health, including structural changes and cognition, have not been fully elucidated. In healthy participants, obese individuals had lower FA than individuals with normal BMI in the corpus callosum,[54,55] an area critical to cognition. Injury to the corpus callosum in patients with stroke is associated with significant cognitive decline.[56] Furthermore, a study in patients with traumatic brain injury demonstrated lower FA in regions of the internal capsule and superior longitudinal fasciculus,[57] regions also affected in individuals with metabolic dysfunction and obesity in

our study. In the patients who were obese in our study, reduced white matter integrity in the critical regions of the corpus callosum, corona radiata, and deep white matter structures paralleled poorer performance on neurocognitive testing for global cognition, memory, abstract reasoning, and visual memory. These findings are supported by our previous work and in that of other cohorts, where both frontal lobe white matter disease and disease in subcortical white matter areas were correlated with cognitive dysfunction in these domains.[58,59] Abnormalities in FA and FW reflecting loss of white matter tract integrity in key tracts of the brain may be a more sensitive marker of damage to regions important in cognition before overt manifestations of abnormalities in neurocognitive testing.

Strengths and Limitations

Strengths of our study include the large population sample, with rigorous uniformity of testing and the ability to study subclinical disease. Prior studies have demonstrated a relationship between diabetes and poor cognitive health.[60,61] To focus on preclinical disease, we excluded individuals with clinical diabetes and assessed a composite of metabolic unhealthiness measures and obesity with brain health. Additionally, in contrast to prior studies evaluating cardiometabolic risk and cognitive function conducted in middle-aged to older adults,[14,62,63] the younger age of our sample offered the opportunity to study the association of cardiometabolic disease on early, subclinical abnormalities in brain health at younger ages than previously studied. Additionally, our study included comprehensive measures of brain MRI and neurocognitive testing, adding to the prior work of other studies on diabetes and obesity in middle-aged samples.[63,64] Although other studies have linked obesity with worse cognitive dysfunction, these have generally conducted limited neurocognitive tests in older samples.[48,65]

Our study results should also be considered in the context of its limitations, including that the relative younger age and health of our sample may have reduced the power to detect differences between groups. Though BMI as a marker for obesity should be given consideration at older ages with decline in muscle mass and height with age,[64] our study participants were of young to middle age. Additionally, it is noteworthy that our cohort consisted of White participants of Western European origin, which may limit generalizability to other racial and ethnic groups. However, although the majority of the literature has been performed in White samples, our results are consistent with those found in Black individuals.[63,66] Furthermore, we may consider that cognitive norms in our study may be skewed with participants with not yet detectable cognitive impairments, and it is possible that our current neuropsychological tests missed cases of subclinical disease. Finally, we are not able to conclude the directionality of our observations between metabolic health, obesity, and structural and cognitive brain abnormalities. The individual MRI and neurocognitive tests assess different regions and facets of brain structure and cognitive function, and thus not all results can be expected to be fully concordant. Our collective findings suggest adverse associations of metabolic health and obesity on brain structure and obesity on cognition, findings associated with poorer brain health and brain aging. Additional confirmatory studies may help support our multiple observations. Future longitudinal studies to follow the structural and cognitive findings of individuals by metabolic health and obesity groups will aid the determination of prognosis and directional relations between metabolic health and brain health.

CONCLUSIONS

Poor metabolic health and obesity are associated with worse brain health in adults without clinical neurologic disease, dementia, or stroke, even in young to middle ages. Our findings underscore the public health implications of optimal levels of cardiovascular risk factors in preventative health and support further investigation of the impact of reducing the burden of cardiometabolic disease to prevent or delay brain aging.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Data S1

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SUPPLEMENTAL MATERIAL

Data S1.

The global cognitive score (PC1) was created using principal component analysis, forcing a single score solution.

Methodology: One of the assumptions of the principal component analysis is that each pair of measures follows a bivariate normal distribution. Therefore, any measures that had a skewed distribution were natural log-transformed, and directionality was reversed such that higher scores reflect superior performance.

Log transformations, Formulas, and Abbreviations used

Log transformations:
Log transformed Trails B (logTrailsB)= -log(LogTrailsB)
Log transformed Hooper Visual Organization Test (LogHVOT) = -log(31-HVOT)

Formulas:
Logical Memory (LM) Combined Recall (LMc) = LM immediate + LM delayed
Visual Reproductions Combined Recall (VRc) = VRc immediate + VRc delayed
Paired Association Learning Combined Recall (PAc)= PAc immediate + PAc delayed

Abbreviations not otherwise specified:
Similarities (Sim)

The PC1 weights (component loadings) were derived using the Framingham Offspring examination cycle 7 Neuropsych data (baseline, n=2551). Participants with prevalent dementia, stroke and other neurological conditions at baseline were excluded (n=123).

Final PC1 formula:
Standardizing measures:
S_LogTrailsB = (logTrailsB + 4.31)/0.45
S_LMc = (LMc - 22.15)/6.74
S_VRc = (VRc - 17.28)/6.27
S_PAc = (PAc - 22.21)/4.51
S_LogHVOT = (LogHVOT + 1.65)/0.52
S_SIM = (SIM - 16.76)/3.55

The global cognitive score was calculated by summing the products of the standardizing measures and the component loadings for each cognitive task.

PC1 = (0.25*S_ logTrailsB) + (0.22*S_LMc) + (0.27*S_VRc) + (0.24*S_PAc) + (0.24*S_LogHVOT) + (0.24*S_SIM)