ARTICLE

Adiposity is related to cerebrovascular and brain volumetry outcomes in the RUN DMC study

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Abstract

Objective

Adiposity predictors, body mass index (BMI), waist circumference (WC), and blood leptin and total adiponectin levels were associated with components of cerebral small vessel disease (CSVD) and brain volumetry in 503 adults with CSVD who were ≥50 years of age and enrolled in the Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort (RUN DMC).

Methods

RUN DMC participants were followed up for 9 years (2006–2015). BMI, WC, brain imaging, and dementia diagnoses were evaluated at baseline and follow-up. Adipokines were measured at baseline. Brain imaging outcomes included CSVD components, white matter hyperintensities, lacunes, microbleeds, gray and white matter, hippocampal, total brain, and intracranial volumes.

Results

Cross-sectionally among men at baseline, higher BMI, WC, and leptin were associated with lower gray matter and total brain volumes, and higher BMI and WC were associated with lower hippocampal volume. At follow-up 9 years later, higher BMI was cross-sectionally associated with lower gray matter volume, and an obese WC (>102 cm) was protective for ≥1 lacune or ≥1 microbleed in men. In women, increasing BMI and overweight or obesity (BMI ≥25 kg/m^2 or WC >88 cm) were associated with ≥1 lacune. Longitudinally, over 9 years, a baseline obese WC was associated with decreasing hippocampal volume, particularly in men, and increasing white matter hyperintensity volume in women and men.

Conclusions

Anthropometric and metabolic adiposity predictors were differentially associated with CSVD components and brain volumetry outcomes by sex. Higher adiposity is associated with a vascular-neurodegenerative spectrum among adults at risk for vascular forms of cognitive impairment and dementias.

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Glossary

BMI = body mass index; **CSVD** = cerebral small vessel disease; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; **FLAIR** = fluid-attenuated inversion recovery; **GMV** = gray matter volume; **HV** = hippocampal volume; **MMSE** = Mini–Mental State Examination; **RUN DMC** = Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort; **STRIVE** = Standards for Reporting and Imaging of Small Vessel Disease; **TBV** = total brain volume; **T2DM** = type 2 diabetes mellitus; **WC** = waist circumference; **WMH** = white matter hyperintensities; **WMV** = white matter volume.

Approximately 50% of the global adult population is overweight or obese according to 2016 estimates, creating an obesity pandemic.[1] Obesity during middle-age is associated with higher risk of several adult life cardiovascular risk factors and events, including hypertension, hyperlipidemias, type 2 diabetes (T2DM), atherosclerosis, and myocardial infarction. These cardiovascular risk factors are subsequently associated with cerebrovascular events such as stroke and late-onset, sporadic dementias,[2] particularly vascular cognitive impairments and vascular forms of dementia.[3]

The biological mechanisms linking obesity to vascular cognitive impairments and dementias and underlying cerebrovascular and neuropathologies are not well understood. However, a potential mechanism is that obesity represents higher amounts of adipose tissue, thus altering peripheral and cerebral circulation, which may be more pronounced with aging.[4] In the brain, this translates to decreased cerebral blood flow and cerebral small vessel disease (CSVD), a major vascular contributor to dementia.[5] A CSVD diagnosis is operationalized by the presence of brain MRI outcomes, including white matter hyperintensities (WMH), lacunes, and microbleeds.

Adipose tissue is the largest endocrine organ in the human body.[6] Anthropometric measurements such as body mass index (BMI) and waist circumference (WC) are used to estimate total and central adiposity, respectively. BMI grossly reflects total adult adiposity,[7] whereas WC reflects the amount of highly bioactive visceral adipose tissue that surrounds internal organs.[8] Secretory products of adipose tissue exhibit vascular and metabolic effects and influence brain structure and function.[6]

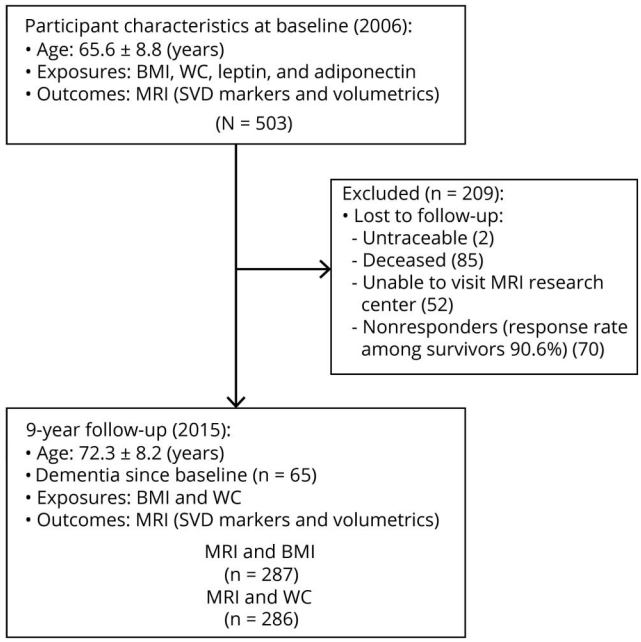
Using data from adults with CSVD who were ≥50 years of age and enrolled in the Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort (RUN DMC), we examined the associations of anthropometric and metabolic adiposity predictors with brain MRI CSVD components (WMH, lacunes, and microbleeds) and volumetry (gray and white matter, hippocampus, and total brain) outcomes to answer 4 questions. First, are adiposity predictors cross-sectionally associated with brain CSVD or volumetry imaging outcomes at 2 time points 9 years apart? Second, does higher adiposity or change in adiposity predict CSVD or volumetry outcomes? Third, do baseline adiposity measures predict 9-year change in brain imaging outcomes? Fourth, does higher adiposity predict dementia in CSVD in a cohort in whom brain CSVD and volumetry imaging outcomes have been associated with dementia?[9,10] Identifying and understanding potential associations between adiposity and CSVD components, both of which are modifiable and increase risk for cognitive impairment and dementias, could facilitate interventions to reduce adverse effects of excess adiposity on brain health.

Methods

Study population

The RUN DMC study prospectively investigates vascular and other factors associated with CSVD and CSVD progression among a baseline sample of 503 adults 50 to 85 years of age with CSVD (figure). Participants were recruited from consecutive patients referred to the Department of Neurology between October 2002 and November 2006 because they presented with symptoms of CSVD. These symptoms were

Figure RUN DMC study design



BMI = body mass index; RUN DMC = Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort; SVD = small vessel disease; WC = waist circumference.

Table 1 Characteristics of participants in the RUN DMC Study

	Baseline 2006		
	All (n = 503)	Men (n = 284)	Women (n = 219)
Demographics			
Age, mean ± SD, y	65.6 ± 8.8	65.7 ± 8.8	65.5 ± 8.9
Education <8 y, n (%)	49 (9.7)	26 (9.2)	23 (10.5)
Depressive symptoms ≥16 on Center of Epidemiologic Studies on Depression Scale, n (%)	167 (33.2)	81 (28.5)	86 (39.3)[a]
MMSE score, mean ± SD	28.1 ± 1.6	28.1 ± 1.7	28.2 ± 1.6
Dementia incidence, n (%)			
Vascular risk factors			
Alcohol consumption, mean ± SD, units/wk	7.9 ± 9.3	10.8 ± 10.3	4.1 ± 6.2[a]
Smoking (ever), n (%)	353 (70.2)	236 (83.1)	117 (53.4)[a]
Lipid-lowering drugs, n (%)	237 (47.1)	143 (50.4)	94 (42.9)
Glucose-lowering drugs, n (%)	66 (13.1)	45 (15.8)	21 (9.6)[a]
Hypertension, n (%)	369 (73.4)	208 (73.2)	161 (73.5)
T2DM, n (%)	75 (14.9)	50 (17.6)	25 (11.4)[a]
Adiposity predictors			
BMI, mean ± SD, kg/m^2	27.2 ± 4.1	27.3 ± 3.8	27.0 ± 4.5
Healthy (BMI <25.0 kg/m^2), n (%)	152 (30.2)	78 (27.5)	74 (33.8)
Overweight (BMI 25.0–29.9 kg/m^2), n (%)	226 (44.9)	139 (48.9)	87 (39.7)
Obese (BMI >30.0 kg/m^2), n (%)	125 (24.9)	67 (23.6)	58 (26.5)
WC, mean ± SD, cm	96.0 ± 12.2	99.9 ± 10.6	91.0 ± 12.4[a]
Healthy WC (men <102 cm, women <88 cm), n (%)	245 (48.7)	154 (54.2)	91 (41.6)[a]
Obese WC (men ≥102 cm, women ≥88 cm), n (%)	258 (52.3)	130 (45.8)	128 (58.4)[a]
Leptin (ng/mL), mean ± SD	23.4 ± 16.2	13.9 ± 10.5	35.7 ± 22.5[a]
Leptin resistance (leptin:BMI)	0.8 ± 0.6	0.5 ± 0.3	1.2 ± 0.7[a]
Adiponectin, mean ± SD, ng/mL	4.9 ± 3.3	3.6 ± 2.2	6.5 ± 3.8[a]
Brain volumetry outcomes			
Total brain volume, mean ± SD, mL	1,060.9 ± 80.1	1,046.0 ± 81.0	1,080.0 ± 74.9[a]
Gray matter volume, mean ± SD, mL	606.2 ± 52.6	593.2 ± 51.4	623.1 ± 49.2[a]
White matter volume, mean ± SD, mL	454.7 ± 46.0	452.9 ± 48.5	457.1 ± 42.5
Hippocampal volume, mean ± SD, mL	7.6 ± 1.0	7.3 ± 1.0	7.9 ± 1.0[a]
CSVD outcomes			
WMH, median (IQR), mL	3.6 (10.0)	3.2 (9.6)	4.1 (10.8)[a]
Microbleeds, n (% any)	83 (16.5)	50 (17.6)	33 (15.1)
Lacunes, n (% any)	132 (26.2)	86 (30.3)	46 (21.0)[a]

Continued

Table 1 Characteristics of participants in the RUN DMC Study *(continued)*

	Follow-up 2015		
	All (n = 287)	**Men (n = 164)**	**Women (n = 123)**
Demographics			
Age, mean ± SD, y	71.3 ± 7.9	71.3 ± 7.9	71.0 ± 7.4
MMSE score, mean ± SD	27.5 ± 3.5	28.1 ± 2.0	28.3 ± 2.0
Dementias, n (%)	14 (4.9)	10 (6.1)	4 (3.3)
Adiposity predictors			
BMI (kg/m^2), mean ± SD	27.2 ± 4.0	27.2 ± 3.6	26.9 ± 4.3
Healthy (BMI <25.0 kg/m^2), n (%)	90 (31.3)	48 (29.3)	42 (34.1)
Overweight (BMI 25.0–29.9 kg/m^2), n (%)	132 (45.9)	80 (48.8)	52 (42.3)
Obese (BMI >30.0 kg/m^2), n (%)	65 (22.6)	36 (21.9)	29 (23.6)
Change in BMI, 2015–2006, mean ± SD, %	0.44 ± 8.3	0.11 ± 6.8	0.88 ± 9.5
WC, mean ± SD, cm	99.1 ± 12.4	102.4 ± 11.2	93.5 ± 12.0[a]
Healthy WC (men <102 cm, women <88 cm), n (%)	122 (42.7)	86 (52.8)	36 (30.1)
Obese WC (men ≥102 cm, women ≥88 cm), n (%)	164 (57.3)	78 (47.9)	86 (69.9)
Change in WC, 2015–2006, mean ± SD, %	4.3 ± 8.7	3.8 ± 8.0	4.9 ± 9.3
Brain volumetry outcomes			
TBV, mean ± SD, mL	1,043.7 ± 78.7	1,025.5 ± 80.8	1,068.0 ± 69.0[a]
GMV, mean ± SD, mL	597.6 ± 50.6	584.67 ± 47.7	617.4 ± 47.4[a]
WMV, mean ± SD, mL	443.8 ± 46.1	439.1 ± 50.6	449.8 ± 39.5
HV, mean ± SD, mL	7.4 ± 1.1	7.1 ± 1.0	7.3 ± 1.0[a]
CSVD outcomes			
WMH, median (IQR), mL	4.7 (10.3)	3.8 (7.6)	5.67 (13.7)
Microbleeds, n (% any)	70 (24.4)	38 (23.2)	32 (26.0)
Lacunes, n (% any)	79 (27.5)	50 (30.4)	29 (23.6)

Abbreviations: BMI = body mass index; CSVD = cerebral small vessel disease; GMV = gray matter volume; HV, hippocampal volume; IQR = interquartile range; MMSE = Mini-Mental State Examination; RUN DMC = Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort; TBV = total brain volume; T2DM = type 2 diabetes mellitus; WC = waist circumference; WMH = white matter hyperintensities; WMV, white matter volume.
[a] Significant at $p < 0.05$ men vs women.

acute such as TIA or lacunar syndromes and subacute manifestations such as cognitive and motor (gait) disturbances.[11] Inclusion criteria were age and the presence of CSVD on neuroimaging (WMH or lacunar infarcts).[11] Patients who were eligible because of a lacunar syndrome were included >6 months after the event to avoid acute effects on outcomes.

Exclusion criteria included (1) dementia; (2) parkinsonism; (3) intracranial hemorrhage; (4) life expectancy <6 months; (5) intracranial space-occupying lesion; (6) psychiatric or other disease interfering with cognitive testing or ability to be followed up; (7) recent or current use of acetylcholinesterase inhibitors, neuroleptic agents, L-dopa, or dopa agonists or antagonists; (8) non-CSVD WMH (e.g., multiple sclerosis); (9) prominent visual or hearing impairment; (10) language barrier; or (11) MRI contraindications, for example, claustrophobia.

Follow-up of participants after 9 years occurred among those who were alive and agreed to participate. Baseline participants were invited to follow-up via post, with a telephone call to schedule their visit at our research center. During their follow-up visit, a subset of baseline assessments were readministered, including a dementia assessment. All tests at baseline and follow-up were performed by 2 trained neurology residents.

Table 2 Logistic regression models estimating cross-sectional associations between adiposity predictors and CSVD outcomes at 9-year follow-up in RUN DMC

	Follow-up 2015				
	CSVD outcomes				
	≥1 Microbleeds[a]			≥1 Lacunes[a]	
	No.	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Continuous adiposity predictors					
BMI	276	0.95 (0.88–1.03)	0.20	1.03 (0.95–1.11)	0.51
Men	161	0.90 (0.80–1.01)	0.09	0.93 (0.83–1.04)	0.19
Women	116	0.99 (0.90–1.11)	0.97	1.17 (1.03–1.32)	0.01
WC	274	0.98 (0.95–1.01)	0.15	1.01 (0.97–1.03)	0.69
Men	157	0.96 (0.92–1.0)	0.05	0.97 (0.94–1.01)	0.19
Women	116	0.99 (0.95–1.03)	0.60	1.04 (0.99–1.09)	0.07
Categorical adiposity predictors					
BMI					
Men vs women					
Healthy BMI, men/women ≤24.9 kg/m^2[b]	47/40	1.0		1.0	
Overweight and obese, men ≥25.0 kg/m^2	113	0.51 (0.23–1.15)	0.11	0.60 (0.26–1.40)	0.23
Overweight and obese, women ≥25.0 kg/m^2	76	1.73 (0.64–4.62)	0.28	6.97 (1.68–28.97)	0.01
WC					
Men vs women					
Healthy WC, men ≤102 cm, women ≤88 cm[b]	85/36	1.0		1.0	
Obese WC, men >102	73	0.42 (0.18–0.97)	0.04	0.32 (0.14–0.75)	0.01
Obese WC, women >88	80	0.79 (0.30–2.08)	0.64	4.66 (1.11–19.42)	0.03

Abbreviations: BMI = body mass index; CI = confidence interval; CSVD = cerebral small vessel disease; OR = odds ratio; RUN DMC = Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort; WC = waist circumference.
Logistic regression models for incident microbleeds were adjusted for age, education, sex, white matter hyperintensity severity, and dementia incidence; incident lacunes were adjusted for age, education, sex, smoking, hypertension, type 2 diabetes mellitus, CSVD severity, and dementia incidence. Nine participants were excluded from microbleeds analyses due to imaging artifacts (motion).
[a] Presence of any microbleeds or lacunes. No significant associations were found for white matter hyperintensities (table e-3 available from Dryad, doi.org/10.5061/dryad.660d317).
[b] Referent category.

Standard protocol approvals, registrations, and patient consents

All participants provided written informed consent. The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study.

Structured interview

A structured interview included questions on demographics, lifestyle, vascular risk factors, and current medication use.

Demographics and lifestyle included education (classified into 7 categories ranging from primary school to an academic degree), marital status, living conditions, and lifestyle habits (alcohol consumption, smoking).

Vascular risk factors and cardiovascular disease included history of hypertension, T2DM, atrial fibrillation, TIA, stroke, myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angiography, aortic prosthesis, vascular prosthesis, carotid endartectomy, and migraine. Family history of myocardial infarction, cerebrovascular disease, and T2DM was recorded.

Current medication use was according to the Anatomical Therapeutic Chemical classification system.[12]

Physical examination

Anthropometric predictors included BMI, calculated as clinically measured body weight in kilograms divided by body height in meters squared. Maximal WC in centimeters

Table 3 Linear regression models estimating baseline cross-sectional associations between adiposity predictors and TBV and GMV in RUN DMC

		Baseline 2006			
		Brain volumetry outcomes			
		TBV		GMV	
	No.	β Coefficient (95% CI)	*p* Value	β Coefficient (95% CI)	*p* Value
Continuous adiposity predictors					
BMI, kg/m^2	503	−0.05 (−0.13 to 0.03)	0.21	−0.16 (−0.24 to −0.09)	0.00
Men	284	−0.12 (-0.23 to 0.04)	0.00	−0.28 (−0.41 to −0.18)	0.00
Women	219	0.01 (−0.08 to 0.09)	0.90	−0.04 (−0.14 to −0.06)	0.48
WC, cm	503	−0.07 (−0.16 to 0.02)	0.11	−0.18 (−0.26 to −0.10)	0.00
Men	284	−0.13 (-0.25 to -0.06)	0.00	−0.25 (−0.40 to −0.16)	0.00
Women	219	−0.02 (−0.11 to 0.08)	0.76	−0.09 (−0.19 to 0.03)	0.16
Leptin, ng/mL	503	−0.18 (-0.26 to -0.07)	0.00	−0.13 (−0.22 to −0.04)	0.00
Men	284	−0.07 (−0.19 to 0.02)	0.11	−0.16 (−0.32 to −0.06)	0.00
Women	219	−0.02 (−0.13 to 0.10)	0.76	−0.05 (−0.19 to −0.08)	0.44
Adiponectin, ng/mL[a]	503	−0.07 (−0.16 to 0.02)	0.11	0.02 (−0.06 to 0.10)	0.65
Men	284	0.04 (−0.04 to 0.14)	0.28	0.06 (−0.05 to 0.17)	0.30
Women	219	0.01 (−0.10 to 0.12)	0.89	−0.03 (−0.17 to 0.10)	0.60
Leptin resistance	503	−0.16 (-0.24 to -0.08)	0.00	−0.11 (−0.18 to −0.03)	0.01
Leptin:BMI, men	284	−0.05 (−0.14 to 0.03)	0.20	−0.13 (−0.24 to −0.02)	0.02
Leptin:BMI, women	219	−0.07 (−0.16 to 0.04)	0.22	−0.08 (−0.19 to 0.05)	0.24
Categorical adiposity predictors					
BMI					
Total sample					
Healthy, ≤24.9 kg/m^2[b]	152	1.0		1.0	
Overweight and obese, ≥25.0 kg/m^2	351	−0.03 (−0.11 to 0.05)	0.53	−0.09 (−0.17 to −0.02)	0.02
Men vs women					
Healthy BMI, ≤24.9 kg/m^2[b]	78/74	1.0		1.0	
Overweight and obese: men ≥25.0 kg/m^2	206	−0.07 (−0.16 to 0.01)	0.08	−0.16 (−0.27 to −0.05)	0.00
Overweight and obese, women ≥25.0 kg/m^2	145	0.03 (−0.06 to 0.12)	0.56	−0.03 (−0.11 to −0.11)	0.96
WC					
Total sample					
Healthy WC, men ≤102 cm, women ≤88 cn[b]	245	1.0		1.0	
Obese WC, men >102 cm, women >88 cm	258	−0.10 (−0.18 to −0.02)	0.01	−0.15 (−0.23 to −0.07)	0.00
Men vs women					
Healthy WC, men ≤102 cm, women ≤88 cm[b]	154/91	1.0		1.0	
Obese WC, men >102 cm	130	−0.12 (−0.20 to −0.03)	0.01	−0.15 (−0.23 to −0.07)	0.00
Obese WC, women >88 cm	128	−0.03 (−0.12 to 0.07)	0.60	−0.06 (−0.17 to 0.06)	0.32

Continued

Table 3 Linear regression models estimating baseline cross-sectional associations between adiposity predictors and TBV and GMV in RUN DMC *(continued)*

		Baseline 2006			
		Brain volumetry outcomes			
		TBV		GMV	
	No.	β Coefficient (95% CI)	*p* Value	β Coefficient (95% CI)	*p* Value
Leptin					
Total sample					
Q1, men ≤7.4 ng/mL, women ≤19.6 ng/mL[b]	127	1.0		1.0	
Q4, men >21.7 ng/mL, women >52.6 ng/mL	126	−0.21 (−0.25 to −0.07)	0.00	−0.17 (−0.20 to −0.04)	0.00
Men vs women					
Q1, men ≤7.4 ng/mL, women ≤19.6 ng/mL[b]	72/55	1.0		1.0	
Q4, men >21.7 ng/mL	71	−0.09 (−0.16 to 0.03)	0.17	−0.19 (−0.24 to −0.02)	0.02
Q4, women >52.6 ng/mL	55	−0.12 (−0.20 to 0.04)	0.18	−0.16 (−0.23 to 0.02)	0.10

Abbreviations: BMI = body mass index; CI = confidence interval; GMV = gray matter volume; Q = quartile; RUN DMC = Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort; TBV = total brain volume; WC = waist circumference.
Linear regression models for TBV and GMV were adjusted for age, education, sex, smoking, and T2DM. Continuous measures of TBV, GMV, WMV, and HV (milliliters). Continuous levels of leptin and adiponectin are categorized in quartiles, and the lowest quartile (Q1) was compared to the highest quartile (Q4).
[a] No significant associations were observed for adiponectin quartiles (data not shown).
[b] Referent category.

was measured without a shirt, in a standing position, between the lowest rib and the iliac crest at the end of usual expiration. Underweight, healthy weight, overweight, and obesity were defined as follows: underweight, BMI <20.00 kg/m^2; healthy, BMI 20.00 to 24.99 kg/m^2; overweight, BMI 25.00 to 29.99 kg/m^2; and obese, BMI ≥30.00 kg/m^2. Central obesity was defined as WC >102 cm for men and >88 cm for women.

Blood pressure measurements included systolic and diastolic pressures obtained in the sitting position. The average of 3 repeated measurements was used.

Blood at baseline was collected after a 12-hour overnight fast, and serum aliquots were stored at −80°C. A lipid panel comprised total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides. Total serum leptin and adiponectin levels were determined with human leptin and adiponectin ELISAs (Laboratory Medicine, Radboud University Medical Center, Nijmegen, the Netherlands).

MRI protocol

MRI was acquired on a 1.5T MRI scanner (2006: Magnetom Sonata, Siemens, Munich, Germany; 2015: Magnetom Avanto, Siemens) with the same head coil used at both time points. The scanning protocol included 3D T1 magnetization-prepared rapid gradient echo imaging (voxel size 1.0 × 1.0 × 1.0 mm) and fluid-attenuated inversion recovery (FLAIR) pulse sequences (2006: voxel size 0.5 × 0.5 × 5.0 mm, interslice gap 1.0 mm; 2015: voxel size 0.5 × 0.5 × 2.5 mm, interslice gap 0.5 mm). To minimize effects of changes in FLAIR sequence, we resliced follow-up FLAIR images to match the slice thickness of baseline images using linear interpolation.[9]

CSVD outcomes

CSVD was rated using Standards for Reporting and Imaging of Small Vessel Disease (STRIVE) criteria for vascular changes on neuroimaging.[13] WMH volumes were calculated with a semiautomatic WMH segmentation method.[14] Segmentations were visually checked for segmentation errors by 1 trained rater blinded to clinical data. The Fazekas scale was used to categorize baseline WMH severity.[15]

Number and location of lacunes and microbleeds were rated manually on FLAIR/T1-weighted and T2*-weighted MRI scans according to the STRIVE criteria by 2 trained raters blinded to clinical data as previously described.[9] Lacunes were defined as hypointense areas >2 and ≤15 mm on FLAIR and T1. This ruled out enlarged perivascular spaces (≤2 mm), except around the anterior commissure, where perivascular spaces can be large, and infraputaminal pseudolacunes. Microbleeds were defined as small (<10-mm diameter), homogeneous, round foci of low signal intensity on T2*-weighted images. Microbleed number per hemisphere was counted. Lesions were not considered microbleeds if they were symmetric hypointensities in the globus pallidus, likely calcifications or iron deposits, flow voids artifacts of the pial blood vessels, or hyposignals in T2* inside a lesion compatible with an infarct or a likely hemorrhagic transformation. Interrater and intrarater reliabilities were excellent.[9] Incident lacunes and microbleeds during the follow-up period were identified.[9]

Table 4 Linear regression models estimating baseline cross-sectional associations between adiposity predictors and WMV and HV in RUN DMC

		Baseline 2006			
		Brain volumetry outcomes			
		WMV		HV	
	No.	β Coefficient (95% CI)	*p* Value	β Coefficient (95% CI)	*p* Value
Continuous adiposity predictors					
BMI	503	0.07 (−0.01 to 0.16)	0.11	−0.08 (−0.16 to −0.01)	0.04
Men	284	0.08 (−0.04 to 0.22)	0.19	−0.12 (-0.26 to 0.01)	0.04
Women	219	0.06 (−0.06 to 0.17)	0.35	−0.06 (−0.17 to 0.06)	0.38
WC	503	0.05 (−0.04 to 0.14)	0.31	−0.11 (−0.20 to −0.02)	0.01
Men	284	0.03 (−0.11 to 0.18)	0.31	−0.10 (−0.26 to 0.02)	0.08
Women	219	0.07 (−0.06– to −0.19)	0.32	−0.11 (−0.23 to 0.02)	0.10
Leptin	503	0.04 (−0.06 to 0.15)	0.42	−0.05 (−0.14 to 0.05)	0.36
Men	284	0.05 (−0.09 to 0.21)	0.43	−0.07 (−0.22 to 0.06)	0.27
Women	219	0.02 (−0.13 to 0.18)	0.74	−0.00 (−0.15 to 0.16)	0.97
Adiponectin[a]	503	0.04 (−0.06 to 0.13)	0.44	0.01 (−0.08 to 0.10)	0.78
Men	284	0.03 (−0.09 to 0.16)	0.62	0.05 (−0.07 to 0.17)	0.44
Women	219	0.04 (−0.10 to 0.20)	0.53	−0.02 (−0.19 to 0.13)	0.73
Leptin resistance, leptin:BMI	503	0.01 (−0.08 to 0.09)	0.92	−0.03 (−0.12 to 0.06)	0.51
Men	284	0.04 (−0.08 to 0.16)	0.48	−0.07 (−0.19 to 0.05)	0.27
Women	219	−0.04 (−0.18 to 0.09)	0.54	0.04 (−0.10 to 0.17)	0.61
Categorical adiposity predictors					
BMI					
Total sample					
Healthy, ≤24.9 kg/m^2[b]	152	1.0		1.0	
Overweight and obese, ≥25.0 kg/m^2	351	0.06 (−0.03 to 0.15)	0.17	−0.03 (−0.12 to 0.05)	0.44
Men vs women					
Healthy BMI, ≤24.9 kg/m^2[b]	78/74	1.0		1.0	
Overweight and obese, men ≥25.0 kg/m^2	206	0.04 (−0.08 to 0.17)	0.46	−0.12 (−0.27 to 0.05)	0.17
Overweight and obese, women ≥25.0 kg/m^2	145	0.08 (−0.05 to 0.19)	0.25	−0.06 (−0.22 to 0.12)	0.54
WC					
Total sample					
Healthy WC, men ≤102 cm, women ≤88 cm[b]	245	1.0		1.0	
Obese WC, men >102 cm, women >88 cm	258	0.03 (−0.06 to 0.12)	0.53	−0.10 (−0.19 to −0.01)	0.02
Men vs women					
Healthy WC, men ≤102 cm, women ≤88 cm[b]	154/91	1.0		1.0	
Obese WC, men >102 cm	130	0.02 (−0.10 to 0.14)	0.53	−0.13 (−0.25 to −0.02)	0.03
Obese WC, women >88 cm	128	0.03 (−0.10 to 0.16)	0.62	−0.07 (−0.20 to 0.07)	0.32
Leptin					
Total sample					

Continued

Table 4 Linear regression models estimating baseline cross-sectional associations between adiposity predictors and WMV and HV in RUN DMC *(continued)*

		Baseline 2006			
		Brain volumetry outcomes			
		WMV		HV	
	No.	β Coefficient (95% CI)	*p* Value	β Coefficient (95% CI)	*p* Value
Q1, men ≤7.4 ng/mL, women ≤19.6 ng/mL[b]	127	1.0		1.0	
Q4, men >21.7 ng/mL, women >52.6 ng/mL	126	0.02 (−0.08 to 0.11)	0.74	−0.11 (−0.18 to 0.02)	0.10
Men vs women					
Q1, men ≤7.4 ng/mL, women ≤19.6 ng/mL[b]	72/55	1.0		1.0	
Q4, men >21.7 ng/mL	71	0.05 (−0.10 to 0.17)	0.74	−0.16 (−0.25 to 0.01)	0.07
Q4, women >52.6 ng/mL	55	−0.04 (−0.20 to 0.13)	0.68	−0.02 (−0.19 to 0.15)	0.82

Abbreviations: BMI = body mass index; CI = confidence interval; HV = hippocampal volume; Q = quartile; RUN DMC = Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort; WC = waist circumference.WMV = white matter volume.
Linear regression models for WMV and HV were adjusted for age, education, sex, smoking, and type 2 diabetes mellitus. Seven participants were excluded from the HV analyses due to imaging artifacts (motion). Continuous measures of WMV and HV (milliliters). Continuous levels of leptin and adiponectin are categorized in quartiles, and the lowest quartile (Q1) was compared to the highest quartile (Q4).
[a] No significant associations were observed for adiponectin quartiles (data not shown).
[b] Referent category.

Brain volumetry outcomes

Volumetry outcomes have been described.[9,11] In brief, gray matter volume (GMV), white matter volume (WMV), hippocampal volume (HV), and CSF volumes were calculated with SPM12 (fil.ion.ucl.ac.uk/spm/) unified segmentation routines on the T1 magnetization-prepared rapid gradient echo images.[16] All images were visually checked for coregistration and segmentation artifacts. GMV, WMV, and CSF volume were computed by summing all voxels belonging to that tissue class multiplied by voxel volume in milliliters. Intracranial volume was determined by summing GMV, WMV, and CSF volume; total brain volume (TBV) was found by summing GMV and WMV. To account for interscan effects, we corrected for differences in intracranial volume between baseline and follow-up. All volumes were normalized to baseline intracranial volume.

Dementia assessment

Dementia screening was performed at the 9-year follow-up.[16] The Mini-Mental State Examination (MMSE)[17] was used as the initial screen for global cognition. Those with a follow-up MMSE score <26 or a decline of ≥3 points from baseline were examined for the presence of dementia at the Radboud Alzheimer Center. If a participant refused examination, a consensus panel consisting of a neurologist, clinical neuropsychologist, and geriatrician made the dementia diagnosis. This panel reviewed all available neuropsychological[11] and brain imaging information, including difference in neuropsychological performance between baseline and follow-up, outcome of the Mini International Neuropsychiatric Interview,[18] the follow-up and/or baseline MRI, and medical record review. In addition, participants' general practitioners and medical specialists were contacted regarding cognitive status. Cognitive tests were interpreted with consideration for age, level of education, and interference with daily living confirmed by family or caregivers. Dementia diagnoses were based on DSM-IV criteria.[19] Dementia onset was the date when clinical symptoms were consistent with the diagnosis.

Data availability

RUN DMC study methods are adequately described herein, and references to previous publications are provided. The RUN DMC study provides deidentified data for replication studies and other forms of analytic inquiry on approval by the study investigators.

Statistical analyses

Cross-sectional descriptive analyses were performed at baseline (2006) and follow-up (2015). Continuous and categorical adiposity predictors were associated with individual brain outcomes for the entire sample and by sex. Means and SDs were computed for continuous variables. Due to skewed distributions, leptin, adiponectin, and WMH were natural log transformed. We calculated leptin resistance as the leptin to BMI ratio (leptin:BMI).[20] Pearson correlation coefficients among adiposity predictors were calculated. We used *t* tests for means comparisons and χ^2 analyses for categorical variables.

We used multivariable linear and logistic regression models to examine cross-sectional associations between individual adiposity predictors and CSVD components and volumetric brain outcomes at examinations in 2006 and 2015. Adiposity predictors included BMI and WC in 2006 and 2015 and leptin and total adiponectin in 2006 only. We used logistic regression analyses to predict the presence vs absence of lacunes and microbleeds. We calculated odds ratios and 95%

confidence intervals . WMH, GMV, WMV, TBV, and hippocampal volume (HV) were considered continuous outcomes in linear regression analyses. We calculated β coefficients and 95% confidence intervals.

Among those who participated at both examinations in 2006 and 2015, 3 longitudinal analyses were performed. These included using (1) baseline adiposity measures to predict follow-up brain imaging outcomes 9 years later, (2) 9-year change (2006–2015) in anthropometry measures in association with brain outcomes at follow-up, and (3) baseline anthropometry measures in association with 9-year change (2006–2015) in brain imaging outcomes. For analyses 1 and 2, multivariable linear and logistic regression models were used as described. In analyses of body weight and BMI change, we categorized the sample a priori by substantial degree of change, either ≥5% or ≥10% increase or decrease from baseline body weight and BMI. For analysis 3, multivariable-adjusted linear mixed models were used. Finally, we used multivariable-adjusted logistic regression analyses of baseline adiposity in association with clinical dementia occurrence over 9 years of follow-up. Baseline characteristics of those who died during follow-up were also described.

Selection of covariates originated from a pool of variables that were potentially biologically relevant or reported in the literature as risk or protective factors for CSVD or brain volumetry outcomes. Our pool consisted of age; sex; educational attainment (primary or less vs higher than primary education); cigarette smoking (ever/never); alcohol intake (units per day); clinically relevant depressive symptom burden (≥16 on the Center of Epidemiologic Studies on Depression Scale or current depression medication use); MMSE score; use of glucose-lowering medications; T2DM (self-reported or T2DM medication use); hypertension (blood pressure ≥140/90 mm Hg or antihypertensive medication use); blood lipid levels; and hypercholesterolemia (cholesterol ≥6.2 mM or lipid-lowering drug use). From this pool, we systematically determined which variables to include in multivariable-adjusted regression models by evaluating each one in age-adjusted regression models in association with brain outcomes. If the variable was associated with an outcome at $p \leq 0.05$, the variable was included as a covariate in the final regression model. As a result, age, sex, education, cigarette smoking, and T2DM were included. In analyses of 2015 brain outcomes, presence of dementia and baseline WMH severity assessed with the Fazekas scale were also included as covariates. Results were considered significant at $p < 0.05$ with 2-tailed tests. SPSS version 22.0 (IBM Corp, Armonk, NY) was used for data analyses.

Results

Baseline and follow-up characteristics of the RUN DMC sample (n = 503) are reported in table 1. The mean baseline age of participants was 65.6 ± 8.8 years and at follow-up was 71.3 ± 7.9 years. We did not evaluate underweight BMI because 2% of participants in 2006 (n = 11 of 503) and 2015 (n = 6 of 287) met the criterion. Dementia was diagnosed in 65 participants during follow-up.

Differences in baseline characteristics between participants in 2006 and the 87 who died during follow-up are presented in table e-1 (available from Dryad, doi.org/10.5061/dryad.660d317). Compared to surviving participants, those who died were older; were more likely to use lipid-, glucose-, and blood pressure–lowering medications; and had lower average MMSE score, higher average WC, and higher prevalence of central obesity and T2DM. Those who died evidenced lower baseline TBV, GMV, WMV, and HV and higher median WMH volume and were more likely to have a Fazekas score of moderate or severe (vs none or mild) or ≥1 lacune.

Adiposity predictors were cross-sectionally associated with CSVD outcomes. At average baseline age of 66 years, leptin was protective for CSVD outcomes in men; the highest (compared to lowest) quartile of leptin was associated with lower WMH volumes and lower odds of ≥1 lacune (table e-2 available from Dryad, doi.org/10.5061/dryad.660d317). Contrastingly, cross-sectional analyses at the 9-year follow-up showed that an obese WC lowered the odds of microbleeds and lacunes in men (table 2). Among women, however, increasing BMI, being overweight or obese based on BMI, or having an obese WC was associated with the presence of ≥1 lacune (table 2). No associations were observed for WMH (table e-3 available from Dryad, doi.org/10.5061/dryad.660d317). Therefore, different adiposity predictors were associated with different CSVD outcomes cross-sectionally at baseline vs cross-sectionally at follow-up; and sex differences were observed.

In relation to brain volumetry outcomes, higher adiposity was cross-sectionally associated with lower brain volumes. Higher BMI and WC, total obesity, and central obesity were associated with lower GMV and TBV in men at average baseline age of 66 years (table 3). Higher serum leptin levels were associated with lower GMV and TBV in men and women. Increasing BMI and WC were also associated with lower HV in men (table 4). A higher estimate of leptin resistance (leptin: BMI), was associated with lower GMV and TBV, particularly in men. At follow-up 9 years later, average age of 71 years, cross-sectional analyses showed higher BMI associated with lower GMV and higher WC with lower HV, particularly in men (table 5). No associations were observed for TBV or WMV (table e-4 available from Dryad, doi.org/10.5061/dryad.660d317).

Longitudinal analyses of baseline adiposity predictors in association with CSVD and brain volumetry (tables e-5–e-7 available from Dryad, doi.org/10.5061/dryad.660d317) outcomes at the 9-year follow-up showed no associations. Similarly, evaluation of change in BMI and body weight over 9

Table 5 Linear regression models estimating cross-sectional associations between anthropometric predictors and brain volumetry outcomes at 9-year follow-up in RUN DMC

		Follow-up 2015			
		Brain volumetry outcomes			
		GMV		HV	
	No.	β Coefficient (95% CI)	*p* Value	β Coefficient (95% CI)	*p* Value
Continuous adiposity predictors					
BMI	287	−0.12 (−0.23 to −0.02)	0.02	−0.02 (−0.11 to −0.08)	0.71
Men	164	−0.14 (−0.29 to −0.03)	0.04	0.05 (−0.09 to 0.19)	0.48
Women	123	−0.09 (−0.22 to 0.07)	0.30	−0.08 (−0.21 to 0.07)	0.32
WC	286	−0.13 (−0.24 to −0.01)	0.03	−0.03 (−0.14 to 0.07)	0.56
Men	163	−0.11 (−0.26 to 0.04)	0.16	0.06 (−0.09 to 0.21)	0.42
Women	123	−0.16 (−0.31 to 0.01)	0.07	−0.12 (−0.28 to 0.03)	0.11
Categorical adiposity predictors					
BMI					
Total sample					
Normal weight, ≤24.9 kg/m^2[a]	88	1.0		1.0	
Overweight and obese, ≥25.0 kg/m^2	199	−0.09 (−0.19 to −0.01)	0.08	0.00 (−0.09 to 0.10)	0.93
Men vs women					
Normal weight, men/women ≤24.9 kg/m^2[a]	47/41	1.0		1.0	
Overweight and obese, men ≥25.0 kg/m^2	117	−0.09 (−0.19 to −0.01)	0.08	0.03 (−0.10 to 0.15)	0.70
Overweight and obese, women ≥25.0 kg/m^2	82			−0.01 (−0.15 to 0.14)	0.95
WC					
Total sample					
Healthy WC, men ≤102 cm, women ≤88 cm [a]	122	1.0		1.0	
Obese WC, men >102 cm, women >88 cm	164	−0.08 (−0.37 to −0.06)	0.18	−0.05 (−0.10 to 0.29)	0.34
Men vs women					
Healthy WC, men ≤102 cm, women ≤88 cm [a]	85/37	1.0		1.0	
Obese WC, men >102 cm	78	−0.08 (−0.37 to −0.06)	0.18	0.14 (−0.01 to 0.52)	0.04
Obese WC, women >88 cm	86	−0.06 (−0.20 to 0.09)	0.46	−0.06 (−0.47 to 0.19)	0.41

Abbreviations: BMI = body mass index; CI = confidence interval; GMV = gray matter volume; HV = hippocampal volume; RUN DMC = Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort; WC = waist circumference.
Linear regression models for GMV and HV were adjusted for age, education, sex, smoking, T2DM, WMH severity, and dementia incidence. Five participants were excluded in the HV analyses due to imaging artifacts (motion). Continuous measures of GMV and HV (milliliters).
[a] Referent category. No significant associations were found for total brain volume and white matter volume (table e-3 available from Dryad, doi.org/10.5061/dryad.660d317).

years showed no association with follow-up CSVD or brain volumetry outcomes (tables e-8 and e-9 available from Dryad, doi.org/10.5061/dryad.660d317). Moreover, more pronounced 5% or 10% change in BMI or body weight over 9 years was considered and was not associated with follow-up CSVD or brain volumetry outcomes (data not shown).

Over 9 years, however, a baseline obese WC was associated with decreasing HV, particularly in men, and increasing WMH volume (table 6) in women and men. Finally, adiposity measures were not associated with dementia.

Discussion

To the best of our knowledge, this is a first report suggesting sex differences underlying cross-sectional associations of anthropometric and metabolic adiposity predictors with

Table 6 Associations between baseline adiposity predictors and 9-year longitudinal repeated measures of HV and WMH in RUN DMC estimated with linear mixed models

		9-y Change in HV, mL		9-y Change in WMH, mL	
Baseline 2006	**No.**	**MD (95% CI)**	***p* Value**	**MD (95% CI)**	***p* Value**
Categorical adiposity predictors					
WC					
Total sample					
Healthy WC, men ≤102 cm, women ≤88 cm[a]	122	−0.07 (0.0 to −0.14)		1.46 (0.32 to 2.61)	
Obese WC, men >102 cm, women >88 cm	164	−0.17 (−0.10 to −0.24)	0.11	3.02 (1.97 to 4.06)	0.03
Men vs women					
Small WC, men ≤102 cm [a]	85	−0.04 (−0.06 to −0.13)		1.05 (0.46 to 2.56)	
Small WC, women ≤88 cm [a]	37	−0.20 (−0.08 to −0.32)		2.20 (0.46 to 3.94)	
Large WC, men >102 cm	78	−0.23 (−0.13 to −0.32)	0.00	2.46 (1.0 to 3.92)	0.16
Large WC, women >88 cm	86	−0.13 (−0.02 to −0.24)	0.47	4.05 (2.50 to 5.60)	0.06

Abbreviations: CI = confidence interval; HV = hippocampal volume; MD = mean difference; RUN DMC = Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort; WC = waist circumference; WMH = white matter hyperintensities
Linear mixed models were adjusted for baseline age, education, sex, smoking, hypertension, and T2DM.
[a] Referent category.

cerebrovascular and brain volumetry outcomes in patients with CSVD. We have addressed several questions. Our first question was whether adiposity was cross-sectionally associated with brain imaging CSVD and volumetry outcomes in adults with CSVD at 2 time points 9 years apart. Using 2 cross-sectional time points 9 years apart, we show that overweight and obesity, as well as higher leptin levels in men with CSVD, are associated with lower brain volumes, particularly in their 60s. However, among a subset of these men who survive into their 70s and are reexamined, higher adiposity is associated with fewer cerebrovascular outcomes, perhaps denoting a survival bias. In contrast, women with CSVD and higher levels of adiposity in their 70s are more likely to experience lacunes. These data illustrate the nuances of following up surviving participants with a clinically diagnosed cerebrovascular phenotype. Most observed cross-sectional associations occurred among men at 2 cross-sectional time points, at an average age 66 years and 9 years later at an average age 71 years. Adverse associations with adiposity diminished with survivorship.

Our second question was whether baseline adiposity or change in adiposity from baseline to follow-up predicted CSVD components or brain volumetry outcomes on follow-up. The answer to this question was no, which may be due to survival bias or attrition of participants at higher risk.

Our third question was whether baseline adiposity measures predict 9-year change in brain imaging outcomes. We found that baseline central obesity WC (defined with sex-specific cutoffs), a known cardiovascular risk factor, predicted loss of HV in men and increasing WMH volume in men and women.

Our final question was whether baseline adiposity predicts dementia. The answer to this question was no. However, previously published RUN DMC analyses have shown that dementia is associated with lower HV and WMV.[10] With continued follow-up of this aging clinical cohort and accrual of more adults with cognitive decline, impairments, or dementias, future analyses of the adiposity exposure may be sufficiently powered for these analyses.

Associations of higher BMI and WC with underlying cerebrovascular pathologies such as WMH,[21] cerebral microbleeds,[22] and lacunes[23] are sparsely reported. However, most data suggest that higher levels of vascular risk factors, including higher BMI and central obesity or visceral adipose, are associated with higher cerebrovascular risk.[24] Higher WC has been associated with CSVD components, notably microbleeds, lacunes, and WMH, in Korean samples.[22,24]

In addition to considering cerebrovascular components of CSVD, we evaluated brain volumetry. Cross-sectional associations between higher anthropometric predictors and lower TBV, GMV, and HV are comparable to reports that higher levels of anthropometric predictors are associated with lower TBV, GMV, and HV.[25–27] Higher BMI and lower GMV have also been associated with lower cognitive function,[28] as has central obesity.[29] Visceral adipose tissue (highly correlated with WC) measured via abdominal MRI has been associated with lower HV in cognitively healthy elderly 55 to 90 years of age.[30] Despite the majority of studies reporting associations between higher adiposity and lower brain volumes, there are conflicting reports. For example, higher BMI was associated

with higher HV in older adults with or at risk for cardiovascular disease.[31]

While cross-sectional associations cannot discriminate cause and effect, observed cross-sectional associations differed 9 years apart. Our findings suggest that higher levels of adiposity, classified as overweight or obese BMI or WC, may be related to earlier brain volumetry outcomes such as lower TBV and GMV and later protection for lacunes and microbleeds in surviving men. In contrast, among women, higher levels of adiposity at follow-up were related to occurrence of lacunes. This finding suggests a cerebrovascular-neurodegenerative spectrum and temporality of brain outcomes associated with adipose predictors that differ between men and women with CSVD and emphasizes that adipose tissue may play endocrine, neuronal, and vascular roles in brain health.[6,32] These roles may be both cause and consequence of cerebrovascular and neurodegenerative pathologies associated with CSVD and its clinical symptoms. Our longitudinal observation that central obesity predicts change in key regional (hippocampus) and type (WMH) of brain volumetry outcomes suggests that higher adiposity is detrimental for brain aging and requires further investigation and replication. Finally, these data underscore the profound influence of selective survival in longitudinal analyses of brain outcomes and imply a role of brain reserve in survival, because those who died during the follow-up period had lower baseline brain volumes.

Metabolic adipose tissue, as manifested by higher blood leptin levels and leptin resistance, is associated with lower TBV and GMV in older adults, particularly men with CSVD. Higher blood leptin levels have been associated with lower GMV in young adults (mean age 32.0 ± 1.0 years)[33] and with lower insula GMV among adults 25 to 40 years of age with a family history of obesity.[34] In contrast, among Japanese elderly, higher blood leptin levels were associated with higher region-specific GMV, including hippocampus.[35] Higher leptin levels have also been shown to protect against age-related cognitive decline[35] and dementia.[36] Because leptin signaling is dysregulated in degenerating hippocampal neurons, potentially indicating neuronal leptin resistance in patients with Alzheimer disease,[37] inconsistent cross-sectional leptin associations with brain outcomes, cognition, and dementias in older men may be obscured. Leptin may play a pivotal role in an aging fat-brain axis and may be a critical biomarker of aging-related changes in satiety, glucose homeostasis, inflammation, vascular function, and memory.[6,38]

Sex differences in total and central obesity are a known phenomenon.[39] Differential storage of white adipose tissue is influenced by sex hormones and fat depot–specific release of hormones and cytokines.[38] Larger WC, denoting a more androgenic hormonal environment, is more common among adult men and postmenopausal women[40,41] and is associated with higher cardiovascular disease risk.[42] Sex-specific associations between anthropometric predictors and brain outcomes may be due to female menopause. The average age at menopause is 52 years in Northern European populations,[43] and our sample most likely included women who were going through the menopausal transition. Menopause influences the sex hormone milieu[44] and body composition,[41] including adipose tissue and blood adipokine levels.

Differential associations between adiposity predictors and brain outcomes may also be dependent on age at measurement and temporality. A changing role of adipose tissue throughout aging and in later life, by age decade, may be a real phenomenon. Our sample was examined on average during their seventh and eighth decades of life. During this aging period, an inflection point in vascular risk factor trajectories has been observed. These trajectories are described for BMI, blood pressure, and blood lipids in association with late-onset sporadic dementias.[45] While we cannot evaluate life-course trajectories in RUN DMC, their potential contribution to a changing risk profile, particularly among women, cannot be ignored. Midlife obesity has been associated with reduced GMV and greater dementia risk, whereas later-life overweight and obesity have been associated with lower dementia risk.[46] Given the cross-sectional findings in RUN DMC, we cannot elucidate causality or gain insights into the temporality of adiposity predictors in relation to brain outcomes. However, there appears to be a potential influence of central obesity on adverse changes in brain volumetry outcomes preceding the later-life at-risk period for dementia, age ≥65 years.

Lack of associations between higher levels of adiposity and CSVD components may be due to attenuation of vascular risk factors among those presenting with cerebrovascular disease, similar to observations in dementia epidemiology during the years closely preceding dementia onset.[45] Given that aging- and dementia-related neurodegenerative events affect homeostatic regulation of energy balance, blood pressure, and other aspects of metabolism, temporal paradoxical associations are often observed between vascular risk factors such as obesity and symptomatic, clinical outcomes.[6,38,46,47]

CSVD is an evolving diagnosis as a result of emerging phenotypic characterization and accumulating mechanistic evidence associated with clinical outcomes. CSVD is a group of pathologic processes with a heterogeneous etiology and pathogenesis involving the small arteries, arterioles, venules, and capillaries of the brain. In 2006, at RUN DMC baseline, CSVD was diagnosed on the basis of the presence of any WMH and any lacunes,[48] with accompanying acute symptoms (TIAs or lacunar syndromes) or subacute manifestations (cognitive, motor [gait], or mood disturbances).[49] Later recognized components of CSVD such as microbleeds were also rated in RUN DMC. Therefore, our approach of evaluating adiposity predictors in association with individual components of CSVD is appropriate and informative for intervention development.

Longitudinal analyses of risk factors for CSVD and its components are challenged because WMH, lacunes, and microbleeds

change erratically over time. In RUN DMC, it was reported[9] that CSVD progression is nonlinear, accelerating over time, and dynamic, with progression interrupted by reduction in some adults who, on average, show progression. RUN DMC has also reported the disappearance of lacunes and microbleeds over 9 years. In RUN DMC, these unexpected changes tended to occur among those presenting with a worse CSVD phenotype at baseline. Because RUN DMC participants who died during the 9-year follow-up had worse baseline CSVD and volumetric phenotypes compared to those who survived and participated in 2015 and there is worsening of CSVD on average among surviving participants, our longitudinal results are likely not influenced by these changes.

Major strengths of our analyses are the following. First, this report is based on 9-year follow-up of men and women presenting with CSVD and with quantified brain volumetry and thorough clinical and risk factor evaluation. Second, brain imaging data were analyzed by raters who were blinded to clinical information, with good interrater and intrarater agreement. Third, statistical analyses were multivariable adjusted. Fourth, our primary predictor, adiposity, was measured in several ways. Using anthropometric and metabolic (leptin and adiponectin) adiposity measures, we observed differential associations. This may point to different mechanistic pathways linking adipose tissue biology to cerebrovascular events and neurodegeneration. Fifth, multiple brain imaging outcomes were investigated. This is important for more precise determination of etiologic mechanisms associated with adiposity.

Despite the aforementioned strengths, there are limitations. First, serum leptin, adiponectin, and lipid levels were not measured at the follow-up examination; blood was collected only at baseline. Second, sociodemographic and health status information was not updated at follow-up in the RUN DMC. Third, nutritional intake and physical activity, known influencers of overweight and obesity, were not measured. Fourth, RUN DMC participants were all diagnosed with CSVD, thus limiting generalizability. It is also known that CSVD brain pathologies exist without symptomatic burden (silent or preclinical CSVD) and are relatively common among elderly. Fifth, the RUN DMC sample is made up of Dutch adults of Northern European ancestry. These results require replication in heterogeneous samples due to global variations in anthropometric and brain characteristics.[50] Sixth, the small number of adults developing dementia render these results inconclusive. Seventh, there were too few underweight participants to evaluate them separately; therefore, our healthy BMI group includes 2% of underweight adults. Finally, no information was available on menopausal status of women.

Our analyses demonstrate sex differences in a potential manifestation of the fat-brain axis and different cross-sectional and longitudinal adiposity-brain associations over a 9-year period in men and women aging with CSVD. Future research is necessary to elucidate biological mechanisms and fat-brain associations over the life course. Clarification of both independent and interdependent vascular vs neurodegenerative mechanisms underpinning the evolving aging brain is imperative.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Adiposity is related to cerebrovascular and brain volumetry outcomes in the RUN DMC study

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