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## Visceral fat is associated with lower brain volume in healthy middle-aged adults

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### Abstract

**Objective**—Midlife obesity has been associated with an increased risk of dementia. The underlying mechanisms are poorly understood. Our aim was to examine the cross-sectional association of body mass index (BMI), waist circumference (WC), waist to hip ratio (WHR) and CT-based measures of subcutaneous (SAT) and visceral (VAT) adipose tissue with various MRI-markers of brain aging in middle-aged community adults.

**Methods**—Participants from the Framingham Offspring cohort were eligible if in addition to having measures of BMI, WC, WHR, SAT and VAT, they had undergone a volumetric brain MRI scan with measures of total brain volume (TCBV), temporal horn volume (THV), white matter hyperintensity volume (WMHV) and MRI-defined brain infarcts (BI). All analyses were adjusted for age, sex and time interval between abdominal CT and brain MRI.

**Results**—In a sample of 733 community participants (mean age 60 years, 53% women), we observed an inverse association of BMI (estimate by standard deviation unit  $\pm$  standard error =  $-0.27 \pm 0.12, p=0.02$ ), WC ( $-0.30 \pm 0.12, p=0.01$ ), WHR ( $-0.37 \pm 0.12, p=0.02$ ), SAT ( $-0.23 \pm 0.11, p=0.04$ ) and VAT ( $-0.36 \pm 0.12, p=0.002$ ) with TCBV, independent of vascular risk factors. The association between VAT and TCBV was the strongest and most robust, and was also independent of BMI ( $-0.35 \pm 0.15, p=0.02$ ) and insulin resistance ( $-0.32 \pm 0.13, p=0.01$ ). When adjusting for C-reactive protein levels the associations were attenuated ( $-0.17 \pm 0.13, p=0.17$  for VAT). No consistently significant association was observed between the anthropometric or CT-based abdominal fat measures and THV, WMHV or BI.

**Interpretation**—In middle-aged community participants we observed a significant inverse association of anthropometric and CT-based measures of abdominal, especially visceral, fat with total brain volume.

## Introduction

Global body mass and obesity, particularly in midlife, are associated with an increased risk of dementia and Alzheimer disease (AD).<sup>1–6</sup> Published data on the association of obesity and body mass index (BMI) with brain volumes are limited, suggesting overall an inverse association of BMI and obesity with temporal lobe volume,<sup>7</sup> total brain volume,<sup>8, 9</sup> and hippocampal volume,<sup>10, 11</sup> in cohorts of less than 300 individuals of various ages and risk profiles. Data on the relation between body mass and MRI-markers of vascular brain injury is equally limited, suggesting a positive association of increasing BMI with incident MRI-defined brain infarcts in patients with white matter disease,<sup>12</sup> and an association of BMI and waist-to-hip ratio with increasing white matter hyperintensity volume.<sup>13, 14</sup>

Different fat compartments carry differential metabolic risks,<sup>15</sup> and there is growing evidence that abdominal obesity and visceral fat are more correlated with vascular risk than global body mass.<sup>16, 17</sup> However, limited data exists demonstrating this concept in association with cognition and dementia. In the Framingham Offspring and the Kaiser Permanente studies, individuals with higher waist-to-hip-ratio or sagittal-abdominal-diameter (two anthropometric markers of abdominal obesity) performed worse on cognitive tests,<sup>18</sup> and had an increased risk of dementia.<sup>19</sup> In the Health-ABC study, computed tomography (CT) measures of subcutaneous fat and total fat mass, but not visceral fat, were associated with worsening global cognitive function.<sup>20</sup> A negative association between waist-to-hip-ratio and hippocampal volume was observed in 122 older individuals.<sup>14</sup> No study has evaluated the association of radiography-based measures of abdominal fat compartments with MRI-markers of brain aging. Interestingly, recent data suggests that higher leptin levels may have a protective effect on brain atrophy and dementia,<sup>21, 22</sup> and, given that leptin expression is higher in subcutaneous than in visceral adipose tissue,<sup>23, 24</sup> we hypothesized that subcutaneous adipose tissue may be less deleterious than visceral adipose tissue for neurodegenerative processes leading to dementia.

The purpose of the present study is to examine the cross-sectional association of BMI, waist circumference, waist to hip ratio, and radiography-based measures of subcutaneous and visceral abdominal fat with MRI measures of total brain volume (TCBV), temporal horn volume (THV), white matter hyperintensity volume (WMHV) and MRI-defined brain infarcts (BI), in middle-aged community participants.

## Methods

### Study sample

The study included participants from the Framingham Offspring Cohort,<sup>25</sup> comprising 5,124 persons examined approximately every 4 years, of which 4,379 were alive at the seventh examination cycle (1998–2001) and 3,539 attended the exam (80.8%). Between 2002 and 2005, as part of an ancillary study, 1,418 Offspring Cohort participants underwent a volumetric multidetector abdominal CT-scan with quantitative measurement of subcutaneous fat and visceral fat volume. Inclusion in the CT study was weighted towards participants from larger Framingham Heart Study families and those residing in the Framingham area, men had to be  $\geq 35$  years old, women  $\geq 40$  years old and non-pregnant, and all participants had to weigh  $< 352$  pounds due to scanner limits. Final inclusion required technically interpretable CT scans ( $n=1,377$ ) and attendance at the seventh examination cycle ( $n=1,355$ ).<sup>26</sup> Between 1999 and 2005, as part of another ancillary study, Offspring Cohort participants alive at the seventh examination cycle and who attended at least one of exam 5, 6, 7 or 8, or had moved away from Framingham but continued to be followed up offsite, were invited to undergo volumetric brain MRI (MRI battery 1). Since 2005, all of them have been invited to undergo a second MRI (MRI battery 2), which was performed in 1399 participants. MRI scans from 2005–2007 only were available for analysis, as data from 2008–2009 were still being processed at this time. As

we did not want our independent variables to be measured after the outcome, only participants who had at least one brain MRI from MRI battery 2 performed after the CT-scan were included in this study. In individuals with several brain MRI scans, we used the measure closest to the date after which the abdominal CT-scan was done. Of the 1355 participants with an abdominal CT-scan, 766 had undergone a brain MRI after the abdominal CT. Of these we excluded subjects with a history of stroke (n=18), dementia (n=1) or other neurological conditions that might confound the measurement of brain volumes (n=14). Hence the sample size for the present analysis was 733 participants (Supplementary Figure 1). Supplementary Table 1 shows the baseline characteristics of participants who attended the seventh examination cycle with (n=1355) and without (n=2184) an interpretable abdominal CT-scan, and of participants with an interpretable abdominal CT-scan who had (n=733) or had not (n=622) also a usable brain MRI-scan performed after the abdominal CT.

### Anthropometric measures and CT measures of body composition

BMI at exam 7 was defined as weight (kg) divided by the square of height (m). Standing waist circumference (WC) at exam 7 was obtained at the level of the umbilicus. Hip circumference was measured at the level of the trochanter major. Waist to hip ratio (WHR) was calculated as the ratio of waist to hip circumferences. Participants underwent eight-slice supine multidetector CT assessment (LightSpeed Ultra, General Electric, Milwaukee, WI). Twenty-five contiguous 5-mm thick slices (120 kVp, 400 mA, gantry rotation time 500 ms, table feed 3:1) were acquired covering 125 mm above the S1 level. Subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) were assessed as previously described (Aquarius 3D Workstation, TeraRecon Inc., San Mateo, CA).<sup>26, 27</sup> Briefly, an image display window was centered at -120 Hounsfield units with a width of -195 to -45 Hounsfield units to identify pixels containing fat. The SAT and VAT compartments were delineated by manually tracing the abdominal muscular wall; excellent inter-reader reproducibility was observed.<sup>28</sup>

### Brain MRI measures

MRI techniques used in the Framingham Offspring Study have been described previously.<sup>29, 30</sup> Briefly, participants were evaluated with a 1 or 1.5-tesla Siemens Magnetom. 3D T1 and double echo proton density (PD) and T2 coronal images acquired in 4-mm contiguous slices were performed. All images were transferred to a centralized reading center (University of California Davis Medical Center) and analyses were performed on QUANTA 6.2, a custom-designed image analysis package operating on a Sun Microsystems Ultra 5 workstation.

Image evaluation was based on a semiautomatic segmentation analysis that involves operator-guided removal of non-brain elements, by tracing of the dura matter within the cranial vault including the middle cranial fossa, but above the posterior fossa and cerebellum. The resulting measure of the cranial vault was defined as the total cranial volume.

Semi-automated analysis of pixel distributions was used to determine the optimal threshold of pixel intensity to best distinguish CSF from brain matter.<sup>31</sup> For segmentation of WMH from other brain tissues, the first and second echo images from T2 sequences were summed and a log-normal distribution was fitted to the summed data. A segmentation threshold for WMH was determined as 3.5 standard deviations (SD) in pixel intensity greater than the mean of the fitted distribution of brain parenchyma.<sup>30</sup> MRI-defined brain infarcts (BI) were defined as an area of abnormal signal intensity in a vascular distribution,  $\geq 3$ mm in size, with a cerebrospinal fluid density on the subtraction image and, for lesions in the basal ganglia area, distinct separation from the circle of Willis vessels.<sup>29, 32</sup> We used size, location, shape and tissue contrast to distinguish BI from dilated perivascular spaces.

## Covariates

Covariates were drawn from exam 7: vascular risk factors (systolic blood pressure, smoking, diabetes mellitus and history of cardiovascular disease, defined as in the Framingham Stroke Risk Profile<sup>33, 34</sup>), physical activity index (PAI),<sup>35</sup> homeostasis model assessment of insulin resistance (HOMA-IR) defined as fasting insulin ( $\mu\text{IU/ml}$ ) x fasting glucose (mmol/l) and serum C-reactive protein (CRP, high-sensitivity assay). CRP and HOMA-IR were log-transformed because of skewed distributions.

## Statistical analyses

Total cerebral brain volume (TCBV) was computed as the ratio of total brain parenchymal volume to totalcranial volume to correct for differences in head size. Hippocampal volume measures were not available on all brain MRI scans done subsequent to the abdominal CT-scan. Therefore temporal horn volume (THV), computed as a ratio to totalcranial volume, was used as a surrogate marker for hippocampal volume.<sup>36</sup> A larger THV corresponds to a smaller hippocampal volume. THV was log-transformed because of a skewed distribution. White matter hyperintensity volume (WMHV) was computed as the ratio of total white matter hyperintensity volume to totalintracranial volume.<sup>30</sup> WMHV was log-transformed because of a skewed distribution. In addition we created (five-year) age-group specific z-scores, zWMHV, and participants with zWMHV>1 were designated as having extensive WMHV (EXT-WMHV).

We standardized the independent variable (BMI, WC, WHR, SAT, and VAT) to a mean of 0 and a SD of 1 (by sex) to facilitate comparisons across adiposity variables. TCBV, THV and WMHV were studied as continuous outcomes, EXT-WMHV and BI were studied as dichotomous outcomes.

The primary analysis was a multivariable linear regression adjusting for age, sex and time interval between abdominal CT and brain MRI, for the associations with TCBV, THV and WMHV. A logistic regression adjusted for the same covariates was run for the associations with EXT-WMHV and BI. These models were run separately for the 4 predictor variables.

In secondary analyses we additionally adjusted for the following potential confounders: vascular risk factors, PAI, BMI, HOMA-IR and CRP (associations with SAT, WC and WHR were not adjusted for BMI due to collinearity). Finally, to assess the robustness of the association between VAT and TCBV we ran secondary analyses stratifying on gender and obesity (BMI  $\geq 30 \text{ kg/m}^2$ ) and in participants without diabetes.

## Results

Sample characteristics are presented in Table 1. Older age, diabetes mellitus and increasing values of systolic blood pressure were associated with increasing tertiles of BMI, WC, WHR, SAT and VAT (data not shown).

The Pearson correlation coefficient between SAT and VAT was  $r=0.58$  ( $p<0.001$ ). Both abdominal CT adipose tissue measures were significantly correlated with BMI ( $r=0.79$ ,  $p<0.001$  for SAT;  $r=0.67$ ,  $p<0.001$  for VAT), WC ( $r=0.80$ ,  $p<0.001$  for SAT  $r=0.71$ ,  $p<0.001$  for VAT) and WHR ( $r=0.19$ ,  $p<0.001$  for SAT;  $r=0.67$ ,  $p<0.001$  for VAT). WC, WHR and BMI were all significantly correlated with each other ( $r=0.72$  for WC and WHR,  $r=0.85$  for WC and BMI,  $r=0.38$  for WHR and BMI,  $p<0.001$ ).

### **Association of anthropometric and radiographic-based measures of adipose tissue with brain volumes**

Higher levels of BMI, WC, WHR, SAT and VAT were associated with smaller total brain volume (TCBV) (Table 2). The inverse associations of BMI and WC with TCBV were maintained when running the analysis in the larger dataset of participants with a brain MRI-scan and anthropometric measures regardless of the availability of radiographic-based measures of adipose tissue (Supplementary Table 2). When adjusting for vascular risk factors, the associations with TCBV were weakened but remained significant. The association of VAT with TCBV remained significant when adjusting for BMI (Table 2). When adjusting for HOMA-IR, the inverse associations of VAT with TCBV remained significant:  $-0.28 \pm 0.13$  ( $p=0.035$ ). When adjusting for CRP levels, the inverse associations of all adiposity measures with TCBV were weakened and no longer significant ( $-0.17 \pm 0.13$ ,  $p=0.17$  for VAT). The inverse association of VAT with TCBV was substantially unchanged within strata defined by gender, presence of obesity or central obesity, absence of diabetes (Supplementary Table 3).

WHR, but not BMI, WC, SAT and VAT, was associated with increasing temporal horn volume (THV), independently of vascular risk factors (Table 2).

### **Association of anthropometric and radiographic-based measures of adipose tissue with MRI-markers of vascular brain injury**

BMI, WC, WHR, SAT and VAT were not significantly associated with white matter hyperintensity volume (WMHV and EXT-WMHV) or with MRI-defined brain infarcts (BI) in our primary model adjusted for age, sex and time interval between abdominal CT and brain MRI (Table 3). In the model adjusted additionally for vascular risk factors and physical activity index there was a weak association of increasing BMI and VAT with a lower frequency of EXT-WMHV (but not with WMHV) and of WC and VAT with a lower frequency of BI (Table 3).

## **Discussion**

### **Principal findings**

In middle-aged Framingham Offspring participants we observed an inverse association of BMI, WC, SAT and VAT with total brain volume (TCBV), independent of vascular risk factors. The association between VAT and TCBV was the strongest and most robust of all, and was also independent of BMI and insulin resistance. When adjusting for CRP levels, the associations were attenuated. No consistently significant association was observed between the anthropometric or radiographic-based measures of adipose tissue and temporal horn volume (THV) or MRI-markers of vascular brain injury. WHR only was associated with increasing THV. An inverse association of borderline significance was observed between BMI, VAT and extensive white matter hyperintensities (EXT-WMHV) and between WC, VAT and MRI-defined brain infarcts (BI), only in the model adjusted for vascular risk factors.

### **In the context of the current literature**

Several studies on samples of less than 300 individuals have recently suggested an association of BMI and obesity with lower total or regional brain volumes, both in older persons and younger or middle-aged adults.<sup>7-9, 37</sup> Our study confirms the inverse association of increasing body mass with lower total brain volume and extends it to a large cohort of over 700 middle-aged community participants. More importantly our data suggests that the association is stronger for central obesity versus global adiposity, and is particularly prominent and robust for the visceral fat component of abdominal obesity.

A few studies on less than 150 participants have suggested an inverse association of BMI<sup>10, 11</sup> and waist-to-hip ratio<sup>14</sup> with hippocampal volume. WHR was associated with increasing THV, a surrogate marker of decreasing hippocampal volume). However, none of the other anthropometric or radiographic-based measures of adipose tissue were associated with THV. As we did not use a direct measure of hippocampal volume we can however not formally exclude the possibility that such associations exist.

An association of BMI and waist-to-hip-ratio with increasing WMH volume has been reported in small series of individuals at high vascular risk.<sup>13, 14</sup> In a recent study including patients with prevalent cerebral white matter disease, increasing BMI was associated with a higher incidence of brain infarcts.<sup>12</sup> In our large sample of middle-aged community participants, anthropometric markers and CT-based measures of abdominal fat did not predict more extensive white matter hyperintensities or a higher prevalence of MRI-defined brain infarcts cross-sectionally.

### Potential mechanisms

The potential mechanisms underlying the inverse association of obesity and particularly visceral abdominal fat with total brain volume are speculative.

Inflammation could be an important mediator. Indeed obesity is highly associated with inflammatory markers.<sup>26</sup> Cytokines such as interleukin 6 and tumor necrosis factor alpha are produced in adipose tissue and induce hepatic production of CRP.<sup>26</sup> Adipose tissue also contains inflammatory cells such as monocytes and macrophages which accumulate in obese states.<sup>26</sup> Inflammation was shown to predict a higher risk of dementia,<sup>38</sup> and several inflammatory markers were recently shown to be inversely associated with TCBV in the Framingham Offspring Study.<sup>39</sup> A recent study also found that persons on anti-inflammatory drugs show significantly smaller age-related volume changes in regions of both gray and white matter compared to controls. In the present dataset, the inverse association of all adiposity measures with TCBV was attenuated after adjusting for CRP, suggesting that this mechanism could indeed be important.

Diabetes and insulin resistance, both strongly related to obesity,<sup>40</sup> are other potential mediators of the inverse association between adiposity and brain volume. In the Framingham Offspring cohort we have recently shown an inverse association of diabetes, fasting glucose and HOMA-IR with TCBV.<sup>41</sup> Our observation that the inverse association of VAT with TCBV was maintained, even though weakened, after adjusting for diabetes and HOMA-IR, indicates that these are probably not the sole mediators of our finding.

Finally, adipose-tissue derived hormones, such as adiponectin, leptin, resistin or ghrelin, could also play a role in the relation between adipose tissue and brain atrophy. In transgenic animal models, leptin receptor deficient rodents were shown to have impaired memory performances,<sup>42</sup> and long term potentiation of neurons in the hippocampus.<sup>43</sup> Leptin has also been shown to reduce the extracellular amyloid beta load and the level of tau phosphorylation in neuronal cells.<sup>44</sup> A positive correlation between plasma leptin levels and gray matter volume in the right hippocampus was identified,<sup>21</sup> and in the Framingham Original cohort we have recently shown that higher circulating leptin levels were significantly associated with a reduced risk of incident dementia and AD, higher TCBV and lower THV.<sup>22</sup>

Whereas the putative mediating effect of inflammation in the inverse association of anthropometric and radiographic-based measures of adipose tissue with brain volume does not appear to be restricted to a specific fat compartment,<sup>26</sup> visceral fat is more likely to mediate insulin resistance,<sup>45, 46</sup> and has a specific pattern of adipose-tissue derived hormone secretion,<sup>23, 24, 47</sup> that could partly explain the stronger inverse association of visceral adipose tissue

with total brain volume. Visceral fat is characterized by an enhanced rate of lipolysis and an increased plasma free fatty acid flux to the hepatic portal circulation, thus exacerbating insulin resistance.<sup>47</sup> The expression profile of adipose-tissue derived hormones has also been shown to differ substantially between visceral and subcutaneous adipose tissue, with a more proatherogenic pattern of gene expression in visceral fat.<sup>48–50</sup> This differential expression could also underlie the differential neurodegenerative effects of adipose tissue derived hormones. Leptin expression for instance has been shown to be lower in visceral compared to subcutaneous adipose tissue.<sup>23, 24</sup> Unfortunately, plasma levels of most adipokines with suspected neurodegenerative effects are not available at the present time in this dataset to formally explore this hypothesis.

### Strengths and limitations

The strengths of this study are the population-based setting, the large sample size, the young age of the participants compared to most previous studies with careful surveillance and exclusion of prevalent stroke and dementia, and the availability of quantitative measures of both MRI markers of brain aging and CT-based abdominal adipose tissue compartments. It is usually assumed that anthropometric measures of central obesity such as waist circumference, waist-to-hip-ratio, or sagittal-abdominal diameter reflect visceral rather than total fat mass, the former being more strongly related to metabolic disorders and vascular disease. However, the validity of these measures is questionable with increasing age,<sup>51</sup> and CT-based measures of abdominal fat compartments allow a more accurate distinction between visceral and subcutaneous fat. The main limitations are the lack of a direct measure of hippocampal volume and the cross-sectional design. The absence of longitudinal measure of change in TCBV did not enable us to formally distinguish between an association of adipose tissue with a dynamic process of accelerated brain atrophy and an adverse effect of adiposity on brain development, as overweight middle-aged adults may have been overweight in childhood.<sup>52</sup> However, we used the ratio of total brain volume to intracranial volume and not the raw measure of total brain volume, making it more likely that our results reflect brain atrophy occurring after the brain has reached its maximum size, reflected in the total intracranial volume.<sup>22</sup> Although the acceptance rate was high, persons included in this study are not perfectly representative of the general population, as they have fewer risk factors than persons excluded. This limitation is common to all population-based studies involving time-consuming examinations and follow-up. Finally, we did not perform any correction for multiple testing as we considered our study as exploratory.

### Implications

First, while lower total brain volume or hippocampal volume and extensive white matter hyperintensities or covert brain infarcts were all shown to be powerful predictors of incident dementia,<sup>53–57</sup> our results suggest that accelerated global brain atrophy, rather than more extensive vascular brain injury, could be the predominant mechanism underlying the association of increased body mass and visceral fat with cognitive decline and dementia. However, only further follow-up of our cohort and additional independent studies will be able to confirm or refute this hypothesis. Indirectly our findings are corroborated by a recent MRI and proton magnetic resonance spectroscopic imaging study performed in 50 healthy middle-aged subjects, showing an inverse association of BMI with concentrations of N-acetylaspartate and choline-containing metabolites, especially in the frontal lobes, pointing to axonal and myelin abnormalities as well as decreased neuronal viability.<sup>58</sup>

Second, whereas abdominal obesity and visceral fat are already recognized as being more important in determining vascular risk than global body mass,<sup>16, 17</sup> our data suggest that they may also be important determinants of the association between overweight and lower total brain volume.

## Conclusions

In a large sample of middle-aged community participants, we observed a significant inverse association of anthropometric markers and CT-based measures of abdominal fat with total brain volume, the most prominent association being observed with visceral fat. Anthropometric and CT-based adiposity measures were not associated with MRI-markers of cerebrovascular disease. Although these findings are preliminary they could improve our understanding of the mechanisms underlying the relationship of obesity with dementia with potentially important implications for prevention strategies.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1**

## Population characteristics in the overall cohort

<i>N</i>	733
Women, %	53
Age at exam 7±SD, years	60±9
Age at CT±SD, years	64±9
Age at MRI±SD, years	67±9
SBP±SD, * mmHg	124±17
Smokers, * %	8
Diabetes mellitus, * %	8
History of cardiovascular disease, * %	9
Time btw. CT and MRI, years	3±1
Time btw. Exam 7 and MRI, years	7±1
serum CRP±SD, * mg/L	3.8±6.2
HOMA-IR±SD, * μIU/mL x mmol/L	4.1±3.3
ApoEε4-carriers, %	25
Body mass index, * kg/m <sup>2</sup>	28±5
Waist circumference, * cm	39±5
Subcutaneous adipose tissue, cm <sup>3</sup>	3001±1351
Visceral adipose tissue, cm <sup>3</sup>	2073±1079

CRP: C-Reactive Protein; CT: Computed Tomography; HOMA-IR: Insulin Resistance measure (see methods); MRI: Magnetic Resonance Imaging; SBP: Systolic Blood Pressure; SD: Standard Deviation;

\* measured at exam 7

Table 2

Association of anthropometric and radiographic-based measures of adipose tissue with MRI brain volumes

		Total brain volume (N=733)		Temporal horn volume (N=733)	
		Estimate* ± SE	P	Estimate* ± SE	P
<b>Body mass index</b>					
per SD	model A	-0.35±0.11	0.002	0.02±0.03	0.448
	model B	-0.27±0.12	0.022	0.002±0.03	0.950
<b>Waist circumference</b>					
per SD	model A	-0.41±0.11	0.003	0.04±0.03	0.131
	model B	-0.30±0.12	0.010	0.02±0.03	0.437
<b>Waist to hip ratio</b>					
per SD	model A	-0.48±0.12	<0.001	0.10±0.03	0.001
	model B	-0.37±0.12	0.002	0.08±0.03	0.006
<b>Subcutaneous adipose tissue</b>					
per SD	model A	-0.29±0.11	<0.001	0.03±0.03	0.262
	model B	-0.23±0.11	0.044	0.02±0.03	0.503
<b>Visceral adipose tissue</b>					
per SD	model A	-0.44±0.11	<0.001	0.05±0.03	0.101
	model B	-0.36±0.12	0.002	0.03±0.03	0.333
	model C	-0.35±0.15	0.023	0.06±0.04	0.138
	model D	-0.31±0.16	0.049	0.05±0.04	0.214

SD: standard deviation; SE: standard error; model A: linear regression adjusted for age, sex and time between CT and MRI; model B: model A additionally adjusted for systolic blood pressure, smoking, diabetes mellitus and history of cardiovascular disease and physical activity index; model C: model A additionally adjusted for BMI; model D: model B additionally adjusted for BMI;

\* Estimates are regression coefficients for total brain volume and temporal horn volume, per SD of increasing adiposity measures.

**Table 3**

Association of anthropometric and radiographic-based measures of adipose tissue with MRI-markers of vascular brain injury

		<u>White matter hyperintensity volume (N=733)</u>		<u>Extensive white matter hyperintensity volume (N=733)</u>		<u>Brain infarcts (N=733)</u>	
		Estimate* ± SE	P	OR [95%CI]	P	OR [95%CI]	P
<b>Body mass index</b>							
per SD	model A	-0.02±0.03	0.595	0.92 [0.77-1.10]	0.352	0.88 [0.71-1.10]	0.274
	model B	-0.04±0.04	0.239	0.83 [0.69-1.00]	0.048	0.83 [0.66-1.06]	0.136
<b>Waist circumference</b>							
per SD	model A	-0.03±0.04	0.352	0.96 [0.81-1.14]	0.635	0.82 [0.65-1.02]	0.075
	model B	-0.06±0.04	0.133	0.87 [0.72-1.05]	0.140	0.77 [0.61-0.98]	0.033
<b>Waist to hip ratio</b>							
per SD	model A	-0.03±0.04	0.453	1.06 [0.88-1.27]	0.536	0.84 [0.67-1.05]	0.120
	model B	-0.05±0.04	0.190	0.98 [0.81-1.19]	0.857	0.80 [0.63-1.01]	0.063
<b>Subcutaneous adipose tissue</b>							
per SD	model A	-0.05±0.04	0.176	0.89 [0.75-1.06]	0.191	0.88 [0.70-1.10]	0.262
	model B	-0.06±0.04	0.077	0.83 [0.69-1.00]	0.052	0.85 [0.67-1.07]	0.166
<b>Visceral adipose tissue</b>							
per SD	model A	-0.02±0.04	0.518	0.90 [0.75-1.08]	0.249	0.81 [0.65-1.02]	0.068
	model B	-0.05±0.04	0.225	0.82 [0.68-1.00]	0.045	0.78 [0.62-0.98]	0.033
	model C	-0.02±0.05	0.741	0.92 [0.72-1.17]	0.501	0.80 [0.60-1.08]	0.149
	model D	-0.02±0.05	0.620	0.89 [0.70-1.15]	0.372	0.80 [0.59-1.08]	0.149

SD: standard deviation; SE: standard error; model A: linear regression (for white matter hyperintensity volume) or logistic regression (for extensive white matter hyperintensity volume and brain infarcts) adjusted for age, sex and time between CT and MRI; model B: model A additionally adjusted for systolic blood pressure, smoking, diabetes mellitus and history of cardiovascular disease and physical activity index; model C: model A additionally adjusted for BMI; model D: model B additionally adjusted for BMI;

\* Estimates are regression coefficients for white matter hyperintensity volume, per SD of increasing adiposity measures.