Journal of the Neurological Sciences 404 (2019) 52–57

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Abdominal fatness and cerebral white matter hyperintensity

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ARTICLE INFO

Keywords:
Small vessel disease
Leukoaraiosis
Obesity
Adipose tissue
Inflammation
Metabolic syndrome

ABSTRACT

Although obesity has been proven as a risk factor of metabolic and cardiovascular diseases, there have been few studies addressing the association between obesity and cerebral white matter hyperintensity (WMH) volume with controversial findings. In this study, we evaluated the relationship between abdominal fat distribution and WMH volume in a neurologically healthy population. We performed an observational study in a consecutive series of subjects who were examined during voluntary health check-ups between January 2006 and December 2013. We directly measured both visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) using abdominal computed tomography. The WMH volumes were also recorded quantitatively. A total of 2504 subjects were included in this study. In multivariate analysis, the relationship between SAT and WMH volume remained significant ($\beta = -0.170$, standard error [SE] = 0.065, $P = .006$) after adjusting for confounding factors. The protective effects of SAT on the WMH volume were more prominent in female participants ($\beta = -0.295$, SE = 0.138, $P = .033$) and in severely obese participants ($\beta = -0.358$, SE = 0.167, $P = .033$). Conclusively, we demonstrated a negative association between SAT and WMH volume in a healthy population.

1. Introduction

Cerebral white matter hyperintensity (WMH) is a subclinical pathology, which represents tissue rarefaction or myelin pallor arising from a loss of axon or gliosis [1]. With the improvement of imaging modalities, WMH has been increasingly identified in the elderly, prior to dementia or stroke [2]. Many studies have suggested several potential mechanisms of the development of WMH (e.g. diffuse hypoperfusion, endothelial dysfunction, glymphatic blockage), however, this process is still not understood [3–5].

Obesity is defined as abnormal or excessive fat accumulation and is associated with atherosclerosis, subclinical inflammation, and cardiovascular morbidity including stroke and dementia [6–8]. WMH, a precursor to dementia and stroke, could have a close association with obesity, but the association of obesity with WMH is somewhat controversial. Some previous studies showed that higher body mass index (BMI) and waist circumference (WC) are associated with WMH, but other studies showed no association [9–11]. These controversial results could have resulted from the fact that body fat distribution, rather than generalized obesity, is more related to cardio-metabolic risks [12].

There have been few studies addressing this issue. A Japanese study of diabetic patients showed that abdominal visceral adipose tissue (VAT) was associated with the presence of WMH [13], and several studies in Korea and Japan of healthy adults also showed that VAT but not abdominal subcutaneous adipose tissue (SAT) or WC are associated with the presence of WMH or lacunes [14–16]. These studies have just focused on the simple presence of WMH lesion rather than the quantitative volumetric assessment of WMH, which can confer more precise

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https://doi.org/10.1016/j.jns.2019.07.016
Received 19 April 2019; Received in revised form 1 July 2019; Accepted 11 July 2019
Available online 12 July 2019

degree of clinical impact by adiposity level.

In this study, we investigated the relationship between abdominal fat distribution, directly measured by abdominal computed tomography (CT), and WMH volume in a neurologically healthy adult population.

2. Methods

2.1. Patients and population

As part of a consecutive registry of health check-ups in the Seoul National University Hospital Health Promotion Center between January 2006 and December 2013, a total of 3241 subjects who were older than 29 years were examined. All of these patients underwent extensive evaluations, including brain magnetic resonance imaging (MRI), brain magnetic angiography (MRA), and laboratory examinations as a spectrum of routine health check-ups at our center. From this population, we selected 2552 participants for whom abdominal fat CT was performed. We excluded 48 patients who had a history of stroke or severe neurological deficits. Finally, a total of 2504 healthy subjects were included in the final analysis. The current study was approved by the Institutional Review Board at the Seoul National University Hospital (IRB No. 1604–072-754). Any data not published within the article will be available from the corresponding author upon reasonable request.

2.2. Clinical assessment

We assessed extensive clinical information regarding the demographic factors, cardiovascular risk factors, and laboratory factors of the participants as follows: age, sex, BMI, waist circumference (WC), menopause (female only), hypertension (use of anti-hypertensive, or ≥ 140 mmHg in systolic blood pressure, or ≥90 mmHg in diastolic blood pressure), diabetes (use of glucose lowering agents or ≥6.5% in hemoglobin A1c levels), hyperlipidemia (use of lipid lowering agents, or ≥240 mg/dL in total cholesterol levels, or ≥160 mg/dL low-density lipoprotein [LDL] cholesterol levels), dyslipidemia (triglyceride ≥150 mg/dL or high-density lipoprotein [HDL] cholesterol < 40 mg/dL in men or < 50 mg/dL in women), ischemic heart disease, current smoking or current alcohol use, and use of antiplatelet medicine [17]. Laboratory examinations regarding the glucose profile, lipid profile, and high-sensitivity C-reactive protein (hs-CRP) levels were also performed after 12 h of overnight fasting.

2.3. Radiological assessment

In this study, all participants underwent both brain MRI, using 1.5-Tesla MR scanners (Signa, GE Healthcare, Milwaukee, WI, USA or Magnetom SONATA, Siemens, Munich, Germany), and Abdominal fat CT scans, using a 16-detector row CT scanner (Somatom Sensation 16, Siemens Medical Solutions, Forchheim, Germany).

In MRI images, the basic slice thickness was 5 mm in the axial plane. We obtained broad MRI acquisitions as follows: T1-weighted images (TR/ TE = 500/11 ms), T2-weighted images (repetition time [TR]/ echo time [TE] = 5000/127 ms), T2 fluid-attenuated inversion recovery images (TR/TE = 8800/127 ms), T2-gradient echo images (TR/TE = 57/20 ms). The volume of WMH was rated quantitatively using Medical Imaging Processing, Analysis, and Visualization (MIPAV, version 7.3.0, National Institutes of Health, Bethesda, MD) by two neurologists (K.-W.N. and H.-Y.J.) who were blinded to clinical information [18].

To obtain the adipose tissue area, we used a technique that has been standardized and validated in our previous studies [8,19]. Briefly, a single slice at the umbilicus level was obtained at 5 mm thickness with a scan time of 0.5 s. Using commercially available CT software (Rapidia 2.8; INFINITT, Seoul, Korea), we calculated the cross-sectional surface area (in cm^2) of the different abdominal compartments. The adipose tissue area was determined electronically using the setting of attenuation ranging from −250 to −50 Hounsfield units. VAT was defined as the intra-abdominal fat that was surrounded by the parietal peritoneum or transversalis fascia, excepting the vertebral column and paraspinal muscles. SAT was calculated by subtracting the VAT area from the total adipose tissue (TAT) area.

2.4. Statistical analysis

The data are displayed as mean [standard deviation] for continuous variables with a normal distribution, and as median [interquartile range] for the others. Continuous variables with skewed data were transformed into a log scale, excepting the WMH volumes. The WMH volume was transformed into a squared root scale, because it has many zero values. Univariate linear regression analyses were conducted for the evaluation of the possible predictors of the WMH volumes. Then, variables with P values < .05 in the univariate analysis were introduced as confounding factors in the multivariate linear regression analysis. To compare the predictive power of the obesity parameters (e.g., BMI, WC, VAT, SAT, and VAT/SAT ratio), we introduced each parameter, respectively, in to the analyses models. We also performed sensitivity analysis using additional adjustment for the BMI and WC.

The adipocyte activity appears to be fairly different between males and females [20–22]. To confirm the sexual difference regarding the effects of adipose tissues on WMH volume, we performed stratified multivariate linear regression analysis by sex.

The severity of obesity is another considerable factor on the adipocyte's role [23,24]. Thus, we used both the TAT tertiles and the degree of obesity, based on the BMI values (e.g., normal weight < 23; 23 ≤ overweight < 25; 25 ≤ obesity I < 30; 30 ≤ obesity II) [25], to conduct stratified analyses according to the severity of obesity. Additionally, to understand the pathophysiologic mechanism between SAT and WMH, we evaluated the association between SAT and cardiovascular risk factors or WMH volumes according to the TAT tertiles. Univariate linear regression analyses were used for analysis. All statistical analyses in this study were performed using SPSS version 23 (IBM SPSS, Chicago, IL, USA) and assisted by professional statisticians (H.K., S.-S.H.). Statistical significance was considered at P < .05.

3. Results

A total of 2504 healthy participants were assessed (mean age: 56 years, male sex: 55%). The median WMH volume was 1.10 [0.20–2.60] mL, and the median volumes of VAT and SAT were 109.83 [75.11–151.25] and 151.22 [115.34–198.32] cm^2, respectively. The baseline characteristics of the cohort are presented in Table 1. In univariate linear regression analysis, WMH volumes were significantly related to age, WC, hypertension, diabetes, current smoking, current alcohol drinking, systolic and diastolic blood pressure, and glucose, HbA1c, total cholesterol, LDL cholesterol and hs-CRP levels, and VAT, SAT, and VAT/SAT ratio (Table 2).

In multivariate analysis, the relationship between SAT and WMH volume remained significant after adjusting for confounding factors (β = −0.099; standard error [SE] = 0.048, P = .039). This result was reinforced when we additionally adjusted the BMI (β = −0.146; SE = 0.061, P = .017) or both the BMI and WC (β = −0.170; SE = 0.062, P = .006) as confounders (Table 3). Furthermore, the protective effects of SAT on WMH volumes were more prominent in female participants (Table 3).

Considering the interaction between the severity of obesity and adipocyte action, we conducted stratified multivariate analysis using the TAT tertiles. The protective effect of SAT was significant only in the highest TAT tertile (β = −0.358; SE = 0.167, P = .033, Table 4). When we used the degree of obesity based on the BMI values instead of TAT tertiles, the relationship between SAT and WMH volume only remained significant in the obesity II group (β = −1.651; SE = 0.606, P = .008, Supplementary Table 1).

Table 1
Baseline characteristics of the cohort.

	Total	Male	Female
Number, n	2504	1378	1126
Age, y	56 ± 9	56 ± 9	57 ± 9
Sex, male, n (%)	1378 (55)	NA	NA
Body mass index, kg/m^2	24.17 ± 3.07	24.59 ± 2.93	23.66 ± 3.16
Waist circumference, cm	86 ± 9	89 ± 8	83 ± 9
Menopause, n (%)	NA	NA	490 (44)
Hypertension, n (%)	564 (23)	337 (24)	227 (20)
Diabetes, n (%)	344 (14)	235 (17)	109 (10)
Hyperlipidemia, n (%)	644 (26)	336 (24)	308 (27)
Dyslipidemia, n (%)	786 (31)	415 (30)	371 (33)
Ischemic heart disease, n (%)	93 (4)	125 (9)	198 (18)
Current smoking, n (%)	429 (17)	395 (29)	34 (3)
Current alcohol drinking, n (%)	1234 (49)	921 (67)	313 (28)
On antiplatelet medication, n (%)	112 (13)	78 (16)	34 (9)
Systolic blood pressure, mmHg	126 ± 16	128 ± 15	125 ± 17
Diastolic blood pressure, mmHg	76 ± 11	78 ± 11	75 ± 11
Glucose, mg/dL	96 ± 23	99 ± 26	93 ± 18
HbA1c, %	5.9 ± 0.8	6.0 ± 0.9	5.8 ± 0.6
Total cholesterol, mg/dL	200 ± 36	197 ± 36	204 ± 37
LDL cholesterol, mg/dL	127 ± 35	127 ± 35	128 ± 35
HDL cholesterol, mg/dL	54 ± 14	51 ± 13	59 ± 14
Triglyceride, mg/dL	120 ± 74	133 ± 84	104 ± 56
hs-CRP, mg/dL	0.18 ± 0.69	0.20 ± 0.70	0.16 ± 0.67
WMH volume, mL	2.53 ± 5.46	2.54 ± 6.17	2.53 ± 4.79
VAT, cm^2	119.96 ± 74.09	138.47 ± 81.12	97.30 ± 56.79
SAT, cm^2	164.17 ± 85.34	141.22 ± 70.93	192.26 ± 92.79
VAT/SAT ratio	0.80 ± 0.43	1.03 ± 0.42	0.53 ± 0.24
TAT, cm^2	284.13 ± 139.41	289.55 ± 137.40	279.69 ± 140.92

NA = not applicable, LDL = low-density lipoprotein, HDL = high-density lipoproteine, hs-CRP = high-sensitivity C-reactive protein, WMH = white matter hyperintensity, VAT = visceral adipose tissue, SAT = subcutaneous adipose tissue, TAT = total adipose tissue.

Table 2
Univariate linear regression analysis between square root-white matter hyperintensity volume and demographic, clinical, laboratory, and radiological factors.

	β (95% CI)	*P*
Age, y	0.054 (0.050 to 0.059)	< 0.001
Sex, male, n (%)	0.013 (−0.071 to 0.097)	0.762
Body mass index, kg/m^2	0.002 (−0.011 to 0.016)	0.729
Waist circumference, cm	0.009 (0.004 to 0.014)	< 0.001
Hypertension, n (%)	0.519 (0.421 to 0.618)	< 0.001
Diabetes, n (%)	0.461 (0.341 to 0.582)	< 0.001
Hyperlipidemia, n (%)	0.078 (−0.018 to 0.174)	0.109
Dyslipidemia, n (%)	0.000 (−0.090 to 0.090)	0.998
Ischemic heart disease, n (%)	0.202 (−0.020 to 0.423)	0.074
Current smoking, n (%)	−0.237 (−0.348 to −0.126)	< 0.001
Current alcohol drinking, n (%)	−0.184 (−0.267 to −0.100)	< 0.001
On antiplatelet medication, n (%)	0.151 (−0.072 to 0.375)	0.185
Systolic blood pressure, mmHg	0.011 (0.008 to 0.013)	< 0.001
Diastolic blood pressure, mmHg	0.010 (0.006 to 0.013)	< 0.001
Glucose, mg/dL[a]	0.750 (0.536 to 0.964)	< 0.001
HbA1c, %[a]	1.291 (0.926 to 1.655)	< 0.001
Total cholesterol, mg/dL	−0.001 (−0.002 to 0.000)	0.031
LDL cholesterol, mg/dL	−0.002 (−0.003 to −0.001)	0.003
HDL cholesterol, mg/dL	−0.001 (−0.004 to 0.002)	0.522
Triglyceride, mg/dL	0.061 (−0.022 to 0.144)	0.150
hs-CRP, mg/dL[a]	0.029 (0.000 to 0.057)	0.046
VAT, cm^2[a]	0.146 (0.074 to 0.217)	< 0.001
SAT, cm^2[a]	−0.094 (−0.179 to −0.009)	0.030
VAT/SAT ratio	0.278 (0.181 to 0.376)	< 0.001
TAT, cm^2[a]	0.026 (−0.066 to 0.117)	0.584

CI = confidence interval, LDL = low-density lipoprotein, HDL = high-density lipoproteine, hs-CRP = high-sensitivity C-reactive protein, VAT = visceral adipose tissue, SAT = subcutaneous adipose tissue, TAT = total adipose tissue.
[a] These variables were introduced as log scale.

In the evaluation about the association between SAT and cardiovascular risk factors and WMH voulmes according to TAT tertiles, SAT showed a negative correlation with diabetes, and triglyceride, glucose, hs-CRP levels, and WMH volumes. Conversely, SAT showed a positive correlation with HDL cholesterol levels (Table 5).

4. Discussion

In this study, we demonstrated that SAT was negatively associated with WMH volume in a neurologically healthy population. Because other obesity parameters revealed no statistical significance, our cohort identified SAT as the most potent predictor of WMH volume. Furthermore, this association was more prominent in female participants and in severely obese participants, in agreement with previous studies [6,21,24,26].

The exact underlying pathophysiologic mechanisms underlying the relationship between SAT and WMH volumes are not clear. However, here, we suggest several plausible explanations: first, SAT may attenuate vascular risk factors, which are well-known risk factors for the development of WMH. Although there are still conflicting views, several studies have demonstrated the protective effects of SAT on metabolic or vascular risk factors, known as the 'metabolic sink' [22,26–29]. This protective effect may result from the less-lipolytic activity of SAT [20], deposing the post-prandial circulatory free fatty acid or glycerol as triglyceride in their tissues [6,23]. Supporting this hypothesis, our cohort showed a negative correlation between SAT and circulating triglyceride and glucose levels, and a positive correlation with HDL cholesterol. Thus, the SAT might act as a surrogate marker of a reduced risk of WMH. Second, endothelial dysfunction, due to subclinical inflammation, could play a role in the pathological mechanism. Adipose tissues are not simple storage organs, they secrete various hormone and substance [8,30]. Compared with the secretion levels in VAT, SAT secretes more protective adiponectin and fewer pro-inflammatory adipokines or tissue factors (e.g., IL-6, IL-8, TNF-a, and PAI-1) [28,30,31]. This hormonal balance may protect the brain environment from a prothrombotic state, platelet adhesion, and endothelial dysfunction [14,30,32,33]. Notably, endothelial dysfunction has recently been highlighted as one of main mechanisms involved in the development of

Table 3
Relationship between body fat distribution and square root-WMH volumes according to sexual differences[e].

	Total		Male		Female	
	(*n* = 2504)		(*n* = 1378)		(*n* = 1126)	
	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*
Model 1[b]						
BMI	−0.002 (0.007)	0.768	−0.005 (0.010)	0.628	−0.004 (0.011)	0.690
WC	0.002 (0.003)	0.437	0.003 (0.004)	0.465	−0.001 (0.004)	0.739
VAT[a]	−0.016 (0.042)	0.713	−0.024 (0.054)	0.661	−0.052 (0.075)	0.487
SAT[a]	−0.099 (0.048)	0.039	−0.055 (0.061)	0.363	−0.153 (0.091)	0.093
VAT/SAT ratio	0.084 (0.055)	0.128	0.059 (0.070)	0.400	0.134 (0.159)	0.402
Model 2 (BMI)[c]						
VAT[a]	−0.013 (0.055)	0.816	−0.011 (0.074)	0.880	−0.052 (0.092)	0.570
SAT[a]	−0.146 (0.061)	0.017	−0.070 (0.087)	0.421	−0.253 (0.128)	0.049
VAT/SAT ratio	0.085 (0.055)	0.122	0.060 (0.070)	0.390	0.132 (0.160)	0.409
Model 3 (BMI + WC)[d]						
VAT[a]	−0.082 (0.062)	0.188	−0.111 (0.083)	0.180	−0.062 (0.100)	0.535
SAT[a]	−0.170 (0.062)	0.006	−0.215 (0.099)	0.029	−0.295 (0.138)	0.033
VAT/SAT ratio	0.065 (0.057)	0.252	0.054 (0.070)	0.436	0.133 (0.160)	0.409

SE = standard error, BMI = body mass index, WC = waist circumference, VAT = visceral adipose tissue, SAT = subcutaneous adipose tissue.
[a] These variables were introduced as log scale.
[b] Adjusted for age, menopause (only in the analysis with female participants), hypertension, diabetes, current smoking and alcohol use, LDL cholesterol and hs-CRP levels.
[c] Added body mass index with Model 1.
[d] Added waist circumference with Model 2.
[e] VAT, SAT, and VAT/SAT ratio were respectively introduced in each model.

Table 4
Relationship between body fat distribution and square root-WMH volume according to TAT[c].

	Univariate analysis		Multivariate analysis	
	β (SE)	*P*	β (SE)	*P*
TAT tertile 1 (*n* = 834)[b]				
VAT[a]	0.107 (0.067)	0.114	−0.113 (0.096)	0.243
SAT[a]	−0.230 (0.077)	0.003	−0.148 (0.089)	0.099
VAT/SAT ratio	0.320 (0.089)	< 0.001	0.028 (0.100)	0.783
TAT tertile 2 (*n* = 827)[b]				
VAT[a]	0.222 (0.105)	0.035	−0.067 (0.133)	0.617
SAT[a]	−0.294 (0.148)	0.046	−0.028 (0.172)	0.868
VAT/SAT ratio	0.149 (0.079)	0.062	−0.023 (0.094)	0.811
TAT tertile 3 (*n* = 843)[b]				
VAT[a]	0.107 (0.067)	0.114	0.118 (0.147)	0.423
SAT[a]	−0.230 (0.077)	0.003	−0.358 (0.167)	0.033
VAT/SAT ratio	0.320 (0.089)	< 0.001	0.180 (0.102)	0.079

SE = standard error, TAT = total adipose tissue, VAT = visceral adipose tissue, SAT = subcutaneous adipose tissue.
[a] These variables were introduced as log scale.
[b] Adjusted for age, body mass index, waist circumference, hypertension, diabetes, current smoking and alcohol use, LDL cholesterol and hs-CRP levels.
[c] VAT, SAT, and VAT/SAT ratio were respectively introduced in each model.

WMH through the occlusion of perforating arterioles or the block of glymphatic drainage from the interstitial fluid [3,5]. Thus, the anti-inflammatory effect of SAT may prevent WMH formation through inflammatory pathways. Lastly, chronic diffuse hypo-perfusion might be involved. SAT has been studied as a negative predictor of atherosclerosis, which can lead to diffuse hypoperfusion of the brain environment [34,35]. Thus, though we have no data supporting this theory, SAT may have a protective role through the reduction of atherosclerosis.

Interestingly, the protective effect of SAT appears to be more prominent in obese subjects. As we mentioned above, SAT showed a significant negative correlation with WMH only in the highest TAT tertile or the obesity II group, who had BMI values above 30. This pattern also

Table 5
Univariate linear regression analysis between SAT and vascular risk factors/white matter hyperintensity volume according to the TAT tertiles.

	Univariate analysis	
	β (SE)	*P*
TAT tertile 1 (n = 834)		
Hypertension	0.047 (0.044)	0.294
Diabetes	−0.123 (0.050)	0.014
Dyslipidemia	0.110 (0.042)	0.009
WMH volumes[a]	−0.047 (0.016)	0.003
Triglyceride[b]	0.011 (0.037)	0.770
HDL cholesterol	0.000 (0.001)	0.720
Glucose[b]	−0.182 (0.082)	0.027
hs-CRP[b]	−0.015 (0.011)	0.174
TAT tertile 2 (n = 827)		
Hypertension	−0.076 (0.019)	< 0.001
Diabetes	−0.139 (0.024)	< 0.001
Dyslipidemia	−0.014 (0.017)	0.414
WMH volumes[a]	−0.016 (0.008)	0.046
Triglyceride[b]	−0.119 (0.016)	< 0.001
HDL cholesterol	0.004 (0.001)	< 0.001
Glucose[b]	−0.284 (0.044)	< 0.001
hs-CRP[b]	−0.014 (0.006)	0.016
TAT tertile 3 (n = 843)		
Hypertension	0.018 (0.026)	0.488
Diabetes	−0.108 (0.0300	< 0.001
Dyslipidemia	−0.046 (0.023)	0.046
WMH volumes[a]	−0.026 (0.010)	0.008
Triglyceride[b]	−0.149 (0.022)	< 0.001
HDL cholesterol	0.006 (0.001)	< 0.001
Glucose[b]	−0.205 (0.058)	< 0.001
hs-CRP[b]	−0.020 (0.008)	0.009

SAT = subcutaneous adipose tissue, TAT = total adipose tissue, WMH = white matter hyperintensity, HDL = high-density lipoprotein, hs-CRP = high-sensitivity C-reactive protein.
[a] These variables were introduced as square root scale.
[b] These variables were introduced as log scale.

occurred between the metabolic risk factors and SAT, as shown in Table 5. We speculate that these phenomena arise from the fact that the SAT's 'metabolic sink' effects have more power when someone reaches a positive energy balance [6,23,36,37]. In line with this explanation, previous studies have also demonstrated a negative association between metabolic syndrome and SAT in severely obese patients in other ethnic groups [24].

Sexual difference is another considerable issue. The total amount and distribution of SAT differs between females and males [21,22,38]. As in previous studies, we provide evidence that the protective effects of SAT are more powerful in females than in males. This could be the simple result of the higher levels of SAT observed in female participants or of the preferential deposition of superficial SAT, which has more prominent 'metabolic sink' effects than the deep SAT area, in females [26].

The current study presents several novel findings as well as confirming the findings of previous studies. However, there are also some caveats to this study. First, the study was designed as a single-center retrospective observational study. Though we had a large sample size and conducted broad evaluations, the possibility of selection bias must be considered and caution should be taken in the generalization of these findings to clinical fields. Second, because this study analyzed the natural cross-sections of traits, we are unable to present evidence of a causal relationship. Further prospective studies are required to identify the underlying pathophysiology involved. Lastly, due to methodological limitations, we could not differentiate SAT into superficial and deep SAT, which have different metabolism characteristics [39]. However, though we also included deep SAT which had intermediate features between superficial SAT and VAT, SAT measurements revealed a strong relationship. Thus, our main conclusion would not change if we divided the SAT into subsections.

In conclusion, we demonstrated a negative association between SAT and WMH volume in a healthy population. This association is more prominent in females and severely obese adults. Given the same favorable association of SAT with various risk factors for the development of WMH, a protective role of SAT is highly expected and the conduction of further longitudinal study is strongly recommended.

Acknowledgements

None.

Disclosures

None.

Source of funding

None.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.07.016.

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