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Metabolic syndrome and localization of white matter hyperintensities in the elderly population

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Abstract

Background: Metabolic syndrome (MetS) is defined as a clustering of metabolic disorders: abdominal obesity, dyslipidemia, hypertension, and hyperglycemia. Although specific components of MetS have been associated with white matter hyperintensities (WMH), less is known about the association between MetS as a whole and WMH, especially in normal aging. We aimed to: (1) investigate this association in a cohort of healthy elderly individuals, and (2) examine the relationship between MetS and the regional distribution of WMH, to further understanding of the relationship between MetS and structural brain changes.

Methods: Analyses were carried out on 308 participants (48.1% men, age: 71.0 ± 3.9 years) from the French longitudinal ESPRIT (Enquête de Santé Psychologique - Risques, Incidence et Traitement) study, who were free of cerebrovascular disease cognitive and functional impairment. Logistic regression models were used to examine the cross-sectional association between MetS (defined using the National Cholesterol Education Program–Adult Treatment Panel III criteria) and (1) WMH volumes, and (2) WMH volumes according to their localization in insulofrontal and temporoparietal regions.

Results: After adjusting for potential confounders, participants with MetS had a twofold increased chance of presenting with high levels of WMH volume compared with those without (odds ratio [OR] = 2.74, 95% confidence interval [CI]: 1.25–6.03). MetS was specifically associated with an increase of temporoparietal WMH volumes, but no association was found between MetS and WMH localized in the insulofrontal region.

Conclusion: Our findings suggest that effective management of MetS may reduce WMH accumulation in brain areas already vulnerable to the aging process.

Keywords

Epidemiology; Observational study; Elderly; Metabolic syndrome; White matter hyperintensities; Alzheimer's disease

1. Introduction

Several epidemiological studies have investigated the association between MetS, defined as a clustering of abdominal obesity, dyslipidemia, hypertension, and hyperglycemia, and onset of dementia or age-associated cognitive decline. Although there is a growing body of evidence suggesting that MetS is a significant risk factor for dementia, and also for progression of mild cognitive impairment to dementia [1–7], studies of its relationship to cognitive performance have given inconsistent results. A predictive role of MetS on cognitive deficit [8,9] and cognitive decline [10–13] has been suggested by some studies, but at least two other studies have shown MetS to be associated with improved cognitive performance [14] and decreased cognitive decline [15]. In addition to differences in study design or the heterogeneity of populations, which may contribute to these conflicting results, one possible explanation not previously examined, to our knowledge, is that MetS has a differential impact on cognitive outcomes depending on whether individuals are aging normally or have comorbid subclinical neurodegeneration.

Normal aging is associated with increased small-vessel cerebrovascular disease, visualized on magnetic resonance imaging (MRI) as WMH [16]. Although specific MetS components have been associated with WMH, less is known about the association between MetS as a whole and WMH. Even if MetS is an empirical concept whose clinical utility has been previously challenged [17], it, nonetheless, remains a powerful predictor of cerebrovascular morbidity [18], which can be reversed by acting on health behaviors such as diet [19].

In the present report, we aimed to investigate the cross-sectional association between MetS, its components, and WMH volume in a cohort of healthy elderly individuals without cognitive or functional impairment at baseline. A further objective was to examine the relationship between MetS and the regional distribution of WMH, to contribute to a better understanding on how vascular risk factors such as MetS might affect brain function. Finally, in supplementary analyses, we explored the question of whether participants with the highest levels of WMH at baseline were at greater risk of developing Alzheimer's disease over 8-year follow-up.

2. Methods

2.1. Study population

The data were derived from the Enquête de Santé Psychologique - Risques, Incidence et Traitement (ESPRIT) study [20], a longitudinal study of neuropsychiatric disorder in community-dwelling French elderly individuals, in which noninstitutionalized participants ($n = 2259$, 65 years) were recruited from the electoral rolls of Montpellier (southern France) between 1999 and 2001. After obtaining written informed consent from all participants, health interviews were administered by trained staff at baseline and after 2, 4, 7, and 10 years of follow-up. Each subject also received a standardized neurological examination, and every second subject aged <80 years was offered an MRI. The study design and procedure were approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre.

Of the 2259 ESPRIT participants, 764 participants underwent MRI examination. To restrict the analyses to healthy elderly participants, those diagnosed as having dementia at inclusion (defined according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [21]), those with mild cognitive impairment [22] (defined using the revised criteria [23]), participants with cognitive impairment (Mini-Mental State Examination [MMSE]: <24), functional impairment (at least one disability on the Instrumental Activities of Daily Living scale [24]), or a significant history of stroke or vascular disease (angina pectoris, myocardial infarction, coronary balloon dilation or artery bypass, stroke, and/or peripheral artery disease surgery) at baseline were excluded. As described in the flowchart diagram (Fig. 1), the present report based on 308 healthy participants with complete data on total and regional WMH volumes, MetS, and other covariates.

2.2. Data collection

2.2.1. Assessment of MetS—MetS was diagnosed at baseline, according to National Cholesterol Education Program—Adult Treatment Panel III criteria [25] based on the presence of three or more of the following: (a) waist circumference: >102 cm (men)/ $<.88$ cm (women); (b) serum triglycerides: 1.7 mM/L; (c) high-density lipoprotein cholesterol: <1.04 mM/L (men)/ <1.29 mM/L (women); (d) systolic/diastolic blood pressure: 130 mm Hg/ 85 mm Hg or use of antihypertensive drugs; (e) fasting blood glucose: 6.1 mM/L or presence of type 2 diabetes or diabetic treatment, as previously described [8].

2.2.2. Measurement of WMH—MRI structural imaging was carried out by fast multislice double-echo T2-weighted two-dimensional axial acquisition, using 4-mm-thick slices with 0.4 mm between-slice spacing that covered the whole brain (30 slices, the upper slice passing through the brain vertex). MRI images (124 slices; 1-mm-thick slices) were also obtained by spoiled gradient echo (SPGR) three-dimensional T1-weighted axial acquisition with two excitations. WMH volume in milliliters was estimated using a semiautomatic three-step protocol method [26, 27] using MRicro software (Chris Rorden, Columbia, SC; available at www.mricro.com) [28]. An experienced reader examined all scans. Another experienced neurologist examined 80 randomly chosen scans to assess interrater reliability.

Interrater and intrarater intraclass correlation coefficients showed good-to-excellent agreement (0.79 and 0.95, respectively).

The localization of WMH in the brain was assessed by a quantitative approach [29]; briefly, the T1-weighted SPGR sequences were spatially normalized into standard atlas space and the inverse transform was applied to a white matter atlas [30], so that regional WMH could be defined in frontal, parietal, occipital, temporal, cerebellum, basal ganglia, and insula regions. For the present analyses, WMH volumes in temporoparietal (obtained by summing the WMH volumes in the temporal region and those in the parietal region) and insulofrontal regions (obtained by summing the WMH volumes in the insular region and those in the frontal region) were considered.

2.2.3. Assessment of covariates—Sociodemographic variables consisted of sex, age, and educational level (four categories: no formal education or primary school, lower-secondary education, higher-secondary education, or university degree). Smoking status (non/former/current smoker), presence of allele 4 of the apolipoprotein E (*APOE*) (having at least one $\epsilon 4$ vs. no $\epsilon 4$) (<http://www.genopole-lille.fr/spip/>), use of lipid-lowering drugs, MMSE score, and total intracranial volume were also considered. Total intracranial volume (mm^3) was determined by segmenting each T1-weighted SPGR image into its component tissue classes (gray matter, white matter, cerebrospinal fluid) with SPM5 (Wellcome Department of Cognitive Neurology, London, UK) [31] and summing the volumes.

We chose covariates based not only on their statistical association with the exposure and/or outcome, but also on whether a covariate may in theory impact the MetS–WMH association. Education attainment, as a marker of socioeconomic status, has been shown to be related to both MetS and WMH. Regarding health behaviors, we made the choice to include smoking habits, which is an important vascular risk factor. Regarding other health factors such as diet or physical activity, which are also important risk factors of MetS, data such as frequency of participation in leisure walks, consumption of fruits and vegetables, and fish intake have been collected at baseline of the study. In preliminary analyses, we found that the adjustment for these covariates did not change the association observed between MetS and WMH, but would lead to a substantial reduced number of the subjects included in the analyses. So, we made the choice to not include these covariates in the present analyses. Finally, regarding health status variable, we included use of lipid-lowering drugs, as it is a common treatment for dyslipidemia and an important factor to adjust for when assessing the association between MetS and health outcome. Even if the analyses were carried out on cognitively healthy subjects, we included the MMSE score as a covariate to preclude the possibility that the MetS–WMH association observed may be biased by cognitive performance distribution at baseline. *APOE* $\epsilon 4/\epsilon X$ —the genetic established risk factor of Alzheimer's disease [AD]—was also included, as it has been shown to be associated with WMH volumes in some studies.

2.3. Statistical analyses

Characteristics of the participants according to MetS status were compared using χ^2 for categorical variables, Student *t* tests for continuous variables normally distributed (i.e., age

and total cranial volume), and Wilcoxon rank-sum test for continuous variables not normally distributed (WMH volumes and performances in MMSE).

As distributions of WMH volumes did not follow Gaussian distribution, total WMH volumes and regional WMH volumes were considered as categorical variables by dichotomizing WMH volumes in two groups corresponding to the 50th percentile of the distribution: high level defined by WMH volume ≥ 0.7 mL (median = 1.75 mL, 25th–75th range: 0.80–1.75 mL) versus low level defined by WMH volume <0.7 mL (median = 0.30 mL, 25th–75th range: 0.10–0.40 mL). Logistic regression models were performed to assess the association between MetS, its components, and levels of WMH volumes.

These models were adjusted for sex, age at baseline, total cranial volume (model 1 [M1]), education, smoking habits, use of lipid-lowering drugs, cognitive performances assessed by the MMSE score, and the presence of at least one allele $\epsilon 4$ of the *APOE* (model 2 [M2]). Interactions between each covariate and MetS were tested and found to be nonsignificant. To further assess whether MetS components may drive the association between MetS as a whole and WMH volume, the latter was examined after adjusting for each MetS component. Furthermore, to assess the potential additive effect of MetS components on WMH volumes, we also ran analyses in which the sum of the MetS components was considered.

To contribute to a better understanding on how vascular risk factors such as MetS might affect brain function, further logistic regression models were performed to assess the association between MetS and the regional distribution of WMH. Two regions of interest were considered: the posterior regions, specifically the temporoparietal ones, as it was evidenced to be the first region burdened by lesions observed in early AD process, [32–34] and the insulofrontal region, as this later is not primarily affected by lesions in the early state of AD process.

In supplementary analyses, we finally assessed whether WMH volumes measured at baseline in these cognitively healthy participants were associated with the risk of developing AD over the 8 years of follow-up. We performed a logistic regression model analysis with AD onset as outcome. Diagnosis of incident cases of AD was made by a neurologist at each wave of the study according to a three-step procedure involving the administration of a battery of neuropsychological tests by trained psychologists, an examination by a neurologist, and a review of all potential cases of dementia by an independent committee of neurologists to obtain a consensus on diagnosis and etiology according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [21].

Analyses were conducted using SAS software, version 9.1 (SAS Institute, Cary, NC).

3. Results

3.1. Characteristics of the participants

Of the 764 participants who underwent an MRI examination (Fig. 1), WMH volumes were estimated for 724. The characteristics of the 416 persons who were excluded from this study owing to stroke, vascular disease, or cognitive or functional impairment at baseline, or for

whom information on MetS or other covariates were missing, were compared with the 308 persons included in the present analysis. Those included were more likely to report high educational attainment (54.2% vs 39.0%, $P < .0001$), to be nonsmokers (61.4% vs 50.0%), and to have lower WMH volumes (1.82 ± 3.15 mL vs 4.88 ± 12.41 mL, $P < .0004$). No significant difference was observed between these two groups regarding MetS status and other covariates.

Prevalence of MetS at baseline in these 308 participants was 11%, and characteristics of the participants as a function of MetS status are shown in Table 1. Analyses of the factors associated with levels of WMH volumes are shown in Table A1.

3.2. Cross-sectional association between MetS, its components, and WMH volumes

Table 1 shows that MetS was significantly associated with higher WMH volumes. By considering high (≥ 0.7 mL) versus low level (<0.7 mL) of WMH volumes, results of logistic regression models showed that participants with MetS were more likely to have higher WMH volumes compared with those without MetS (OR = 2.65, 95% CI: 1.22–5.76, Fig. 2, M1). Further adjustment for education, smoking, use of lipid-lowering drugs, cognitive performance, and *APOE* genotype did not attenuate these results (OR = 2.69, 95% CI: 1.22–5.92, Fig. 2, M2).

Analyses of associations between each MetS component and WMH volume were performed to determine which MetS components were the most associated with total WMH volume (Table A2). Of the five components, only hypertension was significantly associated with increased WMH volumes. We also found that the sum of MetS components increased the odds of having high WMH volume (Table A2).

Further analyses were conducted to examine whether the associations observed between MetS as a whole and WMH volumes might be driven by hypertension. In models in which MetS and hypertension criteria were included simultaneously, we observed that the MetS–WMH volumes relationship remains statistically significant after adjusting for hypertension (OR = 2.43, 95% CI: 1.10–5.40).

3.3. Cross-sectional association between WMH and localization of WMH in the brain

To further determine whether MetS is associated with the localization of WMH in the brain, similar models were performed by considering WMH volumes according to their localization in regions of interest. We examined the association between MetS and WMH according to their posterior (temporoparietal) and anterior (insulofrontal) regions, respectively. Results in the Fig. 2 show that MetS was observed to be associated with increased WMH volume localized in the temporoparietal region ($P = .003$). No significant association was found between MetS and WMH localized in the insulofrontal region ($P = .27$).

3.4. Supplementary analyses: Prospective association between WMH and AD onset

It has been previously shown that the temporoparietal brain regions are the first to manifest accumulating lesions in early AD [32]; we then carried out supplementary analyses in

participants free of cognitive and functional impairment at baseline to assess whether amounts of WMH localized in the temporoparietal regions were more at risk of developing AD over the 8 years of follow-up. Of the 308 participants free of dementia, cognitive impairment, and functional impairment included in the analyses, seven cases of probable or possible AD occurred over the 8 years of follow-up (information was not available for 10 participants). Results of the logistic regression analyses, adjusted for age, sex, and total cranial volume showed that higher levels of WMH in the temporoparietal region (analyzed in continuous way) was associated with an increased odds of developing AD 8 years later (OR = 1.37, 95% CI: 1.03–1.82). However, this result should be interpreted cautiously regarding the very small number of incident cases of AD.

4. Discussion

In this study, which was carried out on a healthy elderly cohort free of cerebrovascular disease, dementia, and cognitive and functional impairment at baseline, we observed that participants with MetS had 2.5-fold increased odds of presenting highest levels of WMH volumes compared with those without, after taking into account multiple potential confounders. MetS was specifically associated with an increased volume of temporoparietal WMH, whereas no significant association was found with insulofrontal WMH volumes. By showing that participants with WMH localized in the temporoparietal regions at baseline were more likely to develop AD over the next 8 years, our finding gives some support to the hypothesis that MetS may be associated with AD process by acting on a neurodegenerative process.

MetS—by definition, a cluster of metabolic abnormalities—is a heterogeneous outcome [18]. As there is evidence of its role as a predictor of cardiovascular mortality and morbidity [35], including stroke [36], several studies suggest that disturbances associated with MetS may promote changes in arteries [37], including silent lacunar infarcts [38–41], intracranial sclerosis [37,38,42,43], and periventricular hyperintensities [26].

The Austrian Stroke Prevention Study, in which participants with high levels of glycated hemoglobin A (who also met several MetS criteria) showed greater rate of brain atrophy [44], which was associated with increased WMH volumes [45], highlighted the potential link between MetS and late-life WMH. In the present report, we first focused on the association between MetS as a whole and brain lesions related to small-vessel cerebrovascular disease. Our results showed that within a healthy general elderly population, MetS was associated with increased WMH volume in the absence of clinical signs, in accordance with a cross-sectional study from Japan, in which MetS as a whole was significantly associated with subcortical white matter lesions [38].

It has been suggested by some studies that MetS could be selectively associated with neurocognitive alterations that are required to diagnose vascular cognitive impairment [11] or vascular dementia, but not AD [1]. However, in the current study, we showed that increased WMH burden in posterior areas in older adults without cognitive or functional impairment was associated with incident AD over an 8-year period. One potential explanation of this observation may involve a mechanistic link between distributed small-

vessel cerebrovascular disease and AD. Other several physiopathological processes underlying these associations, such as microangiopathy, β -amyloid deposition, and oxidative stress, have also been proposed; these processes may interact with each other [29]. At this stage, the exact nature of this relationship remains to be fully elucidated.

Exploring the association between MetS and localization of WMH constitutes an original way to contribute to a better understanding of how vascular risk factors such as MetS might alter both brain structure and then its functional consequences. Our finding indicated that MetS was specifically associated with WMH localized in the temporoparietal, but not in the insulofrontal, region.

The hypothesis that WMH localized in temporoparietal lobes may be associated with early AD pathology is based on a conjecture of several findings, as detailed in the report by Acosta-Cabronero et al [32]. Volumetric and metabolic MRI studies have shown that mesial temporal lobe atrophy and posterior temporoparietal association cortex hypometabolism are established features of AD [46]. Some studies also suggest that the posterior cingulate hypometabolism is the most severe metabolic lesion in very early AD [33]. “As posterior cingulate and mesial temporal lobe regions are connected via the Circuit of Papez, it has been proposed that neuronal degeneration in early AD may involve this neuronal network” [32,33]. This network degeneration would then predict a white matter degeneration connecting these areas, which means degeneration from posterior cingulum to posterior temporoparietal areas and a relative preservation of white matter in frontal area. In line with this hypothesis, we carried supplementary analyses suggesting that participants (free of cognitive and functional impairment at baseline) with higher amounts of temporoparietal WMH were more likely to develop future AD.

A recent study, using functional MRI data, investigated the association between MetS and the deterioration in white matter changes assessed by diffusion tensor imaging [47]. Authors have reported that patients with MetS showed an anterior–posterior pattern of deterioration in white matter changes, involving the frontal lobes [47]. Although WMH have also been described clinically to be associated with dys-executive syndrome, this observation is not in accordance with our findings. Further research using combined methodological MRI approaches and neuropathological data is then required to clarify the link between vascular risk factors and neurodegenerative lesions.

Previous studies have described an association of hypertension and dyslipidemia with WMH [48,49]. In this study, these two components appeared to be the most highly associated with WMH. By showing that MetS as a whole remained associated with WMH even after adjusting for each of these components, and more importantly that the sum of MetS components tended to further increase odds of having high WMH volume over and above its component parts, our finding suggests that the MetS–WMH association is not primarily driven by an individual MetS component, underlining the utility of the concept of MetS.

The present study has some limitations, the first being its cross-sectional design, precluding the possibility of ascertaining the direction of the association between MetS and WMH. Our hypothesis was that MetS would impact on WMH volumes; however, we cannot exclude the

possibility that WMH, owing to underlying cerebrovascular disease, may induce metabolic disorders leading to MetS. Even if we have excluded participants reporting a history of vascular disease from the analyses, a prospective design is needed to establish the temporal sequence of events. The second limitation, common to all studies based on observational data, was that the possibility remains that unmeasured confounders may partly explain part of the association between MetS, its components, and WMH. Furthermore, it is possible that WMH is the surrogate for some other factors not included in the models. A third drawback concerns the generalizability of our finding, as participants of the ESPRIT study are not fully representative of the general elderly population, having a higher educational level and better health conditions owing principally to the exclusion of persons in institutions. The general lower rate of incident dementia cases and cognitive disorders in the ESPRIT study combined with the lower prevalence of MetS in the included participants (11%) compared with the original ESPRIT study sample (14.6%) may have led to an underestimation of the strength of the association. Finally, the small number of incident cases of AD in our study also induced a limitation in terms of statistical power of our analyses. However, this quantitative limit may be compensated by the high-quality screening of dementia cases and its subtypes involving a three-step procedure in which dementia cases were well characterized by neurological examination and not just by an algorithm, as done in many studies.

Despite these limitations, the present report carried out on a healthy general population cohort free from history of vascular disease and stroke and without cognitive and functional impairment at baseline was the first to examine whether MetS was associated with WMH volumes by paying special attention to the localization of WMH. Our results highlight that among participants who at baseline were still not engaged in a pathological cognitive aging process, MetS was positively associated with WMH, especially those localized in the temporoparietal area. Furthermore, those with the highest temporoparietal WMH volumes at baseline were more likely to develop AD over the 8-year follow-up. These original findings support the conclusions of recent public health enquiries into the potential interest of preventive population strategies for AD (<http://consensus.nih.gov/2010/alz.htm>), including early management of MetS and its components, which could reduce AD prevalence by at least delaying onset. Further analyses are now required to determine whether MetS is associated with WMH changes over time.

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Fig. 1.
Flowchart diagram mapping the selection of the 308 healthy elderly participants included in the present analyses.

Fig. 2.

Cross-sectional association between MetS and total WMH volumes and according to their localization in the brain (n = 308 participants). Results of logistic regression estimating odds of high levels of WMH in participants with MetS compared with those without MetS. M1: Model adjusted for sex, age, and total cranial volume. M2: M1+ adjusted for educational level, smoking habits, use of lipid-lowering drugs, cognitive performances in Mini-Mental State Examination, and *APOE* $\epsilon 4/\epsilon X$. Total WMH volumes were dichotomized according to the median = 0.7 mL, with high WMH levels defined by median = 1.75 (25th–50th range: 0.80–1.75), and low WMH levels defined as the reference (median = 0.30, 25th–50th range: 0.10–0.40). Temporoparietal and insulofrontal WMH were dichotomized according to the median values (0.11 and 0.37 mL, respectively). High levels of temporoparietal WMH defined by median = 0.38 (25th–50th range: 0.20–1.29), and low level defined by median = 0.03 (25th–50th range: 0.009–0.06). High levels of insulofrontal WMH defined by median = 1.11 (25th–50th range: 0.61–2.22), and low level defined by median = 0.13 (25th–50th range: 0.06–0.23).

Table 1

Characteristics of participants according to their MetS status at baseline

Characteristics of participants	Without MetS [†] n = 274	With MetS [†] n = 34	P value
Women (n = 163), %	53.3	50.0	.72
Age, M (SD)	71.1 (4.00)	71.1 (3.9)	.94
No academic qualification/ primary school (n = 57), %	17.9	23.5	.56
Current smokers (n = 25), %	8.8	2.9	.13
Use of lipid-lowering drugs (n = 73), %	23.4	26.5	.69
Performances in MMSE, M (SD)	27.7 (1.5)	27.5 (1.7)	.25*
APOE ε4/εX genotype (n = 63), %	20.4	20.6	.98
MetS criteria			
Central obesity (n = 53), %	12.0	66.7	<10 ⁻⁴
High triglycerides (n = 46), %	3.3	47.1	<10 ⁻⁴
Low HDL cholesterol (n = 25), %	7.4	85.1	<10 ⁻⁴
Hypertension (n = 245), %	78.1	99.9	<10 ⁻⁴
High FBG (n = 29), %	5.1	44.1	<10 ⁻⁴
Total cranial volume (mm ³), M (SD)	1465.2 (129.4)	1454.3 (116.9)	.64
Total WMH volume (mL)			
High level (≥ 0.7mL), %	32.3	67.6	.01
Total WMH volume (mL), M (SD)	1.79 (3.19)	2.02 (2.8)	.04*

Abbreviations: MetS, metabolic syndrome; MMSE, Mini-Mental State Examination; APOE ε4/εX, apolipoprotein E (having at least one copy of the allele ε4); HDL, high-density lipoprotein; WMH, white matter hyperintensities; FBG, fasting blood glucose; M (SD), mean (standard deviation).

* P value obtained after performing a Wilcoxon rank-sum test.

[†] Defined using the National Cholesterol Education Program criteria [25].

Table A1

Factors associated with total WMH volumes categorized in tertiles

Characteristics of participants	WMH volumes		P value
	Low levels (<0.7 mL)	High levels (0.7 mL)	
Median (25th–50th percentile)	0.30 (0.10–0.40)	1.75 (0.80–1.75)	
Women, %	53.7	52.0	.76
Age, M (SD)	70.2 (3.7)	72.1 (4.1)	<10 ⁻⁴
No academic qualification/primary school, %	17.5	19.6	.85
Current smokers, %	7.5	8.8	.92
Use of lipid-lowering drugs, %	22.5	25.0	.60
Performances in MMSE, M (SD)	27.8 (1.4)	27.5 (1.6)	.10
<i>APOE</i> ε4 genotype (heterozygote), %	17.5	23.6	.18
Total cranial volume (mL), M (SD)	1460.6 (127.0)	1467.7 (129.3)	.63

Abbreviations: MMSE, Mini-Mental State Examination; *APOE* ε4, ε4 allele of the apolipoprotein E (having at least one copy); WMH, white matter hyper-intensities; M (SD), mean (standard deviation).

Table A2

Association between each MetS component and total WMH volumes

MetS criteria	Total n, (%) exposed	Levels of WMH volumes	P
		OR (95% CI) of having high levels of WMH volumes (> 0.7mL) *	
Central obesity	292, 18.1%	1.57 (0.84, 2.94)	.16
High triglycerides	308, 14.9%	1.25 (0.65, 2.39)	.50
Low HDL cholesterol	308, 8.1%	1.81 (0.77, 4.27)	.17
Hypertension	304, 80.6%	1.87 (1.00, 3.50)	.05
High FBG	324, 9.4%	1.14 (0.51, 2.56)	.75
Number of MetS criteria	288	1.31 (1.01–1.71)	.04

Abbreviations: MetS, metabolic syndrome; HDL, high-density lipoprotein; FBG, fasting blood glucose; OR (95% CI), odds ratio accompanied with its 95% confidence interval.

* Odds ratio adjusted for age at baseline (by year), sex, educational attainment, smoking, use of lipid-lowering drugs, MMSE scores, allele ε4 of apolipoprotein E, and total cranial volume (results of logistic regression models).