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

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**Word Count**: Paper 3596 ; Abstract: 226;

1 Table and 2 figures, 2 online appendix Tables;

ABSTRACT

**Background:** Metabolic syndrome (MetS) is defined as a clustering of metabolic disorders: abdominal obesity, dyslipidemia, hypertension and hyperglycemia. While 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 1) to investigate this association in a cohort of healthy elderly and 2) to examine the relationship between MetS and the regional distribution of WMH, in order to further understanding of the relationship between MetS and structural brain changes.

**Methods:** Analyses were carried out on 308 participants (48.1 % men, 71.0±3.9 years) from the French longitudinal ESPRIT study, free of cerebrovascular disease cognitive and functional impairment. Logistic regression analyses were performed to examine the cross-sectional association between MetS (defined using the NCEP-ATP III criteria) and 1) WMH volumes 2) WMH volumes according to their localization in insulo-frontal and temporo-parietal region.

**Results:** After adjusting for potential confounders, participants with MetS had a 2-fold increased odds of presenting high levels of WMH volume compared to those without (OR=2.74, 95 % CI: 1.25-6.03). MetS was specifically associated with an increase of temporo-parietal WMH volumes, but no association was found between MetS and WMH localized in the insulo-frontal region.

**Conclusion:** Our findings suggest that effective management of MetS may reduceWMH accumulation in brain areas already vulnerable to the ageing process.

**Keywords:** Epidemiology, observational study, elderly, metabolic syndrome, white matter hyperintensities, Alzheimer's diseases

## 1. INTRODUCTION

Several epidemiological studies have investigated the association between metabolic syndrome (MetS), defined as a clustering of abdominal obesity, dyslipidemia, hypertension and hyperglycemia, and onset of dementia or age-associated cognitive decline. While 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 co-morbid subclinical neurodegeneration.

Normal aging is associated with increased small vessel cerebrovascular disease, visualized on magnetic resonance imaging (MRI) as white matter hyperintensities (WMH)[16]. . While 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 cerebro-vascular 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 without cognitive or functional impairment at baseline. A further objective was to examine the relationship between MetS and the regional distribution of WMH, in order 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 disease over 8-year follow-up.

## 2. METHODS

### a. Study population

The data were derived from a longitudinal study of neuropsychiatric disorder in community-dwelling French elderly the ESPRIT Study[20] in which non-institutionalized participants (n=2259, ≥65 y) 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 under the age of 80 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*, fourth edition (DSM-IV) [21]), MCI [22] (defined using the revised criteria [23]), participants with cognitive impairment (MMSE <24), functional impairment (at least one disability on the Instrumental Activities of Daily Living (IADL) 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 flow chart diagram (Figure 1), the present report based on 308 healthy participants with complete data on total and regional WMH volumes, MetS and other covariates

### b. Data Collection

*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 3 or more of

the following: (a) waist circumference: men (women)>102 (88) cm; (b) serum triglycerides (TG):≥1.7 mmol/L; (c) HDL cholesterol: men (women) <1.04 (1.29) mmol/L; (d) systolic/diastolic blood pressure: ≥130 mmHg /≥85 mmHg or use of antihypertensive drugs; (e) fasting blood glucose (FBG):≥6.1 mmol/L or presence of type 2 diabetes or diabetic treatment, as previously described [8].

*Measurement of WMH* MRI structural imaging was carried out by fast multislice double echo T2-weighted 2D axial acquisition, 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; 1mm thick) were also obtained by fast SPGR 3D T1-weighted axial acquisition with 2 excitations. WMH volume in mL was estimated using a semi-automatic 3-step protocol method [26] using MRIcro software[27]. An experienced reader examined all scans. Another experienced neurologist examined 80 randomly chosen scans to assess inter-rater reliability. Inter- and intra-rater 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 [28]; briefly the T1-weighted SPGR sequences were spatially normalized into standard atlas space and the inverse transform was applied to a white matter atlas [29], so that regional WMH could be defined in frontal, parietal, occipital, temporal, cerebellum, basal ganglia and in insula regions. For the present analyses, WMH volumes in temporo-parietal (obtained by summing the WMH volumes in temporal and those in parietal regions) and insulo-frontal regions (obtained by summing the WMH volumes in insular region and those in frontal regions) were considered.

*Assessment of covariates*. Socio-demographic variables consisted of sex, age and educational level (4 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 ε4 of the apolipoprotein E (ApoE4) (having at least one ε4 vs. no ε4) (http://www.genopole-lille.fr/spip/), use of lipids 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 (grey matter, white matter, cerebrospinal fluid) with SPM [30] and summing the volumes.

We chose covariates based not only on their statistical association with the exposure or / and outcome, but also on whether a covariate may in theory impact the MetS-WMH association. Education attainment, as a marker of socio-economic 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 led 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 lipids 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

performances distribution at baseline. ApoE4 -the genetic established risk factor of AD- was also included as it has been shown to be associated with WMH volumes in some studies.

### c. Statistical analyses

Characteristics of the participants according to MetS status were compared using Chi-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 variable by dichotomizing WMH volumes in two groups corresponding to the $50^{th}$ percentile of the distribution: high level defined by WMH volume $\geq$0.7 ml (median = 1.75 ml, $25^{th}$-$75^{th}$ range: 0.80-1.75 ml) versus low level defined by WMH volume<0.7 ml (median = 0.30 ml, $25^{th}$-$75^{th}$ 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 (Model1), education, smoking habits, use of lipid lowering drugs, cognitive performances assessed by the MMSE score and the presence of at least one allele ε4 of the ApoE (Model 2). Interaction between each covariate and MetS were tested and found to be non significant. 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 temporo-parietal ones as it was evidenced to be the first region burdened by lesions observed in early AD process [31-33] and the insulo frontal 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 this cognitively healthy participants were associated with the risk of developing AD over the 8-year of follow-up. We performed a logistic regression model 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 DSM IV[21].

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

## 3. RESULTS

### a. Characteristics of the participants

Of the 764 participants who underwent an MRI examination (Figure 1), WMH volumes were estimated for 724. The characteristics of the416 persons who were excluded from this study due to stroke, vascular disease, 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 %, $p<0.0001$), to be non smokers (61.4% vs. 50.0%) and to have lower WMH volumes (1.82±3.15 mL vs. 4.88±12.41mL, $p<0.0004$). 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 were shown in Appendix-Table A.

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

Table 1, showed that MetS was significant associated with higher WMH volumes. By considering high (≥0.7 mL) vs. 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 to those without MetS (Odds ratio=2.65, 95% CI: 1.22 to 5.76, Figure2, M1). Further adjustment for education, smoking, use of lipid lowering drugs, cognitive performance and Apoe genotype did not attenuate these results (Odds ratio=2.69, 95% CI: 1.22 to 5.92, Figure2, 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 (Appendix-Table B). Of the 5 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 (Appendix-Table B).

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 to 5.40).

**c. 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 volume according to their localization in regions of interest. We examined the association between MetS and WMH according to their posterior (temporo-parietal) and anterior (insulo-frontal) regions respectively. Results in the Figure 2 showed that MetS was observed to be associated with increased WMH volume localized in the temporo-parietal region (p=0.003). No significant association was found between MetS and WMH localized in insulo-frontal region (p=0.27).

**d. Supplementary analyses: Prospective association between WMH and AD onset**

It has been previously shown that the temporo-parietal brain regions are the first to manifest accumulating lesions in early AD [31], 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 temporo-parietal regions were more at risk of developing AD over the 8 year of follow-up. Of the 308 participants free of dementia, cognitive and functional impairment included in the analyses, 7 cases of probable or possible AD occurred over the

eight 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 temporo-parietal (analyzed in continuous way) was associated with an increased odds of developing AD 8 years later volume (OR= 1.37, 95% CI: 1.03 to 1.82). However this result should be interpreted cautiously regarding the very small number of incident cases of AD.

## 4. DISCUSSION

In this study, carried out on a healthy elderly cohort free of cerebro-vascular disease, without dementia, 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 to those without, after taking into account multiple potential confounders. MetS was specifically associated with an increased volume of temporo-parietal WMH, while no significant association was found with insulo-frontal WMH volumes. By showing that participants with WMH localized in the temporo-parietal 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[34], including stroke[35], several studies suggest that disturbances associated with MetS may promote changes in arteries[36], including silent lacunar infarcts[37-40], intracranial sclerosis[36, 37, 41, 42] and periventricular hyperintensities[37].

The Austrian Stroke Prevention Study, in which participants with high glycated hemoglobin A (who also met several MetS criteria), showed greater rate of brain atrophy [43] which was associated with increased WMH volumes [44], 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 [37].

It has been suggested by some studies that MetS could be selectively associated with neurocognitive alterations that are required to diagnose vascular cognitive impairment[45] 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 cerebro-vascular disease and AD. Other several physio-pathological processes underlying these associations such as micro-angiopathy, beta amyloid deposition, and oxidative stress have also been proposed, these processes may interact with each other[28]. 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 temporo-parietal but not in insulo-frontal regions.

The hypothesis that WMH localized in temporo-parietal lobes may be associated with early AD pathology is based on a conjecture of several findings as detailed in Acosta-Calbronero et al ‘s report [31]. Volumetric and metabolic MRI studies have showed that mesial temporal lobe atrophy and posterior temporo-parietal association cortex hypometabolism are established features of AD [46]. Some studies also suggest that the posterior cingulated hypometabolism is the most severe metabolic lesions in very early AD [32]. “As posterior cingulated 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"[31, 32]. This network degeneration would then predict a white matter degeneration connecting these areas, which means a degeneration from posterior cingulum to posterior temporo-parietal 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 temporo-parietal WMH were more likely to develop future AD.

A recent study, using functional MRI data, has investigated the association between MetS and the deterioration in white matter changes assessed by DTI[47]. Authors have reported that patients with MetS showed an anterior-posterior pattern of deterioration in white matter changes, involving the frontal lobes[47]. While WMH have also been described clinically to be associated with dysexecutive syndrome referring to a sub-cortico-frontal burden, this observation is not in accordance with our findings. Further research using combined methodological MRI approaches and neuro-pathological data are then required to clarify the link between vascular risk factors and neurodegenerative lesions.

Previous studies have described an association between hypertension, dyslipidemia and 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, due to underlying cerebrovascular disease, may induce metabolic disorders leading to MetS. Even if we have excluded from the analyses participants reporting a history of vascular disease, 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 generalisability 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 due 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 to 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 term of statistical power of our analyses. However this quantitative limit may be compensate by the high quality of 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 it 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 temporo-parietal area. Furthermore those with the highest temporo-parietal 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, 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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## 6. ACKNOWLEDGEMENTS/CONFLICTS/FUNDING SOURCES

Study sponsorship:

Financial support: The ESPRIT Study is conducted under a partnership agreement between the Institut National de la Santé et de la Recherche Médicale (INSERM) and Sanofi- Aventis. The Fondation pour la Recherche Médicale funded the preparation and initiation of the study. The ESPRIT Study is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, MGEN, Institut de la Longévité, Conseils Régionaux d'Aquitaine et Bourgogne, Fondation de France and Ministry of Research – INSERM Programme 'Cohortes et collections de données biologiques'. Part of this project is financed by grant from the Agence Nationale de la Recherche (project ANR-2006-PNRA -005; ANR2007 LVIE 003;ANR 2007-LVIE-004). Tasnime Akbaraly is supported by the BUPA Foundation, UK. The funders had no role in the design and conduct of the study, collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Disclosures of all authors' financial relationships

The authors report no conflicts of interest.

Author Contributions: FP had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept, design & Acquisition of the data*: KR CB, TNA, SA, FP

*Analysis and interpretation of the data:* TNA, FP, AMD, YS

*Drafting of the manuscript:* TNA & FP

*Critical revision of the manuscript for important intellectual content:* FP, AMD, YS, NS, JM, FAP, CB, AB, SA, KR, TNA

*Statistical analysis:* TNA

## 7. KEYWORDS

Epidemiology, observational study, elderly, metabolic syndrome, white matter hyperintensities, Alzheimer’s diseases

## 8. FIGURE LEGENDS

Figure 1: Flow chart diagram mapping the selection of the 308 healthy elderly participants included in the present analyses.

Figure 2: Cross-sectional association between metabolic syndrome (MetS) and total white matter hyperintensities (WMH) volumes and according to their localisation in the brain (n=308 participants)

Legends

Results of logistic regression estimating odds of being in high levels of WMH in participants with MetS compared to 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 MMSE and allele ε4 of apolipoprotein E .

- Total WMH volumes were dichotomized according to the median=0.7 mL. With High WMH levels defined by median=1.75, $25^{th}$ -$50^{th}$ range: 0.80-1.75 and low WMH levels defined as the reference (median=0.30, $25^{th}$ -$50^{th}$ range: 0.10-0.40).
- Temporo-parietal and insulo-frontal WMH were dichotomized according to the median values (respectively 0.11 and 0.37 ml).
- High levels of temporo-parietal WMH defined by median=0.38, $25^{th}$ -$50^{th}$ range (0.20-1.29), low level defined by median=0.03, $25^{th}$ -$50^{th}$ range (0.009-0.06)
High levels of insulo-frontal WMH defined by median=1.11, $25^{th}$ -$50^{th}$ range (0.61-2.22), low level defined by median=0.13, $25^{th}$ -$50^{th}$ range (0.06- 0.23)

## 9. TABLES

Table 1: Characteristics of participants according to their metabolic syndrome (MetS) status at baseline.

| | | Without MetS *N=274 | With MetS * N=34 | p-value |
|---|---|---|---|---|
| Women (n=163), % | | 53.3 | 50.0 | 0.72 |
| Age, m (SD) | | 71.1 (4.00) | 71.1(3.9) | 0.94 |
| No academic qualification /primary school (n=57), % | | 17.9 | 23.5 | 0.56 |
| Current smokers (n=25)% | | 8.8 | 2.9 | 0.13 |
| Use of lipid lowering drugs (n=73), % | | 23.4 | 26.5 | 0.69 |
| Performances in MMSE, m (SD) | | 27.7 (1.5) | 27.5 (1.7) | 0.25** |
| ApoE4 genotype (heterozygote) (n=63), % | | 20.4 | 20.6 | 0.98 |
| 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 fasting blood glucose (n=29), % | 5.1 | 44.1 | $<10^{-4}$ |
| Total cranial volume ($mm^3$), m (SD) | | 1465.2 (129.4) | 1454.3(116.9) | 0.64 |
| Total WMH Volume (ml) | High level (≥0.7mL), % | 32.3 | 67.6 | 0.01 |
| Total WMH Volume (ml), m (SD) | | 1.79 (3.19) | 2.02 (2.8) | 0.04** |

MetS: metabolic syndrome, MMSE: mini mental state examination; ApoE4: ε4 allele of the apolipoprotein E (having at least one copy), HDL: High-density lipoprotein, WMH: white mater hyperintensities.

m (SD) : mean (standard deviation)
*Defined using the National Cholesterol Education Program (NCEP) criteria [25]
**p-value obtained after performing a Wilcoxon Rank Sum test