White matter lesions as a predictor of depression in the elderly: the 3C-Dijon study.

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The 3C-Dijon study

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Key words: Depression; imaging; elderly; epidemiology; white matter lesions; longitudinal

Number of words in abstract=248
Number of words in the Text=3759
Number of tables = 4

Abstract

Background

There is increasing evidence for a link between cerebrovascular disease and depression in the elderly but the mechanisms are still unknown. This study examines the longitudinal relationship between depression and white matter lesions (WML) in a sample of elderly aged 65 years and over.

Methods

3C-Dijon is a 4-year follow-up population-based prospective study of 1658 subjects. At baseline, lifetime Major Depressive Episode diagnosis was established using "Mini International Neuropsychiatric Interview". At each study wave, severity of depressive symptoms was assessed using Center for Epidemiological Studies-Depression (CES-D) and antidepressants intake was recorded. At baseline, "lifetime major depression" (LMD) was defined as lifetime Major Depressive Episode or antidepressant medication intake. At follow-up, subjects were classified “incident depression” if scoring high at CES-D or antidepressant users.
A baseline, cerebral MRI was performed in order to quantify WML volumes using an automated method of detection. At 4-year follow-up, 1214 subjects had a second MRI.

Results

Cross-sectional analysis showed a significantly higher WML volume in subjects with LMD compared to the others. Adjusted longitudinal analysis showed that increase in WML load was significantly higher in subjects with baseline LMD (2.1 cm^3 vs. 1.5 cm^3, p=0.004). Among subjects free of depression up to baseline (n=956), the higher the baseline WML volume, the higher the risk of developing depression during follow-up (OR per one quartile increase=1.3 (95% CI=1.1-1.7)).

Conclusions

Our data show that depression and WML volumes are strongly related. These results are consistent with the hypothesis of a vascular depression in the elderly.

Introduction

Major depression in elderly subjects is a severe and frequent psychiatric disorder with prevalence in the community-dwelling ranging between 1% and 5% (1). Recent studies suggest that a type of depression might be specific of old age, occurring more frequently after the age of 65 and associated with a strong vascular component (2-6). The vascular depression hypothesis suggests that cerebrovascular pathologies might predispose, precipitate, or perpetuate the development of geriatric depressive syndromes. However, the mechanisms that link cerebrovascular risk factors to depression are still unknown. The dominant interpretation is that subclinical cerebrovascular disease disrupts fronto-subcortical function, which in turn causes a syndrome of late-onset depression (4,7). With recent progress in medical imaging, it is possible to study simultaneously vascular factors and brain changes visible at MRI in relation to depression. To date, only a few studies have investigated the relation between cerebral white matter lesions (WML), the most common form of vascular brain modifications, and depression in the elderly (8-16). Most of those studies have reported an association between greater WML volumes and depression (8-15). However, the relationship between WML load and depression has never been investigated prospectively.

The aim of our study was to investigate the longitudinal association between WML volumes and depression and to assess whether WML localization may influence this relationship in a large population-based sample of elderly. Furthermore, we investigated prospectively the association between higher WML volumes and incident depression risk.

Method

Sample

The 3C study is a multicenter cohort study, conducted in three French cities (Bordeaux, Dijon, and Montpellier), and designed to estimate dementia risk attributable to vascular factors. A sample of non-institutionalized subjects aged 65 years and over was randomly selected from the electoral rolls of each city. Between January 1999 and March 2001, 9294 subjects were enrolled (Bordeaux=2104, Dijon=4931, and Montpellier=2259). The detailed description of the study protocol has been published elsewhere (17). The study protocol was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre. Each participant signed an informed consent. Subjects were followed-up every two years during 4 years.

Among Dijon participants aged less than 80 years old and enrolled between June 1999 and September 2000 (N=2763), a cerebral Magnetic Resonance Imaging (MRI) examination was proposed. Exclusion criteria were conventional: (i) carrying a cardiac pacemaker, valvular prosthesis, or other internal electrical/magnetic device; (ii) history of neurosurgery or aneurysm; (iii) presence of metal fragments in the eyes, brain, or spinal cord; (iv) claustrophobia. Although 2285 subjects agreed to participate (82.7%), because of financial limitations, 1924 examinations were performed. Among subjects who had a MRI, 123 scans could not be used because of poor quality and a further 143 subjects were excluded because depression status was missing.

Compared to the others (N=1105), subjects included in the analyses (N=1658) were on average significantly younger (72.5 (SD=4.1) versus 73.4 (SD=4.0), $p<0.0001$), they were less often women (62.2% versus 71.0%, $p<.0001$), they more often had an

education level above baccalaureate (23.5% versus 17.8%, p<0.0001) and their health was overall better (data not shown).

After 4-year follow-up, 1292 had a second MRI (Follow-up rate=73.7%) and the scans were not valid for 70 of them. Subjects without follow-up MRI (n=436) were older (73.5 versus 72.1, p<0.0001), they had higher prevalence of lifetime major depression at baseline (14.9% versus. 13.4%, P=0.04) and they had a significantly higher WML volume at baseline (6.4 cm^3 versus. 5.3 cm^3, p=0.0002).

Data collected

At each study's wave, data were collected at the participants' home by a trained psychologist during a face-to-face interview using a standardized questionnaire. Information about demographic background, occupation, medical history, drug use (on a regular basis during the last month) and personal habits were collected. Depressive symptomatology was evaluated with the Center for Epidemiological Studies-Depression scale (CES-D) (18), a 20-item depression rating scale that was developed for use in epidemiological studies to assess frequency and severity of depressive symptoms experienced during the past week. High depressive symptomatology was defined as a CES-D score≥17 for men and ≥23 for women based on a validation in a French population (19).

The Mini-International Neuropsychiatric Interview (MINI) (20) was used at baseline to assess the existence of lifetime major depressive episode. The MINI is a short structured diagnostic interview developed jointly by psychiatrists and clinicians in the United States and Europe, for DSM-IV and ICD-10 psychiatric disorders. With an administration time of approximately 15 minutes, it was designed to meet the need

for a short but accurate structured psychiatric interview for clinical trials and epidemiological studies.

The questionnaire included an inventory of all drugs used during the preceding month. To reduce underreporting, participants were asked to show medical prescriptions, drug packages and any other relevant information. The trade names of all drugs were recorded and coded using the World Health Organization Anatomical Therapeutic Chemical classification. Psychotropic drugs included anxiolytics, hypnotics and antidepressants.

At baseline, in order to identify subjects who had lifetime major depression (LMD), we grouped together subjects taking antidepressants and those fulfilling lifetime major depressive episode criteria according to the MINI questionnaire (21).

During subsequent waves of the 3C study (2 and 4 year follow-up), incident cases of depression were identified if having high depressive symptomatology (based on CES-D score) or taking antidepressant at least once during one of the follow-up examinations.

MRI data

MRI acquisition was performed on 1.5 Tesla Magnetom (Siemens, Erlangen). A three-dimensional (3D) high-resolution T1-weighted brain volume was acquired using a 3D inversion recovery fast spoiled-gradient echo sequence (3D IR-SPGR; TR = 97 ms; TE = 4 ms; TI=600 ms; coronal acquisition). The axially reoriented 3D volume matrix size was 256 x 192 x 256 with a 1.0 x 0.98 x 0.98 mm^3 voxel size. T2- and PD- (proton density) weighted brain volumes were acquired using a 2D dual spin echo sequence with two echo times (TR = 4400 ms; TE1 = 16 ms; TE2 = 98 ms). T2 and PD acquisitions consisted of 35 axial slices 3.5 mm thick (0.5 mm between slices

spacing), having a 256 x 256 matrix size, and a 0.98 x 0.98 mm^2 in-plane resolution. This relatively coarse T2/PD image axial resolution was set in order to keep acquisition duration in elderly subjects to a minimum.

Positioning in the magnet was based on a common landmark for all subjects, namely the orbito-metal line, so that the entire brain, including cerebellum and mid-brain, was contained within the field of view of both the T1-weighted and T2/PD-weighted acquisitions. Each subject dataset (T1, T2 and PD) was readily reconstructed, visually checked for major artefacts, before being sent to the database repository (Caen) where it was archived for further analyses.

WML volume estimation

Fully automatic image processing software was developed to detect, measure and localize WML. The MR image analysis contained three major steps: (i) Pre-processing, including registration, non-brain tissue removal and bias field correction, (ii) Detection of white matter hyperintensities in T2 images including removal of false positives, (iii) Post-processing including generation of WML probability maps at the individual and sample levels, morphometry, localization and classification of WML. Careful inspection of initial results on several cases revealed at least two types of voxels wrongly classified as WML by the algorithm (false positives, FP). First, some FPs originated from Cerebro Spinal Fluid (CSF) / Virchow robin spaces having intensities similar to that of WML on T2 images. Removal of such false positives requested a better delineation of the CSF compartment border, which was achieved thanks to the SPM99 (Statistical Parametric Mapping) package. Using the high resolution T1 volume, an optimized CSF mask was generated, aligned on the T2 volume using the spatial normalization matrix (SNM-1MNI), thereby allowing the identification and removal of WML having more than 50% of their voxels overlapping

the CSF mask. Secondly, some FPs were voxels truly belonging to WM but were not hyperintensities. Such FPs correspond to voxels having a very low intensity but a larger probability to belong to the WML than to the WM class (this may happen because WML voxels have a larger variance than those of WM). As a consequence, WML having a mean T2 signal intensity lower than that of white matter were excluded.

Morphological parameters were computed for each detected WML including center of mass coordinates, Euclidian distance to the ventricular system and principal axes dimension. When its distance to the ventricular system was less than 10 mm a WML was labeled as periventricular (PWML), otherwise it was labeled as deep (DWML). Stereotactic coordinates of the center of mass were calculated using the combination of the T1-to-PD/T2 and T1-to-Talairach space registration matrices.

The position of the center of mass with respect to that of the major fissures and sulci in the Talairach atlas (interhemipsheric fissure, Rolando sulcus, Sylvian fissure, parieto-temporal sulcus, occipito-temporal sulcus) was then determined and used to define the hemispheric (left, right) and lobar (frontal, occipital temporal or parietal) localization of each WML.

The volume of WML by lobe was then calculated by summing the volumes of all the lesions detected in each of the lobes. Similarly, a periventricular WML volume and a deep WML volume were estimated.

These measures were obtained for both the baseline and the follow-up scans. The volume of WML detected is highly correlated to the total volume of White Matter. Therefore, in all the analyses, we have adjusted for White Matter volume to take that effect into account.

For prospective analysis, WML volume was studied in four categories based on quartiles distribution.

Covariates

Education level was defined in four categories ranging from primary certificate level (low) to baccalaureate or university degree (high). Subjects were considered as hypertensive if systolic blood pressure (SPB) was 140 mm Hg or higher or diastolic blood pressure (DBP) was 90 mm Hg or higher or they were on antihypertensive medication.

We defined diabetes as self-reported diabetes or fasting blood glucose ≥ 7 mmol/l. Subjects were considered as having a history of cardiovascular disease if they reported a history of stroke or myocardial infarct or arteritis. Tobacco and alcohol consumptions were studied in 3 classes: current, former or abstainer.

Statistical analysis

The cross-sectional analyses were performed on a sample of 1658 subjects. To evaluate the cross-sectional associations with WML volume and LMD prevalence, chi-square test was used for categorical variables and analysis of variance for continuous variables. For multivariate analyses, we performed analyses of covariance adjusting for following potential confounders (based on univariate analyses and literature): sex, age, hypertension, history of cardiovascular disease, alcohol and tobacco consumptions. Separate models were performed to analyze the relationship between depression and WML volumes by type or localization.

The longitudinal association between LMD and progression of WML volumes over 4-year follow-up was evaluated using analyses of covariance adjusting for baseline WML volume and delay between the two MRI examinations, in addition to the potential confounders listed above. Subjects whose WML volume decreased from

more than 6 cm^3 (n= 8) were considered as outliers and excluded from the longitudinal analyses that were performed on a sample of 1214 subjects.

In order to test the assumption that WML might cause depression, logistic regression model was computed to estimate the risk of developing depression during follow-up according to WML volumes quartile at baseline. In those analyses, subjects with LMD or high depressive symptoms at baseline were excluded and 959 subjects remained in the analyses.

All two by two interactions were considered by adding an interaction term in the models but none was significant. We used SAS (release 9.1; SAS Statistical Institute, Cary, NC) for the analyses.

Results

The study sample at baseline is described in Table 1. Mean age of participants was 72.4 years (Standard Deviation (SD) =4.1) and 60.6% of participants were women. Prevalence of LMD was 14.5% and 13.1% of subjects had high depressive symptoms.

Factors associated with LMD are also shown in Table 1. LMD prevalence was higher in women. Mean age did not differ significantly between subjects with LMD (72.7 years (SD=4.0)) and subjects without (72.4 years (SD=4.1)), (p=0.20). Alcohol and tobacco consumptions were significantly related to LMD, prevalence being higher in non smokers (compared to current and former smokers) as well as in former drinkers (compared to current and never drinkers). There was no significant trend for an association between LMD and education level.

Subjects with hypertension, diabetes or history of cardiovascular disease did tend to have LMD more often but the associations were not significant.

LMD prevalence was significantly higher in subjects with high depressive symptoms at the time of interview as well as in subjects with physical impairment.

Mean WML volume was 5.6 cm^3 (SD=5.0) at baseline and it divided up as 1.3 cm^3 (SD=3.7) in deep area, 4.3 cm^3 (SD=1.0) in periventricular area.

WML volume increased linearly with age (r=0.09, p<0.0001) and mean WML volume was significantly higher in subjects with hypertension (6.0 cm^3 in hypertensive versus 4.8 cm^3 in normotensive subjects, p<0.0001).

Table 2 shows the baseline cross-sectional association between WML volume and LMD. After adjusting for potential confounders, WML volumes were on average significantly higher in subjects with LMD compared to subjects without. In separate models by lobar volume, there was a significant association between LMD and higher

WML in the frontal lobe only (p=0.01) whereas a similar but non significant trend was observed in the parietal lobe (p=0.12). In addition, the relationship between WML volume and LMD did not differ according to the type of WML (deep versus periventricular).

Among the 1214 participants included in the longitudinal analyses, baseline LMD prevalence was 13.8 % and baseline mean WML volume was 5.2 cm^3 (SD=4.4). Unadjusted WML volume increase was 1.4 cm^3 (SE=0.08) in subjects without baseline LMD and 2.1 cm^3 (SE=0.20) in subjects with baseline LMD (p=0.0005). The WM total volume increased of 2.3 cm^3 (SD=23.5) between the two MRI and did not differ according to baseline LMD status (p=0.12).

Table 3 shows the adjusted longitudinal relationship between baseline LMD and progression of WML volume over time. After adjusting for potential confounders, progression of WML volume was 0.6 cm^3 higher in subjects with baseline LMD compared to those without and this difference was significant (p=0.004). This association was observed whatever the localization (non significant trend for temporal and parietal lobes) and the type of WML.

Exclusion of subjects who had cognitive impairment (MMSE score <24, n=64) or prevalent dementia (n=8), did not modify the association: progression of WML volume was stronger in subjects having baseline LMD (2.0 cm3, SE=0.3) compared to those without (1.4 cm3, SE=0.3) (p for difference=0.003).

In additional longitudinal analyses, we tried to explore the direction of the relationship between WML and depression. Particularly, to test the hypothesis that high WML volume is a risk factor for depression, we selected a sub-sample of subjects without depression at baseline. Of the 956 subjects fulfilling these criteria, 103 developed a depression during follow-up. Table 4 shows the relationship between WML volumes

at baseline and incident depression risk in subjects free of depression up to baseline examination. We observe that the higher the baseline WML volume, the higher the depression risk during follow-up (p for linear trend =0.01).

Discussion

In this study of elderly subjects, WML severity was associated with lifetime major depression. Actually, cross-sectional analyses showed that subjects with LMD had a mean volume of WML significantly higher than subjects without LMD. The plausibility of this association was strengthened by the longitudinal analyses which showed that the progression of WML volume over 4-year follow-up was significantly higher in subjects with LMD at baseline.

Our cross-sectional findings are in line with most studies in clinically depressed subjects as well as with population-based studies that have reported an association between WML and depression (11,12). Our findings do not support the hypothesis that cerebrovascular risk factors could mediate the association between WML and depression (16). Indeed adjusting for age, hypertension or history of cardiovascular disease does not modify the association between WML and depression and our data do not either show an interaction between cerebrovascular risk factors and WML volume on the risk of depression.

Our longitudinal findings are in contrast with two previous reports that were in favor of an absence of an association. However these researches were based on highly selected samples (22-23) Indeed, the PROSPER study (22) is a clinical trial including 572 non-demented elderly aged 70 and above having an history of cardiovascular disease and the other report (23) is a case-control study comparing a group of 164 depressed subjects to a group of 126 controls. Both studies had observed a cross-sectional association between WML volume and depression but they also both found that change of WML volume over time was not related to baseline depression.

When we performed separate analyses by type of WML (periventricular or deep), our data did not suggest differences in association between LMD and WML volumes. In

the analyses of WML by lobe, cross sectional findings showed a relation between depression and WML volume in the frontal lobe only. Longitudinal WML data suggest that LMD is associated with higher increase in WML volume for frontal, occipital, parietal and temporal lobes although the association does not reach statistical significance for the last two. Other studies have suggested that the relationship between WML and depression is limited to WML localized in the frontal lobe (9,24) or in the deep white matter (11,13-14,25), but these studies were based on small clinical samples. It is therefore likely they did not have enough statistical power to detect WML volume differences between depressed and non depressed groups other than in areas where WML are the most frequent. Furthermore, our results support the hypothesis that WML could play a role in depression occurrence in this population. Actually, we observed that in subjects without any history of depression before enrolment, higher WML volumes at baseline increase the risk of developing depression during follow-up.

Some limitations should be noted to our findings. Compared with the general population aged 65 years or over, the 3C participants have higher education and socio-economic levels, and they are healthier. In addition, subjects who agreed to participate in the MRI substudy also have higher socio-economic conditions and are overall healthier than the 3C subjects who did not have an MRI examination. However, our analyses show that the acceptance rate was high and not associated with LMD prevalence at baseline. But we can not exclude that selection bias might affect the strength of the association between WML and depression. Another potential limitation relates on the use of CES-D and MINI instruments. Indeed, firstly, assessment of psychiatric conditions was not a primary objective of the 3C study and secondly in large scale studies such as ours, it is almost impossible to undertake

extensive psychiatric interviews. Therefore, depression diagnosis is based on diagnostic tools and we can not determine whether depression can be attributed to exogenous or endogenous conditions.

In addition, misclassification of depressed cases can occur as for any diagnosis tool. Although we can not exclude it, it is very unlikely that our findings are spurious and explain by differential misclassification. Misclassification would rather tend to bias the associations toward the null hypothesis and therefore underestimate the true association (26).

In our cross sectional analyses, we defined lifetime major depression based on MINI questionnaire or antidepressant drug intake. One could argue that, in some elderly people, antidepressants are prescribed when they have dementia or cognitive deficits, but no depression and this could bias our findings. However, we have performed sensitivity analyses by excluding subjects taking antidepressants and the results were unchanged. Similarly, longitudinal results were unchanged after we excluded subjects taking antidepressants during follow-up (Mean WML volume progression =1.2 (SE=0.3) in subjects without MDE at baseline compared to mean WML volume progression=2.2 (SE=0.3) in subjects with baseline MDE, $p<0.0001$).

In the 3C study, numerous clinical and socio-demographic data are recorded and in our analyses, we were able to take into account different potential confounders. The fact that the relationship between WML and depression is still significant after all those adjustments reinforces the plausibility of the association. In addition to the adjustments presented in the results section, we have performed additional analyses by adjusting on baseline cognitive performances (assessed by Mini-Mental State Examination) and the results were not modified.

Our study is the first to evaluate the progression of WML in relation to depression in the general population. Moreover, WML volumes were estimated using a fully automatic image processing software which produces reliable and reproducible results. The WML progression we observe over 4-year is compatible with previous reports (27,28). However, this method also has weaknesses. For around 10 % of the sample, WML volume decreased between baseline and 4-year follow-up MRI examinations. This could be artefactual or reflect brain shrinkage for some individuals. We have performed a sensitivity analysis by excluding subjects whose WML volume had decreased between baseline and 4-year follow-up and the associations between WML volumes and depression were unchanged. Other studies having developed automated method of WML detection have also observed the same pattern of decrease in WML load in a small proportion of individuals (27,28). This phenomenon may be due to the difficulty to identify small WML given the relative large thickness of the T2 images.

Overall, our results are in adequacy with the hypothesis of vascular depression in the elderly (2,29,30). The vascular depression hypothesis state that lesions may contribute to the pathogenesis of depression. WML may disrupt neural circuits, or fiber tracts connecting frontal and subcortical regions, such disruption might alter the function of circuits involved in the mood regulation, contributing to the pathogenesis of depression (31). In the 3C study, the relationship between WML volume and LMD was stronger in subjects with vascular risk factors but the interaction term was not significant. Therefore, our findings support the leading theory that emphasizes a vascular cause of depression in the elderly.

In summary, this is the first longitudinal population based-study investigating the relationship between WML volume and WML volume change and depression in the elderly.

In this large longitudinal study in a community sample of subjects aged 65 years and over, we demonstrate that subjects having lifetime major depression have significantly higher WML volumes and their WML volume increase is significantly higher over 4-year follow-up compared to subjects without LMD. Therefore, depressed subjects are at increase risk of numerous adverse outcomes including WML spreading and further studies are needed to understand the underlying mechanisms.

In addition, higher WML volume did predict incident depression in subjects free of any lifetime depression up to baseline examination. These results may have some implications for depression prevention in older individuals but additional epidemiological studies are also needed to address the role of vascular risk factors treatment in such prevention strategy.

ACKNOWLEDGMENTS

The Three-City Study is conducted under a partnership agreement between the Institut National de la Santé et de la Recherche Médicale (INSERM), the Victor Segalen–Bordeaux II University, and Sanofi-Aventis. The Fondation pour la Recherche Médicale funded the preparation and initiation of the study. The 3C Study is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, MGEN, Institut de la Longévité, Conseils Régionaux of Aquitaine and Bourgogne, Fondation de France, and Ministry of Research–INSERM Programme “Cohortes et collections de données biologiques.”

FINANCIAL DISCLOSURE

The authors have nothing to disclose and have no potential conflicts of interest

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Table 1: General characteristics of the participants

	All sample	Lifetime major depression*		
	N	n	%	P[†]
Sex				
Men	653	56	8.6	<0.0001
Women	1005	185	18.4	
Education level				
Low	277	49	17.7	0.25
Medium low	717	106	14.8	
Medium high	314	39	12.4	
High	347	45	13.0	
Living alone				
No	1051	130	12.4	0.001
Yes	604	110	18.2	
History of cardiovascular disease[‡]				
No	1526	221	14.5	0.83
Yes	132	20	15.1	
Hypertension[§]				
No	380	60	15.8	0.43
Yes	1278	181	14.2	
Glycemia[**]				
No	1454	207	14.2	0.52
High	49	8	16.3	
Diabetes	142	25	17.6	
Alcohol consumption				
Yes	1326	170	12.8	<0.0001
No	298	60	20.1	
Former	28	11	39.3	
Tobacco consumption				
Non smoker	1022	172	16.8	0.004
Ex smoker	549	59	10.8	
Current smoker	87	10	11.5	
High depressive symptoms[††]	213	75	35.2	<0.0001
Physical Impairment[‡‡]				
No	1570	221	14.1	0.01
Yes	73	18	24.7	

*Lifetime major depressive episode mesured by the Mini-International Neuropsychiatric Interview (MINI) or use of antidepressive medication

[†] Based on the Chi-square for qualitative variables or analysis of variance for continous variables

[‡] Self reported history of stroke, arterits and myocardial infarction

[§] systolic blood pressure>= 140 mm Hg and/or diastolic blood pressure >= 90 mm Hg or use antihypertensive medication

[**] High defined as 6.1 mmol/l<= glycemia < 7 mmol/l, diabetes defined as reported diabete or treatment for diabete or glycemia >= 7 mmol/l

[††]Measured by the Center For Epidemiological Studies Depression Scale; defined as a score >=17 for men and >=23 for women

[‡‡]Measured using IADL scale

Table 2: Cross-sectional association between White Matter Lesions (WML) volume and lifetime major depression at baseline

	Lifetime major depression *				
	No		Yes		P‡
	Mean	SE	Mean	SE	
N	(n=1417;85.5%)		(n=241;14.5%)		
Mean WML volume	6.8	0.50	7.6	0.54	0.03
Mean WML volume by type					
Periventricular	5.5	0.44	6.1	0.49	0.05
Deep	1.3	0.09	1.5	0.10	0.02
Mean WML volume by lobe					
Frontal	3.1	0.28	3.6	0.30	0.01
Occipital	0.7	0.03	0.7	0.04	0.48
Parietal	1.4	0.13	1.5	0.14	0.12
Temporal	1.6	0.13	1.7	0.14	0.25

SE: Standard Error

*Lifetime major depression episode measured by the Mini-International Neuropsychiatric Interview (MINI) or use of antidepressive medication

‡Analysis of covariance adjusting for sex, age, hypertension, history of cardiovascular disease, alcohol and tobacco consumption, physical impaiment and brain white matter volume

Table 3: Longitudinal relationship between lifetime major depression at baseline and evolution of White Matter Lesions volume during the 4-year follow-up

	Lifetime major depression *				
	No		Yes		P‡
	Mean	SE	Mean	SE	
N	(n=1046; 86.2%)		(n=168; 13.8%)		
WML volume progression	1.5	0.31	2.1	0.35	0.004
WML volume progression by type					
Periventricular	1.2	0.28	1.7	0.31	0.008
Deep	0.02	0.07	0.1	0.08	0.01
WML volume progression by lobe					
Frontal	0.6	0.17	0.8	0.19	0.02
Occipital	0.05	0.04	0.1	0.05	0.02
Parietal	0.3	0.10	0.4	0.11	0.06
Temporal	0.6	0.16	0.7	0.17	0.15

WML = White matter Lesions
SE: Standard Error
* Lifetime major depression episode measured by the Mini-International Neuropsychiatric Interview (MINI) or use of antidepressive medication
‡ Analysis of covariance adjusting for sex, age, hypertension, history of cardiovascular disease, alcohol and tobacco consumptions, delay between MRI examination, WML volume at baseline, physical impairment and brain white matter volume

Table 4: Relation between baseline White Matter Lesion (WML) volume and the risk of incident depression* in subjects with no depression† at baseline (n=956)

WML volume percentile	N	OR (95% CI) ‡
< 25th	242	1
25th - 50th	251	1.2 (0.6-2.3)
50th - 75th	237	1.5 (0.8-2.9)
≥ 75th	226	2.4 (1.3-4.6)

* defined as high depressive symptomatology or antidepressive intake

† i.e. no antidepressant, no high depressive symptomatology and no MDE at baseline

‡ Adjusted for sex, age, hypertension, history of cardiovascular disease, alcohol and tobacco consumptions, baseline CESD score, physical impairment and brain white matter volume