ORIGINAL ARTICLE

Cerebral White Matter Lesions and Depressive Symptoms in Elderly Adults

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Background: There is evidence for a vascular cause of late-life depression. Cerebral white matter lesions are thought to represent vascular abnormalities. White matter lesions have been related to affective disorders and a history of late-onset depression in psychiatric patients. Their relation with mood disturbances in the general population is not known. We investigated the relation between white matter lesions and the presence of depressive symptoms or a history of depression in a population-based study.

Methods: In a sample of 1077 nondemented elderly adults, we assessed the presence and severity of subcortical and periventricular white matter lesions using magnetic resonance imaging, presence of depressive symptoms, and history of depression. Using multiple regression analysis, we examined the relation among white matter lesions, depressive symptoms, and history of depression.

Results: Most of the subjects had white matter lesions. Persons with severe white matter lesions (upper quintile) were 3 to 5 times more likely to have depressive symptoms as compared with persons with only mild or no white matter lesions (lowest quintile) (periventricular odds ratio [OR] = 3.3; 95% confidence interval [CI], 1.2-9.5; subcortical OR = 5.4; 95% CI, 1.8-16.5). In addition, persons with severe subcortical but not periventricular white matter lesions were more likely to have had a history of depression with an onset after age 60 years (OR = 3.4; 95% CI, 1.1-10.7) compared with persons with only mild or no white matter lesions.

Conclusion: The severity of subcortical white matter lesions is related to the presence of depressive symptoms and to a history of late-onset depression.

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FOR THE majority of persons with a depression syndrome the age of onset is in the late 20s, but it is also common to have an onset after age 40 years.[1,2] Between 1% and 2% of elderly persons suffer from a major depression.[3] When a first depressive episode occurs in late life, a different cause is suggested as compared with a younger age of onset.[4] It has been suggested that a cerebrovascular component is probably more important to the cause of late-life depression than genetic or psychological factors.[5-8] Interest in cerebrovascular disease as a risk factor for depression has grown in the past 5 years, and associations between factors such as hypertension and transient ischemic attacks with depression have been reported.[9] Cerebral white matter lesions (WMLs) are thought to result from cerebrovascular brain damage.[10] Within the clinical setting, severity of WML has been related with the presence of depression[11-13] and with poor outcome of depression.[14] Furthermore, when studying persons with a late-life depression, an increased severity of WMLs has been associated with a later age of onset.[5,11,15,16] Although these clinical studies provide clues to the relation between WMLs and depression, they have limitations because of the highly selected study population.

The aim of our study was to investigate whether cerebral WMLs are associated with the presence of depressive symptoms in elderly persons. Furthermore, we investigated whether a history of depression is associated with the severity of WMLs and whether this relation is the same for depressive episodes that started early in life and those that started in late life. The study was conducted among 1077 Dutch persons aged 60 to 90 years.

RESULTS

DEPRESSIVE SYMPTOMS AND WHITE MATTER LESIONS

Characteristics of the 1077 participants of the Rotterdam Scan Study are given in

SUBJECTS AND METHODS

SUBJECTS

Participants of the Rotterdam Scan Study were recruited from 2 large ongoing cohort studies: the Rotterdam Study and the Zoetermeer Study. Both studies have been described in detail elsewhere.[17,18] In short, the Rotterdam Study is a population-based prospective cohort study among 7983 elderly persons, in which all inhabitants of a Rotterdam, the Netherlands, suburb who were older than 55 years were invited to participate. The study had its baseline in 1990 and was designed to study determinants of neurologic, cardiovascular, endocrinologic, and ophthalmologic diseases in elderly adults. The Zoetermeer study is a population-based prospective cohort study among 10 361 persons aged 5 to 91 years at the baseline year (1975) that was originally concerned with prevalence of various chronic diseases.

We invited 1904 subjects aged between 60 and 90 years who were randomly selected in strata of age (5-year strata), sex, and study from a larger pool of subjects in the appropriate age groups from the 2 primary studies. Of these 1904 individuals, 1717 subjects were eligible. Details concerning the Rotterdam Scan Study have been published previously.[19,20] Briefly, 1904 randomly selected subjects were invited by letter and subsequently contacted by telephone. On agreement of participation, a list of contraindications (dementia, contraindications for magnetic resonance imaging [MRI] scanning, blindness) was reviewed to assess eligibility. Dementia assessment was done by an initial screening of cognitive functions (using the Mini-Mental State Examination [MMSE[21]] and the Geriatric Mental Schedule, organic section).[21] Those who scored below the cut-off of 26 on the MMSE or above 0 on the Geriatric Mental Schedule were further evaluated by more extensive neuropsychological tests, and, if indicated, informant interview and review of medical records. Among the eligible participants, 1077 (63%; 563 from the Rotterdam Study, 514 from the Zoetermeer Study) agreed to have an MRI brain scan and were included in these analyses. Responders differed from nonresponders in that they were younger, more educated (5% more subjects had a university-level education, $P=.05$), and had higher baseline MMSE scores (age and sex-adjusted mean difference, 0.4 points, $P < .001$), but equal cholesterol levels, body mass indexes, and blood pressure measurements.[21] The medical ethics committee of the Erasmus University, Rotterdam, approved the protocol, and each participant signed an informed consent form.

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging scanning was performed on a 1.5-T MR VISION System (Siemens, Erlangen, Germany) for subjects from the Rotterdam Study or a 1.5-T MR Gyroscan system (Philips, Best, the Netherlands) for subjects from the Zoetermeer study. The scanning protocol included a series of axial T1-weighted, T2-weighted, and proton-density–weighted images. Details of the scanning protocol have been published previously.[20] To cover the whole brain, sections were 5-mm or 6-mm thick (scanner dependent) with an interslice gap of 20%. The images were printed with a reduction factor of 2.7.

WHITE MATTER LESIONS RATING SCALE

Periventricular and subcortical WMLs were considered present if visible as hyperintense on both proton-density– and T2-weighted images, and not hypointense on T1-weighted images. Details on the scoring method that was used have been described previously.[19,20] Briefly, when the largest diameter of the WML was adjacent to the ventricle, it was defined as periventricular; otherwise, as subcortical. Periventricular WMLs were scored semiquantitatively for 3 separate regions (adjacent to the frontal horns, the lateral walls, and the occipital horns) on a scale ranging from 0 (none) to 3 (large confluent). The total periventricular WML score was the added total of the region-specific scores (score range, 0-9). Subcortical WMLs were counted in 3 categories of size based on their maximal diameter (as appearing on hardcopy): small (< 3 mm), medium (3-10 mm), or large (> 10 mm). Considering them spherical with a fixed diameter, we approximated a total volume score for subcortical WML (score range, 0-29.5).

Other recorded brain features were cerebral atrophy and the presence and number of strokes. Subcortical atrophy was

Table 1. Compared with people without any WMLs, people with WMLs had higher CES-D scores and more often had depressive symptoms (Table 1). When severity of WML was expressed in quintiles, the mean CES-D score of the upper quintile (adjusted for age, sex, and educational level) was higher compared with the lowest quintile (difference in CES-D score, 1.5 [$F_5=5.1$, $P=.03$] for periventricular WML and 1.6 [$F_5=6.8$, $P=.01$] for subcortical WML). There was a linear relation between quintiles of WML severity and mean CES-D scores (age-, sex-, and educational level–adjusted trends: periventricular WML *P*trend=.03; subcortical WML *P*trend=.02). Additionally, when subjects had more severe WMLs, depressive symptoms were more often present (**Figure 1**). In the lowest quintile of WML, only 2% to 3% of all persons met the criteria for depressive symptoms, while in the other quintiles this varied between 7% and 12%. Even when adjusted for the person's cognitive function, severity of cerebral atrophy, and possible presence of stroke, persons with more severe WML were up to 5 times as likely to have depressive symptoms compared with those subjects with only mild WML (**Table 2**). The strength of these associations slightly diminished when subcortical WMLs were studied conditionally on the severity of periventricular WMLs and vice versa (Table 2).

HISTORY OF DEPRESSION AND WHITE MATTER LESIONS

Among persons who reported a previous depression, WML severity was linearly associated with age of onset (for a per-unit increase in periventricular WML severity, the age of onset was 1.3 years later [$P=.02$]; for per-volume unit increase in subcortical WML, age of onset was 1.0 years later [$P=.02$]). More severe WMLs were found in subjects who had had an onset of depression

measured by the ventricle-to-brain ratio (ratio range, 0.21-0.45).[20] Cortical atrophy was rated semiquantitatively (range, 0-15).[20] A stroke was defined as hyperintense on proton-density– and T2-weighted images, while hypointense on T1-weighted images.

Intrareader and interreader studies showed a good to excellent agreement. Weighted κ statistics for periventricular WML severity grades were between 0.79 and 0.90, and for the total cortical atrophy score, the κ statistic was 0.81. Interreader and intrareader-intraclass correlation coefficients for subcortical WML volume scores were 0.88 and 0.95, and for subcortical atrophy, 0.57 and 0.76.

Of all subjects, only 54 (5.0%) had no WMLs at both periventricular and subcortical locations, 217 subjects (20%) were without any sign of periventricular WMLs, and 81 subjects (7.5%) were without any subcortical WMLs.

DEPRESSIVE SYMPTOMS AND HISTORY OF DEPRESSION

Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D).[22] Depressive symptoms were defined as present when the subject scored at or above 16 points on the CES-D.[22] The CES-D questionnaire was completed by 1068 individuals. Subjects who used antidepressant medication and scored below 16 points on the CES-D (n=12) were omitted from the analyses for current depressive symptoms.

All participants were asked for their history of depressive episodes. To obtain more specificity, we carefully excluded normal reactions to stressful events and normal grief. If depressive episodes had occurred, the subjects were asked for the age of onset and whether the episodes had prompted them to seek medical advice. We defined "depression" as those depressive episodes that had required attention of a general practitioner, psychologist, or psychiatrist. This definition includes minor depression as defined by the Research Diagnostic Criteria,[23,24] as well as more severe depression syndromes such as major depression or bipolar depression. We dichotomized the age of onset at the cut-off point of 60 years.[4,15]

Of the 262 persons who reported previous depressive episodes, 193 met our criteria for depression, and of these, 185 remembered the age of onset. Only these latter persons were included in the analyses as having had a depression. As expected, at the time of the interview, persons who reported an onset beyond age 60 were older (mean age, 75.5 years; range, 61.6-89.7 years) than persons who reported an earlier onset (mean age, 68.5 years; range, 59.0-87.1 years).

STATISTICAL ANALYSIS

All analyses were adjusted for age (at the time of MRI), sex, educational level (according to the United Nations Educational, Scientific, and Cultural Organization),[25] and type of MRI scanner. An α level of 5% was used (2-sided). Demographic characteristics and depression variables were compared between persons with and without any WML location using analysis of covariance (ANCOVA). Next, to allow for a nonlinear relation between WML severity and depression variables, we analyzed this relation in scanner-specific quintiles of the WML-severity distribution, also with ANCOVA. A linear relation between severity of WML and age of onset of depression (in years) was analyzed using regression analyses, additionally adjusting for age-square. To quantify the relation between depression variables and severity of WML, risks were calculated (as estimated by the odds ratio [OR]) using logistic regression with the lowest quintile of WML severity as the reference category. For the logistic analysis of the relation between severity of WML and history of depression, the people who had never had depressive episodes were used as the control group. Trend analyses were used to study whether the relations between severity quintiles of WML and history of depression and current depressive symptoms and mean CES-D scores were linear.

Because cognitive impairment, cerebral atrophy, and a history of stroke have been related to WML as well as measures for depression,[26,27] we adjusted for these possible confounders in additional analyses. As periventricular WML and subcortical WML severity were correlated (Spearman rank correlation=0.7, $P<.01$), we additionally analyzed the relations between depression variables and the severity of periventricular WML conditional on the severity of subcortical WML and vice versa by entering both variables simultaneously in the multivariate model. This allows assessment of the independent effects of lesions at these 2 distinct locations on the depression variables.

after age 60 years than in persons who had had an onset before age 60 years, while there was no difference in WML severity between this latter group and persons who had never had depressive episodes (**Figure 2**).

Table 3 illustrates that overall, persons with more severe WMLs did not report more previous depressions. However, when analyzed in strata of age of onset of depression, severity of WMLs was associated with a history of depression with an onset after, but not before age 60 years (>60 years, $P_{trend}=.05$ for subcortical WMLs; $P_{trend}=.13$ for periventricular WMLs; <60 years, $P_{trend}>.70$ for both subcortical and periventricular WMLs). These relations were found to be independent of the person's age, sex, educational level, cognitive function, severity of cerebral atrophy, and possible presence of stroke. The last column of Table 3 illustrates that these associations with subcortical WMLs were independent of the severity of periventricular WMLs, while this was not observed vice versa.

COMMENT

This study relates structural brain alterations of the white matter with indicators of current depression and history of depression. The greatest strength of this study is that it is population-based and includes a large sample of elderly persons to assess the relation between WMLs and depression. We report a significant association between severity of WMLs and the presence of depressive symptoms and history of late-onset depression.

There are some methodological issues that need to be discussed. First there is the possibility of selection bias. Participants of our study were younger than the nonparticipants. Because older age is an established risk factor for the presence and severity of WMLs, people with the most severe WMLs were probably underrepresented in our study. Likewise, persons with current mood distur-

Table 1. Characteristics of Participants Without Any White Matter Lesions and of Participants With Periventricular and/or Subcortical White Matter Lesions*

Characteristic	White Matter Lesions: Absent (n = 54)	White Matter Lesions: Present (n = 1023)	F (*df*)†	*P*†
Mean (SD) age, y	66.8 (4.9)	72.5 (7.4)	31.5 (4)	<.001
Sex (M/F)	22/32	500/523	2.2 (4)	.14
Primary education only	13 (24.1)	350 (34.2)	1.1 (4)	.31
Median score on the MMSE (range)	29 (24-30)	28 (19-30)	0.4 (6)	.51
Presence of cerebral infarcts	4 (7.4)	132 (12.9)	0.1 (5)	.79
Median cortical atrophy grade (range)	0.8 (0.0-2.4)	1.0 (0.0-3.0)	1.7 (5)	.19
Mean (SD) ventricle-brain ratio	0.30 (0.03)	0.32 (0.04)	3.1 (5)	.08
Depression variables				
Mean CES-D score (range)	3.8 (0-14)	5.9 (0-36)	5.8 (5)	.02
Subjects with CES-D scores ≥16	0 (0.0)	79 (7.7)	4.2 (5)	.04
Use of antidepressant medication	1 (1.9)	19 (1.9)	0.0 (5)	.84
History of depression‡	13 (24.1)	180 (17.6)	0.1 (5)	.72
Subject with onsets at <60 y	13 (24.1)	119 (11.6)	1.6 (5)	.21
Subjects with onsets at ≥60 y	0 (0.0)	53 (5.2)	1.7 (5)	.19

*Values are presented as number (percentage) of participants unless otherwise indicated. MMSE indicates Mini-Mental State Examination; CES-D, Center of Epidemiologic Studies Depression Scale.

†Analyses of covariance are adjusted for age, sex, level of education, and type of magnetic resonance scanner used, where appropriate.

‡History of depression is defined as depressive episodes prompting medical attention.

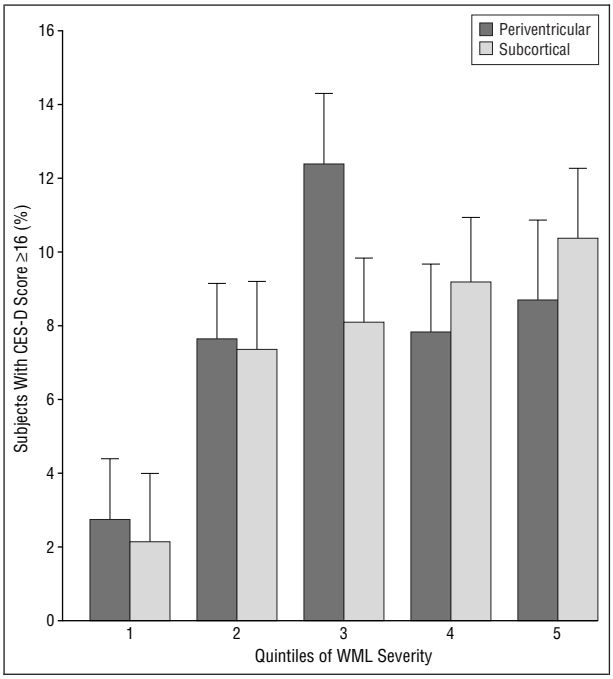

Figure 1. *Presence of depressive symptoms (defined as a Center of Epidemiologic Studies Depression Scale [CES-D] score of ≥ 16) per white matter lesion (WML) severity quintile adjusted for age, sex, and level of education. Total N=1077.*

Table 2. Relation Between Severity of White Matter Lesions (in Quintiles) and Presence of Depressive Symptoms Expressed as Odds Ratios

Location of White Matter Lesions	Quintile	No. of Subjects	OR (95% CI): Model 1	OR (95% CI): Model 2
Subcortical	1st	214	1.0 (Reference)	1.0 (Reference)
	2nd	208	3.9 (1.3-12.1)	3.2 (1.0-9.9)
	3rd	212	4.5 (1.5-13.6)	3.2 (1.0-10.1)
	4th	209	5.0 (1.6-15.1)	3.5 (1.1-11.3)
	5th	209	5.4 (1.8-16.5)	4.5 (1.3-15.8)
Periventricular	1st	251	1.0 (Reference)	1.0 (Reference)
	2nd	279	3.4 (1.3-8.6)	2.6 (1.0-6.8)
	3rd	164	5.7 (2.2-14.8)	3.7 (1.4-10.3)
	4th	201	3.3 (1.2-8.9)	1.9 (0.7-5.8)
	5th	157	3.3 (1.2-9.5)	1.7 (0.5-5.8)

*Odds ratios (OR) and confidence intervals (CI) are adjusted for age, sex, level of education, Mini-Mental State Examination score, presence of stroke, and severity of cerebral atrophy.

†OR and CI were adjusted as in model 1, but were conditional on the severity of either periventricular or subcortical white matter lesions, as applicable.

bances may have been underrepresented.[28] In our sample, the mean score on the CES-D and the percentage of persons who scored at or above the cut-off were lower than those values found by others.[29,30] Although we cannot exclude that the relation between WMLs and depression was different among nonparticipants, we consider this unlikely. If this relation would be the same within nonparticipants, then the probable underrepresentation of both those with the most severely affected brains and depressed individuals may have resulted in underestimating the strength of the association between WMLs and depressive symptoms.

A second issue to consider is our case finding. We used the cut-off of 16 points on the CES-D[31] to define the presence of depressive symptoms. A previous study in an elderly Dutch population that used the same cut-off point reported a sensitivity of 100% and a specificity of 88% for major depression, and a positive predictive value of 13.2% for diagnosis of a *DSM-III* affective disorder.[30] Affective disorders, according to *DSM-III*, are frequently diagnosed among elderly persons. Yet they comprise only the tip of the iceberg of all people with depressed mood.[7] For the definition of a history of depression we used answers from a standardized questionnaire. We ascertained the severity of the reported depressive episodes by carefully attempting to rule out normal reactions to stressful events and by adding to the definition the item of an individual's having consulted a physician. The definition that we used includes the criteria of a minor depression as defined by the Research Diagnostic Criteria,[24] and may include more severe depression. Because the questionnaire is retrospective, it is possible that recall bias has occurred. It may be that subjects with the most severe WMLs more easily forget depressive episodes because of coexisting cognitive problems. This bias, however, would lead to underreporting of depressive episodes, especially in people with the more severe WMLs, and as such an underestimation of the relation between

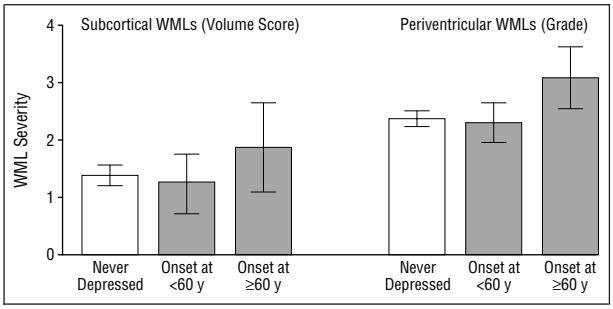

Figure 2. *Severity of white matter lesions (WMLs) in persons without depressive episodes (n=815) and in persons with a history of depression according to age at onset (<60 years [n=132] and ≥60 years [n=53]). Means have been adjusted for age, sex, level of education, and type of magnetic resonance imaging scanner used (95% confidence intervals).*

Table 3. Severity of White Matter Lesions (WMLs) and the Relation With a Positive History of Depression and With Its Age of Onset*

	Positive History of Depression†			
Quintile	Total (n = 185)	Onset <60y (n = 132)	Onset ≥60y (n = 53)	Onset ≥60y‡ (n = 53)
Subcortical WMLs				
1	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
2	1.6 (0.9-2.6)	1.5 (0.9-2.7)	1.9 (0.5-6.7)	1.9 (0.5-7.1)
3	1.4 (0.8-2.3)	1.1 (0.6-2.1)	3.0 (1.0-9.6)	3.3 (0.9-11.5)
4	1.2 (0.7-2.0)	1.0 (0.5-1.9)	2.3 (0.7-7.6)	2.3 (0.6-9.1)
5	1.4 (0.8-2.5)	1.1 (0.5-2.1)	3.4 (1.1-10.7)	3.5 (0.8-14.4)
Periventricular WMLs				
1	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
2	0.8 (0.5-1.3)	0.8 (0.5-1.3)	1.1 (0.4-3.1)	0.8 (0.3-2.4)
3	1.3 (0.7-2.1)	1.1 (0.6-2.0)	2.0 (0.7-5.7)	1.4 (0.4-4.2)
4	1.2 (0.7-2.0)	1.2 (0.6-2.1)	1.5 (0.5-4.3)	0.9 (0.3-3.0)
5	0.9 (0.5-1.6)	0.5 (0.2-1.2)	1.8 (0.6-5.1)	0.9 (0.2-3.5)

**Values are presented as odds ratios (95% confidence intervals) adjusted for age, sex and level of education, Mini-Mental State Examination score, severity of cerebral atrophy, and possible presence of stroke.*

†The group without a history of depressive episodes (n = 815) was used as the control group.

‡Results were conditional on the severity of either periventricular or subcortical WMLs, as applicable.

WML and depressive episodes. Another problem with retrospective questionnaires is that people are more likely to remember the more severe depressive episodes. This would only aid in differentiating between clinically relevant depressive episodes and adequate reactions to grief or anxiety.

We found presence as well as severity of WMLs to be related to the presence of depressive symptoms. This relation was found for subcortical as well as for periventricular WMLs, although more strongly for subcortical WMLs. In this general population, WMLs were related with a history of late onset, but not with early onset of depression, as has been reported in a patient series.[32] When we made the distinction between subcortical and periventricular WMLs we found only subcortical WMLs to be related to a history of late-onset depression, which is also in line with reports from some patient series.[4,11,15,27,33]

One interpretation of our results could be that depressive symptoms are a psychological reaction to declining cognitive function because of WMLs. However, we found the relation to be independent of cognitive status. Another possible explanation is that other cerebral characteristics, correlated to the presence of WMLs, are responsible for the observed association between WMLs and depression. Ventricular enlargement, presence of stroke, and cortical atrophy have been related to mood disturbances.[27] However, the relation found between WML severity and depressive symptoms did not change when we controlled for these possible confounders. We found that subcortical WMLs especially related with indicators of depression. Subcortical pathways, in particular intact corticostriatal connections, are important for the expression of normal mood and motivation,[34,35] making it biologically plausible that subcortical WML, by interrupting these connections, can cause mood alterations. An alternative hypothesis for the association between WMLs and depression would be that it is not the cerebrovascular pathology that leads to the depression, but rather that those subjects who are prone to depression have an increased risk of vascular disease.[36] If this would be the case, we would have expected a more prominent association with early-onset depression than with late-onset depression, making this explanation less likely.[11] Finally, we studied the relation between WMLs and depression within an elderly adult population, which implies that we cannot extrapolate our findings to younger age groups.

In summary, this population-based study of a random sample of elderly subjects demonstrated an increasing risk for depressive symptoms with increasing severity of WMLs. In addition, we found a relation between a history of late-onset depression and severity of mainly subcortical WMLs. These findings can have implications for clinical practice. The presence of depressive symptoms in an elderly individual should prompt physical examination and possibly electrocardiogram monitoring and neuroimaging to search for cerebrovascular risk factors as possible causes for these symptoms. Another implication regards the possible prevention of late-life major depression. Since WMLs are thought to have a mainly cerebrovascular cause,[19,37,38] recognizing this high-risk group may provide an opportunity to prevent depressive symptoms from evolving into a major depressive disorder.[1,29,39]

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