

# White Matter Hyperintensity Progression and Late-Life Depression Outcomes

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**Context:** White matter hyperintensities (WMHs) are bright foci seen in the parenchyma of the brain on T2-weighted cranial magnetic resonance imaging (MRI) scans and are associated with geriatric depression. Because they are associated with age, they should increase in number and size over time. To our knowledge, this is the first longitudinal, volumetric MRI study of WMHs in depression.

**Objective:** To determine if WMH progression over 2 years influences depression outcomes.

**Design:** Over 2 years, depressed subjects received antidepressant treatment according to a naturalistic somatic treatment algorithm designed to offer the best possible treatment to the individual. After the treatment period, depressed subjects were dichotomized based on whether they had reached and sustained remission during this period.

**Participants:** One hundred thirty-three subjects aged 60 years or older meeting DSM-IV criteria for major depressive disorder.

**Measures:** Cranial MRI was obtained at baseline and approximately 2 years later. White matter hyperinten-

sity volume was measured in each hemisphere using a semiautomated segmentation process.

**Outcomes:** Subjects were dichotomized based on achieving or not achieving remission of depressive symptoms, defined as a Montgomery-Åsberg Depression Rating Scale score of 8 or less.

**Results:** The depressed subgroup that achieved and sustained remission had significantly less increases in WMH volume (11.5%) than did the group that did not achieve or sustain remission (31.6%) ( $P=.01$ ). In a regression model, greater change in WMH volume was significantly associated with failure to sustain remission ( $P=.004$ ) even when controlling for baseline depression severity, medical illness severity, age, sex, and race. Education was associated with achieving and sustaining remission ( $P=.02$ ).

**Conclusions:** Greater progression of WMH volume is associated with poor outcomes in geriatric depression. Future work is needed to develop means of slowing the rate of WMH progression and to determine whether this will lead to improved depression outcomes in elderly persons.

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**W**HITE MATTER hyperintensities (WMHs) are bright regions seen in the brain parenchyma on T2-weighted magnetic resonance imaging (MRI) scans. These hyperintense lesions are more common in depressed elderly persons than in age-matched control subjects.<sup>1-10</sup> These lesions are thought to represent injury to white matter tracts and may contribute to the pathogenesis of geriatric depression if they affect the white matter tracts of the neural circuits involved in mood regulation. Studies of small populations have suggested that increased WMH severity is associated with new onset of depression,<sup>11,12</sup> a more

chronic course of depression,<sup>13</sup> and poorer response to short-term antidepressant treatment.<sup>14,15</sup> Autopsy studies have demonstrated that, in depressed elderly persons, these lesions are the result of ischemia.<sup>16</sup> This work has resulted in the "vascular depression" hypothesis of late-life depression,<sup>1,17,18</sup> which postulates that late-life depression in some individuals is mediated through cerebrovascular changes. Despite this work, to our knowledge the relationship between WMH progression over time and depression outcomes has not been systematically studied in larger populations.

In addition to being associated with depression, WMHs are also associated with increased age<sup>19-22</sup> and medical comorbid-

ity.<sup>19,23-25</sup> The few longitudinal studies available use visual rating scales and show that WMH severity seems to worsen over time.<sup>26-29</sup> This increase in WMH disease is associated with hypertension,<sup>26-28</sup> and pharmacological control of hypertension may reduce disease progression.<sup>26</sup> Cross-sectional studies also show greater WMH severity in subjects with uncontrolled hypertension compared with subjects with controlled hypertension or those who are normotensive.<sup>30,31</sup>

Supporting the theory that WMHs represent injury to the brain parenchyma and resultant disruption of neural circuitry, WMHs are associated also with additional neuropsychiatric deficits other than mood dysregulation. Increasing severity of WMH disease is associated with motor difficulties, particularly gait and balance.<sup>32</sup> Greater WMH disease is also associated with impairment in a variety of cognitive domains,<sup>14,19,33-35</sup> although longitudinal studies have not always found similar relationships between cognition and progression of WMHs.<sup>27,29</sup> As greater WMH disease is associated with mood, cognitive, and motor disturbances, it is important to understand how WMH severity changes over time.

We report the results of what is, to our knowledge, the first longitudinal, volumetric MRI study of WMHs in late-life depression. We correlated changes in WMH volume over a 2-year period with outcomes in depressed elderly subjects. We examined the hypothesis that depressed subjects with greater increases in WMH volume would have poorer depression outcomes as manifested by symptom relapse or failure to achieve symptom remission despite aggressive antidepressant treatment.

## METHODS

### SAMPLE

All subjects were participants in the National Institute of Mental Health–sponsored Conte Center for the Neuroscience of Depression at Duke University Medical Center, Durham, NC. Participation was restricted to subjects aged 60 years or older who had a diagnosis of major depressive disorder and a Center for Epidemiologic Studies–Depression Scale<sup>36</sup> score of 16 or less. Exclusion criteria included the following: (1) other major psychiatric illnesses, although comorbid anxiety disorders were allowed if the clinician felt them to be secondary to depression; (2) history of alcohol or other drug abuse or dependence; (3) primary neurologic illnesses, including clinically apparent stroke and dementia; (4) medical illnesses impairing cognitive function, such as untreated hypothyroidism; (5) physical disability precluding cognitive testing; and (6) the presence of a metal implant in the body that precludes MRI.

This study was approved by the Duke University Medical Center institutional review board. After an explanation of the study's purpose and procedures, those who provided written informed consent were enrolled in the study. Subjects were followed up in this intent-to-treat study for 2 years or until withdrawal.

### BASELINE COGNITIVE SCREEN

Subjects were excluded if they had a diagnosis of dementia or if a study geriatric psychiatrist suspected dementia at baseline. Most subjects had Mini-Mental State Examination<sup>37</sup> scores above 24; some severely depressed individuals had scores below 25.

These subjects were followed up through a short-term, 12-week treatment phase; if the scores remained below 25, they were excluded from this study.

## CLINICAL ASSESSMENT PROCEDURES

At baseline, a study geriatric psychiatrist administered a standardized clinical assessment including the Montgomery-Åsberg Depression Rating Scale (MADRS)<sup>38</sup> and the Clinical Global Impression scale.<sup>39</sup> Cognitive status was measured with the Mini-Mental State Examination. The MADRS was repeated every 3 months to monitor treatment response. Other independent variables included age at study enrollment, sex, race, and educational level. Current medications and doses were reviewed. Medical illness was measured by the Cumulative Illness Rating Scale (CIRS),<sup>40</sup> modified for geriatric populations,<sup>41</sup> a clinician-rated assessment of medical illness severity. Subjects additionally completed a self-report questionnaire that asked about the presence or absence of several medical conditions, including diabetes mellitus, heart trouble, and hypertension. These data were self-reported and were developed from questions included in the National Institute of Mental Health Epidemiological Catchment Area program.<sup>42</sup> The term "heart trouble" represents signs and symptoms of cardiac disease, typically heart failure or coronary artery disease. Brain MRI was performed at baseline and after approximately 2 years (mean [SD] time between scans, 716 [79.1] days; minimum time, 600 days; maximum time, 938 days).

## ANTIDEPRESSANT THERAPY

Subjects were treated according to a treatment algorithm, the Duke Somatic Treatment Algorithm for Geriatric Depression approach.<sup>43</sup> This algorithm mimics "real-world" treatment options rather than a more rigid clinical trial design by accounting for past treatments and current severity. Subjects who were never treated are initially prescribed a selective serotonin reuptake inhibitor. If adequate doses of the selective serotonin reuptake inhibitor do not bring sufficient response after 8 to 12 weeks, the recommendation is to switch the treatment to venlafaxine or to augment it with bupropion. Options after a continued, inadequate treatment response include tricyclic antidepressants and lithium carbonate augmentation. At each stage doses are increased as tolerated or required to the maximum approved dose. Electroconvulsive therapy is a treatment option at each algorithm level, dependent on the severity of the subject's depression, the number of failed trials, and the preference of the subject. Subjects were not routinely referred for psychotherapy, although some were already engaged in ongoing psychotherapy at study enrollment while others were referred for individual and/or group psychotherapy, usually cognitive-behavioral psychotherapy.

Study investigators monitored treatment to ensure that the clinical protocol was being followed. Subjects were evaluated every 3 months and more frequently if clinically indicated.

Concurrent medication use was also closely monitored by the treating clinicians. For this study, we considered agents that could affect vascular risk factors, such as antihypertensive, antiplatelet (including aspirin), and antilipid agents.

## DEFINITION OF TREATMENT RESPONSE

Depressed subjects were divided into 3 groups based on response during the 2-year treatment period. All determinations were made using longitudinal MADRS scores, which were obtained at baseline and every 3 months. Subjects were classified as being "remitted" if their MADRS score decreased and remained below a score of 8 throughout the study period. They

were classified as “relapsed” if their MADRS score dropped below 8 but subsequently rose above 10; for this study’s purpose they stayed in the “relapsed” category even if they later again dropped below a score of 8. Subjects were classified as “unremitted” if they persistently exhibited MADRS scores of 8 or higher. If subjects withdrew prior to reaching the 2-year mark, determination of treatment response was based on available data.

To simplify the analyses and increase power in the various groups, we combined the unremitted and relapsed depressed subjects into a “poor outcome” group. Remitted subjects were included in the “good outcome” group. We based this decision on the following 2 factors: (1) clinically, the group that was unremitted or relapsed had a poorer outcome than those who did remit, and (2) there were no statistically significant differences in the demographic or MRI variables between those who did not remit and those who relapsed (data not shown).

## MRI VARIABLES

### MRI Acquisition

Magnetic resonance imaging for this study was performed on 2 scanners, both with magnetic field strength of 1.5 T and both from the same manufacturer (GE Signa; GE Medical Systems, Milwaukee, Wis). One system was an echo-speed version and the other was an NV/i system. Scanning was performed on the echo-speed system until August 1, 2001, and then was transferred to the NV/i system. The radiofrequency coil was of identical design and coverage, but the gradient systems were of slightly different performance characteristics. The echo-speed system had a maximum strength of 23 mT/m, a slew rate of 120 T/m per second, and a 60-cm bore diameter. The NV/i system has a maximum strength of 40 mT/m, a slew rate of 150 T/m per second, and a 55-cm bore diameter. The nominal maximum field of view is 48 cm on both systems. Geometry phantoms were scanned monthly on both systems to ensure that the gradient calibration factors were consistent for the 2 systems. The calibration factors were observed to change no more than 2% in any one axis over the length of the study. Volumes derived from imaging data were corrected by multiplying volumes by a suitable correction factor determined by the volume of the geometry phantom that was acquired closest to the time of a given scan.

All subjects were screened for the presence of cardiac pacemakers, neurostimulators, metallic implants, metal in the orbit, aneurysm clips, or any other condition in which MRI was contraindicated. Padding was used to immobilize the head without causing discomfort. The scanner alignment light was used to adjust the head tilt and rotation so that the axial plane lights passed across the canthomeatal line and the sagittal lights were aligned with the center of the nose. A rapid sagittal localizer scan was acquired to confirm the alignment.

A dual-echo fast spin-echo acquisition was obtained in the axial plane for morphometry. The pulse sequence parameters were as follows: repetition time, 4000 milliseconds; echo times, 30 milliseconds and 135 milliseconds, 32 (16)-kHz (mean [SD]) full-imaging bandwidth; echo train length, 16 milliseconds; a 256 × 256-pixel matrix; 3-mm section thickness; 1 excitation; and a 20-cm field of view. The images were acquired in 2 separate acquisitions with a 3-mm slice gap between sections for each acquisition. The second acquisition was offset by 3 mm from the first so that the resulting data set consisted of contiguous sections.

### MRI Processing

Images were processed at the Duke Neuropsychiatric Imaging Research Laboratory on SUN (Sun Microsystems Inc, Santa

Clara, Calif) workstations. Volume measurements used a Neuropsychiatric Imaging Research Laboratory–modified version of MrX software, which was created by GE Corporate Research and Development, Schenectady, NY, and originally modified by Brigham and Women’s Hospital, Boston, Mass, for image segmentation. The basic segmentation protocol was modified from a version developed by Kikinis et al<sup>44</sup> and has been previously described.<sup>45</sup> Changes to the basic procedures were required for segmenting scans of elderly subjects, and particularly for identifying WMH lesions. These changes have also been previously described.<sup>46</sup>

The WMHs were selected based on a set of explicit rules developed from neuroanatomical guidelines, consultation with a neuroradiologist (J.M.P.), and knowledge of the neuropathological condition of the lesions.<sup>46</sup> Periventricular white matter lesions were defined as regions that were contiguous with lateral ventricle and did not extend into the white matter tracts. Deep white matter lesions were located in the white matter tracts and may or may not have adjoined periventricular lesions. Both were included in measurements of WMH volume. The final step was to run a summarizing software program that calculated the WMH volume within the cerebral hemispheres.

### Training and Reliability

All technicians received extensive training by experienced volumetric analysts. Reliability was established by repeated measurements on multiple MRI scans before raters were approved to process study data. In addition, an ongoing reliability study was conducted to insure that the quality of volumetric analyses was maintained throughout the study. Thus, reliability measures included testing on both the initial and follow-up scans. Intraclass correlation coefficients for WMHs were 0.988 in the left cerebral hemisphere and 0.994 in the right cerebral hemisphere.

## ANALYTIC STRATEGY

Summary statistics were derived for demographic and clinical variables, including MRI results for the entire cohort and the 2 groups dichotomized based on treatment response. Means and SDs were reported for continuous variables and percentages for dichotomous variables. Differences in antidepressant, antihypertensive, antiplatelet, and antilipid medication use were also examined between the depressed groups. We tested for differences between groups using *t* tests for continuous variables and  $\chi^2$  tests for discrete variables. Finally, we developed a logistic regression model using depression outcome as the dependent variable, while change in WMH volume, baseline MADRS score, CIRS score, sex, race, age, and educational level were independent variables. We did not include the Mini-Mental State Examination score in this model because of our exclusion of individuals with low Mini-Mental State Examination scores.

We additionally included baseline WMH volume as an independent variable. As baseline volume contributes toward our measure for percentage change in WMH volume, there was a concern that including this variable may affect our results. For this reason, a separate model was developed without this variable.

## RESULTS

### SAMPLE CHARACTERISTICS

The study sample of 133 subjects was composed mainly of white (93%) women (64%), with a mean age of 68.58 years (**Table 1**). The cohort was highly educated, with

**Table 1. Differences in Demographics and Lesion Volumes of Dichotomized Depressed Subjects\***

Variable	Type of Depressed Subject		Total	P Value
	Unremitted/Relapsed	Remitted		
Sex, No. (%)				.43
Male	26 (33.33)	22 (40.00)	<b>48</b> (36.09)	
Female	52 (66.67)	33 (60.00)	<b>85</b> (63.91)	
Race, No. (%)				.37
White	74 (94.87)	50 (90.91)	<b>124</b> (93.23)	
Other	4 (5.13)	5 (9.09)	<b>9</b> (6.77)	
Age, y	68.40 (6.86)	68.84 (6.94)	68.58 (6.87)	.72
Educational level, y	14.39 (2.15)	13.31 (3.21)	13.94 (2.68)	.03
Baseline MADRS score	26.85 (6.78)	29.02 (8.16)	27.74 (7.43)	.10
Baseline CIRS score	3.96 (2.98)	3.76 (3.09)	3.88 (3.01)	.71
Total WMH volume (baseline)	5.93 (9.16)	8.07 (14.39)	6.82 (11.61)	.30
Total WMH volume (2nd year)	7.83 (11.91)	9.08 (15.78)	8.35 (13.60)	.61
% Change in WMH volume	31.60 (48.02)	11.53 (30.59)	23.29 (42.73)	.01
Left hemisphere WMH volume (baseline)	3.05 (4.80)	3.79 (6.47)	3.36 (5.54)	.45
Left hemisphere WMH volume (2nd year)	3.97 (6.01)	4.33 (7.43)	4.12 (6.61)	.76
% Change in left hemisphere WMH volume	31.27 (48.45)	10.33 (33.44)	22.61 (43.98)	.01
Right hemisphere WMH volume (baseline)	2.87 (4.40)	4.28 (7.97)	3.46 (6.14)	.19
Right hemisphere WMH volume (2nd year)	3.86 (5.95)	4.75 (8.45)	4.23 (7.07)	.48
% Change in right hemisphere WMH volume	33.52 (51.25)	14.25 (35.54)	22.56 (46.26)	.02

Abbreviations: CIRS, Cumulative Illness Rating Scale<sup>40</sup>; MADRS, Montgomery-Åsberg Depression Rating Scale<sup>38</sup>; WMH, white matter hyperintensity.

\*Data are given as the mean (SD) unless otherwise indicated. All WMH volumes are reported in milliliters.  $\chi^2$  Tests with 1 *df* were used to compare discrete variables. Simple *t* tests with 131 *df* were used to compare continuous variables, except for the analysis of educational level that was analyzed using a Satterthwaite *t* test with 87 *df*.

a mean educational level approaching 14 years. Fifty-five depressed subjects (41.4%) were in the good outcome group, in which they remitted and sustained remission over the study period. The initial mean (SD) MADRS score was 27.74 (7.43) (range, 16-53). Seventy-eight subjects (58.6%) were in the poor outcome group; they remitted and relapsed, or did not remit. A separate set of analyses (data not shown) found no statistically significant differences in demographics, mean WMH lesion volume, or change in WMH lesion volume between depressed subjects who relapsed and those who never remitted (the poor outcome group).

There were 69 subjects who had baseline data but did not receive a follow-up MRI scan, so they were excluded from this study. This was the only reason why subjects meeting inclusion criteria were excluded. These subjects were lost to follow-up or withdrew from the study.

Complete data for demographics, baseline clinical measures, and baseline MRI variables was available on all subjects. Ninety-eight subjects had complete MADRS scores over the study period (9 possible observations). Thirty-five subjects were missing MADRS scores; 15 were from the good outcome group, and 20 from the poor outcome group ( $P = .29$ , Fisher exact test). For those missing MADRS scores, the mean (SD) number of scores missing was 1.69 (1.05) (range, 1-5).

#### COMPARISONS BETWEEN DICHOTOMIZED GROUPS BASED ON OUTCOMES

After dichotomizing the 2 depressed groups based on outcomes, we then tested for differences (Table 1). There were no significant differences in demographics and baseline MADRS or baseline CIRS scores between the groups.

The poor outcome group had a significantly higher level of education than the good outcome group. The good outcome group had higher baseline and 2-year WMH volumes than did the poor outcome group, but this difference was not statistically significant.

There was a statistically significant difference in percent change of WMH volume among the groups, although both groups exhibited increases in WMH severity over the 2-year period (Table 1). The poor outcome group had the greatest mean percent change in total WMH severity at 31.6% (left hemisphere, 31.27%; right hemisphere, 33.52%). The good outcome group had the least mean percent change in total WMH severity at 11.5% (left hemisphere, 10.33%; right hemisphere, 14.25%). These differences were statistically significant at  $P < .05$ .

#### MEDICAL COMORBIDITY AND MEDICATION USE

There was little difference in medical comorbidity between the dichotomized groups. An analysis of the self-report of medical illnesses between the poor outcome and good outcome groups found no significant differences in the self-report of heart trouble (12 poor outcome subjects compared with 12 good outcome subjects,  $P = .36$ ), hypertension (30 poor outcome subjects compared with 25 good outcome subjects,  $P = .42$ ), or diabetes mellitus (4 poor outcome subjects compared with 5 good outcome subjects,  $P = .49$ ). The CIRS scores were also comparable (Table 1). To further explore this issue, we investigated baseline use of antihypertensive, antiplatelet (including aspirin), and antilipid agents. When comparing poor outcome subjects with good outcome subjects,



**Table 2. Logistic Regression Model Predicting Outcome Group Assignment**

Parameter	Estimate	SE	P Value	OR (95% CI)
% Change total WMH volume*	1.9405	0.6669	0.0038	6.962 (1.884-25.729)
Baseline WMH volume	0.0122	0.0170	0.4734	1.012 (0.979-1.047)
Sex	-0.2940	0.2162	0.1738	0.555 (0.238-1.296)
Race	0.3478	0.3685	0.3452	2.005 (0.473-8.501)
Age	0.0195	0.0325	0.5487	1.020 (0.957-1.087)
Educational level	-0.1883	0.0787	0.0168	0.828 (0.710-0.967)
Baseline MADRS score	0.0439	0.0275	0.1108	1.045 (0.990-1.103)
Baseline CIRS score	-0.0583	0.0666	0.3811	0.943 (0.828-1.075)

Abbreviations: CI, confidence interval; CIRS, Cumulative Illness Rating Scale<sup>40</sup>; MADRS, Montgomery-Åsberg Depression Rating Scale<sup>38</sup>; OR, odds ratio; WMH; white matter hyperintensity.

\*The total WMH volume is the combined WMH volume of the left and right hemispheres.

there was no statistically significant difference in use of antihypertensive (11 poor outcome subjects compared with 9 good outcome subject,  $P = .72$ ), antiplatelet (18 poor outcome subjects compared with 13 good outcome subjects,  $P = .62$ ), or antilipid agents (22 poor outcome subjects compared with 12 good outcome subjects,  $P = .41$ ).

As various psychotropic medications have been associated with regional brain volume changes,<sup>47-54</sup> we also examined for differences in medication use during the study period between the 2 groups. Poor outcome depressed subjects were more likely to be taking more antidepressants (mean of 2.55 compared with 1.60,  $P < .001$ ) and have a greater number of changes in their antidepressant regimen (mean of 2.78 compared with 1.42,  $P < .001$ ) over the study period than those who did remit. This group was also more likely to be treated with a selective serotonin reuptake inhibitor than the group who remitted ( $P = .02$ ). No significant differences were seen between these 2 groups in the use of tricyclic antidepressants, tricyclic antidepressants, bupropion, or venlafaxine.

### PREDICTORS OF OUTCOME

To further understand the relationship between WMH progression and depression outcomes, we designed a logistic regression model testing for factors contributing toward assignment into either depression outcome group (**Table 2**). In addition to controlling for demographic covariates such as age, sex, and educational level, we also controlled for baseline severity of depression (measured by the MADRS), medical illness severity (measured by the CIRS), and baseline WMH volume. In this model, greater change in WMH severity was associated with depression relapse or failure to remit, with an odds ratio of almost 7 for a 100% increase in WMH volume. Higher levels of education were associated with sustained remission of depression. A similar model that excluded baseline WMH volume exhibited the same associations.

The principal finding of this study is that greater WMH progression is independently associated with poorer depression outcomes over the 2-year assessment period. Previous studies have relied on visual rating scales estimating change of WMH severity. To our knowledge, this is the first study to measure change in WMH volume over time in a large group of depressed elderly persons.

In this study, the rate of WMH volume change—or percent change over 2 years—is significantly related to longitudinal outcomes of depression. In our analysis, only greater percent change in WMH volume predicted assignment into this poor outcome group. There was about a 7-fold increased risk of a poor outcome for every 100% increase in WMH volume; thus, every 1% increase in WMH volume carried with it a 7% increased risk of poor outcome. A higher educational level was associated with achieving and sustaining remission. Sex, race, age, baseline WMH volume, depression severity, and medical illness severity were not associated with outcome.

This study found that percent change in WMH volume is more associated with depression outcomes than is static WMH volume at baseline, as seen in the regression model that failed to detect an association between WMH volume and outcomes. This finding is concordant with previous reports associating greater change in WMH severity with depression onset<sup>11,12</sup> and chronicity.<sup>13</sup> This finding should be viewed in the context that the group who remitted had a greater mean WMH volume at each time point than did the group who relapsed or did not remit, although this difference was not statistically significant. This suggests that WMH volume at any time point has limited predictive value, but what may be more important is where and to what extent lesions are continuing to develop.

So how does WMH progression contribute to depression outcomes? The answer may lie in the location where these WMH are developing. There have been previous reports associating greater WMH disease in specific frontal brain regions with depression.<sup>7,16,55,56</sup> If the hypothesis is correct that WMHs that contribute to depression have their effect by disrupting connections between cortical and subcortical regions involved in mood regulation, further disruption of these circuits may result in depression relapse. Potentially, if enough connecting white matter tracts are impaired, depression may become treatment refractory. This theory deserves more consideration. If accurate, interventions designed to slow WMH progression may result in improved depression outcomes.

What causes this difference in WMH progression? Given that we found no difference in medical illness severity between the 2 groups, the pathophysiological condition behind this difference is difficult to explain. One possibility is that, while the 2 groups may have comparable illness severity, the group that remitted may be more likely to adhere to medical treatments, thus influencing their disease course. As we did not control for medical illness severity, it is possible that subjects with poorer outcomes may have had unidentified or more treatment-resistant vascular diseases. Another possibility is that all treatments for vascular risk

factors such as hypertension may not have equivalent results on WMH progression.<sup>14,19,33-35</sup>

Another possibility is that untreated depression is itself hastening disease progression. Depression is associated with greater platelet activation, which may be associated with ischemic cerebrovascular disease<sup>57,58</sup>; antidepressant treatment may reduce this activation.<sup>59</sup> Depression is also associated with impairment in negative feedback control of the hypothalamic-pituitary-adrenal axis.<sup>60</sup> This results in elevated cortisol levels during depression,<sup>61</sup> which is itself associated with increases in blood pressure, another vascular risk factor.

Our findings regarding education also merit discussion. Although the depressed subjects who achieved remission had a significantly lower level of education than did the depressed subjects who did not achieve remission or relapsed, in the final model higher levels of education improved the odds of achieving remission. This finding is consistent with studies reporting an association between treatment response and the level of education,<sup>62,63</sup> although other studies have failed to associate education with depressive symptoms in elderly subjects.<sup>64,65</sup> Our data should be viewed in the context that this is a highly educated cohort with a mean educational level of almost 14 years. Although the differences in educational level between outcome groups were significant, there may be little practical difference between the small differences in education level seen between our groups.

This study has limitations. Antidepressant treatments were not rigidly controlled, although the treatment algorithm helps assure adequate appropriate treatment for all subjects. Our analytic method did not distinguish between periventricular and deep white matter lesions, nor does it allow the determination where hyperintensities are developing over time. It also did not allow us to determine if increased WMH volumes were due to the development of lesions in new regions or the expansion of old regions. Because hyperintensity location may be the critical difference between depressed and nondepressed individuals, methods of localizing hyperintensities to specific regions should be used in future studies.

One particular weakness important to consider is the measure of medical comorbidity. We examined this question in a variety of ways, including self-report of vascular risk factors, the CIRS score, and examining medication use. We used the CIRS score in the predictive model, as it was more objective and physician rated, but it does not adequately capture more subtle distinctions that could influence hyperintensity progression, such as mean blood pressure over time. It also does not capture other potential contributing risk factors, such as cigarette use. Had these other factors been considered, it may potentially have affected our results.

Despite these limitations, this study appears to validate the "vascular depression" hypothesis of late-life depression<sup>1,17,18</sup> by showing that WMH disease progression is associated with depression outcomes. Given the aging of our population, a better understanding of this complex relationship is critical. Future research should be designed to better clarify the factors that contribute to WMH disease progression and to determine if interventions designed to slow progression result in better de-

pression outcomes. We also plan further research to better understand where lesions that contribute to the pathogenesis of depression develop. Such research will result in a greater understanding of the neural circuitry involved in mood regulation.

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