Published in final edited form as:

Int J Geriatr Psychiatry. 2017 February ; 32(2): 214–221. doi:10.1002/gps.4469.

Effects of white matter integrity and brain volumes on late life depression in the Framingham Heart Study

Wei Qiao Qiu^{1,2,3}, Jayandra J. Himali^{4,5}, Philip A. Wolf^{4,5}, D. Charles DeCarli⁷, Alexa Beiser^{4,5,6}, and Rhoda Au^{4,5}

¹Department of Psychiatry, Boston University School of Medicine, Boston, MA, USA

²Department of Pharmacology, Boston University School of Medicine, Boston, MA, USA

³Alzheimer's Disease Center, Boston University School of Medicine, Boston, MA, USA

⁴Department of Neurology, Boston University School of Medicine, Boston, MA, USA

⁵Framingham Heart Study, Boston University School of Public Health, Boston, MA, USA

⁶Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA

⁷Alzheimer's Disease Center, University of California Davis Medical Center, Sacramento, CA, USA

Abstract

Background—It is unclear whether brain white matter hyperintensities (WMHI) causes or is a result of late life depression. We used the Framingham Heart Study offspring to examine whether indices of brain aging are related to incident depression in the elderly.

Methods—The Center for Epidemiologic Studies Depression Scale (CES-D) was administered along with a brain MRI scan at baseline and was re-administered ($n = 1212$) at an average 6.6 ± 0.6 year follow-up. The outcomes (i) change in CES-D scores from baseline; (ii) depression defined as CES-D ≥ 16 ; (iii) severe depression defined as CES-D ≥ 21 ; and (iv) CES-D cutoff scores and/or on antidepressant were used.

Results—Among those who did not have depression at baseline, 9.1% ($n = 110$) developed depression, 4.0% ($n = 48$) developed severe depressive symptoms, and 11.1% ($n = 135$) were put on antidepressants. When depressive symptoms only was the outcome, we found that baseline WMHI was positively associated with change in CES-D scores and that those with an extensive WMHI at baseline had a high risk of developing severe depressive symptoms; the relationship was strengthened in the absence of cardiovascular diseases. In contrast, when depressive symptoms or taking antidepressant was the outcome, larger total cerebral brain volume and temporal lobe brain volume, but not WMHI, were negatively associated with the development of depression.

Conclusions—Brain WMHI is a probable risk factor for vascular depression in the elderly. The depression outcomes with and without antidepressant were related to different brain pathologies.

Keywords

white matter hyperintensities; brain; late life depression; longitudinal; Framingham Heart Study

Introduction

Late life depression is a clinical syndrome with several etiologies (Alexopoulos *et al.*, 1993; Lebowitz *et al.*, 1997; Ritchie *et al.*, 2000) and can be categorized into subtypes. Vascular depression is the most common subtype and is associated with vascular factors, such as cardiovascular disease (CVD), diabetes, and hypertension (Alexopoulos *et al.*, 1997; Taylor *et al.*, 2013), and presents with comorbid deficits in executive function. Other late life depression subtypes include post-stroke depression, which develops after the onset of cerebral infarct or hemorrhage (Robinson *et al.*, 1987), prodromal depression of Alzheimer's disease (AD) (Berger *et al.*, 1999; Cervilla *et al.*, 2000; Lopez *et al.*, 2003; Ritchie *et al.*, 2000; Wilson *et al.*, 2002), and early-onset depression surviving to an old age.

Although late life depression is found to be associated with different brain pathologies (Alexopoulos *et al.*, 1993), whether these brain pathologies lead to or result from a depression syndrome is largely unknown. Vascular depression is associated with cerebrovascular pathology such as white matter hyperintensities (WMHI) in the brain (Alexopoulos *et al.*, 2005). Despite that it is widely accepted that brain WMHI is an underlying pathology of vascular depression⁵, there is no published study on the longitudinal relationship between MRI-defined WMHI and the development of late life depression. Recurrent major depressive disorder is associated with hippocampal atrophy (Sheline *et al.*, 1999; Steffens *et al.*, 2000) and memory loss (Basso and Bornstein, 1999; MacQueen *et al.*, 2002; Rapp *et al.*, 2005). History of depression has also been associated with neuropathological hallmarks of AD, amyloid plaques, and neurofibrillary tangles (Rapp *et al.*, 2006).

Capitalizing on longitudinal data from the Framingham Heart Study (FHS), we examined which brain structures including WMHI are linked to the development of depressive symptoms, defined by the Center for Epidemiological Studies Depression Scale (CES-D) cutoff scores or being put on antidepressants, in a middle to older age community-based cohort. The CES-D (Radloff, 1977) has been commonly used to detect and quantify depressive symptoms in epidemiology studies (Lyness *et al.*, 1997). A cutoff point of 16 is commonly used to define depression (Boyd *et al.*, 1982). Using a CES-D cutoff score of 21, sensitivity of 92%, and specificity of 87% for clinical diagnosis of depression has been previously reported (de Silva *et al.*, 2014; Fuhrer and Rouillon, 1989).

Methods

Study design and participants

The FHS is a single-site, community-based, prospective cohort study in Framingham, MA. The design and selection criteria of the Framingham Heart Study offspring cohort have been previously described (Kannel *et al.*, 1979). Two thousand eight hundred eighty-three

participants attended the seventh examination cycle (1998–2001) and were given an option for participating in an ancillary study on cognitive aging and dementia. Among them, 1400 subjects, who participated in the ancillary study including having CES-D test at both seventh (1998–2001) and eighth (2005–2008) examinations and having a brain MRI scan at seventh examination, were used for this study analyses. One thousand four hundred eighty-three subjects, who did not attend this ancillary study at either examination cycle or had prevalent stroke or dementia, were excluded. Informed consent was obtained from all study participants, and the study protocol was approved by the Institutional Review Board of Boston University Medical Campus.

We found that participants who comprised the study sample for the study sample ($n = 1400$) were slightly younger, less likely to be women and smokers, and slightly less likely to have medical conditions than those who did not attend the ancillary study and did not have CES-D data that could not be used for the study ($n = 1483$) (Table S1).

Depression

Current depression was defined using CES-D cut scores, and depression status was defined using CES-D cut scores and/or antidepressant use. A cutoff point of 16 was used to define depression and 21 to define severe depression. All medications were coded, and antidepressants including selective serotonin reuptake inhibitors, tricyclic antidepressants, trazodone, venlafaxine, bupropion, and mirtazapine were categorized into one group. For longitudinal analysis, participants who had a CES-D score < 16 and were not on antidepressants at exam 7 comprised the incidence sample for the development of depression. In this group, we used (i) change in CES-D score from exams 7 to 8 as a continuous measure and (ii) defined incident depression as exam 8 CES-D score of 16 or new antidepressant use; incident severe depression was defined as an exam 8 CES-D score of 21 or new antidepressant use.

Brain measurements

The brain MRI protocol has been reported in detail elsewhere (DeCarli *et al.*, 2005; Jefferson *et al.*, 2010). A Siemens 1-T MR machine (Siemens Medical, Erlangen, Germany) with a T2-weighted double spin-echo coronal imaging sequence was used. A central laboratory blinded to demographic and clinical information processed digital information on brain images and quantified the brain data with a custom-written computer program operating on a UNIX, Solaris platform (Sun Microsystems, Santa Clara, CA, USA). The semiautomated segmentation protocol for quantifying total cranial volume, total brain volume, frontal lobar volume, lateral ventricular volume, hippocampal volume (HPV), and WMHI has been described elsewhere (DeCarli *et al.*, 1999), as has the interrater reliabilities for these methods. The units for the brain volumes were defined and controlled as the percentage of total cranial volume. Extensive WMHI was defined as one standard deviation (SD) above age-group means. Each image set undergoes rigorous quality control assessment that includes assessment of the original acquisition quality as well as the quality of the

Table S1. Cross-sectional comparisons of demographic and medical characteristics between those included in the study sample who had CES-D versus those who did not have a CES-D test at seventh examination

image processing. Moreover, each of the analysts is highly trained to maintain rigorous precision with intra-class (analyst) coefficients above 90% for all analyses.

Covariates

Covariates were defined at the seventh examination or through the call-back study for the brain MRI scan. Education was defined with four level categories: no high school degree, high school degree, some college, and a college degree. Living status was dichotomized as whether the participant was living alone or not. Additional characteristics at baseline included age, sex, current cigarettes smoking status, diabetes mellitus (non-fasting blood glucose ≥ 200 mg/dL or fasting blood glucose ≥ 126 mg/dL or use of oral hypoglycemic or insulin), Stage I hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or on antihypertensive treatment), prevalent CVD (coronary heart disease, angina, coronary insufficiency, myocardial infarction, heart failure, and intermittent claudication) and atrial fibrillation. Apolipoprotein E (ApoE) genotyping was conducted on 98% ($n = 1190$) participants from our sample.

Statistical analysis

Analyses were performed using Statistical Analyses System software version 9.3 (SAS Institute, Cary, NC, USA). We performed univariate analyses to describe baseline characteristics in the prevalence sample by depression category (not depressed, depressed, and severely depressed) and used bivariate analyses to compare each of the two depression groups with the comparison group without depression. Mean $\pm$ SD with t -test for the variables with a normal distribution or median (Q1, Q3) with Mann–Whitney test for the variables with a skewed distribution or number (%) with chi square for categorical variables was performed.

To study the development of depression, only participants whose CES-D scores were less than 16 and were not on antidepressants at exam 7 were used ($n = 1212$). We examined longitudinal change as a continuous measure of annualized raw change $[(\text{CES-D measure at exam 8} - \text{CES-D measure at exam 7}) / \text{time interval between exams in years}]$ and then with the development of incident depression (CES-D ≥ 16 or ≥ 21) or new use of antidepressants by exam 8. We used multivariable linear regression to relate each of the brain volume measures to continuous measure of annualized change of CES-D. For the analyses involving development of incident depression, we used multivariable logistic regression models. We then assessed the relationship between each of the total cerebral brain volume, frontal lobar volume, temporal lobar volume, and HPV and the development of incident depression defined as CES-D ≥ 16 and CES-D ≥ 21 , respectively, or on antidepressants by exam 8 by using multivariable logistic regression models. All analyses were adjusted for age at baseline, interval between baseline and MRI assessment, sex, education, and living status (model I) as well as adding baseline CES-D (model II). WMHI was transformed to $\log_{10}$ for multivariate regression because of its skewed distribution. In a secondary analyses, we excluded participants with prevalent CVD and diabetes mellitus ($n = 998$). Significance was set at $p < 0.05$ for all models.

Results

We divided the baseline sample ($n = 1400$) into two groups: (i) 1212 who did not have depression (CES-D score <16) and have not been taking antidepressants served as the no depression control group and (2) 188 who had a CES-D score ≥ 16 or were taking antidepressants were classified as depressed. Further for the depressed group, we identified those with a CES-D score ≥ 21 ($n = 154$) and classified them as severe depression (Table 1). In cross-sectional analyses, we compared the no depression subgroup with both the depressed group and the severely depressed group and found the two depressed groups were younger, had a higher percentage that were women, ApoE4 carriers, and current smokers. There were no differences in other demographic and clinical variables. In brain volumetric measurements, both depressed subgroups had a significantly larger volume of frontal lobe and smaller volume of WMHI, although the absolute values of the volumetric differences were modest and thus unclear whether they are clinically meaningful.

We then used the no depression group at baseline ($n = 1212$) for the longitudinal study analysis. The average (mean $\pm$ SD) age of this subset was 61.0 ± 9.0 years, and other demographic information for the participants was described in the first column of Table 1. One hundred twenty-eight (10.6%) subjects lived alone. There were 255 (21.4%) carrying at least one ApoE4 allele. Medically, 468 (38.7%) had stage I hypertension, 121 (10.1%) had diabetes mellitus, 95 (7.8%) had CVD, and 31 (2.6%) had atrial fibrillation, while 117 (9.7%) had been smoking at baseline. The average time from seventh examination to the time of the brain MRI was 0.74 ± 0.80 years. The average measured brain volumes (mean $\pm$ SD) for this group were as follows: total cerebral brain volume (79.74 ± 3.12), frontal lobe brain volume (36.55 ± 3.27), temporal lobe brain volume (10.58 ± 0.85), and HPV (0.34 ± 0.05) at baseline (Table 1). The median WMHI volume was 0.05 with Q1 of 0.01 and Q3 of 0.08, and 144 participants (11.9%) had extensive WMHI. One hundred forty-three (11.8%) participants had cerebral infarcts.

The average follow-up time from seventh to eighth examination was 6.6 ± 0.6 years. Longitudinally, 110 participants (9.1%) developed depression defined by a CES-D score ≥ 16 , 48 (4.0%) developed severe depressive symptoms defined by a CES-D score ≥ 21 , and 135 (11.1%) were put on antidepressants between two examinations. We first used depressive symptoms as an outcome and found that WMHI volume at baseline (seventh examination), but not infarcts, was positively associated with change of CES-D score ($\beta = +0.06$, SE = 0.03, $t = 1.98$, df = 1197, $p < 0.05$) after adjusting for age, sex, the time duration to have a brain MRI, and the status of living alone (Table 2). After adjusting for the baseline CES-D score (seventh examination), a significant association between WMHI volume and CES-D ≥ 21 was also found (odds ratio (OR) = 1.42, 95% confidence interval (CI) = 1.00, 2.00, $t = 1.98$, df = 1197, $p < 0.05$). For incident depression, we found that extensive WMHI at seventh examination was associated with the development of CES-D ≥ 21 , but not with CES-D ≥ 16 , at eighth examination after adjusting for age, sex, time to MRI, education, living alone without (OR = 2.91, 95% CI = 1.39, 6.09, $X^2 = 5.17$, df = 1, $p < 0.01$) and with (OR = 2.95, 95% CI = 1.38, 6.29, $X^2 = 7.80$, df = 1, $p < 0.01$) adding the baseline CES-D in the model (Table 2), indicating that greater WMHI at baseline was related to the development of severe depression. Interestingly, after excluding the participants who had vascular risk

including stage I hypertension, diabetes, CVD, and atrial fibrillation, the association between extensive WMHI and the development of severe depressive symptoms was strengthened (OR = 1.91, 95% CI = 1.39, 6.09, $X^2 = 7.99$, df = 1, $p < 0.01$) and remained so after adding the baseline CES-D scores into the model (OR = 3.70, 95% CI = 1.65, 8.28, $X^2 = 10.09$, df = 1, $p < 0.01$). Unlike the relationship between WMHI and depression, all brain volumes were not associated with the development of depressive symptoms, for example, CES-D scores or CES-D cutoffs, used as an outcome (data not shown).

Then, when we used either the CES-D cutoff scores or being put on antidepressants as an outcome, the relationships between WMHI volume and the development of depression were no longer significant (Table 3). However, total cerebral brain volume at seventh examination was negatively associated with CES-D ≥ 16 or antidepressant use (OR = 0.78, 95% CI = 0.65, 0.92, $X^2 = 8.24$, df = 1, $p < 0.01$) and with CES-D ≥ 21 or antidepressant use (OR = 0.77, 95% CI = 0.63, 0.93, $X^2 = 7.17$, df = 1, $p < 0.01$). Similar data were found when adding the baseline CES-D scores in the models, indicating that larger total brain volume was protective for the development of depression defined by either depressive symptoms or being put on antidepressants. Additionally, temporal lobe brain volume at baseline was negatively associated with CES-D ≥ 21 or antidepressant use without (OR = 0.83, 95% CI = 0.69, 0.98, $X^2 = 4.61$, df = 1, $p < 0.05$) and with (OR = 0.82, 95% CI = 0.69, 0.98, $X^2 = 4.85$, df = 1, $p < 0.05$) adding the baseline CES-D scores in the model.

Discussion

Late life depression has different subtypes; however, the longitudinal relationships between different brain pathologies and the depression subtypes are not clear. Results from this FHS study sample were consistent with vascular depression as evidenced by the longitudinal relationship of brain WMHI to the development of depression when defined by CES-D cutoff scores (Table 2). When defined by CES-D cutoff scores or taking antidepressants was the depression outcome (Table 3), we found that the relationship of total brain and temporal lobe was in a negative direction to the development of depression, suggesting that larger brain volumes are protective for late life depression.

While a cross-sectional association between brain WMHI and late life depression was reported by several studies (Hoptman *et al.*, 2006; Mettenberg *et al.*, 2012; Sheline *et al.*, 2008; Takahashi *et al.*, 2008), it was unclear whether brain WMHI was a cause or a result of late life depression. Our study provides evidence of an association between brain WMHI and the incident development of depressive symptoms over a 6-year period (Table 2). This finding is likely to be clinically meaningful because (i) the longitudinal study design that excluded all participants with prevalent depression at baseline and (ii) for those with baseline WMHI, the risk of developing late life depression was an almost fourfold increase, even in the absence of CVD (Table 2). The concept of vascular depression was proposed by Alexopoulos *et al.* based on vascular scores including CVD derived from the Cumulative Illness Rating Scale-Geriatrics (Miller *et al.*, 1992), and vascular depression is common in the elderly (Alexopoulos *et al.*, 1997; Alexopoulos *et al.*, 1993; Lebowitz *et al.*, 1997; Ritchie *et al.*, 2000). WMHI volume is a biomarker for cerebrovascular pathology because WMHI is negatively associated with regional cerebral blood flow (Oda *et al.*, 2003) and is

positively associated with subgenual cingulate activity on the affect-reactivity task; it is suggested that white matter ischemia disrupts brain mechanisms of affective regulation (Aizenstein *et al.*, 2011). Because most participants with CVD had been treated with anti-cardiovascular medications, the use of these medications may prevent onset of vascular depression.

When factoring in antidepressant use in addition to depressive symptoms as an outcome for depression, the relationship between extensive WMHI and depression was no longer significant (Table 3). Antidepressant use could equate to current depression, even if CES-D score was low because of treatment. It is possible that brain WMHI is related to antidepressant resistant depression so that only depressive symptoms, but not depression remission induced by antidepressant treatment, were associated with brain WMHI. A previous 2-year longitudinal study found that after antidepressive treatment, those whose symptoms did not remit had increased WMHI volume, while those whose depressive symptoms were in remission did not evidence change in WMHI (Taylor *et al.*, 2003). It has been shown that white matter integrity is inversely associated with remission of late life depression when being treated with antidepressants (Iosifescu *et al.*, 2006; Sheline *et al.*, 2010). A clinical trial showed that microstructural white matter abnormalities lateral to the anterior cingulate are associated with a low rate of remission of geriatric depression to the treatment of citalopram for 12 weeks (Alexopoulos *et al.*, 2002).

Our cross-sectional sample likely included both early-onset and late-onset depressed participants. In contrast to the longitudinal analysis, cross-sectional analysis, which contained both early-onset and late-onset depressed participants, did not show increased brain WMHI in the depressed subgroups (Table 1). Consistently, another study has shown that patients with early-onset depression do not have WMHI abnormality in the brain (Komaki *et al.*, 2008).

Larger total brain and temporal lobe volume appeared protective from developing late life depression including antidepressant usage as an outcome (Table 3). It is possible that larger brain volumes are protective only for antidepressant responsive subtypes of depression, but not likely for antidepressant resistant subtypes like vascular depression defined by brain MRI. Another possibility is that recurrent depression due to not being treated or being resistant to the treatment would lead to brain atrophy, which could explain why brain volumes were related to CES-D cutoff or taking antidepressant defined depression. One earlier study found a cross-sectional association between late life depression and total brain volume (Lin *et al.*, 2005), although another did not (Sheline *et al.*, 2008). Recurrent late life depression is associated with hippocampal atrophy (Sheline *et al.*, 1999; Steffens *et al.*, 2000). These brain regions are also positively associated with impairment of cognitive function and AD, and recurrent depression in the elderly can lead to the damage of these brain area and cognitive decline, especially memory loss (Basso and Bornstein, 1999; MacQueen *et al.*, 2002; Rapp *et al.*, 2005). In addition, for each depressive symptom assessed by the CES-D, risk of developing AD increased by an average of 19% (Dal Forno *et al.*, 2005; Wilson *et al.*, 2002). Thus, recurrent depression without antidepressant treatment or resistant to the treatment may lead to decreased brain volumes, especially those related to cognitive decline and dementia.

The limitation of this study include (i) depression was based on the CES-D score rather than the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition criteria or the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders; (ii) we had no information about the onset and the course of depression; and (iii) CES-D data had been collected every 6–7 years instead of annually so that recurrent depression was not captured fully. A large number of participants did not have CES-D test, so these were not included in the study analyses, although there were no significant differences between the groups with and without the CES-D data. This was a Caucasian sample with relatively low overall cardiovascular risk; higher risk samples as well as ethnic groups with high cardiovascular risk may be needed to study vascular depression defined by brain MRI. The study did not have data on other neurological conditions except stroke and dementia or whether antidepressants were being used for other clinical treatments such as insomnia. Nevertheless, our findings suggest WMHI is a risk factor for the development of brain MRI-defined vascular depression. The clinical meaning of this finding will also depend on the development of a drug-targeting reduction of WMHI in the brain as a strategy for treating and preventing late life depression. The combination of antidepressants and cardiovascular medications may be beneficial for MRI-defined vascular depression.

Acknowledgments

We want to express our thanks to the FHS study staff for their hard work for the acquisition of subjects and the data collection for many years. We also thank Dr. Sudha Seshadri for co-serving as PI with Dr. Philip Wolf and then Dr. Rhoda Au on the National Institute on Aging (NIA) AG-008122 and for her dedication to the FHS study. This work was also supported by the Framingham Heart Study's National Heart, Lung, and Blood Institute contract (N01-HC-25195) and by grants from the National Institute of Neurological Disorders and Stroke, NS-17950 for P. A. W. and from the NIA, AG-16495 for R. A. and AG-022476 for W. Q. Q.

References

- Aizenstein HJ, Andreescu C, Edelman KL, et al. fMRI correlates of white matter hyperintensities in late-life depression. *Am J Psychiatry*. 2011; 168(10):1075–1082. [PubMed: 21799066]
- Alexopoulos GS, Kiess DN, Choi SJ, Murphy CF, Lim KO. Frontal white matter microstructure and treatment response of late-life depression: a preliminary study. *Am J Psychiatry*. 2002; 159(11):1929–1932. [PubMed: 12411231]
- Alexopoulos GS, Meyers BS, Young RC, et al. Clinically defined vascular depression. *Am J Psychiatry*. 1997; 154(4):562–565. [PubMed: 9090349]
- Alexopoulos GS, Meyers BS, Young RC, Mattis S, Kakuma T. The course of geriatric depression with “reversible dementia”: a controlled study. *Am J Psychiatry*. 1993; 150(11):1693–1699. [PubMed: 8105707]
- Alexopoulos GS, Schultz SK, Lebowitz BD. Late-life depression: a model for medical classification. *Biol Psychiatry*. 2005; 58(4):283–289. [PubMed: 16026764]
- Basso MR, Bornstein RA. Relative memory deficits in recurrent versus first-episode major depression on a word-list learning task. *Neuropsychology*. 1999; 13(4):557–563. [PubMed: 10527064]
- Berger AK, Fratiglioni L, Forsell Y, Winblad B, Backman L. The occurrence of depressive symptoms in the preclinical phase of AD: a population-based study. *Neurology*. 1999; 53(9):1998–2002. [PubMed: 10599771]
- Boyd JH, Weissman MM, Thompson WD, Myers JK. Screening for depression in a community sample. Understanding the discrepancies between depression symptom and diagnostic scales. *Arch Gen Psychiatry*. 1982; 39(10):1195–1200. [PubMed: 7125849]

- Cervilla JA, Prince M, Joels S, Mann A. Does depression predict cognitive outcome 9 to 12 years later? Evidence from a prospective study of elderly hypertensives. *Psychol Med*. 2000; 30(5):1017–1023. [PubMed: 12027039]
- Dal Forno G, Palermo MT, Donohue JE, et al. Depressive symptoms, sex, and risk for Alzheimer's disease. *Ann Neurol*. 2005; 57(3):381–387. [PubMed: 15732103]
- de Silva VA, Ekanayake S, Hanwella R. Validity of the Sinhala version of the Centre for Epidemiological Studies Depression Scale (CES-D) in out-patients. *Ceylon Med J*. 2014; 59(1):8–12. [PubMed: 24682190]
- DeCarli C, Massaro J, Harvey D, et al. Measures of brain morphology and infarction in the Framingham Heart Study: establishing what is normal. *Neurobiol Aging*. 2005; 26(4):491–510. [PubMed: 15653178]
- DeCarli C, Reed T, Miller BL, et al. Impact of apolipoprotein E epsilon4 and vascular disease on brain morphology in men from the NHLBI twin study. *Stroke*. 1999; 30(8):1548–1553. [PubMed: 10436099]
- Fuhrer R, Rouillon F. French version of CES-D scale: description and translation of self evaluation. *J Psychiatr Psychol*. 1989; 4:163–166.
- Hoptman MJ, Gunning-Dixon FM, Murphy CF, Lim KO, Alexopoulos GS. Structural neuroimaging research methods in geriatric depression. *Am J Geriatr Psychiatry*. 2006; 14(10):812–822. [PubMed: 17001021]
- Iosifescu DV, Renshaw PF, Lyoo IK, et al. Brain white-matter hyperintensities and treatment outcome in major depressive disorder. *J Br Psychiatry*. 2006; 188:180–185.
- Jefferson AL, Himali JJ, Beiser AS, et al. Cardiac index is associated with brain aging: the Framingham Heart Study. *Circulation*. 2010; 122(7):690–697. [PubMed: 20679552]
- Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham Offspring Study. *Am J Epidemiol*. 1979; 110(3):281–290. [PubMed: 474565]
- Komaki S, Nagayama H, Ohgami H, et al. Prospective study of major depressive disorder with white matter hyperintensity: comparison of patients with and without lacunar infarction. *Eur Arch Psychiatry Clin Neurosci*. 2008; 258(3):160–164. [PubMed: 17990046]
- Lebowitz BD, Pearson JL, Schneider LS, et al. Diagnosis and treatment of depression in late life. Consensus statement update. *JAMA*. 1997; 278(14):1186–1190. [PubMed: 9326481]
- Lin HF, Kuo YT, Chiang IC, Chen HM, Chen CS. Structural abnormality on brain magnetic resonance imaging in late-onset major depressive disorder. *Kaohsiung J Med Sci*. 2005; 21(9):405–411. [PubMed: 16248124]
- Lopez OL, Becker JT, Sweet RA, et al. Psychiatric symptoms vary with the severity of dementia in probable Alzheimer's disease. *J Neuropsychiatry Clin Neurosci*. 2003; 15(3):346–353. [PubMed: 12928511]
- Lyness JM, Noel TK, Cox C, et al. Screening for depression in elderly primary care patients. A comparison of the Center for Epidemiologic Studies-Depression Scale and the Geriatric Depression Scale. *Arch Intern Med*. 1997; 157(4):449–454. [PubMed: 9046897]
- MacQueen GM, Galway TM, Hay J, Young LT, Joffe RT. Recollection memory deficits in patients with major depressive disorder predicted by past depressions but not current mood state or treatment status. *Psychol Med*. 2002; 32(2):251–258. [PubMed: 11866320]
- Mettenburg JM, Benzinger TL, Shimony JS, Snyder AZ, Sheline YI. Diminished performance on neuropsychological testing in late life depression is correlated with microstructural white matter abnormalities. *Neuroimage*. 2012; 60(4):2182–2190. [PubMed: 22487548]
- Miller MD, Paradis CF, Houck PR, et al. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. *Psychiatry Res*. 1992; 41(3):237–248. [PubMed: 1594710]
- Oda K, Okubo Y, Ishida R, et al. Regional cerebral blood flow in depressed patients with white matter magnetic resonance hyperintensity. *Biol Psychiatry*. 2003; 53(2):150–156. [PubMed: 12547471]
- Radloff L. The CES-D scale: a self report depression scale for research in the general population. *Appl Psychol Meas*. 1977; 1:385–401.

- Rapp MA, Dahlman K, Sano M, et al. Neuropsychological differences between late-onset and recurrent geriatric major depression. *Am J Psychiatry*. 2005; 162(4):691–698. [PubMed: 15800140]
- Rapp MA, Schnaider-Beeri M, Grossman HT, et al. Increased hippocampal plaques and tangles in patients with Alzheimer disease with a lifetime history of major depression. *Arch Gen Psychiatry*. 2006; 63(2):161–167. [PubMed: 16461859]
- Ritchie K, Ledesert B, Touchon J. Subclinical cognitive impairment: epidemiology and clinical characteristics. *Compr Psychiatry*. 2000; 41(2 Suppl 1):61–65. [PubMed: 10746906]
- Robinson RG, Bolduc PL, Price TR. Two-year longitudinal study of poststroke mood disorders: diagnosis and outcome at one and two years. *Stroke*. 1987; 18(5):837–843. [PubMed: 3629640]
- Sheline YI, Pieper CF, Barch DM, et al. Support for the vascular depression hypothesis in late-life depression: results of a 2-site, prospective, antidepressant treatment trial. *Arch Gen Psychiatry*. 2010; 67(3):277–285. [PubMed: 20194828]
- Sheline YI, Price JL, Vaishnavi SN, et al. Regional white matter hyperintensity burden in automated segmentation distinguishes late-life depressed subjects from comparison subjects matched for vascular risk factors. *Am J Psychiatry*. 2008; 165(4):524–532. [PubMed: 18281408]
- Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci*. 1999; 19(12):5034–5043. [PubMed: 10366636]
- Steffens DC, Byrum CE, McQuoid DR, et al. Hippocampal volume in geriatric depression. *Biol Psychiatry*. 2000; 48(4):301–309. [PubMed: 10960161]
- Takahashi K, Oshima A, Ida I, et al. Relationship between age at onset and magnetic resonance image-defined hyperintensities in mood disorders. *J Psychiatr Res*. 2008; 42(6):443–450. [PubMed: 17588605]
- Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Mol Psychiatry*. 2013; 18(9):963–974. [PubMed: 23439482]
- Taylor WD, Steffens DC, MacFall JR, et al. White matter hyperintensity progression and late-life depression outcomes. *Arch Gen Psychiatry*. 2003; 60(11):1090–1096. [PubMed: 14609884]
- Wilson RS, Barnes LL, Mendes de Leon CF, et al. Depressive symptoms, cognitive decline, and risk of AD in older persons. *Neurology*. 2002; 59(3):364–370. [PubMed: 12177369]

Cross-sectional comparisons of demographic, medical characteristics, and brain volumes between those with and without depression in the Framingham Heart Study sample at exam 7

Table 1

	CES-D <16	CES-D 16 or on antidepressants	Test scores <i>t</i> -test or χ^2 (df)	<i>I</i> CES-D 21 or on antidepressants	Test scores <i>t</i> -test or χ^2 (df)
Total number	1212	188	–	154	–
Age, year, mean $\pm$ SD	60 $\pm$ 9	59 $\pm$ 8	2.75 (1398) **	58 $\pm$ 8	3.38 (1364) ***
Female, number (%)	635 (52.4)	137 (72.9)	27.60 (1) ***	111 (72.1)	21.36 (1) ***
Education, number (%)					
Non-high school	26 (2.2)	3 (1.6)	3.54 (2)	1 (0.6)	2.77 (2)
High School graduate and some college	666 (54.9)	117 (62.2)		93 (60.4)	
College graduate	520 (42.9)	68 (36.2)		60 (39)	
ApoE4, number (%)	255 (21.4)	52 (28.1) *	4.12 (1) *	43 (28.5)	3.85 (1) *
Smoking, number (%)	117 (9.7)	27 (14.4)	3.91 (1) *	24 (15.6)	5.19 (1) *
Living alone, number (%)	128 (10.6)	25 (13.3)	1.24 (1)	19 (12.3)	0.44 (1)
Medical conditions, number (%)					
Stage I hypertension	468 (38.7)	74 (39.4)	0.04 (1)	58 (37.7)	0.06 (1)
Diabetes mellitus	121 (10.1)	21 (11.2)	0.21 (1)	19 (12.4)	0.75 (1)
Cardiovascular disease	95 (7.8)	14 (7.5)	0.03 (1)	14 (9.1)	0.29 (1)
Atrial fibrillation	31 (2.6)	4 (2.1)	Fisher's <i>I</i>	4 (2.6)	Fisher's <i>I</i> ²
Brain MRI measures, mean $\pm$ SD					
Time from exam 7 to MR, years	0.74 $\pm$ 0.80	0.70 $\pm$ 0.82	1.01 (1398)	0.70 $\pm$ 0.80	–0.68 (1364)
TCBV	79.72 $\pm$ 3.15	79.96 $\pm$ 2.91	–1.01 (1398)	80.05 $\pm$ 2.86	–1.25 (1364)
FBV	36.51 $\pm$ 3.26	37.17 $\pm$ 3.31	–2.55 (1398) *	37.26 $\pm$ 3.40	–2.67 (1364) **
TBV	10.57 $\pm$ 0.85	10.70 $\pm$ 0.81	–1.94 (1398)	10.74 $\pm$ 0.79	–2.34 (1364) *
HPV	0.34 $\pm$ 0.05	0.34 $\pm$ 0.06	0.15 (1386)	0.34 $\pm$ 0.05	0.25 (1352)
WMHl, median [Q1,Q3]	0.05 [0.01, 0.08]	0.04 [0.01, 0.07]	1.13 (1395) ³	0.04 [0.01, 0.07]	1.94 (1361) * ³
Cerebrovascular pathology, number (%)					
Cerebral infarcts	143 (11.8)	20 (10.6)	0.21 (1)	17 (11.04)	0.08 (1)

	CES-D <16	CES-D 16 or on antidepressants	Test scores <i>t</i> -test or χ^2 (df)	CES-D 21 or on antidepressants	Test scores <i>t</i> -test or χ^2 (df)
Extensive WMHI	144 (11.9)	20 (10.6)	0.25 (1)	15 (9.7)	0.62 (1)

CES-D, Center for Epidemiologic Studies Depression Scale; TCBV, total cerebral brain volume; FBV, frontal lobe brain volume; TBV, temporal lobe brain volume; HPV, hippocampal volume; WMHI, white matter hyperintensities volume.

Comparisons were conducted between CES-D <16 subgroup and either CES-D 16/antidepressants or CES-D 21/antidepressants subgroups. Statistical significance was shown.

¹ CES-D 21/antidepressants subgroup was derived from the CES-D 16/antidepressants subgroup by having a CES-D 21. Mean $\pm$ SD with *t*-test or number (%) with Wald chi square (χ^2) are presented.

² Fisher's exact test was used.

³ Median (Q1, Q3) with Mann-Whitney test was used.

* $p < 0.05$

** 0.001 $p < 0.01$

*** $p < 0.001$

Table 2

Significant relationships between brain volumes and the development of incident depression by eighth examination

All subjects (<i>n</i> = 1212)	CES-D score change	CES-D 16	CES-D 21
	Estimate ± SE	OR [95% CI]	OR [95% CI]
Cerebral infarcts			
M1	0.02 ± 0.08	0.62 [0.30, 1.25]	0.33 [0.08, 1.36]
M2	−0.01 ± 0.08	0.78 [0.37, 1.62]	0.42 [0.10, 1.80]
WMHI			
M1	0.06 ± 0.03[*], <i>t</i> (1197) = 1.98	1.07 [0.86, 1.34]	1.27 [0.92, 1.77]
M2	0.06 ± 0.03[*], <i>t</i> (1197) = 1.98	1.17 [0.93, 1.48]	1.42 [1.00, 2.00][*], <i>X</i>² (1) = 3.92
Extensive WMHI			
M1	0.15 ± 0.08	1.38 [0.79, 2.40]	2.91 [1.39, 6.09]^{**}, <i>X</i>² (1) = 5.17
M2	0.14 ± 0.08	1.60 [0.89, 2.88]	2.95 [1.38, 6.29]^{**}, <i>X</i>² (1) = 7.80
Excluding subjects who had vascular diseases (<i>n</i> = 998)			
Extensive WMHI			
M1	0.13 ± 0.09	1.33 [0.71, 2.52]	1.91 [1.39, 6.09]^{**}, <i>X</i>² (1) = 7.99
M2	0.12 ± 0.08	1.60 [0.89, 2.88]	3.70 [1.65, 8.28]^{**}, <i>X</i>² (1) = 10.09

CES-D, Center for Epidemiologic Studies Depression Scale; WMHI, white matter hyperintensities volume.

Subjects who did not have CES-D >16 and had not been taking antidepressants by seventh examination were used for the longitudinal analysis. WMHI volume was log transformed in multivariate regression analyses. Multivariable linear regression was used to relate each of the brain volume measures to continuous measure of CES-D change. For the analyses involving development of incident depression defined by a cutoff CES-D score, multivariable logistic regression model was used.

M1: model 1 adjusted for age, sex, time to MRI, education, and living alone.

M2: model 2 adjusted for age, sex, time to MRI, education, living alone, and CES-D at seventh examination.

Only those models with statistical significance are bold and shown with *t*-score (df) or chi square (*X*²) (df).

^{*}
p < 0.05.

^{**}
0.001 *p* < 0.01.

Table 3

Significant relationships between brain volumes and the development of incident depression and/or being put on antidepressants by eighth examination

All subjects <i>n</i> = 1212	CES-D 16 or antidepressants	CES-D 21 or antidepressants
	OR [95% CI]	OR [95% CI]
WMHI		
M1	1.07 [0.91, 1.26]	1.07 [0.89, 1.29]
M2	1.13 [0.95, 1.34]	1.11 [0.92, 1.34]
TCBV		
M1	0.78 [0.65,0.92] **, X^2 (1) = 8.24	0.77 [0.63,0.93] **, X^2 (1) = 7.17
M2	0.80 [0.67,0.95] *, X^2 (1) = 6.21	0.79 [0.65,0.96] *, X^2 (1) = 5.68
FBV		
M1	0.93 [0.78, 1.10]	0.85 [0.70, 1.03]
M2	0.94 [0.79, 1.11]	0.85 [0.70, 1.04]
TBV		
M1	0.89 [0.75, 1.03]	0.82 [0.69, 0.98] *, X^2 (1) = 4.85
M2	0.89 [0.76, 1.04]	0.83 [0.69, 0.98] *, X^2 (1) = 4.61
HPV		
M1	0.97 [0.83, 1.12]	0.91 [0.77, 1.07]
M2	0.98 [0.84, 1.14]	0.92 [0.77, 1.08]

CES-D, Center for Epidemiologic Studies Depression Scale; WMHI, white matter hyperintensities volume; TCBV, total cerebral brain volume; FBV, frontal lobe brain volume; TBV, temporal lobe brain volume; HPV, hippocampal volume. Subjects who did not have CES-D>16 and had not been taking antidepressants by seventh examination were used for the longitudinal analysis. WMHI volume was log transformed in multivariate regression analyses; Multivariable logistic regression models were used to study the relationship between brain measurements and development of incident depression defined by a cutoff CES-D score or being put on antidepressants.

M1: model 1 adjusted for age, sex, time to MRI, education, and living alone.

M2: model 2 adjusted for age, sex, time to MRI, education, living alone, and CES-D at seventh examination.

Only those models with statistical significance are bold and shown with chi square (X^2) (df).

* $p < 0.05$

** 0.001 $p < 0.01$