History of depression, depressive symptoms, and medial temporal lobe atrophy and the risk of Alzheimer disease

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ABSTRACT

Background: Depression may increase risk for Alzheimer disease (AD), but it is not clear whether this risk is mediated by structural brain changes. We determined whether history of depressive episodes and presence of depressive symptoms were associated with smaller hippocampal and amygdalar volumes and with increased risk for incident AD.

Methods: Within the Rotterdam Scan Study 503 persons, aged 60–90 years at baseline and without dementia, reported their history of depressive episodes. Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression Scale. Volumetric assessment of the hippocampus and amygdala was performed using three-dimensional MRI. All subjects were followed for an average of 6 years for development of AD, diagnosed according to National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria.

Results: A total of 134 subjects (26.6%) reported a history of depression (88 reported an onset <60 years and 46 a late onset). Multiple linear regression analyses did not reveal a significant association with hippocampal or amygdalar volume for any of the depression parameters. During follow-up, 33 persons developed AD. Cox regression analyses showed that subjects with early onset depression had an increased risk for AD (HR 3.76; 95% CI 1.41 to 10.06), independent of hippocampal and amygdalar volume, whereas this risk was 2.34 (95% CI 0.82 to 6.69) in subjects with a late-onset depression. Depressive symptoms at baseline were not associated with increased risk for AD.

Conclusion: History of depression, and particularly an early onset, but not presence of depressive symptoms increased the risk for Alzheimer disease. This risk was not mediated by smaller hippocampal or amygdalar volumes. ***Neurology*® 2008;70:1258–1264**

GLOSSARY

AD = Alzheimer disease; **CAMDEX** = Cambridge Examination for Mental Disorders of the Elderly; **CES-D** = Center for Epidemiologic Studies Depression Scale; **HASTE** = half-Fourier acquisition single-shot turbo spin-echo; **HPA** = hypothalamic-pituitary-adrenal; **ICV** = intracranial volume; **MMSE** = Mini-Mental State Examination.

Alzheimer disease (AD) is the most common cause of dementia and may affect 40% of people aged 85 years and over.[1] It has been estimated that with the increase of the elderly population, the prevalence of AD will triple to 13 million people in the United States alone in the next 50 years.[1] In up to 50% of patients with AD, depression is comorbid, resulting in more adverse consequences for both patient and caregivers.[2] Because depression may also precede a clinical diagnosis of AD by several years, one of the explanations for this comorbidity is that in a subgroup of patients with AD depression has contributed to the development of AD.[3] It has been hypothesized that depression increases the risk for AD through hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, which may occur in patients with depression.[4] Prolonged exposure to glucocorticoids with repeated depressive episodes would then lead to hippocampal atrophy and subsequently develop-

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ment of AD.[5] Animal studies suggest biologic plausibility for a direct detrimental effect of glucocorticoids on the hippocampus.[6] Evidence from observational studies is indirect with a majority of studies finding smaller hippocampal and amygdalar volumes in patients with major depressive disorder or posttraumatic stress disorder.[7-10] In addition, it has been observed that elevated levels of glucocorticoids are related to smaller hippocampal volumes and impaired memory.[11] Prospective studies that found an association between depression and development of AD were sometimes suggestive of depression being a prodromal symptom,[12-14] while others suggested a causal relationship.[15] The results of these studies were not always consistent, however, and most of them did not jointly examine history of depression, hippocampal and amygdalar volume, and subsequent development of AD.

One aim of the present study was to examine whether a history of depression, age at onset of depression, and presence of depressive symptoms at baseline were associated with smaller hippocampal and amygdalar volumes on MRI. The second aim was to examine whether these depression measures were associated with increased risk for incident AD, and whether hippocampal and amygdalar volume mediated these associations. We used data from the prospective population-based Rotterdam Scan Study, in which elderly individuals without dementia and with hippocampal and amygdalar measurements at baseline were followed for an average of 6 years for development of dementia.

METHODS

Rotterdam Scan Study. The Rotterdam Study is a large population-based cohort study in The Netherlands that started in 1990 and investigates the prevalence, incidence, and determinants of chronic diseases among elderly participants.[16] The study was approved by the medical ethics committee of the Erasmus Medical Center, Rotterdam, The Netherlands. From 1995 to 1996, we randomly selected 965 living members (aged 60 to 90 years) of this cohort in strata of sex and age (5 years) for participation in the Rotterdam Scan Study, a study on age-related brain changes on MRI. As part of the eligibility criteria we excluded individuals who were demented, blind, or had MRI contraindications. This left 832 persons eligible for participation. Among these, 563 persons gave their written informed consent to participate in the present study (response rate: 68%).[17] The 269 persons who were not willing to participate were on average 3.2 years older ($p < 0.001$); were more likely to be female (9% more women; $p = 0.02$); were more likely to have a low level of education (15% more; $p < 0.001$); and scored on average 0.5 points lower on the Mini-Mental State Examination (MMSE) ($p = 0.001$) than those who did participate in the study.

Depression measures. Participants were asked for their history of depressive episodes. If depressive episodes had occurred, the subjects were asked for the age at 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.[18] Age at first onset was dichotomized into early onset (before age 60 years) and late onset (at age 60 or above) depression.[18] At baseline, we assessed depressive symptoms with the Center for Epidemiologic Studies Depression Scale (CES-D).[19,20] The conventional cutoff score of 16 or higher was used to indicate presence of depressive symptoms.

MRI measurements. All subjects underwent T1, T2, and proton-density weighted images in a 1.5 Tesla MR unit (VISION MR, Siemens, Erlangen, Germany). For volumetric measurements of the hippocampus, a custom-made, inversion recovery–double-contrast, three-dimensional, half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequence was included (inversion time, 440 msec; repetition time, 2,800 msec; 128 contiguous sagittal slices of 1.2 mm; acquisition matrix, 192 × 256 pixels; and field of view, 256 × 256 cm). Two HASTE modules were sequentially acquired after the inversion pulse (effective echo times of 29 msec and 440 msec). Each HASTE module combined nonselective radiofrequency excitations to provide a short interecho spacing of 3.9 msec. The first HASTE module was used for the hippocampal and amygdalar volume measurement.

Hippocampal and amygdalar volume assessment. Coronal slices (1.5 mm, no interslice gap) were reconstructed from the HASTE sequence in such a way that they were perpendicular to the long axis of the hippocampus. The left and the right hippocampus and amygdala were manually outlined on each slice with a mouse-driven cursor.[21] Outlining proceeded from posterior to anterior. We started to outline the hippocampus at the point where the crux of the fornices was in full profile. Included in the region of interest for the hippocampus were the subiculum, the CA1 through CA4 sectors of the hippocampus proper, and the gyrus dentatus. The alveus could often be used to separate boundaries of the hippocampus from the overlying amygdala. The anterior boundary of the amygdala was defined as the plane including the most anterior part of the temporal stem. Absolute volumes (mL) were calculated by multiplying the areas on each slice by the slice thickness. Two readers, who were blinded to clinical information, measured the scans. Intra- and interrater correlation coefficients have been reported and showed good reproducibility.[22] We corrected for head size differences across individuals by dividing the raw volumes by the subject's intracranial volume (ICV) and subsequently multiplying this ratio by 1,000. ICV was automatically assessed by summing gray, white matter and CSF voxels; the cerebellum was excluded.[23] We summed the left and right side to yield total volumes because the analyses did not suggest laterality of effects.

Other MRI variables. White matter lesions were considered present if visible as hyperintense on proton-density and T2-weighted axial images, without prominent hypointensity on T1-weighted scans.[24] Periventricular white matter lesions were scored semiquantitatively from 0 to 9.[24] We defined infarcts as focal hyperintensities on T2-weighted images.[25] Infarcts in the white matter also had to have corresponding hypointensities on T1-weighted images in order to distinguish them from white matter lesions. Subcortical brain atrophy was calculated by averaging the ventricle-to-brain ratio on T1-weighted images at the frontal horns, the occipital horns, and the caudate nucleus.

Other measurements. At the research center, age, gender, and highest attained level of education of the participant were assessed. Level of education was assessed on an eight-point ordinal scale ranging from uncompleted primary education to university education. General cognitive functioning was assessed by means of the MMSE.[26] Subjective memory complaints were assessed by 10 questions regarding everyday memory problems experienced in the preceding month.[27] For instance, the participant was asked, "Have there been moments during the last month that you felt very forgetful?" All answers were coded as yes or no. The answers to the questions were summed to obtain the total number of memory complaints (range 0–10).

Ascertainment of dementia and AD. All participants were free of dementia at baseline and we followed the cohort for incident dementia.[21,25,28] Briefly, participants were screened at follow-up visits (1997–1999, 1999–2000, 2002–2003) with the MMSE[26] and the Geriatric Mental Schedule[29] and when screen positive assessed with the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX) interview.[30] Participants suspected of dementia were examined by a neurologist and underwent extensive neuropsychological testing. The MRI at baseline was not used in diagnosing dementia. To avoid missing dementia cases among the persons who did not come to the research center, we also continuously monitored the medical records of all participants at the general practitioners' offices and the Regional Institute for Ambulatory Mental Health Care to obtain information on diagnosed dementia. Follow-up was complete until January 1, 2005. A diagnosis of dementia and AD was made by a panel that consisted of a neurologist, neuropsychologist, and research physician and used standard criteria.[31,32]

Study sample. Complete MRI data, including a three-dimensional MRI sequence, were obtained in 511 persons. Fifty-two subjects had no HASTE sequence, mainly because they became claustrophobic during the MRI examination. In addition, 25 subjects had missing data on ICV or depression measures. Thus, the study sample consisted of 486 subjects. The 77 subjects with missing data were not significantly different from the 486 subjects with respect to distribution of age, gender, level of education, CES-D score, white matter lesions, and subcortical atrophy.

Data analysis. Baseline characteristics were compared across groups of history of depressive episodes (no history; early onset; late onset) using analysis of variance or Kruskal-Wallis (if distributions were skewed) for continuous variables, and 2 × 2 tables for categorical variables.

The cross-sectional associations of history of depression and current symptoms of depression with hippocampal and amygdalar volume were estimated using multiple linear regression analyses with total hippocampal and amygdalar volume, respectively, as the outcome variable. First, we examined whether a history of depression was associated with hippocampal and amygdalar volumes. Second, we examined whether an early onset (<60 years) compared to no history of depression, and whether a late onset (60 years or above) compared to no history of depression were associated with hippocampal and amygdalar volumes. Third, we examined whether current depressive symptomatology (CES-D 16+ vs CES-D < 16) were associated with hippocampal and amygdalar volumes. All analyses were adjusted for age, gender, level of education, MMSE score, and subjective memory complaint score, and additionally adjusted for deep white matter lesions (as a continuous variable), periventricular lesion score (as a continuous variable), brain infarcts (present vs absent), and subcortical brain atrophy (as a continuous variable).

The prospective associations of history of depression and current symptoms of depression with risk of AD were estimated using Cox regression analyses with delayed entry and age as the timescale.[33] The age at onset of dementia was set at the date on which clinical symptoms allowed the diagnosis of dementia. Duration of follow-up for each participant was calculated from baseline examination until death, diagnosis of dementia, or the end of follow-up, whichever came first. The proportional hazards assumption was checked using a log vs log minus log plot, and was not violated. In the first model we adjusted for age (timescale), gender, level of education (as a continuous variable), MMSE (as a continuous variable), and subjective memory complaint score (as a continuous variable). In the second model we also adjusted for total hippocampal and amygdalar volume (as continuous variables) to examine whether the risk was mediated by hippocampal or amygdalar volume. In the third model, we also adjusted for white matter lesions (as a continuous variable), periventricular lesion score (as a continuous variable), brain infarcts (present vs absent), and subcortical brain atrophy (as a continuous variable) to account for possible vascular origin of depression. Finally, we examined the specificity of the results for risk of AD by repeating all analyses with all-cause dementia as the outcome. Analyses were performed using SPSS, version 14 (SPSS, Inc., Chicago, IL) and SAS, version 9 (SAS Institute, Inc., Cary, NC).

RESULTS

Of the 486 subjects in the study sample, 130 (26.7%) reported a history of depression, of whom 84 (64.6%) reported an early onset, and 46 (35.4%) a late onset. Thirty-five subjects (7.8%) scored 16 or higher on the CES-D at baseline. Subjects reporting an early onset depression were younger than those with a late onset of depression or no history of depression (table 1). Also, they had higher CES-D scores at baseline than subjects without a history of depression but lower CES-D scores than subjects with a late onset. Subjects with a late onset more often had brain infarcts, deep white matter lesions, periventricular lesions, and subcortical atrophy on MRI than those with an early onset of depression.

Table 1 Baseline characteristics of the study sample (n = 486) according to history of depression

	History of depressive episodes		
	No history (n = 356)	Early onset (n = 84)	Late onset (n = 46)
Age, y, mean ± SD	74.3 ± 8.0	68.5 ± 6.3	76.5 ± 6.3
Female, %	46.9	50.0	63.0
Educational level,* mean ± SD	2.9 ± 1.6	2.9 ± 1.7	2.5 ± 1.6
Memory complaint score, mean ± SD	2.3 ± 2.4	2.6 ± 2.5	2.4 ± 2.5
MMSE score, mean ± SD	27.7 ± 2.2	28.0 ± 1.7	27.4 ± 2.2
CES-D 16+, %	3.7	13.1	25.0
Age at first episode, y, mean ± SD	NA	45.8 ± 11.3	68.8 ± 7.3
Infarcts present on MRI, %	29.8	21.4	34.8
Deep white matter lesions, mL, median (range)	0.40 (0–29.5)	0.15 (0–12.5)	0.86 (0–15.0)
Periventricular lesions, score, median (range)	2.0 (0–9)	2.0 (0–9)	2.5 (0–9)
Subcortical atrophy, mean ± SD	0.31 ± 0.04	0.30 ± 0.04	0.32 ± 0.04
ICV, mL, mean ± SD	1,132.7 ± 121.6	1,139.4 ± 115.1	1,108.5 ± 95.9
Total amygdalar volume, mean ‰ of ICV ± SD	4.04 ± 0.65	4.06 ± 0.62	4.14 ± 0.50
Total hippocampal volume, mean ‰ of ICV ± SD	5.62 ± 0.82	5.77 ± 0.70	5.72 ± 0.86

*Range from 0 (less than primary education) to 7 (university education).
MMSE = Mini-Mental State Examination; CES-D = Center for Epidemiologic Studies Depression Scale.

Depression measures with hippocampal and amygdalar volume. Linear regression analysis adjusted for age, gender, level of education, MMSE score, and subjective memory complaint score showed no significant difference in the adjusted mean total hippocampal volume between subjects who reported no history of depression and those who did (5.64‰ of ICV vs 5.69‰ of ICV; adjusted difference −0.05; 95% CI −0.21 to 0.10). Similarly, no difference was observed in total amygdalar volume (adjusted difference −0.003; 95% CI −0.12 to 0.13). When history of depression was divided into early and late onset, subjects with no history of depression had an adjusted mean total hippocampal volume of 5.64‰ of ICV; subjects with an early onset had an adjusted mean total hippocampal volume of 5.67‰ of ICV (mean difference −0.03; 95% CI −0.22 to 0.15), and those with a late onset 5.72‰ of ICV (mean difference −0.08; 95% CI −0.31 to 0.15). The adjusted mean total amygdalar volume in subjects with no history of depression was 4.05‰ of ICV; for subjects with an early onset of depression it was 3.98‰ of ICV (mean difference 0.07; 95% CI −0.07 to 0.22), and 4.17‰ of ICV in those with a late onset depression (mean difference −0.19; 95% CI −0.42 to 0.04).

Current depressive symptoms, as indicated by CES-D scores of 16 or higher, were not significantly associated with hippocampal volume. The adjusted mean volume in subjects without depressive symptoms was 5.64‰ of ICV and in subjects with depressive symptoms it was 5.81‰ of ICV (mean difference −0.17; 95% CI −0.43 to 0.10). The adjusted mean total amygdalar volume in persons with CES-D scores below the cutpoint of 16 was 4.05‰ of ICV, and it was 4.08‰ of ICV in those with scores of 16 or higher (mean difference −0.03; 95% CI −0.25 to 0.19).

Adding deep white matter lesions, periventricular lesion score, brain infarcts, and subcortical brain atrophy to all models did not materially change the results (data not shown).

Depression measures with incident AD and all-cause dementia. During a total of 2,854 person-years of follow-up (mean per person, 5.9 ± 1.6 years), 44 persons developed dementia, 33 of whom developed AD. Seven persons were diagnosed with vascular dementia and 4 persons with other types of dementia. The mean follow-up time for subjects without a history of depression was 5.8 ± 1.6 years; for subjects with an early onset of depression the mean follow-up time was 6.1 ± 1.5 years; and for subjects with a late onset 6.1 ± 1.6 years. Cox regression analyses adjusted for age, sex, educational level, MMSE, and subjective memory complaints showed that having a history of depression increased the risk of AD (HR 2.46; 95% CI 1.15 to 5.26). This risk did not materially change after adjustment for hippocampal and amygdalar volume (HR 2.97; 95% CI 1.33 to 6.61). When we divided the group with a history of depression into early and late onset, subjects with an early onset of depression particularly were at increased risk of developing AD (HR 3.70;

Table 2 Risk (hazard ratios with 95% CIs) of dementia and Alzheimer disease (AD) associated with history of depression and presence of depressive symptoms

	Cases/ person-year	AD Model 1, HR (95% CI)*	AD Model 2, HR (95% CI)†	Cases/ person-year	All-cause dementia Model 1, HR (95% CI)*	All-cause dementia Model 2, HR (95% CI)†
No history of depression/ history of depression	21/2,057 12/797	1 (reference) 2.46 (1.15–5.26)	1 (reference) 2.97 (1.33–6.61)	28/2,057 16/797	1 (reference) 2.44 (1.26–4.71)	1 (reference) 2.86 (1.45–5.63)
No history depression	21/2,057	1 (reference)	1 (reference)	28/2,057	1 (reference)	1 (reference)
Early onset	7/516	3.70 (1.43–9.58)	3.76 (1.41–10.06)	8/516	3.23 (1.36–7.70)	3.37 (1.39–8.17)
Late onset	5/281	1.71 (0.62–4.74)	2.34 (0.82–6.69)	8/281	1.98 (0.87–4.54)	2.51 (1.08–5.85)
Not depressed	27/2,640	1 (reference)	1 (reference)	36/2,640	1 (reference)	1 (reference)
CES-D 16+	6/214	1.02 (0.40–2.64)	1.36 (0.49–3.76)	8/214	1.20 (0.52–2.79)	1.35 (0.55–3.30)

*Adjusted for age (time scale), sex, level of education, general cognitive functioning, and subjective memory complaint score.
†Additionally adjusted for total hippocampal and amygdalar volume on MRI.

95% CI 1.43 to 9.56), whereas this increased risk was less pronounced in subjects with a late onset of depression (HR 1.71; 95% CI 0.62 to 4.74). Additional adjustments for hippocampal and amygdalar volume again did not materially change the results (table 2). When using all-cause dementia as the outcome, the results did not change, although the relation between late-onset depression and dementia reached statistical significance after adjusting for hippocampal and amygdalar volumes (table 2).

Presence of depressive symptoms at baseline was not associated with risk of incident AD or all-cause dementia. Per point increase on the CES-D, the HR for AD was 0.99 (95% CI 0.95 to 1.04) and the HR for all-cause dementia was 0.99 (95% CI 0.94 to 1.03) in the first model, and did not change after additional adjustment for hippocampal and amygdalar volume. When analyzed as a dichotomous variable, high CES-D scores were also not significantly associated with risk of AD or all-cause dementia (table 2).

Adding deep white matter lesions, periventricular lesion score, brain infarcts, and subcortical brain atrophy to all models did not materially change the results (data not shown).

DISCUSSION This prospective population-based study showed that a history of depression, and in particular a first onset before age 60, increased the risk of developing AD and all-cause dementia. History of depression was not associated with hippocampal or amygdalar volumes at baseline and these volumes did not mediate the increased risk for AD associated with history of depression. Depressive symptoms at baseline were not associated with hippocampal and amygdalar volumes, and did not increase the risk of developing AD.

Before we interpret our findings, several strengths and limitations of the study need to be addressed. Strengths of this study are the large sample size with many MRI parameters, the population-based sample of elders without dementia at baseline, its prospective design, and the complete follow-up ascertainment of dementia. In addition, since we had measures of hippocampal and amygdalar volumes on MRI as well as incident AD, we were able to determine whether these volumes mediated a relation between depression and AD.

A limitation of the study may be that we had to rely on self-report of history of depressive episodes. It has been reported that agreement between self-reported depression and clinical diagnosis may be limited and that cases of depression may be missed when relying on self-report.[34] This will most likely result in overrepresentation of the more severe depressive episodes. In our study, some of the milder depressive episodes may thus have been classified as having no history of depression, resulting in an underestimation of the observed relation. Another limitation is that we did not have follow-up measures of hippocampal and amygdalar volume, and we therefore do not know to what extent smaller hippocampal and amygdalar volumes represented loss of volume or pre-existing smaller volumes.

We did not find that having a history of depression was associated with smaller hippocampal or amygdalar volumes. Our findings are in contrast with a number of clinical studies in patients with major depression or post-traumatic stress disorder that observed that compared to controls, these patients had unilateral or bilateral smaller hippocampal and amygdalar volumes on MRI, although absence of a relation has also been observed.[7-10,35-37] It is also possible that patients with severe clinical depression have smaller volumes and that we had too few cases of severe depression to find a significant relation.

We also did not find that depressive symptoms at baseline increased risk for dementia or AD. Several epidemiologic studies, although not all,[12,13] showed that clinical depression or depressive symptoms at baseline increased the risk for dementia and AD during follow-up.[14,38-40] This discrepancy in findings may be explained by difference in depression measures between studies. It is possible that only more severe depressive symptoms or clinical depression is associated with increased dementia risk. In our study, the number of persons scoring above the clinical cut-off on the CES-D was relatively low. Also, our study population consisted of subjects who, compared to those who did not participate, were relatively young and had somewhat better cognitive functioning at baseline. This may have reduced the number of incident dementia cases. As a result, we may have had limited statistical power to find a significant association with incident AD.

The finding that early onset depression particularly increased the risk for AD and all-cause dementia could be interpreted as being supportive of the hypothesis that depression is a true risk factor for AD. From the glucocorticoid cascade hypothesis[41] it would be predicted that depression leads to AD through a damaging effect on the hippocampus. We thus expected that the risk for AD associated with depression would be attenuated after adjusting for hippocampal and amygdalar volume. However, we did not find a significant association between history of depression and hippocampal and amygdalar volume at baseline, nor did adjusting for these parameters reduce the risk of AD. Also, the risk estimates were fairly similar for all-cause dementia and thus not suggestive of specificity for AD, and adjustment for vascular MRI parameters did not alter the risk estimates. Another possibility is that the effect of depression is not through the hippocampus or the amygdala but through other brain structures. An alternative explanation for our findings could be that early onset depression and AD are not causally related, but that another, unknown factor leads to increased risk of both depression and AD. At baseline, subjects who reported a history of depression before age 60 were on average 6 years younger than subjects without a history of depression. Since the follow-up time was comparable among the three groups, these subjects developed depression as well as dementia at a younger age.

In this prospective population-based study of nondemented elders, history of depression and in particular and early onset, but not presence of depressive symptoms increased risk for dementia and AD. This risk was not mediated by smaller hippocampal or amygdalar volumes. Future studies should determine whether early onset depression is a true risk factor for development of AD or whether a third factor causes both depression and dementia.

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