

Use of Hippocampal and Amygdalar Volumes on Magnetic Resonance Imaging to Predict Dementia in Cognitively Intact Elderly People

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Context: The recent focus on the development of preventive interventions for Alzheimer disease has fueled the search for biomarkers of presymptomatic disease. Patients with Alzheimer disease and mild cognitive impairment have marked atrophy of the hippocampus and amygdala compared with healthy elderly people. Whether atrophy of these structures is also present in persons without cognitive impairment who later develop dementia is unknown.

Objective: To assess whether volumetric assessment of the hippocampus and amygdala using magnetic resonance imaging (MRI) predicts dementia in elderly people without cognitive impairment.

Design: Longitudinal cohort study.

Setting: A general community in the Netherlands.

Participants: Five hundred eleven persons, aged 60 to 90 years, free of dementia at baseline were followed up during 3043 person-years (mean per person, 6.0 years). We performed volumetric assessment of the hippocampus and amygdala, obtained information about daily memory problems, and performed extensive neuropsychological testing in all study participants.

Main Outcome Measure: Dementia, as assessed by repeated neuropsychological screening and monitoring of medical records.

Results: Thirty-five persons developed dementia (26 with Alzheimer disease). Hippocampal and amygdalar volumes were strongly associated with the risk of dementia; the age-, sex-, and education-adjusted hazard ratio per 1-SD decrease in volume was 3.0 (95% confidence interval, 2.0-4.6) for the hippocampus and 2.1 (95% confidence interval, 1.5-2.9) for the amygdala. The hazard ratios associated with atrophy were similar in persons without memory complaints or low cognitive function at baseline. Compared with those remaining free of dementia, baseline brain volumes were 17% smaller in persons who received a clinical diagnosis of dementia within 2 to 3 years after MRI and still 5% smaller in those whose conditions were diagnosed 6 years after MRI.

Conclusion: Atrophy of the hippocampus and amygdala on MRI in cognitively intact elderly people predicts dementia during a 6-year follow-up.

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ALZHEIMER DISEASE IS THE most common cause of dementia in late life. Strategies to prevent or delay the disease are under development.¹ Once available, it will be important to identify people at high risk of developing dementia who may benefit from such therapies. Magnetic resonance imaging (MRI) of the brain is one potential tool for detecting the preclinical stage of the disease. Pathologically, Alzheimer disease is characterized by dense accumulation of neurofibrillary tangles and amyloid plaques in the medial temporal lobe,² leading to neuronal loss that is visible as atrophy on MRI.³ Several studies have shown marked reductions in hippocampal and amygdalar volumes on MRI in pa-

tients with overt Alzheimer disease^{4,5} compared with healthy elderly individuals. Patients with mild cognitive impairment (MCI), who are at high risk of developing Alzheimer disease,⁶ also have smaller hippocampal volumes than healthy elderly people.⁷⁻¹⁰ The question remains whether hippocampal atrophy can also predict subsequent development of Alzheimer disease at an earlier stage, before the first occurrence of memory complaints and MCI. We addressed this question by studying the longitudinal relationship between volumes of the hippocampus and amygdala on MRI and incident dementia in the general population. By taking into account memory complaints and neuropsychological performance at baseline, we sought to investigate whether at-

rophy on MRI predicts dementia even in people without cognitive problems. We used data from the population-based Rotterdam Scan Study,¹¹ in which 511 elderly individuals without dementia underwent volumetric MRI assessments of the hippocampus and amygdala and who were then followed up for an average period of 6 years.

METHODS

PARTICIPANTS

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.¹¹ From 1995 to 1996, we randomly selected 965 living members (aged 60-90 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.¹² As part of the eligibility criteria, we excluded individuals who had dementia,¹² were 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%). Complete MRI data, including a 3-dimensional MRI sequence, were obtained in 511 persons.¹³ The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, the Netherlands.

MRI ASSESSMENTS

At baseline examinations from 1995 to 1996, a 3-dimensional MRI sequence covering the whole brain was made using a 1.5-T MRI unit.¹³ We reformatted coronal slices (1.5-mm contiguous slices) from this 3-dimensional MRI sequence in such a way that they were perpendicular to the long axis of the hippocampus. The left and right hippocampus and amygdala were manually outlined on each slice with a mouse-driven cursor.¹³ Absolute volumes were calculated by multiplying the areas on each slice by the slice thickness. We summed the left and right sides to yield total volumes because the analyses did not suggest laterality of effects. As a proxy for head size, we measured the intracranial cross-sectional area on a reformatted middle sagittal MRI slice.¹³ Two readers (T.d.H. and colleague) who were blinded to clinical information measured the 511 images. Intrarater and interrater correlation coefficients have been reported¹³ and showed good reproducibility. We corrected for head size differences across individuals by dividing the raw volumes by the subject's calculated head size and subsequently multiplying this ratio by the average head size area (men and women separately).⁵

ASCERTAINMENT OF INCIDENT DEMENTIA

All 511 participants were free of dementia at baseline, and we followed up the cohort for incident dementia.¹² Briefly, participants were screened at follow-up visits (1997-1999, 1999-2000, and 2002-2003) with the Mini-Mental State Examination (MMSE) and the Geriatric Mental Schedule, and when the screen was positive for dementia we assessed participants with the Cambridge Examination for Mental Disorders of the Elderly interview. Participants who were thought to have dementia were examined by a neurologist and underwent extensive neuropsychological testing. The MRI at baseline was not used in diagnosing dementia. The number of participants who could be examined in person at the follow-up visits were 430, 378,

and 289, respectively, in 1997-1999, 1999-2000, and 2002-2003. 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 511 participants at the general physicians' offices and the Regional Institute for Ambulatory Mental Health Care (Rotterdam) to obtain information on diagnosed dementia; follow-up was complete until January 1, 2003. A diagnosis of dementia and Alzheimer disease was made by a panel that consisted of a neurologist, neuropsychologist, and research physician and used standard criteria.^{14,15} The onset of dementia was defined as 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.

OTHER MEASUREMENTS

Because memory impairment is the first detectable neuropsychological sign of incipient Alzheimer disease,⁶ we questioned persons on memory complaints. This was done by a single question: "Do you have complaints about your memory performance?" This question has been previously shown to predict incident dementia.¹⁶ Objective memory performance was assessed using a 15-word verbal learning task. First, 3 trials of 15 similar words were administered to test immediate recall. Delayed recall was tested with interference from other neuropsychological tests 15 minutes later.¹⁷ For each participant, we calculated *z* scores based on the results of the memory test (the *z* score equals the individual test score minus the mean test score divided by the standard deviation). We constructed a compound score for memory performance by averaging the *z* scores of the total of the 3 immediate recall trials and the delayed recall trial of the 15-word verbal learning task.¹² Additionally, we administered tests that assess psychomotor speed: the Stroop test, the Letter-Digit Substitution Test, and the Paper and Pencil Memory Test.¹² A compound score for psychomotor speed was calculated by averaging the *z* scores of the first part of the Stroop, the correct number on the Letter-Digit Substitution Test, and the first part of the Paper and Pencil Memory Test. Finally, a compound score for global cognitive function was calculated by averaging the *z* scores of the memory test and the tests for psychomotor speed.

We defined MCI as having (1) memory complaints and (2) objective memory impairment: memory *z* score greater than 1.5 SD below age- and education-specific means. These criteria are similar to the frequently used Petersen criteria of MCI¹⁸ except that we lacked corroboration of the memory complaint by an informant. The mean \pm SD MMSE score in persons with MCI was 26.5 ± 2.2 , which is equal to the MMSE scores in a study of persons with MCI studied by Petersen et al.¹⁹ In persons with MCI, the mean \pm SD *z* score was -1.61 ± 0.43 for memory, -0.31 ± 0.89 for psychomotor speed, and -0.87 ± 0.62 for global cognitive function.

We evaluated other characteristics on brain MRI that have previously been associated with dementia.¹² White matter lesions were considered present if visible as hyperintense on proton density and T2-weighted axial images, without prominent hypointensity on T1-weighted studies. Periventricular white matter lesions were scored semiquantitatively from 0 to 9.¹² We defined infarcts as focal hyperintensities on T2-weighted images. Infarcts in the white matter also had to have corresponding hypointensities on T1-weighted images 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.

With Cox proportional hazards models, we calculated adjusted hazard ratios of dementia per standard deviation decrease in volumes on MRI. We also made age- and sex-specific tertiles of volumes, which we denote as severe, moderate, and no atrophy. To investigate how long before clinical onset of dementia atrophy is noticeable, we calculated the difference in baseline brain volume for each person who developed dementia compared with those who were still alive and free of dementia in the cohort at the time of diagnosis. We then grouped those who developed dementia into 3 equally sized groups based on the time between baseline and clinical onset of dementia (median time since baseline, 2.0, 4.9, and 6.3 years) and plotted the average volume difference in these groups against the median time until onset of dementia. In the basic model, we adjusted for age, sex, and level of education. Additional adjustments included periventricular white matter lesions, brain infarcts, and subcortical atrophy on MRI.¹² Analyses were repeated after excluding persons with MCI at baseline. Then we excluded persons with a low performance on memory tasks at baseline (>1 or >1.5 SDs below age- and education-adjusted means), and finally, we excluded persons with memory complaints at baseline.

Table 1. Baseline Characteristics of the Study Sample*

Characteristic	Value (N = 511)
Age, mean (SD), y	73.4 (8.0)
Women	251 (49)
Primary education only	157 (31)
Memory complaint	159 (31)
Hypertension†	270 (52)
Diabetes mellitus‡	41 (8)
Atrial fibrillation on ECG	13 (2.5)
Brain infarct on MRI	143 (28)
Periventricular white matter lesions on MRI, mean (SD) (severity range, 0-9)	2.7 (2.2)
Subcortical brain atrophy on MRI, mean (SD), average ventricle-brain ratio	0.31 (0.04)
Hippocampal volume on MRI, mean (SD), mL	6.38 (0.88)
Amygdala volume on MRI, mean (SD), mL	4.57 (0.72)

Abbreviations: ECG, electrocardiogram; MRI, magnetic resonance imaging.

*Data are given as number (percentage) of patients unless otherwise indicated.

†Defined as systolic blood pressure of 160 mm Hg or higher or diastolic blood pressure of 95 mm Hg or higher or use of antihypertensive medications.

‡Defined as use of antidiabetic medication or a random glucose level of 200 mg/dL (11.1 mmol/L) or higher.

Table 1 presents the baseline characteristics of the study sample. There were 143 participants (28%) who had a brain infarct on MRI, of whom 28 had experienced symptoms of a cerebrovascular accident. For the other participants, the brain infarcts on MRI were “silent.”¹² Other neurologic disorders were present in 5 participants (1%) who had Parkinson disease and 2 participants who had epilepsy. Sixteen persons (3%) fulfilled criteria of MCI at baseline, a prevalence in line with other community studies.⁶ **Table 2** gives the baseline cognitive function in the whole cohort and in participants, excluding persons with MCI, those with low memory performance, and those with memory complaints. As expected, cognitive function was better in these latter groups.

During a total of 3043 person-years of follow-up (mean per person, 6.0 years), 35 persons developed dementia, of whom 26 received a clinical diagnosis of Alzheimer disease. Persons with incident dementia had at baseline a low MMSE score (mean±SD, 26.2±2.6), memory z score (mean±SD, -1.00±0.80), psychomotor speed z score (mean±SD, -0.60±0.79), and global cognitive z score (mean±SD, -0.78±0.60).

Persons with severe atrophy of the hippocampus or the amygdala had the highest risk of developing dementia and Alzheimer disease, independent of other brain MRI measures (**Table 3** and **Table 4**). In people with no hippocampal atrophy, the incidence rate of dementia was 4.8 per 1000 person-years, whereas in people with severe hippocampal atrophy, the incidence rate was 21.6 per 1000 person-years. The risk of dementia increased 3-fold per 1-SD decrease in hippocampal volume (age-, sex- and education-adjusted hazard ratio, 3.0; 95% confidence interval [CI], 2.0-4.6). For the amygdala we found incidence rates of 2.9 per 1000 person-years in people with no atrophy and 19.4 per 1000 person-years in people with severe atrophy. The risk of dementia doubled per 1-SD decrease in amygdalar volume (age-, sex- and education-adjusted hazard ratio, 2.1; 95% CI, 1.5-2.9). The risk of dementia associated with atrophy was similar in persons without MCI, low performance on memory tasks, or memory complaints at baseline (**Figure 1**). Hippocampal and amygdalar atrophy were not associated with low speed performance (data not shown), but hippocampal atrophy was associated with

Table 2. Baseline Cognitive Function*

Cognitive Function	All Participants (N = 511)	Participants Without			
		MCI† (n = 495)	Memory Impairment >1.5 SDs‡ (n = 471)	Memory Impairment >1.0 SD‡ (n = 413)	Memory Complaints (n = 351)
Mini-Mental State Examination score	27.7 (2.1)	27.8 (2.1)	27.9 (1.9)	28.1 (1.8)	27.8 (2.1)
Memory function, z score	0	0.05 (0.90)	0.10 (0.86)	0.25 (0.80)	0.10 (0.92)
Psychomotor speed, z score	-0.02 (0.84)	-0.01 (0.84)	0.02 (0.83)	0.04 (0.85)	0.03 (0.80)
Global cognitive score, z score	-0.01 (0.72)	0.01 (0.71)	0.05 (0.68)	0.13 (0.67)	0.06 (0.68)

Abbreviation: MCI, mild cognitive impairment.

*Data are presented as mean (SD).

†Defined as presence of memory complaints and memory performance of more than 1.5 SDs below the age- and education-adjusted means in memory tests.¹⁸

‡Defined as scoring greater than 1.5 or 1.0 SD below the age- and education-adjusted means of the memory test.

Table 3. Baseline Hippocampal Atrophy on MRI and Risk of All-Cause Dementia and Alzheimer Disease*

Hippocampus Atrophy Severity†	All-Cause Dementia				Alzheimer Disease		
	No. of Patients	HR (95% CI)		No. of Patients	HR (95% CI)		
		Adjusted for Age, Sex, and Education	Adjusted for Age, Sex, Education, and Other MRI Measures‡		Adjusted for Age, Sex, and Education	Adjusted for Age, Sex, Education, and Other MRI Measures‡	
None (n = 169)	5	1.0	1.0	4	1.0	1.0	
Moderate (n = 173)	9	1.8 (0.6-5.4)	1.9 (0.6-5.6)	6	1.5 (0.4-5.4)	1.6 (0.4-5.6)	
Severe (n = 169)	21	4.5 (1.7-12.1)	3.9 (1.5-10.5)	16	4.6 (1.5-13.9)	4.0 (1.3-12.0)	
P for trend§		.001	.004		.002	.008	

Abbreviations: CI, confidence interval; HR, hazard ratio; MRI, magnetic resonance imaging.

*Values are adjusted HRs of dementia with 95% CIs compared with no atrophy.

†Based on age- and sex-specific tertiles.

‡The MRI measures adjusted for were severity of periventricular white matter lesions, brain infarcts, and severity of subcortical atrophy.

§P value of linear trend analysis.

Table 4. Baseline Amygdalar Atrophy on MRI and Risk of All-Cause Dementia and Alzheimer Disease

Amygdala Atrophy Severity	All-Cause Dementia				Alzheimer Disease		
	No. of Patients	HR (95% CI)		No. of Patients	HR (95% CI)		
		Adjusted for Age, Sex, and Education	Adjusted for Age, Sex, Education, and Other MRI Measures‡		Adjusted for Age, Sex, and Education	Adjusted for Age, Sex, Education, and Other MRI Measures‡	
None (n = 170)	3	1.0	1.0	2	1.0	1.0	
Moderate (n = 171)	13	4.4 (1.3-15.5)	4.2 (1.2-14.7)	10	5.2 (1.1-23.8)	4.8 (1.1-22.1)	
Severe (n = 170)	19	7.3 (2.2-25.0)	6.0 (1.7-20.8)	14	8.6 (1.9-38.0)	7.0 (1.6-31.8)	
P for trend§		.001	.003		.002	.007	

Abbreviations: CI, confidence interval; HR, hazard ratio; MRI, magnetic resonance imaging.

*Values are adjusted HRs of dementia with 95% CIs compared with no atrophy.

†Based on age- and sex-specific tertiles.

‡The MRI measures adjusted for were severity of periventricular white matter lesions, brain infarcts, and severity of subcortical atrophy.

§P value of linear trend analysis.

low memory performance.¹⁷ In persons with memory performance greater than 1.5 SDs below age- and education-adjusted means, the mean ± SD hippocampal volume was 6.00 ± 1.09 mL, which was 0.38 mL smaller than in all participants (Table 1). The mean ± SD amygdalar volume was 4.50 ± 0.82 mL, similar to that of the whole group. We also analyzed the association between MRI volumes and incident dementia within persons with low cognitive performance at baseline, although small numbers prevent firm conclusions. In persons with MCI (16, of whom 5 developed dementia), the age-, sex-, and education-adjusted hazard ratio per 1-SD decrease was 14.3 (95% CI, 1.2-169.0), yet the model for amygdalar volume did not converge. In the group with memory impairment greater than 1.5 SDs below age- and education-adjusted means (29, of whom 8 developed incident dementia), the hazard ratio was 6.7 (95% CI, 1.7-25.8) per 1-SD decrease in hippocampal volume and 2.9 (95% CI, 1.3-6.5) per 1-SD decrease in amygdalar volume.

Figure 2 shows that persons who developed dementia had significantly smaller hippocampal and amygdalar volumes at baseline than persons without incident dementia. Volume reduction at baseline was inversely associated with time until onset of dementia.

COMMENT

In this large population-based cohort study in elderly people, we found that atrophy of the hippocampus and amygdala on MRI predicted dementia and Alzheimer disease during a 6-year follow-up, even in persons without memory complaints or low cognitive performance at baseline. The strength of our study is the large population and the long follow-up duration. The number of persons who developed dementia was, as expected, based on incident rates in other general populations.²⁰

The in vivo use of MRI volumes of the hippocampus in Alzheimer disease has been validated by histologic studies that showed correlations with postmortem neuronal loss and Alzheimer disease.^{3,21} After early MRI studies²² had showed atrophy of the hippocampus in patients with dementia of moderate severity, later studies^{7,10,23} found atrophy in patients with milder dementia. Atrophy on MRI is also observed in high-risk populations, such as patients with MCI^{8-10,24,25} or persons at risk of autosomal dominant familial Alzheimer disease.^{26,27} Within patients who have MCI, hippocampal atrophy severity predicts conversion to dementia independently of neuro-

psychological performance.^{18,28} We show that hippocampal and amygdalar atrophy on MRI increases the risk of dementia during a long follow-up period, even in people who have not yet developed memory complaints or cognitive impairment. This is in line with the hypothesis that there is a long presymptomatic period in the development of Alzheimer disease. Our data show that atrophy of structures in the medial temporal lobe is detectable at least 6 years before clinical onset. Although pathologic studies² have suggested that the amy-

dala is affected slightly later in the Alzheimer disease process than the hippocampus, we found amygdalar atrophy to a similar extent as hippocampal atrophy in persons who develop dementia. Cross-sectional studies^{29,30} in patients with mild Alzheimer disease also showed hippocampal and amygdalar atrophy to an equal degree. Some investigators,³¹ although not all,⁹ have advocated the use of atrophy of the entorhinal cortex on MRI in predicting Alzheimer disease because neuropathologic features of Alzheimer disease can be found in this region even before changes occur in the hippocampus.² We were thus far unable to reliably assess the entorhinal cortex on MRI in such a large series.

Concerning the extent of atrophy, we found in those destined to develop dementia volume reductions between 17% and 5%, depending on how long before the diagnosis of dementia the MRI was conducted. In persons with mild to moderate Alzheimer disease, volume reductions compared with healthy elderly persons are between 25% and 40%,²² suggesting that atrophy rates accelerate in patients with Alzheimer disease.^{25,32} In a study²⁷ of 5 middle-aged persons who developed familial Alzheimer disease within 3 years, a 16% volume difference in medial temporal lobe structures with healthy controls was observed, which fits well with our results in elderly persons. Our results did not change when we took concurrent vascular brain changes on MRI into account, suggesting that vascular brain disease and atrophy on MRI reflect different underlying processes that both independently predict dementia in late life. However, this does not exclude the possibility that vascular brain disease and atrophy act synergistically to push a person over a threshold to develop dementia symptoms. Atrophy and vascular brain disease are correlated in elderly people,³³ and hence large samples and repeated brain imaging and cognitive testing are necessary to fully disentangle their effects on cognitive decline and risk of dementia.

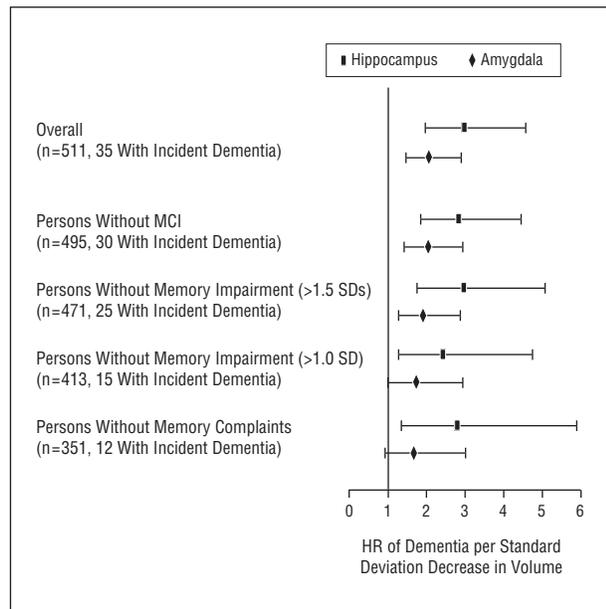


Figure 1. Risk of dementia with smaller hippocampal and amygdalar volumes on magnetic resonance imaging (hazard ratios [HRs] per standard deviation decrease with 95% confidence intervals [error bars]). Analyses were performed in the whole population, in persons without mild cognitive impairment (MCI), in persons without memory impairment (scoring >1.5 SDs or 1 SD below age- and education-adjusted means), and in persons without memory complaints. Adjustments were made for age, sex, and education.

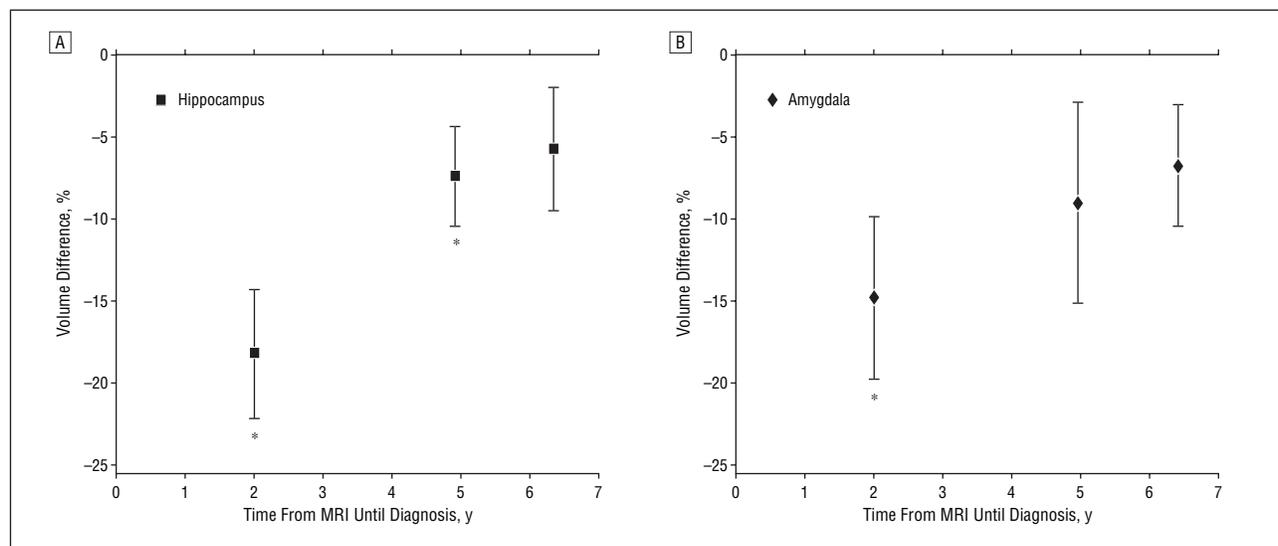


Figure 2. Volume difference at baseline magnetic resonance imaging (MRI) in the hippocampus (A) and amygdala (B) of persons who developed dementia (n=35) at different time points after baseline compared with people who were free of dementia and alive. We made tertiles according to time after baseline that the diagnosis was made and plotted the differences (with standard error [error bars]) at the median time point in these tertiles. Adjustments were made for age, sex, and education. Asterisk indicates $P < .05$.

The emergence of potentially disease-modifying therapies for Alzheimer disease highlights the need to identify high-risk persons who may benefit from such therapies. Treatment and preventive interventions yield the largest benefit early in the disease process, at a stage when brain damage is not extensive and there are no or only a few symptoms. Our study suggests that structural brain imaging can help identify people at high risk for developing dementia, even before they have any memory complaints or measurable cognitive impairment. However, we must bear in mind that most people with atrophy did not develop dementia, even after 6 years. Further prospective population studies are therefore required to find additional biomarkers, including other brain imaging parameters, that alone or in combination with clinical and genetic characteristics can help separate those who are at risk for developing dementia from those who are not.

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