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Sex-Related Reserve Hypothesis in Alzheimer's Disease: Changes in Cortical Thickness with a Five-Year Longitudinal Follow-Up

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Abstract

Background: Sex effects on the progression of Alzheimer's disease (AD) have received less attention than other demographic factors, including onset age and education.

Objective: The aim of this study was to investigate whether sex affected cortical thinning in the disease progression of AD.

Methods: We prospectively recruited 36 patients with early-stage AD and 14 people with normal cognition. All subjects were assessed with magnetic resonance imaging at baseline, Year 1, Year 3, and Year 5. We performed cortical thickness analyses using surface-based morphometry on magnetic resonance imaging.

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SUPPLEMENTARY MATERIAL

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Results: Women with AD showed more rapid cortical thinning in the left prefrontal cortex, bilateral medial frontal cortices, bilateral temporo-parietal association cortices, and bilateral lateral temporal lobe over 5 years than men with AD, even though there was no difference in cortical thickness at baseline. In contrast, there were no regions of significantly more rapid atrophy in men with AD.

Conclusions: Our findings suggest that women deteriorate faster than men in the progression of AD.

Keywords

Alzheimer's disease; cognitive reserve; cortical thickness; longitudinal study; sex

INTRODUCTION

Alzheimer's disease (AD) is the most common type of dementia, with prevalence increasing every year [1]. Factors known to alter the risk of developing AD include sex as well as age, educational level, and vascular risk factors. Women are more susceptible to AD [2] and incidence of AD for women is twice the rate for men [3]. Many studies have reported sex differences in risk factors, response to cholinesterase inhibitors, and clinical course of AD, although the results were not completely consistent [4–7].

Women and men demonstrate brain structural and functional differences, not only throughout development and aging, but also during the progression of neurodegeneration. For example, men have been found to have larger brain volumes, a greater number of neurons [8], and better visuospatial abilities [9], while women exhibit better performance at verbal memory tasks [10, 11] and more efficient neural processing [12]. However, studies on the effects of sex on cortical atrophy in AD patients have produced inconsistent results. While some studies have reported that cortical thinning in AD patients was more prominent in anterior cingulate, frontal, and parietal cortices in men than in women [13–15], other studies have reported either opposite results [14, 16–18] or no sex differences in cortical thickness [19, 20].

Although brain changes have been found to be associated with many complex factors, there have been only a few longitudinal studies investigating sex differences in the progression of AD [17, 21, 22]. Previous studies from our group suggested that sub-groups with better premorbid performance showed steeper rates of cortical thinning after the development of AD compared to others [23, 24]. For example, early-onset AD patients exhibited steeper rates of parietal cortical thinning than late-onset AD patients [23]. Highly-educated AD patients also revealed steeper rates of cortical thinning in medial frontal, temporal, and parietal regions than poorly-educated AD patients [24]. We, therefore, aimed to determine whether sex affected cortical thinning in AD patients. Given that men have better visuospatial abilities [9] and women have better performance on verbal memory tasks [11], we hypothesized that women with AD would have faster cortical thinning in the medial temporal lobe while men with AD would have faster cortical thinning in the parietal lobe.

METHODS

Participants

We prospectively recruited 36 patients with AD to participate in the Alzheimer Disease and Positron Emission Tomography (ADAPET) study, which has been described in detail in previous studies [23, 25]. The patients met the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV; [26] and the criteria for probable Alzheimer's disease proposed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; [27]. Early-stage AD patients (Clinical Dementia Rating [CDR] = 0.5 or 1) with a caregiver were enrolled into this longitudinal study. None had a family history suggestive of an autosomal dominant disease. We excluded patients with other brain structural lesions on magnetic resonance imaging (MRI), such as territorial infarction, intracranial hemorrhage, brain tumor, hydrocephalus, or severe white matter hyperintensities.

At the initial visit, patients underwent clinical interviews, neurological examination, Mini-Mental Status Examination (MMSE), Clinical Dementia Rating (CDR), and conventional brain MRI scans. We assessed sex through their medical records and interviews. Secondary causes of cognitive deficits were ruled out by laboratory tests including complete blood count, blood chemistry, vitamin B12, folate, syphilis serology, and thyroid function tests.

We recruited 14 healthy volunteers with normal cognition (NC) who were spouses of the AD patients without history of neurological or psychiatric illnesses and neurologic deficits. This NC group exhibited normal cognition on the neuropsychological testing.

This study was approved by the Institutional Review Board of Samsung Medical Center. We obtained informed consent from all patients and control participants.

Image acquisition and cortical thickness measurement

Three-dimensional T1-weighted Turbo Field Echo MRI images from 50 participants (36 patients with probable AD and 14 NC) were acquired using the same MRI scanner (Philips 3.0T Achieva) with the same imaging parameters (sagittal slice thickness = 1.0 mm, overcontiguous slice acquisition with 50% overlap; no gap; repetition time = 9.9 ms; echo time = 4.6 ms; flip angle = 8°; and matrix size = 240 × 240 pixels, reconstructed to 480 × 480 over a field of view of 240 mm). Images were processed by the standard Montreal Neurological Institute anatomic pipeline. Further image processing methods for cortical thickness measurement were described in a previous study [28].

Follow-up evaluations with neuroimaging

In the ADAPET study, patients performed high-resolution T1-weighted MRI scans at baseline and repeated at 1, 3, and 5 years from baseline. Of the 36 AD patients at baseline, 34, 27, and 17 patients completed the first, third, and fifth year of follow-up procedures, respectively. Nineteen patients were excluded during longitudinal follow-up, due to consent withdrawal (n = 6), stroke (n = 2), newly-developed breast cancer (n = 1), death (n = 5),

immobilization from progression of AD ($n = 3$), and MRI acquisition failures ($n = 2$). Of the 14 NCs at baseline, 13, 13, and 12 completed the first, third, and fifth year of follow-up procedures, respectively. Two NCs were excluded due to consent withdrawal and stroke. One participant at baseline and four participants at 3 years from baseline were excluded due to technical problems with cortical thickness estimation. The total number of subjects (women with AD, men with AD, women with NC, and men with NC) that participated in cortical thickness analysis is illustrated in Fig. 1.

Statistical analysis

Differences in demographic data between groups were assessed using Student's *t*-tests for continuous variables and Chi-square tests for dichotomous variables. In order to compare baseline differences in mean cortical thickness between groups, we performed an analysis of covariance (ANCOVA) including age, education, disease duration, onset age (early onset versus late onset), presence of APOE $\varepsilon 4$ genotype, and intracranial volume (ICV) as covariates. In order to assess differences in longitudinal changes in mean cortical thickness between groups over five years, we used mixed effects model. Mixed effects models allowed for the analyses of all available data despite missing values. The mean cortical thickness values at each evaluation time were the dependent variables. Fixed effects variables included age, education, disease duration, ICV, onset age (early onset versus late onset), presence of APOE4 genotype, groups (sex in AD and sex in NC), time (years from baseline assessment), and the interaction between groups and time. Patients were entered as the random effects variable. The interaction between groups and time provided an estimate of whether there was a statistically significant difference in the change in mean cortical thickness between groups over time. Demographic data and mean cortical thickness analyses were performed using PASW (Predictive Analysis Software) 22.0 (SPSS, Chicago, IL, USA).

In order to compare the topography of cortical thickness, the Surfstat package created by Dr. Keith Worsley (http://www.math.mcgill.ca/keith/surfstat) was used. Group differences at baseline and the interaction between groups and time were tested by general linear mixed effects models. Each subject's native-space cortical thickness at every vertex was tested, accounting for the effects of age, education, disease duration, onset age (early onset versus late onset), presence of APOE $\varepsilon 4$ genotype, and ICV. A correction for performing multiple comparisons was made using the false discovery rate (FDR) theory [29] ataq value of 0.05 after pooling the *p* values.

RESULTS

Demographic and clinical characteristics

Demographics and clinical data are presented in Table 1. There were no differences in baseline age, proportion of early onset AD, MMSE, CDR, and CDR-Sum of Boxes (CDR-SOB) between women and men with AD. Women with AD had fewer years of education and shorter duration of disease compared to men with AD. No differences were found in these demographic characteristics between women and men with normal cognition.

Comparisons of baseline cortical thickness between women and men with AD and normal cognition

There were no differences in total mean cortical thickness between women and men with AD at baseline (Table 2). Also, there were no regions with significantly different cortical thickness at baseline when comparing women and men with AD (Fig. 2A). There were no differences in total and regional cortical thickness between women and men with normal cognition at baseline (Table 2, Fig. 2B).

Comparisons of longitudinal change in cortical thickness and cognition between women and men with AD and normal cognition

When comparing total cortical thinning over 5 years, women with AD tended to show more rapid decline than men with AD, although no significant interaction between groups and time was observed in AD patients (women versus men; $\beta = -0.02$, $p = 0.138$). Figure 3A provides statistical maps of vertices that showed significant group-by-time interactions in cortical thickness during five years of follow-up. Over five years, women with AD showed more rapid cortical thinning in the left dorsolateral frontal cortex, left superior temporal gyrus, bilateral temporo-parietal association cortices (Left > Right), bilateral anterior cingulate gyri, bilateral medial frontal cortices, and bilateral occipital cortices than did men with AD. The men with AD did not show more rapid decline in any regions compared to women with AD. Over the follow-up periods, women and men in the NC group did not show significantly different changes of either total or regional cortical thickness (Fig. 3B).

There were no differences in changes in scores of neuropsychological tests between women and men with AD (Supplementary Table 1).

DISCUSSION

In the present study, we investigated sex effects on the progression of AD. We found that women with AD showed more accelerated cortical thinning over five years than men with AD, although baseline comparisons showed no differences in cortical thickness between women and men in either the AD or NC groups. From these results, we suggest that women might exhibit more rapid deterioration than men as the disease progresses, as women have similar cortical thickness in the early stage of AD compared with men.

Several cross-sectional studies have shown inconsistent results regarding the effect of sex on brain structures in patients with AD. While some studies have reported that cortical thinning was more severe in men with AD [13, 15], others have found greater thinning in women with AD [14]. In line with previous studies [19, 20, 28], we found no differences in cortical thickness at baseline between men and women with early-stage AD after controlling for age, education, disease duration, onset age (early onset versus late onset), presence of APOE $\varepsilon 4$ genotype, and ICV. These previous studies included heterogeneous AD patients, with variability in characteristics such as disease duration, age, educational level, and disease severity; these different epidemiological and clinical characteristics could influence the course of disease, and contribute to inconsistent findings regarding sex effects on AD. As AD is a degenerative disease, longitudinal evaluation is more valuable than cross-sectional

evaluation of the understanding of disease progression and the effects of demographic and clinical characteristics on AD.

Our major finding was that women showed more rapid cortical thinning than men as AD progressed. While the exact pathomechanism has not been fully established, our finding is in line with a pathologic study showing that women with AD had more neurofibrillary tangles than men [30]. Our findings might be explained by a sex-related cognitive reserve hypothesis. That is, individuals with higher cognitive reserve show greater resistance to pathologic burden before the clinical manifestation of AD. However, once clinical symptoms present, the rate of progression for those with greater reserve is faster than for those with lower cognitive reserve. In previous studies, women with mild cognitive impairment showed better verbal memory function than men despite similar levels of brain hypometabolism [11] and similar AD pathology burden [31] indicative of greater cognitive reserve. Women's advantage in verbal memory is sustained during hippocampal atrophy [10] and metabolic deficits in the mild cognitive impairment stage of AD, but is eliminated when hippocampal atrophy and metabolic deficits become more severe in AD. Also, another study showed that healthy women have more economical 'small-world' architecture denoted by higher local clustering and shorter path lengths between nodes than men [12], suggesting that women have more efficient neural processing for regional tasking. Alternatively, differences may be explained by hormonal effects. Specifically, in pre-menopausal women, estrogen has mitochondrial protection effects against amyloid-β through antioxidant enzyme upregulation [32, 33], but women lose these protective effects as they experience menopause and become more vulnerable to the toxicity of amyloid-β [33–35].

Women with AD showed more rapid cortical thinning in left dorsolateral frontal cortex, left superior temporal gyrus, bilateral temporo-parietal association cortices, bilateral cingulate gyri, bilateral medial frontal cortices, and bilateral occipital cortices than men. These regions are known to be responsible for cognitive functions which are lost as AD progresses [36, 37]. Superior temporal cortex, temporo-parietal association cortices, and occipital cortices are associated with visuospatial function [38], while dorsolateral frontal cortex, left superior temporal, medial frontal, and anterior cingulate gyrus are associated with executive function and attention.

This study has some limitations. First, the patients were selected from a single center and since this was a longitudinal study, several patients withdrew during the five-year period resulting in a relatively small number of patients, therefore limiting the generalizability of the results. Second, women with AD showed lower educational level than men with AD, which might underestimate our findings. In fact, a previous study from our group suggested that AD patients with higher education levels showed more accelerated cortical thinning than those with lower education levels [24]. Third, women with AD had trends as younger and higher proportion of APOE genotype than men with AD which leaves open the possibility that our findings might be driven by these factors. Thus, we adjusted all of these factors as covariates although these factors were not different between two groups. Fourth, there were differences in the disease duration between women with AD and men with AD. A previous study suggested that the rate of cortical thinning was steep in the early stage of AD and in the later stage of AD, that of cortical thinning was steady, which is consistent with a

sigmoidal pattern [39]. This argument is mitigated to some degree by controlling for disease duration in the analyses. Finally, we could not assess the correlation between neuropsychological test scores and changes in brain structure in the present study due to the small number of patients. To address these limitations, further studies should be done with more patients in the future.

In conclusion, as disease progresses, cortical thinning was more prominent and significant in women with AD than in men. These findings are noteworthy for understanding and predicting the prognosis of AD patients and for making decisions about the care of patients in the clinic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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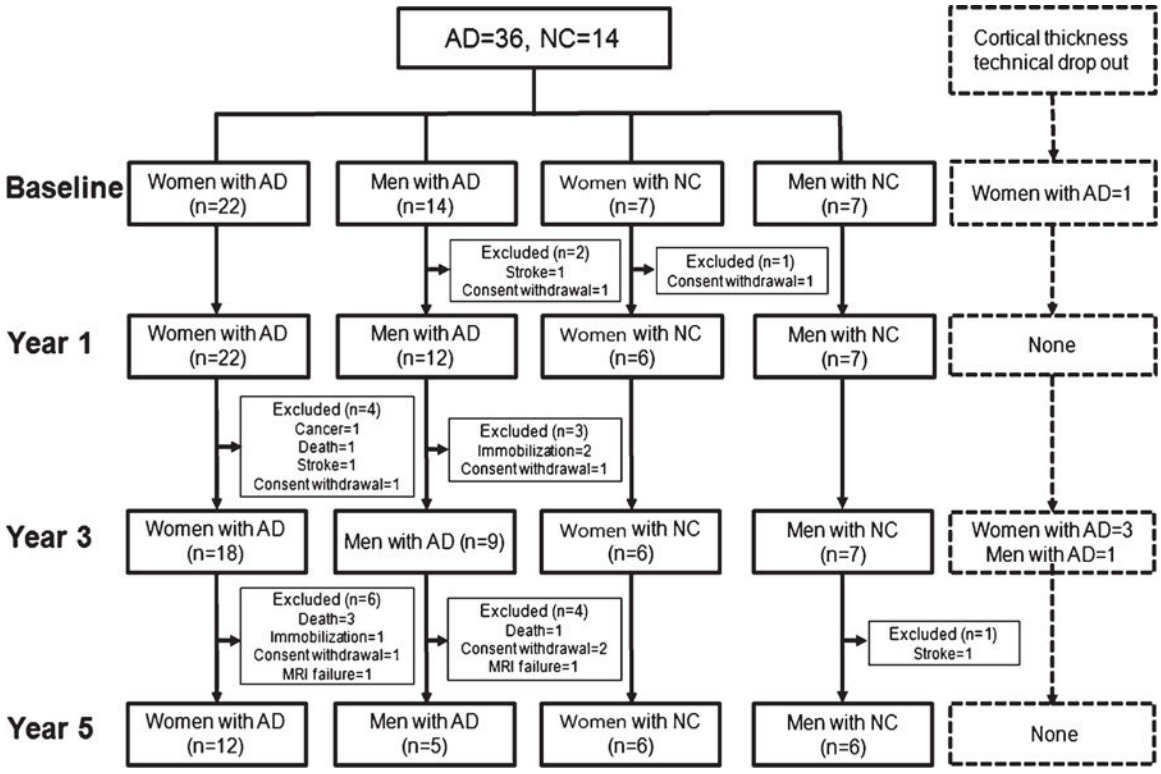

Fig. 1.

Study flow diagram. AD, Alzheimer's disease; NC, normal cognition.

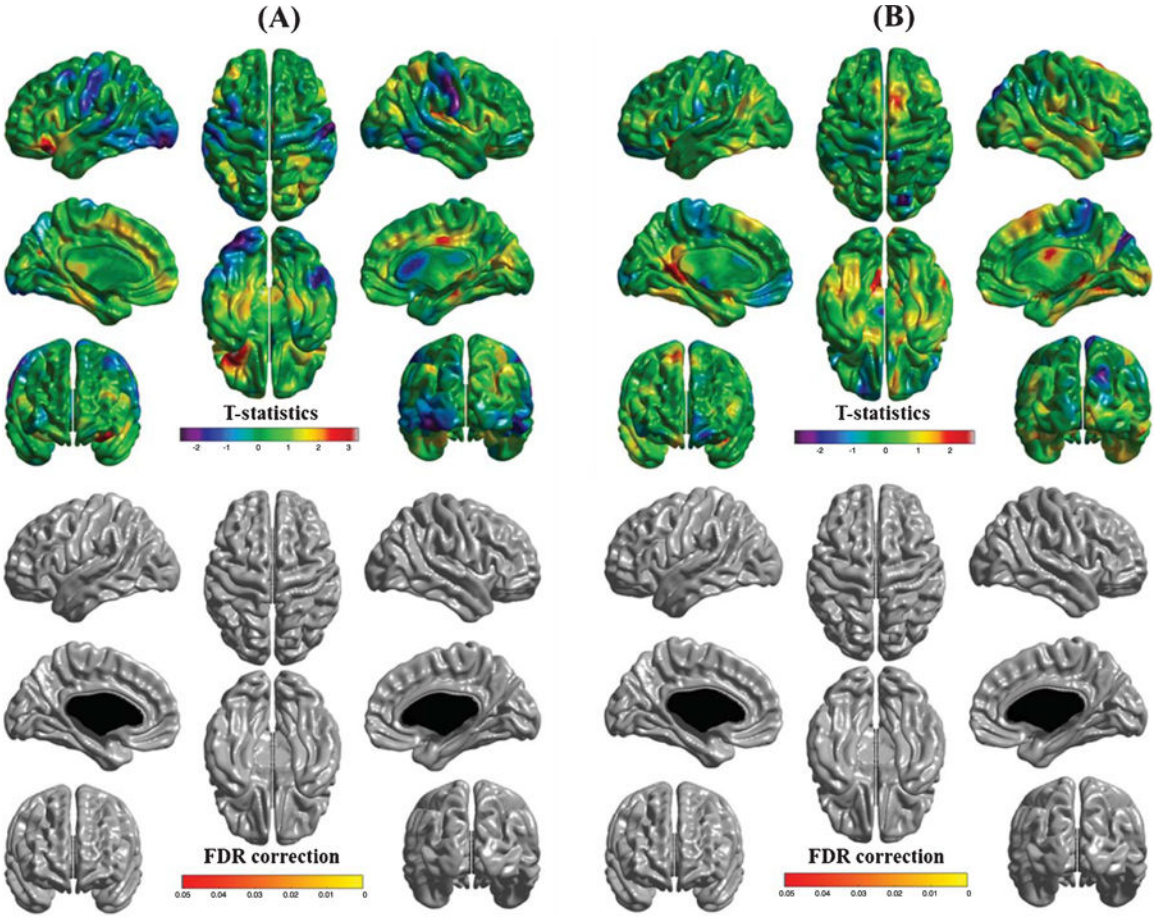

Fig. 2.

A statistical map of baseline differences in cortical thickness (Top: T-map, Bottom: FDR corrected $p < 0.05$). A) Women versus men with AD. B) Women versus men with normal cognition. Regional differences at baseline were analyzed by ANCOVA with adjustment for age, education, duration of disease, onset age (early onset versus late onset), presence of APOE4 genotype, and intracranial volume as covariates. AD, Alzheimer's disease; NC, normal cognition.

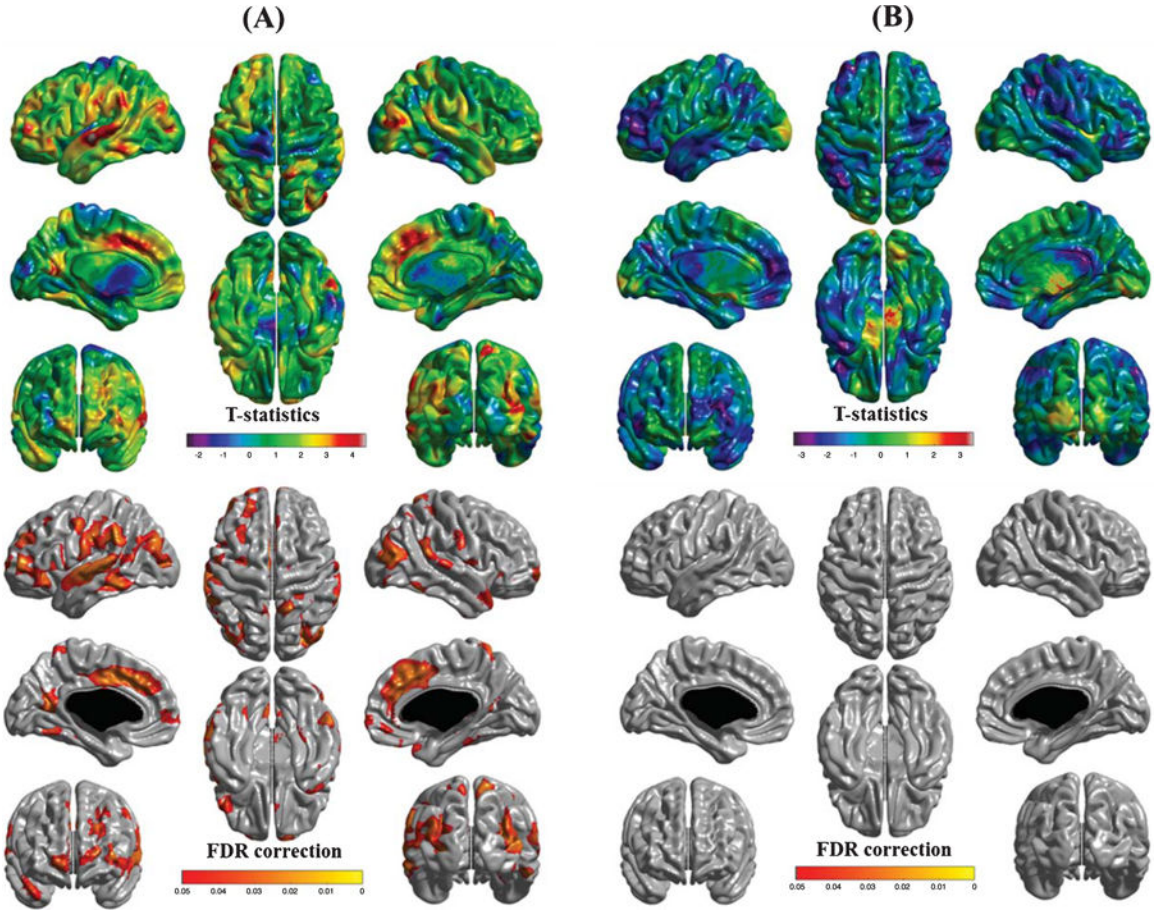

Fig. 3.

A statistical map of longitudinal decrease (group-by-time interaction) in cortical thickness from baseline to Year 1, 3, and 5 (Top: T-map, Bottom: FDR corrected $p < 0.05$). A) Women versus men with AD. B) Women versus men with normal cognition. The group-by-time interaction was analyzed by mixed effects modeling using the general linear model with age, education, disease duration, onset age (early onset versus late onset), presence of APOE4 genotype, time, group and intracranial volume as covariates. AD, Alzheimer's disease; NC, normal cognition.

Table 1

Demographic and clinical characteristics at baseline

	AD			NC		
	Women (*n* = 22)	**Men (*n* = 14)**	***p***	**Women (*n* = 7)**	**Men (*n*=7)**	***p***
Baseline age (y)[a]	68.4±8.8	73.1±5.6	0.079	66.0±6.2	68.3±9.1	0.592
Education (y)	9.2±4.4	13.9±3.2	0.001	10.6±5.8	13.9±2.9	0.211
EOAD proportion (%)	40.9 %	35.7%	0.518	N/A	N/A	N/A
Duration of disease (y)	3.0±1.8	5.2±2.9	0.016	N/A	N/A	N/A
MMSE	20.6±3.3	21.4±3.3	0.485	29.6±0.5	28.9±1.1	0.140
CDR	0.8±0.3	0.9±0.2	0.325	0.0±0.0	0.0±0.0	>0.999
CDR-SOB	4.9±1.9	4.4±1.8	0.491	0.1±0.2	0.1±0.2	>0.999
ApoE ε4 genotype[b,c]	14/22 (63.6)	5/13 (38.5)	0.149	1/7 (14.3)	1/7 (14.3)	>0.999
Use of AChE inhibitor	21/22 (95.5)	13/14 (92.9)	0.740	N/A	N/A	N/A
Use of memantine	3/22 (13.6)	4/14 (28.6)	0.270	N/A	N/A	N/A

[a] Values are mean ± SD or

[b] numbers of cases with percentages in parentheses.

[c] APOE ε4 genotyping was performed in 49 participants because one AD patient refused the test.

AChE inhibitor, acetylcholinesterase inhibitor; AD, Alzheimer's disease; APOE, apolipoprotein; CDR, Clinical Dementia Rating; CDR-SOB, Clinical Dementia Rating sum-of-boxes; MMSE, Mini-Mental State Examination; N/A, not applicable; NC, normal cognition.

Table 2

Baseline differences in cortical thickness between men and women adjusted by age, education, disease duration, onset age (early onset versus late onset), presences of APOE $\varepsilon 4$ genotype, and intracranial volume

	AD			NC		
Regions	**Women (*n* = 22)**	**Men (*n* = 14)**	***p***	**Women (*n* = 7)**	**Men (*n*=7)**	***p***
Total (mm)	2.84±0.14	2.84±0.14	0.425	3.02±0.12	3.01±0.08	0.984
Frontal lobe (mm)	2.99±0.14	2.99±0.12	0.576	3.17±0.15	3.15±0.12	0.908
Temporal lobe (mm)	3.04±0.17	2.99±0.15	0.385	3.25±0.10	3.26±0.11	0.740
Parietal lobe (mm)	2.75±0.16	2.76±0.19	0.525	2.92±0.11	2.91±0.08	0.902
Occipital lobe (mm)	2.51±0.14	2.55±0.18	0.431	2.67±0.14	2.67±0.07	0.743

AD, Alzheimer's disease; n, numbers; NC, normal cognition.