

Sex Differences in the Clinical Manifestations of Alzheimer Disease Pathology

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Context: Sex differences in risk of clinically diagnosed Alzheimer disease (AD) have been studied extensively, but little is known about the relation of the pathologic indices of AD to the clinical manifestations of the disease in men compared with women.

Objective: To test whether the relation of AD pathology to the clinical manifestations of the disease differs in men and women.

Design: Longitudinal, clinicopathologic cohort study.

Participants and Setting: Analyses were conducted on 141 older Catholic clergy members who underwent detailed annual clinical evaluations and brain autopsy at death. The number of neuritic plaques, diffuse plaques, and neurofibrillary tangles in a 1-mm² area sampled from 4 cortical regions was counted, and a global measure of AD pathology (range, 0-2.98 U) and specific measures of each pathology were derived.

Main Outcome Measures: Clinical diagnosis of probable AD and level of global cognitive function at the last evaluation before death.

Results: Women had more global AD pathology than did men ($P=.04$), due primarily to more neurofibrillary tangles ($P=.02$). At the last evaluation before death, 57 persons met clinical criteria for probable AD (34 [60%] of them women). In logistic regression models, sex was not related to odds of clinical AD (odds ratio [OR], 1.35; 95% confidence interval [CI], 0.56-3.25), but the relation of global AD pathology to clinical diagnosis differed for men and women. Each additional unit of AD pathology was associated with a nearly 3-fold increase in the odds of clinical AD in men (OR, 2.82; 95% CI, 1.03-7.65) compared with a more than 20-fold increase in the odds of clinical AD in women (OR, 22.67; 95% CI, 5.11-100.53). Results were unchanged after controlling for potential confounders or using level of cognition as the outcome.

Conclusion: These data suggest that AD pathology is more likely to be clinically expressed as dementia in women than in men.

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ALZHEIMER DISEASE (AD) IS the leading cause of dementia in older people. Despite years of research, the question of whether men and women differ in risk of disease remains controversial. Prospective studies of disease risk have had mixed results. Of 8 population-based studies with at least 2 years of observation,¹⁻⁸ 5 reported a greater risk of AD in women^{1,2,5-7} and the other 3 found no difference.^{3,4,8} There are several potential explanations for the discrepant results. Because more women live to ages at which the disease is common, some studies may not have had sufficient numbers of cases of disease in older men to adequately adjust for the confounding effect of age. Men and women also differ with respect to education, occupation, and re-

lated lifestyle variables that are also associated with risk of AD. These variables may not be completely accounted for by statistical analyses. Other issues include methodological differences between incidence studies, including observation time, number of evaluations, attrition rate, and diagnostic accuracy.

Few studies⁹⁻¹² have examined sex differences in the pathologic indices of AD. These studies have also had mixed results, with most indicating no sex differences.^{9,10,12} Although the amount of AD pathology may not differ for men and women, we are unaware of a previous study that addressed the critical question regarding whether the relation between AD pathology and clinical status proximate to death differs for men and women. We used clinical and postmortem data from the Re-

ligious Orders Study¹³ to examine the relation of AD pathology to clinical diagnosis of AD and level of cognition in men compared with women.

METHODS

Subjects were older Catholic nuns, priests, and brothers in the Religious Orders Study, a longitudinal clinicopathologic study of aging and AD. The study involves annual clinical evaluations and brain donation at death. It was approved by the institutional review board of Rush University Medical Center, Chicago, Ill.

Since January 1994, more than 1000 persons have completed the baseline clinical evaluation, and participation in follow-up has exceeded 95% among survivors. At the time of these analyses, 196 persons had died and 181 of them (92%) had undergone brain autopsy. Data from the first consecutive 168 autopsies were available for analysis. Postmortem data collection, which typically occurs several months after the autopsy, was ongoing for the remaining 13 persons.

CLINICAL EVALUATION

Each participant had a uniform evaluation that included the procedures recommended by the Consortium to Establish a Registry for Alzheimer Disease.¹⁴ The evaluation included a medical history, neurologic and neuropsychological examinations, and review of brain scan information when available, as previously described.¹⁵⁻¹⁷ Participants were evaluated in person by a board-certified or board-eligible neurologist or geriatrician. On the basis of this evaluation, participants were classified with respect to AD and other common neurologic disorders that can contribute to cognitive impairment, using the criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.¹⁸ Follow-up evaluations, identical in all essential details, were performed annually by examiners blinded to previously collected data. At the time of death, all available clinical data were reviewed blinded to postmortem data, and a summary diagnostic opinion was rendered regarding the most likely clinical diagnosis at the time of death.

NEUROPSYCHOLOGICAL PERFORMANCE TESTING

A set of 19 cognitive function tests was selected to assess functions commonly affected by aging and AD. Composites of 2 or more tests were used in analyses to minimize floor and ceiling effects and other sources of measurement error. We formed a global measure based on all 19 tests and specific measures of episodic memory (based on 7 tests), semantic memory (4 tests), working memory (4 tests), perceptual speed (2 tests), and visuospatial ability (2 tests). Raw scores on each test were converted to *z* scores by using the baseline mean and standard deviation, and the *z* scores were averaged to form the composite measures. Further information about the individual tests and the derivation of the cognitive measures is published elsewhere.^{16,19}

APOLIPOPROTEIN E GENOTYPING

Blood was collected with acid citrate dextrose anticoagulant and stored at room temperature until it underwent lymphocyte separation within 24 hours. The DNA was extracted from approximately 3 million cells and amplified. Apolipoprotein (APOE) genotyping was performed by an investigator blinded to all clinical

and postmortem data following the method of Hixson and Vernier,²⁰ as previously described.^{21,22}

NEUROPATHOLOGICAL EVALUATION

Brains were removed in a standard fashion and cut coronally with the use of a Plexiglas jig into 1-cm-thick slabs as described previously.^{21,23} Tissue blocks from 1 hemisphere were fixed for 3 to 14 days in paraformaldehyde. Tissues from the midfrontal, superior temporal, and medial temporal lobes (including the entorhinal cortex); hippocampus; inferior parietal cortex; basal ganglia; and thalamus were embedded in paraffin, sectioned at 6 μ m, and stained with a modified Bielschowsky silver stain.²⁴

Neuritic plaques, diffuse plaques, and neurofibrillary tangles were counted in 4 cortical areas, including the midfrontal, superior temporal, entorhinal, and inferior parietal cortices, by a board-certified neuropathologist (J.A.S.) or trained technician blinded to all clinical data. To determine the density of each pathologic index, each slide was scanned for the region containing the largest number of the structure of interest. Then, using a 10 \times magnification eyepiece graticule to mark a 1-mm² area, the total number of structures was counted under \times 100 total magnification and this number was recorded, resulting in 12 individual measures of pathology for each person. With this procedure, the different pathologic markers were unlikely to come from the same location on each slide. Because of the complexity involved in counting plaques and tangles from tissue stained with the Bielschowsky silver stain,²¹ we examined interrater reliability in 40 cases, which ranged from $r=0.89$ to $r=0.93$ for the individual indices, supporting the reproducibility of these measures.

Because we wanted an overall indicator of the burden of AD pathology (range, 0-2.98 U) with minimal measurement error, a global measure of AD pathology was used in the analyses. The raw scores from each of the 3 pathologic indices from each of the 4 regions were converted to standard scores (by dividing each by the standard deviation of the entire deceased cohort) and averaged to yield summary measures of neuritic plaques, diffuse plaques, and neurofibrillary tangles. Because the 3 summary neuropathologic indices were strongly related (Spearman rank correlation coefficients ranged from 0.45 to 0.80; for all, $P<.001$), we also created a global measure of AD pathology by averaging the summary measures of neuritic plaques, diffuse plaques, and neurofibrillary tangles. Further information about the counting procedures and the derivation of the summary measures is published elsewhere.^{21,23,25}

We assessed the validity of the global AD pathology summary measure by comparing it with other established methods commonly used to stage and classify AD pathology. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) system,²⁶ National Institute on Aging (NIA)-Reagan Institute²⁷ criteria, and Braak staging²⁸ are currently accepted measures for determining the spectrum of AD pathology, but their distributions are not optimal for analytic purposes. Because both CERAD and NIA-Reagan Institute criteria were developed to assess the level of certainty that dementia is due to AD pathology, these criteria were modified to include only pathologic measures without diagnosis or age, the latter of which is a covariate in the analyses. With respect to CERAD criteria, 47 persons had a diagnosis of definite AD, 52 were considered probable AD, 9 were considered possible AD, and 33 were categorized as no AD, and the Spearman rank correlation coefficient with the global AD pathology measure was 0.80 ($P<.001$). The NIA-Reagan Institute criteria indicated a high likelihood that dementia, if present, was attributable to AD pathology in 29 persons, an intermediate likelihood in 62, a low likelihood in 47, and no AD in 3. The correlation between NIA-Reagan

Institute criteria and the AD pathology measure was 0.79 ($P < .001$). Finally, 11 brains were staged as Braak stage I-II, 42 brains were staged as Braak stage III-IV, and 87 brains were staged as Braak stage V-VI, with a correlation of 0.69 ($P < .001$) between Braak stage and the AD pathology score. These results support the idea that the global measure of AD pathology used in this study represents a metrically sound method of summarizing the traditional pathological hallmarks of AD.

To measure old microscopic infarctions, hematoxylin-eosin-stained slides of the 4 cortical regions were evaluated. For each brain we identified the age, volume (in cubic millimeters), and location of all cerebral infarctions visible to the naked eye as previously described.²³ Ischemic lesions with small amounts of hemorrhage were included. For these analyses, we included all old cortical and subcortical gray and white matter cerebral infarctions. Microscopic strokes and acute and subacute infarctions were not included.

Additional evaluations were conducted to quantify Lewy bodies. Six-micrometer sections of the midbrain, including a hemisection of the substantia nigra, were immunohistochemically stained with antibodies to α -synuclein using alkaline phosphatase as the chromogen as previously described.²⁹ Lewy bodies were counted across the complete hemisection of the substantia nigra. Extraneuronal Lewy bodies and Lewy neurites were not counted.

STATISTICAL ANALYSIS

We used unpaired, 2-tailed t tests to analyze sex differences in age at death, education, Mini-Mental State Examination³⁰ score at death, interval from last clinical evaluation to death, and post-mortem interval. All other analyses included terms for age at death and education.

To determine whether men and women had different levels of AD pathology, we constructed separate linear regression models examining the association of sex with the summary measures of global AD pathology, neuritic plaques, diffuse plaques, and neurofibrillary tangles.

In a series of logistic regression models, we examined the association of sex, AD pathology, and their interaction with the clinical diagnosis of AD proximate to death as the outcome. All models included an indicator for male sex (where 0 indicated female; 1, male). In an initial model, we assessed whether sex and global AD pathology were independently related to clinical AD. We then added a term for the interaction of sex with global AD pathology to test whether the association of AD pathology with clinical AD differed in men and women. To determine whether results varied by neuroanatomic region, we repeated these models with regional indices of AD pathology, separately for frontal, temporal, parietal, and entorhinal cortices.

We conducted additional analyses to examine other factors that might account for the interaction of sex with AD pathology. In 2 separate logistic regression models that used clinical AD as the outcome, each with terms for sex, global AD pathology, and their interaction, we added a term for the interaction of age and AD pathology, and then a term for the interaction of education and AD pathology. In each analysis, we examined whether the interaction of sex with AD pathology remained significant.

We also examined other covariates, including genetic and other common age-related pathological findings, to determine whether they confounded the interaction of sex with AD pathology. First, we examined whether *APOE* allele status might have contributed to the interaction of sex and AD pathology by adding terms for possession of at least 1 *APOE* $\epsilon 4$ allele and the interaction of $\epsilon 4$ and AD pathology. Then we examined macroscopic cerebral infarctions (ie, stroke) and Lewy bodies, both coded as binary variables (eg, 0 indicates no; 1, yes) in all analyses. In separate

Table 1. Selected Characteristics of Men and Women*

Characteristic	Men (n = 64)	Women (n = 77)	P Value†
Age at death, y	83.5 (6.8)	86.2 (5.9)	.02
Education, y	18.2 (4.0)	17.8 (3.4)	.49
MMSE score (proximate to death)	26.2 (3.7)	27.1 (2.4)	.10
Interval between testing and death, mo	7.8 (7.4)	9.3 (7.9)	.23
Postmortem interval, h	8.0 (9.5)	7.1 (5.3)	.52

Abbreviation: MMSE, Mini-Mental State Examination.

*Data are presented as mean (SD) unless otherwise indicated.

†Based on unpaired, 2-tailed t tests.

logistic regression models with clinical AD as the outcome and terms for sex, AD pathology, and their interaction, we first added a term for the presence of stroke, and then a term for the presence of Lewy bodies. In subsequent analyses, we added a term for the interaction of cerebral infarctions and AD pathology to one model and then, in another model, we added a term for the interaction of Lewy bodies and AD pathology.

To determine whether the effects observed with the global measure were present for some types of AD pathology but not others, we repeated the core logistic regression models using summary measures of neuritic plaques, diffuse plaques, and neurofibrillary tangles as the outcome.

We conducted a similar series of analyses with level of global cognition proximate to death as the outcome rather than clinically diagnosed AD, and we used linear regression because of the continuous outcome measure. We first examined the relation of sex and global AD pathology to global cognitive function proximate to death. We then added a term for the interaction of sex with AD pathology to determine whether the association of AD pathology with cognitive function differed in men and women. Finally, we repeated these analyses for each of the specific cognitive domains.

All models were validated graphically and analytically. Analyses were carried out using SAS statistical software.³¹

RESULTS

Because we wanted to examine the relation between AD pathology and the clinical expression of AD in men and women, we excluded persons with clinical conditions other than AD (eg, Parkinson disease, delirium, or stroke) thought to be causing cognitive impairment (in 3 subjects) or dementia (in 6), or contributing to cognitive impairment in those with clinical AD (in 18).

Of the 168 persons with postmortem data, analyses were conducted on the remaining 141 persons, of whom 64 were men and 77 were women. Women were slightly older at death than men, but characteristics were otherwise comparable (**Table 1**).

SEX AND AD PATHOLOGY

We first examined whether men and women differed in levels of AD pathology in a series of linear regression models adjusted for age and education. Women had slightly more global pathology (parameter estimate = -0.25, $P = .04$) than men. This appeared to be due primarily to more neurofibrillary tangles (parameter estimate = -0.33, $P = .02$).

Table 2. Effect of 1 U of AD Pathology on Odds of Clinically Diagnosed AD Proximate to Death in Men and Women*

Pathologic Measure†	OR (95% CI)	P Value
1 U of global AD pathology		
Men	2.82 (1.03-7.65)	.04
Women	22.67 (5.11-100.53)	<.001
1 U of neuritic plaques		
Men	2.50 (1.09-5.72)	.03
Women	11.37 (3.60-35.92)	<.001
1 U of diffuse plaques		
Men	1.76 (0.93-3.30)	.08
Women	3.62 (1.60-8.18)	.002
1 U of neurofibrillary tangles		
Men	1.39 (0.45-4.28)	.56
Women	13.41 (3.19-56.39)	<.001

Abbreviations: AD, Alzheimer disease; CI, confidence interval; OR, odds ratio.

*Based on logistic regression models that controlled for age at death and education and included an interaction for sex and AD pathology measure.

†See the "Neuropathological Evaluation" subsection of the "Methods" section for an explanation of the scoring.

There was a trend for neuritic plaques (parameter estimate = -0.26, $P = .09$) but no relation to diffuse plaques (parameter estimate = -0.15, $P = .33$).

SEX, GLOBAL AD PATHOLOGY, AND CLINICAL AD PROXIMATE TO DEATH

Fifty-seven persons met clinical criteria for probable AD (34 [60%] of them women), 31 persons met clinical criteria for mild cognitive impairment¹⁵ (18 [58%] of them women), and 53 people had no cognitive impairment (25 [47%] of them women) proximate to death. In an initial logistic regression analysis controlling for age and education, sex was not related to odds of AD (odds ratio [OR], 1.35; 95% confidence interval [CI], 0.56-3.25) and global AD pathology was strongly related to odds of clinical AD (OR, 7.05; 95% CI, 3.23-15.38). We then added a term for the interaction of sex with AD pathology to test whether the relation of AD pathology to clinical disease differed in men compared with women (**Table 2**). The interaction term was significant. Each 1-U increase in AD pathology was associated with a nearly 3-fold increase in the odds of clinical AD in men (OR, 2.82; 95% CI, 1.03-7.65). By contrast, there was a more than 20-fold increase in the odds of clinical AD in women (OR, 22.67; 95% CI, 5.11-100.53). This is illustrated graphically by plotting the predicted probability of having clinical AD at different levels of global AD pathology in men and women (**Figure 1**). As can be seen, at lower levels of pathology the risk of clinical disease is similar or slightly higher in men compared with women, but at moderate to high levels of pathology, disease risk is greater in women than in men. In separate analyses by region, the interaction between sex and AD pathology was significant in the temporal and parietal neocortex, with trends in the frontal neocortex and entorhinal cortex (data not shown).

To ensure that age and education^{25,32,33} did not account for our results, we repeated the core analysis with a term added for the interaction of age with AD pathol-

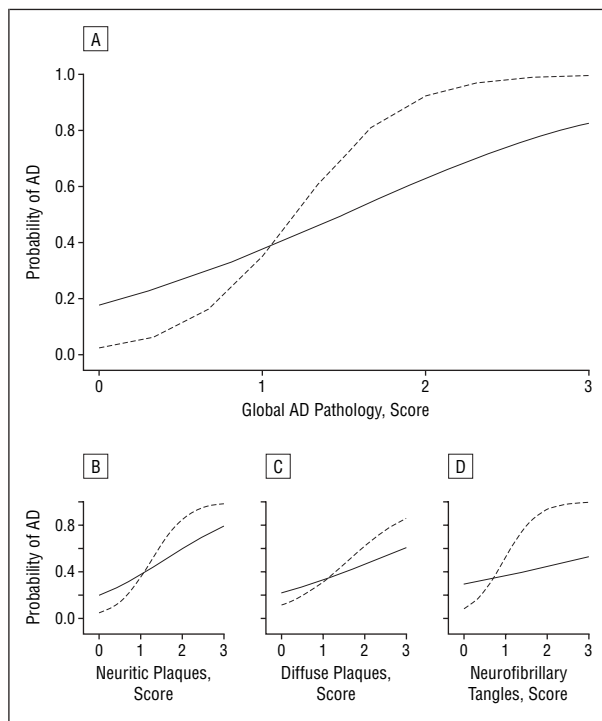


Figure 1. Probability of clinically diagnosed Alzheimer disease (AD) proximate to death as a function of level of global AD pathology (A), neuritic plaques (B), diffuse plaques (C), and neurofibrillary tangles (D) in men (solid line) and women (dashed line). See the "Neuropathological Evaluation" subsection of the "Methods" section for an explanation of the scoring.

ogy, and again with a term added for the interaction of education with AD pathology. The interaction of sex with AD pathology remained significant (for both, $P = .02$).

OTHER COVARIATES

APOE ε4 Allele

Apolipoprotein ε4 allele status has been shown to be an important risk factor for AD,^{34,35} especially among women.^{36,37} Eighteen (28%) of the men and 24 (31%) of the women had at least 1 APOE ε4 allele in our sample. To determine whether possession of an ε4 allele might account for the sex difference in the relation of AD pathology to clinical disease, we repeated the core analysis, first with a term for the possession of at least 1 ε4 allele and second, in a separate model, with a term added for the interaction of ε4 with AD pathology. In each of these analyses, the interaction of sex with AD pathology remained significant (for both, $P = .02$).

Cerebral Infarctions

Because cerebral infarctions are common in older people,³⁸ are associated with dementia,²³ and may be more common in men,^{39,40} we examined whether the sex difference in the clinical manifestation of AD pathology could be modified by stroke pathology. We repeated the core analysis with a term added for infarction (present in 40 people [28.4%] on postmortem examination). In this analysis, there was no main effect for infarction (most

likely because we excluded people with clinically diagnosed stroke that was thought to contribute to dementia or cognitive impairment), and the interaction of sex with global AD pathology remained ($P = .008$). We also examined a model that included a term for the interaction of stroke and global AD pathology and the results were unchanged.

Lewy Bodies

To determine whether the sex difference in the clinical manifestation of AD pathology could be modified by another common neuropathologic lesion of old age, we examined the effect of Lewy bodies (present in 21 [14.9%] of our subjects). We repeated the core analysis with a term added for Lewy bodies, and in a second model we added a term for the interaction of Lewy bodies and global AD pathology, and the interaction of sex with AD pathology was not substantially changed.

SEX, SPECIFIC TYPES OF AD PATHOLOGY, AND CLINICAL AD

To determine whether the sex difference in the clinical expression of AD pathology varied across types of pathology, we repeated the analyses using summary measures of neuritic plaques, diffuse plaques, and neurofibrillary tangles in place of the global measure of AD pathology. Each type of AD pathology was related to the odds of clinical AD proximate to death (OR [95% CI] for neuritic plaques, 4.90 [2.50-9.61]; for diffuse plaques, 2.41 [1.43-4.06]; and for neurofibrillary tangles, 4.51 [2.15-9.45]).

When a term for the interaction of sex with the pathology index was added, the interaction was significant for neuritic plaques ($P = .04$) and neurofibrillary tangles ($P = .02$) but not for diffuse plaques ($P = .17$) (data not shown). As shown in Table 2, each 1-U increase in neuritic plaques was associated with a more than 2-fold increase in the odds of clinical AD in men compared with a more than 11-fold increase in women. Similarly, a 1-U increase in neurofibrillary tangles was associated with a less than 2-fold increase in the odds of clinical AD in men compared with a more than 13-fold increase in women. The results are illustrated in Figure 1.

SEX, AD PATHOLOGY, AND COGNITIVE FUNCTION PROXIMATE TO DEATH

Because the clinical manifestations of AD develop gradually over a period of years, separating normality from disease can be difficult, and among those with disease, levels of impairment vary widely. Therefore, to ensure that our results were not due to bias or imprecision in clinical classification of AD, we also examined the relation of sex and AD pathology with level of global cognition proximate to death. At the last clinical evaluation before death, the global cognitive score ranged from -4.19 to 1.29, with higher scores indicating better function. In a linear regression model adjusted for age and level of education, sex was not significantly related to level of cognition (parameter estimate = -0.15, $P = .29$) but global AD pathology was ($P < .001$). With each 1-U increase in pa-

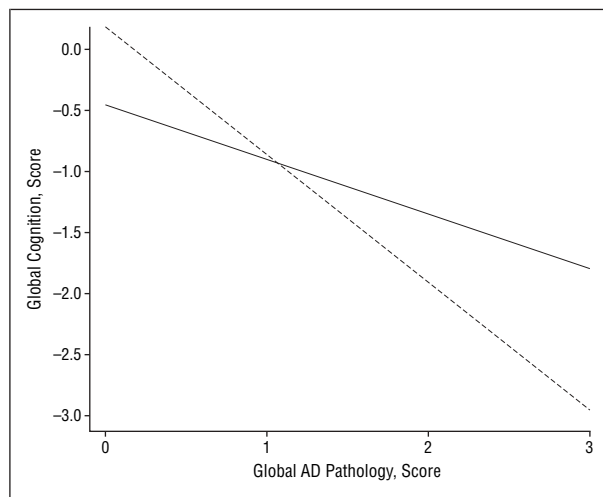


Figure 2. Level of global cognitive function proximate to death as a function of global Alzheimer disease (AD) pathology in men (solid line) and women (dashed line). See the "Neuropathological Evaluation" subsection of the "Methods" section for an explanation of the global AD pathology scoring. For global cognitive function, higher scores indicate better function.

thology, the cognitive score was reduced by an average of 0.81 U (95% CI, -0.62 to -1.01).

We then repeated the analysis with a term added for the interaction of sex with AD pathology. The interaction was significant ($P = .004$). With each additional unit of global AD pathology, the global cognitive score was reduced by an average of 0.45 U in men (95% CI, -0.75 to -0.14) compared with a reduction of 1.04 U in women (95% CI, -1.29 to -0.80). This effect is shown in **Figure 2**. To determine whether sex differences might exist for some cognitive domains and not others, we repeated these analyses with specific cognitive domains as the outcome and the results remained the same. With each additional unit of global AD pathology, the cognitive function scores in episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability were reduced significantly more in women than in men (for all, $P < .05$).

COMMENT

In a group of 141 older persons who underwent detailed clinical evaluations proximate to death, we found that the association between AD pathology and clinical AD was substantially stronger in women than in men. On a global measure of AD pathology that ranged from 0 to 3, each additional unit of pathology increased the odds of clinical AD nearly 3-fold in men compared with more than 20-fold in women. This effect was observed for neuritic plaques and neurofibrillary tangles but not diffuse plaques. The findings suggest that AD pathology is more likely to be expressed clinically as dementia in women than in men.

Most research on sex differences in AD has been restricted to persons with clinically diagnosed disease.¹⁻⁸ Some studies have found an increased risk of AD among women^{1,2,5-7} but others have not,^{3,4,8} most likely owing to methodologic differences between studies. Some studies have compared the level of AD pathology at autopsy among persons coming to the attention of the health care system,⁹⁻¹² but again results have been mixed. We also

did not find sex differences in the odds of clinical AD, but we did find slightly higher levels of AD pathology in women compared with men. We are not aware of previous research examining sex differences in the likelihood that AD pathology will be expressed clinically as AD or cognitive impairment.

Our results suggest that the clinical manifestation of AD is stronger in women than in men. Understanding why the association between AD pathology and dementia differs in men and women could yield important clues about the pathophysiology of AD or eventually lead to sex-specific preventive or therapeutic strategies.

Clinical AD is not a discrete entity and can be subject to diagnostic imprecision, particularly in persons with mild cognitive impairment. Therefore, we used 2 complementary outcomes: clinically diagnosed AD proximate to death and level of global cognition proximate to death, which allowed us to examine severity and gradations of function. The fact that these 2 outcomes yielded comparable results makes it unlikely that the observed sex difference in the association of AD pathology with clinical AD was due to bias or imprecision in clinical classification.

Because age is strongly related to AD, the substantial sex difference in longevity complicates studies of sex differences in the disease. In the present study, the mean sex difference in age at death was less than 3 years, and we controlled for this variable in analyses. In addition, we explicitly tested whether an interaction of age with AD pathology accounted for the observed interaction of sex with AD pathology. It did not. It seems unlikely, therefore, that sex differences in age influenced our results.

Although the sex difference in the clinical manifestation of AD pathology was not unexpected, it was stronger than anticipated and its bases are uncertain. Other forms of pathology may disproportionately contribute to dementia in men compared with women. Men are known to have more cardiovascular disease,^{41,42} and some data suggest that Parkinson disease and Lewy bodies are more common in men.^{43,44} All 3 diseases can contribute to cognitive impairment. However, in our sample men did not have more infarcts or Lewy bodies, and in analyses that controlled for the presence of either infarct or stroke and the presence of Lewy bodies, we still found a stronger association between AD pathology and clinical AD for women.

Another possibility is that women have a relative lack of some protective factor, such as the estrogen deficiency of postmenopausal women, which could increase their vulnerability to AD pathology. For example, data from studies with mice lacking estrogen receptors suggest that the up-regulation of estrogen is a crucial element in protecting the brain from injury.^{45,46} Finally, although we statistically controlled for the effect of having an $\epsilon 4$ allele, the complex interaction of *APOE* genotype and other biological mechanisms might be one of several factors modifying the pathway from pathology to clinical disease in women. More research is needed to explore these and other possibilities.

Several factors increase our confidence in the findings. Participants underwent detailed structured clinical evaluations proximate to death with more than 90% participation in brain autopsy. Comparable results were obtained with clinically diagnosed AD and level of global

cognition as outcomes, suggesting that the observed sex difference was not due to bias or imprecision in clinical classification. Furthermore, analyses controlled for potentially confounding demographic (ie, age and education) and genetic (ie, *APOE* $\epsilon 4$) factors. Finally, uniform structured procedures were followed with blinding to previously collected data, as well as to postmortem data, reducing the potential for bias.

Our study has some limitations. First, this cohort is a selected group of participants who differ in important ways from the general US population. It will be important, therefore, to replicate these findings in more diverse groups. However, we are not aware of any reasons that the findings might be due to the unique nature of our study group with one exception: the relative homogeneity among our participants may have provided additional control over lifestyle and socioeconomic variables with the potential to confound the association of sex with AD. Second, because our cohort consisted of volunteers and the presence of neuropsychiatric symptoms was judged to be rare, our analyses were restricted to cognitive manifestations of AD. It is possible that sex differences also exist for non-cognitive clinical features. Population-based studies with a greater frequency of neuropsychiatric symptoms associated with AD are needed to explore this issue further.

Most studies of sex differences in AD focus on differences in risk of disease. Few studies have examined whether the relation between pathologic indices of AD and the clinical manifestation of the disease differs for men and women. We found a stronger relation between pathology and clinical AD in women than in men. These findings suggest that AD pathology is more likely to be expressed clinically as dementia in women.

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