Gender Differences in Alzheimer Disease: Brain Atrophy, Histopathology Burden, and Cognition

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Abstract
Multiple studies suggest that females are affected by Alzheimer disease (AD) more severely and more frequently than males. Other studies have failed to confirm this and the issue remains controversial. Difficulties include differences in study methods and male versus female life expectancy. Another element of uncertainty is that the majority of studies have lacked neuropathological confirmation of the AD diagnosis. We compared clinical and pathological AD severity in 1028 deceased subjects with full neuropathological examinations. The age of dementia onset did not differ by gender but females were more likely to proceed to very severe clinical and pathological disease, with significantly higher proportions having a Mini-Mental State Examination score of 5 or less and Braak stage VI neurofibrillary degeneration. Median neuritic plaque densities were similar in females and males with AD but females had significantly greater tangle density scores. In addition, we found that AD-control brain weight differences were significantly greater for females, even after adjustment for age, disease duration, and comorbid conditions. These findings suggest that when they are affected by AD, females progress more often to severe cognitive dysfunction, due to more severe neurofibrillary degeneration, and greater loss of brain parenchyma.

Key Words: Amyloid plaque; Brain weight; Cognition; Neuritic plaque; Neurofibrillary tangle; Phosphorylated tau.

INTRODUCTION
For generations, clinical and basic science research often neglected to analyze for male–female differences, and often have failed to include females at all. In response to this, the United States Congress approved the Revitalization Act in the early 1990s, requiring the inclusion of women in National Institutes of Health-funded clinical research (1). The ideal today in clinical research is to have equal distributions of males and females, and many studies are trying to understand how health conditions and medications might differentially affect females and males.

Alzheimer disease (AD) is the most common cause of dementia in the elderly. Many studies have reported that females have a higher risk of developing AD (2–6), and that they are more severely affected (2, 6, 7). Yet, this concept is mired in controversy due to conflicting published results (8–13). Differences in experimental design and study populations may be responsible for some of the discrepant results, while, additionally, most studies have lacked pathological confirmation of the diagnosis of AD, thereby creating additional uncertainty. In this study, we used clinical and autopsy data to explore differences between male and females in terms of cognition, AD-specific histopathology and its impact on the neural parenchyma.

MATERIALS AND METHODS
Subjects were all volunteers in the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND), a longitudinal clinicopathological study of normal aging, cognition, and movement in the elderly since 1996 in Sun City, Arizona. Autopsies are performed by the Banner Sun Health Research Institute, Sun City, Arizona (JRF, AJI, LIS, KJD, CMB, SJ, TGB, GES); Department of Economics, Arizona State University, Tempe, Arizona (EVA, JW); Neurological Institute, Phoenix, Arizona (MNS); Mayo Clinic Arizona, Scottsdale, Arizona (RJC, CHA, BKW, ED-D); Department of Neurology, University of Arizona, Tucson, Arizona (SZR, GLA); and Banner Alzheimer Institute, Phoenix, Arizona (ADB, KC, EMR). Send correspondence to: Geidy E. Serrano, PhD, Banner Sun Health Research Institute, 10515 W Santa Fe Drive, Bldg. B, 3rd Floor, Sun City, AZ 85351. E-mail: Geidy.Serrano@bannerhealth.com.

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Institute Brain and Body Donation Program (BBDP; www.brainandbodydonationprogram.org). Subsets of the Program are funded by the US National Institute on Aging Arizona Alzheimer’s Disease Core Center and the US National Institute of Neurological Disorders and Stroke National Brain and Tissue Resource for Parkinson’s Disease and Related Disorders. Cognitively normal volunteer subjects are all recruited from the communities of greater Phoenix, Arizona through public relations activities. Many AZSAND subjects with cognitive impairment, dementia, or movement disorders are also community-derived while some are enrolled through neurologists’ practices or dementia clinics. All subjects sign Institutional Review Board-approved informed consents allowing both clinical assessments during life and several options for brain and/or body organ donation after death. Most subjects are clinically characterized with annual standardized test batteries consisting of general neurological, cognitive, and movement disorders components, including the Mini-Mental State Examination (MMSE). Subjects for the current study were chosen by searching the BBDP database for cases with a clinical or neuropathological criteria for a defined neurodegenerative disease. Those disorders where these were available. Non-AD conditions were diagnosed using standard clinico-pathological criteria with international consensus criteria for each disorder. Subjects with clinicopathologically defined AD as well as Parkinson disease, Alzheimer disease, vascular dementia, progressive supranuclear palsy, corticobasal degeneration, multiple system atrophy, dementia with Lewy bodies, hippocampal sclerosis, frontotemporal lobar degeneration with TDP-43 proteinopathy (FTLD-TDP), Pick disease, and Huntington disease.

The complete neuropathological examination was performed using standard AZSAND methods (15, 16). Brain weights were determined at autopsy, after removal of 10–30 cc of ventricular cerebrospinal fluid but prior to fixation. The gender-specific AD-control brain weight difference was expressed for each AD subject as the ratio (converted to a percentage) of that individual’s brain weight as compared with the mean brain weight of all control subjects of the same gender. Neuropathological examinations were performed in a standardized manner and consisted of gross and microscopic observations, the latter including assessment of frontal, parietal, temporal, and occipital lobes, all major diencephalic nuclei and major subdivisions of the brainstem, cerebellum, and spinal cord (the latter only for those with whole-body autopsy). Following fresh slicing and subsequent fixation in cold 10% neutral-buffered formalin for 36–60 hours, histological preparations included large-format (3 × 5 cm), 40–80 μm-thick, cryoprotected frozen sections as well as paraffin-embedded 6-μm sections. Both sets were stained with hematoxylin and eosin; the former set was also stained for senile plaques, neurofibrillary changes, and other neuronal and glial tauopathies using thioflavin S, Gallyas and Campbell-Switzer methods (15, 17, 18). In all cases, an additional set of paraffin sections was immunohistochemically stained for phosphorylated α-synuclein (p-syn), while staining for phosphorylated TDP-43 (p-TDP43) was done only for subjects judged after initial neuropathological examination to be at risk for FTLD-TDP (19–23). Neuritic plaque and neurofibrillary tangle densities were graded blindly as recommended by The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) with separate semiquantitative density estimates of none, sparse, moderate, or frequent (24). All scores were converted to a 0–3 scale for statistical purposes. Regions scored included cortical gray matter from frontal (F), temporal (T), parietal (P), hippocampal CA1 (H), and entorhinal (E) regions. Neurofibrillary degeneration was staged on the thick frozen sections by the original method of Braak (18, 25), and neuropathological AD diagnoses were made when neuritic plaque densities and Braak stage met “intermediate” or “high” criteria according to National Institute on Aging/Reagan Institute criteria (26–28). Non-AD conditions were diagnosed using standard clinicopathological criteria with international consensus criteria for those disorders where these were available.

### Statistical Methods
Univariate analyses were used as an initial screen to indicate which variables might be significantly affected by gender and also have significant relationships with AD-control brain weight difference and/or MMSE score. For comparing group measures, the Mann–Whitney U-Test, 1-way analysis

| Diagnosis/Gender (N) | Age at Death (SD) | MMSE (SD) | Cognitive Sx, Age Onset (SD) | Cognitive Sx, Years Duration (SD) | Education Years (SD) |
|---------------------|------------------|-----------|-----------------------------|---------------------------------|----------------------|
| ND-Female (126)     | 85.8 (9.3)*      | 29.0 (1.0)*| NA                          | NA                              | 15.0 (2.4)*          |
| ND-Male (166)       | 83.1 (9.2)       | 27.8 (2.0) | NA                          | NA                              | 14.8 (2.9)           |
| AD-Female (345)     | 83.5 (9.6)       | 12.2 (9.1) | 74.7 (10.6)                 | 8.8 (5.0)                       | 14.0 (2.5)           |
| AD-Male (391)       | 81.3 (7.6)*      | 13.4 (8.4) | 73.7 (8.9)                  | 7.7 (4.1)*                      | 15.2 (2.8)*          |

*MMSE, Mini-Mental State Examination; Sx, symptoms; NA, not applicable; ND, nondemented controls; AD, Alzheimer disease.

*p < 0.05 for comparison of all groups.

*p < 0.001 for gender comparisons within AD subjects.
of variance (ANOVA), Kruskal–Wallis ANOVA, and contrast analysis were used as appropriate. The chi-squared test was used to compare proportions and Spearman’s method was used to test univariate correlations. Variables that were significantly affected on this initial screen by gender, or that correlated significantly with AD-control brain weight difference and/or MMSE score, were included in multivariable logistic regression models.

**RESULTS**

Of deceased AZSAND subjects, 28% of women versus 30% of men had a final clinicopathological diagnosis of AD (not significantly different [ns]). The group age means differed significantly with the youngest group (males with AD) having a mean age of 81.3 years, whereas for the oldest group (control females), the mean age was 85.8 years (p < 0.05) (Table 1). Both AD and control female groups were significantly older than their respective male groups (p < 0.01); however, in both genders the age difference between control and AD subjects was of the same magnitude (ns). The mean age of onset of cognitive symptoms was 74.7 for females and 73.7 for males (ns); females with AD survived significantly longer after symptom onset (8.8 vs 7.7 years; p < 0.01).

The CERAD neuritic plaque density score showed a significant gender-related difference only within the control group, with significantly greater densities in females (Table 2; p < 0.05); this difference was significant even after adjustment for age and cognitive symptom duration. As compared with males with AD, females with AD had higher Braak stage (p < 0.05) even after adjustment for age and cognitive symptom duration. Furthermore, females as a group were significantly more likely to reach the highest Braak neurofibrillary stage (Fig. 1, p < 0.001) and significantly less likely to be in the lowest Braak stage (Fig. 1, p < 0.05). These differences also persist after adjusting for age and cognitive symptom duration (p < 0.05).

As expected, females had significantly lower brain weights, and AD brain weights were significantly lower than those of controls (Fig. 2, Table 2; p < 0.05). A contrast analysis indicated that the AD-control brain weight difference was significantly greater for females (p < 0.001). Spearman’s correlations indicated that some variables, including years of education, cognitive symptom age of onset, and total infarct volume, did not correlate significantly with AD-control brain weight difference (Table 3). The 7 variables that correlated significantly with AD-control brain weight difference, including gender, age at death, years since cognitive symptom onset, postmortem interval, multiple diagnoses, neuritic plaque density, and Braak stage (Table 3), were progressively added to logistic regression models, with all models including up to 6 variables (when the 6-variable equation omitted Braak stage) achieving significance (Table 4).

As expected, both females and males with AD had significantly lower MMSE scores than controls (Table 1; p < 0.05). The male–female AD difference between mean MMSE scores approached the significance level (13.4 vs 12.2, respectively; p = 0.07) and a higher proportion of females had very severe cognitive impairment as defined by MMSE scores of 5 or less (Fig. 3; p < 0.05). MMSE scores did not correlate with education years, neuritic plaque density, or multiple diag-

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**TABLE 2. Pathological Characteristics of Study Subjects**

| Diagnosis-Gender (N) | Brain Weight (SD) | Within-Gender AD-Control Brain Weight Difference (%) | Plaque Density (SD) | Braak NF (SD) | Total Infarct Volume in mm³ (SD) | % Cases Multiple Dx (N) | Postmortem Interval, in Hours (SD) |
|----------------------|-------------------|-----------------------------------------------------|---------------------|--------------|---------------------------------|------------------------|----------------------------------|
| ND-Female (126)      | 1126.3 (98.0)     | 9.0 (11.6)                                          | 1.4 (1.2)           | 3.0 (1.0)    | 12.7 (66.7)                     | NA                    | 3.7 (3.1)                       |
| ND-Male (166)        | 1255.8 (111.1)    | 5.6 (11.0)                                          | 1.1 (1.1)           | 2.7 (1.2)    | 4.1 (23.3)                      | NA                    | 4.7 (11.5)                      |
| AD-Female (345)      | 1024.2 (124.4)    | 9.0 (11.6)                                          | 2.8 (0.4)           | 5.1 (1.0)    | 11.6 (51.7)                     | 28.7 (98)             | 4.7 (6.7)                       |
| AD-Male (391)        | 1188.6 (133.5)    | 5.6 (11.0)                                          | 2.7 (0.4)           | 4.7 (1.2)    | 4.2 (25.4)                      | 32.0 (125)            | 6.5 (10.7)                      |

Braak NF, Braak neurofibrillary tangle stage; Dx, diagnoses; NA, not applicable; ND, no dementia.

*p < 0.05 for gender comparisons within AD subjects.

*p < 0.05 for comparison of all groups; analysis of variance.

*p < 0.001 for % brain weight difference; contrast analysis.

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**FIGURE 1. Distribution of neurofibrillary degeneration severity by Braak stage. A higher proportion of females (black) were classified as having the highest (stage VI) Braak neurofibrillary stage (**p < 0.001). A higher proportion of males (gray) were classified as having the lowest (stage I) nonzero stage (*p < 0.05).**
Several studies suggest that females are at higher risk of developing AD (29–31), whereas other analyses, such as that done in the Rotterdam study, propose that only the very oldest (>90 years) females have a higher risk (32). Furthermore, Kukull et al (8), Rocca et al (9), and Knopman et al (33) did not find any incidence differences between males and females. It is well accepted that females have a longer life expectancy than males; therefore, some results finding higher AD severity, prevalence, and incidence rates in females might be due only to a higher prevalence of very old females in the population. Additionally, analysis based only on the oldest of subjects may be idiosyncratic and/or limited by small sample size.

The AZSAND is not a random sample of the local or US population and, therefore, results may not be readily generalizable. All autopsy studies (except those of court-ordered autopsies) are subject to volunteer bias (34–36). While the control subjects are all derived from people living independently in the communities of greater Phoenix, those with cognitive impairment and dementia are a more selected subset because they are often referred from neurologists’ offices or dementia clinics. It is expected, however, that the increased diagnostic precision and specific histopathological lesion measurement obtained through neuropathological examination confer distinct advantages to autopsy studies such as this one (37–39).

It is well known that cognition declines with aging, and while some studies suggest that this decline is more noticeable in females (30, 40–44), this has not been replicated by all studies (45–47). Barnes et al (6, 7) reported no gender differences in the rate of cognitive decline but suggest that AD pathology is more likely to result in cognitive dysfunction in females than in males. Similarly, Salehi et al (48) found gender differences in AD-related pathology, but others reported no pathological differences between women and men (49–51).

Contradictory results between studies could be explained by differences in experimental design, experimental analysis, and study populations. Relatively few studies have looked at gender differences in AD pathology (6, 7, 48–51) and many that explored cognitive function and incidence rate lacked pathological confirmation of the diagnosis of AD (3–5, 8–10, 30, 43, 44, 52). The accuracy of the clinical diagnosis of AD is low enough, with sensitivity ranging from 71% to 87% and specificity ranging from 44% to 71% (37), to increase the likelihood of false negative findings in studies lacking neuropathological diagnosis confirmation.

This study supports previous published investigations that have suggested that females may be more severely affected by AD than males. In AZSAND subjects, age of cognitive symptom onset did not significantly differ by gender but females were more likely to proceed to very severe disease, both clinically and pathologically, with a significantly higher proportion of females progressing to MMSE scores of 5 or less and to the highest Braak stage of neurofibrillary degeneration (Figs. 1, 3). Neuritic plaque density also tended to be greater in females but the statistical significance of this was limited to control subjects. These results closely parallel those of Barnes et al (6) who also found a higher female tangle burden.

While plaques and tangles may be specific markers of AD pathology, the most proximal cause of cognitive dysfunc-
 tion is likely to be loss of neural parenchyma. Loss of neural parenchyma is commonly expressed, at the gross anatomical level, by brain weight and volume. Numerous studies over many decades have documented how brain volume and weight loss starts as early as in middle age, and how this phenomenon seems to be amplified by neurological disorders such as AD (53–56). To our knowledge, this is the first study that has compared gender-specific AD-control brain weight differences. Even after adjusting for several potential confounders, including age, neuritic plaque densities, disease duration, and presence or absence of multiple diagnoses, the AD-control brain weight difference in AZSAND subjects was found to be significantly greater for women than men. Although both control groups are similarly older than their counterpart AD groups, both female groups are older, on average, than both male groups. Age-related brain atrophy could be synergistic with AD-related brain atrophy, resulting in an accelerated loss of brain weight with increasing age in patients with AD. However, in this study we used multiple regression equations to demonstrate that age did not independently contribute to AD-control brain weight differences when gender was a covariable. Gender at least partially influences the brain weight loss observed in AD and its influence seems to be even stronger than age, in particular with AD. Likewise, it is well known that many dementia subjects who meet criteria for a diagnosis of AD also meet criteria for a diagnosis of other diseases, such as Parkinson disease, dementia with Lewy bodies, vascular dementia, and progressive supranuclear palsy. Therefore, we postulated that this variable could also affect AD-control brain weight differences even though the percentage of females with more than 1 diagnosis did not differ from that in males. On our 2-factor correlation analysis, the correlation of multiple diagnoses with brain weight difference is significant but failed to reach significance on our multivariable analysis.

The loss of significance in our multivariable models including Braak stage indicates that a greater severity of neurofibrillary changes in women may be at least partially responsible for females’ greater AD-control brain weight difference as well as greater MMSE score decline. Nevertheless, logistic regression equations including only gender and Braak stage demonstrated that gender itself may have a significant and independent influence on the observed brain weight difference. Over the past few decades, a variety of studies have suggested that estrogen protects against synaptic loss. One can speculate that the sharp loss of estrogen observed at menopause could be accelerating the synaptic loss observed with aging and AD, consequently leading to a higher brain weight loss. Taken together, these results suggest that females not only develop more AD-specific pathology, espe-

| Variable | Complete Equation | Gender Values |
|----------|-------------------|--------------|
| OR; 95% CI; p Value | OR; 95% CI; p Value |
| Gender | 1.3; 1.1–1.6; 0.01 | 0.6; 0.5–0.8; 0.001 |
| Gender + Braak stage | 0.2; 0.4–0.4; <0.001 | 0.7; 0.5–0.9; 0.019 |
| Gender + Expired age + PMI + Neuritic plaques + Cognitive symptoms, years duration + Multiple diagnoses | 0.1; | 0.7; |
| Gender + Expired age + PMI + Neuritic plaques + Cognitive symptoms, years duration + Multiple diagnoses + Braak stage | 0.01–0.07; 0.02 | 0.6–1.0; 0.05 |

CI, confidence interval; for gender, females had an assigned value; OR, odds ratio.

| Variable | Spearman rho (\(\rho\)) | p Value |
|----------|--------------------------|---------|
| Gender | 0.102 | 0.0172 |
| % brain weight difference | 0.200 | 0.000001 |
| Age | 0.178 | 0.0000287 |
| Braak stage | −0.230 | 0.0000000564 |
| Cognitive symptoms, years | −0.266 | 0.000000000308 |
| Cognitive symptoms, age onset | −0.279 | 0.0000000000362 |
| Neuritic plaque density | −0.0723 | 0.0910 |
| Multiple diagnoses | 0.0588 | 0.170 |
| Education | 0.0144 | 0.763 |

FIGURE 3. Mini-Mental State Examination (MMSE) scores distribution. A higher proportion of females (black) had very severe cognitive impairment as defined by MMSE scores of 5 or less (*\(p<0.05\)). All other paired comparisons are not significantly different.
cally neurofibrillary tangles, but as a result they also suffer a
greater AD-related loss of brain parenchyma and cognitive function.

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TABLE 6. Factors Affecting Mini-Mental State Examination Difference, Multivariable Analysis

| Variable | Complete Equation OR; 95% CI; p Value | Gender Values OR; 95% CI; p Value |
|----------|--------------------------------------|-----------------------------------|
| Gender   | 0.623; 0.465–0.834; 0.001; 0.6; 0.5–0.8; 0.001 | 0.7; 0.5–0.9; 0.019 |
| Gender + Braak | 0.2; 0.4–0.4; <0.001; 1.5; 1.0–2.3; 0.05 | |
| Gender + Age + Cognitive symptoms, years + Cognitive symptoms, age onset + % brain weight difference | 0.07; 0.01–0.5; 0.007 | 0.2; 1.5; 0.01–2.1; 1.0–2.2; 0.07 |
| Gender + Age + Cognitive symptoms, years + Cognitive symptoms, age onset + % brain weight difference + Braak | 0.1 | 0.4–0.4; 0.5–0.9; 0.007 |

CI, confidence interval; for gender, females had an assigned value; OR, odds ratio.
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