*Research article*

# Greater burden of Alzheimer's Co-pathology in women with Parkinson's disease dementia

Journal of Parkinson's Disease
2026, Vol. 16(6): 1191–1200
© The Author(s) 2026
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1877718X261470295
journals.sagepub.com/home/pkn

**Nathaniel Dunckley[1], Erika D. Driver-Dunckley[2], Nan Zhang[3], Geidy E. Serrano[1], Holly A. Shill[4], Shyamal H. Mehta[2], Christine Belden[1], Cecilia Tremblay[1], Alireza Atri[1,5], Charles H. Adler[2] and Thomas G. Beach[1]**

## Abstract

**Objective:** To investigate sex differences in Alzheimer's disease (AD) related pathology among autopsy-confirmed Parkinson's disease (PD) cases.

**Background:** AD and PD frequently co-occur in older adults, yet the influence of sex on AD pathology in the context of PD remains unexplored.

**Methods:** All subjects were enrolled in the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) and Brain and Body Donation Program (BBDP) and had annual standardized research clinical assessments by neuropsychologists, subspecialty behavioral and movement disorders neurologists, as well as comprehensive neuropathological examinations after death.

**Results:** Among 230 autopsy-confirmed PD cases, females exhibited greater amyloid plaque pathology burden than males, regardless of a co-occurring AD diagnosis. Specifically, females with PD had significantly higher mean cortical total plaque scores (mean 6.5/15 vs. 4.9/15, $p = 0.045$) and greater CERAD neuritic plaque density (mean 1.7/3 vs. 1.3/3, $p = 0.035$). Females were also more likely to have a higher cortical plaque burden (plaque total $\geq$ 5: 56.8% vs. 39.7%, $p = 0.015$). In multivariable logistic regression models, female subjects showed greater than twice the odds of having an amyloid plaque burden $\geq$5 compared to males (OR = 2.18; 95% CI = 1.17–4.06; $p = 0.014$), when controlling for ApoE $\epsilon$4 status, Lewy body density score, and age at death.

**Conclusions:** Female sex is associated with increased amyloid plaque pathology in PD, independent of ApoE $\epsilon$4 status. These findings highlight a sex-specific vulnerability to AD pathology in PD patients and support the need for sex-informed approaches to reseach in mixed neurodegenerative disease.

## Plain Language Summary

**Women with Parkinson's Disease Dementia have higher rates of Alzheimer's related brain pathology.** This study explored whether the amount of Alzheimer's-related brain changes differs between males and females with Parkinson's disease. The brains of 230 deceased individuals who had Parkinson's disease were examined. Throughout their lives, these people received regular clinical evaluations by neurology specialists and, after their death, autopsies were performed. The study found that women with Parkinson's disease Dementia had a higher "burden" of Alzheimer's disease-associated amyloid pathology in their brains compared to men with Parkinson's disease Dementia. This was true even if they had not been formally diagnosed with Alzheimer's disease. In conclusion, these findings show that women with Parkinson's disease Dementia are more vulnerable to developing Alzheimer's-like brain changes than men with Parkinson's disease Dementia.

[1]Banner Sun Health Research Institute, Banner Health, Sun City, AZ, USA
[2]Department of Neurology, Parkinson's Disease and Movement Disorders Center, Mayo Clinic, Scottsdale, AZ, USA
[3]Section of Biostatistics, Department of Quantitative Health Sciences, Mayo Clinic, Scottsdale, AZ, USA
[4]Department of Neurology, Barrow Neurological Institute, Phoenix, AZ, USA
[5]Department of Neurology, Center for Mind/Brain Medicine, Brigham & Women's Hospital & Harvard Medical School, Boston, MA, USA

**Corresponding author:**
Erika Driver-Dunckley, Mayo Clinic, 13400 East Shea Blvd, Scottsdale, AZ 85251 United States.
Email: driverdunckley.erika@mayo.edu

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (https://us.sagepub.com/en-us/nam/open-access-at-sage).

**Keywords**
neurodegeneration, pathophysiology, basal ganglia, biochemistry, cell biology

Received: 16 December 2025; accepted: 5 July 2026

## Introduction

Alzheimer's disease (AD) and Parkinson's disease (PD) are prevalent among neurodegenerative disorders in aging populations, each contributing uniquely to cognitive and motor decline. While AD is primarily characterized by β-amyloid plaques and tau neurofibrillary tangles, PD is defined by dopaminergic neurodegeneration and the accumulation of α-synuclein aggregates.[1] These pathologies often co-occur within the same individuals, particularly in older adults with PD who subsequently also develop dementia. Autopsy studies frequently reveal overlapping AD and PD pathology, suggesting a shared or compounding mechanism of neurodegeneration.[2] Neuropathological data from the Arizona Brain and Body Donation Program (BBDP) indicates that over half of PD dementia cases exhibit significant comorbid AD pathology, evident by both amyloid plaque and tau pathology.[3]

Sex is an essential biological variable in both diseases. Men are more frequently affected by PD, while women are more likely to develop AD and may experience faster cognitive decline with more extensive tau and amyloid pathology.[4–6] The mechanisms underlying these sex differences are complex, potentially involving hormonal and genetic factors. Despite known disparities in disease prevalence and progression, limited research has examined whether sex influences AD pathology in patients with PD.

In this study, we analyzed clinical, cognitive, and neuropathological data from a large autopsy-confirmed cohort of PD patients, assessing differences in β-amyloid plaque and tau pathology burden, in relation to ApoE genotype, between males and females. This analysis aims to determine whether the well-documented pattern of increased AD pathology in women persists even in the context of comorbid PD, which could enhance clinical awareness and inform more nuanced models of disease progression.

## Materials and methods

### Research subjects

Approval of this study was obtained from the Institutional Review Boards (IRB) of Banner Sun Health Research Institute. Participants provided informed consent and were enrolled in the AZSAND/BBDP at Banner Sun Health Research Institute (www.brainandbodydonationprogram.org).[2,7] Recruitment primarily targeted independently living retirees in Maricopa County, Arizona, particularly the Sun Cities, resulting in a predominantly Caucasian, middle to high income demographic. Along with neurological controls, individuals with dementia and parkinsonism were also recruited.

### Clinical assessments

Research-dedicated physical, neurological, cognitive, and movement examinations have been previously detailed.[2,7] Participants underwent at least one research visit; with most completing several annual visits. Standardized neuropsychological test batteries covered global assessments and specific cognitive domains.[2] Subspecialist cognitive-behavioral neurologists perform comprehensive evaluations leading to a cognitive diagnosis at the consensus conference involving neuropsychologists, neurologists and cognitive neurology subspecialists. All participants receive annual standardized movement disorders examination, including the Unified Parkinson's Disease Rating Scale (UPDRS, original version) and a clinical diagnosis by movement disorders fellowship-trained neurologists (EDD, CHA, SHM, HAS). Assessment of smell, sleep, and autonomic function along with medical comorbidities were conducted as previously published.[2] This study examined clinical diagnoses from the first and last examination visits, as well as the final clinical diagnosis which is made after death at a consensus conference, by review of all prior clinical assessments as well as review of the private medical records, prior to availability of the neuropathological examination results.

### Case selection

Subjects included in this study had completed neuropathological examinations between 2008 and 2023, with at least one complete set of AZSAND/BBDP clinical assessments, including a final clinical diagnosis (considering all available clinical data before autopsy results) and a final clinicopathological diagnosis (with autopsy results considered).

### Tissue processing and neuropathologic diagnosis

Autopsies were conducted by AZSAND/BBDP. Both clinical and neuropathological methods have previously been published.[2,7] The same neuropathologist (TGB), blinded to clinical findings, conducted all neuropathological examinations. A clinicopathological diagnosis of PD required two or more cardinal clinical signs, as well as Lewy bodies and pigmented neuron loss in the substantia nigra.[8] Dementia with Lewy bodies (DLB) was distinguished from PD with dementia according to consensus criteria

published by the DLB Consortium[9]; the diagnosis of DLB was assigned if dementia was diagnosed prior to or within one year of the onset of parkinsonism and if the distribution and density of Lewy body (LB)-type pathology met "intermediate" or "high" criteria. Subjects with LB-related histopathology were classified according to the Unified Staging System for Lewy Body Disorders (USSLB).[10,11] Neuropathological AD diagnoses were defined using the criteria according to the National Institute on Aging – Alzheimer's Association (NIA-AA) combined with a history of clinical dementia.[12] Formaldehyde-fixed paraffin-embedded sections were stained with hematoxylin and eosin (H & E) and immunohistochemical stains for phosphorylated a-synuclein and phosphorylated TDP-43.[2,7] Large-format, formaldehyde-fixed sections (40–80 μm-thick) were also stained with H & E, as well as with methods targeting amyloid plaques and neurofibrillary tangles, including Gallyas silver, Thioflavin-S and Campbell-Switzer silver stains.[2,7] The dataset further included summary regional brain density measures for total amyloid plaques and neurofibrillary (NF) tangles (for both: summary score of 5 regional semi-quantitative 0–3 density scores for a maximum possible total of 15 in frontal, temporal and parietal lobes plus hippocampal CA1 and entorhinal/transentorhinal area), and assignment of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuritic plaque density, Braak neurofibrillary stage, and AD neuropathological change levels of Low, Intermediate or High, as described previously.[2,12]

### Statistical analysis

The analyses utilized SAS statistical software (Version 9.4 SAS Institute Inc., Cary, NC) and Sigma Plot 12.0 (Systat Software, Inc., San Jose, CA, USA). Group comparisons used the Kruskal-Wallis test, Chi-square test or Fisher's exact test as appropriate. Multivariable logistic regression was used to further assess the sex association with greater presence of plaque burden after adjusting for potential confounders (age at death and ApoE status). For all tests, 0.05 was chosen as the criterion for statistical significance.

## Results

We analyzed 230 autopsy-confirmed PD cases (74 females, 156 males), comparing clinical and pathological characteristics by sex. There were no significant sex differences in PD symptom onset age, disease duration, Hoehn & Yahr stage, or UPDRS scores. Age at death was also similar between groups (mean $81.8 \pm 6.7$ years in females vs. $80.4 \pm 7.0$ years in males; $p = 0.094$), as was the proportion with a coexistent diagnosis of Alzheimer's disease (32.4% in females vs. 30.1% in males; $p = 0.724$). In contrast, males had a significantly higher prevalence of REM sleep behavior disorder (RBD) compared to females (66.9% vs. 42.9%; $p = 0.043$). Olfactory function, assessed using the University of Pennsylvania Smell Identification Test (UPSIT), was significantly better in females (mean $16.0 \pm 5.2$) than in males ($13.0 \pm 4.8$; $p = 0.002$), although both groups demonstrated overall olfactory impairment. Additionally, years of education differed by sex, with males having completed more years of schooling than females ($15.9 \pm 2.8$ vs. $14.7 \pm 2.6$ years; $p = 0.003$) (Table 1).

*Comorbid variables.* Rates of comorbid hypertension, diabetes, obesity, depression, anxiety, and hyperlipidemia were similar between groups, although males had higher rates of sleep apnea (21.2% vs. 2.7%; $p < 0.001$), smoking (52.6% vs. 18.9%, $p < 0.001$), and alcohol consumption (66.0% vs. 47.3%, $p = 0.007$). Rates of minor traumatic brain injury were similar between groups (33.8% females vs. 34.6% males; $p = 0.901$) and family histories of dementia or parkinsonism were also not statistically significant. [Table 2].

*Cognitive function.* No statistically significant sex differences were observed in cognitive test scores or dementia diagnosis rates; except on the AVLT total learning score; females scored higher compared to males ($30.9 \pm 12.2$ vs. $24.4 \pm 10.2$, $p = 0.003$). MMSE scores were equivalent ($22.7 \pm 6.9$ in females vs. $22.0 \pm 6.3$ in males; $p = 0.190$). At final clinical evaluation, 55.4% of female subjects and 68.6% of male subjects had a dementia diagnosis, a difference that was not significant ($p = 0.089$). Similarly rates of MCI were not statistically different (13.5% females vs. 12.8% males; $p = 0.089$). [Table 3].

*Alzheimer's disease and Lewy body pathology.* Female subjects had significantly greater amyloid plaque burdens than male subjects. Figure 1 provides an example of amyloid plaque density. The mean total plaque score was higher in females ($6.5/15 \pm 5.4$) than in males ($4.9/15 \pm 5.5$; $p = 0.045$). A larger proportion of females also met criteria for a dichotomously higher plaque burden (plaque total $\geq 5$: 56.8% vs. 39.7%, $p = 0.015$). CERAD neuritic plaque density was also significantly higher in female subjects (mean $1.7/3 \pm 1.2$ vs. $1.3/3 \pm 1.2$; $p = 0.035$), with more females classified as having frequent neuritic plaques (37.8% vs. 26.3%). The Thal amyloid phase was significantly different between the two groups (mean 2.0 (1.5) vs. 1.6 (1.5), $p = 0.034$). In line with higher Thal phases, females were more likely than males to have amyloid plaques in the striatum, substantia nigra and cerebellar cortex. In contrast, tau pathology did not differ significantly between sexes. Total tangle burden was similar between females and males ($5.7/15 \pm 3.0$ in females vs. $5.1/15 \pm 2.4$ in males; $p = 0.353$), and Braak neurofibillary stage did not differ by sex ($p = 0.459$). Likewise, there were no

**Table 1.** Clinical characteristics.

| | Sex | | | |
|---|---|---|---|---|
| | Female(N = 74) | Male(N = 156) | Total(N = 230) | P-value |
| **Death Age (y)** | | | | 0.094[a] |
| N (Missing) | 74 (0) | 156 (0) | 230 (0) | |
| Mean (SD) | 81.8 (6.7) | 80.3 (7.0) | 80.8 (6.9) | |
| Median (IQR) | 82 (79, 86) | 81 (76, 85) | 81 (76, 85) | |
| Range | 65.0, 97.9 | 60.5, 101.6 | 60.5, 101.6 | |
| **PD Symptom Onset Age (y)** | | | | 0.749[a] |
| N (Missing) | 73 (1) | 148 (8) | 221 (9) | |
| Mean (SD) | 66.7 (10.8) | 66.2 (11.2) | 66.4 (11.1) | |
| Median (IQR) | 68 (61, 74) | 67 (59, 73) | 68 (60, 73) | |
| Range | 38.5, 87.7 | 37.3, 95.5 | 37.3, 95.5 | |
| **PD Symptom Disease Duration (years)** | | | | 0.320[a] |
| N (Missing) | 73 (1) | 148 (8) | 221 (9) | |
| Mean (SD) | 15.0 (7.2) | 14.1 (7.3) | 14.4 (7.3) | |
| Median (IQR) | 15 (10, 19) | 13 (9, 19) | 14 (9, 19) | |
| Range | 1.6, 32.6 | 0.5, 44.5 | 0.5, 44.5 | |
| **UPDRS II Total Off** | | | | 0.992[a] |
| N (Missing) | 64 (10) | 121 (35) | 185 (45) | |
| Mean (SD) | 20.5 (10.1) | 20.7 (8.9) | 20.7 (9.3) | |
| Median (IQR) | 20 (12, 29) | 21 (15, 26) | 21 (14, 27) | |
| Range | 1.0, 40.0 | 0.0, 42.0 | 0.0, 42.0 | |
| **UPDRS III Total Off** | | | | 0.995[a] |
| N (Missing) | 51 (23) | 102 (54) | 153 (77) | |
| Mean (SD) | 41.7 (21.7) | 42.0 (16.7) | 41.9 (18.5) | |
| Median (IQR) | 45 (23, 60) | 42 (31, 53) | 42 (28, 54) | |
| Range | 2.0, 78.0 | 1.0, 82.0 | 1.0, 82.0 | |
| **Hoehn & Yahr** | | | | 0.422[a] |
| N (Missing) | 71 (3) | 148 (8) | 219 (11) | |
| Mean (SD) | 3.5 (1.2) | 3.4 (1.1) | 3.4 (1.1) | |
| Median (IQR) | 3 (3, 4) | 3 (3, 4) | 3 (3, 4) | |
| Range | 0.0, 5.0 | 0.0, 5.0 | 0.0, 5.0 | |
| **Education (y)** | | | | 0.003[a] |
| N (Missing) | 68 (6) | 142 (14) | 210 (20) | |
| Mean (SD) | 14.7 (2.6) | 15.9 (2.8) | 15.5 (2.8) | |
| Median (IQR) | 15 (12, 16) | 16 (14, 18) | 16 (13, 18) | |
| Range | 10.0, 20.0 | 8.0, 24.0 | 8.0, 24.0 | |
| **UPSIT (0–40)** | | | | 0.002[a] |
| N (Missing) | 34 (40) | 88 (68) | 122 (108) | |
| Mean (SD) | 16.0 (5.2) | 13.0 (4.8) | 13.8 (5.1) | |
| Median (IQR) | 16 (12, 19) | 12 (10, 16) | 13 (10, 17) | |
| Range | 7.0, 27.0 | 5.0, 30.0 | 5.0, 30.0 | |
| **SCOPA-Aut Total (0–100)** | | | | 0.053[a] |
| N (Missing) | 44 (30) | 92 (64) | 136 (94) | |
| Mean (SD) | 27.0 (11.8) | 31.7 (12.6) | 30.2 (12.5) | |
| Median (IQR) | 27 (19, 34) | 31 (22, 39) | 30 (20, 36) | |
| Range | 6.3, 55.0 | 7.2, 68.5 | 6.3, 68.5 | |
| **RBD**, n (%) | | | | 0.043[b] |
| N (Missing) | 60 (14) | 133 (23) | 193 (37) | |
| Questionnaire | 14 (23.3%) | 41 (30.8%) | 55 (28.5%) | |
| History | 12 (20.0%) | 45 (33.8%) | 57 (29.5%) | |
| **RLS**, n (%) | | | | 0.983[b] |
| N (Missing) | 74 (0) | 155 (1) | 229 (1) | |
| Yes | 19 (25.7%) | 40 (25.8%) | 59 (25.8%) | |

[a]Kruskal-Wallis p-value; [b]Chi-Square p value.

PD: Parkinson's disease, UPDRS: Unified Parkinson's Disease Rating Scale, UPSIT: University of Pennsylvania Smell Identification Test, SCOPA-AUT: Scales for Outcomes in Parkinson's Disease-Autonomic, RBD: REM Sleep Behavior Disorder, RLS: Restless Legs Syndrome.

**Table 2.** Comorbidities and family history.

| | Sex | | | |
|---|---|---|---|---|
| | Female(N = 74) | Male(N = 156) | Total(N = 230) | P-value |
| Hypertension, n (%) | | | | 0.132[a] |
| | 49 (66.2%) | 87 (55.8%) | 136 (59.1%) | |
| Diabetes, n (%) | | | | 0.242[a] |
| | 8 (10.8%) | 26 (16.7%) | 34 (14.8%) | |
| Hyperlipidemia, n (%) | | | | 0.951[a] |
| | 40 (54.1%) | 85 (54.5%) | 125 (54.3%) | |
| Obesity, n (%) | | | | 0.402[a] |
| | 12 (16.2%) | 19 (12.2%) | 31 (13.5%) | |
| Traumatic Head Injury, n (%) | | | | 0.901[a] |
| | 25 (33.8%) | 54 (34.6%) | 79 (34.3%) | |
| Depression, n (%) | | | | 0.123[a] |
| | 51 (68.9%) | 91 (58.3%) | 142 (61.7%) | |
| Anxiety or Panic Disorder, n (%) | | | | 0.432[a] |
| | 32 (43.2%) | 59 (37.8%) | 91 (39.6%) | |
| Sleep Apnea, n (%) | | | | <.001[a] |
| | 2 (2.7%) | 33 (21.2%) | 35 (15.2%) | |
| Smoking, n (%) | | | | <.001[a] |
| | 14 (18.9%) | 82 (52.6%) | 96 (41.7%) | |
| Alcohol use, n (%) | | | | 0.007[a] |
| | 35 (47.3%) | 103 (66.0%) | 138 (60.0%) | |
| Family history of Dementia, n (%) | | | | 0.331[b] |
| N (Missing) | 67 (7) | 144 (12) | 211 (19) | |
| No | 62 (92.5%) | 138 (95.8%) | 200 (94.8%) | |
| Yes | 5 (7.5%) | 6 (4.2%) | 11 (5.2%) | |
| Family history of PD, n (%) | | | | 1.000[b] |
| N (Missing) | 67 (7) | 144 (12) | 211 (19) | |
| No | 60 (89.6%) | 130 (90.3%) | 190 (90.0%) | |
| Yes | 7 (10.4%) | 14 (9.7%) | 21 (10.0%) | |

[a]Chi-Square p-value; [b]Fisher Exact p-value.
PD: Parkinson's disease.

significant sex differences in Unified Lewy body stage or overall Lewy body density (Table 3).

*Subgroup analyses by cognitive Status.* In the PD subgroup without dementia (cognitively normal or MCI; $n = 82$), no significant sex differences were observed in Lewy body stage, Braak stage, plaque burden, or other neuropathologic measures (Supplemental Table 1). In contrast, among subjects with Parkinson's disease dementia (PDD; $n = 148$), several sex differences emerged (Supplemental Table 2). Females demonstrated greater Lewy body density ($31.0 \pm 6.7$ vs. $28.8 \pm 6.2$; $p = 0.030$). Notably, Alzheimer's disease-related pathology was significantly more pronounced in females with PDD. Females had higher total plaque burden ($7.6 \pm 5.6$ vs. $5.5 \pm 5.6$; $p = 0.028$), were more likely to meet criteria for elevated plaque burden (plaque total $\geq 5$: 63.4% vs. 43.9%; $p = 0.034$), and had higher CERAD neuritic plaque density ($1.9 \pm 1.2$ vs. $1.4 \pm 1.2$; $p = 0.018$). Thal amyloid phase was also significantly higher in females ($2.4 \pm 1.4$ vs. $1.7 \pm 1.5$; $p = 0.019$), with a greater proportion of females in higher Thal phase groupings ($p = 0.020$). In contrast, tangle burden and Braak stage did not differ significantly between sexes.

*Multivariable analysis of plaque burden.* Implementing ROC analysis, the final pathology diagnosis of AD was used as the outcome to find the optimal cut-off of total plaque score to differentiate AD vs. non-AD. From this a plaque score of >=5 was chosen as the optimal cut-off for AD diagnosis. In multivariable logistic regression models adjusting for age at death, ApoE ϵ4 status, and Lewy body density score, female sex was associated with more than a two-fold increase in the odds of having elevated plaque burden (plaque total $\geq 5$) compared to males (OR 2.18, 95% CI 1.17–4.06; $p = 0.014$). The presence of an ApoE ϵ4 allele was a strong independent predictor of higher plaque burden (OR 6.79, 95% CI 3.25–14.19; $p < 0.001$), while increasing age at death was also associated with greater plaque burden (OR 1.05 per year, 95% CI 1.00–1.10; $p = 0.032$) (Table 4). An interaction term between sex and Lewy body density score was initially included to assess potential effect modification but was not statistically significant ($p = 0.086$) and was therefore removed from the

**Table 3.** Cognitive function and pathology.

| | Sex | | | |
|---|---|---|---|---|
| | Female(N = 74) | Male(N = 156) | Total(N = 230) | P-value |
| **Final Dx: Alzheimer's disease (AD)**, n(%) | | | | 0.724[a] |
| Yes | 24 (32.4%) | 47 (30.1%) | 71 (30.9%) | |
| **Final Dx: Cognitive Status**, n (%) | | | | 0.089[a] |
| NL | 23 (31.1%) | 29 (18.6%) | 52 (22.6%) | |
| MCI | 10 (13.5%) | 20 (12.8%) | 30 (13.0%) | |
| DEM | 41 (55.4%) | 107 (68.6%) | 148 (64.3%) | |
| **CAS MMSE** | | | | 0.190[b] |
| N (Missing) | 64 (10) | 130 (26) | 194 (36) | |
| Mean (SD) | 22.7 (6.9) | 22.0 (6.3) | 22.2 (6.5) | |
| Median (IQR) | 25 (20, 28) | 24 (19, 26) | 24 (19, 27) | |
| Range | 0.0, 30.0 | 0.0, 30.0 | 0.0, 30.0 | |
| **MMSE score 5 or less**, n (%) | | | | 0.398[c] |
| Missing | 10 | 26 | 36 | |
| No | 61 (95.3%) | 127 (97.7%) | 188 (96.9%) | |
| Yes | 3 (4.7%) | 3 (2.3%) | 6 (3.1%) | |
| **Clinical Dementia Rating (CDR)** | | | | 0.076[b] |
| N (Missing) | 49 (25) | 104 (52) | 153 (77) | |
| Mean (SD) | 0.9 (1.0) | 1.1 (0.9) | 1.0 (0.9) | |
| Median (IQR) | 1 (0, 1) | 1 (1, 2) | 1 (1, 2) | |
| Range | 0.0, 3.0 | 0.0, 3.0 | 0.0, 3.0 | |
| **MoCA** | | | | 0.154[b] |
| N (Missing) | 20 (54) | 50 (106) | 70 (160) | |
| Mean (SD) | 20.6 (5.9) | 19.3 (13.3) | 19.7 (11.6) | |
| Median (IQR) | 20 (17, 26) | 20 (13, 23) | 20 (14, 24) | |
| Range | 6.0, 29.0 | 4.0, 99.0 | 4.0, 99.0 | |
| **AVLT Total Learning** | | | | 0.003[b] |
| N (Missing) | 55 (19) | 110 (46) | 165 (65) | |
| Mean (SD) | 30.9 (12.2) | 24.4 (10.2) | 26.6 (11.3) | |
| Median (IQR) | 30 (20, 39) | 23 (17, 32) | 27 (19, 34) | |
| Range | 9.0, 62.0 | 0.0, 48.0 | 0.0, 62.0 | |
| **Unified LB Stage**, n (%) | | | | 0.743[a] |
| 2.1 | 4 (5.4%) | 9 (5.8%) | 13 (5.7%) | |
| 2.2 | 3 (4.1%) | 3 (1.9%) | 6 (2.6%) | |
| 3 | 26 (35.1%) | 62 (39.7%) | 88 (38.3%) | |
| 4 | 41 (55.4%) | 82 (52.6%) | 123 (53.5%) | |
| **Braak Stage (0–6)** | | | | 0.937[b] |
| N (Missing) | 74 (0) | 155 (1) | 229 (1) | |
| Mean (SD) | 3.3 (1.0) | 3.2 (1.0) | 3.3 (1.0) | |
| Median (IQR) | 3 (3, 4) | 3 (3, 4) | 3 (3, 4) | |
| Range | 1.0, 6.0 | 0.0, 5.0 | 0.0, 6.0 | |
| **Braak Stage (0–6)**, n (%) | | | | 0.468[c] |
| Missing | 0 | 1 | 1 | |
| 0 | 0 (0.0%) | 1 (0.6%) | 1 (0.4%) | |
| 1 | 3 (4.1%) | 10 (6.5%) | 13 (5.7%) | |
| 2 | 11 (14.9%) | 20 (12.9%) | 31 (13.5%) | |
| 3 | 28 (37.8%) | 51 (32.9%) | 79 (34.5%) | |
| 4 | 25 (33.8%) | 66 (42.6%) | 91 (39.7%) | |
| 5 | 6 (8.1%) | 7 (4.5%) | 13 (5.7%) | |
| 6 | 1 (1.4%) | 0 (0.0%) | 1 (0.4%) | |
| **Sum LB Density** | | | | 0.107[b] |
| N (Missing) | 62 (12) | 142 (14) | 204 (26) | |
| Mean (SD) | 28.9 (7.1) | 27.5 (6.7) | 27.9 (6.8) | |
| Median (IQR) | 30 (23, 35) | 29 (23, 33) | 29 (23, 33) | |
| Range | 5.0, 39.0 | 7.0, 40.0 | 5.0, 40.0 | |
| **Plaque Density**, n (%) | | | | 0.141[a] |
| frequent | 28 (37.8%) | 41 (26.3%) | 69 (30.0%) | |

(continued)

**Table 3.** Continued.

| | Sex | | | |
|---|---|---|---|---|
| | Female(N = 74) | Male(N = 156) | Total(N = 230) | P-value |
| moderate | 12 (16.2%) | 27 (17.3%) | 39 (17.0%) | |
| sparse | 15 (20.3%) | 26 (16.7%) | 41 (17.8%) | |
| zero | 19 (25.7%) | 62 (39.7%) | 81 (35.2%) | |
| **Plaque Total** | | | | 0.045[b] |
| N (Missing) | 74 (0) | 156 (0) | 230 (0) | |
| Mean (SD) | 6.5 (5.4) | 4.9 (5.5) | 5.4 (5.5) | |
| Median (IQR) | 7 (0, 12) | 2 (0, 11) | 3 (0, 12) | |
| Range | 0.0, 15.0 | 0.0, 15.0 | 0.0, 15.0 | |
| **Total Plaque >= 5**, n (%) | | | | 0.015[a] |
| Yes | 42 (56.8%) | 62 (39.7%) | 104 (45.2%) | |
| **Tangle Total** | | | | 0.353[b] |
| N (Missing) | 74 (0) | 153 (3) | 227 (3) | |
| Mean (SD) | 5.7 (3.0) | 5.1 (2.4) | 5.3 (2.6) | |
| Median (IQR) | 6 (4, 7) | 5 (3, 7) | 6 (4, 7) | |
| Range | 0.5, 14.5 | 0.0, 11.5 | 0.0, 14.5 | |
| **CERAD Neuritic Plaque Density** | | | | 0.035[b] |
| N (Missing) | 74 (0) | 156 (0) | 230 (0) | |
| Mean (SD) | 1.7 (1.2) | 1.3 (1.2) | 1.4 (1.2) | |
| Median (IQR) | 2 (0, 3) | 1 (0, 3) | 1 (0, 3) | |
| Range | 0.0, 3.0 | 0.0, 3.0 | 0.0, 3.0 | |
| **CERAD Neuritic Plaque Density**, n (%) | | | | 0.141[a] |
| 0 | 19 (25.7%) | 62 (39.7%) | 81 (35.2%) | |
| 1 | 15 (20.3%) | 26 (16.7%) | 41 (17.8%) | |
| 2 | 12 (16.2%) | 27 (17.3%) | 39 (17.0%) | |
| 3 | 28 (37.8%) | 41 (26.3%) | 69 (30.0%) | |
| **Thal Phase**, n (%) | | | | 0.034[b] |
| N (Missing) | 73 (1) | 155 (1) | 228 (2) | |
| Mean (SD) | 2.0 (1.5) | 1.6 (1.5) | 1.7 (1.5) | |
| Median (IQR) | 2 (0, 3) | 1 (0, 3) | 2 (0, 3) | |
| Range | 0.0, 5.0 | 0.0, 5.0 | 0.0, 5.0 | |
| **Thal Phase**, n (%) | | | | 0.160[a] |
| Missing | 1 | 1 | 2 | |
| Phase 0 (A0) | 19 (26.0%) | 61 (39.4%) | 80 (35.1%) | |
| Phase 1 (A1) | 5 (6.8%) | 18 (11.6%) | 23 (10.1%) | |
| Phase 2 (A1) | 14 (19.2%) | 22 (14.2%) | 36 (15.8%) | |
| Phase 3 (A2) | 28 (38.4%) | 39 (25.2%) | 67 (29.4%) | |
| Phase 4 (A3) | 4 (5.5%) | 11 (7.1%) | 15 (6.6%) | |
| Phase 5 (A3) | 3 (4.1%) | 4 (2.6%) | 7 (3.1%) | |
| **Thal Phase Group,** n (%) | | | | 0.058[a] |
| Missing | 1 | 1 | 2 | |
| Phase 0/1/2 (A0/A1) | 38 (52.1%) | 101 (65.2%) | 139 (61.0%) | |
| Phase 3/4/5 (A2/A3) | 35 (47.9%) | 54 (34.8%) | 89 (39.0%) | |
| **TDP-43**, n (%) | | | | 0.668[a] |
| Missing | 29 | 60 | 89 | |
| no | 24 (53.3%) | 51 (53.1%) | 75 (53.2%) | |
| undx | 15 (33.3%) | 27 (28.1%) | 42 (29.8%) | |
| yes | 6 (13.3%) | 18 (18.8%) | 24 (17.0%) | |
| **ApoE e4 Copies**, n (%) | | | | 0.939[c] |
| Missing | 3 | 10 | 13 | |
| 0 | 53 (74.6%) | 110 (75.3%) | 163 (75.1%) | |
| 1 | 17 (23.9%) | 35 (24.0%) | 52 (24.0%) | |
| 2 | 1 (1.4%) | 1 (0.7%) | 2 (0.9%) | |

[1]Chi-Square p-value; [b]Kruskal-Wallis p-value; [c]Fisher Exact p-value.
MMSE: Mini-Mental Status Examination, MoCA: Montreal Cognitive Assessment, AVLT: Auditory Verbal Learning Test, LB: Lewy Body, CERAD: The Consortium to Establish a Registry for Alzheimer's Disease.

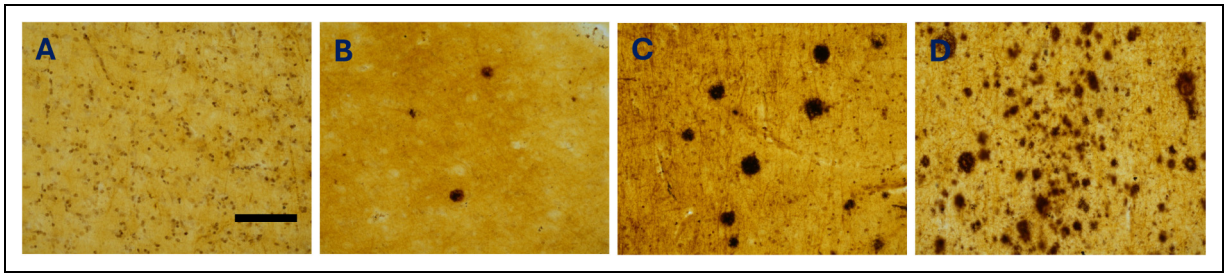



**Figure 1.** Photomicrographs illustrating the semi-quantitative scale for amyloid plaque density. Sections of superior frontal gyrus stained with the Campbell-Switzer silver method. A = None; B = Sparse; C = Moderate; D = Frequent. Scale bar in A (80 μm) serves for all panels.

**Table 4.** Greater Alzheimer's disease (AD) plaque burden in females.

| Variable | Level | OR (95% CI) | P value |
|---|---|---|---|
| Sex | Female vs. Male | 2.10 (1.04, 4.22) | 0.038 |
| Death Age | Every one unit increase | 1.06 (1.01, 1.11) | 0.027 |
| ApoE e4 | Yes vs. No | 5.66 (2.55, 12.57) | <.001 |
| Sum of Lewy body density score | Every one unit increase | 1.10 (1.04, 1.16) | <.001 |

Implementing ROC analysis, the final pathology diagnosis of AD was used as the outcome to find the optimal cut-off of total plaque score to differentiate AD vs. non-AD. From this a plaque score of >=5 was chosen as the optimal cut-off for AD diagnosis.

final model. In the adjusted model, female sex remained independently associated with increased odds of elevated AD plaque burden (OR 2.10, 95% CI 1.04–4.22; $p = 0.038$), confirming the robustness of this association after accounting for Lewy body pathology.

## Discussion

This autopsy-based study of individuals with Parkinson's disease, found no sex differences in clinical features, demographics, or comorbidities. However, female subjects exhibited significantly greater AD-related pathology, particularly amyloid plaque burden. This was observed across multiple measures including total plaque score, CERAD neuritic plaque density, and Thal amyloid phase. These differences were robust and remained significant after adjustment for age, ApoE ϵ4 status, and Lewy body density. Importantly, this increased plaque burden in females was not accompanied by differences in tau pathology, as measured by tangle burden and Braak stage. This suggests that sex differences in PD may be driven more by amyloid-related processes than by tau pathology, at least within this cohort. The multivariable analysis further strengthens this conclusion. Female sex was independently associated with approximately a two-fold increased odds of elevated plaque burden, even after controlling for major contributors such as ApoE ϵ4 genotype and age. While ApoE ϵ4 was the strongest predictor of plaque burden overall, the persistence of a sex effect suggests additional biological mechanisms beyond known genetic risk factors.

An important finding of this study is that sex differences appear to be stage-dependent, emerging primarily in the context of PDD rather than earlier disease stages. Among PD subjects without dementia (cognitively normal or MCI), there were no significant sex differences in Lewy body stage, Braak stage, amyloid plaque burden, or other neuropathologic measures. In contrast, among subjects with PDD, females demonstrated greater Lewy body density and, more prominently, significantly higher AD-related amyloid pathology. These findings suggest that sex-related vulnerability to amyloid pathology may play a key role in the development of dementia in PD, rather than influencing early disease processes. This interpretation is consistent with the broader literature indicating that mixed pathologies, particularly AD co-pathology, are major determinants of cognitive impairment in PD.[3] The observation of higher Lewy body density in females with PDD further suggests that the interaction between synuclein and amyloid pathology may be particularly relevant in this group. While Lewy body pathology alone is a key driver of PD, the combination of increased synuclein burden and greater amyloid deposition in females may produce a cumulative or synergistic effect on cognitive decline. These findings suggest that women may be more susceptible to amyloid-driven pathology in the context of PD, echoing patterns observed in clinically diagnosed AD populations.[4]

Global cognitive performance and rates of dementia did not differ significantly between sexes, despite females demonstrating a superior performance on measures of verbal learning (AVLT). The absence of sex-based differences in

tau pathology may partly explain the lack of differences in overall cognitive impairment, given the well-established relationship between neurofibrillary tangles and cognitive decline. In AD, higher neuritic plaque densities are also associated with greater cognitive impairment; however, this relationship appeared less pronounced in females with PD in our cohort. This attenuation may reflect the relatively small sample size and will require further study. Alternatively, these findings may suggest a degree of relative cognitive resilience in females, potentially reflecting sex-related cognitive reserve or compensatory mechanisms. Similar observations have been reported in AD, where females may tolerate a greater burden of neuropathology before exhibiting clinical symptoms.[6]

Strengths of this study include a well-characterized autopsy cohort with comprehensive neuropathological assessments and detailed clinical data, allowing for robust comparisons by sex and cognitive status. Limitations include the relatively modest sample size for subgroup analyses and the inability to account for unmeasured factors that may contribute to observed sex differences.

In summary, this study demonstrates that female sex is independently associated with greater AD-related pathology in PD, particularly in the context of dementia. While clinical features are largely similar between sexes, underlying neuropathological differences suggest that females may experience a distinct disease trajectory characterized by increased amyloid burden. These findings underscore the importance of considering sex as a biological variable in PD research and highlight the need to account for mixed pathologies in both clinical practice and therapeutic development.

## Acknowledgments

We are extremely grateful to the efforts of the AZ SANDS staff and affiliates, and especially to the study participants, and their study partners, without whom this research would not have been possible.

## ORCID iD


Erika D. Driver-Dunckley https://orcid.org/0000-0003-3938-0648

## Ethical considerations

This study was approved by Banner Sun Health Research Institute's designated Institutional Review Boards (IRB). IRB#1132516 and date of approval 08/01/2025. All subjects completed informed consent and were enrolled in the AZSAND/BBDP at Banner Sun Health Research Institute.

## Consent to participate

This study was approved by Banner Sun Health Research Institute's designated Institutional Review Boards (IRB). All subjects completed informed consent and were enrolled in the AZSAND/BBDP at Banner Sun Health Research Institute.

## Consent for publication

Not applicable.

## Funding

The Arizona Study of Aging and Neurodegenerative Disorders (AZSAND)/Brain and Body Donation Program (BBDP) are supported by the National Institute of Neurological Disorders and Stroke (U24 NS072026 National Brain and Tissue Resource for Parkinson's Disease and Related Disorders), the National Institute on Aging (P30 AG019610 and P30 AG072980, Arizona Alzheimer's Disease Core Center), the Arizona Department of Health Services (contract 211002, Arizona Alzheimer's Research Center), the Arizona Biomedical Research Commission (contracts 4001, 0011, 05-901 and 1001 to the Arizona Parkinson's Disease Consortium), the Michael J. Fox Foundation for Parkinson's Research, and Mayo Clinic Foundation.

## Declaration of conflicting interest

NAD

## Supplemental material

Supplemental material for this article is available online.

## References

1. Irwin DJ, White MT, Toledo JB, et al. Neuropathologic substrates of Parkinson disease dementia. *Ann Neurol* 2012; 72: 587–598.
2. Beach TG, Adler CH, Sue LI, et al. Arizona study of aging and neurodegenerative disorders and brain and body donation program. *Neuropathology* 2015; 35: 354–389.
3. Beach TG, Serrano GE, Driver-Dunckley ED, et al. Parkinson Disease Neuropathological Comorbidities: Prevalences from Younger-Old to Older-Old, with Comparison to Non-Demented, Non-Parkinsonian Subjects. medRxiv *2025*; PMID: 39867383 PMCID: PMC11759614. DOI: 10.1101/2025.01.13.25319971
4. Filon JR, Intorcia AJ, Sue LI, et al. Gender differences in Alzheimer disease: brain atrophy, histopathology burden, and cognition. *J Neuropathol Exp Neurol* 2016; 75: 748–754.
5. Ferretti MT, Iulita MF, Cavedo E, et al. Sex differences in Alzheimer disease—the gateway to precision medicine. *Nat Rev Neurol* 2018; 14: 457–469.
6. Barnes LL, Wilson RS, Bienias JL, et al. Sex differences in the clinical manifestations of Alzheimer disease pathology. *Arch Gen Psychiatry* 2005; 62: 685–691.
7. Beach TG, Sue LI, Walker DG, et al. The sun health research institute brain donation program: description and experience, 1987–2007. *Cell Tissue Bank* 2008; 9: 229–245.
8. Dickson DW, Braak H, Duda JE, et al. Neuropathological assessment of Parkinson's disease: refining the diagnostic criteria. *Lancet Neurol* 2009; 8: 1150–1157.

9. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB consortium. *Neurology* 2017; 89: 88–100.
10. Adler CH, Beach TG, Zhang N, et al. Unified staging system for Lewy body disorders: clinicopathologic correlations and comparison to braak staging. *J Neuropathol Exp Neurol* 2019; 78: 891–899.
11. Beach TG, Adler CH, Lue L, et al. Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction. *Acta Neuropathol* 2009; 117: 613–634.
12. Montine TJ, Phelps CH, Beach TG, et al. National institute on aging-Alzheimer's association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. *Acta Neuropathol* 2012; 123: 1–11.