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# Sex Differences for Clinical Correlates of Alzheimer's Pathology in People with Lewy Body Pathology

**Ece Bayram, MD, PhD**[1], **David G. Coughlin, MD, MTR**[1], **Irene Litvan, MD, MSc, FAAN, FANA**[1]

[1]Parkinson and Other Movement Disorders Center, Department of Neurosciences, University of California San Diego

## Abstract

**Background:** Lewy body (LB) dementias have limited clinical diagnostic accuracy due to frequent co-pathologies contributing to clinical heterogeneity. Although sex differences in clinical prevalence and frequency of pure LB pathology were shown, differences for clinicopathological correlations are less known.

**Objectives:** Determining sex differences for clinical associations of Alzheimer's disease (AD) co-pathology in those with LB pathology

**Methods:** Data was from National Alzheimer's Coordinating Center for 223 women and 468 men with limbic or neocortical LB, separated into two groups as those with high likelihood and low/intermediate likelihood for LB clinical phenotype based on pathology. Clinical associations of sex and interaction of sex and pathology for the clinical phenotype were analyzed.

**Results:** More severe AD co-pathology was associated with worse cognitive decline and lower likelihood of LB disease clinical phenotype. Women with more severe AD co-pathology and tau had worse cognitive decline and higher likelihood of AD clinical phenotype than men. Men with more severe AD co-pathology had lower likelihood of LB clinical phenotype than women. Interaction of sex and pathology was more pronounced in those aged between 70 and 80.

**Conclusions:** AD co-pathology lowers the likelihood of LB clinical phenotype for both women and men, however, men may be at higher risk of LB disease underdiagnosis and women at higher risk of dementia. The use of both LB and AD biomarkers, even when LB or AD pathology is not clinically expected, is necessary for the accurate clinical diagnosis of both LB diseases and AD.

**Corresponding author:** Ece Bayram MD, PhD, 9500 Gilman Dr MC 0886, La Jolla, CA 92093, USA, Phone: +1 858 246 2546, drecebayram@gmail.com.

Authors' Roles

1. Research Project: A Conception, B Organization, C Execution
2. Statistical Analysis: A Design, B Execution, C Review and Critique
3. Manuscript: A Writing of the first draft, B Review and Critique

EB: 1A, 1B, 1C, 2A, 2B, 2C, 3A
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## Introduction

Following Alzheimer's disease (AD), Lewy body (LB) diseases are the second most common family of neurodegenerative dementing disorders and include Parkinson's disease, Parkinson's disease dementia and dementia with Lewy bodies(1–3). These diseases share a spectrum of overlapping clinical features, genetic risk factors, and the common neuropathological hallmark of alpha-synuclein positive Lewy bodies and Lewy neurites. Currently, neuropathological confirmation remains the gold standard in diagnosing LB disease(4–6) and clinical diagnostic accuracy for dementia with Lewy bodies and early stage-Parkinson's disease remains at only about 50%(7,8), which significantly limits efforts to assign patients at early stages to clinical trials for disease-modifying agents. AD co-pathology is commonly observed at autopsy and impacts clinical phenotype, potentially leading to clinical underdiagnosis of LB disease(9). In those with both LB and AD pathologies, higher neurofibrillary tangle burden has been associated with lower likelihood of LB dementia clinical diagnosis(10–12) likely due to associated alterations in cognitive profiles and lower likelihood of having LB core features like visual hallucinations(13–15).

Sex has also been associated with phenotypic differences for those with pure LB pathology, and frequency of AD co-pathology in those with LB pathology(16,17). Compared to men, mixed LB and AD pathology is more common in women(17), pure LB pathology is less likely to lead to LB clinical phenotype and more likely to present with AD clinical phenotype in women(16). In AD, women have greater tau burden than men with similar cognitive impairment(18), and women can bear more tau before developing cognitive decline(19,20). However, interactive effect of sex and AD co-pathology, particularly tau, in those with LB pathology remains unknown. To do so, we analyzed sex differences for the associations between AD co-pathology and LB disease core clinical features, including cognitive fluctuations, visual hallucinations, rapid eye movement sleep behavior disorder (RBD) and parkinsonism(4–6) using the large scale, multicentered data from autopsy-validated individuals collected by National Alzheimer's Coordinating Centers (NACC). We also assessed sex-specific Braak tau staging associations with clinical features. As sex difference for prevalence of LB dementia may be age-dependent, with higher prevalence in men for those younger than 70 to 75 years of age and prevalence increasing for women with age(21–23), we investigated the age impact by additional analysis of age-stratified groups. We hypothesized that those with more AD pathology will be less likely to have LB clinical phenotype and rates of misdiagnosing patients with LB pathology will be higher in women compared to men.

## Methods

### Participants

We obtained the data from NACC Uniform Data Set (UDS) and Neuropathology Data Set including UDS visits conducted between September 2005 and August 2019 at 39 past and present AD research centers(24–27). Only individuals with a limbic (transitional) or neocortical (diffuse) LB pathology, and available Braak tau staging data were included. Presence or lack of AD neuropathology was not an exclusion criterion. Individuals with any other neuropathologic diagnoses that may lead to cognitive decline (e.g., multiple

system atrophy, frontotemporal lobar degeneration, other tauopathies, TAR DNA binding protein-43 pathology, pigment-spheroid degeneration/neurodegeneration with brain iron accumulation, trinucleotide repeat diseases) were excluded. Patients with prion disease, leukodystrophy, multiple sclerosis or other demyelinating diseases, contusion/traumatic brain injury, neoplasm or central nervous system infections were excluded. Based on these criteria, 223 women and 468 men from 35 past and present AD research centers in the NACC were included (Figure 1).

Women and men were divided into two groups based on the staging of LB and AD pathologies (LB-AD and LB+AD)(5). AD neuropathologic change staging in NACC is based on NIA-AA guidelines, and we used Braak tau staging for those lacking AD neuropathologic change staging(28). LB-AD group consisted of individuals with a high likelihood for LB clinical phenotype(5) (94 women, 256 men), including individuals with (1) neocortical LB and NIA-AA none/low/intermediate AD neuropathologic change (or Braak tau<V) (74 women, 202 men), and (2) limbic LB and NIA-AA none/low AD neuropathologic change (or Braak tau<III) (20 women, 54 men). LB+AD group consisted of individuals with an intermediate or a low likelihood for LB disease phenotype (129 women, 212 men), including individuals with (1) neocortical LB and NIA-AA high AD neuropathologic change (or Braak tau >IV) (117 women, 178 men), and (2) limbic LB and NIA-AA intermediate/high AD neuropathologic change (or Braak tau>II) (12 women, 34 men).

### Clinical assessments

Cognitive status (normal cognition, mild cognitive impairment, dementia), and clinical diagnosis at last visit were included as provided by NACC. CDR® Dementia Staging Instrument-Sum of Boxes (CDR-SOB) scores at last visit were used for cognitive decline severity. Clinician report of LB disease core clinical features (cognitive fluctuations, visual hallucinations, RBD, parkinsonism) at any visit during follow-up was included.

### Neuropathological assessments

Neuropathological variables consisted of LB pathology staging(5) and AD pathology staging including Thal phase (amyloid-β plaque score), Braak tau stage (neurofibrillary tangle stage) and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score (neuritic plaque score)(28). Level of substantia nigra neuron loss ranging from 0 (none) to 3 (severe) was included, given its association with clinical phenotype in LB diseases(5).

### Statistical analysis

IBM SPSS version 28.0 (Armonk, NY: IBM Corp) and R version 4.0.3(29) were used. Sex and pathology group differences for demographics and neuropathology were assessed with Welch's t tests for continuous, Mann Whitney U for ordinal and Chi-square tests for categorical variables. Effects of sex and pathology groups on clinical features were assessed using generalized linear models (GZLM) including features with potential impact on clinical phenotype, and that differ between the sexes as covariates. Clinical associations of Braak tau stage were assessed individually for women and men with logistic and linear regression. Interaction of sex and Braak tau for clinical features was assessed with GZLM.

Age-stratified analyses included the same models for individuals <70, between 70 and 80, and >80 years. False discovery rate (FDR) was used for multiple comparison correction, alpha level was set at .05 for significance.

### Data availability statement

Data supporting the findings are available from NACC. Data are available to all researchers following approval of a data request submitted to NACC (naccdata.org).

## Results

Demographics, clinical and neuropathology features are presented in Table 1, Supplementary Tables 1–2, and Figure 2.

### Sex comparisons for demographics, clinical and neuropathology features

Women were older at last visit, had cognitive decline at an older age, and died older than men (t=−4.46, t=−3.71, t=−4.67, respectively; $p$<.001 for all). Women and men had similar years of education, length of follow-up, duration between last visit and death, duration of cognitive decline, and duration between death and brain removal ($p$>.10 for all). Ratios of women and men with recent or past hypertension, diabetes, hypercholesterolemia and obesity (body mass index≥30) at last visit were similar (Supplementary Table 1). Similar ratios of women and men were using antihypertensive or blood pressure, diabetes, antipsychotic, anxiolytic, sedative or hypnotic agents within two weeks of the last visit. Higher ratios of men had a history of smoking and alcohol abuse, and were using lipid-lowering medications, non-steroidal anti-inflammatory drugs, anticoagulant or antiplatelet agents, antidepressants, AD medications and antiparkinson agents than women.

Women and men had similar LB and amyloid pathology staging (Thal phase) ($\chi^2$=2.09, $p$=.22; U=7509, $p$=.065). Similar ratios of women and men had vascular pathologies and hippocampal sclerosis ($\chi^2$=2.41, $p$=.75; $\chi^2$=0.038, $p$=.37). Women had higher Braak tau staging (U=40569, $p$<.001), higher CERAD scores (U=45460, $p$=.008), and less substantia nigra neuron loss (U=7072, $p$=.012) than men. Women were less likely to be demented ($\chi^2$=16.61, $p$=.002), have LB core clinical features (cognitive fluctuations $\chi^2$=9.50, $p$=.005; visual hallucinations $\chi^2$=15.8, $p$<.001; RBD $\chi^2$=30.4, $p$<.001; parkinsonism $\chi^2$=23.4, $p$<.001) and clinical LB diagnosis, but more likely to have clinical AD diagnosis during follow-up ($\chi^2$=38.3, $p$<.001). 8.5% (n=19) of women and 4.5% (n=21) of men did not have clinical diagnosis of LB disease or AD despite having LB pathology with or without AD pathology (Supplementary Table 2).

### Pathology group comparisons for demographics, clinical and neuropathology features

Women in LB-AD and LB+AD had similar demographics. Higher ratio of women in LB-AD was using antiparkinson agents. LB+AD women were more likely to be demented, spent a longer time with cognitive decline and had higher CDR-SOB than LB-AD women. Neocortical LB pathology was more common in LB+AD women; level of substantia nigra neuron loss was similar for LB-AD and LB+AD women. LB+AD women were less likely to

have clinical LB, more likely to have clinical AD diagnosis than LB-AD women. Presence of LB core clinical features did not differ across groups (Figure 2).

Men in LB-AD and LB+AD had similar demographics, age at cognitive decline, duration of cognitive decline, and similar ratios of neocortical LB pathology. Higher ratio of men in LB-AD had obesity and was using antiparkinson agents. Compared to LB-AD men, LB+AD men had higher CDR-SOB, less substantia nigra neuron loss, higher likelihood of clinical LB, lower likelihood of clinical AD diagnosis. LB+AD men were less likely to have cognitive fluctuations, visual hallucinations, RBD and parkinsonism than LB-AD men (Figure 2).

### Effects of sex and pathology groups on clinical features

Because age at last visit, smoking and alcohol abuse history, substantia nigra neuron loss level differed between women and men, and due to cognitive associations of education and LB location (neocortical vs limbic)(30), subsequent GZLM were adjusted for these variables. Compared to men, women were less likely to have parkinsonism, clinical LB diagnosis, dementia, and had lower CDR-SOB (Table 2). LB+AD was associated with increased likelihood and severity of dementia, clinical AD, lower likelihood of clinical LB diagnosis, and LB core clinical features.

LB+AD was associated with increased likelihood and severity of dementia, clinical AD diagnosis for women more than men (Table 2). LB+AD was associated with lower likelihood of cognitive fluctuations, visual hallucinations, RBD, parkinsonism and clinical LB diagnosis more for men than women.

### Sex-specific Braak tau stage associations and interaction of sex and Braak tau stage for clinical features

For women, higher tau staging was associated with a greater likelihood and severity of dementia at last visit, younger age at cognitive decline onset, longer time with cognitive decline, clinical AD; lower likelihood for RBD, parkinsonism, and clinical LB diagnosis during follow-up (Supplementary Table 3). For men, higher tau staging was associated with a greater likelihood and severity of dementia at last visit, clinical AD during follow-up; lower likelihood for cognitive fluctuations, visual hallucinations, RBD, parkinsonism, and clinical LB diagnosis during follow-up.

GZLM were adjusted for age at last visit, education, smoking and alcohol abuse history, CERAD score, substantia nigra neuron loss level education and LB location. Tau staging increased the likelihood of clinical AD diagnosis and CDR-SOB for women more than men (Supplementary Table 3, Figure 3). There were no significant sex and tau interaction for other features.

### Age-stratified analyses

Sex differences for individuals <70, between 70 and 80, and >80 years of age at last visit are shown in Supplementary Table 4. For those <70 at last visit, compared to men, women had higher Braak tau staging and were less likely to have a smoking history. For those between

70 and 80, women had higher Braak tau staging, were less likely to be demented, have clinical LB diagnosis and LB core clinical features than men. For those >80, women were older at last visit and death, less likely to have a smoking history, parkinsonism and clinical LB diagnosis than men. Other variables were similar for women and men.

All GZLM were adjusted for age at last visit, education, LB pathology location and level of substantia nigra neuron loss (Supplementary Table 5). For those <70, LB+AD was associated with higher likelihood of dementia and clinical AD diagnosis, lower likelihood of clinical LB diagnosis, RBD and parkinsonism. LB+AD was associated with lower likelihood of parkinsonism more for men than women.

For those between 70 and 80, men were more likely to have clinical LB diagnosis whereas women had higher CDR-SOB; LB+AD was associated with higher likelihood of clinical AD diagnosis, lower likelihood of clinical LB diagnosis and LB core clinical features. LB+AD was associated with lower likelihood of cognitive fluctuations, visual hallucinations and RBD more for men than women and with higher likelihood of clinical AD diagnosis more for women than men.

For those ≥70, LB+AD was associated with more severe dementia more for women than men. For those >80, LB+AD was associated with higher likelihood and severity of dementia, higher likelihood of clinical AD diagnosis; LB+AD was associated with higher likelihood of dementia more for women than men.

## Discussion

In this study, we assessed the association of AD co-pathology with clinical features and the interaction between sex and AD co-pathology on clinical phenotype in a large cohort of autopsy-validated LB disease patients. We found that having a more severe AD co-pathology was associated with lower likelihood of LB core clinical features and clinical LB disease diagnosis, higher likelihood of dementia and clinical AD diagnosis with sex modifying these associations. With more severe AD co-pathology or higher tau staging, women had worse cognitive decline and were more likely to have AD clinical phenotype than men; with more severe AD co-pathology, men were less likely to have LB disease phenotype than women. These findings emphasize a sex difference for clinicopathological correlations of AD co-pathology and tau burden in individuals with limbic or neocortical LB pathology.

Sex represents an important factor for both AD and LB disease prevalence, presentation and progression(31–33). Sex differences observed here, including higher tau and neuritic plaque density in women, and more substantia nigra neuron loss in men, were consistent with prior autopsy studies(17,34). Given that AD co-pathology in LB disease lowers the likelihood of LB disease phenotype(5) and pure LB pathology is associated with LB disease phenotype more for men than women(16), women were less likely to have LB core clinical features and clinical LB disease diagnosis than men in our analysis. Over 85% of women and 75% men in LB+AD group were clinically diagnosed with AD, which is in accordance with prior reports on AD co-pathology leading to AD clinical phenotype in those with LB pathology(5,12). Amygdala-predominant LB cases were excluded as this

pattern of synucleinopathy is typically observed in the setting of severe AD pathology, is unlikely to result in LB disease phenotype, and there may be biochemical differences in alpha-synuclein accumulated in this entity(5,35). Despite limbic or neocortical LB pathology in all our participants, rates of accurately identifying those with LB pathology in the setting of higher levels of AD neuropathology at the clinic remained at 39% for women and 64% for men, supporting that AD co-pathology lowers the likelihood of LB disease phenotype, making accurate clinical diagnoses difficult(5). Individuals with no or low levels of AD neuropathological change and LB pathology being clinically misdiagnosed with AD will inevitably impact the care provided, expectations in terms of the prognosis and findings of clinical trials targeting particular disease mechanisms. Clinical underdiagnosis of LB disease in women is likely due to higher frequency of AD co-pathology and LB pathology not frequently leading to a typical LB disease phenotype in women. These observations highlight the need for in vivo molecularly specific biomarkers to identify patients with co-pathologies during life even when LB pathology is not clinically expected. Such stratification may be necessary to assemble biologically homogenous populations for clinical trials of disease-modifying agents.

Association between more severe AD co-pathology and higher likelihood for dementia and more severe dementia, being amplified in women, suggest that previously reported sex-specific cognitive associations of pure AD pathology(32) also occur when LB pathology is accompanied by AD pathology. In LB dementia, tau has been associated with worse overall cognition and lower likelihood of inattention and executive dysfunction typical for LB dementia phenotype and instead is associated with worse episodic memory and naming which are more characteristic of AD(10,36). Our findings are in accordance with these previous reports. In AD, women may harbor greater tau burden before onset of cognitive decline, but once they reach higher levels of pathology, women decline faster than men(18–20,32). In mild cognitive impairment, women have a stronger association between verbal memory and tau burden, particularly in left hemisphere(37). We found that in those with limbic or neocortical LB pathology, higher tau staging was associated with worse dementia severity for women more than men. Our analyses evaluating the association between tau and LB core clinical features show that clinicopathological associations of tau in those with LB pathology are not only limited to cognition but can also be found for other LB disease features.

Prevalence studies have suggested that dementia with LB is more common for men until the age of 70 to 75, and this sex difference for prevalence declines with older age(21–23). Although our aim was not to investigate prevalence, as available data in NACC may not be representative of the elderly population, we performed age-stratified analyses to evaluate clinicopathological correlations across different age groups. Ratio of women with clinical LB disease diagnosis decreased with age, and for those aged 70 and older, women were less likely to be clinically diagnosed with LB disease compared to men. Interaction of sex and pathology differed across the age groups, and majority of significant interactions were found for those aged 70 and older. AD co-pathology was associated with worse dementia particularly for women aged 70 or older, compared to men. AD co-pathology was associated with lower likelihood of LB core features particularly for men between the ages 70 and 80, compared to women. However, these age-stratified analyses need to be interpreted

cautiously, given the differences across the age groups for the sample sizes. While sources of these differences cannot be elucidated in this study, LB dementia is a complex disease with genetic and environmental risk factors that predispose to it(38). AD co-pathology in LB disorders is similarly complex; there is likely age-related factors that predispose to its development but in certain in vivo studies some species of alpha-synuclein are capable of cross-seeding tau pathology(39), and positron emission tomography studies suggest a different distribution of tau pathology in LB disorders than AD(40,41), implying that the interaction may be more direct and complex. It is not possible from the data collected in NACC study to discern when AD co-pathology arises in these patients and longitudinal prospective studies with molecularly specific biomarker collection are needed.

There are several limitations to this study. Our analyses only included clinician reports of LB core clinical features(4–6), due to significant amounts of missing data for other features that may help with clinical identification of LB disease (e.g., autonomic disturbances, impairment in individual cognitive domains, assessment of clinical features with validated scales(42)). Clinical diagnosis data should be interpreted cautiously as clinical diagnosis in NACC is based on available diagnostic criteria at the time of the visits, and this data was included in our analysis as is. NACC data with available neuropathological assessments represent predominantly older data. Accuracy of clinical diagnosis can likely increase after implementation of up-to-date clinical diagnostic criteria combined with currently available LB and AD biomarkers, which are strong predictors of underlying pathology(43–47). Clinical diagnosis and cognitive status in NACC are determined by a single clinician, a group of clinicians or an ad hoc consensus group using available data which may include a combination of detailed or brief neurological examination, neuropsychological testing, participant report, co-participant report, and clinical opinion(24,26,27). Although the consistent use of more comprehensive assessments for all individuals would deem our findings more reliable(48), level of data used to determine the cognitive status of each participant are unknown. Time of onset can help with clinical diagnosis(49) and differ for men and women(50), although we did not have this level of detail for LB core clinical features and were unable to account for this in our analysis. Medications reported in NACC reflect the medications being used within the two weeks of the visit. Detailed data on history of medication use and comorbidities could not be included in our analysis due to limited data in NACC. Other neuropathologies such as hippocampal atrophy, TDP-43 and vascular burden have been associated with clinical phenotype in LB disorders and AD(9,51–57). Although we excluded participants with other neurodegenerative pathological diagnoses available in NACC(25), we were unable to control for neuropathologies not encoded in the dataset. Current forms in NACC(24) do not include the quantification and tracking of vascular burden, which may have important implications for the clinical phenotype in LB disorders(53). Our pathology groups were based on the likelihood of LB dementia phenotype using LB and AD neuropathologic change staging(5), and LB pathology location (limbic vs neocortical) was included as a covariate in our statistical models as LB pathology location has been associated with phenotypic differences. Compared to limbic LB, neocortical LB has been associated with more rapid cognitive decline and higher risk of dementia(30). Larger samples are needed to differentiate the impact of AD co-pathology for those with limbic or neocortical LB pathology. In addition, level of LB pathology burden

has also been associated with different clinical phenotypes(58) and could not be assessed in our analysis. There are studies in AD showing sex-specific cognitive associations of regional tau pathology(18,59), and we were unable to conduct such regional analyses in our study, as only Braak neurofibrillary tangle staging data were available for tau burden. Currently available advanced neuropathology methods allow for assessment of tau and LB pathology burden level in different regions(60) and can guide future studies to better understand sex-specific clinicopathological correlations.

In conclusion, our findings show that sex modifies the associations between AD co-pathology and clinical phenotype in patients with LB pathology. Tau appears to be an important factor for both women and men with LB pathology, with significant associations with clinical phenotype including cognitive and behavioral features. Although AD co-pathology increases the risk of clinical underdiagnosis of LB disease in men more than women, women with limbic and neocortical LB pathology continue to be at higher risk of LB disease underdiagnosis with or without AD co-pathology compared to men. Additionally, significant association between AD co-pathology and cognition, especially for women, implicates that sex-specific tau effect in AD extends to those with LB pathology. Women may withstand the cognitive effect of LB pathology more than men, with tau co-pathology being the more impactful pathology for cognition in women with LB pathology. There is a need to improve clinical diagnostic approaches and implementing alpha-synuclein-specific biomarkers to improve diagnostic accuracy in LB diseases and AD, particularly in women.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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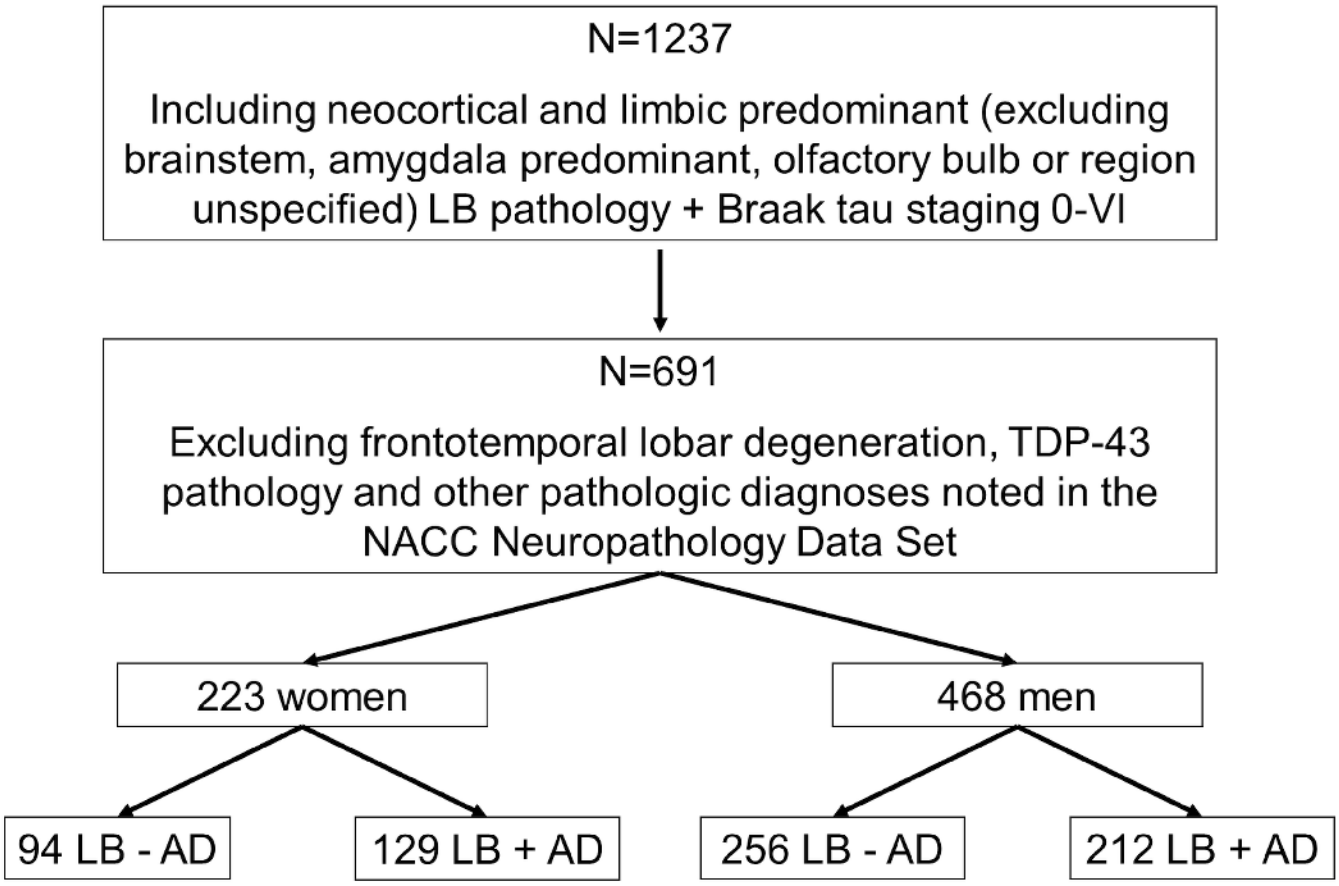


**Figure 1.**
Flowchart showing the selection criteria and number of individuals at each step

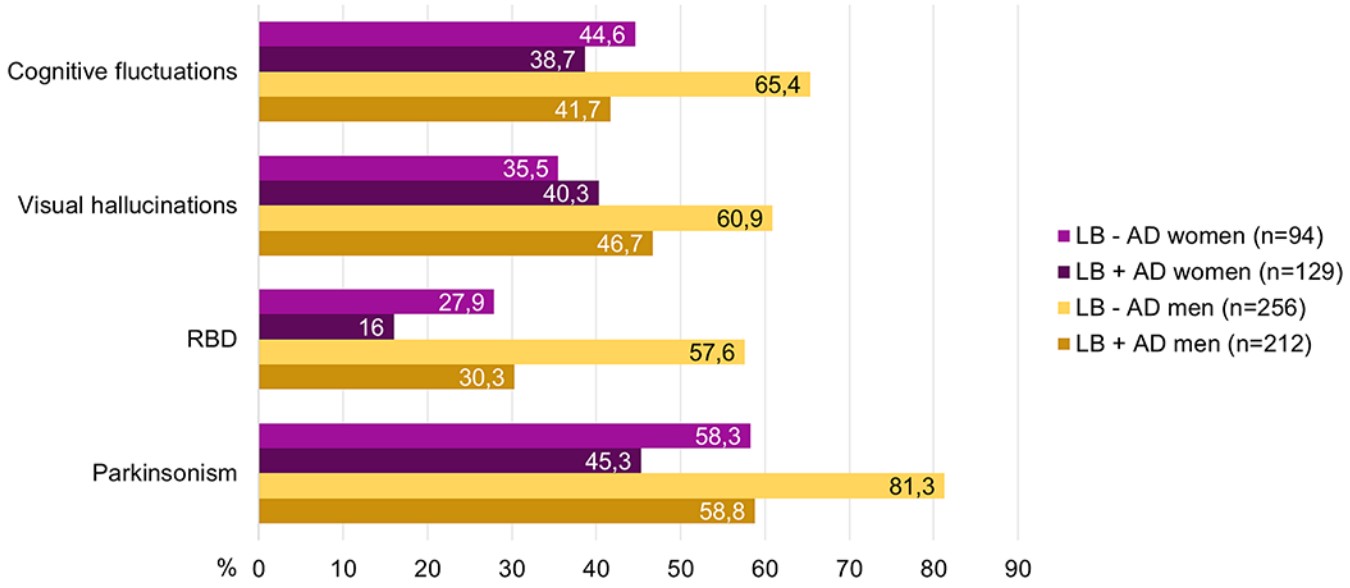


**Figure 2.**

Percentage of women (n=223) and men (n=468) with a high likelihood for LB disease phenotype based on pathology (LB - AD) and those with intermediate or low likelihood (LB + AD) presenting with LB disease core clinical features at any visit during follow-up.

Data was available from 3171 women (65 LB - AD, 106 LB + AD) and 364 men (208 LB - AD, 156 LB + AD) for cognitive fluctuations; 222 women (93 LB - AD, 129 LB + AD) and 468 men (256 LB - AD, 212 LB + AD) for visual hallucinations; 168 women (68 LB - AD, 100 LB + AD) and 360 men (205 LB - AD, 155 LB + AD) for RBD; and 178 women (72 LB - AD, 106 LB + AD) and 389 men (219 LB - AD, 100 LB + AD) for parkinsonism.

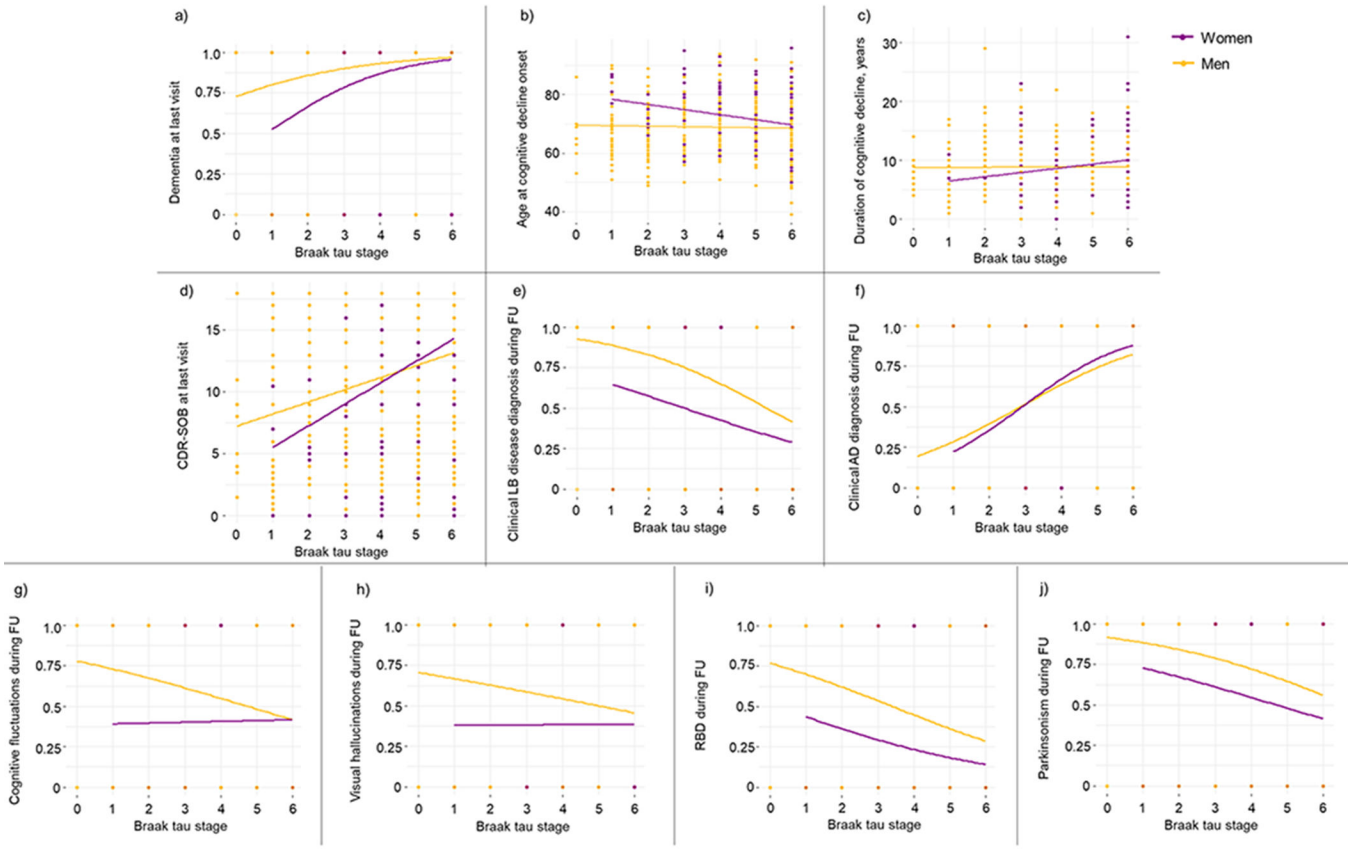


**Figure 3.**

Association between Braak tau stage and a) dementia diagnosis at last visit, b) age at onset of cognitive decline, c) duration of cognitive decline, d) CDR® Dementia Staging Instrument-Sum of Boxes (CDR-SOB) at last visit e) clinical Lewy body (LB) disease diagnosis during follow-up (FU), f) clinical Alzheimer's disease (AD) diagnosis during FU, g) cognitive fluctuations during FU, h) visual hallucinations during FU, i) REM sleep behavior disorder (RBD) during FU, j) parkinsonism during FU for women and men. Logistic regression curves are used for categorical outcome variables, and scatter plots with regression lines are used for numerical outcome variables. Plots depict uncorrected models; corrected models are reported in Supplementary Table 3.

**Table 1.**

Demographics, clinical and neuropathology features of women (n=223) and men (n=468)

| Demographics, clinical and neuropathology features | Women (n=223) | | | | Men (n=468) | | | |
|---|---|---|---|---|---|---|---|---|
| | All | LB - AD (n=94) | LB + AD (n=129) | LB - AD vs LB + AD | All | LB - AD (n=256) | LB + AD (n=212) | LB - AD vs LB + AD |
| Age at last visit | 79.9 (10.0) | 81.0 (9.2) | 79.2 (10.5) | t=−1.38, *p*=.37 | 76.4 (8.9) | 76.9 (8.6) | 75.8 (9.2) | t=−1.38, *p*=.31 |
| Age at death | 81.5 (9.8) | 82.5 (9.1) | 80.7 (10.3) | t=−1.36, *p*=.35 | 77.9 (8.8) | 78.4 (8.5) | 77.2 (9.1) | t=−1.37, *p*=.30 |
| Education | 16.2 (11.6) | 15.9 (9.2) | 16.4 (13.1) | t=0.39, *p*=.79 | 15.9 (3.1) | 15.9 (3.1) | 15.9 (3.0) | t=−0.047, *p*=.99 |
| Length of follow-up, years | 3.1 (3.1) | 3.3 (3.2) | 2.9 (3.0) | t=−0.97, *p*=.49 | 2.7 (2.5) | 2.9 (2.5) | 2.4 (2.5) | t=−1.89, *p*=.15 |
| Interval between last visit and death, months | 18.8 (20.2) | 18.3 (20.8) | 19.1 (19.8) | t=0.29, *p*=.86 | 17.3 (17.2) | 17.1 (16.9) | 17.6 (17.6) | t=0.34, *p*=.89 |
| Cognition at last visit (%) | | | | $\chi^2$=28.2, *p*<.001 * | | | | $\chi^2$=10.62, *p*=.040 * |
| Cognitively normal [a] | 18 (8.1) | 17 (18.1) | 1 (0.8) | | 10 (2.1) | 8 (3.2) | 2 (1.0) | |
| MCI | 9 (4.0) | 7 (7.4) | 2 (1.6) | | 29 (6.2) | 23 (9.0) | 6 (2.8) | |
| Dementia | 196 (87.9) | 70 (74.5) | 126 (97.7) | | 429 (91.7) | 225 (87.9) | 204 (96.2) | |
| Age at onset of cognitive decline | 71.9 (10.2) | 73.5 (9.7) | 70.9 (10.4) | t=−1.87, *p*=.16 | 68.8 (9.0) | 69.3 (8.8) | 68.3 (9.2) | t=−1.20, *p*=.38 |
| Duration of cognitive decline, years | 9.1 (4.5) | 7.9 (4.0) | 9.8 (4.7) | t=3.08, *p*=.009 * | 8.8 (3.7) | 8.8 (4.0) | 8.8 (3.4) | t=−0.090, *p*=1.00 |
| Cognitive fluctuations [b] (%) | 70 (40.9) | 29 (44.6) | 41 (38.7) | $\chi^2$=0.59, *p*=.57 | 201 (55.2) | 136 (65.4) | 65 (41.7) | $\chi^2$=20.3, *p*<.001 * |
| Visual hallucinations [b] (%) | 85 (38.3) | 33 (35.5) | 52 (40.3) | $\chi^2$=0.53, *p*=.58 | 255 (54.4) | 156 (60.9) | 99 (46.7) | $\chi^2$=9.48, *p*=.007 * |
| RBD [b] (%) | 35 (20.8) | 19 (27.9) | 16 (16.0) | $\chi^2$=3.50, *p*=.16 | 165 (45.8) | 118 (57.6) | 47 (30.3) | $\chi^2$=26.4, *p*<.001 * |
| Parkinsonism [b] (%) | 90 (50.6) | 42 (58.3) | 48 (45.3) | $\chi^2$=2.92, *p*=.21 | 278 (71.5) | 178 (81.3) | 100 (58.8) | $\chi^2$=23.7, *p*<.001 * |
| Clinical diagnosis (%) | | | | $\chi^2$=39.4, *p*<.001 * | | | | $\chi^2$=54.3, *p* <.001 * |
| Only LB disease | 43 (19.3) | 29 (30.9) | 14 (10.9) | | 158 (33.8) | 116 (45.3) | 42 (19.8) | |
| Only AD | 118 (52.9) | 33 (35.1) | 85 (65.9) | | 150 (32.1) | 48 (18.8) | 102 (48.1) | |
| LB and AD | 43 (19.3) | 15 (16.0) | 28 (21.7) | | 139 (29.7) | 81 (31.6) | 58 (27.4) | |
| CDR®-Sum of Boxes | 11.9 (6.3) | 8.9 (6.6) | 14.1 (5.0) | t=6.41, *p*<.001 * | 11.1 (5.6) | 9.9 (5.5) | 12.6 (5.3) | t=5.44, *p*<.001 * |
| Neocortical LB (%) | 191 (85.7) | 74 (78.7) | 117 (90.7) | $\chi^2$=6.34, *p*=.047 * | 380 (81.2) | 202 (78.9) | 178 (84.0) | $\chi^2$=1.94, *p*=.32 |
| Thal phase | 4.1 (1.2) | 3.3 (1.5) | 4.7 (0.4) | U=356, *p*<.001 * | 3.7 (1.7) | 2.9 (1.8) | 4.7 (0.8) | U=1289, *p*<.001 * |
| Braak tau stage | 4.6 (1.4) | 3.3 (1.1) | 5.6 (0.6) | U=414, *p*<.001 * | 4.0 (1.7) | 2.8 (1.2) | 5.4 (0.7) | U=1375, *p*<.001 * |

| Demographics, clinical and neuropathology features | Women (n=223) | | | | Men (n=468) | | | |
|---|---|---|---|---|---|---|---|---|
| | All | LB - AD (n=94) | LB + AD (n=129) | LB - AD vs LB + AD | All | LB - AD (n=256) | LB + AD (n=212) | LB - AD vs LB + AD |
| CERAD score | 2.2 (1.0) | 1.7 (1.0) | 2.6 (0.7) | U=2666, $p$<.001 * | 2.0 (1.1) | 1.4 (1.1) | 2.7 (0.8) | U=10174, $p$<.001 * |
| Substantia nigra neuron loss | 1.8 (1.4) | 1.8 (1.4) | 1.8 (1.5) | U1159=, $p$=1.00 | 2.2 (1.7) | 2.3 (1.5) | 2.2 (1.9) | U=3212, $p$=.042 * |
| Presence of ischemic, hemorrhagic, or vascular pathology (%) | 218 (98.2) | 91 (96.8) | 127 (99.2) | $\chi^2$=1.78, $p$=.33 | 449 (97.8) | 244 (98.0) | 205 (97.6) | $\chi^2$=0.74, $p$=.87 |
| Presence of hippocampal sclerosis[b] (%) | 5 (2.2) | 1 (1.1) | 4 (3.1) | $\chi^2$=2.21, $p$=.51 | 8 (1.7) | 2 (0.8) | 6 (2.8) | $\chi^2$=3.22, $p$=.34 |
| Time between death and brain removal, hours | 12.1 (10.0) | 13.2 (12.2) | 11.2 (7.7) | t=−0.88, $p$=.51 | 13.9 (13.0) | 13.6 (13.2) | 14.2 (12.8) | t=0.29, $p$=.91 |

Values are presented as mean (standard deviation) or count (percentage). LB: Lewy body, AD: Alzheimer's disease, LB - AD: high likelihood for Lewy body disease phenotype based on pathology; LB + AD: low or intermediate likelihood for Lewy body disease phenotype based on pathology, MCI: mild cognitive impairment, RBD: REM sleep behavior disorder.

The $p$ values are FDR-corrected. Statistical significance is marked with *.

[a]The count (percentage) for cognitively normal individuals include those with and without a clinical diagnosis of LB disease. Cognitively normal individuals without a clinical diagnosis of AD or LB disease are shown in Supplementary Table 1.

[b]Data was available from 171 women (65 LB - AD, 106 LB + AD) and 364 men (208 LB - AD, 156 LB + AD) for cognitive fluctuations; 222 women (93 LB - AD, 129 LB + AD) and 468 men (256 LB - AD, 212 LB + AD) for visual hallucinations; 168 women (68 LB - AD, 100 LB + AD) and 360 men (205 LB - AD, 155 LB + AD) for RBD; 178 women (72 LB - AD, 106 LB + AD) and 389 men (219 LB - AD, 100 LB + AD) for parkinsonism; 92 women (42 LB - AD, 50 LB + AD) and 164 (91 LB - AD, 73 LB + AD) men for hippocampal sclerosis.

**Table 2.**

Main sex and pathology group effects and interaction of sex and pathology group (LB - AD, LB + AD) on clinical features[a]

| Clinical features as outcomes | Main sex effect | Main pathology group effect | Sex and pathology group interaction effect |
|---|---|---|---|
| Dementia diagnosis at last visit | B=1.40, $p$=.030 * | B=1.24, $p$=.017 * | $G^2$=9.56, $p$=.011 * |
| Age at onset of cognitive decline | B=−1.01, $p$=.34 | B=−0.50, $p$=.38 | $G^2$=1.41, $p$=.54 |
| Duration of cognitive decline | B=0.69, $p$=.48 | B=0.60, $p$=.36 | $G^2$=1.33, $p$=.51 |
| Clinical LB disease diagnosis during FU | B=1.75, $p$=.010 * | B=−1.59, $p$<.001 * | $G^2$=27.4, $p$<.001 * |
| Clinical AD diagnosis during FU | B=0.73, $p$=.21 | B=2.18, $p$<.001 * | $G^2$=37.2, $p$<.001 * |
| Cognitive fluctuations during FU | B=0.56, $p$=.34 | B=−1.20, $p$=.001 * | $G^2$=11.0, $p$=.007 * |
| Visual hallucinations during FU | B=0.76, $p$=.24 | B=−0.73, $p$=.033 * | $G^2$=9.41, $p$=.011 * |
| RBD during FU | B=0.85, $p$=.23 | B=−1.66, $p$<.001 * | $G^2$=17.2, $p$<.001 * |
| Parkinsonism during FU | B=1.53, $p$=.033 * | B=−1.44, $p$<.001 * | $G^2$=17.5, $p$<.001 * |
| CDR®-Sum of Boxes at last visit | B=3.58, $p$=.025 * | B=2.96, $p$=.002 * | $G^2$=17.4, $p$<.001 * |

LB - AD: high likelihood for Lewy body disease phenotype based on pathology; LB + AD: low or intermediate likelihood for Lewy body disease phenotype based on pathology, LB: Lewy body, AD: Alzheimer's disease, FU: follow-up, RBD: REM sleep behavior disorder.

The $p$ values are FDR-corrected. Statistical significance is marked with *.

[a]Models to investigate the reported findings included age at last visit, education, smoking and alcohol abuse history, LB pathology location (neocortical vs limbic) and level of substantia nigra neuron loss as covariates