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Sex differences in dementia with Lewy bodies: focused review of available evidence and future directions

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Abstract

In this review, we summarize the current knowledge on sex differences in dementia with Lewy bodies (DLB) relating to epidemiology, clinical features, neuropathology, biomarkers, disease progression, and caregiving. While many studies show a higher DLB prevalence in men, this finding is inconsistent and varies by study approach. Visual hallucinations may be more common and occur earlier in women with DLB, whereas REM sleep behavior disorder may be more common and occur earlier in men. Several studies report a higher frequency of parkinsonism in men with DLB, while the frequency of fluctuations appears similar between sexes. Women tend to be older, have greater cognitive impairment at their initial visit, and are delayed in meeting DLB criteria compared to men. Women are also more likely to have Lewy body disease with co-existing AD-related pathology than so-called “pure” Lewy body disease, while men may present with either. Research is mixed regarding the impact of sex on DLB progression. Biomarker and treatment research assessing for sex differences is lacking. Women provide the majority of caregiving in DLB but how this affects the caregiving experience is uncertain. Gaining a better understanding of sex differences will be instrumental in aiding future development of sex-specific strategies in DLB for early diagnosis, care, and drug development.

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Human and animal rights

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Keywords

dementia with Lewy bodies; dementia; Lewy body disease; sex

1. Introduction

Neurodegenerative diseases have documented sex differences in clinical phenotype, time to diagnosis, pathology, and treatment [1, 2]. For example, Alzheimer disease (AD) is more common in women [3-5]. This can partly relate to longevity differences, but women may have greater neurofibrillary tangle (NFT) pathology [6] and higher CSF total tau and Aβ42 levels [7] than men. Parkinson disease (PD) is more common in men [8-10]. Dementia with Lewy bodies (DLB) is more commonly diagnosed in men [11-13], resulting in fewer women in DLB cohorts. This has historically precluded the examination of sex differences in DLB. However, longstanding DLB programs and recent multicenter collaborations now have large cohorts available for examining potential sex differences [14-20]. A better understanding of sex differences in DLB is important for early disease detection, symptomatic management, caregiver support, and eventual implementation of personalized therapies.

In this review, we highlight current research on sex differences in DLB including epidemiology, clinical presentation, pathology, biomarkers, progression, management, and caregiving. Search criteria included peer-reviewed DLB research studies identified through EMBASE and PubMed published in English prior to July 2022. We excluded research solely on PD, AD, or other dementias. DLB studies were included if results had sex- or gender-specific analyses. While “sex” (biology) and “gender” (a socially-based construct) are related terms, they have different meanings but many studies used the terms interchangeably. Thus, the review focuses on identified sex differences in DLB with further comment on the potential role of gender in the discussion.

2. Sex differences in Clinical and Population Cohorts

DLB accounts for approximately 3.5% to 9.6% of dementia cases in epidemiologic studies [12, 21-24]. Clinical DLB samples typically have more men [11-13, 25], a pattern observed in some population studies [12] but not others [16, 21, 22] (Table 1). Some variability may relate to differences in community versus clinical populations. Specialty clinic DLB cohorts typically include more individuals with parkinsonism and/or REM sleep behavior disorder (RBD), which are more commonly diagnosed in men [12, 26-30]. Community samples often include older individuals with a greater proportion of women. In older patients with DLB, the sex ratio is more likely to be equal or higher for women. For those <75, a DLB diagnosis is more common in men [12, 16, 31]. Geographic location may also be relevant, although the basis for this is unclear. For example, Japanese multicenter DLB studies [32-34], French cohorts [16] and British samples [23, 35] showed more balanced sex ratio than U.S. cohorts.

It is unknown whether race or ethnicity affects cohort sex differences. An autopsy study of 81 Black and 154 White community participants from longitudinal aging studies revealed no differences in sex or in the frequency and distribution of Lewy body pathology [36]. In a National Alzheimer’s Coordinating Center (NACC) study comprised of 1,782 White, 130

Black, and 122 Hispanic participants, women represented only 26% of White participants with cognitive impairment due to Lewy body pathology, compared to 60% identifying as Black and 41% identifying as Hispanic [37]. More work is needed to determine whether this reflects disease-specific differences, geographic variation, and/or recruitment patterns.

3. Clinical Features

3.1 Cognitive Function and Dementia:

DLB is characterized by impairments in attention and visual perceptual abilities, while memory and naming tend to be relatively preserved compared to patients with AD [38-40]. Lower memory and naming scores occur in DLB with AD-related pathology compared to DLB without AD-related pathology, and co-pathology is common in women with DLB [41, 42].

In a study of individuals with clinically probable DLB [43], men (n=101) had higher Mini Mental State Examination (MMSE) scores than women (n=133) (19.7 ± 4.6 vs. 18.0 ± 5.7, p=0.029), suggesting less severe cognitive impairment despite similar clinical presentation, disease duration, and age at onset [17]. In a European DLB Consortium sub-analysis (n=375), DLB participants with an AD-CSF profile were more likely to be female, older and with lower MMSE scores than those without an AD-CSF profile [44]. In the Amsterdam Dementia Cohort, women with DLB (n=39/223, 17%) had lower CSF Aβ42, as well as worse MMSE and animal fluency scores, but did not differ from men on other cognitive tasks [18]. This pattern was also shown in a NACC DLB study [20], wherein women had a higher Braak NFT stage, neuritic plaque frequency and Clinical Dementia Rating Scale Sum of Boxes scores at the last visit. Overall, data on differences in cognitive function between sexes in DLB are limited, but suggest that women may have worse MMSE scores, possibly relating to higher degrees of AD-related pathology.

3.2 Cognitive Fluctuations.

Men and women with DLB have similar reported rates of cognitive fluctuations [14, 15, 17, 18, 20] (Table 2) based on the Mayo Fluctuation Scale [15], the Clinician Assessment of Fluctuation and One Day Fluctuation Assessment Scale scores [45], or history-taking [14, 17, 18, 20]. Reliable biomarkers of fluctuations in DLB are lacking [46]. In a NACC study of pathologically-defined DLB, there was also no sex effect on the presence of cognitive fluctuations during follow-up, but AD co-pathology reduced the likelihood of cognitive fluctuations more in men than women [20]. There is no convincing evidence of sex differences in the point prevalence or longitudinal progression of fluctuations in DLB, but how this is affected by co-pathology requires further study.

3.3 REM Sleep Behavior Disorder (RBD).

RBD can occur decades before the onset of cognitive or motor features of DLB [15, 47]. In clinical sleep center samples, isolated RBD is more common in men [48-50]. A population study found a prevalence of 1% with no sex differences [48], however, suggesting RBD may be under-detected in women. Men with DLB are more likely to have a history of RBD (46-84%) than women (21-55%) [14, 15, 17, 18, 20] (Table 2). This may be due to greater

muscle phasic activity in men during REM sleep [50] and more vigorous dream-related movements that can cause injury [51-53]. In both men and women with DLB, RBD occurs less frequently in the presence of AD co-pathology [20]. In a longitudinal study at the Mayo Clinic, RBD emerged at a younger age in men than women (median 64 vs. 68 years) [15]. Although RBD developed before the other core DLB features in both sexes, it typically preceded cognitive symptom onset in men and was more likely to develop concurrently with cognitive symptoms in women [15]. The absence of RBD was associated with delays in diagnosis of probable DLB in both sexes [15]. These findings suggest that men with DLB and RBD may have a longer identifiable preclinical phase and window of opportunity for intervention.

3.4 Visual hallucinations (VH).

In DLB, VH may be more common in women (38-82%) than men (38-76%), with significant differences in 4 of 7 studies (Table 2) [15, 18, 54, 55]. However, this is not found in some autopsy [14, 20] or clinical samples [17]. While men were more likely to have VH compared to women in pathologically-defined DLB in the NACC, this sex difference disappeared after correcting for demographics and pathology staging [20]. In the presence of AD co-pathology, VH likelihood reduced further for men than women [20]. In both the clinical and pathologic subsets of a Mayo Clinic longitudinal study of clinically probable DLB [15], the time from cognitive symptom onset to developing VH was shorter in women than men. RBD typically preceded the development of VH for both men and women. However, women developed VH within the same time frame as fluctuations and parkinsonism, while men were more likely to develop VH after the other three core features of RBD, parkinsonism, and fluctuations [15]. Overall, research is mixed regarding sex differences in VH, with a suggestion that VH may occur more frequently and earlier in women with DLB. More research is needed regarding potential differences, such as use of dopaminergic treatments and follow-up duration (as VH may appear later in men).

3.5 Parkinsonism.

Several studies report a higher prevalence of parkinsonism in men than women with DLB (Table 2) [14, 15, 17, 18, 54]. In one study, sex differences for parkinsonism were statistically significant at diagnosis (59.0% men vs. 44.4% women, p=0.027), but not symptom onset (5.0% men vs. 4.5% women) [17]. In another clinically-defined DLB cohort, parkinsonism was more common in men (91% men vs. 83% women, p=0.025), but the difference was not significant in the autopsied subset (89% men vs. 88% women, p=0.83) [15]. In a NACC pathologically-defined cohort, parkinsonism was less common in women with DLB [20]. In the setting of AD co-pathology, parkinsonism was less common in both sexes, but particularly in men [20]. Two DLB studies reported that women had lower rates of treatment for parkinsonism [15, 20], but milder symptom severity may be a confounder [15]. While women with DLB appear more likely to develop VH and parkinsonism concurrently, it remains unclear whether this timing makes women with DLB at greater risk for adverse effects from dopaminergic therapy (e.g., worsening hallucinations) and consequently, under-treatment of motor symptoms.

3.6 Supportive features.

In patients with DLB, Capgras syndrome appears equally likely in men and women [56], but depression and auditory hallucinations may be more common in women [17]. There were no sex differences in severe neuroleptic sensitivity reactions in a small DLB sample [57]. In another study, men more commonly had hyposmia and syncope in early DLB, but there were no sex-based differences in constipation or orthostatic hypotension [17].

3.7 Clinical subtypes.

Recent studies use data-driven approaches to identify clinical DLB subtypes (as opposed to pathological or imaging subtypes), with varying findings related to sex. In a study of 81 individuals with probable DLB, cluster analysis yielded three subtypes: cognitive predominant, neuropsychiatric-predominant, and parkinsonism-predominant [58]. Male:female representation was not statistically different across groups [58]. In a factorial analysis using 107 participants in the European DLB consortium [59], hierarchical clustering identified four subtypes: Cluster 1: Aβ and cerebrovascular pathologies, medial temporal atrophy, and cognitive fluctuations; Cluster 2: posterior atrophy, poor cognitive performance, and parkinsonism; Cluster 3: tau pathology, posterior atrophy, and low parkinsonism frequency; and Cluster 4: cognitive fluctuations, higher MMSE scores, virtually normal AD biomarkers, and the least regional brain atrophy and cerebrovascular pathology. While the overall cohort was predominantly men (n=77/107, 72%), Cluster 4 was more common in women (n=12/19, 63%), though most patients in Cluster 4 came from one center [59]. Currently it remains uncertain whether these subtypes are clinically meaningful and whether there are true sex differences between groups.

4. Diagnosis of DLB

Individuals with DLB frequently experience diagnostic delays [60]. Sex differences in emergence of DLB core features [15, 42] may explain missed or delayed diagnoses in women. In a NACC study examining pathologically-defined DLB cohorts (excluding individuals with more severe AD co-pathology), women were older than men but manifested fewer core DLB features and were less likely to be diagnosed with probable DLB during life [14]. Delayed diagnosis in women may relate to milder parkinsonism and lower rates of RBD in women compared to men [15]. Diagnosis timing, however, may relate more to the presence or absence of RBD than sex per se: individuals without RBD met criteria for probable DLB later, irrespective of sex [15]. Compared to men, women with DLB tend to present at an older age, show greater cognitive impairment at their initial visit, and have a later emergence of two or more core features needed for a clinical diagnosis of probable DLB [14, 15, 18].

How underlying neuropathology intersects with sex to affect diagnostic timing is uncertain. In one study, DLB was diagnosed earlier in a neuropathologic subgroup of Lewy body disease without neocortical tangles, where individuals were disproportionately male and more likely to have RBD, greater parkinsonism severity, and relatively preserved memory and naming [42]. A NACC study found that sex did not affect the age of dementia onset in “pure” Lewy body disease (with Braak stage 0-II Alzheimer pathology). Male sex,

depression, and apolipoprotein E4 (ApoE-e4) status predicted earlier dementia onset in Lewy body disease with Braak stage III-VI pathology [61]. When evaluating pathologically-defined DLB in another NACC study, more severe AD co-pathology was associated with lower likelihood of DLB core clinical features and clinical DLB diagnoses, and a higher likelihood of dementia and clinical AD diagnoses, in both sexes. Sex modified the degree of these associations [20].

5. Neuropathology

DLB neuropathology includes Lewy-related pathology in brainstem-limbic regions or diffusely extending to the neocortex [43, 62]. At least 50% of people with DLB have co-existing AD-related pathology [11, 41, 62]. When Aβ and tau pathology are present in DLB, the burden may still be lower than that of AD [62-64]. Lewy body disease without neocortical AD-related pathology often shows a male predominance, while men and women are similarly represented in pathologic subgroups of Lewy body disease with neocortical AD-related pathology [15, 42, 61, 65, 66]. In a NACC study, women and men had similar Lewy body and amyloid staging, but women had higher Braak Tau staging and less nigral neuronal loss than men [20].

Whether differential hormonal influences on α-synuclein may contribute to sex differences in neocortical LB pathology is an area of active study. Most studies of hormonal influences on α-synuclein have been conducted in PD [9, 67]. Sex hormones, especially estriol, contain antioxidant properties that harbor anti-aggregation and fibril-destabilizing effects on α-synuclein in vitro [68]. Women may be protected against α-synucleinopathies pre-menopause, after which α-synuclein aggregation accelerates with decreasing estradiol levels, especially during the second half of menopause [4]. Whether the older age of onset of DLB in women [12, 16, 31] relates to these hormonal differences remains unknown.

6. Biomarkers

6.1 DLB Biomarkers.

While skin biopsy and CSF RT-QuIC are promising synuclein biomarkers [69], limited research evaluates sex differences in these assays. A small 2012 study reported lower levels of CSF α-synuclein in women with DLB versus controls, but no difference in men with DLB versus controls [70]. A recent study found lower CSF α-synuclein levels in women compared to men [18]. Notably, both studies used ELISA techniques rather than newer approaches assessing α-synuclein seeding activity (e.g., RT-QuIC).

Apart from polysomnography to investigate RBD, there is minimal research on sex differences for indicative (dopamine transporter imaging, ^{123}I-metaiodobenzylguanidine cardiac scintigraphy) or supportive (MRI, electroencephalography, fluorodeoxyglucose-positron emission tomography) biomarkers [43]. In a study examining DAT-SPECT in patients with parkinsonian disorders including DLB, correcting for age and sex did not improve sensitivity or specificity [71]. Studies of MRI atrophy patterns in DLB often control for sex rather than investigating it as a variable of interest [72, 73]. In individuals with probable DLB from the European DLB cohort, male sex was associated with

abnormal frontal cortical atrophy but sex did not predict atrophy in medial temporal or posterior cortices [74]. In DLB, female sex has been associated with higher white matter hyperintensity volumes but not with infarct frequency [66, 75, 76]. These findings highlight the need to evaluate for potential biomarker differences between sexes in DLB, not just control for sex as a confounding variable.

6.2 AD-related Biomarkers.

Age-adjusted AD-CSF biomarker analysis from 223 patients with DLB within the Amsterdam Dementia Cohort revealed women had lower levels of Aβ42 compared to men, but there were no differences in total or phosphorylated tau concentrations [18]. In a multicohort DLB study, women were more likely to have positive imaging biomarkers using Pittsburgh compound B and Tau-PET ([^{18}F]AV-1451) or CSF Aβ42 and phosphorylated tau, including dual amyloid and tau positivity. The presence of Aβ pathology was associated with greater cognitive impairment and participants with positive tau biomarkers demonstrated fewer core clinical DLB features [54]. Additional Tau-PET [77] and Amyloid-PET [78] studies included 77-86% male participants and did not specifically report sex differences. There is clearly a need for research into biomarkers of AD pathology in DLB.

6.3 Genetics.

ApoE-e4 is associated with an increased dementia risk in the synucleinopathies [79, 80]. In an autopsy-confirmed cohort of 652 patients with Lewy body disease (31% with dementia and parkinsonism, 43% with dementia without parkinsonism, 26% with parkinsonism without dementia), ApoE-e4 status was more common in those with a Thal phase of III-V and with neocortical tangle pathology (Braak NFT stage IV-VI). ApoE-e4 has also been associated with more severe Lewy-related pathology, even in cases with low AD pathology [81]. In one study of clinically probable DLB, women carried the ApoE-e4 allele more frequently than men [18], but another study showed no sex differences in the proportion of ApoE-e4 carriers [14]. GBA mutations are associated with an increased susceptibility for Lewy body disease and dementia [82, 83]. Some studies suggest that GBA mutations are associated with earlier symptom onset in men with DLB [84, 85]; however, a recent meta-analysis found no sex differences in GBA variants in DLB [86]. More work is needed to better understand the clinical heterogeneity of DLB and how it relates to genetic factors in men and women.

7. Progression

7.1 Clinical Progression.

Studies examining sex differences in cognitive progression have mixed findings, even within the same cohort. A study including 835 participants with probable DLB from the European DLB Consortium (54% male) did not find sex significant differences in the rate of decline on the MMSE over two years [87]. In a subgroup analysis (n=100), however, men had a more rapid MMSE decline over two years [87, 88]. Other studies have not found an effect of sex on cognitive decline [89-92]. It is possible that decline relates more to pathology than sex given that faster cognitive decline is associated with an AD-CSF profile [88] and the synergistic effects of α-synuclein, amyloid-β, and tau pathologies [11, 42, 93].

7.2 Survival.

Whether sex affects survival in DLB remains unclear. In an autopsy-confirmed DLB sample, women had shorter median survival following dementia onset than men (6.6 versus 8.1 years), though women died at an older age [94]. In a clinical cohort, however, sex did not affect median survival after first presentation with cognitive impairment in DLB (men: 3.57 years, women: 3.81 years) [95]. Similarly, sex was not a significant predictor of survival in a clinically-defined NACC DLB cohort [96] and duration of cognitive decline was similar between sexes in a pathological NACC study [20]. Discrepancies may relate to differences in cohort identification. In another NACC study with neuropathological data, male sex was associated with shorter survival in individuals with transitional or diffuse Lewy body disease pathology, but there was no difference in survival by sex in the subset of individuals with an antemortem diagnosis of probable DLB. Most of this sample had a Braak NFT stage of IV or greater [97].

Sex differences in clinical progression and survival are likely influenced by the extent of Lewy-related and AD-related pathology [62, 97]. Increased CSF phosphorylated tau is linked to shorter survival and faster rates of cognitive decline among individuals with DLB [88, 98, 99]. Additionally, while available studies focus on potential biological sex differences, survival is also influenced by gender roles, relating to the presence, identity, and involvement of caregivers and whether the person with DLB requires residential/institutional care.

8. Management

Under-representation of women in DLB clinical trials limits assessment of potential sex differences in treatment response. Completed studies on Clincialtrials.gov (accessed December 2, 2022) report only ~15-37% female participants in DLB drug trials. Additionally, although 15% of the sample in a trial of nelotanserin for RBD were female, none of the female participants were randomized to the treatment group [100]. Similarly, studies examining nucleus basalis of Meynert deep brain stimulation for DLB included 0-17% female participants [101, 102]. Reasons for low female participation are likely complex, relating to prevalence of DLB diagnoses in countries where trials are performed, the fact that women meet DLB diagnostic criteria less often and later than men, and potential differences in caregiving structures for men versus women.

9. Caregiving

While population-based studies of caregivers of individuals with DLB are lacking, 67-90% of caregivers in identified DLB studies were women [103-107]. Most of these caregivers were spouses, but a substantial minority were daughters and daughters-in-law [103-105, 108]. Men also serve as caregivers, but little is known about their unique experiences.

Higher caregiver burden in DLB is associated with dementia severity [103], neuropsychiatric symptoms (including sleep disturbance) [104-106, 108, 109], need for assistance with activities of daily living [105, 108, 109], caregiver anxiety [104], and social isolation [105]. Whether sex affects caregiving in DLB is uncertain. In one study combining caregivers of

individuals with DLB and AD, female caregivers reported higher relative stress than male caregivers [108]. In a study combining caregivers of individuals with DLB, PD dementia, and AD, sex was significantly correlated with caregiver burden, but not after adjusting for multiple comparisons [103]. Caregiver sex was not associated with pre-loss grief in a recent study in DLB [107]. Given that sex and gender likely align for many study participants, these results may reflect gender roles as well as potential biological differences affecting caregiving. Biological sex differences (e.g. physical stature, potentially affective symptoms) have caregiving implications, but so does gender (e.g. relating to societal and familial roles).

10. Limitations

This is a focused review of existing literature and while it is unlikely that publications specifically targeting sex differences in DLB were overlooked, studies in which sex was examined in secondary analyses may have been missed. The review also focused on sex rather than gender, as studies specifically evaluating gender were scarce.

11. Future Directions

This review focused on sex-related differences in DLB because research on gender in this context is lacking. While sex refers to biological distinctions (sex chromosomes, X and Y), gender is based on psychosocial, environmental, and cultural influences [110]. In the fields of dementia and AD, examples of gender-related differences in risk factors include education, income, marital status, smoking, depression, diet/exercise, and cerebrovascular comorbidities [111, 112]. Gender may also affect clinical diagnosis of dementia, as gender differences in functional roles can affect timing of recognizing functional decline [113]. While sex and gender intersect, more studies are needed to distinguish sex and gender effects in DLB, especially pertaining to modifiable risk factors and patient and caregiving experiences.

Clinical awareness of possible sex differences in clinical presentation and biomarker status of DLB will support more accurate and timely diagnoses, including at prodromal stages. Identification of endophenotypes of DLB, based on unique combinations of demographic and clinical features, along with pathological biomarkers, would inform diagnostic criteria revision, understanding of expected disease progression, and prediction of treatment response. Consideration of differential effects of sex and gender on individuals living with DLB and their caregivers [114-116] supports a trend towards individualized care and fulfillment of unmet needs (Table 3). Moving forward, DLB clinical trials should stratify randomization by sex so that women participants are not solely allocated to the placebo arm [100]. Excluding individuals with DLB and AD co-pathology also risks exacerbating under-representation of women in DLB trials [114, 115]. Clinical trial results should include sex/gender-specific data to identify whether treatment differences exist and allow for future meta-analyses.

12. Conclusions

DLB impacts women living with and caring for others living with the disease (Figure 1). Current literature supports sex differences in clinical presentations, pathology, and clinico-pathological correlations, informing efforts for early detection, appropriate counseling, and patient and caregiver support. Additional research is needed to address the presented gaps in the current understanding of potential sex and gender differences in biomarkers and treatment responses in DLB.

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Highlights

- Better understanding sex differences in DLB will aid diagnosis and management.
- RBD and parkinsonism may be more common in men.
- Visual hallucinations appear more common in women.
- Delayed DLB diagnosis may be more frequent in women.
- Women are more likely to have mixed Lewy body and Alzheimer-related pathologies.

Figure 1. Sex differences in DLB

Women with dementia with Lewy bodies (DLB) tend to be older, have greater cognitive impairment at their initial visit, and meet DLB criteria later when compared to men. Women with DLB may also be more likely to experience visual hallucinations than men, with visual hallucinations starting concurrently with parkinsonism and cognitive fluctuations. While the illustration includes a shadowed cat to visually represent the hallucination, hallucinations appear real to the individuals experiencing them. Parkinsonism can be milder in women with DLB than in men, one reason women might be diagnosed later. Caregivers in DLB are commonly women, reflecting either spouses or daughters and daughters-in-law. Caregiver burden can be affected by dementia severity, neuropsychiatric symptoms, and need to assist with activities of daily living, but whether sex affects caregiver burden is uncertain. Little is known about the experiences of DLB in individuals from diverse backgrounds. The illustration of two women of non-white race does not imply that DLB disproportionately affects Black women or that women from these backgrounds have a different experience.

Table 1.

Sex demographic profiles in sample DLB studies

Reference	Country	Referral base	Study type	Diagnostic criteria used	Epidemiology (if reported)	Men/ women ratio	Term Used in Publication (Sex or Gender) [b]
Population-based studies							
Yue et al., 2016 [117]	China	Door-to-door in rural China	Cross-sectional, door-to-door, population-based study across 56 villages in Ji County	DSM-IV criteria	Prevalence/total population, % (95% CI) Men: 1.22 (0.78–1.65) Women: 0.91 (0.57–1.25) Prevalence/dementia population, % (95% CI) Men: 15.15 (10.16–20.15) Women: 7.45 (4.79–10.10)	**Men: n=30 (51.7%)** Women: n=28 (48.3%)	**Sex**
Savica et al., 2013 [12]	U.S.	Medical records-linkage system of the Rochester Epidemiology Project (REP)	Retrospective study	DLB Consortium 3rd Consensus Criteria	Incidence/all ages, Rate per 100,000 person-years Men: 4.8 Women: 2.2 Incidence/over 65 years old, Rate per 100,000 person-years Men: 54.2 Women: 16.2	**Men: n=43 (67%)** Women: n=21 (33%)	**Sex**
Williams et al., 2006 [94]	U.S.	Recruited via word of mouth, public service announcements, and referrals from physicians in the St. Louis area	Prospective longitudinal study	DLB Consortium 1st Consensus Criteria and neuropathology confirmation	N/A	**Men: n=38 (60%)** Women: n=25 (40%)	**Gender**
Goodman et al., 2017 [118]	U.S.	Centers for Medicare & Medicaid (CMS) administrative enrollment and claims data for 100% of Medicare beneficiaries enrolled in the fee-for-service (FFS) program	Retrospective study	ICD-9 codes with 331.82 or 332.0 + 331.0 [a]	N/A	**Women: n= 85,234 (50.5%)** Men: n= 83,395 (49.5%)	**Sex**
Rahkonen et al., 2003 [119]	Finland	Random sample drawn from “Kuopio 75+” population health survey study in the city of Kuopio	Population healthy survey study	DLB Consortium 1st Consensus Criteria	N/A	**Women: n=26 (87%)** Men: n=4 (13%)	**Sex**
Gascón-Bayarri et al., 2007 [120]	Spain	Population-based in El Prat del Llobregat, in the Barcelona’s Metropolitan Area, in Catalonia, Spain	Population-based survey study	DLB Consortium 1st Consensus Criteria	Overall DLB prevalence: 9.09 (5.18-14.55) Men: 0.4 Women:1.2	**Women: n=13 (87%)** Men: n=2 (13%)	**Sex**
Secondary care / large database studies							

Reference	Country	Referral base	Study type	Diagnostic criteria used	Epidemiology (if reported)	Men/ women ratio	Term Used in Publication (Sex or Gender) [b]
Gan et al., 2021 [121]	China	Nine memory clinics in the China Lewy Body Disease Collaborative Alliance	Retrospective study	DSM-IV criteria	N/A	**Male: n=177 (50.9%)** Female: n=171 (49.1%)	**Sex/Gender** [b]
Yang et al., 2018 [122]	Taiwan	DLB patient data obtained between 2000-2013 from the Taiwan National Health Insurance Research Database (NHIRD)	Retrospective study	ICD-9-CM code 331.82, or following 1-year rule of having parkinsonism and dementia (ICD-9-CM does 332, 333, 290.0, 290.1, 290.2, 290.3, 294.1, 3331.0)	Incidence/all ages, Rate per 100,000 person-years Men 7.06 Women 7.14	**Men: n=438 (50.2%)** Women: n=434 (49.8)	**Sex**
Utsumi et al., 2020 [17]	Japan	Outpatient psychiatry clinic in Sunagawa City Medical Center	Retrospective study	DLB Consortium 4th Consensus Criteria	N/A	**Women: n=133 (57%)** Men: n=101 (43%)	**Gender**
Breitve et al., 2016 [89]	Norway	Outpatient clinics of old age psychiatry and geriatric medicine in western Norway	Longitudinal study	DLB Consortium 3rd Consensus Criteria	N/A	**Men: n=40 (55.6%)** Women: n=32 (44.4%)	**Sex**
Rongve et al., 2016 [123]	Norway	Outpatient geriatric, psychiatric and neurology clinics in western Norway	Five-year prospective cohort study	DLB Consortium 3rd Consensus Criteria	N/A	**Men: n=35 (52.2%)** Women: n=32 (47.8%)	**Sex**
Aarsland et al., 2008 [124]	Norway	Outpatient clinics in neurology, geriatric medicine and old age psychiatry in the counties of Rogaland and Hordaland in Western Norway	Retrospective cohort study	DLB Consortium 3rd Consensus Criteria	N/A	**Women: n=20 (51.3%)** Men: n=19 (48.7%)	**Gender**
Farina et al., 2009 [125]	Italy	Eight Italian memory clinics	Mixed retrospective and prospective study	DLB Consortium 1st Consensus Criteria	N/A	**Men: n=52 (51%)** Women: n=50 (49%)	**Sex**
Choudhury et al., 2021 [15]	U.S.	Mayo Clinic Alzheimer's Disease Research Center (ADRC)	Prospective longitudinal cohort study	DLB Consortium 4th Consensus Criteria	N/A	**Men: n=370 (76%)** Women: n=118 (24%)	**Sex**
Bayram et al., 2021 [14]	U.S.	Neuropathologicall y confirmed cases from the National Alzheimer's Coordinating Center (NACC) database	Retrospective study	DLB Consortium 4th Consensus Criteria for neuropathology associated with a high likelihood of exhibiting a DLB phenotype	N/A	**Men: n=156 (74%)** Women: n=55 (26%)	**Sex**
Kane et al., 2018 [23]	U.K.	Nine participating psychiatry of old age/memory clinic services in the UK	Retrospective case series		Overall DLB prevalence 4.6 (4.0–5.2)	**Men: n=113 (54.6%)**	**Sex**

Reference	Country	Referral base	Study type	Diagnostic criteria used	Epidemiology (if reported)	Men/ women ratio	Term Used in Publication (Sex or Gender) [b]
		across four NHS hospital trusts in East Anglia and North-East England			• 113 M/94 F (54.6% M) Overall DLB incidence 4.8 (4.0–5.7) • 62 M/61 F (50.4% M)	Women: n=94 (45.4%)	
Price et al., 2017 [95]	U.K.	Cambridge and Peterborough NHS Foundation Trust (CPFT), which provides secondary mental healthcare	Retrospective naturalistic cohort study	DLB Consortium 3rd Consensus Criteria	N/A	**Women: n=129 (51.4%)** Men: n=122 (48.6%)	**Sex**
Mouton et al., 2018 [16]	France	French National Alzheimer database (Banque Nationale Alzheimer [BNA]), which stores information from French memory centers and private practice neurologists	Repeated cross-sectional study	DLB Consortium 3rd Consensus Criteria	N/A	**Women: n=5,635 (54.7%)** Men: n=4,674 (45.3%)	**Sex/Gender** [b]
van de Beek et al., 2020 [18]	Netherlands	Amsterdam Dementia Cohort (patient selection based on CSF availability)	Retrospective study	DLB Consortium 4th Consensus Criteria	N/A	**Men: n=184 (83%)** Women: n=39 (17%)	**Sex**

DLB=dementia with Lewy bodies; CI=Confidence Interval; ICD=International Classification of Diseases; DSM=Diagnostic and Statistical Manual of Mental Disorders

[a] Method of defining dementia allowed beneficiaries to be classified as having more than one dementia subtype.

[b] Sex and gender terms were used interchangeably, though authors' interpretations seemed to suggest biological definition of "sex".

Table 2.

DLB core features in men and women

Reference	Cohort (Total N, % men)	RBD (N, %)		p-value	Parkinsonism (N, %)		p-value	Visual hallucinations (N, %)		p-value	Fluctuations (N, %)		p-value
		Men	Women		Men	Women		Men	Women		Men	Women	
Choudhury et al., 2021 [15]	488 (76)	311 (84)	61 (52)	**<0.001**	335 (91)	98 (83)	**0.025**	244 (66)	97 (82)	**0.001**	286 (77)	87 (74)	0.43
Bayram et al., 2021 [a] [14]	110 (50)	28 (51)	16 (29)	>0.29	47 (86)	42 (76)	>0.29	35 (64)	22 (40)	**<0.05**	31 (56)	27 (49)	>0.29
Bayram et al., 2022 [b] [20]	691 (68)	165 (45.8)	35 (20.8)	**<0.001**	278 (71.5)	90 (50.6)	**<0.001**	255 (54.4)	85 (38.3)	**<0.001**	201 (55.2)	70 (40.9)	**<0.005**
Utsumi et al., 2020 [17]	234 (43)	76 (76)	66 (50)	**<0.001**	60 (59)	59 (44)	**0.027**	77 (76)	109 (82)	NS	54 (54)	78 (58)	NS
Van de Beek et al., 2020 [18]	223 (83)	99 (73)	11 (55)	0.17	130 (73)	23 (62)	0.28	69 (38)	23 (59)	**0.02**	119 (84)	29 (94)	0.26
Ferreira et al., 2020 [54]	416 (69)	210 (73)	79 (61)	0.48	253 (88)	107 (83)	**0.023**	152 (53)	93 (72)	**0.04**	230 (80)	112 (87)	0.53
Chiu et al., 2018 [c] [55]	152 (57)	N/A	N/A	N/A	N/A	N/A	N/A	39 (45)	39 (60)	**0.028**	N/A	N/A	N/A

DLB=dementia with Lewy bodies; NS=not significant (p-value not provided)

[a] Showing data from the study's matched subsamples (by age, education, tau burden; n=55 women, n=55 men); in the overall cohort, additional statistically significant sex differences were found for RBD (men 56% vs. women 29%, p<0,01), and parkinsonism (men 92% vs. women 76%, p<0.01) (Bayram et al., 2021).

[b] Unlike their prior study [14] that excluded individuals with Braak tau staging > III, this study [20] included pathologically-confirmed DLB sample with all Braak tau stages 0-VI.

[c] As this study focused on sex differences in DLB in visual hallucinations only, there are no available data on sex differences in other DLB core features.

Table 3.

Gaps and Research Opportunities Relating to Sex and Gender in DLB

Knowledge or Care Gap	**Potential Research Opportunities**
Differences in presenting phenotype and clinicopathological correlations	Large-scale clinicopathologic studies with assessment of both sex and gender
Risk Factors	- Studies examining genetic risk factors (e.g. APOE, GBA) - Studies investigating hormonal influences (pregnancy, menopause, estrogen/hormone replacement therapy, androgen-deprivation treatment, transgender health, etc.) - Evaluation of environmental exposures, comorbidities (cerebrovascular risk factors, etc.), demographics (education, ethnicity/race, age, etc.) and how they may differ by sex/gender
Under- or misdiagnosis	Studies of pragmatic approaches to increase recognition of DLB generally and with sex- and gender-specific considerations
Biomarker differences by sex/gender	Targeted recruitment of diverse populations for biomarker studies and subanalyses by sex and gender
Progression	Natural history studies with diverse recruitment (including by sex/gender) and associated subanalyses
Treatment	- Stratifying by sex/gender during randomization - Inclusion of biomarkers in DLB treatment trials (as this may be different by sex and affect treatment response) - Assessment of treatment response by sex/gender
Caregiving	- Research on differential caregiver experiences by sex and gender, access to healthcare/resources, and potential value of specific interventions