Sex differences in clinical cognitive impairment with Lewy bodies: a Chinese multicenter study

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Abstract

Background: Research on sex ratios of Lewy body dementia is controversial, established in small samples, and rarely focused on prodromal stage. The objective is to investigate the clinical sex ratios (men/women) and their associations with clinical features among individuals with mild cognitive impairment with Lewy bodies (MCI-LB), dementia with Lewy bodies (DLB), Parkinson’s disease with mild cognitive impairment (PD-MCI), and Parkinson’s disease with dementia (PDD) in China.

Methods: We conducted a multicenter cohort study, including 1038 individuals with probable MCI-LB, DLB, PD-MCI, or PDD diagnosis from 22 memory clinics in China from January 2018 to March 2022, and recorded their demographic and clinical data by reviewing medical records. Descriptive and regression analyses were used to calculate the sex ratio (men/women), and its associations with demographic and clinical data.

Results: In this study, men comprised 35.14% (men/women sex ratio = 0.54) for MCI-LB, 46.72% (men/women sex ratio = 0.88) for DLB, 63.56% (men/women sex ratio = 1.74) for PD-MCI, and 52.40% (men/women sex ratio = 1.10) for PDD. Sex ratios roughly increased with age. Men had more parkinsonism (p = 0.000) and less fluctuating cognition (p = 0.024) in MCI-LB, and those with PD-MCI had more RBD (p = 0.001). Women with PD-MCI had lower MMSE scores (β ± standard error = −1.24 ± 0.58, p = 0.04), more irritability (0.95 ± 0.46, p = 0.04) and fluctuating cognition (−3.41 ± 1.31, p = 0.01), and less parkinsonism (−2.10 ± 0.97, p = 0.03) than men after adjusting for demographic and cardiometabolic conditions.

Conclusion: There were more women in DLB and MCI-LB, and more men in PD-MCI and PDD. The sex distribution, demographic, and clinical characteristics differed, which strengthened the independence and heterogeneity of the four diseases, and indicated sex-sensitive strategies for management of dementia necessary.

Highlights

- There are significant sex differences in Chinese population with cognitive impairment in Lewy body disease.

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Women were more common in dementia with Lewy bodies and mild cognitive impairment with Lewy bodies cases, had more frequent and severe neuropsychiatric symptoms, and poorer cognition than men.

Men predominant in Parkinson’s disease with mild cognitive impairment and Parkinson’s disease with dementia cases, and performed more frequent RBD and parkinsonism than women.

Dementia with Lewy bodies vs. Parkinson’s disease with dementia, and mild cognitive impairment with Lewy bodies vs. Parkinson’s disease with mild cognitive impairment are distinct disease forms and should not be confused.

**Keywords:** Gender, Sex ratio, Lewy body disease, Mild cognitive impairment, Parkinson’s disease
mandatory; while the Neuropsychiatric Inventory (NPI) assessment [15], magnetic resonance imaging (MRI) visual rating scales [Medial Temporal lobe Atrophy (MTA) [23] and Fazekas scales [24]], and Apolipoprotein E (APOE) genotype test were optional. The detailed information is shown in Table 1 and Additional file 1: eAppendices 2 and 3.

The Ethics Committees of the 22 centers approved all research activities in this multicenter study and waived informed consent because the data were pseudonymized from registers. The procedures were performed in accordance with the ethical standards of the Committee on Human Experimentation.

**Diagnostic criteria**

Probable DLB: diagnosed if a patient had two or more core clinical features of DLB with or without the presence of a proposed biomarker (positive FP-CIT SPECT or dopamine transporter PET, and/or meta-iodobenzylguanidine scan, and/or polysomnographic confirmation of REM sleep without atonia) or only one core clinical feature plus one or more proposed biomarkers [25]. Since the consensus of the criteria for MCI-LB were in development at the time of first diagnosis, so probable MCI-LB was initially defined with a combination of MCI criteria using Petersen’s criteria in 2011 [26] and DLB criteria by McKeith in 2017 [1], with a MMSE ≥ 20 and CDR score of ≥ 0.5 [27]. The final diagnosis of probable MCI-LB was confirmed by two experienced neurologists double-blinded.

Probable PDD: diagnosed according to the clinical criteria for probable PDD, developed by the Movement Disorder Society in 2007 [28].

Probable PD-MCI: diagnosed by the diagnostic criteria developed by the Movement Disorder Society Task Force level I or level II diagnosis [29].

All patients with cognitive impairment in Lewy body disease mentioned in this study had a probable diagnosis. According to the international consensus of the “one-year rule”, DLB should be diagnosed when cognitive impairment precedes parkinsonism or begins within a year of parkinsonism, and PDD should be diagnosed when parkinsonism precedes cognitive impairment by more than one year.

**Statistical analyses**

Descriptive analyses were conducted by number (proportion, %) for qualitative variables and mean [± standard deviation (SD)] or median (interquartile range) after normality tests for quantitative variables. The sex ratios were calculated by men (number)/women (number). Variables associated with diagnosis (MCI-LB, DLB, PD-MCI, and PDD) were tested using analysis of variance for quantitative variables and Chi-squared tests for qualitative variables. For comparisons of groups, Student’s t-test was used for normally distributed data and a Mann–Whitney U-test for nonparametric data. Qualitative variables were assessed using a Chi-squared test. The R × C contingency tables were used for the comparison of rates among the four groups according to the diagnoses (MCI-LB, DLB, PD-MCI, and PDD), and Fisher’s exact test (R × C) was used for samples with theoretical frequencies less than one in Table 3. The P-values were corrected by Bonferroni correction.

Linear and logistic regression analyses were conducted to evaluate sex differences in demographic and clinical outcome measures, and represent the data with β ± standard error (SE). Firstly, we used two linear regression models with sex as the factor, and with demographics (age at cognitive impairment, age at parkinsonism, interval between cognitive impairment and parkinsonism, and course of disease, MRI visual scales [MTA scores (both in left and right)], and clinical assessments (C-MMSE, MoCA, ADL, CDR, and NPI and its subitems) as main outcome measures. Then logistic regressions were used to explore the relationship between four clinical core features as the dependent variables and sex ratio with other possible explicative variables in Model 2 [education, cardiometabolic conditions (hypertension, type 2 diabetes mellitus (T2DM), heart disease, and stroke), smoking and alcohol consumption, and age at last visit and course of disease]. The reference modality was “men.”

The IBM SPSS for Windows (version 25.0; IBM Corporation, Armonk, NY, USA) was used for statistical analyses, with p < 0.05 considered significant at the two-tailed α level.

**Results**

**Demographic and clinical characteristics**

According to our selection criteria, we assembled four groups in this study: MCI-LB (n = 74, mean age at last visit = 70.46 ± 7.30), DLB (n = 533, mean age at last visit = 72.05 ± 8.22), PD-MCI (n = 118, mean age at last visit = 64.69 ± 8.26), and PDD (n = 313, mean age at last visit = 68.06 ± 7.88). The demographic and clinical characteristics of the patients are shown in Table 2. Men had longer course of disease (p = 0.000), higher proportions of stroke (p = 0.009), smoking (p = 0.000) and alcohol consumption (p = 0.000) than women. Men performed better in C-MMSE (p = 0.006) and MoCA (p = 0.009) and had less depression (p = 0.000). We did not find any sex
Table 1  Demographic and clinical information collection in this multicenter study

| Items                                | Subitems                                      | Other information                                                                                                                                                                                                 |
|--------------------------------------|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Demographic data                     | Sex                                           | Men or women                                                                                                                                                                                                      |
|                                      | Age at last visit                             | The age at patients’ last visit at each center                                                                                                                                                                    |
|                                      | Educational years                            |                                                                                                                                                                                                                  |
|                                      | Onset age                                     | The onset ages were recorded according to patients’ and/or caregivers’ chief complaints. We conducted the onset ages of cognitive impairment (n = 1038) and parkinsonism (n = 781) in this study.   |
|                                      | Interval between cognitive impairment and parkinsonism | The absolute value of onset age of cognitive impairment minus onset age of parkinsonism among the target patients. There were 781 pieces of data were analyzed, since a total of 781 patients (418 men and 363 women; 19 patients in MCI-LB, 331 patients in DLB, 118 patients in PD-MCI and 313 patients in PDD) had parkinsonism in this study. |
|                                      | Course of disease                             | Age at last visit minus onset age                                                                                                                                                                                  |
| Sex ratio                            | Sex ratio                                     | Sex ratios mean the number of men divided women (men/women).                                                                                                                                                       |
| Clinical core features               | Fluctuating cognition                         | The presence was diagnosed with three or more “yes” responses required for structured questions from caregivers confirmed by the Mayo Fluctuations Composite Scale.                                              |
|                                      | Visual hallucinations                         | The hallucinations item of 12-item NPI was used to determine the presence of hallucination, as complaining about by the patient and/or caregiver with specifically formed and detailed VH and illusions.|
|                                      | Parkinsonism                                  | This is diagnosed by having one or more spontaneous cardinal features of parkinsonism included bradykinesia, rest tremor or rigidity evaluated by the motor section (Part III) of the Movement Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS). |
|                                      | RBD                                           | It can be confirmed by caregivers who mentioned five or more behaviors that are mentioned in the RBD screening questionnaire (RBD-SQ), or this patient was diagnosed by an overnight video polysomnography. |
| Cognitive status                     | MCI or dementia                               |                                                                                                                                                                                                                  |
| Clinical diagnosis at last visit      | Probable MCI-LB, DLB, PD-MCI or PDD           | The diagnostic criteria and clinical core features assessments are detailed described below.                                                                                                                        |
| Neuropsychological assessments       | Mini-Mental State Examination (Chinese version) | Scores range from 0 (severe impairment) to 30 (no impairment). It is used to evaluate global cognitive function.                                                                                                                                                        |
|                                      | Montreal Cognitive Assessment                 | Scores range from 0 (severe impairment) to 30 (no impairment). It is used to evaluate global cognitive function.                                                                                                                                                        |
|                                      | The Activities of daily living                | Scores range from 20 (no impairment) to 80 (severe dysfunction), it is used to evaluate the functional status.                                                                                                                                                          |
|                                      | The Clinical Dementia Rating                  | Scores range from 0.5 (MCI), 1.0 (mild), 2.0 (moderate) to 3.0 (severe), it is used to evaluate the severity of dementia.                                                                                                                                              |
|                                      | Neuropsychiatric Inventory*                   | Each subscale ranges between 0 (NPS) and 12 and the total composite score between 0 (no NPS) and 144, it is used to evaluate the presence and severity of NPS. A total of 451 patients (61 patients with MCI-LB, 339 with DLB, 15 with PD-MCI and 36 with PDD) underwent NPI assessment in this study. |
difference in the demographic information, APOE ε4 status, MTA and Fazekas scores, and ADL, CDR, and NPI scores. The sex-specific characteristics of the four groups are displayed in Additional file 1: Table S1. Women were younger at last visit (p = 0.04), had a shorter course of disease (p = 0.000), and lower scores of MTA (p = 0.001 in left, p = 0.009 in right) than men in PDD cases.

**Sex ratios**

Men comprised 35.14% (sex ratio = 0.54) for MCI-LB, 46.72% (sex ratio = 0.88) for DLB, 63.56% (sex ratio = 1.74) for PD-MCI, and 52.40% (sex ratio = 1.10) for PDD. The onset age-specific (Fig. 1a) and age at last visit-specific (Fig. 1b) sex ratios for individual diagnostic groups were shown. Women were more common among patients with MCI-LB who developed the disease between the ages of 65 and 75, whereas more men developed PD-MCI before 75 years.

**Associations between sex and demographic and clinical features**

We evaluated the associations between sex and demographic and clinical features in Table 4. Women with PD-MCI were younger when complaining of cognitive impairment (β ± SE = −2.64 ± 0.97, p = 0.007) and parkinsonism (−2.60 ± 1.05, p = 0.01) than men after adjusting for education and cardiometabolic conditions; however, we found no such sex difference of age for DLB, or PDD groups. Women with PD-MCI were more likely to have lower score of C-MMSE (−1.24 ± 0.58, p = 0.04), more irritability (0.95 ± 0.46, p = 0.04) and FLC (−3.41 ± 1.31, p = 0.01), and less parkinsonism (−2.10 ± 0.97, p = 0.03) than men after adjusting for age at last visit, education, course of disease, and cardiometabolic conditions in favor of men increased with education in patients with MCI-LB, DLB, and PDD.

Sex differences were also found in core clinical features of the four groups (Fig. 2). Compared with women, men with MCI-LB had more parkinsonism (53.85% vs 10.42%, p = 0.000), less FLC (11.54% vs 39.58%, p = 0.024), and those with PD-MCI had more RBD (53.33% vs 23.26%, p = 0.001). Men and women with DLB or PDD had similar rates of FLC, parkinsonism, VHs, and RBD.

**Table 1 (continued)**

| Items                  | Subitems                      | Other information                                                                 |
|------------------------|-------------------------------|-----------------------------------------------------------------------------------|
| MRI visual rating scales | Medial Temporal lobe Atrophy* | Scores range from 0 (no atrophy) to 4 (severe volume loss of hippocampal volume, it is used to evaluate the visual regional brain atrophy in the hippocampus, parahippocampal gyrus, entorhinal cortex and the surrounding cerebrospinal fluid spaces. Multiple planar oblique coronal (perpendicular to the axis of the hippocampus), transverse and coronal position reconstructions were made of 3D T1-weighted images for diagnostic multisequence MRI. All of the MRI readings were reviewed by two experienced neuroradiologists double-blindly, and the final rating scores were averaged. A total of 922 patients (74 patients with MCI-LB, 480 with DLB, 107 with PD-MCI and 261 with PDD) completed MRI visual rating scales. |
| Fazekas scales*        |                               | Scores range from 0 (no or single punctate lesion) to 3 (large confluent lesions), it is used to reflect the whole white matter lesion. The numbers of participants, the principles of MRI parameters and review are the same as described above. |
| APOE genotype*         |                               | Genomic DNA was extracted from peripheral blood stored at −80 °C, and the APOE gene was amplified by polymerase chain reaction. All genotypes were determined without knowledge of the patient status. A total of 167 patients (40 patients with MCI-LB, 111 with DLB, 0 with PD-MCI and 16 with PDD) had the APOE genotype test. |

* It means the items or subitems were optional to provide.

RBD rapid eye movement sleep behavior disorder, MCI mild cognitive impairment, MCI-LB mild cognitive impairment with Lewy bodies, DLB dementia with Lewy bodies, PD-MCI Parkinson’s disease with mild cognitive impairment, PDD Parkinson’s disease dementia, NPS neuropsychiatric symptoms, MRI magnetic resonance imaging, APOE apolipoprotein E.
Table 2 Demographic and clinical characteristics of participants

| Characteristics a | All n = 1038 | Men n = 514 | Women n = 524 | t/Z/χ² | p-value |
|-------------------|-------------|------------|--------------|--------|---------|
| Age at last visit, mean (SD), y | 69.89 ± 8.45 | 70.18 ± 8.26 | 69.61 ± 8.63 | -1.26 | 0.21 |
| Age at CI, mean (SD), y | 67.78 ± 8.14 | 68.17 ± 7.92 | 67.39 ± 8.34 | -1.63 | 0.10 |
| Age at PARK b, mean (SD), y | 66.78 ± 8.14 | 66.83 ± 9.04 | 66.16 ± 9.57 | -0.13 | 0.26 |
| Interval between CI and PARK b, mean (SD) c | 2.95 ± 2.56 | 2.96 ± 2.61 | 2.93 ± 2.50 | -0.15 | 0.88 |
| Education, mean (SD), y | 8.90 ± 4.54 | 10.09 ± 4.00 | 7.73 ± 4.74 | -1.17 | 0.24 |
| Course of disease, mean (SD), y | 3.05 ± 2.26 | 3.15 ± 2.40 | 2.95 ± 2.12 | -7.50 | 0.000 |
| Cardiometabolic conditions d | | | | |
| Hypertension | 275 (32.54%) | 127 (31.28%) | 148 (33.71%) | 0.57 | 0.45 |
| T2DM | 100 (11.83%) | 50 (12.32%) | 50 (11.39%) | 0.17 | 0.68 |
| Heart disease | 116 (13.73%) | 52 (12.81%) | 64 (14.58%) | 0.56 | 0.46 |
| Stroke | 109 (12.90%) | 65 (16.01%) | 44 (10.02%) | 6.73 | 0.009 |
| Smoking e | 139 (16.45%) | 118 (29.06%) | 21 (4.78%) | 90.48 | 0.000 |
| Alcohol consumption f | 109 (12.90%) | 97 (23.89%) | 12 (2.73%) | 84.04 | 0.000 |
| APOE ε4 carriers g | 56 (33.53%) | 17 (30.91%) | 39 (34.82%) | 0.25 | 0.62 |
| MTA scores, mean (SD) h | | | | |
| Left | 1.19 ± 0.73 | 1.20 ± 0.77 | 1.18 ± 0.70 | -0.03 | 0.98 |
| Right | 1.18 ± 0.75 | 1.19 ± 0.79 | 1.18 ± 0.71 | -0.19 | 0.85 |
| Fazekas scales, mean (SD) i | 1.17 ± 0.69 | 1.16 ± 0.71 | 1.18 ± 0.68 | -0.57 | 0.57 |
| C-MMSE, mean (SD) j | 17.86 ± 6.88 | 18.37 ± 7.07 | 17.36 ± 6.65 | -2.77 | 0.006 |
| MoCA, mean (SD) J | 12.89 ± 6.51 | 13.44 ± 6.62 | 12.34 ± 6.35 | -2.76 | 0.006 |
| ADL, mean (SD) k | 30.91 ± 12.86 | 30.47 ± 12.69 | 31.35 ± 13.02 | -1.66 | 0.10 |
| CDR, mean (SD) k | 1.57 ± 0.83 | 1.53 ± 0.84 | 1.60 ± 0.83 | -1.40 | 0.16 |
| NPI scores, mean (SD) l | 12.93 ± 13.01 | 11.73 ± 12.44 | 13.93 ± 13.42 | -1.91 | 0.05 |
| Delusions | 161 (35.94%) | 71 (34.98%) | 90 (36.73%) | 0.15 | 0.67 |
| Hallucinations | 336 (75.00%) | 154 (75.86%) | 182 (74.29%) | 0.15 | 0.70 |
| Agitation | 117 (26.12%) | 51 (25.12%) | 66 (26.94%) | 0.19 | 0.66 |
| Depression | 182 (40.63%) | 64 (31.53%) | 118 (48.15%) | 12.74 | 0.000 |
| Anxiety | 161 (35.94%) | 70 (34.48%) | 91 (37.14%) | 0.34 | 0.56 |
| Euphoria | 33 (7.37%) | 17 (8.37%) | 16 (6.53%) | 0.55 | 0.46 |
| Apathy | 172 (38.39%) | 78 (38.42%) | 94 (38.37%) | 0.00 | 0.99 |
| Disinhibition | 53 (11.83%) | 23 (11.33%) | 30 (12.24%) | 0.09 | 0.77 |
| Irritability | 154 (34.38%) | 75 (36.95%) | 79 (32.24%) | 1.09 | 0.30 |
| Aberrant motor behavior | 134 (29.91%) | 58 (28.57%) | 76 (31.02%) | 0.32 | 0.57 |
| Night-time behavior disturbances | 321 (71.65%) | 153 (73.37%) | 168 (68.57%) | 2.53 | 0.11 |
| Appetite and eating abnormalities | 112 (25.00%) | 47 (23.15%) | 65 (26.53%) | 0.68 | 0.41 |

Bold means that the significant P values
P-value means the comparison between men and women by Mann–Whitney U test or χ² test
CI cognitive impairment, PARK parkinsonism, SD standard deviation, ML memory loss, MDs movement disorders, T2DM type 2 diabetes mellitus, APOE apolipoprotein E, MTA medial temporal lobe atrophy, C-MMSE the Mini-Mental State Examination (Chinese version), MoCA the Montreal Cognitive Assessment, ADL the Activity of Daily Living Scale, CDR the clinical dementia rating, NPI the Neuropsychiatric Inventory

* Unless otherwise indicated, data are expressed as number (%) of patients

In the statistical analysis, 781 patients (418 men and 363 women) had parkinsonism and the information of interval between cognitive impairment and parkinsonism; 406 men and 439 women completed cardiometabolic conditions, smoking and alcohol consumption investigation; 55 men and 112 women underwent APOE genotype tests; 449 men and 473 women underwent MTA and Fazekas visual evaluation; 203 men and 245 women underwent NPI assessment

Model 2. Being female independently increased the risks of higher NPI score (β ± SE = 6.04 ± 1.72, p = 0.001), especially delusions (0.87 ± 0.34, p = 0.01), hallucinations (0.83 ± 0.36, p = 0.02), depression (1.10 ± 0.31, p = 0.000), and anxiety (0.80 ± 0.27, p = 0.003) in DLB. Moreover, being female was related to higher scores of MTA (both left, p = 0.03 and right, p = 0.05) and Fazekas (p = 0.04) in
Fig. 1 Age-specific sex ratios in patients with MCI-LB, DLB, PD-MCI and PDD. The onset age-specific (a) and age at last visit-specific (b) sex ratios are shown in this figure. And the numbers of participants in each group are described at Additional file 2. MCI-LB mild cognitive impairment with Lewy bodies, DLB dementia with Lewy bodies, PD-MCI Parkinson’s disease with mild cognitive impairment, PDD Parkinson’s disease dementia

Table 3 The education- and number of core features-specific sex ratios in patients with MCI-LB, DLB, PD-MCI and PDD

|                | MCI-LB (n = 74) | DLB (n = 533) | PD-MCI (n = 118) | PDD (n = 313) | $\chi^2$ | Cramer’s V | P-value |
|----------------|-----------------|---------------|------------------|--------------|---------|------------|---------|
| **Education years** |                 |               |                  |              |         |            |         |
| 0 year         |                 |               |                  |              |         |            |         |
| Men            | 1               | 4.55          | 7                | 13.73        | 1       | 100.00     | 8       | 24.24   |
| Women          | 21              | 95.45         | 44               | 86.27        | 0       | 0.00       | 25      | 75.76   |
| 1–6 years      |                 |               |                  |              |         |            |         |
| Men            | 3               | 15.79         | 55               | 47.83        | 12      | 70.59      | 34      | 48.57   |
| Women          | 16              | 84.21         | 60               | 52.17        | 5       | 29.41      | 36      | 51.43   |
| $\geq$ 7 years |                 |               |                  |              |         |            |         |
| Men            | 22              | 66.67         | 187              | 50.95        | 62      | 62.00      | 122     | 58.10   |
| Women          | 11              | 33.33         | 180              | 49.05        | 38      | 38.00      | 88      | 41.90   |
| **Num. of core features** |               |               |                  |              |         |            |         |
| One            |                 |               |                  |              |         |            |         |
| Men            | 10              | 30.30         | 24               | 47.06        | 9       | 56.25      | 14      | 58.33   |
| Women          | 23              | 69.70         | 27               | 52.94        | 7       | 43.75      | 10      | 41.67   |
| Two            |                 |               |                  |              |         |            |         |
| Men            | 9               | 31.03         | 97               | 43.11        | 50      | 63.29      | 54      | 68.35   |
| Women          | 20              | 68.97         | 128              | 56.89        | 29      | 36.71      | 25      | 31.65   |
| Three          |                 |               |                  |              |         |            |         |
| Men            | 7               | 58.33         | 81               | 49.69        | 14      | 66.67      | 80      | 42.55   |
| Women          | 5               | 41.67         | 82               | 50.31        | 7       | 33.33      | 108     | 57.45   |
| Four           |                 |               |                  |              |         |            |         |
| Men            | 0               | 0.00          | 47               | 50.00        | 2       | 100.00     | 16      | 72.73   |
| Women          | 0               | 0.00          | 47               | 50.00        | 0       | 0.00       | 6       | 27.27   |

Bold means that the significant P values

MCI-LB mild cognitive impairment with Lewy bodies, DLB dementia with Lewy bodies, PD-MCI Parkinson’s disease with mild cognitive impairment, PDD Parkinson’s disease dementia, Num. number of patients, Pro. proportion
PD-MCI, but lower scores of MTA (both left, $p = 0.003$ and right, $p = 0.02$) in PDD.

**Discussion**

In the present study, DLB and MCI-LB were more prevalent in women than men, while PD-MCI and PDD were more prevalent in men than women. Women had more frequent depression, shorter course of disease, and lower C-MMSE and MoCA scores than men. In addition, being female was associated with severe neuropsychiatric symptoms (NPS) in DLB, and lower MTA and Fazekas scores in PDD. This multicenter study first described the sex-specific characteristics of LBD in the prodromal and dementia stages, reflecting the clinical practice of LBD in China to a certain extent.

**Sex ratios in cognitive impairment in Lewy body disease**

We found that women were more common in DLB (64.86%), while men were slightly predominant in PDD with a proportion of 52.40%, which tended to differ for Western populations. A retrospective cohort in UK aiming to evaluate mortality of DLB showed a slight women predominance (51.4%) [10]. Mouton et al. [3] conducted a cross-sectional clinical study with 10,309 DLB and showed women comprising 54.7% for DLB. Traditionally, scientific literature on sex distribution in dementia has reported a more pronounced or roughly equal prevalence of men in DLB and PDD [2]. Mouton et al. also demonstrated a predominance of men (54.6%) in PDD, in line with previous literature reporting a more pronounced prevalence of men in PDD (in Sweden, $n = 297$, 61.3% were men [5]; in China, $n = 107$, 57.9% were men [8]). We firstly reported the sex ratios in MCI-LB and PD-MCI, and found a strong women predominance with 35.14% (sex ratio $= 0.54$) for MCI-LB, and a strong male predominance with 63.56% (sex ratio $= 1.74$) for PD-MCI. In addition, the sex ratios varied in different groups classified by age and education years. With the increase of age, in terms of the age at last visit or at onset, sex ratios in favor of men generally showed a rising trend in patients with MCI-LB, DLB, PD-MCI and PDD. PD was significantly prevalent in men, thus it was easy to understand that PD-MCI and PDD, as cognitive disorders progressing from PD, have a higher proportion in men than in women. Women accounted for the majority of DLB patients between 60 and 75 years of age, although the sex ratio gradually decreased with age. However, the sex ratio
Table 4  Regression models of sex, demographic and clinical features

| Characteristics                | MCI-LB       | DLB         | PD-MCI       | PDD          |
|--------------------------------|--------------|-------------|--------------|--------------|
|                                | Model 1      | Model 2     | Model 1      | Model 2      | Model 1      | Model 2      | Model 1      | Model 2      |
| Women vs. men (Ref)            |              |             |              |              |              |              |              |              |
| Demographics                   |              |             |              |              |              |              |              |              |
| Age at CI, y                   | 1.49 ± 2.40  | -           | - 1.05 ± 0.87| - 1.47 ± 1.75| - 2.64 ± 0.97**|              |              |              |
| Age at PARK, y                 | -            | 28.02 ± 4.07***| - 0.46 ± 1.03| - 1.98 ± 1.92| - 2.60 ± 1.05* |              |              |              |
| Interval between CI and PARK, y| 2.72 ± 2.76  | 0.54 ± 0.25*| 0.49 ± 0.67  | - 0.02 ± 0.42| -            |              |              |              |
| Course of disease, y           | 0.05 ± 0.78  | 0.34 ± 0.20 | 0.28 ± 0.55  | - 0.53 ± 0.35| -            |              |              |              |
| MRI visual scales              |              |             |              |              |              |              |              |              |
| MTA scores                     |              |             |              |              |              |              |              |              |
| Left                           | -            | - 0.09 ± 0.18| - 0.02 ± 0.07| 0.19 ± 0.09* | - 0.20 ± 0.07**|              |              |              |
| Right                          | -            | - 0.01 ± 0.18| - 0.02 ± 0.08| 0.18 ± 0.09* | - 0.16 ± 0.07*|              |              |              |
| Fazekas scales                 | 0.14 ± 0.26  | - 0.01 ± 0.07| 0.23 ± 0.11* | - 0.08 ± 0.07| -            |              |              |              |
| Clinical assessments           |              |             |              |              |              |              |              |              |
| C-MMSE                         | -            | -           | 0.45 ± 0.67  | 0.05 ± 0.28  | - 0.02 ± 0.74|              |              |              |
| MoCA                           | -            | - 1.01 ± 0.54| 0.28 ± 0.55  | 0.61 ± 0.47  | - 0.03 ± 0.67|              |              |              |
| ADL                            | -            | -           | -            | 0.95 ± 1.51  | - 0.30 ± 1.53|              |              |              |
| CDR                            | -            | -           | -            | - 0.08 ± 0.08| - 0.02 ± 0.09|              |              |              |
| NPI                            | 3.63 ± 2.04  | 6.04 ± 1.72**| -           | -            | - 1.82 ± 4.46|              |              |              |
| Delusions                      | 0.45 ± 0.26  | 0.87 ± 0.34*| -           | -            | 0.12 ± 0.60  |              |              |              |
| Hallucinations                 | 0.61 ± 0.44  | 0.83 ± 0.36*| -           | -            | 0.43 ± 1.01  |              |              |              |
| Agitation                      | 0.33 ± 0.43  | 0.17 ± 0.22  | -           | -            | - 0.004 ± 0.13|              |              |              |
| Depression                     | 0.26 ± 0.35  | 1.10 ± 0.31***| -           | -            | 0.02 ± 0.03  |              |              |              |
| Anxiety                        | 0.28 ± 0.20  | 0.80 ± 0.27**| -           | -            | - 1.01 ± 0.66|              |              |              |
| Euphoria                       | 0.07 ± 0.13  | - 0.15 ± 0.10| -           | -            | 0.03 ± 0.06  |              |              |              |
| Apathy                         | - 0.29 ± 0.31| 0.49 ± 0.33  | -           | -            | 0.06 ± 1.30  |              |              |              |
| Disinhibition                  | 0.31 ± 0.23  | 0.02 ± 0.13  | -           | -            | 0.13 ± 0.10  |              |              |              |
| Irritability                   | 0.95 ± 0.46* | 0.25 ± 0.24  | -           | -            | 0.42 ± 0.48  |              |              |              |
| Aberrant motor behavior        | 0.33 ± 0.29  | 0.91 ± 0.34**| -           | -            | 0.63 ± 0.60  |              |              |              |
| Night-time behavior disturbances| 0.002 ± 0.37| 0.59 ± 0.36  | -           | -            | 0.13 ± 1.22  |              |              |              |
| Appetite and eating abnormalities | 0.33 ± 0.31| 0.27 ± 0.24  | -           | -            | 0.71 ± 0.50  |              |              |              |
| Core clinical features         |              |             |              |              |              |              |              |              |
| RBD                            | -            | 0.05 ± 1.11  | 0.23 ± 0.24  | - 1.85 ± 0.53**| - 0.28 ± 0.29|              |              |              |
| Parkinsonism                   | -            | -           | - 0.61 ± 0.25*| -           | 2.10 ± 0.97* |              |              |              |
| Fluctuating cognition          | -            | 3.41 ± 1.31**| - 0.26 ± 0.23| 0.70 ± 0.50  | 0.55 ± 0.30  |              |              |              |
| Visual hallucinations          | - 1.01 ± 0.99| 0.08 ± 0.27  | 0.33 ± 0.49  | 0.50 ± 0.38  |              |              |              |              |
in favor of females increased with age for DLB patients older than 75 years old in Mouton et al.’s research, as in our study. We supposed that women might be more likely to seek help for dementia in China [30], or have more neuropsychiatric symptoms [31] that are noted during the course of the disease, which led to women predominance. Moreover, these differences may be due to either one or a combination of study design, sample-size, as well as potential ethnorial, genetic, environmental and occupational factors. We also found that the proportion of men gradually rose both in DLB and PDD with increased education level. This finding may be due to the educational imbalance between older Chinese men and women [32], in that men were educated longer than women. 

DLB is diagnosed by clinical symptoms and biomarkers according to current criteria, and the “1-year rule” is remaining supported to distinguish DLB from PDD in clinical practice. Cases of suspected DLB presenting with dementia alone, that is without parkinsonism, may also have been missed and classified as AD, particularly if no other core feature was reported in the patient’s records. Moreover, for those DLB patients with neuropsychiatric symptoms, more “mental disorders” will be diagnosed and treated in the department of psychiatry. Neuropathological studies reported that men were more likely to have pure neocortical (“diffuse”) or intermediate (“limbic”) Lewy body pathologies, whereas women had more AD pathology and cerebrovascular disease [7, 33], and thus more women would also be classified as AD. There are reasons to believe that the clinically suspected DLB is underestimated, particular in women, and women might account for a larger proportion of DLB.

**Sex difference in clinical features**

Formal studies demonstrated a significant but controversial association between clinical symptoms and sex in DLB, but associations have not been extensively studied for PDD, MCI-LB, or PD-MCI. In this clinical multicenter cohort, women had a non-significantly higher proportion of VHSs, and no sex differences were found in other core clinical features. Chiu et al. [11] showed that VHSs were more common in women with clinical DLB adjusted for age and disease severity, with the same finding in the cohort of van de Beek [34]. In a Japanese study with 234 clinical DLB patients [35], VHSs and FLC were non-significantly more prevalent for women, while parkinsonism (p = 0.027) and RBD (p = 0.000) were more prevalent for men. In a pathological DLB study [36] based on the NACC Neuropathology Data Set, fewer women had VHSs (p = 0.009), RBD (p = 0.007), or parkinsonism (p = 0.007) compared with men. In patients with MCI-LB, we found that RBD was the most common but with no sex difference; women had more FLC (39.58% vs 11.54%, p = 0.024) and men had more parkinsonism (53.85% vs 10.42%, p = 0.000). We also found that RBD was the second most common clinical feature after parkinsonism and was more frequent for men (53.33% vs 23.26%, p = 0.001) with PD-MCI. In the prodromal and dementia stages of LBD, patients show different sex predominance in core clinical features. Previous studies in patients with PD and PDD showed that RBD was more common in men [12, 37], and its presence and severity were associated with decreased cerebrospinal fluid (CSF) alpha-synuclein level [38, 39]. Although Yu et al. [39] showed that men had lower CSF alpha-synuclein levels (1429 ± 164 vs 1831 ± 60, p = 0.02) than men, and only one longitudinal study [40] revealed a significant correlation between estimated changes in alpha-synuclein level and RBD-SQ scores (p = 0.001, data not available), we still do not know how sex influences occurrence of RBD by influencing alpha-synuclein levels. The FLCs included memory, attention, executive functions, language, and visuospatial function fluctuation during the day and over weeks. Women with MCI-LB had worse cognitive function in the current study, possibly contributing to the women’s predominance of FLC. The frequency of FLC in MCI-LB cases has not been determined.

**Table 4 (continued)**

In the statistical analysis of Model 1 and Model 2, 62 patients with MCI-LB, 437 patients with DLB, 104 patients with PD-MCI, and 242 patients with PDD were analyzed for the age at CI, course of disease, C-MMSE, MOCA, ADL, and CDR, as well as four core clinical features; 17 patients with MCI-LB, 292 patients with DLB, 104 patients with PD-MCI, and 242 patients with PDD were analyzed for the age at PARK and the interval between CI and PARK; 62 patients with MCI-LB, 434 patients with DLB, 102 patients with PD-MCI, and 236 patients with PDD were analyzed for MRI visual scales; and 61 patients with MCI-LB, 339 patients with DLB, 12 patients with PD-MCI, and 36 patients with PDD were analyzed for NPI. Data represent β ± standard error by linear regressions (a) or logistic regressions (b). *p < 0.05, ** p < 0.01, *** p < 0.001

**Model 1:** with correction for education, cardiometabolic conditions (hypertension, type 2 diabetes mellitus, heart disease, stroke), smoking and alcohol consumption by linear regressions

**Model 2:** Model 1 with correction for age at last visit and course of disease

**MCI-LB mild cognitive impairment with Lewy bodies, DLB dementia with Lewy bodies, PD-MCI Parkinson’s disease with mild cognitive impairment, PDD Parkinson’s disease dementia, CI cognitive impairment, PARK parkinsonism, MRI Magnetic Resonance Imaging, MTA medial temporal lobe atrophy, C-MMSE the Mini-Mental State Examination (Chinese version), MoCA the Montreal Cognitive Assessment, ADL the Activity of Daily Living Scale, CDR the clinical dementia rating, NPI the Neuropsychiatric Inventory, RBD rapid eye movement sleep behavior disorder
Consistent with previous literature [12, 41], NPS occurred frequently and severely in DLB female cases in our cohort. Several studies also showed that, even in the earliest disease stages, NPS can be present [27, 42, 43], but we found no significant sex differences in patients with MCI-LB. The PDD patients showed significant sex differences with more hippocampal and white-matter damage in men, possibly because 17β-estradiol (E2) conveys neuroprotective effects on the hippocampal and cardio-cerebral vascular system in women [44, 45]. Previous studies have demonstrated that estradiol levels have effect on cognition and memory during menopause transition, and women could have better cognitive and memory performance in relevant tasks after estradiol-based hormone therapy (E2-HT) [46–48]. According to the baseline information of Cardiovascular Risk factors, Aging and Dementia cohort [47], women who had used E2-HT for >5 years had better scores in global cognition, episodic memory, and psychomotor speed tests at baseline than women who had used E2-HT for less than five years or non-users. A prospective, randomized, double-blind, placebo-controlled trial in Korea [48] showed that, when comparing with the control group, menopausal hormone therapy using percutaneous E2 gel and micronized progesterone could significantly reduce the deterioration of MoCA score, and increase the scores of MMSE and MoCA at 24 months for women with MCI. Confusingly, women were associated with higher scores of MTA (both left and right) and Fazekas in PD-MCI, but lower scores of MTA (both left and right) in PDD in linear regression models after adjusting for demographic and clinical features. This may be due to “phased” estradiol protection mechanisms, meaning that premenopausal women maintain high levels of estradiol to protect the hippocampal and cardio-cerebral vascular system, but for a period after menopause (“MCI window”), women show a sudden drop of estradiol levels, a period of time when women have more severe brain damage. However, with the increase of age and entering another stage after menopause (“dementia window”), this kind of damage tends to be gentle in elderly women. The authors consider this hypothesis bold and interesting, and a mechanism worth exploring.

Strength and limitations
The main strength of this study is that this is the first multicenter study in China utilizing a large sample size and focuses on the prodromal stage of LBD. These findings reflect clinical facts, also can represent the clinical characteristics of cognitive impairment in Lewy body disease in Eastern populations and enrich the literature that predominantly compiled of patients from European descent. The clinical diagnosis was made by a physician experienced in neurodegenerative disease, largely supported using PET–CT and CSF biomarkers, as well as regular follow-up to improve diagnostic accuracy. All of the clinical information was reviewed from medical records, which reduced recall bias.

Uncertainty may also occur in deciding how patients exhibiting both MCI/dementia and parkinsonism are best categorized. There are few comparative studies on MCI-LB and PD-MCI, and having no definitive differential diagnostic criteria for them. Thus, we are still referring to the “one-year rule”, similar to that used to separate DLB and PDD, to distinguish some clinical MCI-LB and PD-MCI cases if the onset and order of parkinsonism and cognitive impairment can be clearly established [25]. There were significant neuropathological differences between DLB and PDD, as DLB had greater severity of CAA than PDD [49] and showed higher seeding activity of disease-associated alpha-synuclein than PD [50]. Nevertheless, the diagnosis was based on clinical findings rather than postmortem finding, which might cause diagnostic bias in this study. Additionally, the lack of Unified Parkinson Disease Rating Scale records further affected our research on motor symptoms in cognitive impairment in Lewy body disease. Insufficient accumulation of PET–CT and CSF biomarkers in each center, and incomplete information also affected our further analysis. Finally, the cohort was all Chinese patients in memory clinics but not a community cohort, and had low number of subjects in MCI stage, which might lead to the sampling bias, as well as possible differences with other regions and so limited the generalizability.

Perspectives and significance
This multicenter clinical cohort indicated sex differences in cognitive impairment in Lewy body disease, wherein women were predominant in DLB and MCI-LB cases, and men predominant in PD-MCI and PDD cases. Women seemed to have more frequent and severe NPS, and poorer cognition in DLB. These findings reinforce the arguments that DLB is a distinct disease from PDD, and is not the same disease even in the prodromal stage, thus it should not be confused. More importantly, due to the sex differences in clinical symptoms, it is essential for adopting sex-sensitive strategies for management of dementia. Further research to explore the role of sex differences in the pathogenesis of LBD may contribute to the sex-specific treatment of dementia.
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Author contributions
YJ had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design were performed by YJ and ZS. All authors contribute to collect medical records, and the acquisition, analysis, or interpretation of data. YJ wrote the first draft of the manuscript, and ZC, XL, and YL contributed to the critical revision of the manuscript for important intellectual content. Statistical analysis was performed by ZC and SJ. Fundings were obtained from YJ and ZS. All authors read and approved the final manuscript.

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Availability of data and materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The Ethics Committees approved all research activities in this cohort study and waived informed consent because the data were pseudonymized from registries. The procedures were performed in accordance with the ethical standards of the Committee on Human Experimentation.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no conflict of interest.

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Additional file 1: eAppendix 1. Information of participating clinics, eAppendix 2. Details of APOE genotyping. eAppendix 3. MRI parameters and review. Table S1. Sex-specific characteristics of the four groups

Additional file 2: Onset age groups (years old) and Age at last visit groups (years old).

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