

Biological sex differences in clinical Parkinsonian signs and Parkinson's disease pathology in community-dwelling older adults



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BACKGROUND

- Several prior studies reveal substantial differences in the clinical manifestations of Parkinson's disease (PD) between men and women
- Whether biological sex differences also exist in age-related Parkinsonism signs and Parkinson's disease neuropathology remains to be elucidated

Objective

To investigate sex differences in age-related Parkinsonism signs (total & sub-scores) and Parkinson's Disease pathology (Lewy bodies & nigral neuronal loss) in a large cohort of community-dwelling older adults

METHODS

Study population (N=2,234)

- ✓ Participants from 3 ongoing RADC cohort studies:
 - Religious Orders Study (ROS; 1994-present)
 - Rush Memory and Aging Project (MAP; 1997-present)
 - Minority Aging Research Study (MARS; 2004-present)
- ✓ No known dementia at study enrolment
- ✓ Complete evaluation of Parkinsonian signs close to death
- ✓ Complete brain autopsy
- ✓ Non-missing Parkinson's Disease pathology

Outcomes

- **Parkinsonism signs** assessed using a 26-item modified version of the motor portion of the United Parkinson's Disease Rating Scale. **Sub-scores:** *gait* (6 items), *bradykinesia* (8 items), *rigidity* (5 items), *tremor* (7 items). **Global score:** average of the 4 sub-scores (range=0-100).
 - Global and gait scores had skewed distributions; a square root transformation was considered
 - Bradykinesia, rigidity, and tremor were infrequent and treated as binary variables (absent vs. present)
- **Presence of PD pathology:** *Lewy bodies* (LB) categorized into three mutually exclusive LB sub-groups (nigral, limbic, neocortical); *nigral neuronal loss* (moderate-to-severe); and *PD tissue diagnosis* defined as having any type of LB and moderate-to-severe nigral neuronal loss.

Statistical analyses

- **Linear regression models** for the transformed global score of Parkinsonism signs and gait sub-score
- **Logistic regression models** for all other binary outcomes
 - Core models: sex (ref.=women), age-at-death, education
 - Fully-adjusted models: further controlled for ADNC (intermediate/high likelihood), LATE-NC (stages 2 or 3), macro-/micro-infarcts, and moderate-to-severe CAA, arteriosclerosis, atherosclerosis.

RESULTS

Table. Characteristics of participants proximate to death in the whole sample and by sex.

Characteristics	All (N=2,234)	Men (n=686)	Women (n=1,548)
Demographics			
Age at death, mean (SD), years	90.3 (6.7)	88.3 (6.6)	90.4 (6.6)
Education, mean (SD), years	16.3 (3.6)	17.1 (3.9)	15.9 (3.4)
Non-Latino White, %	90	92	90
Clinical, proximate to death			
Interval last exam, median (IQR), years	1.4 (0.7;3.0)	1.1 (0.6;2.5)	1.5 (0.7;3.2)
Global Parkinsonian score [‡] , median (IQR)	13.8 (7.5;21.7)	13.8 (7.2;21.6)	13.8 (7.8;21.7)
Parkinsonian gait score [‡] , median (IQR)	36.4 (18.5;51.9)	33.3 (14.8;50.0)	36.4 (22.2;51.9)
Bradykinesia*, %	39	37	40
Rigidity*, %	19	24	17
Tremor*, %	28	38	24
Resting tremor*, %	11	13	10
Postural tremor*, %	37	49	31
Clinical diagnosis of dementia, %	42	38	43
Neuropathology			
Post-mortem interval, median (IQR), hours	7.1 (5.3;11.2)	7.0 (5.0;11.5)	7.2 (5.4;11.0)
Presence of Lewy bodies, %			
Nigral predominant	21	26	19
Limbic type	21	24	20
Neocortical type	14	16	13
Nigral neuronal loss (moderate/severe), %	11	14	9
Pathologic diagnosis of PD, %	8	11	7

Abbreviations: IQR, interquartile-range; PD, Parkinson disease; SD, standard deviation.

[‡]Global and gait scores exhibited skewed distributions; a square root transformation was considered

*Bradykinesia, rigidity, and tremor were infrequent and treated as binary variables (present vs. absent)

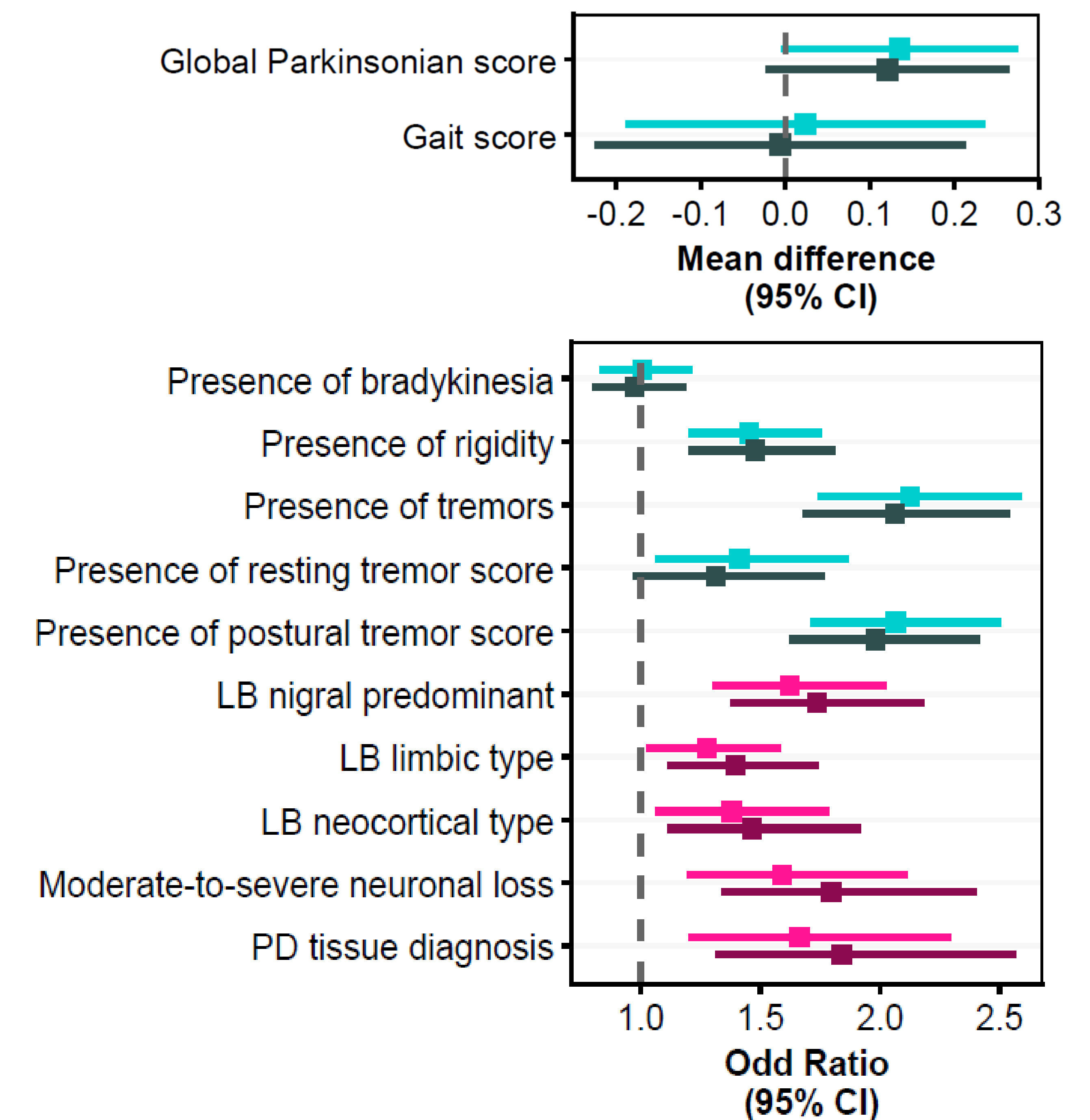
- Close to death, men had greater odds of rigidity (OR=1.48 [1.20;1.81], $P=0.0002$) and postural tremors (OR=1.98 [1.62;2.42], $P<0.0001$) than women, after controlling for demographics, ADNC and other neuropathologies (**Figure**). We did not find sex differences in other Parkinsonian's signs (gait, bradykinesia; all P -values>.09).
- A death, men had greater odds of any type of LB (all P -values<.004) and nigral neuronal loss (OR=1.80 [1.34;2.41], $P<0.0001$) than women, after controlling for demographics and neuropathologies (**Figure**).
- All the associations mentioned above remained after false discovery rate correction.

CONCLUSIONS

- These findings indicate that men are more likely than women to exhibit rigidity and postural tremors. Men also have higher odds of developing all types of Lewy bodies and experiencing loss of nigral neurons, even when accounting for multiple common age-related neuropathologies.
- To our knowledge, this large cross-sectional study is the first to emphasize the influence of sex on susceptibility and the progression of Parkinson's disease pathology in older populations
- **Limitations:** Not population representative; predominantly older White volunteers.
- **Strengths:** Large study group from 3 cohorts with harmonized design and study protocols; bias reduction by including a large number of age-related neuropathologies in the models.

Figure. Multivariable-adjusted associations of Parkinsonian signs proximate to death and Parkinson's disease neuropathologies in **men compared to women** (N=2,234). LB, Lewy bodies; PD, Parkinson's disease.

Estimates are derived from separate linear regression models (top panel) and logistic regression models (bottom panel). Core models were adjusted for sex; (reference=women) and controlling for age-at-death (years, continuous) and education (years, continuous). Fully-adjusted models were further adjusted for ADNC, LATE-NC, CAA, arteriosclerosis, atherosclerosis, chronic macro-infarcts and micro-infarcts.



Thank you
Merci

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