

Sex differences for Lewy body dementia phenotype considering Lewy body and Alzheimer’s disease pathology staging

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Background

- Both Lewy body (LB) and Alzheimer’s disease (AD) pathology staging impacts the likelihood of having LB dementia (LBD) and AD phenotype.
- Compared to males with limbic/neocortical LB pathology, females are less likely to have an LBD phenotype.
- Compared to females with similar LB and AD pathology staging, AD co-pathology reduces the LBD phenotype likelihood for males.

Objective: Expand sex comparison to the full range of LB/AD pathology level (McKeith 2017 criteria, Table 1) for LBD core clinical features including cognitive fluctuations, visual hallucinations, REM sleep behavior disorder (RBD), and parkinsonism

Table 1. Lewy body dementia phenotype likelihood based on Lewy body and Alzheimer’s disease pathology staging (LB/AD pathology level)				
		Alzheimer’s disease neuropathologic change		
		NIA-AA none-low/ Braak NFT stage 0-II	NIA-AA intermediate/ Braak NFT stage III-IV	NIA-AA high/ Braak NFT stage V-VI
Lewy body pathology	Diffuse/neocortical	High	High	Intermediate
	Transitional/limbic	High	Intermediate	Low
	Brainstem-predominant/	Low	Low	Low
	Amygdala-predominant	Low	Low	Low
	Olfactory bulb only	Low	Low	Low
NIA-AA: National Institute on Aging-Alzheimer’s Association guidelines for Alzheimer’s disease neuropathologic assessment (Montine et al. 2012), NFT: neurofibrillary tangle				

Methods

Data from the National Alzheimer’s Coordinating Center (NACC) for 206 females and 324 males excluding people with other neurodegenerative diagnoses contributing to cognitive decline.

Majority of cohort was Non-Hispanic (96%), White (92%).

- Groups were based on LB/AD pathology level:
- Low: 128 females, 158 males
 - Intermediate: 50 females, 79 males
 - High: 28 females, 87 males

Interaction between sex and LB/AD pathology level for clinical outcomes were assessed with generalized linear models adjusting for age at last visit.

Results

- Females died older and had fewer years of education ($p=.027$, $p<.001$).
- Females had higher levels of AD co-pathology and lower levels of LB pathology staging ($p<.001$, $p=.017$).
- Higher LB/AD pathology level was associated with
 - Higher likelihood of LBD clinical diagnosis ($\beta=1.39$ females; $\beta=1.73$ males)
 - Lower likelihood of AD clinical diagnosis ($\beta=-1.30$ females, $\beta=-1.43$ males)
 - Higher likelihood of cognitive fluctuations ($\beta=0.93$ females, $\beta=1.00$ males)
 - Higher likelihood of visual hallucinations ($\beta=0.76$ females, $\beta=0.86$ males)
 - Higher likelihood of RBD ($\beta=0.76$ females, $\beta=1.39$ males)
 - Higher likelihood of parkinsonism ($\beta=0.98$ females, $\beta=1.44$ males)more so for males ($p<.001$ for all) (Table 2, Figure).

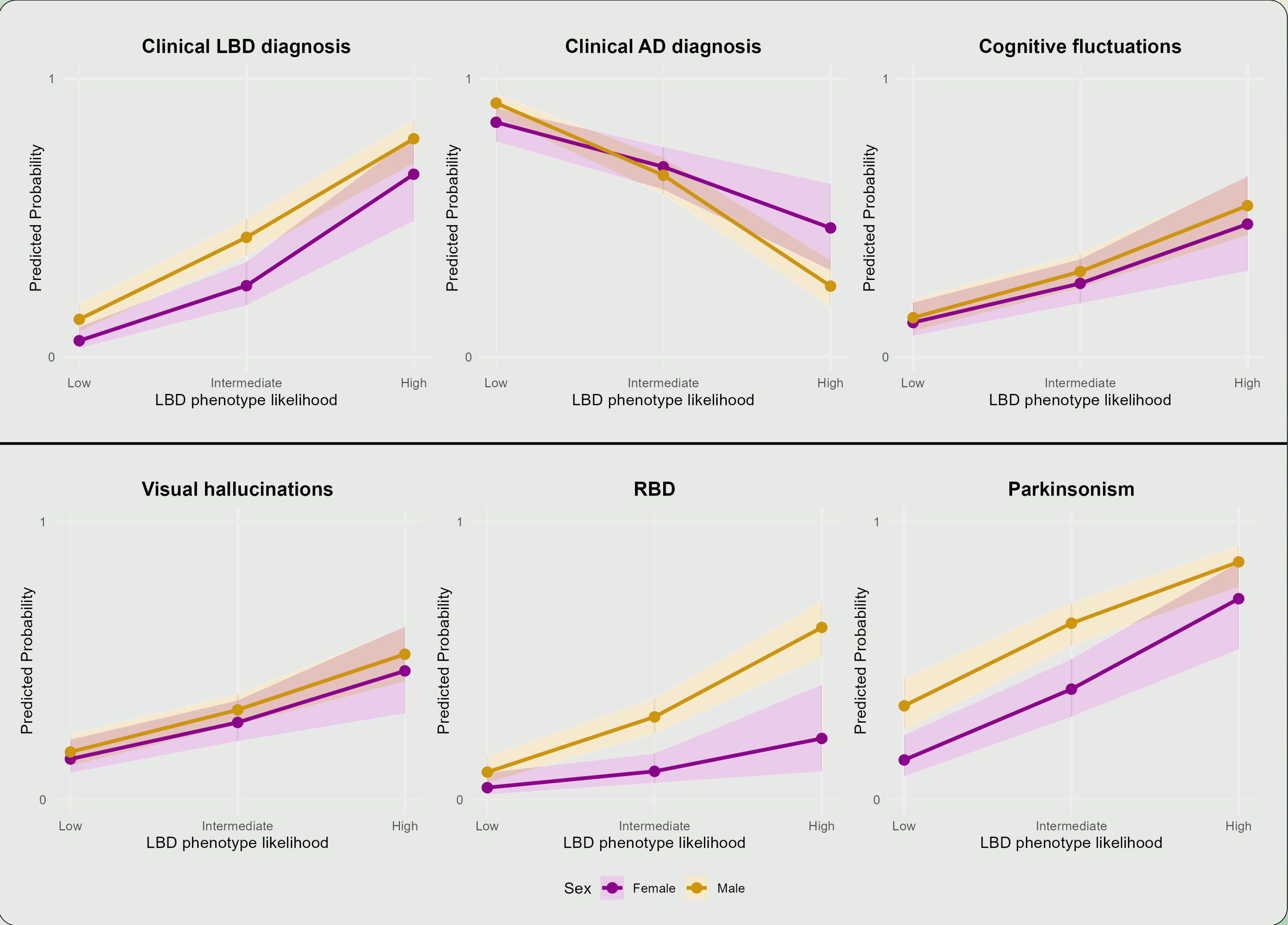
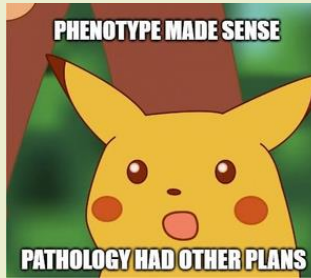


Table 2. Demographics, neuropathology, and clinical features for LBD phenotype likelihood groups			
	Low (n=128 F vs 158 M)	Intermediate (n=50 F vs 79 M)	High (n=28 F vs 87 M)
Demographics			
Age at death [§]	71.5 (11.9) vs 69.3 (11.0)	73.8 (10.9) vs 70.9 (8.4)	75.1 (10.7) vs 71.1 (7.9)
Age at last visit	74.8 (12.7) vs 73.2 (12.1)	76.5 (11.1) vs 73.7 (8.8)	77.2 (10.0) vs 74.6 (8.5)
Years of education [§]	15.1 (3.0) vs 16.5 (2.8)	15.5 (2.3) vs 16.4 (2.8)	14.4 (2.6) vs 16.0 (3.2)
Neuropathology			
LB pathology staging ^{§†}			
Olfactory only	17.5% vs 14.2%		
Amygdala-predominant	42.5% vs 43.9%	-	-
Brainstem-predominant	16.7% vs 27.0%	-	-
Limbic	23.3% vs 14.9%	8.0% vs 10.1%	10.7% vs 14.9%
Neocortical	-	92.0% vs 89.9%	89.4% vs 85.1%
AD pathology staging ^{§†}			
Thal amyloid phase ^a	5 (4-5) vs 5 (4-5)	5 (5-5) vs 5 (4-5)	3 (3-4) vs 3 (2-4)
Braak NFT stage ^a	6 (5-6) vs 6 (5-6)	6 (5-6) vs 6 (5-6)	4 (3-4) vs 3 (2-4)
CERAD neuritic plaque score ^a	3 (3-3) vs 3 (3-3)	3 (3-3) vs 3 (3-3)	2 (1-3) vs 1 (0-2)
Clinical Diagnosis			
LBD ^{§††}	7.0% vs 13.3%	20.0% vs 43.0%	71.4% vs 78.2%
AD ^{§††}	82.0% vs 89.9%	80.0% vs 70.9%	35.7% vs 23.0%
Clinical Features			
Cognitive fluctuations ^{§††}	11.7% vs 13.3%	18.0% vs 19.0%	46.4% vs 50.6%
Visual hallucinations ^{§††}	15.6% vs 16.5%	20.0% vs 32.9%	53.6% vs 51.7%
RBD ^{§††}	5.5% vs 9.5%	0.0% vs 22.8%	25.8% vs 56.3%
Parkinsonism ^{§††}	9.4% vs 19.0%	22.0% vs 39.2%	60.7% vs 69.0%
^a Median (interquartile range) noted. Statistical significance for sex effect is marked with §, pathology group effect is marked with †, and sex and pathology group interaction is marked with * for $p<.05$. F: female, M: male, NFT: neurofibrillary tangle, LBD: Lewy body dementia, AD: Alzheimer's disease, RBD: rapid eye movement sleep behavior disorder.			

Conclusions

- Females with LB pathology have higher levels of AD co-pathology and lower likelihood of LBD phenotype.
- Even for females with similar LB/AD pathology level as males, females are less likely to have an LBD phenotype, including a lower likelihood for all LBD core clinical features.
- Clinical features may fall short in identifying LB pathology during life, particularly in females.

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