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ORIGINAL RESEARCH

Disease Progression and Longitudinal Clinical Outcomes of Lewy Body Dementia in the NACC Database

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ABSTRACT

Introduction: As the identification of Lewy body dementia (LBD) is often confirmed post-mortem, there is a paucity of evidence on the progression of disease antemortem. This study aimed to comprehensively assess the course of LBD over time across cognitive, functional, and neuropsychiatric outcomes using real-world data.

Methods: Adults with at least one visit to an Alzheimer's Disease Center with a diagnosis of mild cognitive impairment/dementia (index date), indication of LBD, and at least one follow-up visit were identified in the National Alzheimer's Coordinating Center database (September 2005–June 2020). Participant characteristics, medication use, comorbidities, and changes in outcomes were assessed over a 5-year follow-up period and stratified by disease severity based on the Clinical Dementia Rating (CDR®) Dementia Staging Instrument-Sum of Boxes (CDR-SB) score at index.

Results: A total of 2052 participants with LBD (mean age at index 73.4 years) were included (mild, 219; moderate, 988; severe, 845). Mean annualized increase over 5 years was 0.9 points for CDR-Global Score, 5.6 points for CDR-SB, 10.4 points for the Functional Activities Questionnaire, and 2.0 points for the Neuropsychiatric Inventory-Questionnaire. Disease progression was greater among participants with moderate and severe LBD at index compared with those with mild LBD.

Conclusion: Participants with LBD experienced decline across all outcomes over time, and impairment increased with disease severity. Findings highlight the substantial clinical burden associated with LBD and the importance of earlier diagnosis and effective treatment. Further research is needed to understand the predictors of cognitive and functional decline in LBD which may help inform clinical trials.

Keywords: Lewy body dementia; Clinical outcomes; Cognitive impairment; Disease progression; Longitudinal data

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Key Summary Points

Why carry out this study?

Progression of Lewy body dementia (LBD) over time across cognitive, functional, and neuropsychiatric outcomes is not well understood.

Previous studies on clinical outcomes among people with LBD have mainly focused on a single outcome or focused on smaller cohorts.

This retrospective study reported participant characteristics, medication use, comorbidities, and changes in outcomes over a 5-year follow-up period.

What was learned from the study?

Participants with LBD experienced significant decline in cognitive, functional, and neuropsychiatric outcomes over time, and impairment increased with disease severity.

These findings highlight the substantial clinical burden associated with LBD and the importance of earlier diagnosis and effective treatment.

INTRODUCTION

Lewy body dementia (LBD) accounts for 5% to 10% of all dementia cases [1] and is characterized by progressive cognitive decline, neuropsychiatric symptoms, and motor symptoms consistent with Parkinson's disease (PD) [2–4]. LBD encompasses dementia with Lewy bodies (DLB) and PD dementia (PDD) [5], and as a result of its progressive nature, the disease is associated with a substantial clinical burden. People with LBD experience lower quality of life [6], higher and earlier mortality [7, 8], higher hospitalization rates [9], and greater variability in cognitive decline relative to patients with Alzheimer's disease (AD) [10], as well as high healthcare resource utilization and costs [11].

LBD is often underdetected and misdiagnosed. Despite the availability of specific diagnostic criteria, accurate diagnosis of LBD remains challenging, particularly at early stages, because of various factors including overlapping pathologies with AD and vascular dementia, atypical disease presentation, underuse of biomarkers, and insufficient neuropsychological evaluation [4, 12]. Furthermore, for patients diagnosed with LBD, there are currently no disease-modifying therapies available and treatments indicated for LBD target specific symptoms [13–15]. Other treatments have been used off-label to manage LBD-related symptoms (e.g., memantine, anti-Parkinson agents, quetiapine), though evidence regarding their overall effectiveness is limited [13, 16]. As a result, there is a substantial unmet clinical need among people with LBD.

Prior studies on clinical outcomes among people with LBD have generally focused on a single outcome such as decline in cognition [10, 17–20], functional activities [21, 22], or neuropsychiatric symptoms [23, 24]. A large, longitudinal international study found that the mean annual decline in Mini-Mental State Examination (MMSE) score in people with DLB was approximately 2 points [20]; notably, a decrease of 1–3 points is indicative of clinically meaningful decline [25, 26]. Over a 5-year follow-up period even people diagnosed with mild DLB reported a 4.4-point decline in the MMSE score, which occurred faster in DLB compared with AD [17]. In a different study, Vik-Mo and colleagues reported that LBD was associated with greater neuropsychiatric and psychotic symptoms than other forms of dementia, including AD [24]. Within the LBD cohort, people with DLB presented with more severe and widespread cognitive dysfunction than those with PDD based on MMSE and Montreal Cognitive Assessment (MoCA), particularly in attention, visuospatial and executive function, and language domains [19], highlighting the severity of disease.

As the identification of LBD is often confirmed postmortem, there is a paucity of evidence documenting the progression of disease

antemortem [27, 28]. In particular, broad, real-world assessments that comprehensively capture the heterogeneous disease course of LBD across multiple cognitive, functional, and neuropsychiatric domains are scarce. Such insight has the potential to assist healthcare stakeholders to optimize care as well as inform clinical trials aimed at developing novel therapies for this difficult-to-treat patient population. Therefore, this study sought to assess the clinical features of LBD, including disease characteristics, medication use, comorbidities, and progression trajectories in terms of changes in cognition, function, and neuropsychiatric symptoms over time using real-world data. The results were reported for the cohort of patients with LBD overall, and also stratified by disease severity based on the Clinical Dementia Rating (CDR®) Dementia Staging Instrument Sum of Boxes (CDR-SB) score at the time of initial cognitive decline diagnosis.

METHODS

Data Source

This study used data from 30 Alzheimer's Disease Centers (ADCs) through the US National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) and the neuropathology (NP) dataset. Since 1999, the NACC has collected data from past and present ADCs supported by the US National Institute on Aging/National Institutes of Health [29]. The UDS includes participants with a range of cognitive status and contains information on demographics, medical and family history, as well as clinical information on cognitive, motor, functional, and neuropsychiatric status. Data for UDS are collected prospectively on an approximately annual basis and recorded directly by trained clinicians. Data were de-identified and compliant with the patient confidentiality requirements of the Health Insurance Portability and Accountability Act; as a result, approval from an ethics committee was not required.

The NP dataset contains autopsy data for a subset of participants from the UDS. In addition to age and date of death, the NP dataset includes information regarding the presence of neuropathological features for most major dementias [30].

Sample Selection

The study population included NACC participants with at least one ADC visit between September 2005 and June 2020 with a diagnosis of mild cognitive impairment (MCI) or dementia. The index date was defined as the date of the first visit with an indication of cognitive impairment. Participants were required to have an indication of LBD on or after the index date defined as any of the following: (1) primary, contributing, or non-contributing LBD etiology; (2) biomarker evidence of LBD on a dopamine transporter (DAT) scan (i.e., decreased striatal dopamine binding); or (3) evidence of LBD pathology postmortem. Additionally, participants were required to have at least one follow-up visit after the index date with non-missing data for the outcomes of interest in order to assess changes in disease progression over time (Fig. 1). The overall LBD cohort was stratified into three subgroups based on the CDR-SB score on the index date: mild (CDR-SB score 0–0.5); moderate (CDR-SB score 1–4); severe (CDR-SB score $\geq$ 4.5), in accordance with validated threshold values for identifying dementia in patients with PD [31].

Study Measures and Outcomes

Participant characteristics were evaluated on the index date and included demographics (e.g., age, sex, race, ethnicity), select comorbidities, *APOE ε4* genotype status, and self-reported medication use. Cognitive characteristics included age at onset of cognitive decline based on clinician assessment, clinical assessment of symptoms, CDR-Global Score (CDR-GS), CDR-SB score, and MoCA score (which replaced MMSE in the NACC database in March 2015) [32–34]. For patients with only MMSE scores available in the data, MMSE scores were mapped into MoCA scores using a published conversion algorithm validated in people with PD to generate uniform summary measures across the

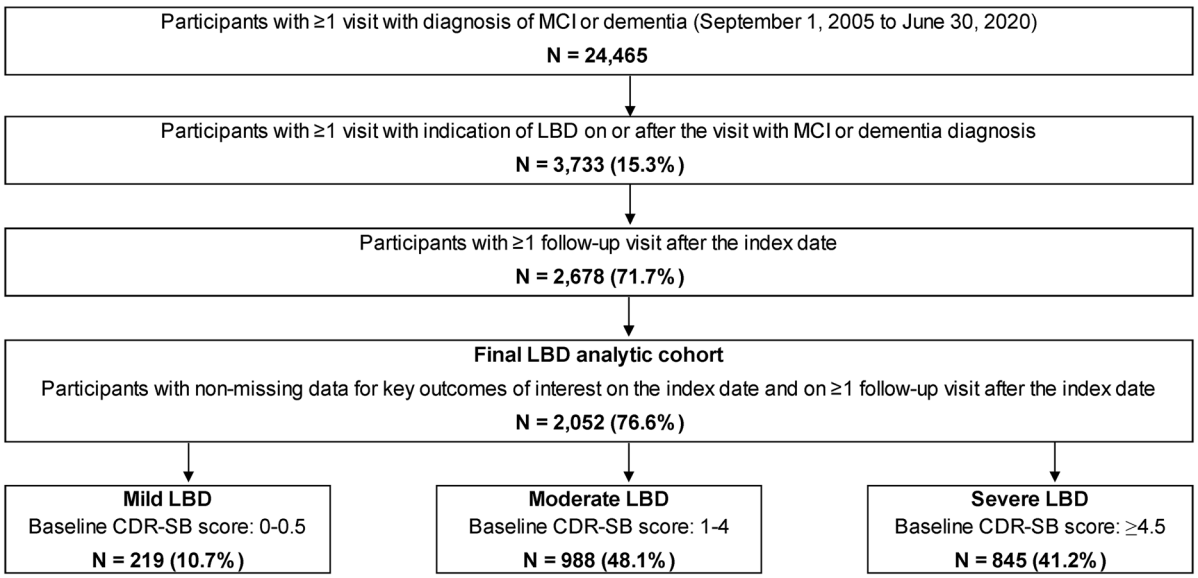


Fig. 1 Sample selection. *CDR-GS* Clinical Dementia Rating Global Score, *CDR-SB* Clinical Dementia Rating Sum of Boxes, *LBD* Lewy body dementia, *MCI* mild cognitive impairment, *MoCA* Montreal Cognitive Assessment, *NPI-Q* Neuropsychiatric Inventory-Questionnaire. LBD indication was defined as the presence of LBD etiology (primary, contributing, or non-contributing), biomarker evidence of LBD on a dopamine transporter (DAT) scan, or presence of LBD pathology postmortem. The index date was defined as the date of the first visit with indication of cognitive impairment (based on the earliest visit with clinician's documentation of presence of cognitive decline, or the date of MCI/dementia diagnosis during subsequent visits, whichever occurred first). Participants were required to have non-missing data on at least one follow-up visit after the index date for CDR-GS, CDR-SB, MoCA, NPI-Q, changes in falls, tremors, and slowness

different time periods [35]. If one MMSE score could be mapped onto multiple MoCA scores, the lower MoCA score was used.

Functional outcomes that were analyzed included the Functional Assessment Questionnaire (FAQ) score (which quantifies participants' ability to perform essential daily activities, such as preparing meals and managing personal finances; a score of ≥ 9 indicates impaired function [36]), level of independence, and PD symptoms (e.g., bradykinesia, gait disorder, posture instability). Neuropsychiatric outcomes that were analyzed included the total Neuropsychiatric Inventory-Questionnaire (NPI-Q) severity score (higher scores indicating greater symptom severity [37–40]) and the proportions of participants with specific neuropsychiatric symptoms included in the NPI-Q (e.g., delusions, hallucinations, depression). Outcomes were assessed at each visit after the index visit.

Statistical Analysis

Participant characteristics and outcomes were summarized descriptively using means and standard deviations for continuous variables and frequencies and percentages for categorical variables. The assessment of outcomes at each follow-up visit was conducted among participants with non-missing values for the outcome at the given visit. For the stratified analyses by CDR-SB score at index, statistical differences were evaluated using chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables for all characteristics except for cognitive assessments because they differed across the three subgroups by design. Mean changes in outcomes during the follow-up visits and the annualized mean change from the index date were described for each CDR-SB subgroup. While ADC visits are typically

Table 1 Participant characteristics of the LBD cohort at the index visit, overall and stratified by CDR-SB

	Overall *N* = 2052	Mild LBD (CDR-SB 0–0.5) *N* = 219	Moderate LBD (CDR-SB 1–4) *N* = 988	Severe LBD (CDR-SB ≥ 4.5) *N* = 845	*P* value
Socio-demographic characteristics					
Age at index (years)	73.4 ± 9.2	75.9 ± 8.3	73.1 ± 9.2	73.1 ± 9.4	*
Male	1385 (67.5%)	144 (65.8%)	701 (71.0%)	540 (63.9%)	
Race					
White	1875 (91.4%)	197 (90.0%)	926 (93.7%)	752 (89.0%)	
Black or African American	115 (5.6%)	15 (6.8%)	43 (4.4%)	57 (6.7%)	
Other	57 (2.8%)	6 (2.7%)	18 (1.8%)	33 (3.9%)	
Hispanic ethnicity	112 (5.5%)	14 (6.4%)	39 (3.9%)	59 (7.0%)	
Education (years)	15.5 ± 3.4	16.4 ± 2.9	15.7 ± 3.2	15.0 ± 3.7	*
Marital status					
Married	1596 (77.8%)	157 (71.7%)	796 (80.6%)	643 (76.1%)	
Widowed	262 (12.8%)	33 (15.1%)	105 (10.6%)	124 (14.7%)	
Divorced	117 (5.7%)	19 (8.7%)	49 (5.0%)	49 (5.8%)	
Other	66 (3.2%)	9 (4.1%)	34 (3.4%)	23 (2.7%)	
Living situation					
Lives with spouse or partner	1582 (77.1%)	157 (71.7%)	785 (79.5%)	640 (75.7%)	
Lives alone	249 (12.1%)	49 (22.4%)	127 (12.9%)	73 (8.6%)	
Lives with a relative or friend	142 (6.9%)	12 (5.5%)	46 (4.7%)	84 (9.9%)	
Other	75 (3.7%)	1 (0.5%)	28 (2.8%)	46 (5.4%)	
Additional characteristics and medical history					
LBD indication type					*
Primary LBD etiology	876 (42.7%)	107 (48.9%)	496 (50.2%)	273 (32.3%)	
LBD pathology postmortem	723 (35.2%)	64 (29.2%)	282 (28.5%)	377 (44.6%)	
Contributing or non-contributing LBD etiology, or LBD biomarker evidence	453 (22.1%)	48 (21.9%)	210 (21.3%)	195 (23.1%)	

Table 1 continued

	Overall *N* = 2052	Mild LBD (CDR-SB 0–0.5) *N* = 219	Moderate LBD (CDR-SB 1–4) *N* = 988	Severe LBD (CDR-SB ≥ 4.5) *N* = 845	*P* value
Smoking					
Always non-smoker	1078 (52.5%)	115 (52.5%)	523 (52.9%)	440 (52.1%)	
Past smoker	807 (39.3%)	87 (39.7%)	388 (39.3%)	332 (39.3%)	
Current smoker	49 (2.4%)	3 (1.4%)	18 (1.8%)	28 (3.3%)	
Unknown	118 (5.8%)	14 (6.4%)	59 (6.0%)	45 (5.3%)	
APOE ε4 genotype status					*
No copy	919 (44.8%)	129 (58.9%)	456 (46.2%)	334 (39.5%)	
1 copy	686 (33.4%)	55 (25.1%)	326 (33.0%)	305 (36.1%)	
2 copies	193 (9.4%)	10 (4.6%)	78 (7.9%)	105 (12.4%)	
Unknown	254 (12.4%)	25 (11.4%)	128 (13.0%)	101 (12.0%)	
Select comorbidities					
Hypercholesterolemia	1094 (53.3%)	124 (56.6%)	524 (53.0%)	446 (52.8%)	
Hypertension	1028 (50.1%)	120 (54.8%)	469 (47.5%)	439 (52.0%)	
Depression	991 (48.3%)	68 (31.1%)	471 (47.7%)	452 (53.5%)	*
Traumatic brain injury	263 (12.8%)	25 (11.4%)	112 (11.3%)	126 (14.9%)	
Diabetes	223 (10.9%)	23 (10.5%)	95 (9.6%)	105 (12.4%)	
Alcohol abuse	133 (6.5%)	7 (3.2%)	55 (5.6%)	71 (8.4%)	
Sleep disorders	90 (4.4%)	14 (6.4%)	50 (5.1%)	26 (3.1%)	
AD medications					
Memantine	494 (24.1%)	13 (5.9%)	162 (16.4%)	319 (37.8%)	*
Cholinesterase inhibitors	1102 (53.7%)	37 (16.9%)	480 (48.6%)	585 (69.2%)	*

Table 1 continued

	Overall $N = 2052$	Mild LBD (CDR-SB 0–0.5) $N = 219$	Moderate LBD (CDR-SB 1–4) $N = 988$	Severe LBD (CDR-SB ≥ 4.5) $N = 845$	*P* value
Other medications					
Anti-Parkinson agents	343 (16.7%)	32 (14.6%)	198 (20.0%)	113 (13.4%)	*
Antidepressants	826 (40.3%)	55 (25.1%)	398 (40.3%)	373 (44.1%)	*
Anti-psychotic agents	167 (8.1%)	5 (2.3%)	56 (5.7%)	106 (12.5%)	*
Anxiolytics, sedatives, or hypnotic agents	306 (14.9%)	23 (10.5%)	170 (17.2%)	113 (13.4%)	

Means and standard deviations are shown for continuous characteristics; counts and percentages are shown for categorical characteristics, unless otherwise noted

Some numbers may not add to the totals due to missing values

AD Alzheimer's disease, *CDR-SB* Clinical Dementia Rating Sum of Boxes, *LBD* Lewy body dementia

*Denotes $p < 0.001$ based on Wilcoxon rank-sum tests for continuous characteristics and chi-square tests for categorical characteristics among three groups. *P* values were not assessed for characteristics where at least one of the cells had a count of zero

12 months apart, some participants had variable time between visits. For example, 21% of the sample had visits that were 6–11 months apart and 9% had visits 18 months or more apart. To account for this variability, the annualized change was calculated using linear extrapolation or interpolation of the change in scores between visits. To explore the implications of sample attrition over time, a sensitivity analysis was conducted whereby the overall LBD cohort was restricted to participants with complete information for all outcomes of interest except FAQ for at least five visits. All analyses were conducted using SAS Enterprise Guide version 7.15 and R version 3.6.1.

RESULTS

A total of 2052 participants met all inclusion criteria and among them, 219 (10.7%) had mild LBD, 988 (48.1%) had moderate LBD, and 845 (41.2%) had severe LBD (Fig. 1).

Characteristics at Index Visit

Characteristics among participants with LBD overall and stratified by CDR-SB score at index are summarized in Table 1. Most participants were male (67.5%) and the mean age on the index date was 73 years. Participants with mild LBD were significantly older than participants with moderate and severe LBD (76 vs. 73 and 73 years, respectively; $p < 0.001$). Less than half (42.7%) of the participants had a primary LBD etiology, 35.2% were identified with LBD pathology postmortem, 22.1% had a contributing or non-contributing LBD etiology, or biomarker evidence of LBD on a DAT scan. Most participants either had no copy of *APOE ε4* (44.8%) or had one copy (33.4%), 9.4% had two copies, and 12.4% had an unknown number.

The three most common comorbid conditions were hypercholesterolemia (53.3%), hypertension (50.1%), and depression (48.3%). The proportion of participants with LBD using AD medications increased with disease severity.

Table 2 Clinical outcomes of the LBD cohort at the index visit, overall and stratified by CDR-SB

	Overall *N* = 2052	**Mild LBD (CDR-SB 0–0.5)** *N* = 219	**Moderate LBD (CDR-SB 1–4)** *N* = 988	**Severe LBD (CDR-SB ≥ 4.5)** *N* = 845	***P* value**
CDR-SB score[†]	4.0 ± 3.1	0.4 ± 0.2	2.4 ± 1.0	6.9 ± 2.7	–
MoCA score[†]	19.5 ± 6.6	24.8 ± 3.4	22.1 ± 4.8	15.0 ± 6.4	–
Age of start of cognitive decline (years)[†]					–
Mean ± SD	69.0 ± 9.7	72.8 ± 8.4	69.3 ± 9.7	68.0 ± 9.8	
Missing, %	4.5%	26.5%	3.1%	0.4%	
Predominant symptom first recognized as a decline in cognition[†]					
Memory	1446 (70.5%)	127 (58.0%)	686 (69.4%)	633 (74.9%)	–
Judgment, planning, problem solving	208 (10.1%)	9 (4.1%)	114 (11.5%)	85 (10.1%)	–
Language	109 (5.3%)	13 (5.9%)	61 (6.2%)	35 (4.1%)	–
Visuospatial function	92 (4.5%)	6 (2.7%)	39 (3.9%)	47 (5.6%)	–
Attention/concentration	90 (4.4%)	5 (2.3%)	56 (5.7%)	29 (3.4%)	–
No impairment in cognition	72 (3.5%)	55 (25.1%)	17 (1.7%)	0 (0.0%)	–
Other	15 (0.7%)	0 (0.0%)	10 (1.0%)	5 (0.6%)	–
Fluctuating cognition	10 (0.5%)	0 (0.0%)	4 (0.4%)	6 (0.7%)	–
Orientation	1 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	–
Mode of onset of cognitive symptoms[†]					
Gradual	1908 (93.0%)	152 (69.4%)	933 (94.4%)	823 (97.4%)	–
No impairment in cognition	75 (3.7%)	56 (25.6%)	18 (1.8%)	1 (0.1%)	–
Subacute	31 (1.5%)	3 (1.4%)	15 (1.5%)	13 (1.5%)	–
Abrupt	21 (1.0%)	3 (1.4%)	13 (1.3%)	5 (0.6%)	–
Other	3 (0.1%)	0 (0.0%)	3 (0.3%)	0 (0.0%)	–
Functional assessments					
FAQ score, mean ± SD	12.7 ± 9.6	1.5 ± 3.6	8.3 ± 6.7	20.7 ± 6.4	*
FAQ score range, %					*
≥ 9 (impaired function)	708 (34.5%)	7 (3.2%)	209 (21.2%)	492 (58.2%)	
< 9 (normal function)	483 (23.5%)	153 (69.9%)	304 (30.8%)	26 (3.1%)	

Table 2 continued

	Overall $N = 2052$	Mild LBD (CDR-SB 0–0.5) $N = 219$	Moderate LBD (CDR-SB 1–4) $N = 988$	Severe LBD (CDR-SB ≥ 4.5) $N = 845$	*P* value
Missing	861 (42.0%)	59 (26.9%)	475 (48.1%)	327 (38.7%)	
Level of independence					
Able to live independently	743 (36.2%)	196 (89.5%)	464 (47.0%)	83 (9.8%)	
Requires some assistance with complex activities	916 (44.6%)	19 (8.7%)	455 (46.1%)	442 (52.3%)	
Requires some assistance with basic activities	335 (16.3%)	4 (1.8%)	65 (6.6%)	266 (31.5%)	
Completely dependent	58 (2.8%)	0 (0.0%)	4 (0.4%)	54 (6.4%)	
Any PD symptoms present‡	1308 (63.7%)	122 (55.7%)	636 (64.4%)	550 (65.1%)	
Bradykinesia	859 (41.9%)	76 (34.7%)	424 (42.9%)	359 (42.5%)	
Gait disorder	785 (38.3%)	65 (29.7%)	371 (37.6%)	349 (41.3%)	
Posture instability	606 (29.5%)	40 (18.3%)	295 (29.9%)	271 (32.1%)	*
Right arm rigidity	703 (34.3%)	55 (25.1%)	336 (34.0%)	312 (36.9%)	
Left arm rigidity	686 (33.4%)	55 (25.1%)	315 (31.9%)	316 (37.4%)	
Right hand slowness	655 (31.9%)	49 (22.4%)	317 (32.1%)	289 (34.2%)	
Left hand slowness	691 (33.7%)	53 (24.2%)	344 (34.8%)	294 (34.8%)	
Right hand tremors	255 (12.4%)	28 (12.8%)	132 (13.4%)	95 (11.2%)	
Left hand tremors	222 (10.8%)	23 (10.5%)	110 (11.1%)	89 (10.5%)	
Meaningful changes in falls	324 (15.8%)	20 (9.1%)	146 (14.8%)	158 (18.7%)	
Meaningful changes in tremors	549 (26.8%)	44 (20.1%)	300 (30.4%)	205 (24.3%)	*

Table 2 continued

	Overall $N = 2052$	Mild LBD (CDR-SB 0–0.5) $N = 219$	Moderate LBD (CDR-SB 1–4) $N = 988$	Severe LBD (CDR-SB ≥ 4.5) $N = 845$	*P* value
Meaningful changes in slowness	835 (40.7%)	59 (26.9%)	419 (42.4%)	357 (42.2%)	*
Neuropsychiatric assessments					
NPI-Q total score	4.8 ± 4.6	1.8 ± 2.6	4.0 ± 3.8	6.5 ± 5.2	*

Means and standard deviations are shown for continuous characteristics; counts and percentages are shown for categorical characteristics, unless otherwise noted

Some numbers may not add to the totals due to missing values

CDR Clinical Dementia Rating, *CDR-GS* Clinical Dementia Rating Global Score, *CDR-SB* Clinical Dementia Rating Sum of Boxes, *FAQ* Functional Activities Questionnaire, *LBD* Lewy body dementia, *MoCA* Montreal Cognitive Assessment, *NPI-Q* Neuropsychiatric Inventory-Questionnaire, *PD* Parkinson's disease, *SD* standard deviation

*Denotes $p < 0.001$ based on Wilcoxon rank-sum tests for continuous characteristics and chi-square tests for categorical characteristics among three groups. *P* values were not assessed for characteristics where at least one of the cells had a count of zero

†*P* values were not assessed for cognitive characteristics because by design the stratification by severity level was based on the cognitive status on the index date

‡PD symptoms included presence of bradykinesia, gait disorder, posture instability, right/left arm rigidity, right/left hand slowness, right/left hand tremors

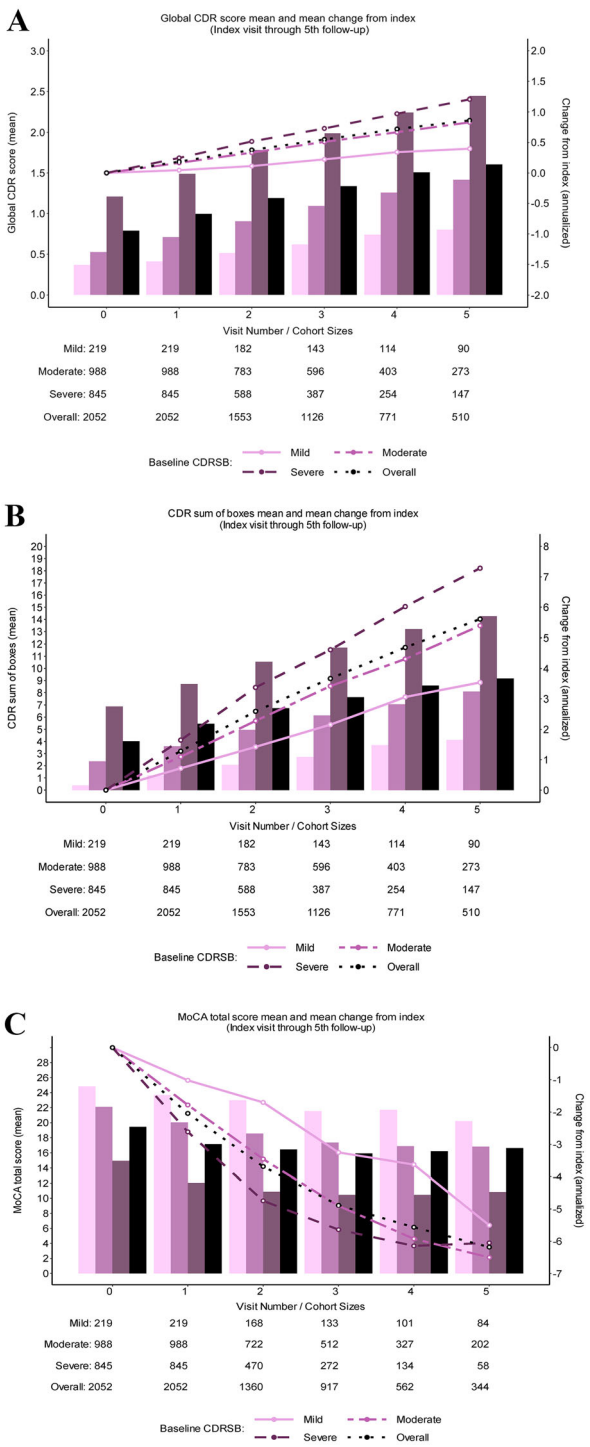
The use of memantine among participants with mild, moderate, and severe LBD was 5.9%, 16.4%, and 37.8%, respectively; the use of cholinesterase inhibitors was 16.9%, 48.6%, and 69.2%, respectively. Other medications that were common during the baseline period were antidepressants (mild, 25.1%; moderate, 40.3%; severe, 44.1%) and anti-Parkinson agents (mild, 14.6%; moderate, 20.0%; severe, 13.4%).

Clinical outcomes at the index visit are summarized in Table 2. The mean age at onset of cognitive decline was slightly higher among participants with mild LBD compared with those with moderate and severe (mild, 73; moderate, 69; severe, 68 years).

In general, participants with mild LBD had better cognitive, functional, and neuropsychiatric performance at index relative to participants with moderate and severe LBD as indicated by a higher mean MoCA score and lower mean CDR-GS, CDR-SB, FAQ, and NPI-Q scores (Table 2). The proportion of participants with impaired function (FAQ score ≥ 9) was almost 20 times lower among those with mild vs. severe LBD (mild, 3.2%; moderate, 21.2%; severe, 58.2%). The proportion of participants requiring some assistance with basic or complex activities was also the lowest for mild LBD (mild, 10.5%; moderate, 52.6%; severe, 83.8%). More than half of participants in each subgroup had any PD symptoms present at baseline (mild, 55.7%; moderate, 64.4%; severe, 65.1%).

Study Outcomes

Outcome assessments at follow-up visits 1, 3, and 5 after the index visit are summarized in Supplementary Material Table S1. Overall, hypertension, hypercholesterolemia, and depression remained the most common comorbid conditions post-index. The use of memantine and cholinesterase inhibitors remained stable over the 5-year follow-up period for the overall LBD cohort and was lowest among participants with mild relative to severe LBD. The use of anti-Parkinson agents was slightly higher among participants with mild and moderate LBD relative to those with severe

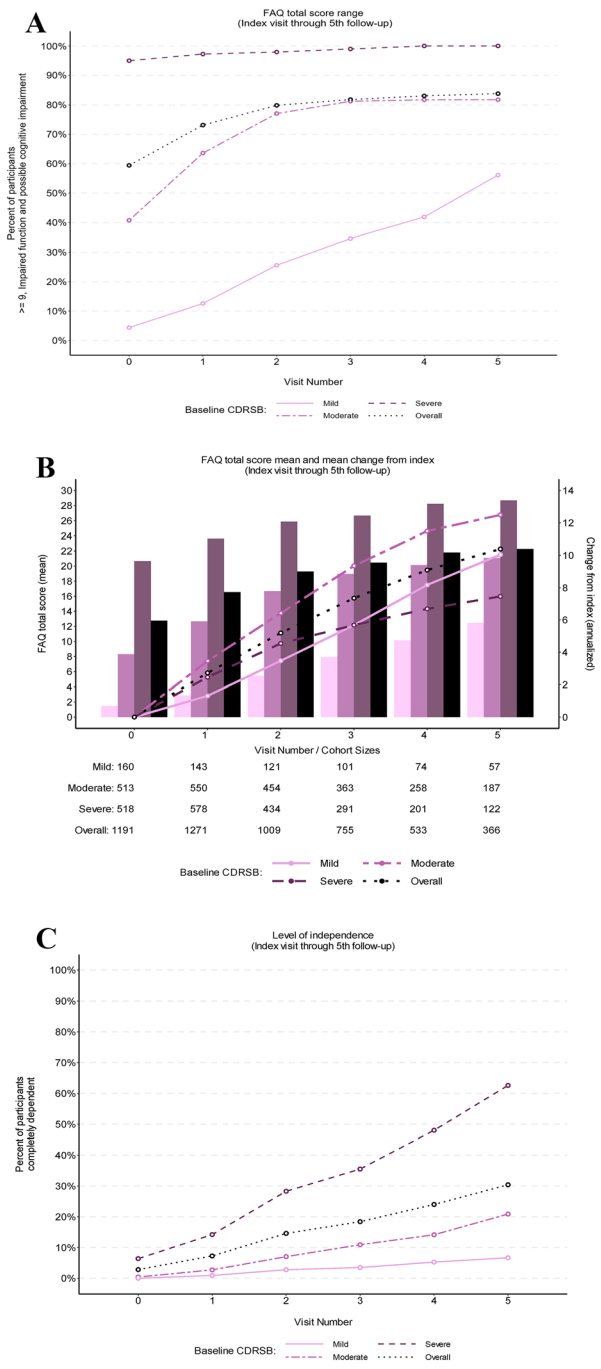


◀**Fig. 2** Change in **a** CDR-GS, **b** CDR-SB, and **c** MoCA scores over time stratified by CDR-SB at index. *CDR* Clinical Dementia Rating, *CDR-GS* Clinical Dementia Rating Global Score, *CDR-SB* Clinical Dementia Rating Sum of Boxes, *MCI* mild cognitive impairment, *MoCA* Montreal Cognitive Assessment. Participants with CDR-SB score of 0–0.5 on the index date were considered to have impairment of mild severity ("mild LBD"), while those with CDR-SB scores of 1–4 and $\geq$ 4.5 were considered to have impairment of greater severity ("moderate LBD" and "severe LBD", respectively) [31]

LBD, while antidepressant use was lower among participants with mild LBD relative to those with moderate and severe LBD.

Cognitive, functional, and neuropsychiatric outcomes generally worsened over time for the overall LBD cohort and the deterioration was greater among participants with moderate and severe LBD compared with those with mild LBD. In particular, CDR-GS and CDR-SB scores increased over time for all subgroups and the magnitude of change was highest for participants with severe LBD at each follow-up visit post-index. The mean annualized increase in CDR-GS and CDR-SB over 5 years relative to the index visit increased with LBD severity (ranging from 0.4 to 1.2 and from 3.5 to 7.3, respectively). The mean annualized decrease in MoCA score over 5 years relative to the index visit was 5.5 for mild LBD, 6.5 for moderate LBD, and 6.1 for severe LBD (Fig. 2).

Overall, the proportion of participants classified as having impaired function (FAQ score of $\geq$ 9) increased from visit 1 to 5 post-index from 8.2% to 35.6% for those with mild LBD, 35.4% to 56.0% for those with moderate LBD, and 66.5% to 83.0% for those with severe LBD. The mean annualized increase in the total FAQ score over 5 years relative to the index visit was 10.0, 12.5, and 7.5 for mild, moderate, and severe LBD. The proportion of participants classified as completely dependent also increased with disease severity from visit 1 to 5 post-index from 0.9% to 6.7% for mild, 2.7% to 20.9% for moderate, and 14.2% to 62.6% for severe LBD (Fig. 3). The cumulative proportion of participants experiencing meaningful changes in falls,



◀**Fig. 3** Change in **a** FAQ score ≥ 9, **b** total FAQ score, and **c** dependence in daily activities over time stratified by CDR-SB at index. *CDR-SB* Clinical Dementia Rating Sum of Boxes, *FAQ* Functional Activities Questionnaire. Participants with CDR-SB score of 0–0.5 on the index date were considered to have impairment of mild severity ("mild LBD"), while those with CDR-SB scores of 1–4 and ≥ 4.5 were considered to have impairment of greater severity ("moderate LBD" and "severe LBD", respectively) [31]. FAQ score of ≥ 9 (dependent in ≥ 3 activities) was used to indicate impaired function [36]

tremors, and slowness was also higher for those with severe LBD: 50.3%, 47.6%, and 75.5% by visit 5 post-index, respectively. The proportion of participants with any PD symptoms post-index was stable among those with mild LBD (57.1–57.8% from visit 1 to 5 post-index) and declined for those with moderate and severe LBD from 68.3% to 49.8% and from 71.7% to 38.1%, respectively. The mean annualized increase in the total NPI-Q score over 5 years relative to the index visit was 1.6, 2.2, and 1.9 for mild, moderate, and severe LBD, indicating slightly increased severity of neuropsychiatric symptoms (Fig. 4). The proportion of participants with specific neuropsychiatric symptoms was relatively stable over time across the three LBD subgroups (Supplementary Material Table S1).

The number of participants with available data on outcomes after the first follow-up visit post-index declined over time, with approximately 41%, 28%, and 17% of participants remaining in the mild, moderate, and severe subgroups, respectively, by visit 5. Findings from the sensitivity analysis in participants with complete information for outcomes of interest for at least five visits (n = 287) were consistent with the annualized mean change in outcomes for the overall LBD cohort (Supplementary Material Figs. S1–S6).

DISCUSSION

This comprehensive study reported participant characteristics, treatment patterns, and

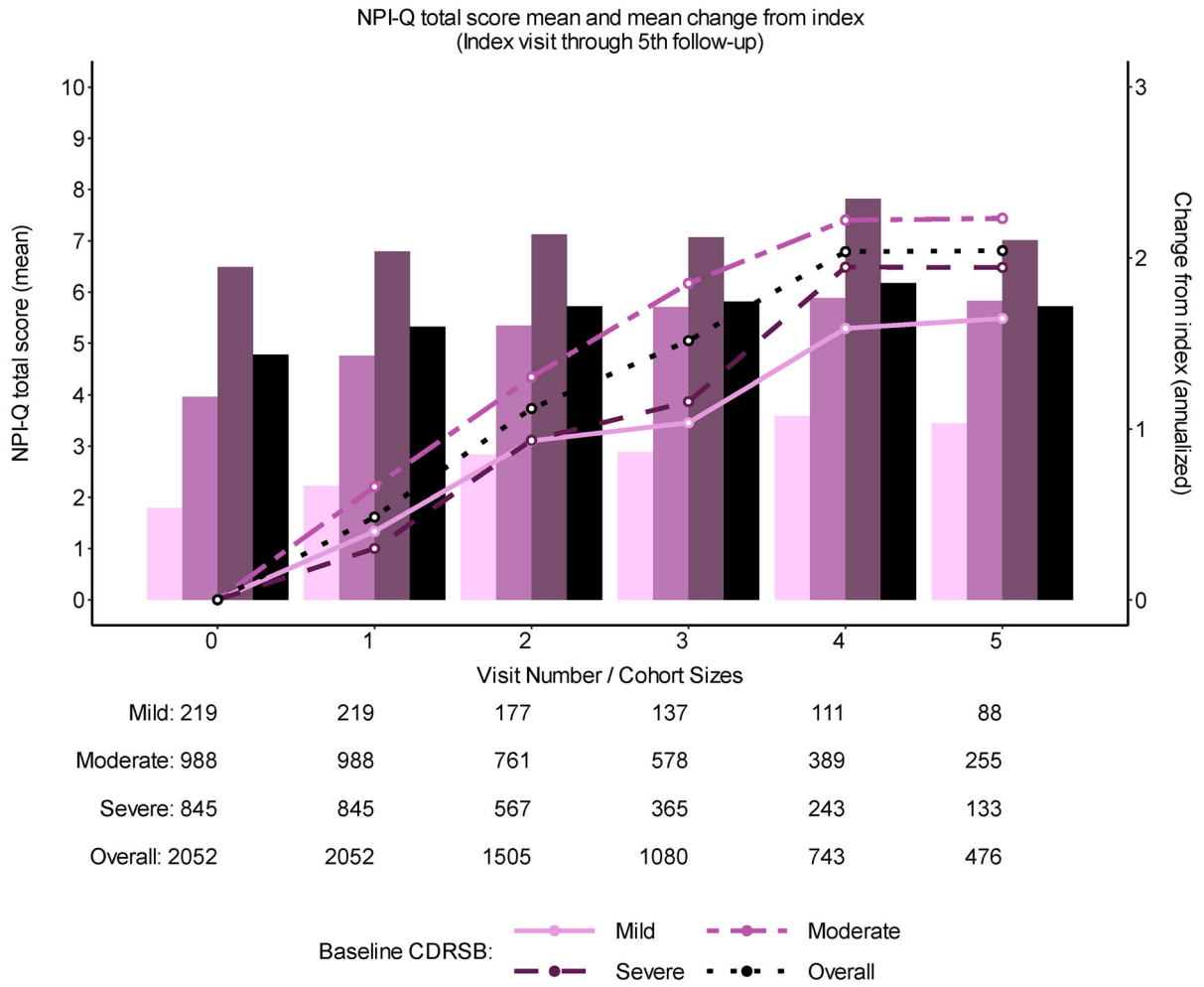


Fig. 4 Change in NPI-Q score over time stratified by CDR-SB at index. *CDR-SB* Clinical Dementia Rating Sum of Boxes, *MCI* mild cognitive impairment, *NPI-Q* Neuropsychiatric Inventory-Questionnaire. Participants with CDR-SB score of 0–0.5 on the index date were considered to have impairment of mild severity ("mild LBD"), while those with CDR-SB scores of 1–4 and ≥ 4.5 were considered to have impairment of greater severity ("moderate LBD" and "severe LBD", respectively) [31]

progression over time among a diverse cohort of older adults with LBD in the USA. Participants with LBD experienced decline in multiple cognitive, functional, and neuropsychiatric outcomes over time. The worsening in cognition and function based on CDR-GS, CDR-SB, MoCA, and FAQ scores was largest among participants with moderate and severe LBD at the time of diagnosis relative to those with mild LBD, indicating potential acceleration of cognitive and functional decline as the disease progresses. Approximately 5 years following the index date, 60.2% of all participants with LBD had impaired function based on their FAQ score. Additionally, the level of dependence increased over time with disease severity, such that over half of participants required assistance with both basic and complex activities and 30% were completely dependent at visit 5 post-index. The proportion of participants with specific neuropsychiatric symptoms remained relatively stable across the three LBD subgroups over time, though the total NPI-Q score worsened slightly relative to the index visit, indicating an

increased severity of neuropsychiatric symptoms. The annualized mean change in outcomes was consistent with the main results for the overall LBD cohort and showed decline in different domains, further highlighting the progressive nature of LBD across a wide spectrum of clinical features. These findings also illustrate the need for therapies that address the wide range of symptoms specific to LBD or help slow disease progression.

The demographic characteristics and comorbidity profiles of the LBD cohort overall and stratified by disease severity based on the CDR-SB score at the index visit were largely similar. The age at onset of cognitive decline was slightly higher among participants with mild LBD compared with those with moderate and severe, which could be likely driven by a higher proportion of participants with PDD vs. DLB in the mild group or potentially greater AD co-pathology in the severe group. About a third of participants were identified with LBD pathology postmortem, and the proportion was slightly higher among those with severe LBD, highlighting the challenges of early and accurate diagnosis of people with LBD. Previous findings from autopsy studies have suggested that DLB pathology occurs in about 20–25% of dementia cases in older adults [41]. While the clinical diagnosis of LBD is largely based on obtaining accurate clinical history and timeline of symptoms, postmortem autopsy is currently the only way to make a conclusive diagnosis and even then overlapping pathology is often seen [12].

Despite more than half of participants having PD symptoms present at the time of initial cognitive decline diagnosis, the use of anti-Parkinson agents was low, and remained so over time. This finding is likely driven by concerns about the limited benefit of dopaminergic medications in LBD, including low likelihood of motor improvement and risk of psychosis exacerbation [42]. The most commonly used medications at index among the overall LBD cohort were cholinesterase inhibitors (53.7%) and antidepressants (40.3%). The use of memantine and cholinesterase inhibitors increased with disease severity both at index and during the follow-up period and was generally higher among participants with severe LBD. The low use of symptomatic treatments in this population also highlights the need for improved therapies focusing on the treatment of symptoms specific to LBD [43], as well as those targeting the pathological mechanisms of the disease, potentially before symptoms and clinical signs develop [44]. While about half of the overall LBD cohort had any PD symptoms present during the follow-up period, a decrease was observed for the severe LBD subgroup from 71.7% to 38.1% at visits 1 to 5 post-index, respectively. This is likely driven by attrition of participants over time, suggesting that those with severe LBD and motor impairments may be more likely to be lost to follow-up because of the severity of their condition. Indeed, in the sensitivity analysis, the proportion of participants with LBD who had PD symptoms increased from 53.0% to 66.2% at visits 1 to 5 post-index, respectively.

This is one of the few studies to comprehensively document the disease progression trajectories with respect to cognitive, functional, and neuropsychiatric outcomes among people with LBD. While most of the previous literature on LBD focused on single outcomes [10, 17, 20, 21], aspects of our findings are consistent with prior studies. Previous research evaluating annual decline in MMSE scores reported a similar decline of 2 to 4 points among patients with LBD [17, 20]. In terms of functional decline, we found that the 1-year change in FAQ score ranged from 1 to 3 points, which is consistent with findings from Gill and colleagues [21].

It is well documented that decline in cognitive, functional, and neuropsychiatric function may potentially have a negative impact on other outcomes. For example, a recent health state transition model evaluating LBD disease progression found that reducing the annual risk of transitioning from mild to severe DLB by 40% decreased time institutionalized and increased time to death [45]. Further studies are needed to assess how different rates of progression in cognitive, functional, and neuropsychiatric outcomes by disease severity at initial assessment may affect healthcare resource use, costs, and survival over time as well as to

evaluate the disease burden of LBD compared with other neurodegenerative diseases such as AD or PD or a control cohort. It is also important to understand the predictors of cognitive and functional decline among people with LBD overall and any differences in the underlying pathological processes between DLB and PDD subtypes. Such information may help in defining more homogenous groups of participants with LBD for recruitment in clinical trials targeting specific disease mechanisms [46]. Nevertheless, taken together, our study findings provide valuable insights into the disease trajectories of older adults with LBD under the current standard of care and highlight the need for better diagnostic tools to identify LBD in early stages. These observations could in turn inform future clinical trials for potential disease-modifying treatments for LBD as well as policy interventions to improve care management for older adults with LBD in the USA.

This study was subject to certain limitations. Although the study utilized data from a diverse set of participants across 30 ADCs in the USA, the results may not be generalized to the entire US population as NACC participants represent a clinic-based convenience sample and tend to be highly educated. Furthermore, individual ADCs recruit and enroll participants according to their own protocols and the varying inclusion/exclusion criteria may introduce bias into the sample. More than a third of participants in the LBD cohort were identified with LBD pathology postmortem and did not have a formal LBD diagnosis antemortem. As a result, the study sample may not adequately reflect the broader population of people with LBD encountered in real-world clinical practice. Additionally, the study sample was broadly categorized as having LBD based on clinician assessment of the dementia etiology recorded in the database. However, it was not feasible to differentiate between DLB and PDD—two related yet distinct subtypes of LBD which may result in different disease progression trajectories than the overall LBD cohort. The proportion of participants with available data declined considerably over time. Although the precise reason for attrition is unavailable in the data, participants with worsening cognitive impairment, neuropsychiatric symptoms, and difficulty with functional activities may be more likely to be lost to follow-up [47]. Consequently, the long-term decline in all outcomes, particularly in later years following the index date, may be underestimated. In addition, the medication use assessed in this study is self-reported (or informant-reported) and therefore should be interpreted with caution. Finally, all analyses were descriptive and did not adjust for differences in participants' baseline characteristics or compare outcomes relative to participants without LBD. Further research is warranted to investigate factors associated with disease progression over time using multivariate models such linear mixed models.

CONCLUSION

Findings from this study highlight the substantial clinical burden associated with LBD. The demographic characteristics and comorbidity profiles of the LBD cohort overall and stratified by disease severity were largely similar and a third of participants were identified with LBD pathology postmortem. Participants with LBD experienced progression across several cognitive, functional, and neuropsychiatric outcomes, including CDR-GS, CDR-SB, MoCA, FAQ, NPI-Q, and dependence in daily activities. The decline was particularly pronounced for measures of function and cognition and was even greater among participants with moderate and severe LBD compared with those with mild LBD. While the use of cholinesterase inhibitors and memantine increased with disease severity, the proportion of patients using anti-Parkinson agents remained low over time. Timely and accurate diagnosis of LBD and better understanding of the disease trajectory may help improve patient care and also inform clinical trials aimed at developing disease-modifying and improved symptomatic therapies for this patient population.

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Compliance with Ethics Guidelines. Data were de-identified and compliant with the patient confidentiality requirements of the Health Insurance Portability and Accountability Act; as a result, approval from an ethics committee was not required.

Data Availability. The datasets analyzed during the current study are not publicly available, as they are subject to a data use agreement between Analysis Group, Inc., and the National Alzheimer's Coordinating Center (NACC). Information about the data used in this study, including detailed descriptions and the process for obtaining them, is available at https://www.alz.washington.edu/.

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