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Clinical Features of Alzheimer Disease With and Without Lewy Bodies

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Abstract

IMPORTANCE—Lewy bodies are a frequent coexisting pathology in late-onset Alzheimer disease (AD). Previous studies have examined the contribution of Lewy bodies to the clinical phenotype of late-onset AD with variable findings.

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OBJECTIVE—To determine whether the presence of Lewy body pathology influences the clinical phenotype and progression of symptoms in longitudinally assessed participants with AD.

DESIGN, SETTING, AND PARTICIPANTS—Retrospective clinical and pathological cohort study of 531 deceased participants who met the neuropathologic criteria for intermediate or high likelihood of AD according to the National Institute on Aging–Ronald Reagan Institute guidelines for the neuropathologic diagnosis of AD. All participants had a clinical assessment within 2 years of death. The data were obtained from 34 AD centers maintained by the National Alzheimer Coordinating Center and spanned from September 12, 2005, to April 30, 2013.

EXPOSURES—Standardized neuropathologic assessment and then brain autopsy after death.

MAIN OUTCOMES AND MEASURES—Clinical and neuropsychiatric test scores.

RESULTS—The mean (SD) age at death was statistically significantly younger for participants who had AD with Lewy bodies (77.9 [9.5] years) than for participants who had AD without Lewy bodies (80.2 [11.1] years) ($P = .01$). The mean (SD) age at onset of dementia symptoms was also younger for participants who had AD with Lewy bodies (70.0 [9.9] years) than for participants who had AD without Lewy bodies (72.2 [12.3] years) ($P = .03$). More men than women had AD with Lewy bodies ($P = .01$). The frequency of having at least 1 *APOE* ε4 allele was higher for participants who had AD with Lewy bodies than for participants who had AD without Lewy bodies ($P = .03$). After adjusting for age, sex, education, frequency of plaques (neuritic and diffuse), and tangle stage, we found that participants who had AD with Lewy bodies had a statistically significantly higher mean (SD) Neuropsychiatric Inventory Questionnaire score (6.59 [1.44] [95% CI, 3.75–9.42] vs 5.49 [1.39] [95% CI, 2.76–8.23]; $P = .04$) and a statistically significantly higher mean (SD) Unified Parkinson Disease Rating Scale motor score (0.81 [0.18] [95% CI, 0.45–1.17] vs 0.54 [0.18] [95% CI, 0.19–0.88]; $P < .001$) than did participants who had AD without Lewy bodies.

CONCLUSIONS AND RELEVANCE—Participants with both AD and Lewy body pathology have a clinical phenotype that may be distinguished from AD alone. The frequency of Lewy bodies in AD and the association of Lewy bodies with the *APOE ε4* allele suggest potential common mechanisms for AD and Lewy body pathologies.

The 2 neuropathological hallmarks of Alzheimer disease (AD) are the extracellular Aβ plaques and the intracellular neurofibrillary tangles, of which the latter is composed of hyperphosphorylated tau protein.[1] Lewy bodies are intraneuronal cytoplasmic inclusions comprising aggregates of α-synuclein[2,3] and are readily detected by immunohistochemistry using anti–α-synuclein antibodies. In up to 50% of cases of sporadic late-onset AD, comorbid Lewy bodies are found.[2] Lewy bodies are frequent in the setting of moderate-to-severe levels of AD neuropathologic change.[2–4]

Neuroanatomical studies indicate that Lewy body accumulation follows a stereotypic pattern starting in the brainstem nuclei/olfactory regions and progressing to limbic areas and, in the most advanced stages, to the neocortex.[5,6] In contrast to this stereotypical pattern, Lewy bodies in AD may also be found concentrated in the amygdala without significant involvement of the brainstem or neocortical regions,[2,3] a distribution that has been called *AD with amygdala Lewy bodies*.[3,7] These cases with both Lewy body and AD pathology are

variously termed *Lewy body variant of AD*, *AD with dementia with Lewy bodies*, or *AD with Lewy bodies*.[8] In the present study, we use the term *AD with Lewy bodies* because *AD with dementia with Lewy bodies* has been considered as a generic term for all dementia with Lewy bodies,[5] and AD with Lewy bodies more precisely reflects our focus on the pathological differences between AD with and AD without Lewy bodies. Despite established clinical diagnostic criteria for AD,[9] a clinical diagnosis of AD often differs from neuropathologic findings.[10–13] Many studies have focused on the influence of Lewy body pathology in the clinical phenotype of AD within consistent results.[8,1418] There is controversy as to whether there are differences in parkinsonian features,[8,14,16,19,20] cognitive deficits,[16,17,19–21] cognitive decline,[8,14] and the presence of visual hallucinations[8,17,18,20,22] between AD with Lewy bodies and AD without Lewy bodies (eTable in the Supplement). These diverse findings may partly reflect the relatively small sample sizes used in some of these studies or the limitations with the clinical or neuropathological data.[8,14,16–18,23,24] We analyzed the demographic and clinical characteristics of a large, well-characterized cohort of participants with neuropathological AD to determine the influence of concomitant Lewy bodies during life.

Methods

Participants

We analyzed participant data submitted to the National Alzheimer Coordinating Center (NACC), University of Washington, Seattle.[25,26] The NACC (supported by grant U01 AG016976 to the principal investigator [PI] W. Kukull, PhD) is responsible for maintaining a database of information obtained from participants enrolled in AD centers funded by the National Institute on Aging (NIA).[25] The NACC data sets used in our study were the Uniform Data Set (UDS)[27,28] and the Neuropathology Data Set.[28] Clinical and neuropathological data submitted to the NACC from participants 50 years of age or older at last AD center assessment and who died and came to autopsy within 2 years of their last clinical assessment served as the sample for our study. Participants with missing data on the Neuropsychiatric Inventory Questionnaire (NPI-Q),[29] the Geriatric Depression Scale (GDS),[30] and the Unified Parkinson Disease Rating Scale (UPDRS) motor score[31] were excluded from the sample because these variables were our primary outcomes. Our Figure shows a flowchart for the inclusion or exclusion of participants.

Standard Protocol Approvals, Registrations, and Patient Consents

Research using the NACC database was approved by the University of Washington institutional review board. Written informed consent was obtained from all participants before death.

Neuropathologic Criteria

Participants meeting study inclusion criteria had neuropathologic AD; thus, they met the NIA–Reagan Institute criteria for intermediate or high likelihood of AD neuropathologic change, which causes dementia.[32] The criteria for dementia with Lewy bodies by McKeith et al[6] categorizes Lewy body pathology into brainstem, limbic, neocortical, and unspecified types. Lewy body densities are incorporated into the criteria. Because pilot analyses

indicated that stratification by Lewy body subtype would be underpowered, we combined all the Lewy body subtypes in McKeith et al[6] into AD with Lewy bodies. The plaque and tangle scores in the NACC Neuropathology Database were derived from a semiquantitative assessment of lesions according to the NIA–Reagan Institute criteria.[26]

Clinical Assessments

Demographic features from the NACC UDS included age at symptomatic onset of AD, age at death, sex, education, and *APOE* ε4 status. Age at death and age at symptomatic onset of AD were also recorded for participants who met neuropathological criteria for AD.[32] Disease duration was calculated based on age at onset and age at death from the NACC UDS. Data on a clinical diagnosis of dementia with Lewy bodies was obtained from the UDS. *APOE* ε4 data were available for a subsample of participants. A Clinical Dementia Rating (CDR)[33] was ascertained for each participant by an experienced clinician who used an algorithm based on information obtained from the participant and a collateral source (eg, spouse or adult child). This interview examined any decline due to cognitive changes in 6 different domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care). A global CDR was derived from ratings using all domains (0 = normal cognition, 0.5 = very mild dementia, 1 = mild dementia, 2 = moderate dementia, and 3 = severe dementia).

We also obtained scores from the CDR sum of boxes (CDR-SB, a quantitative general index more detailed than the global score[34]), the UPDRS motor score,[31] and the NPI-Q.[29] The NPI-Q is a retrospective (up to 1 month) caregiver informant interview covering 12 neuropsychiatric symptom domains.[29] The severity of each NPI-Q item was rated as none, mild (produces little distress in the patient), moderate (more disturbing to the patient but can be redirected by the caregiver), and severe (very disturbing to the patient and difficult to redirect). The NPI-Q was used for 493 participants. We conducted 2 separate analyses of the NPI-Q. In the first analysis, one group was classified as having no (none) symptoms, and the other as having any (mild, moderate, or severe) symptoms. In the second analysis, one group was classified as having lower (none or mild) symptom severity, and the other as having higher (moderate or severe) symptom severity. For subanalysis of participants with neuropathological AD who had mild dementia (CDR of 0.5 or 1) or normal cognition (CDR of 0), we analyzed the GDS,[30] Mini-Mental State Examination,[35] and the UDS Neuropsychological Battery[36] from the NACC UDS. The battery included the Wechsler Memory Scale–Revised Logical Memory Ia Story Units Recalled and Logical Memory IIa–Delayed Story Units Recalled,[37] the Boston Naming Test,[38] and the Animal Naming Test.[39] Many participants with greater severity of dementia could not complete some of the assessments. Therefore, we conducted subanalyses on a sample of participants who were less severely demented before death.

Statistical Analysis

Statistical analysis was performed using SPSS (version 20.0) for Mac (IBM). Unadjusted analyses for comparison of demographic features between participants who had AD with Lewy bodies and participants who AD without Lewy bodies were performed using χ^2 and *t* tests. A general linear model was fitted to analyze group differences while adjusting for

demographic factors. Age, sex, education in years, frequency (none, sparse, moderate, or frequent) of Aβ (diffuse and neuritic) plaques and neurofibrillary tangles (Braak and Braak neurofibrillary stage) were included in the model. Three stages (brainstem, limbic, and neocortical) were determined by counting Lewy bodies in multiple brain areas according to the criteria of McKeith et al.[6] The staging is comparable to the Consortium to Establish a Registry for Alzheimer's Disease and NIA–Reagan Institute staging schemes.[6] Individual Lewy body counts are not available in the NACC data set, so Lewy body pathology in AD was analyzed using the staging criteria of McKeith et al.[6] We repeated the analyses, adjusting for the presence of at least 1 *APOE* ε4 allele. $P \leq .05$ was regarded as statistically significant. For a sensitivity analysis, we fit the model for the subsample of participants who were cognitively normal or had mild dementia.

Results

Participant Characteristics

Of the 531 participants in our sample, 316 (59.5%) had AD without Lewy bodies, and 215 (40.5%) had AD with Lewy bodies (Table 1). The mean (SD) age at death was statistically significantly younger for participants who had AD with Lewy bodies (77.9 [9.5] years) than for participants who had AD without Lewy bodies (80.2 [11.1] years) ($P = .01$). The mean (SD) age at onset of dementia symptoms was also younger for participants who had AD with Lewy bodies (70.0 [9.9] years) than for participants who had AD without Lewy bodies (72.2 [12.3] years) ($P = .03$). More men than women had AD with Lewy bodies ($P = .01$). There were no statistically significant differences in education and duration of AD between participants who had AD with Lewy bodies and participants who had AD without Lewy bodies. The frequency of having at least 1 *APOE* ε4 allele was higher for participants who had AD with Lewy bodies than for participants who had AD without Lewy bodies ($P = .03$). There were no statistically significant differences in neuritic and diffuse plaques and tangles between the 2 groups. Of the 316 participants who had AD without Lewy bodies, 14 (4.4%) received a diagnosis of dementia with Lewy bodies (7 participants for whom it was the primary cause of death and 7 participants for whom it was the contributing cause of death) at the clinical assessment preceding death. Of the 215 participants who had AD with Lewy bodies, 51 (23.7%) received a diagnosis of dementia with Lewy bodies (39 participants for whom it was the primary cause of death and 12 participants for whom it was the contributing cause of death) at the clinical assessment preceding death.

In the subsample with sufficient cognitive data for analyses, there was a total of 160 participants: 100 participants who had AD without Lewy bodies and 60 participants who had AD with Lewy bodies. The mean (SD) age at death was significantly younger for participants who had AD with Lewy bodies (80.2 [8.9] years) than for participants who had AD without Lewy bodies (85.2 [9.9] years) ($P = .002$). The mean (SD) age at onset of dementia was also younger for participants who had AD with Lewy bodies (74.4 [9.9] years) than for participants who had AD without Lewy bodies (80.4 [11.2] years) ($P = .001$). Because this subsample was composed of participants with normal cognition or very mild dementia (CDR of 0 or 0.5), it is likely that they died of complications of something other than AD, which accounts for the older mean age at death. The prevalence of women was

lower in the group of participants who had AD with Lewy bodies (31.7%) than in the group of participants who had AD without Lewy bodies (51.0%) (P = .02). There were no statistically significant differences between participants who had AD with Lewy bodies and participants who had AD without Lewy bodies in mean (SD) years of education (15.3 [3.6] vs 15.4 [2.9] years; P = .95) and mean (SD) duration of AD (5.8 [3.5] vs 4.7 [4.0] years; P = .09). The frequency of having at least 1 *APOE* ε4 allele was higher for participants who had AD with Lewy bodies (46.1%) than for participants who had AD without Lewy bodies (37.3%) (P = .03). In contrast to the results of the total sample, the frequency of neuritic plaques was statistically significantly higher for participants who had AD with Lewy bodies than for participants who had AD without Lewy bodies (P = .02). Diffuse plaque (P = .08) and tangle (P = .39) distributions were not statistically significantly different between the 2 groups.

Comparison of Clinical Scale Scores Between Groups After Adjustment for Covariates

After adjusting for age, sex, education, frequency of plaques (neuritic and diffuse), and tangle stage, we found that participants who had AD with Lewy bodies had a statistically significantly higher mean (SD) NPI-Q score (6.59 [1.44] vs 5.49 [1.39]; P = .04) and a statistically significantly higher mean (SD) UPDRS motor score (0.81 [0.18] vs 0.54 [0.18]; P < .001) than did participants who had AD without Lewy bodies (Table 2). There was no statistically significant difference in the CDR-SB between the 2 groups of total participants (Table 2). In the subanalysis, we found that only the mean (SD) GDS (6.91 [1.41] vs 5.12 [1.31]; P = .001) and the mean (SD) UPDRS motor score (0.63 [0.21] vs 0.26 [0.19]; P < .001) were statistically significantly different between participants who had AD with Lewy bodies and participants who had AD without Lewy bodies such that participants with Lewy bodies had a greater number of depressive features based on the GDS and motor symptomology (Table 2).

After rerunning the analyses with the addition of *APOE* ε4 status in the models, we found that the mean (SD) UPDRS motor score was statistically significantly higher among participants who had AD with Lewy bodies (0.6 [0.2]) than among participants who had AD without Lewy bodies (0.42 [0.19]) (P = .02) (Table 3). In the subanalysis, similar results were found for the GDS (with a mean [SD] score of 7.02 [1.64] for participants who had AD with Lewy bodies vs 5.21 [1.5] for participants who had AD without Lewy bodies; P = .02) and the UPDRS motor score (with a mean [SD] score of 0.64 [0.19] for participants who had AD with Lewy bodies vs 0.33 [0.18] for participants who had AD without Lewy bodies; P < .001) (Table 3).

When individual NPI-Q items were evaluated as having no symptoms vs any symptoms, severity of delusion (P < .001), hallucination (P < .001), and aberrant motor disturbance (P = .04) had higher odds ratios in AD with Lewy bodies than in AD without Lewy bodies. When analyzed using mild vs severe categories, we found that severity of delusions (P = .01), hallucinations (P = .01), motor disturbances (P = .02), and sleep behavior problems (P = .045) were associated with higher odds ratios in AD with Lewy bodies than in AD without Lewy bodies. Severity of NPI-Q items in AD with Lewy bodies is described in Table 4.

There were no statistically significant differences among the 3 motor subtypes from the UPDRS motor score in AD with Lewy bodies (with AD without Lewy bodies as reference).

Discussion

We found younger ages at death and at symptomatic onset of AD among participants who had AD with Lewy bodies compared with participants who had AD without Lewy bodies. Men were more likely than women to have AD with Lewy bodies. The likelihood of having at least 1 *APOE* ε4 allele was higher among participants who had AD with Lewy bodies than among participants who had AD without Lewy bodies. Overall, the NPI-Q scores indicated more behavioral problems, and the UPDRS motor scores poorer motor performance, among participants who had AD with Lewy bodies compared with participants who had AD without Lewy bodies. As captured on the NPI-Q, delusions, hallucinations, aberrant motor behaviors, and sleep behavior problems were more severe among participants who had AD with Lewy bodies than among participants who had AD without Lewy bodies.

In contrast to our results, most neuropathological AD studies[8,14,15,17,19,22,23,40] have found no significant differences in age at symptomatic onset of AD or in age at death between participants who had AD with Lewy bodies and participants who had AD without Lewy bodies. With one exception,[22] all of these other studies[8,14,15,17,19,23,40] had a sample size less than half of our sample size, which could explain why there were no statistically significant differences in age at onset of cognitive symptoms or in age at death. In the study by Weiner et al[22] with a sample size similar to our own, participants were selected based on a clinical diagnosis of dementia while they were living. In contrast, we selected participants based solely on a neuropathologic diagnosis of AD, and some participants therefore had preclinical AD (CDR of 0) or received a CDR of 0.5, which is consistent with a diagnosis of mild cognitive impairment.[41] It is therefore possible that differences in age at symptomatic onset of AD and in age at death will more likely be found in samples of participants with a lower average level of cognitive impairment close to the time of death.

We found that the frequency of clinically diagnosed dementia with Lewy bodies was higher among participants who had AD with Lewy bodies than among participants who had AD without Lewy bodies. This finding suggests that the clinical phenotype of neuropathologic AD with Lewy bodies is probably similar to that of dementia with Lewy bodies. Our sample also had a higher percentage of men among the participants who had AD with Lewy bodies than among the participants who had AD without Lewy bodies. This finding is similar to that of other comparative studies that showed a predominance of male patients with a Lewy body variant of AD[18,19] or that, even though not statistically significant, still showed a slightly higher proportion of men than women with a Lewy body variant of AD.[8,14,16]

In our sample, the presence of at least 1 *APOE* ε4 allele was higher among participants who had AD with Lewy bodies than among participants who had AD without Lewy bodies; however, another study[23] indicated that at least 1 *APOE* ε4 allele was more frequently observed in AD without Lewy bodies than in AD with Lewy bodies. Yet other findings suggest that the frequency of at least 1 *APOE* ε4 allele among individuals with

neuropathologic AD is not different between those with and those without Lewy bodies.[18,40] *APOE* ε4 has been known to be a disease-modifying gene, associated with younger ages of AD onset.[42] Laboratory studies indicate that mismetabolism of the amyloid beta precursor protein (*APP*) gene may trigger Lewy body formation.[43–45] Occasionally, there is pathological discordance with a single gene defect; within a single family, some *APP* mutation carriers may develop Lewy body pathology and others may not, yet all may have AD pathology.[38,44]

Differences in NPI-Q total scores were only statistically significant in the model that did not adjust for *APOE* ε4. Participants who had AD with at least 1 *APOE* ε4 allele have a greater risk than noncarriers for developing neuropsychiatric symptoms, especially delusions and hallucinations.[46] Although *APOE* ε4 carriers have a high rate of cognitive decline and a more severe CDR than noncarriers,[47,48] there was no statistically significant difference in CDR-SB in our study. Among the other clinical measures examined, only the UPDRS motor score showed a statistically significant difference between the 2 groups; this result was similar in the subanalysis. The GDS in the subanalysis also showed statistically significant differences between the 2 groups in the adjusted analyses. Some other studies[22,49] have shown a higher number of depressive features in the Lewy body variant of AD and in dementia with Lewy bodies compared with AD.

When examining the individual NPI-Q items, we found that delusions, hallucinations, and aberrant motor disturbances were more severe in AD with Lewy bodies. This is consistent with studies[8,22] that indicate that patients with Lewy bodies had higher frequencies of hallucinations, delusions, depression, and confusion. Although other studies[17,18,20] have reported no differences.

The strengths of our study included the use of a large, well-characterized sample composed of data collected from AD centers across the United States. Nevertheless, our study had some limitations. Not all participants who originally enrolled had complete data for the GDS, Mini-Mental State Examination, and UDS Neuropsychological Battery. These participants with missing data tend to be those with more severe dementia. As a result, we analyzed these variables only among participants with a CDR (0, 0.5, or 1) to avoid bias. There may have been bias associated with using a convenience sample (eg, our participants were more highly educated than persons in the general US population).[50,51]

Conclusions

In conclusion, our findings suggest that Lewy body–related phenotypes within AD may be useful in distinguishing the presence of comorbid Lewy body pathology. Future research should apply the AD with Lew bodies phenotype found here to another sample with autopsy-proven AD in order to confirm that this phenotype does in fact predict the presence of Lewy bodies. The frequency of Lewy bodies in AD and the association of Lewy bodies with the *APOE ε4* allele suggest potential common mechanisms for AD and Lewy body pathologies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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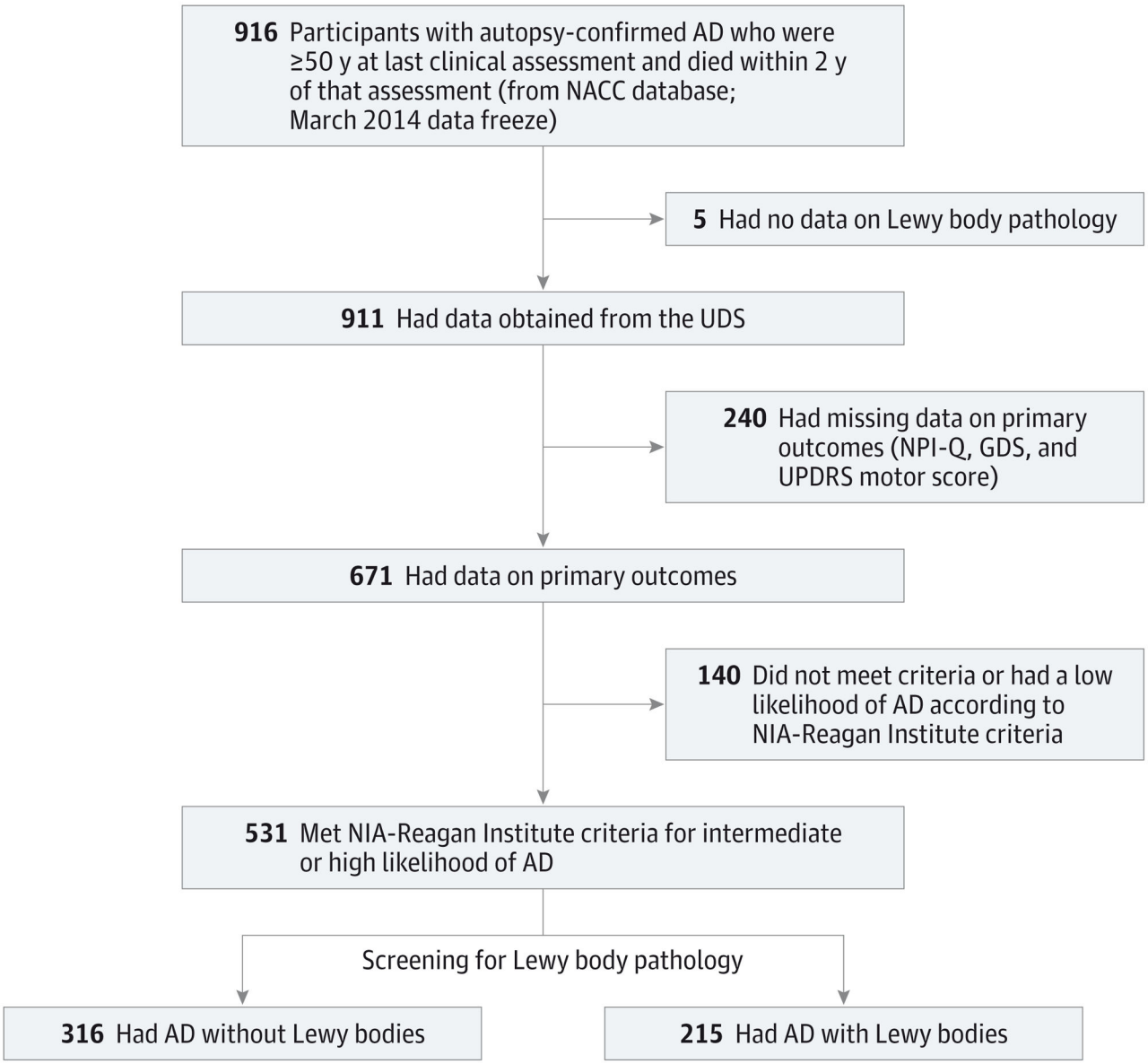

Figure.

Participant Flowchart Showing Selection Criteria and Classification According to the Presence or Absence of Lewy Body Pathology

Abbreviations: AD, Alzheimer disease; NACC, National Alzheimer Coordinating Center; UDS, Uniform Data Set; NPI-Q, Neuropsychiatric Inventory Questionnaire; GDS, Geriatric Depression Scale; UPDRS, Unified Parkinson Disease Rating Scale; NIA, National Institute on Aging.

Table 1

Demographic and Clinical Characteristics of Participants at Last Clinical Assessment

Characteristic	Participants Who Had AD			*P* Value
	Total (n = 531)	Without Lewy Bodies (n = 316)	With Lewy Bodies (n = 215)	
Age at death, mean (SD), y	79.2 (10.6)	80.2 (11.1)	77.9 (9.5)	.01
Female sex, No. (%)	237 (44.6)	156 (49.4)	81 (37.7)	.01
Education, mean (SD), y	15.2 (4.9)	15.4 (5.7)	14.9 (3.4)	.24
Disease duration,[a] mean (SD), y	8.0 (4.9)	7.9 (4.7)	8.0 (4.0)	.93
Age at onset,[a] mean (SD), y	71.3 (11.4)	72.2 (12.3)	70.0 (9.9)	.03
At least 1 *APOE* ε4 allele, No. (%)	217 (57.1)[b]	118 (37.3)	99 (46.1)	.03
Neuritic plaques, No. (%)				
None	2 (0.4)	2 (0.6)	0 (0)	.053
Sparse	32 (6.0)	24 (7.6)	8 (3.7)	
Moderate	118 (22.2)	61 (19.3)	57 (26.5)	
Frequent	379 (71.4)	229 (72.5)	150 (69.8)	
Diffuse plaques, No. (%)				
None	7 (1.3)	4 (1.3)	3 (1.4)	.30
Sparse	38 (7.2)	29 (9.2)	9 (4.2)	
Moderate	95 (17.9)	55 (17.4)	40 (18.6)	
Frequent	353 (66.5)	205 (64.9)	148 (68.8)	
Braak and Braak neurofibrillary tangle stage, No. (%)				
0–2	6 (1.1)	5 (1.6)	1 (0.5)	.21
3–4	134 (25.2)	73 (23.1)	61 (28.4)	
5–6	391 (73.6)	238 (75.3)	153 (71.2)	

Abbreviation: AD, Alzheimer disease.

[a] For 524 participants.

[b] For 380 participants.

Table 2

Clinical Scores After Adjusting for Age, Sex, Education, Frequency of Plaques and Tangles

	Participants Who Had AD Without Lewy Bodies		Participants Who Had AD With Lewy Bodies		
Test	**Mean (SE) Score**	**95% CI**	**Mean (SE) Score**	**95% CI**	***P* Value**
Total sample (n = 531)					
NPI-Q (n = 493)	5.49 (1.39)	2.76–8.23	6.59 (1.44)	3.75–9.42	.04
UPDRS motor score (n = 531)	0.54 (0.18)	0.19–0.88	0.81 (0.18)	0.45–1.17	<.001
CDR-SB (n = 531)	9.17 (1.21)	6.80–11.54	9.78 (1.25)	7.33–12.23	.16
Subanalyses of sample of participants with CDR 0, 0.5, or 1 (n = 160)					
GDS (n = 147)	5.12 (1.31)	2.54–7.71	6.91 (1.41)	4.13–9.69	<.001
NPI-Q (n = 149)	3.73 (1.87)	0.04–7.42	4.35 (2.00)	0.40–8.30	.42
MMSE (n = 150)	25.30 (2.38)	20.62–30.00	24.29 (2.54)	19.30–29.32	.27
UPDRS (n = 160)	0.26 (0.19)	−0.13 to 0.64	0.63 (0.21)	0.22–1.04	<.001
CDR-SB (n = 160)	3.25 (1.10)	1.08–5.43	3.82 (1.18)	1.48–6.16	.21
Logical memory (n = 148)	7.14 (1.80)	3.59–10.69	7.05 (1.94)	3.22–10.88	.91
Long-term memory units (n = 146)	5.87 (1.90)	2.11–9.64	6.50 (2.06)	2.44–10.57	.44
Boston Naming Test (n = 140)	22.55 (2.94)	16.74–28.37	22.17 (3.16)	15.92–28.42	.74
Animal fluency (n = 151)	13.78 (2.37)	9.09–18.50	13.20 (2.57)	8.16–18.32	.59

Abbreviations: AD, Alzheimer disease; CDR-SB, Clinical Dementia Rating sum of boxes; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; NPI-Q, Neuropsychiatric Inventory Questionnaire; UPDRS, Unified Parkinson Disease Rating Scale.

Table 3

Clinical Scores After Adjusting for Age, Sex, Education, Frequency of Plaques and Tangles, and *APOE* ε4 Status

	Participants Who Had AD Without Lewy Bodies		Participants Who Had AD With Lewy Bodies		
Test	**Mean (SE) Score**	**95% CI**	**Mean (SE) Score**	**95% CI**	***P* Value**
Total sample (n = 531)					
NPI-Q (n = 351)	5.95 (1.5)	3.0–8.9	6.78 (1.59)	3.65–9.90	.18
UPDRS motor score (n = 380)	0.42 (0.19)	0.04–0.80	0.60 (0.20)	0.20–0.99	.02
CDR-SB (n = 380)	8.47 (1.26)	6.00–10.94	8.38 (1.33)	5.77–10.99	.86
Subanalyses of sample of participants with CDR 0, 0.5, or 1 (n = 160)					
GDS (n = 147)	5.21 (1.50)	2.23–8.18	7.02 (1.64)	3.76–10.30	.02
NPI-Q (n = 149)	3.38 (1.71)	−0.01 to 6.77	3.09 (1.87)	−0.62 to 6.80	.73
MMSE (n = 150)	24.74 (2.49)	19.81–29.70	24.49 (2.70)	19.14–29.84	.82
UPDRS (n = 160)	0.33 (0.18)	−0.02 to 0.68	0.64 (0.19)	0.25–1.02	<.001
CDR-SB (n = 160)	3.62 (1.16)	1.32–5.93	3.62 (1.27)	1.10–6.15	>.99
Logical memory (n = 148)	6.72 (1.96)	2.82–10.61	7.53 (2.15)	3.25–11.81	.41
Long-term memory units (n = 146)	5.46 (2.11)	1.26–9.66	7.09 (2.33)	2.46–11.70	.13
Boston Naming Test (n = 140)	23.85 (2.87)	18.14–29.56	22.76 (3.16)	16.48–29.04	.42
Animal fluency (n = 151)	13.66 (2.53)	8.63–18.68	13.44 (2.79)	7.89–18.98	.86

Abbreviations: AD, Alzheimer disease; CDR-SB, Clinical Dementia Rating sum of boxes; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; NPI-Q, Neuropsychiatric Inventory Questionnaire; UPDRS, Unified Parkinson Disease Rating Scale.

Table 4

Likelihood of Having More Severe Symptoms on Each NPI-Q Item After Adjusting for Age, Sex, Education, and Frequency of Plaques and Tangles[a]

	None vs Any Symptoms		Mild vs Severe	
NPI-Q Item	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Delusion	2.286 (1.496–3.492)	<.001	2.133 (1.243–3.661)	.01
Hallucination	2.849 (1.791–4.534)	<.001	2.188 (1.196–4.004)	.01
Agitation	1.186 (0.803–1.753)	.39	0.852 (0.545–1.332)	.48
Depression	0.749 (0.510–1.100)	.14	1.033 (0.636–1.680)	.90
Anxiety	1.421 (0.964–2.094)	.08	1.309 (0.835–2.054)	.24
Euphoria	0.679 (0.322–1.431)	1.43	0.764 (0.242–2.410)	.65
Apathy	1.146 (0.782–1.680)	.49	1.370 (0.927–2.025)	.11
Disinhibition	1.267 (0.821–1.955)	.29	0.925 (0.512–1.672)	.80
Irritability	0.898 (0.610–1.323)	.59	1.157 (0.722–1.855)	.54
Aberrant motor behavior	1.56 (1.030–2.363)	.04	1.799 (1.121–2.887)	.02
Sleep behavior problems	1.291 (0.881–1.893)	.19	1.552 (1.011–2.383)	.045
Appetite and eating	0.966 (0.655–1.426)	.86	1.254 (0.794–1.980)	.33

Abbreviations: OR, odds ratio; NPI-Q, Neuropsychiatric Inventory Questionnaire.

[a]The severity of each symptom was evaluated in 2 ways: one looked at no symptoms vs any symptoms, and the other looked at mild (none to mild) vs severe (moderate to severe) symptoms.