Comparison of symptomatic and asymptomatic persons with Alzheimer disease neuropathology

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ABSTRACT

Objectives: We sought to identify demographic and clinical features that were associated with expression of symptoms in the presence of Alzheimer disease (AD) neuropathologic changes.

Methods: We studied 82 asymptomatic (Clinical Dementia Rating global score = 0) and 824 symptomatic subjects (Clinical Dementia Rating score >0) with low to high AD neuropathologic changes at autopsy who were assessed at 1 of 34 National Institute on Aging–funded Alzheimer's Disease Centers. All subjects underwent a clinical examination within 1 year of death. Logistic regression was used to evaluate factors associated with the odds of being asymptomatic vs symptomatic.

Results: Asymptomatic subjects tended to have low neurofibrillary tangle scores but a wide range of neuritic plaque frequencies. There were, however, a few asymptomatic subjects with very high tangle and neuritic plaque burden, as well as symptomatic subjects with few changes. In the multivariable model, asymptomatic subjects were older (odds ratio [OR] = 1.04; 95% confidence interval [CI] = 1.01–1.07), had lower clinical Hachinski Ischemic Score (OR = 0.82; 95% CI = 0.69–0.97), were less likely to have an *APOE* ε4 allele (OR = 0.36; 95% CI = 0.16–0.83), and had lower neurofibrillary tangle score (OR = 0.28; 95% CI = 0.17–0.45) compared with symptomatic subjects.

Conclusions: Dissociating clinical symptoms from pathologic findings better allows for investigation of preclinical AD. Our results suggest that although the severity of the pathology, particularly neurofibrillary tangles, has a large role in determining the extent of symptoms, other factors, including age, *APOE* status, and comorbidities such as cerebrovascular disease also explain differences in clinical presentation. *Neurology*® 2013;80:2121–2129

GLOSSARY

AA = Alzheimer's Association; **Aβ** = β-amyloid; **AD** = Alzheimer disease; **CAA** = cerebral amyloid angiopathy; **CDR** = Clinical Dementia Rating; **CERAD** = Consortium to Establish a Registry for Alzheimer's Disease; **CI** = confidence interval; **DAT** = dementia of the Alzheimer type; **DLB** = dementia with Lewy bodies; **MCI** = mild cognitive impairment; **NACC** = National Alzheimer's Coordinating Center; **NIA** = National Institute on Aging; **OR** = odds ratio; **UDS** = Uniform Data Set.

The National Institute on Aging (NIA) recently urged prioritization of research to better define the preclinical stage of Alzheimer disease (AD) and to determine factors that predict emergence of clinical impairment.[1] The reasons why persons with similar degrees of β-amyloid (Aβ) deposition and neurofibrillary tangles have different clinical expressions remain incompletely understood.[1–4]

The importance of this issue has been highlighted by recent changes in the neuropathologic definition of AD. Prior classification schemes such as CERAD (Consortium to Establish a Registry for Alzheimer's Disease)[5] and NIA–Reagan Institute[6] emphasized the presence of clinical symptoms along with AD neuropathologic features in order to assign a likelihood that the neuropathologic changes contributed to the clinical phenotype, thus discounting the presence of pathology in preclinical stages. The NIA–Alzheimer's Association (AA) guidelines for the neuropathologic assessment of AD were released in 2012.[7,8] These guidelines dissociate the clinical syndrome of dementia of the Alzheimer type (DAT) from the underlying AD

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neuropathologic change, which is an important step toward the acknowledgment that AD neuropathologic change precedes the onset of symptoms by several years.[1,7]

The new neuropathologic definitions give us an opportunity to better define and characterize persons with AD who have not yet developed DAT symptoms. We sought to use this opportunity to identify factors that were associated with clinical manifestations of mild cognitive impairment (MCI) due to AD and overt AD dementia in a large database of persons with autopsy findings consistent with AD.

METHODS

Study sample. Data for this analysis came from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) and Neuropathology Data Set, which had been collected at 34 current and past Alzheimer's Disease Centers between September 2005 and September 2012. The UDS contains clinical and demographic information on subjects with normal cognition, MCI, AD dementia, and other etiologies. Detailed descriptions of UDS data have been published previously.[9] UDS subjects may also consent to autopsy. For those who have an autopsy, neuropathologic features are recorded and submitted to the NACC.

The NIA-AA criteria for neuropathologic AD introduce an "ABC score," which served as the basis for defining neuropathologic AD in this cohort.[7] Braak stage (B score) for neurofibrillary tangles[10] and CERAD neuritic plaque frequency[5] (C score) were recorded in the Neuropathology Data Set. However, a Thal phase[11] for Aβ plaques (A score) is not currently included. Thus, to include the most frequent plaque type, we included "diffuse plaque," which is most likely an early form of Aβ plaque formation and is defined as plaques with no apparent dystrophic neurites, as detected by silver impregnation methods, ubiquitin, or tau immunohistochemistry. All types of Aβ plaques, including diffuse plaques, are also readily identified using Aβ immunohistochemistry.

Using the variable descriptions in the database, subjects with "sparse," "moderate," or "frequent" diffuse plaques were considered to have a Thal Aβ plaque phase of 1 or higher and met inclusion criteria for this study. Likewise, subjects with sparse, moderate, or frequent neuritic plaques had a neuritic plaque C score of 1 or higher and also met study inclusion criteria. Limiting the sample to subjects with either diffuse or neuritic plaques approximates to the inclusion of all subjects meeting NIA-AA criteria for low to high AD neuropathologic change. Thus, the study sample included only those subjects with amyloid plaques, excluding those without, regardless of clinical diagnosis.

Participants with incidental or amygdala-only Lewy bodies were included. However, subjects with a primary neuropathologic diagnosis of dementia with Lewy bodies (DLB) were excluded because these people were judged to have clinical symptoms primarily due to non-AD neurodegeneration and would confound the analysis.

Clinical symptoms were categorized using the Clinical Dementia Rating (CDR) global score.[12] The CDR is an instrument that grades subjects' cognitive and functional abilities. The clinician, incorporating input from an informant who knows the subject well, evaluates the subject's performance in 6 domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Impairment in each of the 6 domains is evaluated by the clinician as none (0), questionable or very mild (0.5), mild (1), moderate (2), and severe (3). An algorithm combines the scores from the individual items to give a global score.[13] Subjects with a CDR global score of 0 at their last clinical assessment were considered to have normal cognition, and thus comprised the "asymptomatic group." Subjects with a score of 0.5 or higher were considered to exhibit clinical characteristics consistent with MCI due to AD or AD dementia and comprised the "symptomatic group." To best correlate clinical symptoms and neuropathologic features, the analytic sample was limited to subjects who died within 1 year of the last UDS clinical assessment.

Several characteristics were considered as possible sources of differences among asymptomatic and symptomatic subjects. Demographics included subject age (at last clinical assessment), sex, race, and duration of education. Clinical characteristics included history of depression, family history of dementia, *APOE* ε4 allele status, and the modified Hachinski Ischemic Score.[14] Finally, the neuropathologic features assessed included the NIA-AA neurofibrillary tangles (B score) and neuritic plaques (C score), as well as presence of vascular pathology, presence of one or more microinfarcts, and the presence of Lewy bodies.

Standard protocol approvals, registrations, and patient consents. Written informed consent was obtained from all participants. Research using the NACC database was approved by the University of Washington Institutional Review Board.

Statistical analysis. The relationship between each characteristic and cognitive status (asymptomatic vs symptomatic) was first evaluated individually using logistic regression with generalized estimating equations, a popular method used to account for the clustering of subjects within a unit, which in this case was the Alzheimer's Disease Center. The regression models were run with an independent correlation structure and robust standard errors.

Characteristics found to be significant at the 0.10 α level in the bivariate analyses were included in a full multivariable model. To address the possible effects of missing data, additional multivariable models were run excluding *APOE* status and excluding both *APOE* and Hachinski Ischemic Score. All analyses were performed using R 2.14.2 "geeglm" package.[15]

RESULTS

Between September 2005 and September 2012, 1,775 UDS subjects had died and undergone autopsy. Of those, 1,436 had at least some diffuse or neuritic plaques (339 excluded because of lack of amyloid pathology). After excluding subjects with >1 year between death and last UDS visit, the analytic sample came to include 906 subjects. Of these, 82 (9%) were asymptomatic and 824 (91%) were symptomatic.

Characteristics of the asymptomatic and symptomatic subjects and the sample as a whole are displayed in table 1. Most subjects were white and had some college education. Mean age at last clinical assessment was higher for asymptomatic (86.2 ± 8.2 [SD] years) than symptomatic subjects (81.3 ± 11.2 years), and asymptomatic subjects had a lower frequency of carrying at least one *APOE* ε4 allele.

The figure displays the distribution of B and C scores among the symptomatic and asymptomatic participants. It should be noted that the NIA-AA

Table 1 Frequency (%) of demographic characteristics

Characteristic	All (n = 906)	Asymptomatic (n = 82)	Symptomatic (n = 824)
Age at last visit, y			
<60	38 (4.2)	0 (0.0)	38 (4.6)
60–69	103 (11.4)	3 (3.7)	100 (12.1)
70–79	191 (21.1)	15 (18.3)	176 (21.4)
80–89	372 (41.1)	32 (39)	340 (41.3)
90+	202 (22.3)	32 (39)	170 (20.6)
Education: at least some college[a]	625 (69.8)	65 (79.3)	560 (68.9)
Race[a]			
White	854 (94.7)	81 (98.8)	773 (94.3)
Black	28 (3.1)	0 (0.0)	28 (3.4)
American Indian, Alaskan	1 (0.1)	0 (0.0)	1 (0.1)
Asian	9 (1.0)	0 (0.0)	9 (1.1)
Multiracial	10 (1.1)	1 (1.2)	9 (1.1)
Sex: female	411 (45.4)	46 (56.1)	365 (44.3)
APOE: at least one ε4 allele[a]	366 (48.7)	12 (16.2)	354 (52.2)

[a] Eleven subjects with missing data on education; 4 subjects with missing data on race; 154 subjects with missing data on *APOE* ε4 frequency.

staging scheme compresses 7 Braak stages into 4 "B" stages (0–3), which improves interrater reliability.[7] The majority of symptomatic participants were at the high end of B and C scores, with B score of 3 (Braak stage V–VI) and frequent CERAD neuritic plaques. The asymptomatic subjects tended to have B score of 1 to 2 (Braak stage I–IV) but a wide range of neuritic plaque frequencies. There were, however, a few asymptomatic subjects with high B and C scores, as well as symptomatic subjects with low B and C scores.

The frequencies of several neuropathologic features are described in table 2. As expected, having both the highest B score (3/3) and highest C score (3/3) was much more common in symptomatic than asymptomatic participants (49.5% vs 2.4%). A similar pattern was shown for diffuse plaques where symptomatic participants had a higher proportion of frequent diffuse plaques compared with asymptomatic subjects. There was minimal difference in the frequency of various cerebrovascular pathologies.

Several demographic and clinical characteristics were significantly associated with cognitive status in the bivariate analyses. The odds of being asymptomatic were increased for subjects who were older, had more education, had lower Hachinski Ischemic Score, did not have a recent history of depression, did not have an *APOE* ε4 allele, had lower B and C scores, and did not have Lewy body pathology (table 3). Race could not be modeled because of extremely small cell frequencies; all but one of the nonwhite subjects were symptomatic.

A full model (table 4) was fit using all of the predictors found to be significant in the bivariate models. In this model, the odds of being asymptomatic were significantly increased with older age, lower Hachinski Ischemic Score, no *APOE* ε4 allele, and lower B score. The association with age was such that the odds of being asymptomatic for a person aged 75 years was 75% higher than for a person aged 65. The effect of B score was quite marked; the odds of being asymptomatic more than tripled with each one stage decrease in B (neurofibrillary tangle) score.

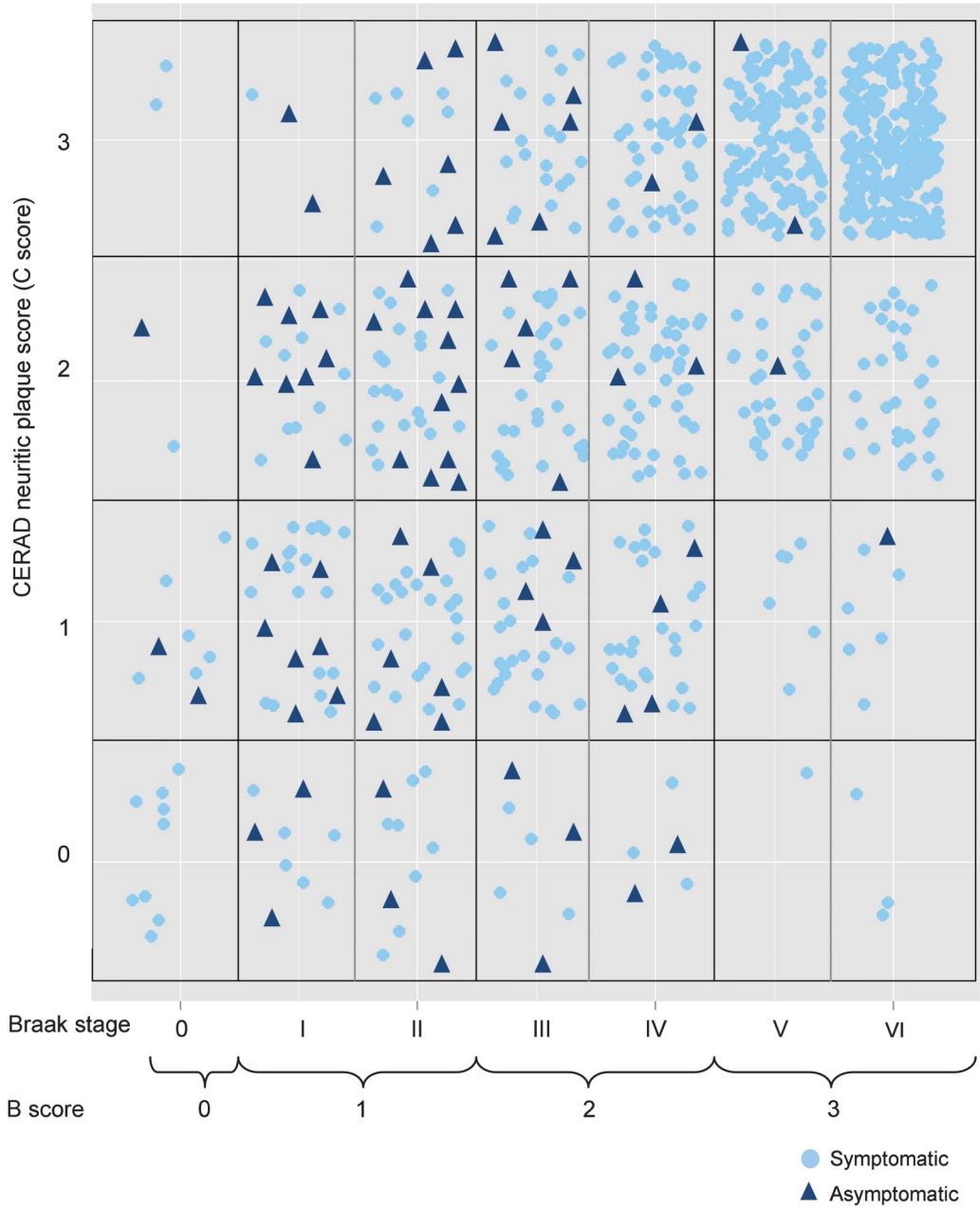
Because performing logistic regression required a complete case sample and much of the missing data were on *APOE* ε4 allele status and Hachinski Ischemic Score, the multivariable models were repeated excluding *APOE* and excluding both *APOE* and Hachinski Ischemic Score. Results, shown in table 4, were nearly identical to those in the full model, but depression became significant. In both models, the odds of being asymptomatic approximately doubled when the subject did not have a recent history of depression.

DISCUSSION We sought to identify characteristics that were associated with symptoms among persons with underlying neuropathologic features of AD, as defined by the 2012 NIA-AA criteria. Our analysis revealed significant associations with several antemortem characteristics: compared with symptomatic subjects, asymptomatic subjects were older and had lower frequency of 1 or 2 *APOE* ε4 alleles, no history of depression, and fewer conditions consistent with vascular dementia.

There was a strong role for pathology in determining extent of clinical presentation. In bivariate analyses, neurofibrillary tangle (B) scores, neuritic plaque (C) scores, Lewy bodies, and amyloid angiopathy were all associated with increased odds of being symptomatic. However, in the multivariable model, only neurofibrillary tangle (B) score was associated with symptoms. The odds of being symptomatic increased 3-fold with every 1-point increase in neurofibrillary tangle (B) score. Nonetheless, the effect was incomplete as several asymptomatic subjects had pronounced pathology. Although highly correlated with being asymptomatic on bivariate analysis, neuritic plaque frequency became insignificant in the full model. In previous clinicopathologic and imaging studies, neurofibrillary tangles were similarly found to be more closely associated with cognitive decline than neuritic plaques.[16–21]

AD often occurs along with other neurodegenerative processes. A recent autopsy study of the oldest old found an association between presence of infarct pathology and symptoms.[22] However, presence of microinfarcts was not associated with symptoms in our study. This might be explained by differences in the study samples, especially in terms of age,[17] or

Figure Distribution of B and C scores among asymptomatic and symptomatic subjects with neuropathologic Alzheimer disease



CERAD = Consortium to Establish a Registry for Alzheimer's Disease.

differences in pathologic interpretation of lesions.[5] Likewise, cerebral amyloid angiopathy (CAA) has been variably reported to be associated with increased risk of cognitive decline.[23,24] The current study showed no independent effect of CAA once the extent of AD neuropathologic change was adjusted for, as shown previously.[25]

Interestingly, the presence of clinical vascular features on Hachinski Ischemic Score was significantly associated with symptoms whereas cerebrovascular pathology at autopsy was not. This difference could be attributable to the fact that vascular pathology was recorded as present vs absent. Within the category "present," there may have been a range of severities and the simplification of absent vs present may have obscured a true relationship. Likewise, the Hachinski Ischemic Score captures features, such as emotional incontinence and somatic complaints, that may not necessarily represent a stroke on pathologic examination.

Depression was also associated with symptoms. Several studies have shown a relationship between depressive symptoms and clinical expression of AD.[26–29] There is also evidence that depression could be associated with the pathology of the disease itself.[30]

Table 2 Frequency (%) of neuropathologic characteristics

Characteristic	Asymptomatic (n = 82)	Symptomatic (n = 824)
Neurofibrillary tangle B score and neuritic plaque C score frequency[a]		
Braak III or IV, moderate neuritic plaques	8 (9.8)	81 (9.8)
Braak III or IV, frequent neuritic plaques	8 (9.8)	73 (8.9)
Braak V or VI, moderate neuritic plaques	1 (1.2)	71 (8.6)
Braak V or VI, frequent neuritic plaques	2 (2.4)	408 (49.5)
Braak <III and/or none–sparse neuritic plaques	63 (76.8)	187 (22.7)
Diffuse plaque frequency[b]		
None	2 (2.4)	18 (1.9)
Sparse	20 (24.4)	131 (14.0)
Moderate	21 (25.6)	172 (18.4)
Frequent	23 (28.1)	534 (57.1)
Ischemic, hemorrhagic, or vascular pathology[c]		
Not present	14 (17.1)	136 (16.5)
Present	68 (82.9)	687 (83.4)
Large infarct[d]		
Not present	74 (90.2)	741 (89.9)
Present	8 (9.8)	81 (9.8)
Microinfarcts[e]		
Not present	65 (79.3)	658 (79.9)
Present	17 (20.7)	165 (20.0)
Amyloid angiopathy[f]		
Not present	45 (54.9)	268 (32.5)
Mild	24 (29.3)	242 (29.4)
Moderate	8 (9.8)	178 (21.6)
Severe	4 (4.9)	112 (13.6)
Lewy body pathology[g]		
Not present	75 (91.5)	591 (71.7)
Present	7 (8.5)	228 (27.7)

[a] Four symptomatic subjects (0.4%) were missing Braak stage or Consortium to Establish a Registry for Alzheimer's Disease neuritic plaque score.
[b] Sixteen asymptomatic subjects (19.5%) and 81 symptomatic subjects (8.7%) were not assessed for diffuse plaques.
[c] One symptomatic subject (0.1%) was not assessed for ischemic, hemorrhagic, or vascular pathology. "Ischemic, hemorrhagic, or vascular pathology" includes multiple subcategories. Three common subcategories are shown. Persons with ischemic, hemorrhagic, or vascular pathology may have one or more of these subcategory conditions.
[d] Two symptomatic subjects (0.2%) were not assessed for large infarcts.
[e] One symptomatic subject (0.1%) was not assessed for microinfarcts.
[f] One asymptomatic subject (1.2%) and 24 symptomatic subjects (2.9%) were not assessed for amyloid angiopathy.
[g] Five symptomatic subjects (0.6%) were not assessed for Lewy body pathology.

However, it may not be possible, in the data available for the current study, to separate preexisting depression from symptoms of AD. We do not have data on lifetime experience with depression before development of symptoms (or for comparable time periods for asymptomatic persons).

The role of *APOE* was also interesting, in that it was strongly associated with symptoms even after adjusting for extent of underlying neuropathology. The residual effect of *APOE* after adjustment for neurofibrillary tangle (B) score and neuritic plaque (C) score may be attributable to the inability to adjust for Aβ (Thal phase) score in our data, or there may be another effect for which we are not able to account.[31] For example, the presence of an *APOE* ε4 allele may be associated with pathology not captured here, such as greater levels of Aβ oligomers, which in turn have been linked to dementia symptoms after adjustment for amyloid plaque pathology.[32]

The association of older age with being asymptomatic seems counterintuitive, given increased AD incidence with increased age. This finding may be

Table 3 Odds of asymptomatic AD at last clinical assessment by characteristic: Logistic regression run separately for each characteristic

Predictor	No.	OR	95% CI[a]	*p* Value
Age at death	906	1.05	(1.02–1.07)	<0.0001
Education (at least some college vs no college)	895	1.73	(0.98–3.06)	0.06
Depression (present within the past 2 y vs absent)	889	0.37	(0.21–0.63)	<0.0001
Hachinski Ischemic Score	714	0.85	(0.73–0.98)	0.03
Family history (present vs absent)	885	0.71	(0.46–1.12)	0.14
Sex (F vs M)	906	1.61	(1.03–2.50)	0.04
APOE (at least one ε4 vs no ε4)	752	0.18	(0.09–0.33)	<0.0001
B score (continuous)	902	0.27	(0.21–0.35)	<0.0001
C score (continuous)	904	0.48	(0.39–0.59)	<0.0001
Vascular pathology (present vs not present)	823	0.96	(0.51–1.81)	0.90
Multiple microinfarcts (present vs not present)	905	1.04	(0.60–1.82)	0.88
Lewy body pathology (present vs not present)	901	0.24	(0.11–0.52)	0.0003
Amyloid angiopathy (present vs not present)	881	0.40	(0.25–0.65)	0.0002

Abbreviations: AD = Alzheimer disease; CI = confidence interval; OR = odds ratio.
[a] Calculated using robust standard errors.

related to a somewhat increased severity for early-onset AD. It might also be attributable to a healthy survivor effect, with asymptomatic persons having a longer life expectancy compared with the symptomatic. Finally, this finding might be attributable to selection bias regarding those who enroll as normal controls.

On bivariate analysis, no college education and male sex were borderline significant predictors of symptoms. Although these variables were not significant in the multivariable models, the effect sizes were fairly large, suggesting that there might be an association that our study was underpowered to detect. Several previous studies have shown evidence of protective effect of increased cognitive reserve in AD[2,33–35] and differences in presentation by sex, although not consistently.[36–39]

Before drawing conclusions from the data, the limitations of the study must be addressed. First, retrospectively fitting preexisting UDS data to the 2012 NIA-AA criteria has shortcomings. We were not able to derive an Aβ plaque (Thal phase) score. Using the surrogate of any diffuse plaques was a reasonable proxy for Thal phase ≥1, and thus a reasonable inclusion criterion. Nonetheless, it might have led to underassessment of cases that would have, in reality, met NIA-AA criteria. For example, some of the older autopsies used silver staining methods, thioflavin T, or Congo red, less-sensitive methods for detecting diffuse Aβ plaques than immunohistochemistry. Unfortunately, the staining methods are not available in the NACC neuropathology database, so we were

Table 4 Multivariable logistic regression models for odds of asymptomatic AD

	Full model (n = 559)		Without *APOE* (n = 665)		Without *APOE* and HIS (n = 845)	
Predictor	OR	95% CI[a]	OR	95% CI[a]	OR	95% CI[a]
Age at last visit	1.04	(1.01–1.07)	1.05	(1.02–1.08)	1.05	(1.02–1.08)
Education (at least some college vs no college)	1.46	(0.71–2.99)	1.52	(0.76–3.07)	1.82	(0.91–3.63)
Depression (present within the past 2 y vs absent)	0.65	(0.33–1.26)	0.51	(0.26–0.99)	0.43	(0.23–0.80)
Sex (F vs M)	1.21	(0.66–2.21)	1.47	(0.82–2.63)	1.39	(0.81–2.36)
HIS	0.82	(0.69–0.97)	0.81	(0.69–0.96)	—	—
APOE (ε4 vs no ε4)	0.36	(0.16–0.83)	—	—	—	—
B score (continuous)	0.28	(0.17–0.45)	0.26	(0.16–0.42)	0.23	(0.15–0.36)
C score (continuous)	0.92	(0.62–1.36)	0.95	(0.64–1.42)	1.04	(0.72–1.51)
Lewy body pathology (present vs not present)	0.68	(0.24–1.97)	0.67	(0.27–1.65)	0.56	(0.24–1.31)
Amyloid angiopathy (present vs not present)	0.69	(0.37–1.28)	0.57	(0.32–1.04)	0.66	(0.38–1.15)

Abbreviations: AD = Alzheimer disease; CI = confidence interval; HIS: Hachinski Ischemic Score; OR = odds ratio.
[a] Calculated using robust standard errors.

unable to account for this protocol variation. Consequently, variation in staining methods between centers could have led to the exclusion of some subjects with AD neuropathologic (Aβ) changes not detected by silver and other stains. Moreover, based on prior AD classification schemes, there was likely a tendency to not perform special stains for diffuse plaques in asymptomatic subjects. This is indicated in our data by the fact that 19.5% of asymptomatic subjects did not have diffuse plaques assessed, compared with 8.7% of symptomatic subjects (table 2). However, the additional inclusion of subjects based on neuritic plaque (C) score ≥1 likely included most subjects with AD neuropathology who would have been misclassified because of lack of assessment of diffuse plaques or use of silver or other stains alone. Thus, we believe that with our inclusion criteria, most of the subjects in the NACC neuropathology database who had AD neuropathology were captured and that there was very little chance of misclassification of subjects without AD neuropathologic changes. Still, we were not able to stratify by Aβ plaque (A) Thal phase in the multivariable analysis, subsequently underassessing extent of Aβ deposition.

Second, there were considerable numbers of missing values for Hachinski Ischemic Score and *APOE*, which decreased the sample size. We performed sensitivity analyses excluding these variables, thus increasing the sample size. The findings from all 3 analyses were similar, supporting the likelihood that these are valid and robust findings.

Third, there are possibly biases in the nature of UDS subjects, especially among those who agree to autopsy, which limit our ability to draw inferences. For example, more highly educated subjects are more likely to enroll as normal controls, limiting our ability to draw inferences about the effect of education and cognitive reserve. In addition, there was only one nonwhite subject in the control group, prohibiting us from making inferences about the effect of race.

Fourth, there may have been confounding based on presence of Lewy bodies. Although Lewy body pathology is a common comorbidity in AD, to exclude the confounding influence of a second neurodegenerative disease, we excluded cases with a diagnosis of DLB. However, cases with incidental Lewy bodies were included. It is possible that some of these cases may now be recognized as a distinct entity called AD with amygdala Lewy bodies.[40]

Fifth, persons were classified as symptomatic vs asymptomatic. Dichotomization of an inherently continuous measure such as cognition is not ideal. However, we believe that use of the CDR as an outcome measure provides an objective and clinically relevant differentiation of people with and without recognizable cognitive symptoms.

Despite these limitations, these data allow us to draw reasonable conclusions regarding factors associated with clinical presentation of DAT in persons with AD neuropathology. There is obviously a very strong effect of neuropathology, with a 3-times-higher risk of becoming symptomatic for each point increase in neurofibrillary tangle (B) score. However, the effect is incomplete, with several asymptomatic subjects having very pronounced pathology. With persons with primary diagnosis of DLB excluded, there is no additional effect of the presence of Lewy bodies on likelihood of symptoms. There is no additional, independent effect of the presence of CAA after adjusting for extent of underlying AD neuropathology. Other factors that had a role in expression of symptoms included age and depression. The role of *APOE* is interesting, in that it was strongly associated even after adjusting for extent of underlying AD neuropathology. Future studies could add to this work by including a more diverse subject sample, especially for asymptomatic controls, and utilizing serial images to better assess the extent of cerebrovascular pathology at the time of cognitive assessment.

AUTHOR CONTRIBUTIONS

S.E. Monsell contributed to the study concept and design, statistical analysis, interpretation of data, and drafting the manuscript. C. Mock contributed to the study concept and design, interpretation of data, and drafting the manuscript. C.M. Roe, N. Ghoshal, and J.C. Morris contributed to the study concept and design and editing of the manuscript for content. N.J. Cairns contributed to the study concept and design, interpretation of data, and editing of the manuscript for content. W. Kukull contributed to the study concept and design and editing of the manuscript for content.

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DISCLOSURE

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