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FEATURED ARTICLE

Neuropathological lesions and their contribution to dementia and cognitive impairment in a heterogeneous clinical population

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Abstract

Introduction: Alzheimer disease (AD) and related dementias are characterized by damage caused by neuropathological lesions in the brain. These include AD lesions (plaques and tangles) and non-AD lesions such as vascular injury or Lewy bodies. We report here an assessment of lesion association to dementia in a large clinic-based population.

Methods: We identified 5272 individuals with neuropathological data from the National Alzheimer's Coordinating Center. Individual lesions, as well as a neuropathological composite score (NPCS) were tested for association with dementia, and both functional and neurocognitive impairment using regression models.

Results: Most individuals exhibited mixed pathologies, especially AD lesions in combination with non-AD lesions. All lesion types were associated with one or more clinical outcomes; most even while controlling for AD pathology. The NPCS was also associated with clinical outcomes.

Discussion: These data suggest mixed-type pathologies are extremely common in a clinic-based population and may contribute to dementia and cognitive impairment.

KEYWORDS
Alzheimer disease, amyloid angiopathy, cognitive decline, dementia, hippocampal sclerosis, Lewy bodies, neuritic plaques, neurofibrillary, neuropathology, tangles, vascular dementia

1 | INTRODUCTION

Alzheimer disease (AD) is the most common cause of dementia, accounting for 60% to 80% of all dementia cases. AD and related dementias (ADRDs) affect >50 million individuals worldwide.[1] Upon autopsy, most AD dementia patients show the hallmark brain lesions of AD: neurofibrillary tangles[2–4] and amyloid plaques, including both diffuse plaques[4] and neuritic plaques.[3,5,6] Often, patients display other non-AD neuropathological lesions such as Lewy bodies,[7,8] cerebral amyloid angiopathy,[9–13] arteriolosclerosis,[11,14,15] hippocampal sclerosis,[15,16] and vascular brain injury.[9,12,17] These "related dementias" contribute to cognitive impairment and have been reported to increase risk for dementia when comorbid with AD.[18–23]

Neuropathological lesions are often considered as distinct disease processes, occurring in isolation. However, there is increasing evidence that dementia of mixed pathologies is more common than previously recognized. Community-based studies, such as the Honolulu-Asian Aging Study,[24] 90+ study,[18] the Adult Changes in Thought (ACT) study,[25] and the Religious Orders Study (ROS) and Rush Memory and Aging Project (MAP)[22,26] have highlighted the continuum of dementia by investigating the effects and commonality of mixed neuropathologies in dementia. These studies show an estimated 50% to 75% of dementia cases have multiple lesion types present at death.[18,19,21–23,25] These studies show some inconsistencies, possibly from the small sample size for many of the studies, or due to differences in study design (Table S1 in the Supporting Information).

One key study showed that in addition to AD lesions, neocortical Lewy bodies, hippocampal sclerosis, low brain weight, and microinfarcts were associated with cognitive impairment in analyses of two population-based autopsy cohorts.[24] The first population was a predominantly non-Hispanic white and female group with 334 participants from the 1997 Nun Study[17]; the second population was a predominantly Japanese American and male group with 774 participants from the 2002 Honolulu-Asia Aging Study.[27] Here, we tested the findings of these earlier studies using a clinic-based population from the NIH-funded Alzheimer Disease Research Centers (ADRCs), together with data from the National Alzheimer's Coordinating Center (NACC).[28–35] Compared to previous studies, our sample size is larger, and more heterogeneous, composed of both male and female participants (46.30% female), and includes some racial/ethnic diversity (Table S1). In addition, our sample is more geographically representative as it includes participants from the 28 nationwide ADRCs, spanning 17 states. Further, we consider additional neuropathologic lesions that have not been studied in previous works.

2 | METHODS

2.1 | Study participants

Participants were enrolled and assessed clinically through the nationwide ADRC program. The ADRCs consist of NIH-funded memory and aging clinics throughout the United States that provide diagnosis and medical services to dementia patients and their families, as well as

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RESEARCH IN CONTEXT

1. Systematic review: The authors began with a literature review. The contribution of lesion comorbidity and mixed pathology has been highlighted in previous studies, but predominantly in community cohorts. We explore similar associations in a larger and more heterogeneous clinic-based cohort.

2. Interpretation: Mixed pathologies in AD dementia are common and are associated with more severe functional and neurocognitive impairment in a large clinic-based cohort of 5272 individuals.

3. Future directions: With these results, we are interested in (1) investigating the rate of progression and cognitive decline as a function of neuropathologic lesion combinations, (2) integrating genetic information to identify genetic variants associated with neuropathologic lesions, and (3) exploring determinants of AD resilience to cognitive decline, resistance to neuropathology, and other dementias.

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participate in dementia and aging-related research. Participants are enrolled and assessed by individuals sites under a consistent protocol and data are then transferred to the NACC. Data for this study were derived from the Uniform Data Set (UDS) of the NACC, together with the NACC neuropathology form (accessed July 2019).[30] As such, this study consists of individuals who presented at memory and aging clinics, who consented to inclusion in research, and later went on to participate in an autopsy program. While the ADRCs are not an intentionally operated for the support of longitudinal cohort studies, participants often visit the clinic multiple times over many years, leading to multiple clinical assessments for most participants.

The UDS consists of participant clinical, medical, and demographic data. The neuropathology form includes detailed information on neuropathological features from brain autopsy reports.[31] In this analysis, we consider all participants with both UDS and neuropathology form (N = 5272). For participants with more than one clinical assessment we only consider the clinical data from their final visit (eg, last assessment prior to death). All participants (or representatives) provided written informed consent; all protocols and assessments were performed with approval by the appropriate institutional internal review boards.

2.2 | Neuropathology phenotypes and variable coding

2.2.1 | Primary neuropathology phenotypes

Lesion types, variables used, and coding are described in detail in Supplemental Text 1. Briefly, lesion types studied include neurofibrillary tangles, neuritic plaques, diffuse plaques, Lewy bodies, cerebral

amyloid angiopathy, arteriolosclerosis, hippocampal sclerosis, and vascular brain injury (as measured by infarcts/lacunes, hemorrhages, microinfarcts, and white matter rarefaction).[3] Specific NACC variables and code mappings used are noted in Supplemental Text 1. Lesions were scored into three categories of increasing severity and numerical value ranging from none or mild (0) to moderate (0.4) to severe (1).[24] Because of differences in form version coding in the UDS, hippocampal sclerosis is represented as a binary variable of absent or present.

2.2.2 | Vascular brain injury

For vascular brain injury the relevant variables were coded into binary variables and then summed up (ranging from 0 to 4). Then, we assigned those with a sum of 0 as none/mild (0), 1 as moderate (0.4), and 2 to 4 as severe (1) to better align with the other variable coding).

2.2.3 | Neuropathology composite score

A neuropathology composite score (NPCS) was created by summing the 8 lesion scores noted above; thus, ranging from 0 to 8.

2.2.4 | Other variables and codings

We also considered brain weight on autopsy (NACC variable NPW-BRWT) as in previous studies[24] (Supplemental Text 2). Analyses are described in the Supplementary Material but were excluded here due to high levels of missing data. Individuals were broadly categorized by degree of AD neuropathology according to NIA-AA Alzheimer's disease neuropathologic change (ADNC), when available (NACC variable NPADNC). When unavailable we used the neurofibrillary tangles, neuritic plaques, and diffuse plaques to categorize individuals using NIA-REAGAN/CERAD criteria.

Those lacking all AD lesions were "No AD Pathology"; those with any combination of AD lesions were "Any AD Pathology"; those with either a low ADNC or AD pathology not meeting NIA-REAGAN criteria were further classified as "Low AD Pathology"; those with intermediate/high ADNC or meeting NIA-REAGAN criteria were classified as "Intermediate or high AD Pathology."

2.3 | Clinical outcomes

Dementia was derived from the NACC variable NACCUDSD, an outcome assessed entirely from clinical data. Neurocognitive impairment was measured by the Mini-Mental State Examination (MMSE)[35,36] (NACCMMSE variable), which ranges from 0 to 30 with lower scores indicating poorer cognitive function. Functional impairment was measured by the Clinical Dementia Rating (CDR®) Dementia Staging Instrument[37] sum of boxes (CDR-SOB) as measured by the NACC variable CDRSUM, which ranges from 0 to 18, with higher scores indicating poorer functioning.

TABLE 1 Characteristics of the participants

Demographics				
Total number of participants, N				5272
Sex, % F				46.30%
Hispanic, %				3.77%
African American, %				3.68%
Age at final exam, mean (SD)				78.52 (±11.14)
Clinical characteristics				
Number of visits, mean (SD)				3.28 (±2.31)
Years from final exam to death, mean (SD)				2.65 (±2.07)
Individuals with dementia, N (%)				4106 (78%)
MMSE score, mean (SD)				17.52 (±9.14)
CDR-SOB score, mean (SD)				8.88 (±6.18)
Neuropathology characteristics	**None/ Mild (%)**	**Moderate (%)**	**Severe (%)**	**Missing (%)**
Neurofibrillary tangles	24.8	22.3	51.5	1.4
Neuritic plaques	36.1	18.7	45.1	0.1
Diffuse plaques	25.9	15.4	51.5	7.2
Lewy bodies	65.5	3.9	26.4	4.2
Cerebral amyloid angiopathy	67.4	19.4	11.0	2.2
Arteriolosclerosis	50.2	28.1	12.4	9.2
Hippocampal sclerosis	84.5	–	11.7	3.8
Vascular brain injury	41.1	32.8	19.9	6.2
NPCS, mean (SD)	2.98 (±1.70)			

Abbreviations: CDR-SOB, Clinical Dementia Rating Sum of Boxes; MMSE, Mini-Mental State Examination; NPCS, Neuropathology Composite Score; SD, standard deviation.

2.4 | Exclusion criteria

Individuals were excluded if they had no UDS form completed, did not have the NACC neuropathology form (must have version 9 or 10), were missing more than three neuropathology variables of interest, and/or were <50 years old by their last clinic visit.

2.5 | Assessing missingness

Overall variable-level missingness is low (see Table 1). We used the MICE package version 3.11 in R to impute the indices of the missing NP variables.[38] The outcome variables (NACCUDSD, NACCMMSE, and CDRSUM) were not included in the prediction matrix of the imputation scheme. Clinical outcome variables were not imputed.

2.6 | Atypical neuropathological findings

Cognitive resilience was defined as those with a high burden of neuropathological lesions but who maintained cognitive function. High

lesion burden was defined as the upper quartile of the NPCS among the cognitively intact (no dementia, mild cognitive impairment [MCI], or other cognitive impairment per the NACCUDSD variable, with minimal impairment per the CDR-SOB and, if available, MMSE). Minimal cognitive impairment was defined as an MMSE of 24 or higher per previous reports[39,40] and a CDR-SOB of 4 or less per previous reports.[41]. Neuropathological resistance was defined as those with no or minimal pathological burden (lower quartile of NPCS) despite advanced age (upper quartile of age). Other dementias were defined as dementia (per NACCUDSD) with no or minimal neuropathological lesions (median or lower NPCS among the cognitively intact).

2.7 | Statistical analyses

Statistical analyses were conducted in R version 4.0.2.[42] Spearman correlation and the corrgram R package were used to assess correlations.[43] Primary outcome variables were dementia, functional impairment via CDR-SOB, and cognitive impairment via MMSE.

2.7.1 | Analysis of dementia outcome

Logistic regression was used to model the association between dementia and the neuropathologic lesions. For this analysis we only included individuals with a status of either dementia or normal cognition; MCI or other mild impairment were excluded (NACCUDSD). In total, 4106 participants (87%) had dementia and 612 (13%) had normal cognition (Total N = 4718).

2.7.2 | Analysis of neurocognitive and functional impairment outcomes

Linear regression was used to model the association between neurocognitive or functional impairment and the neuropathologic lesions using the raw scores of the MMSE and CDR-SOB as linear outcomes. The MMSE data were available for 4032 individuals and CDR-SOB for 5272. To replicate analyses performed in White et al., we also considered impairment as an ordinal trait as part of a supplemental analysis.[24]

2.7.3 | Statistical models

For each clinical outcome two primary models were used: (1) a full model with each lesion as a separate variable, and (2) a model with the NPCS. Covariates for age at clinical exam, sex, a binary variable for African American race/ethnicity, and a binary variable for Hispanic/Latino race/ethnicity were included in all models. Age at exam and age at death were nearly collinear ($R^2 = 0.98$); therefore, we only included age at exam in the models. A sensitivity analysis of age at death is described in the Supplemental Material. In primary models, the variables were treated as additive terms and therefore the odds ratios (ORs) and betas reflect a one-unit change in the variable (none/mild vs severe in lesions; 0 to 1 to 2, etc in the NPCS). For the dementia model, pseudo R^2 was estimated using the DescTools package in R.[44,45] To test the robustness of these models the supplemental material contains several secondary analyses: ordinal parameterizations of lesions (Table S2), ordinal parameterizations of clinical outcomes (Table S3), no imputed/missing data (Table S4).
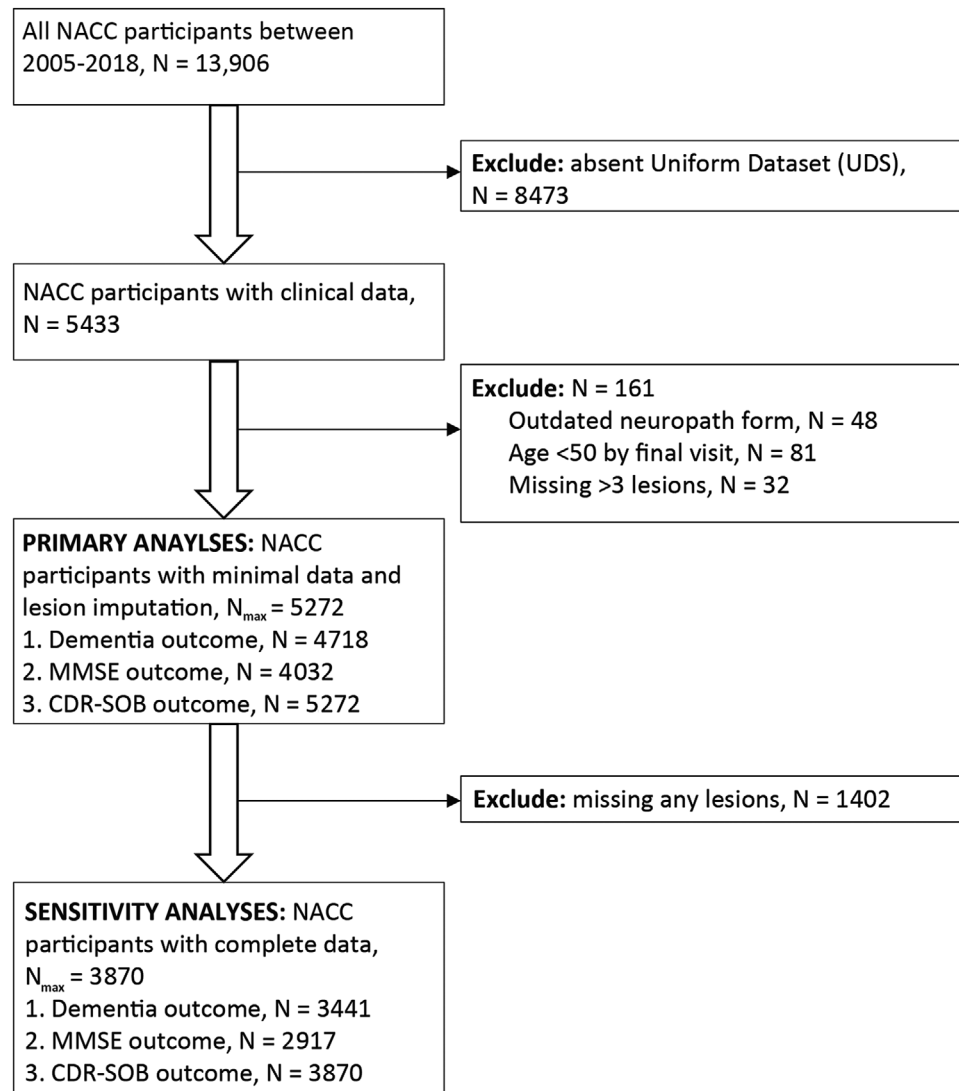
3 | RESULTS

3.1 | Cohort characteristics

The full dataset consisted of 5272 individuals. The majority of participants (72%) had multiple clinic visits ranging from 2 to 13 with a median of 3 assessments. Only the MMSE and CDR-SOB from the final assessment before death were used in this study. Age at final exam ranged from 50 to 110 years old with a mean of 78.5 (±11.1). Time interval between each follow-up exam varied. Additionally, time interval between final exam and death varied, ranging from 0 to 13 years with a mean of 2.65 years (±2.08) (Figure S1). Descriptive statistics and exclusion criteria are shown in Table 1 and Figure 1. AD lesions were the most common lesion types, with 4448 individuals (84%) presenting with one or more AD lesions. Vascular lesions were the next most common, with 52.9% of participants positive for vascular brain injury and 40.5% positive for arteriolosclerosis. Only 229 participants (4%) were negative for all lesion types. The average NPCS in the full imputed dataset (N = 5272) was 2.98 (±1.7) (Figure 2). Figure 2A shows the distribution of the total burden of neuropathology as measured by the NPCS. When this burden is split by quartiles (Figure 2B) it was evident that the AD lesions drove most of the distribution, particularly the middle quartiles. The non-AD lesions were not appreciably different between the 2nd and 3rd quartiles, but, as expected, increased in the 4th quartile. The three AD lesions were highly correlated with each other, and moderately correlated with CAA, a related amyloidosis; vascular brain injury and arteriolosclerosis were also correlated (Figure S2).

Among the cognitively intact (no dementia, CDR-SOB ≤4, and MMSE ≥24 if available; N = 604) neuropathological lesions were very common (Figure S3). Only 9% of the cognitively intact had no lesions; 33% had one or more moderate lesions (with none severe); and 40% had one or more severe lesions. The median NPCS was 1.4 among this group, indicating that at least half the cognitively intact had neuropathological lesions greater than one severe and one mild/moderate lesion (Figure S3).

Mixed pathologies were very common in the full dataset (Table 2). Of those with any AD pathology (neurofibrillary tangles, neuritic plaques, diffuse plaques; N = 4448), 87% had at least one non-AD lesion present (N = 3870), and 61% (N = 2728) had one or more severe non-AD lesions. The rates of mixed pathology did not vary greatly between those deemed "low" AD pathology versus "intermediate/high" AD pathology (Table 2).

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┌─────────────────────────────────┐
│ All NACC participants between   │
│ 2005-2018, N = 13,906           │
└─────────────────────────────────┘
                │
                │          ┌──────────────────────────────────────┐
                ├─────────▶│ Exclude: absent Uniform Dataset (UDS),│
                │          │ N = 8473                              │
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│ NACC participants with clinical │
│ data, N = 5433                  │
└─────────────────────────────────┘
                │
                │          ┌──────────────────────────────────────┐
                │          │ Exclude: N = 161                      │
                ├─────────▶│    Outdated neuropath form, N = 48    │
                │          │    Age <50 by final visit, N = 81     │
                │          │    Missing >3 lesions, N = 32         │
                ▼          └──────────────────────────────────────┘
┌─────────────────────────────────┐
│ PRIMARY ANAYLSES: NACC          │
│ participants with minimal data  │
│ and lesion imputation,          │
│ $N_{max}$ = 5272                │
│ 1. Dementia outcome, N = 4718   │
│ 2. MMSE outcome, N = 4032       │
│ 3. CDR-SOB outcome, N = 5272    │
└─────────────────────────────────┘
                │
                │          ┌──────────────────────────────────────┐
                ├─────────▶│ Exclude: missing any lesions, N = 1402│
                │          └──────────────────────────────────────┘
                ▼
┌─────────────────────────────────┐
│ SENSITIVITY ANALYSES: NACC      │
│ participants with complete      │
│ data, $N_{max}$ = 3870          │
│ 1. Dementia outcome, N = 3441   │
│ 2. MMSE outcome, N = 2917       │
│ 3. CDR-SOB outcome, N = 3870    │
└─────────────────────────────────┘
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FIGURE 1 Flow chart of exclusion criteria and analyses. The flowchart shows exclusion criteria and sample sizes in the dataset. The primary dataset allows three or fewer missing lesions to be imputed and analyzed. The clinical outcomes have varying sample sizes as we do not impute the outcome variables. The "complete" data do not allow any missing lesions and were only used in some of the sensitivity analyses. Abbreviations: CDR-SOB, Clinical Dementia Rating Sum of Boxes; MMSE, Mini-Mental State Examination; NACC, National Alzheimer's Coordinating Center

TABLE 2 Categorization of the participants by types of AD pathologic changes and comorbid lesions

			AD pathology	
		No AD pathology	Low	Int/High
Comorbid non-AD lesions	None	229 (28%)	155 (17%)	423 (12%)
	Moderate only	254 (31%)	281 (31%)	861 (24%)
	1 severe	263 (32%)	291 (32%)	1386 (39%)
	2 or more severe	78 (9%)	178 (20%)	873 (25%)
Total		824	905	3543

For participants with NACC neuropathology form v10, Low versus Int/High pathology was assessed through NIA-AA ADNC categorization (NACC variable NPADNC). For individuals with form v9, NIA-REGAN/CERAD diagnostic criteria were used: "Low" being AD lesions present, but not meeting NIA-REGAN criteria; "Int/High" being AD pathology meeting NIA-REGAN criteria.

(A)

(B)
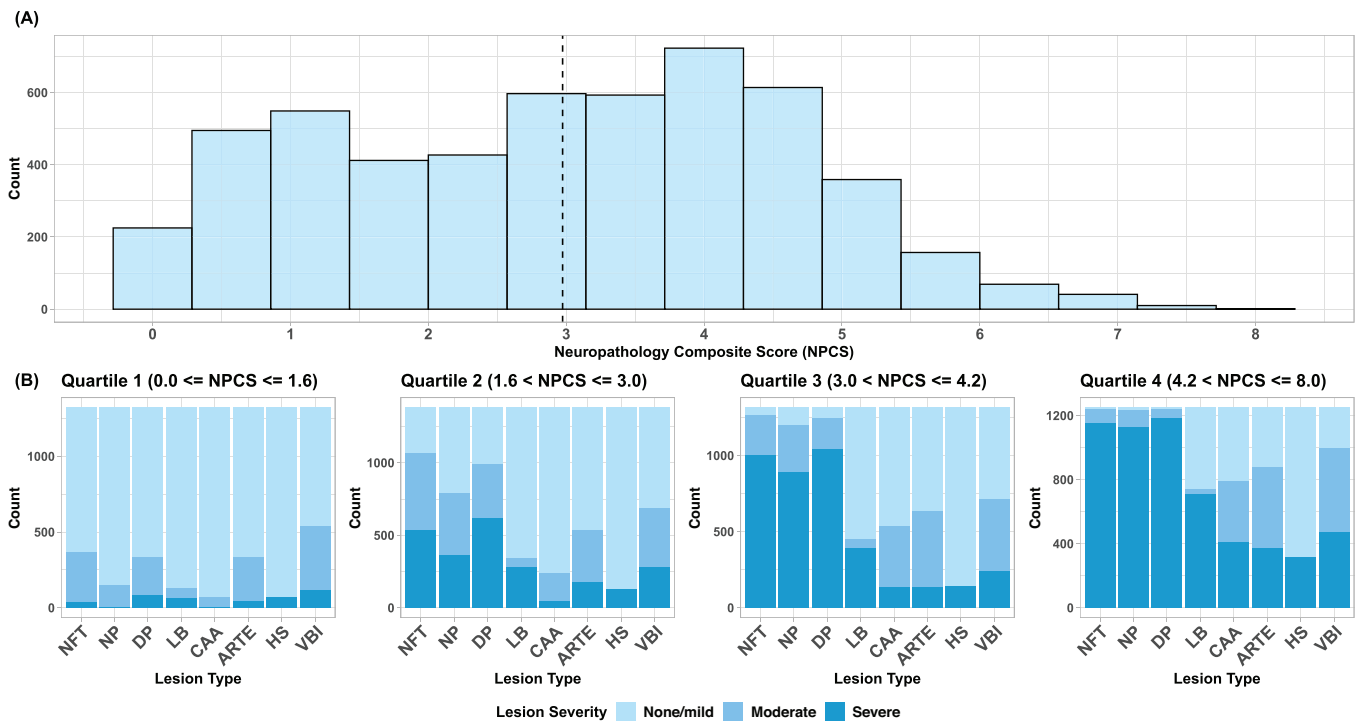
FIGURE 2 Distributions of neuropathology composite score (NPCS) and lesion severity. (A) Shows the overall distribution of the NPCS (N = 5272). The dashed line notes the mean NPCS of 2.98 (±1.7 SD). This histogram represents the distribution of the NPCS from one imputation with the multivariate imputation by chained equation (MICE) package in R software. Other distributions will vary slightly in number per bin, but will follow the same general shape of this distribution. (B) Shows the distribution of individual lesions, split by quartile of the NPCS. Abbreviations: ARTE, arteriolosclerosis; CAA, cerebral amyloid angiopathy; DP, diffuse plaques; HS, hippocampal sclerosis; LB, Lewy bodies; NFT, neurofibrillary tangles; NP, neuritic plaques; NPCS, neuropathology composite score; VBI, vascular brain injury

3.2 | Association between lesions and dementia

In our analyses of dementia (N = 4718) we observed a significant association between neurofibrillary tangles, neuritic plaques, and dementia (tangles, OR = 11.46, P-value < 2E-16; neuritic plaques, OR = 2.33, P-value = 2.56E-05) (Table 3); these ORs reflect a one-unit change in the variable (none/mild vs severe). Among the other non-AD lesion, hippocampal sclerosis showed the strongest association (OR = 7.37, P-value = 3.39E-12), followed by arteriolosclerosis (OR = 2.4, P-value = 7.59E-6). Neither diffuse plaques nor vascular brain injury as assessed by the NACC variables collected was associated with dementia in the full model. The NPCS also showed a significant association with dementia (OR = 2.39, P-value < 2E-16) when modeled as an additive effect (on the log scale).

We assessed model fit using the McKelvey and Zavoina pseudo R^2 estimates. Four models were assessed: a "null" reduced model (age, sex race/ethnicity), an AD model (reduced model plus AD lesions), a full model (reduced model plus all neuropath variables), and an NPCS model (reduced model plus NPCS). The R^2 values were 0.225, 0.495, 0.590, and 0.518, respectively, (see Supplemental Text 3). To replicate White et al., we also analyzed the NPCS as a categorical variable (quartiled, with 0 NPCS as a referent group).[24] This model showed a stronger association with dementia among individuals with upper® quartiles of NPCS relative to those with lower (Q4 vs referent: OR = 50.43,

P-value = < 2E-16.; Q2 vs referent: OR = 6.18, P-value = 1.55E-14; see Table S2 for details).

3.3 | Association between lesions and neurocognitive impairment

In our assessment of MMSE (N = 4032), neurofibrillary tangles showed the strongest association (β = -6.84, P-value < 2E-16; Table 3). Vascular brain injury was not associated with MMSE. Similar results were seen in the ordinal logistic regression models (see Table S3). In the full model, all 8 lesions and covariates capture 29% of the variability in the MMSE outcome (R^2 = 0.286). Meanwhile, the reduced model (covariates only) explained only 9.8% of the variability of MMSE (R^2 = 0.098) and the AD model explained 26.5% (R^2 = 0.265). This means that the remaining five non-AD lesions explain an additional 2% of the total MMSE variability after accounting for AD, age, sex, and race/ethnicity. The NPCS was significantly associated with MMSE (β = -2.01, P-value < 2E-16), and the model explained 23.5% of the variation in MMSE (R^2 = 0.235). Finally, to replicate White et al., we analyzed the NPCS as an ordinal factor split by quartiles.[24] As in the ordinal analysis for dementia, the effect sizes for upper quartiles of NPCS had stronger associations with MMSE than lower quartiles (Table S2).

TABLE 3 Association between neuropathology lesions and clinical endpoints

	Dementia (N = 4718)			MMSE (N = 4032)			CDR-SOB (N = 5272)		
	OR	95% CI	P-value	β	SE	P-value	β	SE	P-value
Age	0.90	0.89-9.12	<2E-16	0.23	0.01	<2E-16	−0.12	0.01	<2E-16
Sex	0.65	0.53-8.05	6.56E-05	0.59	0.25	1.88E-02	−0.17	0.15	2.65E-01
Hisp	1.86	1.00-3.47	5.18E-02	−3.03	0.66	5.12E-06	2.60	0.40	6.68E-11
AA	0.67	0.40-1.13	1.37E-01	−2.94	0.66	9.51E-06	1.07	0.40	7.94E-03
NFT	11.46	7.91-11.66	<2E-16	−6.84	0.43	<2E-16	4.16	0.27	<2E-16
NP	2.33	1.57-3.46	2.46E-05	−2.14	0.47	4.66E-06	1.54	0.29	1.23E-07
DP	0.88	0.64-1.20	4.26E-01	1.27	0.42	2.40E-03	−1.19	0.26	5.41E-06
LB	2.25	1.67-3.03	8.92E-08	−0.91	0.30	2.21E-03	0.49	0.18	6.27E-03
CAA	1.80	1.14-2.84	1.19E-02	−1.97	0.42	2.62E-06	0.84	0.25	8.03E-04
ARTE	2.40	1.64-3.51	7.59E-06	−1.66	0.42	9.60E-05	1.25	0.25	8.79E-07
HS	7.37	4.25-12.78	3.39E-12	−2.64	0.38	6.64E-12	2.22	0.23	<2E-16
VBI	1.09	0.82-1.45	5.72E-01	0.64	0.36	7.80E-02	−0.54	0.22	1.55E-02
Age	0.91	0.90-0.91	<2E-16	0.24	0.01	<2E-16	−0.14	0.01	<2E-16
Sex	0.68	0.56-0.85	3.45E-03	0.45	0.26	8.08E-02	−0.04	0.16	8.10E-01
Hisp	2.21	1.21-4.05	1.01E-02	−3.52	0.68	2.83E-07	2.90	0.41	1.32E-12
AA	0.70	0.42-1.16	1.70E-01	−2.74	0.68	6.23E-05	0.98	0.41	1.82E-02
NPCS	2.39	2.21-2.59	<2E-16	−2.01	0.08	<2E-16	1.19	0.05	<2E-16

The upper portion of the table shows results from the full models with lesions parameterized individually, including imputed data. The bottom portion of the table notes the NPCS model. Effect sizes are presented as odds ratios (OR) for the dementia outcome and βs for MMSE and CDR-SOB outcomes. Bolded items denote P-value < 0.05. Note that reduced MMSE is indicative of increased impairment, hence the negative effect sizes under the MMSE model.

Abbreviations: AA, African American; ARTE, arteriolosclerosis; CAA, cerebral amyloid angiopathy; CDR-SOB, Clinical Dementia Rating Sum of Boxes; CI, confidence interval; DP, diffuse plaques; Hisp, Hispanic/Latino; HS, hippocampal sclerosis; LB, Lewy bodies; MMSE, Mini-Mental State Examination; NFT, neurofibrillary tangles; NP, neuritic plaques; NPCS, neuropathology composite score; SE, standard error; VBI, vascular brain injury.

3.4 | Association between lesions and functional impairment

Analyses of CDR-SOB (N = 5272) showed similar results as MMSE analyses. Neurofibrillary tangles showed the strongest effect, followed by hippocampal sclerosis, neuritic plaques, and arteriolosclerosis (Table 3), with diffuse plaques and vascular brain injury effect sizes in the opposite direction from the other lesions. Similar results were seen in the ordinal logistic regression models (see Table S3). In the full model, 24% of the variability in the CDR-SOB is explained ($R^2 = 0.237$) while the "null" reduced model explained only 8.1% of the variability ($R^2 = 0.081$) and the AD model (3 AD lesions + covariates) explained 21.4% of the variability ($R^2 = 0.214$). Finally, the NPCS was significantly associated with CDR-SOB ($\beta = 1.19$, P-value ≤ 2E-16); the NPCS model with covariates explained 19% of the variability in CDR-SOB ($R^2 = 0.188$). As in the ordinal analyses for dementia and MMSE, the effect sizes for upper quartiles of NPCS had stronger associations with CDR-SOB than lower quartiles (Table S2).

3.5 | Atypical clinical and neuropathological findings

There were 604 cognitively intact individuals (Figure S3). Rates of cognitive resilience (high burden of pathology while maintaining cog-

nitive function) were moderate: 154 participants (25% of all cognitively intact subjects). Few individuals met criteria for neuropathological resistance (advanced age with minimal pathology, NPCS ≤1.4). Only 158 individuals (11% of the 1416 individuals over age 86 at last visit) remained cognitively intact with minimal pathology. Other dementias (dementia with minimal neuropathology) occurred in 749 participants (18% of 4106 with dementia, with NPCS ≤1.4). Many of these had clinical diagnoses for other dementias (eg, frontotemporal lobar degeneration, progressive supranuclear palsy, etc); however, in 29% of these individuals, AD was still clinically diagnosed as the primary disease etiology (NACC variable NACCETPR) (Table S5).

3.6 | Time interval sensitivity analysis

One potential limitation to our approach is that the interval between the last clinical assessment and death may impact the effect size estimates in the statistical modeling. Specifically, longer intervals between clinical assessment and death may increase heterogeneity and decrease the magnitude of associations. To test this we performed a sensitivity analysis on interval between last clinical assessment and death (see Supplemental Text 4 and Figure S1). Briefly, we did note a reduction in the magnitude of effect sizes when using the full dataset, relative to those restricted to shorter intervals (see Tables S6 to S9).

However, overall the effect sizes were largely robust against longer intervals.

4 | DISCUSSION

We present here a large study of the neuropathology in the aging brain (N = 5272) of a clinic-based population. This study confirms the high rate of AD lesions and related dementia lesions in combination. Most individuals showed some combination of AD lesions (84%) and very few individuals completely lacked the assessed pathologic changes (4%). The percentage of individuals with AD lesions is higher than seen in community-based studies, such as ROS (60.6) and MAP (59%),[22] but very similar to what has been seen in other considerably smaller (N = 392) clinic-based cohorts like the clinical core of ROS (83.7%).[22] Of the individuals with AD pathologic changes, 70% had at least one severe lesion from a related dementia. The rate of mixed pathologies is higher than most rates previously reported in other cohorts, likely a reflection of the more heterogeneous clinical populations. Compared to community-based cohorts, individuals in NACC had more Lewy Bodies, more hippocampal sclerosis, and more mixed pathology. This study also found a high rate of lesions among the cognitively intact, consistent with findings from previous studies.[18,22,24,26] It is not clear if this is due to cognitive resilience (either from cognitive reserve or compensation) or "censoring" due to death.

We observed a strong association between increasing severity of individual lesions and dementia, neurocognitive impairment (MMSE), and functional impairment (CDR-SOB). The largest effect sizes were seen in neurofibrillary tangles, neuritic plaques, and hippocampal sclerosis. The effect sizes of neurofibrillary tangles and neuritic plaques align well with previous findings in community-based studies.[18,24,26] Hippocampal sclerosis is often understudied in combination with the primary AD lesions. In the few community-based studies that do include hippocampal sclerosis, similar effect sizes were seen.[18,24,26] Its relatively large contribution to dementia severity indicates it should regularly be included in neuropathologic studies of dementia. The findings were also consistent across a variety of modeling and analysis approaches (see Supplemental Material), lending support to the robustness of the findings.

Diffuse plaques were not associated with the dementia outcome in the full model, likely because of the high correlation between the AD lesions (see Figure S2). A reduced model including diffuse plaques (but lacking tangles and neuritic plaques) did show association with dementia (P-value ≤2E-16). Vascular brain injury was also not significantly associated with dementia in the full model, though the effect size was positive. This may be due to inconsistencies in how vascular phenotypes were assessed or coded across ADRCs or could represent a truly weaker effect on dementia outcome (and thus weaker statistical power). A reduced model that included vascular brain injury did show a nominal association with dementia (OR = 1.37, P-value = 0.01), suggesting some of the signal from vascular brain injury may be captured by the correlation with the arteriolosclerosis phenotype (R^2 = 0.38; see Figure S2).

In the models of MMSE and CDR-SOB diffuse plaques and vascular brain injury showed effects in the opposite direction than the other lesions types (ie, they look "protective"). This change in direction, however, was not seen in reduced models (diffuse plaques alone, or vascular brain injury alone). Sensitivity analyses suggest that the direction change is due to the correlations among lesions (diffuse correlated with other AD lesions; vascular brain injury correlated with arteriolosclerosis; see Tables S10 and S11) rather than a real "protective" effect. Correlated independent variables in a multivariate regression can have very different main effects relative to simple linear regression of a single variable. In particular, if the variable coding does not reflect the true underlying association (eg, linear coding vs a multiplicative or threshold-based effect, or unaccounted interactions) the second variable may pick up residual signal in an unanticipated direction. In this case, the diffuse plaque variable is likely picking up residual effects left over from the other AD lesions, and vascular brain injury is picking up residual effects from arteriolosclerosis. The implication is that, in terms of clinical impact and risk, the AD lesions should not be modeled in isolation. Similarly, the vascular phenotype should not be modeled in isolation either. Future studies should explore other, more granular ways of assessing these lesions, their interactions, and modeling their associations with clinical outcomes.

For the MMSE and CDR-SOB models, we observed increases in the total variability explained when adding the 5 non-AD lesions to an AD lesions only model. The dementia models showed similar increase in goodness of fit when adding the related-dementia lesions (see Supplemental Text 3). This confirms that, while AD lesions dominate the models, there is still utility in assessing and modeling other brain lesions. This study also confirms the cumulative effect of multiple lesion types. In particular, upper quartiles of NPCS showed much stronger associations with MMSE and CDR-SOB than lower quartiles (Table S2). This effect was seen across all three clinical outcomes (dementia, neurocognitive decline, and functional impairment). As such, we recommend, whenever possible, the assessment of multiple neuropathological lesions and types in autopsy programs, even beyond the primary outcomes (eg, assessing Lewy bodies and vascular endpoints in a primarily AD/dementia cohort).

The ascertainment scheme of this study does limit the generalizability. The dataset is weighted towards those with AD or memory impairment and thus is not representative of the general population. Additionally, while the study does include individuals from underrepresented populations (notably African American and Hispanic), the rate of participation in autopsy programs from these populations tends to be low. We also note that more detailed and specific neuropsychiatric and functional measures may improve analyses. For example, the MMSE has been updated to the Montreal Cognitive Assessment (MoCA) in more recent versions of NACC protocols,[46] and more advanced psychometric approaches are available for assessing impairment in specific cognitive domains (eg, executive, memory predominant, visuospatial, etc).[47–49]

Taken together, these results confirm the utility of neuropathological collections and show mixed-type pathologies may be an important contributor to the likelihood and severity of dementia in clinic-based

populations. Further approaches are required to understand the role of these lesions in rates and progression of disease, influence on impairment in specific neuropsychiatric domains, the role of mitigating factors such as education, and the contribution of genetic factors such as *APOE* genotype or other genetic risk factors.

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CONFLICT OF INTEREST

MC reports no conflicts of interest.

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