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RESEARCH ARTICLE

Subtypes of multiple-etiology dementias and the heterogeneous impact of *APOE* variants

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Abstract

INTRODUCTION: Multiple-etiology dementias (MEDs) are frequently identified at autopsy but often missed in clinical diagnosis, limiting the efficiency of dementia research and treatment. This study aimed to characterize subtypes of MEDs, evaluate clinical underdiagnosis, and assess the heterogeneous impact of apolipoprotein E (*APOE*) variants on mortality across MED subtypes.

METHODS: Data from the National Alzheimer's Coordinating Center (NACC) repository, which includes standardized clinical and autopsy assessments, were analyzed using competing risks survival models.

RESULTS: Pure Alzheimer's disease (AD) neuropathology was rare, whereas mixed neuropathologies were common and frequently misdiagnosed as AD alone. *APOE* ε4 decreased mortality risk in decedents without AD neuropathology and increased mortality in decedents with mixed AD neuropathology, but not in those with AD alone. *APOE* ε2 increased mortality in decedents having vascular neuropathology with cerebral amyloid angiopathy.

DISCUSSION: Heterogeneity in MEDs remains substantially underrecognized clinically. The effects of *APOE* variants vary by dementia subtype, emphasizing the need for refined diagnostic tools and personalized dementia treatment and care approaches.

KEYWORDS
APOE, clinical etiology, competing risks, heterogeneity, mixed dementia, multiple-etiology dementias, neuropathology, survival analysis

R01AG056031, R01AG056531, R01AG067523, R01AG066870, R21AG067549

Highlights

- Autopsy data revealed that pure Alzheimer's disease (AD) neuropathology is rare, whereas mixed pathologies are highly prevalent and frequently misdiagnosed as AD alone in clinical settings, underscoring the limitations of current diagnostic practices.
- Comprehensive neuropathological characterization of multiple-etiology dementia (MED) subtypes is crucial for uncovering the true complexity of dementia, which is often masked in clinical assessments. This approach enables a more accurate understanding of disease mechanisms and progression.
- We found that apolipoprotein E (*APOE*) ε4 was associated with increased mortality risk in AD with co-pathologies, but not in pure AD without other neuropathologies. Conversely, *APOE* ε4 was associated with decreased mortality risk in decedents who did not have AD neuropathology. *APOE* ε2 was protective in some AD-related subtypes but was associated with higher mortality risk in cerebral amyloid angiopathy with other vascular neuropathologies, highlighting the heterogeneous impact of genetic risk factors across subtypes.
- The differential effects of *APOE* variants across MED subtypes emphasize the need to evaluate biomarkers and risk factors within the context of underlying neuropathological profiles rather than broad clinical categories.
- These findings reinforce the need to develop and implement more refined, subtype-specific biomarkers and diagnostic protocols to enable precision prevention and personalized treatment strategies for the diverse forms of MED.

1 | BACKGROUND

Dementia is an umbrella term for a range of symptoms associated with neurocognitive disorders. These disorders often impair memory, language, mood, and social skills. They not only affect patients but also result in significant distress for caregivers and families. Without a cure or effective treatment, the consequences for an aging population will continue to grow. The most common types of sporadic (late-onset) dementia include Alzheimer's disease (AD), vascular dementia (VaD), Lewy body disease (LBD), and frontotemporal degeneration (FTD).[1,2] Collectively, these are referred to as Alzheimer's disease and related dementias (ADRD).[2,3] In many older adults, the brain exhibits multiple coexisting pathologies, resulting in mixed or multiple-etiology dementia (MED), which is present in the majority of postmortem dementia cases.[4,5,6,7] However, diagnosing MED in living patients remains difficult due to overlapping clinical features and shared risk factors across dementia types.[8,9,10]

Postmortem neuropathological assessment is widely considered as the "gold standard" for ADRD diagnosis. The National Alzheimer's Coordinating Center (NACC) database contains comprehensive data from more than 50,000 participants collected from more than 42 Alzheimer's Disease Research Centers (ADRCs) over more than 20 years and includes detailed postmortem neuropathological assessments for more than 7000 decedents. Thus, the NACC dataset provides a valuable and ideal resource to systematically characterize the complexity and heterogeneity of ADRD etiology and more accurately summarize ADRD pathological subtypes, which has never been done before. The refined ADRD pathological subtypes can be used to assess the heterogeneous effects of ADRD biomarkers across different etiological groups and ADRD subtypes on disease risk, progression, and outcomes including mortality. They provide a platform for comparing the effects of apolipoprotein E (*APOE*) variants on mortality risk across distinct neuropathological categories, especially in the context of competing risks of mortality, an area where knowledge gaps remain and where competing risk analysis has been underutilized. Furthermore, discrepancy and underdiagnosis of AD with multiple-etiological dementia using clinical etiological assessments can be quantified more precisely using the detailed NACC postmortem neuropathological data. The clinical underestimation and underdiagnosis of MEDs are of significant clinical importance and reflect a growing area of concern and research focus.[11,12,13,14,15] For example, there are significantly different responses as well as major toxicities and adverse effects associated with anti-amyloid antibody therapy for patients with AD pathology alone versus those with both AD and comorbid cerebral amyloid angiopathy (CAA) and other vascular pathology.[16,17]

Cardiovascular disease (CVD) is a leading cause of death and AD is the fourth leading cause of death among women and sixth leading cause overall.[18] Ignoring CVD and other causes of death as major competing risks in survival analysis of mortality risk often results in both underestimation bias and overestimation bias on risk effects of genetic

RESEARCH IN CONTEXT

1. **Systematic review**: Multiple-etiology dementias (MEDs) are common at autopsy but often clinically underdiagnosed. In-depth characterization of subtypes of MEDs are useful to assess the heterogeneous effects of biomarkers for improving differential diagnosis protocols and personalized treatment strategies. Although the apolipoprotein E (*APOE*) ε4 variant is generally known as the most potent genetic risk factor for late-onset Alzheimer's disease (AD), its differential impact on mortality across MED and non-AD dementia subtypes has not been systematically studied.
2. **Interpretation**: This study uses the National Alzheimer's Coordinating Center (NACC) database to quantify the clinical underdiagnosis of MED and to explore how *APOE* variants differentially influence mortality risk across distinct dementia subtypes. The results show that mixed pathologies are both prevalent and frequently misclassified, and that the *APOE* ε4 and ε2 variants have variable effects on mortality depending on the underlying neuropathology. These findings underscore the complex interplay between genetics and heterogeneity in mortality risk as well as other disease outcomes.
3. **Future directions**: Improved assessment and developments of existing and novel biomarkers are needed to support more accurate diagnoses of subtypes of MEDs and personalized treatment strategies.

variants and other biomarkers in various competing risk groups. Carrying at least one copy of the *APOE* ε4 allele is well known as the most potent genetic risk factor of sporadic AD; however, the differential effects of *APOE* ε4 across various ADRD or MED subtypes have never been systematically assessed. Characterizing MED neuropathological subtypes and the often-overlooked heterogeneous effects of *APOE* ε4 within MEDs can provide a deeper understanding of the complexity of MEDs, which is crucial for refining diagnostic methods and developing targeted, effective treatments. In addition, there are effective treatment and prevention measures of CVD and other top causes of death, but there is still no cure for AD. Developing targeted preventive strategies and accurate early diagnostic tools requires refining ADRD and MED subtypes and advancing biomarkers that can distinguish these subgroups.

In this study, we sought to address these knowledge gaps by systematically characterizing neuropathological subtypes of MED, quantifying their clinical underdiagnosis. Using various competing risks survival models, we evaluated the heterogeneous effects of *APOE* variants on mortality across MED subgroups using age at death as event time and birth date as time zero, with autopsy-based neuropathological findings treated as competing causes of death. We employed different strategies to adjust for selection bias via autopsy propensity scores, for robust estimation of the effects of *APOE* variants.

2 | METHODS

2.1 | Study cohort

This study used data from the June 2023 data freeze of the NACC data repository (https://www.naccdata.org/). All studies and experimental protocols conducted by each ADRC contributing to NACC were approved by their respective institutional review boards prior to the initiation of the studies. Written informed consent was obtained from all study participants at each ADRC. At all participating sites, all studies and methods were conducted in accordance with the principles expressed in the Declaration of Helsinki. The NACC data repository includes de-identified data from the past and present participating ADRCs.

In this study, the NACC database was used to evaluate the underdiagnosis of MEDs and to examine the impact of *APOE* variants on mortality risk related to age at death with different MED and ADRD subtypes. The NACC is a centralized data repository, collaboration, and communication hub for the National Institute on Aging's (NIA) ADRC Program. It maintains a large relational database that uses the Uniform Data Set (UDS)[19] to provide standardized clinical data and the NACC Neuropathology Form to provide standardized neuropathological data.[20,21]

As of the June 2023 data freeze, there were 48,605 participants enrolled in the NACC since 2005 (Table 1 and Figure 1). Of those, 35,505 were not indicated to be dead, 5535 died but did not have a recorded brain autopsy, and 7565 had died and had brain autopsy data (Table 1 and Figure 1). Among the 7565 decedents with brain autopsies, there were 7380 decedents with complete autopsy assessed AD neuropathology data, including 6842 of whom died within 5 years of their last clinical visit, as well as 1125 who died in 2018 or later (i.e., within 5 years of the NACC 2023 data freeze) and 298 decedents who died within 1 year of their last clinical visit in 2020 or later. A subset of 25,117 living participants and 6547 autopsied decedents with available *APOE* genotyping was analyzed in the competing risks survival models.

2.2 | Clinical diagnoses

The clinical NACC data include etiological diagnoses in addition to the cognitive status (e.g., cognitively unimpaired, mild cognitive impairment [MCI], or dementia) for each participant on Form D1: Clinical Diagnosis from the UDS. Biomarker findings were added to version 3 of the UDS but are still only available for a small proportion of participants. In the Etiologic Diagnoses section for all three versions of the UDS, the presence of etiological diagnoses can be noted, with each one being recorded individually as the primary, contributing, or non-contributing cause of the observed cognitive impairment. Each

TABLE 1 National Alzheimer's Coordinating Center (NACC) participant demographics and characteristics.

	All participants ($n = 48,605$)	Living participants ($n = 35,505$)	Deceased ($n = 13,100$)	
			Not autopsied ($n = 5535$)	Autopsied ($n = 7565$)
Age at baseline				
Mean [SD]	71.74 (10.44)	70.28 (10.02)	76.20 (9.82)	75.32 (11.02)
Median (IQR)	72 [66, 79]	71 [65, 77]	77 [70, 83]	77 [68, 83]
Follow-up time, years				
Mean [SD]	3.27 (3.78)	3.17 (3.89)	3.20 (3.48)	3.77 (3.40)
Median (IQR)	2 [0, 5]	2 [0, 5]	2 [0, 5]	3 [1, 6]
Months from last visit to death				
Mean [SD]	22.34 (24.39)	NA	24.94 (25.53)	20.44 (23.35)
Median (IQR)	13 [7, 29]		15 [8, 33]	12 [6, 26]
Sex, *n* (%)				
Male	20,892 (43%)	14,118 (40%)	2752 (50%)	4022 (53%)
Female	27,713 (57%)	21,387 (60%)	2783 (50%)	3543 (47%)
Education, *n* (%)				
12 years or fewer	12,123 (25%)	8473 (24%)	1925 (35%)	1725 (23%)
13 to 16 years	19,936 (41%)	14,595 (41%)	2101 (38%)	3240 (43%)
More than 16 years	16,173 (33%)	12,210 (34%)	1456 (26%)	2507 (33%)
Unknown/missing	373 (< 1%)	227 (< 1%)	53 (< 1%)	93 (< 1%)
Race, *n* (%)				
White	38,239 (79%)	26,826 (76%)	4396 (79%)	7017 (93%)
Black or African American	6296 (13%)	5217 (15%)	800 (14%)	279 (4%)
Asian	1346 (3%)	1187 (3%)	91 (2%)	68 (< 1%)
Multiracial	1521 (3%)	1275 (4%)	119 (2%)	127 (2%)
All others	333 (< 1%)	299 (< 1%)	21 (< 1%)	13 (< 1%)
Unknown/missing	870 (2%)	701 (2%)	108 (2%)	61 (< 1%)
Ethnicity, *n* (%)				
Non-Hispanic	44,255 (91%)	31,787 (90%)	5206 (94%)	7262 (96%)
Hispanic	4138 (9%)	3565 (10%)	306 (6%)	267 (4%)
Unknown/missing	212 (< 1%)	153 (< 1%)	23 (< 1%)	36 (< 1%)
***APOE*, *n* (%)**				
ε3/ε3	17,990 (37%)	12,705 (36%)	2077 (38%)	3208 (42%)
ε2/ε3, ε2/ε2	3374 (7%)	2461 (7%)	352 (6%)	561 (7%)
ε3/ε4, ε2/ε4, ε4/ε4	14,730 (30%)	9951 (28%)	1854 (33%)	2925 (39%)
Unknown/missing	12,511 (26%)	10,388 (29%)	1252 (23%)	871 (12%)
Baseline cognitive diagnosis, *n* (%)				
Cognitively unimpaired	19,415 (40%)	16,595 (47%)	1232 (22%)	1588 (21%)
Cognitively impaired not MCI	2130 (4%)	1771 (5%)	191 (3%)	168 (2%)
MCI	10,748 (22%)	8457 (24%)	1092 (20%)	1199 (16%)
Dementia	16,312 (34%)	8682 (24%)	3020 (55%)	4610 (61%)

Abbreviations: IQR, interquartile range; MCI, mild cognitive impairment; SD, standard deviation.

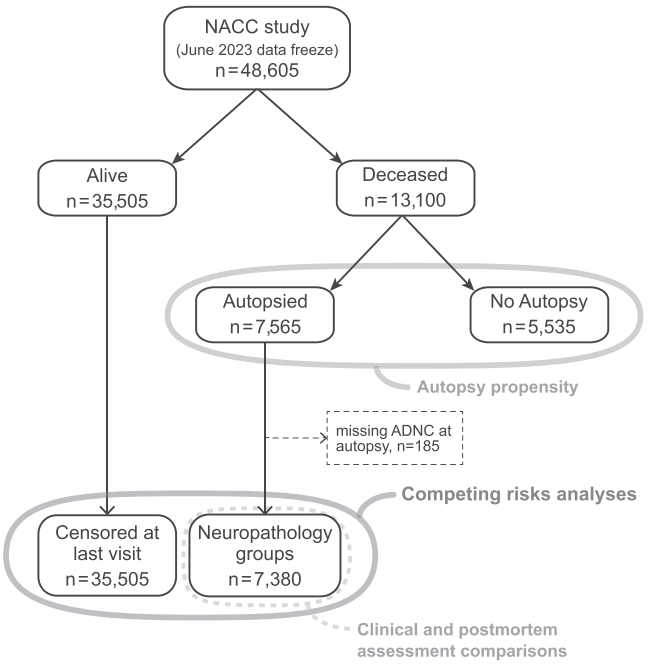

FIGURE 1 Study flow chart. Starting with the entire the National Alzheimer's Coordinating Center (NACC) sample as of the June 2023 data freeze, the flow of the study is broken down to show the sample used to derive the autopsy propensity scores, analyze the competing risks models, and compare the clinical etiology and postmortem neuropathology assessments.

presumptive etiologic diagnosis is coded in the database as: 0 = No (assumed assessed and found not present) or 1 = Yes.

The clinical etiology diagnoses variables were first grouped into diagnostic categories: AD diagnosis (AD); vascular dementia diagnosis (VaD)—including presence of stroke, probable or possible vascular dementia, and vascular brain injury; Lewy body disease (LBD); frontotemporal dementia (FTD); psychiatric diseases (PSY)—including bipolar disorder, schizophrenia, anxiety, post-traumatic stress syndrome (PTSD) and other psychiatric disease; and all other etiological conditions (OTH) from the UDS Form (Table S1). These categories were then organized into 6 groups and 14 subgroups as detailed in Figure 2A. The six groups were mutually exclusive and included: AD alone (AD), AD with VaD and no other etiologies (ADV), all other multiple etiologies with AD (AD.MED), VaD alone (VaD), all other non-AD dementia etiologies (OD), and no etiology noted (none).

2.3 | Autopsy assessed neuropathology

The NACC Neuropathology Form[20] versions 1 to 11, was used to characterize postmortem dementia neuropathologies as: AD neuropathology (ADnp); vascular disease neuropathology (VaDnp)—including atherosclerosis, arteriosclerosis, hemorrhages and microbleeds, infarcts and lacunes, and microinfarcts[22,23]; cerebral amyloid angiopathy (CAA); Lewy body neuropathology (LBDnp); frontotemporal dementia neuropathology (FTDnp); tauopathies and TAR DNA-binding protein 43 (TauTDP); and hippocampal sclerosis (HipSc) (Table S2).

In the NACC neuropathology dataset, AD neuropathology was assessed by the NIA Reagan criteria (variable: NIAR) from 2005 to 2013 in form versions V1 through V9 and by the ABC score, which is a combination of measures of amyloid plaques, Braak stages, and CERAD (Consortium to Establish a Registry for Alzheimer's Disease) neuritic plaque scores (variable: NPADNC), from 2011 to 2023 in form versions V10 and V11. The main difference between these two methods is that the NIA Reagan includes assessments of the Braak stages and CERAD neuritic plaque scores,[24] whereas the ABC score includes the Thal phases as a measure of amyloid plaques (A score) in addition to the Braak stages (B score) and CERAD neuritic plaque scores (C score).[25] Only one person in the NACC dataset had both measures. A logistic model of NIA Reagan scores (none or low vs intermediate or high) regressed on Braak stages (none to VI) and neuritic plaque scores (none to frequent) resulted in logistic-model derived NIA Regan binary scores that predicted none/low versus intermediate/high ABC scores with 98% accuracy. This indicated that the binary measures of the NIA Reagan and ABC scores were highly correlated, and thus, were combined as a binary measure of AD neuropathology (none or low vs intermediate or high).

The dementia neuropathologies detected in the post-mortem examination were organized into 6 groups, and 24 subgroups as detailed in Figure 2B. The six groups were mutually exclusive and included: (1) AD neuropathology alone (AD), (2) AD and vascular neuropathology with no other neuropathologies (ADV), (3) all other AD multiple-etiology combinations (AD.MED), (4) vascular neuropathology alone (VaD), (5) all other non-AD dementia neuropathologies (OD), and (6) no substantial dementia neuropathology noted (noNP). The 24 mutually exclusive subgroups included each neuropathology alone and the combinations of neuropathologies with 70 or more decedents per group (e.g., Alzheimer's disease plus vascular dementia [AD+VaD], vascular dementia plus cerebral amyloid angiopathy [VaD+CAA], Alzheimer's disease plus vascular dementia plus cerebral amyloid angiopathy [AD+VaD+CAA], AD+VaD+CAA+LBD).

2.4 | *APOE* genotyping

Two mutually exclusive binary variables were created for the *APOE* gene from the variable NACCAPOE: *APOE* ε4 as ε4 carriers (ε2/ε4, ε3/ε4, and ε4/ε4) versus non-carriers (ε2/ε2, ε2/ε3, and ε3/ε3) and *APOE* ε2 as ε2 carriers (ε2/ε2 and ε2/ε3) versus non-carriers (ε3/ε3, ε2/ε4, ε3/ε4, and ε4/ε4).

2.5 | Statistical analyses

The study subjects and subgroup breakdown are shown in the study flow chart (Figure 1). All models were tested for violations of the model assumptions, and any violations were rectified and described here. Extensive sensitivity analyses were performed on the sample including

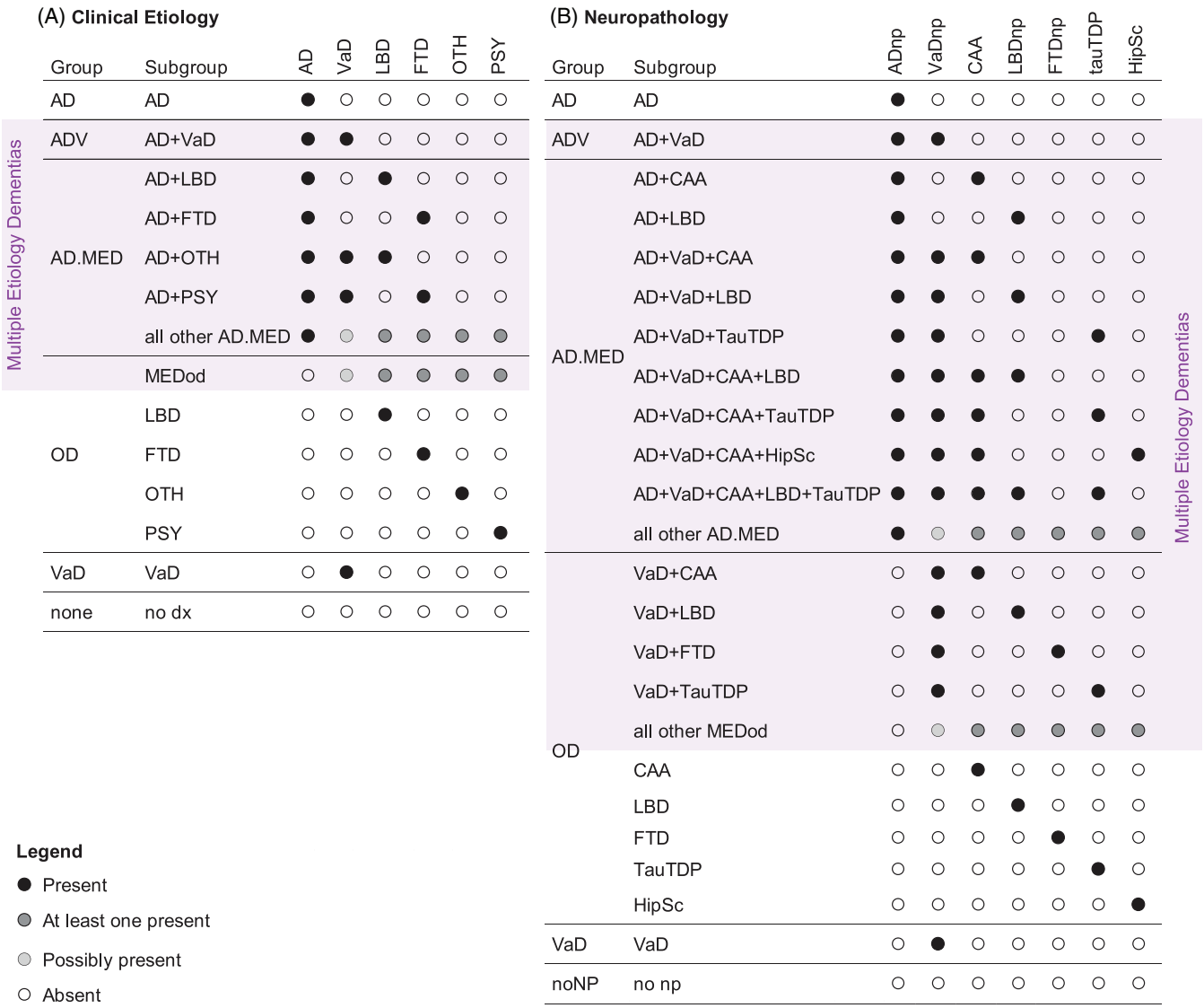

FIGURE 2 Clinical etiology and neuropathology groups. The 6 clinical etiology groups and 14 subgroups are shown in panel (A) on the left and the 6 postmortem neuropathology groups and 24 subgroups are shown in panel (B) on the right. In both (A) and (B), groups with multiple etiologies are shown in the shaded area. The types of clinical etiology diagnoses and postmortem neuropathologies are shown in the columns. A solid black circle indicates that the diagnosis or neuropathology is present, a dark gray circle indicates that at least one of the diagnoses or neuropathologies is present in the group, a light gray circle indicates that the clinical diagnosis or neuropathology is possibly present (i.e., it may be present or absent), and the open circle indicates that the diagnoses or neuropathologies are absent for that group.

all 48,605 NACC participants. All analyses were performed in R Studio (version 2025.5.0.496, R version 4.4.1)[26] with the specific packages as noted. Statistical estimation results are reported with 95% confidence intervals (CIs) and statistical significance was defined as a two-sided p-value < 0.05.

There are various reasons why a person may or may not have had a brain autopsy, some of which would contribute to selection bias and others not. For example, in some cases, consent may have been provided but it may not have been feasible to perform a brain autopsy within 24 hours of death, whereas in other cases consent to autopsy may have been declined either by the participant while they were still alive or by their families after their death. We derived autopsy propensity scores, which estimate each individual's probability of having an autopsy using a logistic regression. Autopsy propensity scores were used as a stratifying variable or through inverse probability weighting in the competing risks survival models to adjust for potential selection bias arising from the non-random selection to have a brain autopsy at death. The logistic model regressors were selected using the Least Absolute Shrinkage and Selection Operator (LASSO)[27] method from among 53 demographic and clinical variables measured at baseline (enrollment). The final propensity model included race (White vs all others), education (12 years or less, more than 16 years, and 13 to 16 years as the reference group), and the baseline global Clinical Dementia Rating (CDR® Dementia Staging Instrument) score in addition to baseline age and sex. Neither *APOE* ε4 nor *APOE* ε2 status was significantly associated with autopsy participation.

Although the propensity scores were derived based on baseline covariates of participants who were known to have died, they were predicted for the entire cohort to use as a stratifying or subclassification variable in the competing risks survival analyses. The resulting autopsy propensity scores, $e(\boldsymbol{x}) = P(z = 1|\boldsymbol{x})$, were the conditional probability of autopsy ($z = 1$) given a vector of observed covariates $\boldsymbol{x}$ as obtained from the logistic regression. This autopsy propensity score was used to derive the inverse probability weighting (IPW)[28] and also was used to divide the population into 10 percentile groups as the stratification strata or subclassification groups.[29]

We used four different Cox proportional hazards (Cox PH)–based competing risks models to examine how *APOE* variants relates to age at death with specific neuropathological diagnoses treated as competing risks. The neuropathology contributing to mortality typically took many years or decades to develop not resulting from death itself. The models adjusted for autopsy selection bias using the autopsy propensity scores, but they differed in how those scores were applied and what type of competing-risk models and effect they estimated on the competing risks.[30,31] The first model was used to examine the subdistribution hazard ratios (SHRs) from the Fine and Gray model and the other three were used to examine cause-specific hazard ratios (CSHRs). We report the Fine and Gray model and one of the cause-specific models that incorporated autopsy propensity score strata to address selection bias due to non-random autopsy selection,[29,32,33] whereas the other two cause-specific models applied IPW for selection bias adjustment.[28] It is known that, given the propensity score $e = e(\boldsymbol{x})$, the distribution of $\boldsymbol{x}$ is the same for $z = 1$ (autopsied) and $z = 0$ (not autopsied), that is, $P(\boldsymbol{x}, z|e) = P(\boldsymbol{x}|e)P(z|e)$ as explained in Equation (1) of Rosenbaum and Rubin.[29] Thus subclassification (or stratification) based on propensity score will balance all relevant observed covariates $\boldsymbol{x}$.[29] In fact, five subclasses (or strata) constructed from propensity score might suffice to remove over 90% of the biases due to imbalanced covariates as reported by Rosenbaum and Rubin.[29] The very large sample size in the NACC dataset affords a large number of strata (or subclasses as called in Rosenbaum and Rubin[29]) if needed. Overall, when the number of strata is 10 or above, the results are not sensitive to the number of strata, and the impact of potential selection bias on the hazard ratio (HR) of *APOE* variants can be balanced out across strata in the stratified analysis because subjects have similar distribution of covariates and have comparable autopsy propensity scores within each of the strata. Thus we selected the stratified analyses using autopsy propensity score strata as a robust approach to the Cox PH–based competing risk model in assessing the heterogenous effect (i.e., HR) of *APOE* variants on mortality risk while adjusting for selection bias due to non-random selection in autopsy participation. Stratified Cox PH type models allow each autopsy propensity stratum to have its own baseline hazard function, while assuming that the effect of *APOE* variants is constant across strata. This assumption is reasonable in our models because *APOE* was not significantly related to autopsy propensity in the NACC data. This is also an assumption in the typical IPW-based approach. If baseline hazards are similar across strata, the global Cox PH assumption holds, and IPW can potentially yield more precise HR estimates. However, when baseline hazards differ substantially between strata, the global Cox PH assumption may be violated, making the typical IPW approach for Cox PH models potentially invalid and leading to unstable estimates. For robustness, it is desirable to see whether both the stratification (or subclassication) and IPW approaches yield equivalent estimates of the HRs for *APOE* variants on mortality risk. Thus, we employed a comparative strategy, fitting cause-specific Cox PH models using both stratification and IPW, and we also reported the robust stratified Fine and Gray model, since the SHRs provide a natural connection to absolute risk.

APOE ε4 status (ε2/ε4, ε3/ε4, and ε4/ε4 vs all others) and *APOE* ε2 status (ε2/ε2 and ε2/ε3 vs all others) were the primary predictors of interest in all models. Sex and baseline age at study entry, dementia status, and Clinical Dementia Rating Sum of Boxes (CDR-SB) scale were included as covariates. Age at death was used as the event time and age at the last clinical visit was used as the censoring time for those alive at the end of follow-up. We also accounted for potential left truncation bias, since individuals could only be observed after surviving to their age at study entry. To account for this, one of the cause-specific models with IPW uses study-entry age as the left-truncation time.[34]

The Fine and Gray model was used to examine the impact of *APOE* variants on the cumulative incidence of death with each neuropathology profile over time. The SHR estimated the effect of *APOE* ε4 and *APOE* ε2 on the probability of dying with a specific neuropathological diagnosis, accounting for the presence of competing outcomes. The SHRs were estimated using the R packages "cmprsk" (version 2.2-12) and "crrSC" (version 1.1.2).

Subgroup analyses are of interest in precision medicine. The impact of *APOE* ε4 status on mortality in the six competing risk groups was also evaluated using Fine and Gray models separately in subgroups split by median study entry age (<72 vs 72+), sex, and race/ethnicity (non-Hispanic White vs underrepresented racial minorities).

The estimated hazard function of the autopsy propensity score stratified competing risks model takes the form:

$$h_k\left(t_{ijk}, \boldsymbol{X}_{ijk}\right) = h_{0jk}\left(t_{ijk}\right)\exp(\hat{\boldsymbol{\beta}}'_k \boldsymbol{X}_{ijk})$$

where, for each subject i in autopsy propensity stratum j and competing risk group k, t is the age at death or censoring, $h_{0jk}(t_{ijk})$ is the baseline hazard (which can be either subdistribution hazard or cause-specific hazard), $\hat{\boldsymbol{\beta}}'_k$ is the vector of estimated model coefficients for competing risk group k, and $\boldsymbol{X}_{ijk}$ is a vector of *APOE* ε4, *APOE* ε2, and the other covariates.[32,33]

Cause-specific hazard models were used to estimate the association of *APOE* ε4 and *APOE* ε2 with the instantaneous risk of dying with a specific neuropathological diagnosis. The cause-specific Cox PH model with IPW was fit by maximizing a weighted partial likelihood:

$$\left\{\frac{\exp\left(\hat{\boldsymbol{\beta}}'_k \boldsymbol{X}_{ik}\right)}{\sum_{j\in R(t)} \hat{w}_j \exp\left(\hat{\boldsymbol{\beta}}'_k \boldsymbol{X}_{jk}\right)}\right\}^{\hat{w}_i}$$

where, for each subject i in competing risk group k, $R(t)$ is the risk set at time t and $\hat{\boldsymbol{\beta}}'_k$ is the vector of estimated model coefficients for competing risk group k accounting for confounding and

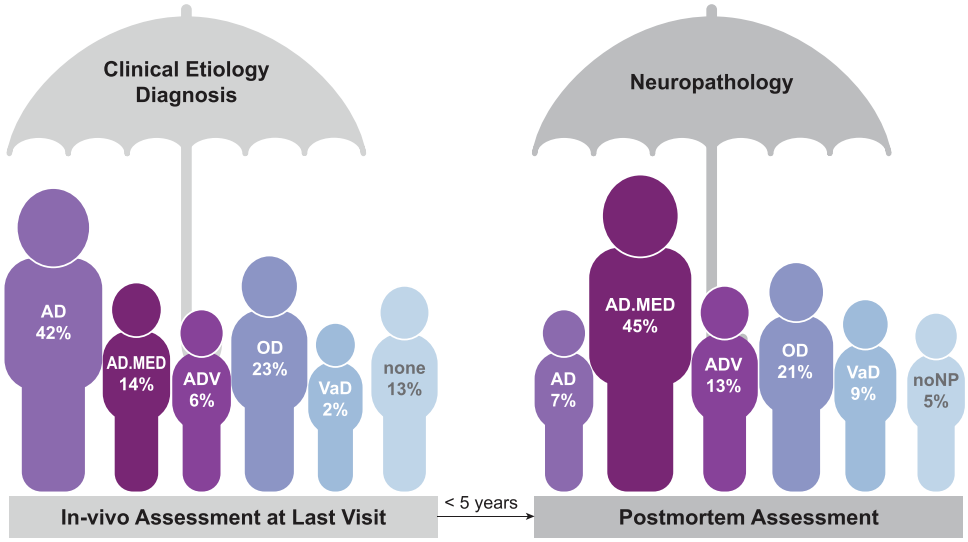

FIGURE 3 Clinical etiology and postmortem neuropathology group proportions ($n = 6512$). For participants who died within 5 years of their last clinical evaluation, the six mutually exclusive clinical etiology groups are shown on the left, and the six mutually exclusive neuropathology groups are shown on the right. Although 42% of decedents had a clinical etiology diagnosis of Alzheimer's disease (AD) alone, only 7% of decedents had AD neuropathology alone. Conversely, only 20% (14% + 6%) of decedents had a clinical etiology diagnosis of AD with another dementia (AD.MED or ADV), whereas 58% (45% + 13%) of decedents had AD with another dementia neuropathology (AD.MED or ADV).

selection bias measured by the autopsy propensity through the estimated IPW ($\hat{w}_i$) calculated as the inverse of the autopsy propensity scores, $e(\boldsymbol{x}) = P(z = 1|\boldsymbol{x})$, for autopsied decedents (i.e., $1/e(\boldsymbol{x})$) and as $1/(1-e(\boldsymbol{x}))$ for non-autopsied participants.[28] The CSHR with 95% confidence interval (CI) estimated using robust standard errors are reported for the weighted cause-specific Cox PH models adjusting for IPW. The R package "survival" (version 3.8-3) was used for all cause-specific Cox PH models.

Extensive sensitivity analyses for all competing risks models were performed. Because all study findings were essentially the same, we chose to report only the competing risks analyses results among those with *APOE* genotype data. For example, sensitivity analyses of various models were performed on the sample including all 48,605 NACC participants with all non-autopsied participants included as censored and with *APOE* status coded as ε3/ε3 (as the reference group), ε4 carriers (ε2/ε4, ε3/ε4, and ε4/ ε4), ε2 carriers (ε2/ε2 and ε2/ε3), or missing *APOE* status. Overall, the study findings are stable among all sensitivity analyses.

3 | RESULTS

3.1 | Comparison of clinical etiology and postmortem neuropathology assessments

Among 6842 autopsied decedents who died within 5 years of their last clinical visit, 2872 (42%) had a clinical etiology diagnosis of AD alone, 439 (6%) had a clinical etiology diagnosis of AD with VaD (ADV), 952 (14%) had any other mixture of AD with other dementias (AD.MED), 152 (2%) were presumed to have VaD etiology alone, 1542 (23%) had other non-AD dementias (OD), and 885 (13%) had no clinical etiology identified at their last clinical visit (Figure 3). At autopsy, however, the neuropathological assessments for the same decedents showed notable discrepancies, with 476 (7%) having AD neuropathology alone, 879 (13%) with AD and VaD neuropathology (ADV), 3108 (45%) having any other mixture of AD with other neuropathologies (AD.MED), 603 (9%) with VaD neuropathology alone, 1405 (21%) with other non-AD neuropathologies (OD) including MED without AD, and 371 (5%) with no dementia neuropathology identified (Figure 3).

In recent years, among the 1125 decedents who died within 5 years of a final clinical visit occurring in 2018 or later, 434 (39%) had a clinical diagnosis of AD alone, whereas only 58 (5%) had AD neuropathology alone at autopsy. In contrast, 191 (17%) were clinically diagnosed with AD.MED, whereas 576 (51%) showed AD.MED neuropathology postmortem. Finally, among the 298 decedents who died within 1 year of their final clinical visit occurring in 2020 or later, 112 (37%) had a clinical diagnosis of AD alone but only 11 (4%) had AD neuropathology alone at autopsy, and 53 (18%) were clinically diagnosed with AD.MED, whereas 163 (55%) had AD.MED neuropathology postmortem.

3.2 | Clinical underdiagnosis of AD.MED and VaD neuropathology

Overall, in 7380 autopsied decedents, multiple etiology dementia of AD with another co-pathology (AD.MED and ADV) was severely underdiagnosed in 76% of decedents with 58% (1987 of 3450) of AD.MED and 52% (478 of 924) of ADV neuropathology groups being diagnosed at their last clinical visit with presumed AD etiology alone (Figure S1 and Figure S2A). VaD neuropathology alone had only been correctly diagnosed in vivo in 8% (52 of 630) of decedents, with 41% (261 of 630) being underdiagnosed with no identified etiology and 51% being

misdiagnosed clinically with a different etiology (Figure S2A). In a comparison of the neuropathology and clinical etiology subgroups, LBD neuropathology alone had been correctly diagnosed in vivo in 48% (39 of 81) of decedents and FTD neuropathology alone had been correctly diagnosed in vivo in 41% (60 of 147) of decedents (Figure S1).

The 7380 autopsied decedents were also divided into two groups, and the neuropathology assessments and clinical etiology diagnoses were compared among the 5742 decedents who had a cognitive diagnosis of dementia at their last clinical visit versus in the 1638 decedents who were not demented at their last clinical visit. Among the demented decedents, the clinical etiology diagnoses had underdiagnosed 74% of the AD.MED and ADV neuropathology groups. In this subsample, only 7% (16 of 243) of the group with VaD neuropathology had been correctly identified in vivo (Figure S2B). Although many of the 1638 non-demented decedents did not have a clinical etiology diagnosis, among those who did receive a diagnosis, 78% of AD.MED and ADV neuropathology groups and 73% of the VaD neuropathology group were misdiagnosed with a different clinical etiology (Figure S2C).

In the subsample of 6842 autopsied decedents who died within 5 years of their last clinical visit, 1759 (61%) of the 2872 individuals diagnosed with AD alone at their final visit were actually found to have mixed AD neuropathology (AD.MED) at autopsy (Figure S2D). The clinical underdiagnoses of mixed etiology dementia has not been improved much in recent years. Although the proportion of participants clinically diagnosed with AD.MED increased from 13% before 2018 to 17% in 2018 and later, the proportion of decedents with AD.MED neuropathology at autopsy also increased from 44% before 2018 to 51% in 2018 and later. Among those with an AD diagnosis alone in 2018 or later who died within 5 years of their last visit, 304 of 434 (70%) were found to have AD.MED neuropathology at death (Figure S2E). Similarly, AD.MED neuropathology was underdiagnosed in decedents who died within 1 year of their last clinical visit in 2020 or later, where of the 112 decedents who had an AD diagnosis alone at their last visit, 82 (73%) were found to have AD.MED neuropathology at death (Figure S2F).

3.3 | *APOE* genotype distributions in neuropathology subgroups

The distribution of *APOE* genotypes was examined among the 24 neuropathology subgroups in 6547 autopsied decedents who had *APOE* genotype data. The subgroups with VaD neuropathology had the highest relative proportions of ε3 homozygotes, whereas subgroups with either AD or CAA (i.e., the union of the two) neuropathology had lower proportions of ε3 homozygotes (Figure S3). The ε2/ε3 and ε2/ε2 allele combinations were more prevalent among cases of non-AD multiple etiologies (otherMEDod) including VaD with CAA neuropathology. The presence of an ε4 allele was most prevalent among cases with AD and CAA neuropathology (Figure S3). Overall, pure AD was relatively rare, and 51% of these cases did not carry an ε4 allele, whereas 47% were ε3/ε3. Among pure VaD cases, >95% carried at least one ε3 allele, and 69% were ε3/ε3.

3.4 | Competing risks survival model with 24 competing risk groups

The 24 mutually exclusive autopsy-assessed neuropathology subgroups allowed for the examination of death with different dementia types. By using these subgroups as causes of competing risks, we assessed how *APOE* ε4 status (ε4 carriers vs non-carriers) and *APOE* ε2 status (ε2/ε2 and ε2/ε3 vs all others) were differentially associated with mortality risk for specific dementia types. For example, death with pure AD or death with AD and CAA co-pathology (AD+CAA) could be examined separately as different competing risks. The analyses were conducted in 6547 autopsied decedents with competing risks of death and 25,117 living participants (as censored observations) with available *APOE* genotyping data.

The Fine and Gray SHR model included *APOE* ε4 and *APOE* ε2 as the primary variables of interest; sex, baseline age, dementia status, and CDR-SB as covariates; and the 10 autopsy propensity score categories as model strata. The SHRs with the corresponding 95% CIs from the Fine and Gray model examining the impact of *APOE* ε4 and *APOE* ε2 on mortality risk in the 24 competing risk groups are shown in Figure 4.

Although the groups of individuals who died with AD and CAA co-pathology (e.g., AD+VaD+CAA, AD+VaD+CAA+LBD, AD+VaD+CAA+TauTDP, AD+VaD+CAA+HipSc, and AD+VaD+CAA+LBD+TauTDP) had the highest SHRs for mortality risk associated with *APOE* ε4, the association did not reach statistical significance in the competing risk groups of AD alone and some other groups with AD but without CAA neuropathology (e.g., AD+VaD+LBD, AD+VaD+TauTDP) as shown in Figure 4. Conversely, *APOE* ε4 was statistically significantly associated with lower mortality risk (SHR <1 and 95% CI <1) in the competing risk groups that did not have either AD or CAA neuropathology (Figure 4). *APOE* ε2 was statistically significantly associated with higher mortality risk in the competing risk groups with both VaD and CAA (VaD+CAA) and with mixed non-AD neuropathologies (MED.od), and showed only a statistically significant protective effect in the groups with AD alone, AD+LBD and the AD+VaD+TauTDP groups (Figure 4). The CSHR from the three Cox PH models were in the same direction for all SHRs that reached statistical significance (Table S3).

3.5 | Fine and gray competing risks analysis with six competing risk groups

The competing risks of death were then examined in the Fine and Gray survival model with the six autopsy-assessed neuropathology groups as the competing risks in the sample of 31,664 with 6547 autopsied decedents and 25,117 living participants as censored observations. The model included *APOE* ε4 status and *APOE* ε2 status as the primary variables of interest; sex, baseline age, dementia status, and CDR-SB as covariates; and the 10 autopsy propensity score categories as model strata. The SHRs with the corresponding 95% CIs for *APOE* ε4 and *APOE* ε2 are shown in Figure 5A.

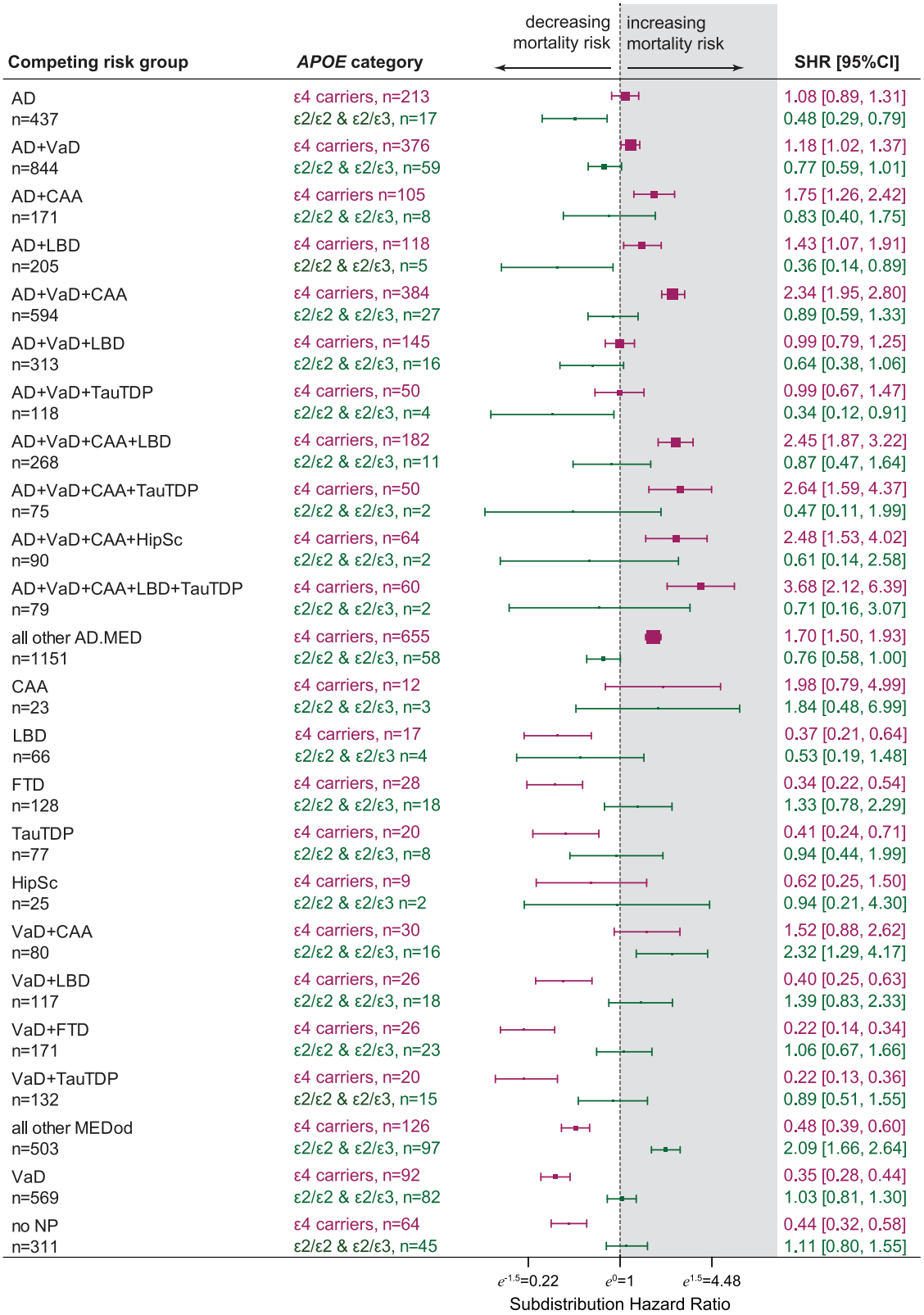

FIGURE 4 Apolipoprotein E (*APOE*)–related mortality risk across 24 neuropathology subgroups. *APOE* ε4 was associated with the highest mortality risk in the competing risk groups with Alzheimer's disease plus vascular dementia plus cerebral amyloid angiopathy (AD+VaD+CAA), both with and without other neuropathologies, but did not reach significance in some other Alzheimer's disease plus vascular dementia (AD+VaD) combinations without cerebral amyloid angiopathy (CAA). In contrast, *APOE* ε4 was associated with lower mortality risk in groups without either Alzheimer's disease (AD) or CAA. *APOE* ε2 was significantly associated with higher mortality in mulitple etiology non-AD dementia (MEDod) and vascular dementia plus cerebral amyloid angiopathy (VaD+CAA), and was protective in pure AD and some other groups that did not have CAA.

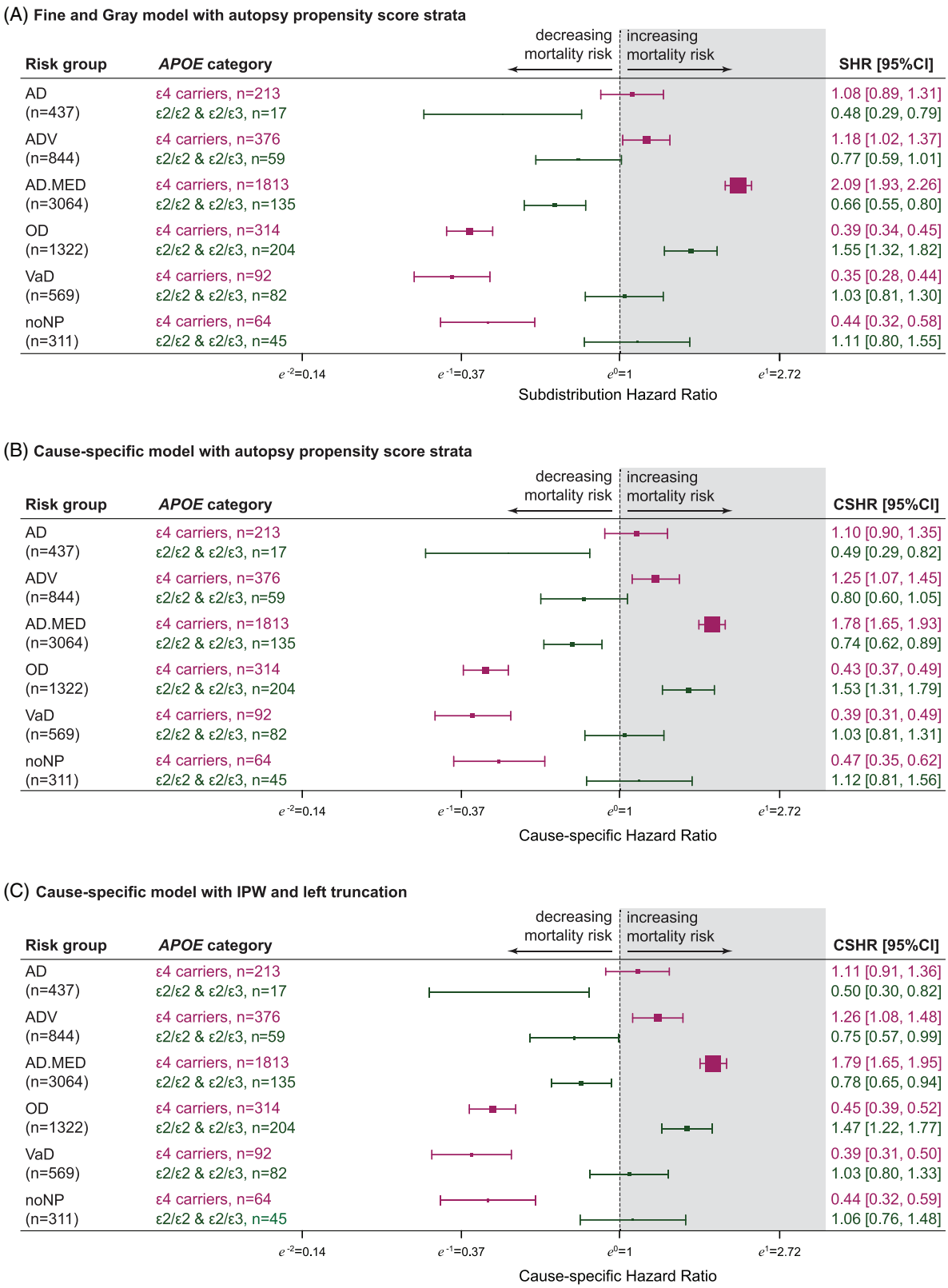

FIGURE 5 Forest plots of apolipoprotein E (*APOE*)–related mortality risk across six neuropathology groups. The top panel (A) shows the subdistribution hazard ratios (SHRs) and their 95% confidence intervals (CIs) for *APOE* ε4 and *APOE* ε2 on mortality risk from the Fine and Gray model. The model included sex, baseline age, baseline Clinical Dementia Rating Sum of Boxes (CDR-SB), and baseline dementia status as covariates as well as autopsy propensity score strata. In the mixed Alzheimer's disease (AD) neuropathology groups (AD.MED and ADV), *APOE* ε4 carriers had significantly increased mortality risk, but *APOE* ε4 carriers had significantly decreased mortality risk in all three non-AD competing risk groups (OD, vascular dementia [VaD], and no neuropathology [noNP]). Conversely, *APOE* ε2 carriers had significantly increased mortality risk in the

APOE ε4 was significantly associated with higher mortality risk among the groups with AD with co-pathologies—AD and VaD neuropathology (ADV) and those with AD mixed with other neuropathologies (AD.MED)—but did not reach significance in the group with AD neuropathology alone (AD) (Figure 5A). Among all of the groups that did not have AD neuropathology (OD, VaD, and noNP), however, *APOE* ε4 was significantly associated with lower mortality risk (Figure 5A). Opposite effects among the competing risks groups were also observed for *APOE* ε2, which was significantly associated with lower mortality risk in the AD and the AD.MED groups, and with higher mortality risk in the group with other non-AD dementia pathology (OD) (Figure 5A). Sensitivity analysis in all 48,605 NACC participants yielded SHRs consistent in direction and significance with those from the primary sample of 31,664.

3.6 | Fine and Gray competing risks subgroup analyses by age, sex, and race/ethnicity

Subgroup analyses are of interest in precision intervention or prevention. Competing risk models of the six neuropathology groups as the competing risks and with *APOE* ε4 and *APOE* ε2 as regressors, were analyzed separately within subgroups defined by baseline (i.e., study entry) median age groups (<72 vs 72+), sex, and race/ethnicity (non-Hispanic White [NHW]} vs underrepresented racial minorities). For the group with mixed AD neuropathology (AD.MED), evidence of *APOE* ε4-related mortality risk was the strongest (95% CIs further from 1) in decedents who were younger than the median age of 72 at baseline, but *APOE* ε4 did not reach significance for the group with AD neuropathology alone (AD) for either age group or in the younger group with AD and VaD neuropathology (ADV) (Figure 6A). Although *APOE* ε4 carriers had reduced mortality risks (95% CIs below 1) among all the groups without AD neuropathology (OD, VaD, and noNP), the evidence of effect was stronger in decedents who were 72 or older at baseline for the VaD group but was weaker in decedents with no substantial dementia pathology (noNP) (Figure 6B). In the models with subgroup analysis separated by sex, the evidence of protective effect of *APOE* ε4 on mortality in the group with VaDnp only was stronger among men, but the evidence of protective effect of *APOE* ε4 was stronger in women than men in the noNP group (Figure 6B). In the models for subgroup analysis where subgroups were separated by race/ethnicity, the evidence of mortality risk associated with *APOE* ε4 was stronger in the racial/ethnic underrepresented racial minorities (URMs) than in NHW decedents in the pure AD competing risk group despite sample size differences but was stronger in NHWs compared to URMs in the AD.MED group consistent with sample size differences (Figure 6C).

3.7 | Cause-specific competing risks analysis with strata

The competing risks of death were then examined in the cause-specific survival model with the six neuropathology groups as the competing risks in the sample of 31,664 with 6547 autopsied decedents and 25,117 living participants as censored observations. The model included *APOE* ε4 status (ε4 carriers vs non-carriers) and *APOE* ε2 status (ε2/ε2 and ε2/ε3 vs all others) as the primary variables of interest; sex, baseline age, dementia status, and CDR-SB as covariates; and the 10 autopsy propensity score categories as model strata. The CSHR with the corresponding 95% CIs for *APOE* ε4 and *APOE* ε2 are shown in Figure 5B.

The effects for *APOE* ε4 and *APOE* ε2 were consistent with the Fine and Gray model (Table S4). *APOE* ε4 was a significant risk factor (CSHR 95% CI above 1) for mortality in the ADV and AD.MED groups but significantly protective (CSHR 95% CI below 1) in the OD, VaD, and noNP groups. *APOE* ε2 was a significant risk factor for mortality in the OD group but significantly protective in the AD and AD.MED groups (Figure 5B and Table S4). Sensitivity analysis in all 48,605 NACC participants yielded CSHRs consistent in direction and significance with those from the primary sample of 31,664.

3.8 | Cause-specific competing risks analysis with IPW

The competing risks of death were further examined using inverse probability weighting (IPW) derived from autopsy propensity scores in the cause-specific survival model with the six neuropathology groups as the competing risks in the sample of 31,664, with 6547 autopsied decedents and 25,117 living participants as censored observations. The model included *APOE* ε4 status (ε4 carriers vs non-carriers) and *APOE* ε2 status (ε2/ε2 and ε2/ε3 vs all others) as the primary variables of interest. The model with age truncation included sex, baseline dementia status, and CDR-SB as covariates, and the model without age truncation included baseline age in addition to the other covariates. The 95% CIs for the CSHR were calculated using the robust standard errors. The CSHR and 95% CI of all regressors for the cause-specific model with age truncation and IPW are shown in Table 2.

competing risk group with other non-AD dementia neuropathology (OD) but it was associated with significantly decreased mortality risk in the pure AD and AD.MED groups. The middle panel (B) shows the cause-specific hazard ratios (CSHRs) and their 95% CIs for *APOE* ε4 and *APOE* ε2 on mortality risk from the Cox PH cause-specific model. The model included sex, baseline age, baseline CDR-SB, and baseline dementia status as well as autopsy propensity score strata. The effects of *APOE* ε4 and *APOE* ε2 on mortality were similar to the Fine and Gray model for all competing risk groups. The bottom panel (C) shows the CSHRs and 95% CIs for *APOE* ε4 and *APOE* ε2 on mortality risk from the Cox PH cause-specific model with inverse probability weighting (IPW) and baseline age truncation. The model included sex, baseline CDR-SB, and baseline dementia status as covariates. The effects of *APOE* ε4 and *APOE* ε2 on mortality were similar to the Fine and Gray model and the cause-specific model with autopsy propensity strata for all competing risk groups.

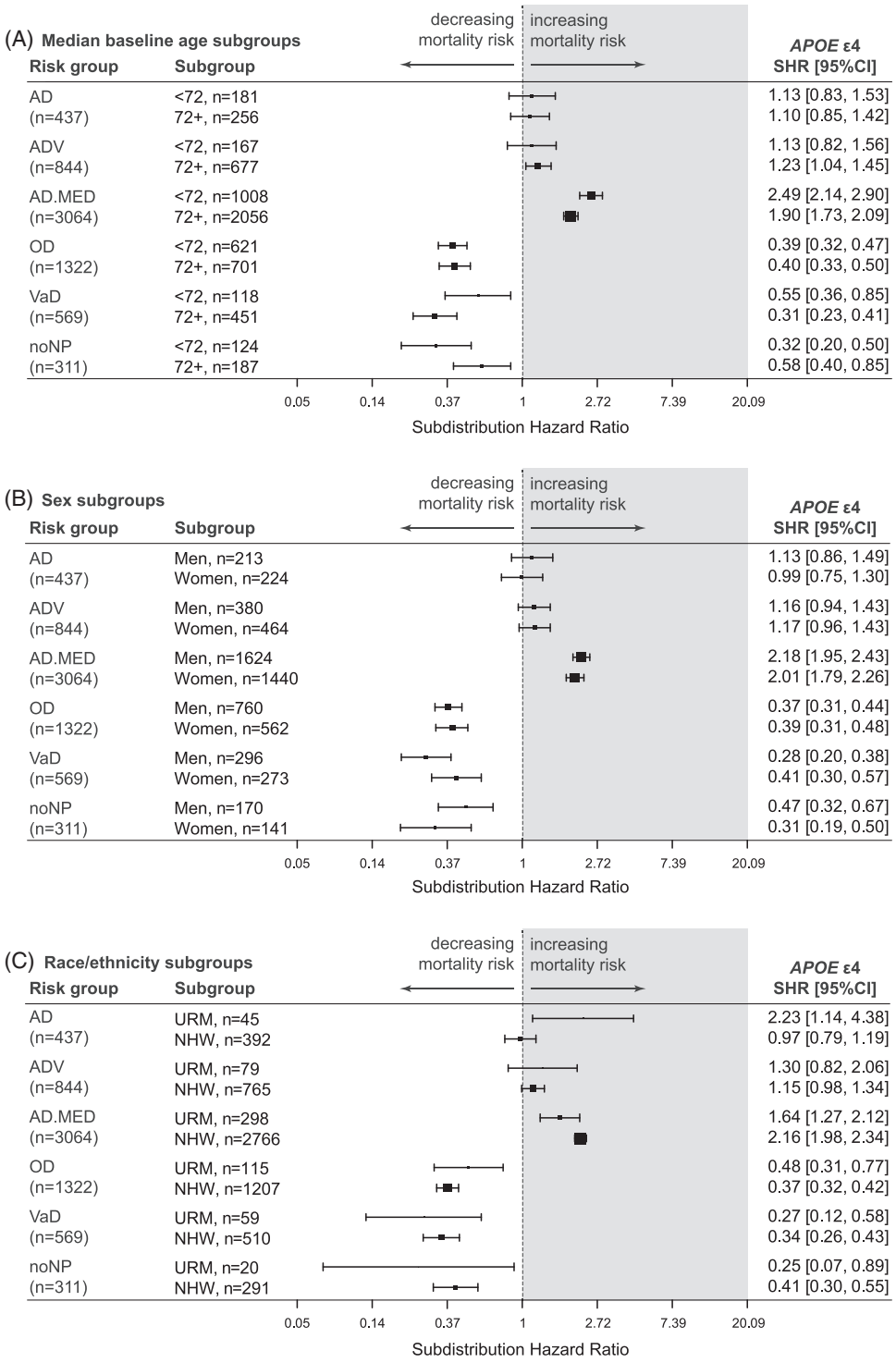

FIGURE 6 Forest plots of *APOE* ε4–related mortality risk within age, sex, and race/ethnicity subgroups across six neuropathology groups. The top panel (A) shows the mortality risk associated with *APOE* ε4 from the Fine and Gray model analyzed in subgroups subdivided by the baseline median age of 72 as a cutpoint. The evidence of mortality risk associated with *APOE* ε4 was weaker with older baseline age in the mixed Alzheimer's disease (AD) (AD.MED) and no neuropathology (noNP) groups and more protective in the group with vascular neuropathology (VaD), suggesting an age-related attenuation of ε4 effects as vascular neuropathology prevalence increases. The middle panel (B) shows the mortality risk associated with *APOE* ε4 from the Fine and Gray model analyzed in subgroups separated by sex. Although the evidence of effect of *APOE* ε4 was weaker among women than among men in the VaD group, it was weaker among men than among women in the noNP group. The bottom panel (C) shows the mortality risk associated with *APOE* ε4 from the Fine and Gray model analyzed in subgroups separated by race/ethnicity. *APOE* ε4 was associated with significant mortality risk among underrepresented racial/ethnic minority (URM) decedents in the pure AD competing risk group but did not reach statistical significance for non-Hispanic White (NHW) decedents in the same competing risk group despite sample size differences.

TABLE 2 Cause-specific model with inverse probability weighting (IPW).

Risk group	Regressor	CSHR [95% CI]	
		With left truncation	Without left truncation*
AD (*n*=437)	*APOE* ε4 status: ε4 carrier	1.11 [0.91, 1.36]	1.12 [0.91, 1.38]
	APOE ε2 status: ε2/ε2 and ε2/ε3	0.50 [0.30, 0.82]†	0.47 [0.28, 0.78]†
	Sex: Female	0.78 [0.64, 0.95]†	0.75 [0.62, 0.92]†
	Baseline CDR-SB	1.12 [1.09, 1.15]‡	1.14 [1.11, 1.17]‡
	Baseline dementia: demented	3.43 [2.59, 4.53]‡	4.63 [3.44, 6.23]‡
ADV (*n*=844)	*APOE* ε4 status: ε4 carrier	1.26 [1.08, 1.48]‡	1.27 [1.07, 1.49]‡
	APOE ε2 status: ε2/ε2 and ε2/ε3	0.75 [0.57, 0.99]†	0.71 [0.53, 0.96]†
	Sex: Female	0.80 [0.69, 0.93]†	0.78 [0.67, 0.90]†
	Baseline CDR-SB	1.12 [1.10, 1.14]‡	1.13 [1.10, 1.15]‡
	Baseline dementia: demented	1.76 [1.40, 2.20]‡	2.18 [1.72, 2.77] ‡
AD.MED (*n*=3064)	*APOE* ε4 status: ε4 carrier	1.79 [1.65, 1.95]‡	1.81 [1.62, 2.01]‡
	APOE ε2 status: ε2/ε2 and ε2/ε3	0.78 [0.65, 0.94]†	0.74 [0.59, 0.92]†
	Sex: Female	0.64 [0.59, 0.69]†	0.60 [0.55, 0.66]†
	Baseline CDR-SB	1.10 [1.09, 1.11]‡	1.14 [1.12, 1.15]‡
	Baseline dementia: demented	3.87 [3.48, 4.29]‡	5.64 [4.90, 6.48]‡
OD (*n*=1322)	*APOE* ε4 status: ε4 carrier	0.45 [0.39, 0.52]†	0.45 [0.39, 0.52]†
	APOE ε2 status: ε2/ε2 and ε2/ε3	1.52 [1.29, 1.78]‡	1.47 [1.22, 1.77]‡
	Sex: Female	0.56 [0.50, 0.63]†	0.55 [0.49, 0.63]†
	Baseline CDR-SB	1.08 [1.06, 1.10]‡	1.10 [1.08, 1.12]‡
	Baseline dementia: demented	3.86 [3.26, 4.58]‡	5.02 [4.15, 6.07]‡
VaD (*n*=569)	*APOE* ε4 status: ε4 carrier	0.39 [0.31, 0.50]†	0.39 [0.31, 0.50]†
	APOE ε2 status: ε2/ε2 and ε2/ε3	1.06 [0.83, 1.35]	1.03 [0.80, 1.33]
	Sex: Female	0.62 [0.52, 0.74]†	0.61 [0.51, 0.73]†
	Baseline CDR-SB	1.09 [1.05, 1.13]‡	1.08 [1.05, 1.12]‡
	Baseline dementia: demented	0.89 [0.65, 1.21]	1.02 [0.74, 1.41]
noNP (*n*=311)	*APOE* ε4 status: ε4 carrier	0.43 [0.32, 0.59]†	0.44 [0.32, 0.59]†
	APOE ε2 status: ε2/ε2 and ε2/ε3	1.08 [0.78, 1.51]	1.06 [0.76, 1.48]
	Sex: Female	0.59 [0.47, 0.74]†	0.58 [0.46, 0.73]†
	Baseline CDR-SB	1.12 [1.08, 1.17]‡	1.13 [1.08, 1.18]‡
	Baseline dementia: demented	0.82 [0.56, 1.21]	0.97 [0.65, 1.44]

Abbreviations: AD, Alzheimer's disease; AD.MED, multiple etiology dementia with Alzheimer's disease and other dementia neuropathology; ADV, Alzheimer's disease and vascular dementia co-pathology; CDR-SB, Clinical Dementia Rating Sum of Boxes; noNP, no neuropathology; OD, other non-AD dementia neuropathology; VaD, vascular dementia.

*The model without left truncation was adjusted for age at study entry as a covariate.

†Significantly reduced mortality risk.

‡Significantly increased mortality risk.

The effects for *APOE* ε4 and *APOE* ε2 in the cause-specific IPW models with and without age truncation were essentially identical to each other (Table S4). The effects for *APOE* ε4 were similar to the Fine and Gray model and the cause-specific model with autopsy propensity strata, where *APOE* ε4 was a significant risk factor (CSHR 95% CI above 1) for mortality in the ADV and AD.MED groups but significantly protective (CSHR 95% CI below 1) in the OD, VaD, and noNP groups (Figure 5C and Table S4). The results for *APOE* ε2 were slightly different from the stratified models where the protective effect in decedents with ADV was in the same direction and the HR reached nominal significance in the IPW model (Figure 5C and Table S4).

In terms of covariates in the cause-specific models with IPWs, female sex was associated with significantly decreased mortality, higher baseline CDR-SB (i.e., greater cognitive impairment) was associated with significantly increased mortality across all competing risk groups, and having dementia at baseline was associated significantly increased mortality in the AD neuropathology groups (AD, ADV, and AD.MED) and in the group with other non-AD dementia

neuropathologies (Table 2). Sensitivity analyses in all 48,605 NACC participants yielded CSHRs consistent in direction and significance with those from the primary sample of 31,664.

4 | DISCUSSION

This study uses the NACC dataset to assess subtypes of multiple-etiology dementia and ADRD, highlighting substantial discrepancies between clinical dementia diagnoses and neuropathological findings at death. We used logistic regression-based autopsy propensity scores to reduce autopsy participation related selection bias. Using the neuropathology subtypes of MED and ADRD, this study further examines how *APOE* ε4 and ε2 alleles differentially influence disease outcome and mortality risk in the context of specific combinations of neuropathologies. These analyses revealed that the effect of *APOE* genotypes on mortality varies depending on the presence and combination of underlying dementia neuropathologies.

Although *APOE* ε4 was significantly associated with higher mortality in individuals who had both AD neuropathology and CAA, it was not significantly associated with increased mortality in individuals who had AD neuropathology alone or had AD.MED without CAA (Figure 4). This suggests that the presence of CAA is one of the key drivers of mortality risk in ε4 carriers. In fact, *APOE* ε4 carriers without significant AD pathology had a significantly lower risk of death.[35] *APOE* ε4 was often reported as associated with higher mortality in all-cause survival analysis, which generally masks major heterogeneities across competing groups.[36,37]

When we subdivided by median enrollment age, the evidence on influence of *APOE* ε4 on mortality in decedents with mixed AD neuropathology weakened among older individuals, whereas the protective effect of *APOE* ε4 on mortality in decedents with VaD neuropathology alone strengthened among older individuals. This evidence of heterogeneous effects of *APOE* ε4 may reflect two converging effects: the increasing prevalence of vascular pathology with advanced age and a diminishing effect of ε4 on mortality in the oldest old. This finding is concordant with reported observations that the effect of *APOE* ε4 on mortality decreases with age longevity[38,39] along with the observations that cases of cerebrovascular disease and hippocampal sclerosis (HS-Aging) increase with age but incident cases of AD decrease with age [Figure 5].[40,41]

We found that the impact of *APOE* ε2 on mortality also varied by neuropathology group. Only the groups with multiple neuropathologies in addition to AD (AD.MED) or with AD neuropathology alone had significantly lower mortality risk associated with *APOE* ε2. In contrast, *APOE* ε2 was associated with significantly higher mortality risk in the group with mixed VaD and CAA neuropathology (Figure 4). This result may be related to reported associations of *APOE* ε2 with spontaneous intracerebral hemorrhage.[42,43,44] About 10% to 15% of strokes are due to intracerebral hemorrhage, which is associated with a high short-term mortality rate.[45,46,47] Thus, although *APOE* ε2 may appear to reduce mortality in individuals with pure AD pathology, it may confer vulnerability in contexts involving cerebrovascular disease—particularly where CAA is also present. These findings underscore the importance of considering neuropathological heterogeneity when interpreting *APOE* genotype effects.

Taken together, these findings indicate that the impact of *APOE* genotypes on disease outcomes and mortality depends not only on the presence of AD neuropathology but also on the presence of non-AD multiple etiology dementias. *APOE* ε4 can be protective; *APOE* ε2 can be harmful. Instead, their effects are related to the presence of other coexisting neuropathologies, particularly vascular lesions, and may be further shaped by other factors. It is important to note that many of these contributing conditions, including vascular disease and CAA, are influenced by many modifiable risk factors such as cholesterol levels, blood pressure, and lifestyle choices (e.g., sleep). The 2024 Lancet Commission emphasizes that targeting these modifiable risk factors can significantly reduce dementia burden.[9]

These findings have major implications for dementia prevention and management. Although no cure currently exists for AD, many of the most common comorbid conditions contributing to mortality in individuals with mixed AD neuropathology, particularly vascular contributors, are preventable or treatable using lifestyle modifications and specific medications. Recognizing that genetic risk interacts with lifestyle factors and the underlying mixed pathology can inform more individualized approaches to prevention and care.

Beyond mortality, our results reinforce the diagnostic challenges posed by multiple-etiology dementias. Although 42% of decedents had been clinically diagnosed with AD alone, only 7% had pure AD neuropathology at autopsy. The majority had mixed neuropathologies, most of which went undiagnosed during life. Among decedents with multiple pathologies, 76% had been diagnosed with a single dementia type at their last clinical visit. Furthermore, mixed neuropathologies were underdiagnosed in more than 70% of participants not labeled as having dementia clinically, suggesting that neuropathological changes often preceded or go undetected clinically despite the absence of cognitive symptoms.

Although there is a time gap between the final clinical assessment and the autopsy, 75% of individuals in the NACC sample died within 2.25 years of their last clinical evaluation. Given that dementia-related neuropathologies typically develop over many years or decades before clinical symptoms emerge,[48,49] it is reasonable to assume that most of the observed neuropathologies were already present at the time of the final diagnosis. Furthermore, the rate of underdiagnosis was high, even among the subsample of decedents who died within 1 year of their last clinical evaluation in 2020 or later. In addition, the neuropathological lesions observed at clinical visits are unlikely to disappear in autopsy due to the lack of effective disease-modifying treatments for AD.

This underdiagnosis of mixed dementias underscores the need for more precise, pathology-informed diagnostic tools that can differentiate among overlapping syndromes during life. Clinicians often rely on the most prominent presenting features, which can mask underlying co-pathologies. Consequently, treatment plans, prognostic assessments, and clinical trial enrollments may be based on incomplete or inaccurate information. Accurate, early detection of mixed

pathologies is essential for targeting appropriate interventions, especially in cases where modifiable factors play a key role.

Our results suggest that incorporating *APOE* genotyping into clinical models could help identify vulnerable subgroups of individuals at greater risk from specific mixed ADRD pathologies. For example, given that about 20% to 24% of non-demented seniors carry at least one copy of the *APOE* ε4 alleles in worldwide populations,[50] ε4 carriers with suspected CAA or ε2 carriers with vascular risk factors may benefit from more aggressive cardiovascular monitoring or preventive strategies. Moreover, applying a competing risks framework allows researchers to assess the impact of individual factors across heterogeneous disease processes, enabling more targeted assessments of therapeutic potential and safety. There exists potential for modifying comorbid pathologies to slow down the overall ADRD progression in some vulnerable subgroups of patients in the competing risk setting.

This study has several limitations. The NACC cohort is not fully representative of the general population. The existing NACC participants tend to be more educated, less racially and ethnically diverse, and often enroll due to cognitive concerns. In addition, survivor bias may influence the results, as individuals who remain in longitudinal studies until death may differ from those who drop out earlier, particularly in age-related analyses. These limitations underscore the importance of validating findings in future studies across more representative and diverse cohorts. In addition, using competing risks analyses, we assessed the significant heterogeneous effect of *APOE* variants on mortality risk typically masked in the existing all-cause mortality analyses. Assessing the effect of *APOE* variants on survival after clinical diagnoses of MED would also be of clinical importance. Therefore, a meaningful follow-up study could use NACC autopsy data to confirm clinical diagnoses, and using competing risk models to adjust for left and right truncation via IPW.[51,52]

A major strength of this study is the robustness of the findings across different models, strategies for adjusting for selection bias using autopsy propensity scores, and sensitivity analyses. Despite differing interpretations of subdistribution and cause-specific hazards, our results consistently showed decreased *APOE* ε4–related mortality risk in subjects without AD neuropathologies and increased mortality risk with mixed AD plus other dementia neuropathologies.

In summary, this study highlights the widespread underdiagnosis of MEDs and the complexity of interpreting *APOE*-related disease outcome and mortality risks. *APOE* ε4 and ε2 do not exert uniform effects across all dementia types and across the human lifespan. Instead, their influence on mortality depends on the specific combinations of underlying neuropathologies. These findings support a more integrated and individualized model of dementia diagnosis and prognosis, one that goes beyond single etiological labels and accounts for the interplay between genetics, pathology, and modifiable risk factors. Moving toward such models will require continued investment and investigation in autopsy-confirmed datasets, and novel biomarkers capable of detecting and distinguishing subtypes of MEDs early and in vivo. Improving diagnostic precision during life is essential for tailoring prevention and interventions, refining clinical trials, and ultimately addressing the full complexity of dementia.

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CONSENT STATEMENT

All studies and experimental protocols conducted by each Alzheimer's Disease Research Center (ADRC) contributing to the National Alzheimer's Coordinating Center (NACC) were approved by their

respective institutional review boards prior to the initiation of the studies. Written informed consent was obtained for all study participants at each ADRC. At all participating sites, all studies and methods were conducted in accordance with the principles expressed in the 1964 Declaration of Helsinki and its later amendments. This study addresses the heterogeneity of the disease and at-risk populations by highlighting the frequent underdiagnosis of mixed dementia pathologies, particularly among older adults, and by showing that genetic risk factors such as *APOE* ε4 and ε2 have differential effects on mortality and pathology across diverse subgroups. It underscores the importance of considering age, genetic background, and coexisting vascular conditions in understanding disease risk and in clinically and demographically varied populations.

CONFLICT OF INTEREST STATEMENT

Author disclosures are available in the Supporting Information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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