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RESEARCH ARTICLE

Exploring epidemiological risk factors for cerebral amyloid angiopathy: Considerations for monoclonal antibody therapy in people with Alzheimer's disease

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Abstract

INTRODUCTION: Cerebral amyloid angiopathy (CAA) increases the risk of amyloid-related imaging abnormalities in Alzheimer's disease (AD) patients receiving anti-amyloid-beta therapies, emphasizing the need to identify its risk factors.

METHODS: Data were collected from three cohort studies, and a machine learning model was developed to predict CAA occurrence using the selected risk factors.

RESULTS: The AD neuropathologic changes (ADNC)-CAA association was significantly positive in the cross-sectional analysis. When stratified by selected risk factors, this association was generally stronger among females, smokers, people with a history of stroke/memory complaints, apolipoprotein E (APOE)-ε4 carriers, and those without diabetes/heart conditions. In the longitudinal analysis of the association between potential risk factors and CAA, a higher risk of CAA was observed among males, older individuals, smokers, people with diabetes/heart conditions, lower Mini-Mental State Examination (MMSE) scores, and APOE-ε4 carriers compared to their respective reference groups.

DISCUSSION: Our study identified risk factors for cerebral amyloid angiopathy, informing potential prevention strategies.

KEYWORDS
Alzheimer's disease, amyloid-related imaging abnormalities, cerebral amyloid angiopathy, neuropathology

Highlights

- ADNC were significantly positively associated with the risk of CAA.
- The ADNC-CAA association was generally stronger among females, smokers, people with a history of stroke/memory complaints, APOE-ε4 carriers, and those without diabetes or heart conditions.

- Longitudinally, higher CAA risk was observed among males, older individuals, smokers, people with diabetes/heart conditions/lower MMSE scores, and APOE-ε4 carriers compared to their reference groups.

1 | INTRODUCTION

Cerebral amyloid angiopathy (CAA) is a disorder characterized by the accumulation of amyloid-beta (Aβ) peptides in the walls of cerebral blood vessels, which weakens the vasculature and significantly increases the risk of intracerebral hemorrhages.[1,2] CAA often occurs sporadically and can be found in cognitively normal older adults, and it is more frequently observed in people with Alzheimer's disease (AD).[3] A rare complication of the disease is CAA-related inflammation (CAA-ri), which occurs spontaneously and can trigger amyloid-related imaging abnormalities (ARIA). Currently, a probable CAA diagnosis is achieved using MRI based on the Boston Criteria v2.0,[4] and a definitive diagnosis is only achievable via *post mortem* examination.[1] The MRI findings of CAA and CAA-ri closely resemble ARIA-H (brain microhemorrhage) and ARIA-E (brain edema), respectively.[5,6] Both forms of ARIA have been observed in AD patients receiving anti-Aβ monoclonal antibody drugs (MABs, e.g., lecanemab and donanemab), with ARIA-E (lecanemab 13%, donanemab 24%) and ARIA-H (lecanemab 17%, donanemab 31%) appearing to relate to the presence of CAA.[7,8] The exact pathophysiological mechanisms underlying this link are not yet clearly understood, although putative mechanism and models have been proposed by Sperling et al.[9] and Hampel et al.[6]

The known risk factors for CAA include age and APOE-ε4.[1,10] In addition, males are more likely to experience an earlier onset of CAA and hemorrhage than females.[11] However, no study has yet comprehensively evaluated potential risk factors for CAA from multiple perspectives, including neuropathological changes, demographic factors, lifestyle factors, medical comorbidities, and other factors, across multiple cohorts. Gaining a deeper understanding of these risk factors carries two significant clinical implications: (1) guiding the development of preventative strategies for CAA, which may reduce the risk of ARIA, and (2) providing evidence for future risk assessment of CAA for individuals considering anti-Aβ MAB treatment. Here, utilizing data from participants of the Religious Orders Study (ROS), the Rush Memory and Aging Project (MAP), and the Minority Aging Research Study (MARS), we examined the cross-sectional associations between neuropathological changes and CAA. Identifying neuropathology highly associated with CAA that have a better diagnostic approach can potentially facilitate the diagnosis of the coexisting CAA. We also explored longitudinal associations between demographic/lifestyle/medical history and CAA. The identified risk factors were used for the development and validation of a machine learning model to predict CAA. Our study comprehensively explores the risk factors for CAA, where a CAA prediction model has also been developed.

2 | METHODS

2.1 | Data sources

This study adheres to the STROBE guideline for observational research[12] and analyzed data collected from older adults in three ongoing community-based cohorts: (1) The ROS, initiated in 1994, recruited older Catholic nuns, priests, and brothers from across the United States[13]; (2) The MAP, which began in 1997, enrolled older adults from subsidized senior housing and retirement communities in Chicagoland and northeastern Illinois[13]; (3) The MARS, launched in 2004, focused on African American older adults.[14] Each study was approved by the Institutional Review Board of Rush University Medical Centre. All participants were free from dementia at enrollment and provided informed consent, including an optional body donation agreement under the Anatomical Gift Act. All these studies share a large common core of data, which has been harmonized at item level.[13]

2.2 | Exposure and outcome

We are interested in neuropathological risk factors (exposures), including: (1) AD neuropathologic changes (ADNC)[15]; (2) transactive response DNA-binding protein 43 kDa (TDP-43) pathology[16]; (3) hippocampal sclerosis[17]; (4) macroinfarcts[18]; (5) microinfarcts[19]; (6) cerebral atherosclerosis[20]; (7) arteriolosclerosis[21]; and (8) Lewy body disease pathology (LBP).[22]

Our outcome of interest is CAA,[23] which is analyzed for both the presence of pathology (no/yes) and severity (none/mild/moderate/severe). The neuropathological evaluation and classification have been summarized in Table 1. We are also interested in demographic (D), lifestyle (L), medical comorbidities (M), and other (O) risk factors (DLMO; details available in eTable S1), which are collectively referred to as the DLMO risk factors. All neuropathology data were obtained at *post mortem* by neuropathologists, and DLMO risk factors were obtained from the baseline records.

2.3 | Statistical analyses

Data analyses were conducted using Stata (version 17.0) and R (version 4.3.1). All tests were two-sided, with significance set at $p < 0.05$. The chi-squared test (for qualitative variables) and ANOVA (for quantitative variables) were used to compare the characteristics of participants with and without CAA. Exposure and outcome variables were treated as dichotomous or ordinal variables where applicable (Table 1 and

RESEARCH IN CONTEXT

1. **Systematic review**: We systematically searched Embase, Global Health, and Ovid MEDLINE from 1980 to April 24, 2024 for studies on risk factors for cerebral amyloid angiopathy (CAA). The search used MeSH terms and keywords such as "Alzheimer's disease," "cerebral amyloid angiopathy," "cerebral hemorrhage," "amyloid-related imaging abnormalities (ARIA)," "lecanemab," "donanemab," and "anti-Aβ monoclonal antibody." Few studies explored CAA risk factors.
2. **Interpretation**: Our study uses data from three aging cohorts to comprehensively evaluate multiple CAA risk factors. In addition, we developed a machine learning model to predict CAA occurrence based on these identified risk factors.
3. **Future directions**: Enhancing our understanding of CAA risk factors is essential for improving the safety of anti-amyloid-beta treatments in patients with Alzheimer's disease. Future studies should validate these findings in datasets that include a more diverse population.

eTable S1). Odds ratios (ORs) from logistic regression were used to measure the cross-sectional association between neuropathology risk factors and CAA. Likelihood ratio tests (LRTs) were employed to assess the effect modification by the DLMO risk factors on the ADNC-CAA association. Associations of baseline DLMO risk factors with risk of CAA were assessed through Poisson regression models[24] using robust error variance.[25] The effect modification by ADNC on these associations was evaluated using Wald tests (WTs). Both cross-sectional and longitudinal models were adjusted for the DLMO risk factors. Given the strong relationship between CAA and AD observed in previous studies,[26,27] each AD-related neuropathological change (ADNC [Aβ plaque, NP, NFT], and TDP-43 pathology) may act as a confounder in analyses of their association with the risk of CAA. Therefore, a sensitivity analysis was conducted, where each AD-related neuropathological change was sequentially adjusted to control for potential confounding bias.

2.4 | Machine learning model development

We employed a structured machine learning pipeline tailored for analyzing the predictive ability of features informed by epidemiological analysis (DLMO risk factors) of the data collected in the ROS/MAP/MARS studies. The preprocessing step addressed missing data (6% per column in the dataset) using the missRanger package in R for imputation. This method leverages random forest algorithms to predict missing values by identifying patterns and correlations within the data, thereby providing more accurate estimates than traditional techniques. For model construction, we employed a 10-fold stratified cross-validation approach to mitigate overfitting. We evaluated the performance of six machine learning models from the scikit-learn library, logistic regression, decision tree, support vector machine, random forest, gradient boosting, and Gaussian Naive Bayes, using the area under the receiver operating characteristic (ROC-AUC) curve. No significant differences in model performance were observed. To ensure reproducibility, all procedures involving data splitting (90% data construction, 10% data for internal validation) and model training were conducted with a fixed random seed, and default parameters were applied throughout, while both internal and external validation results were presented. This process is graphically presented in eFigure S1.

3 | RESULTS

Of the 4642 participants in the ROS/MAP/MARS studies, 2118 participants with *post mortem* neuropathology data were included in the cross-sectional analyses. In addition, 2048 participants with ≥12 months of follow-up time were included in the longitudinal analyses. Participant characteristics are summarized in Table 2. There are no missing data for sex, age at baseline, education, race, Aβ plaque, or medical conditions. Among the participants, 69% are female, and 91% are Caucasian. The mean age at baseline is 79.9 years (standard deviation [SD] 7.2), and the average follow-up is 9.9 years (SD 5.9). Interestingly, among 1653 CAA-positive individuals, 128 (7.7%) showed no Aβ plaques upon *post mortem* evaluation. Fewer than 6% of values are missing for other factors.

3.1 | Cross-sectional analysis

3.1.1 | Neuropathology risk factor-CAA associations

The distribution of neuropathological changes in the study participants is shown in Table 2, where the participants are grouped by their CAA diagnosis (no/yes). This distribution is also presented in Figure 1 and eFigure S2, where participants are grouped according to their CAA severity (none/mild/moderate/severe). Participants with ADNC, Aβ plaque (Thal phases 4&5), moderate/frequent NP, NFT (Braak stages V&VI), or TDP-43 pathology[16] in the neocortical region had a higher proportion of CAA (all $p < 0.001$). The distribution of the remaining neuropathological changes across CAA diagnostic status or severity levels showed no significant findings (Table 2 and eFigure S2).

Controlling for DLMO risk factors, associations were observed between NP (OR 8.71 [6.69-11.32], $p < 0.001$), Aβ plaque (OR 7.28 [95% confidence interval (CI) 5.48–9.68], $p < 0.001$), NFT (OR 2.93 [2.21–3.88], $p < 0.001$), TDP-43 (OR 1.42 [1.09–1.84], $p = 0.01$), and odds of CAA (any severity). These associations increased as neuropathology advanced in stage (Figure 2 and eTable S2). When examining CAA severity separately (eTable S3), Aβ plaque, NP, and NFT remained associated with mild, moderate, and severe CAA, with increasing association strength as CAA severity rose. Notably, Aβ

TABLE 1 *Post mortem* neuropathology assessment and types of variables.

Neuropathological changes	Description	Types of variables used in the present study
Cerebral amyloid angiopathy (CAA)	CAA pathology was examined in four neocortical regions (midfrontal, midtemporal, angular, and calcarine cortices) using immunohistochemistry. Arterioles and capillaries were assessed.[23,24] Paraffin-embedded sections were stained for amyloid-β (Aβ) with the following monoclonal antibodies: **4G8** (1:9000; Covance Labs, Madison, WI), **6F/3D** (1:50; Dako North America Inc., Carpinteria, CA), and **10D5** (1:600; Elan Pharmaceuticals, San Francisco, CA).[23] A semiquantitative scale was developed to classify CAA pathology into four levels of severity (none, mild, moderate, severe) based on the number of amyloid deposits and the number of vessels involved, with cutoffs determined by neuropathologists.[23]	**Dichotomous variable**: No (without CAA), Yes (mild to severe CAA)
	0 = no deposition; 1 = scattered segmental but no circumferential deposition; 2 = circumferential deposition in up to 10 vessels; 3 = circumferential deposition in up to 75% of the region; 4 = circumferential deposition in over 75% of the total region. **None**: average = 0; **Mild**: average <1.5 (between 0.25 and 1.4); **Moderate**: average 1.5 to 2.5; **Severe**: average > 2.5. The CAA score for each region was determined by taking the higher of the meningeal and parenchymal scores. These regional scores were then averaged to provide a continuous measure of overall CAA pathology.[23]	**Ordinal variables**: None, Mild, Moderate, Severe
AD neuropathologic change (ADNC)	The National Institute on Aging-Alzheimer's Association (NIA-AA) criteria for ADNC are based on a combination of three pathologic hallmarks of AD: **amyloid-β plaque** (Aβ plaque, detected using immunohistochemistry), **neurofibrillary tangles** (NFT, visualized using Bielschowsky silver stain), and **neuritic plaque** (NP, visualized using thioflavin S or modified Bielschowsky).[15] The neuropathologist determines the overall severity of AD, into four categories: no AD, low, intermediate, and high severity.	**Dichotomous variable**: No (no AD/low severity), Yes (intermediate/high severity)
Amyloid-ß (Aß) plaque	Based on a 6-level measure of Aß deposits involving different regions of the brain.[15] 1. No Aß plaques 2. Thal phase 1: Neocortex only 3. Thal phase 2: Neocortex + hippocampus 4. Thal phase 3: Neocortex (with or without hippocampus) + basal ganglia 5. Thal phase 4: Neocortex (with or without hippocampus) + basal ganglia + substantia nigra 6. Thal phase 5: Neocortex (with or without hippocampus) + basal ganglia (with or without substantia nigra) + cerebellum	**Dichotomous variable**: No (without Aß plaques), Yes (Thal phase 1 to 5) **Ordinal variables**: Without, Thal phase 1&2, Thal phase 3, Thal phase 4&5
Neuritic plaque (NP)	The NP score is based on semiquantitative estimates of NP density.[15] 1. No NP 2. Sparse NP 3. Moderate NP 4. Frequent NP	**Dichotomous variable**: No (without NP), Yes (sparse, moderate, frequent NP) **Ordinal variables**: Without, Sparse, Moderate, Frequent
Neurofibrillary tangle (NFT)	The Braak score is based on measures of NFT pathology in different regions of the brain.[15] 1. Braak stage 0 – No NFTs 2. Braak stages I or II – NFTs primarily confined to the entorhinal region 3. Braak stages III or IV – Involvement of limbic regions, such as the hippocampus 4. 3) Braak stages V or VI – Moderate to severe involvement of neocortical regions	**Dichotomous variable**: Braak stages 0 to II, Braak stages III to VI **Ordinal variables**: Braak stage 0 to II, Braak stage III or IV, Braak stage V or VI

(Continues)

TABLE 1 (Continued)

Neuropathological changes	Description	Types of variables used in the present study
Transactive response DNA binding protein 43 kDa (TDP-43)	TDP-43 immunohistochemistry was conducted on eight brain regions—amygdala, entorhinal cortex, CA1 and dentate gyrus of the hippocampus, anterior temporal pole cortex, midtemporal cortex, orbitofrontal cortex, and midfrontal cortex—using the phosphorylated monoclonal antibody **TAR5P-1D3** (pS409; 1:1000, Ascension, Munich, Germany) TDP-43 antibody.[16] Four stages of TDP-43 distribution were summarized as: 1. None 2. Amygdala only 3. Amygdala + limbic 4. Amygdala + limbic + neocortical	**Dichotomous variable**: None or amygdala only, Extending beyond amygdala **Ordinal variables**: Without, Amygdala, Amygdala + Limbic, Amygdala + Limbic + Neocortical
Hippocampal sclerosis	Hippocampal sclerosis is defined as severe neuronal loss and gliosis in CA1 and/or the subiculum. It is assessed unilaterally in a coronal section of the mid hippocampus at the level of the lateral geniculate body.[17]	**Dichotomous variable**: No, Yes
Macroinfarcts	Slabs were inspected with the naked eye for the presence of macroinfarcts. All grossly visualized and suspected macroscopic infarcts were dissected for histologic confirmation.[18]	**Dichotomous variable**: No, Yes
Microinfarcts	Six cortical regions (midfrontal, middle temporal, entorhinal, hippocampal, inferior parietal, anterior cingulate cortices), two subcortical regions (anterior basal ganglia, thalamus), and the midbrain in one hemisphere were examined for microinfarcts using 6 μm paraffin-embedded sections stained with hematoxylin/eosin.[19]	**Dichotomous variable**: No (without microinfarcts), Yes (with microinfarcts)
Cerebral atherosclerosis	After paraformaldehyde fixation, the circle of Willis at the base of the brain was examined for the presence of atherosclerosis, including the vertebral, basilar, posterior cerebral, middle cerebral, and anterior cerebral arteries, along with their proximal branches.[20] Four stages of cerebral atherosclerosis distribution were summarized as: 1. None – No significant atherosclerosis observed 2. Mild – Small amounts of atherosclerosis in up to several arteries (typically less than 25% vessel involvement) without significant occlusion 3. Moderate – Atherosclerosis present in up to half of all visualized major arteries, with less than 50% occlusion of any single vessel 4. Severe – Atherosclerosis present in more than half of all visualized arteries and/or more than 75% occlusion of one or more vessels	**Dichotomous variable**: No (without cerebral atherosclerosis), Yes (mild to severe cerebral atherosclerosis) **Ordinal variables**: Without, Mild, Moderate, Severe
Arteriolosclerosis	Sections in the anterior basal ganglia region were inspected for arteriolosclerosis, with histological changes defined by intimal deterioration, smooth muscle degeneration, and fibrohyalinotic thickening of arterioles, resulting in the narrowing of the vascular lumen.[21] Four stages of arteriolosclerosis distribution were summarized as: 1. Without 2. Mild 3. Moderate 4. Severe	**Dichotomous variable**: No (without arteriolosclerosis), Yes (mild to severe arteriolosclerosis) **Ordinal variables**: Without, Mild, Moderate, Severe
Lewy Body diseases pathology (LBP)	Immunohistochemistry was used to examine LBP in seven brain regions (midfrontal, midtemporal, inferior parietal, anterior cingulate, entorhinal cortices, amygdala, and midbrain). Paraffin-embedded sections were immunostained for brain tissue using α-synuclein (Zymed; 1:50).[22] McKeith criteria were modified to assess the following categories of Lewy body disease: 1. Not present 2. Nigral-predominant 3. Limbic-type 4. Neocortical-type	**Dichotomous variable**: No (without LBP), Yes (Nigral-predominant, Limbic-type or Neocortical-type) **Ordinal variables**: Without, Nigral-predominant, Limbic-type, Neocortical-type

TABLE 2 Characteristics of study participants.

	Cerebral amyloid angiopathy (CAA)[a]			
Measures	**No (*n* = 465)**	**Yes (*n* = 1653)**	***p*-value**	**All (*n* = 2118)**
Alzheimer's disease neuropathological changes (ADNC)			**<0.001**	
No	330 (71.7)	388 (24.1)		718 (34.6)
Yes	130 (28.3)	1225 (76.0)		1355 (65.4)
Amyloid-ß plaque (Aß plaque)			**<0.001**	
Without Aß plaques	191 (41.1)	128 (7.7)		319 (15.1)
Thal phase 1&2[b]	139 (29.9)	242 (14.7)		381 (18.0)
Thal phase 3[b]	80 (17.2)	528 (31.9)		608 (28.7)
Thal phase 4&5[b]	55 (11.8)	755 (45.7)		810 (38.2)
Neuritic plaque (NP)			**<0.001**	
Without neuritic plaque	277 (59.8)	211 (13.0)		488 (23.4)
Sparse	37 (8.0)	128 (7.9)		165 (7.9)
Moderate	98 (21.2)	675 (41.6)		773 (37.1)
Frequent	51 (11.0)	607 (37.5)		658 (31.6)
Neurofibrillary tangle (NFT)			**<0.001**	
Braak stage 0 to II[c]	146 (31.5)	199 (12.3)		345 (16.6)
Braak stages III or IV[c]	287 (62.0)	890 (54.9)		1177 (56.5)
Braak stages V or VI[c]	30 (6.5)	532 (32.8)		562 (26.9)
Transactive DNA-Binding Protein-43 (TDP-43) pathology			**<0.001**	
none	248 (55.5)	705 (44.6)		953 (47.0)
amygdala	86 (19.2)	278 (17.6)		364 (18.0)
amygdala + limbic	38 (8.5)	172 (10.9)		210 (10.3)
amygdala + limbic + neocortical	75 (16.8)	425 (26.9)		500 (24.7)
Hippocampal sclerosis			0.17	
No	423 (92.4)	1454 (90.2)		1877 (90.7)
Yes	35 (7.6)	157 (9.8)		192 (9.3)
Macroinfarcts			0.58	
No	289 (62.8)	1036 (64.2)		1325 (63.9)
Yes	171 (37.2)	577 (35.8)		748 (36.1)
Microinfarcts			0.53	
No	320 (69.6)	1097 (68.0)		1417 (68.4)
Yes	140 (30.4)	516 (32.0)		656 (31.6)
Arteriolosclerosis			0.51	
Without arteriolosclerosis	158 (34.4)	537 (33.3)		695 (33.5)
Mild	156 (33.9)	529 (32.8)		685 (33.0)
Moderate	100 (21.7)	404 (25.0)		504 (24.3)
Severe	46 (10.0)	144 (8.9)		190 (9.2)
Cerebral atherosclerosis			0.47	
Without cerebral atherosclerosis	94 (20.3)	292 (17.7)		386 (18.3)
Mild	235 (50.8)	828 (50.2)		1063 (50.3)
Moderate	110 (23.8)	439 (26.6)		549 (26.0)
Severe	24 (5.2)	90 (5.5)		114 (5.4)

(Continues)

TABLE 2 (Continued)

Measures	Cerebral amyloid angiopathy (CAA)[a]			
	No ($n = 465$)	Yes ($n = 1653$)	p-value	All ($n = 2118$)
Lewy Body diseases pathology (LBP)			0.65	
Without Lewy Body disease	355 (78.5)	1184 (76.1)		1539 (76.6)
Nigral-predominant[d]	9 (2.0)	27 (1.7)		36 (1.8)
Limbic-type[d]	32 (7.1)	120 (7.7)		152 (7.6)
Neocortical-type[d]	56 (12.4)	225 (14.5)		281 (14.0)
Sex, *n* (%)			0.81	
Female	320 (68.8)	1147 (69.4)		1467 (69.3)
Male	145 (31.2)	506 (30.6)		651 (30.7)
Age at baseline, mean [SD]	78.6 [7.5]	80.38 [7.2]	0.20	79.9 [7.2]
Education, *n* (%)			0.67	
≤12 years	95 (20.4)	322 (19.5)		417 (19.7)
13-18 years	266 (57.2)	929 (56.2)		1195 (56.4)
>18 years	104 (22.4)	402 (24.3)		506 (23.9)
Race			**<0.001**	
Caucasians	406 (87.3)	1530 (92.6)		1936 (91.4)
Non-Caucasians	59 (12.7)	123 (7.4)		182 (8.6)
Alcohol consumption, *n* (%)			0.52	
None/infrequent drinker	318 (68.4)	1170 (70.8)		1488 (70.3)
Occasional drinker	40 (8.6)	143 (8.7)		183 (8.6)
Frequent drinker	107 (23.0)	340 (20.5)		447 (21.1)
Smoking status, *n* (%)			0.07	
No	293 (64.0)	1123 (68.5)		1416 (67.5)
Yes	165 (36.0)	516 (31.5)		681 (32.5)
Hypertension			**0.03**	
No	214 (46.1)	856 (51.8)		1070 (50.6)
Yes	250 (53.9)	796 (48.2)		1046 (49.4)
Diabetes			**0.02**	
No	388 (83.6)	1448 (87.7)		1836 (86.8)
Yes	76 (16.4)	204 (12.4)		280 (13.2)
Heart conditions			0.77	
No	412 (88.8)	1458 (88.3)		1870 (88.4)
Yes	52 (11.2)	193 (11.7)		245 (11.6)
Stroke			0.20	
No	400 (89.3)	1444 (91.3)		1844 (90.8)
Yes	48 (10.7)	138 (8.7)		186 (9.2)
Cancer			0.53	
No	299 (65.6)	1098 (67.2)		1397 (66.8)
Yes	157 (34.4)	537 (32.8)		694 (33.2)
Claudication			0.51	
No	419 (92.5)	1522 (93.4)		1941 (93.2)
Yes	34 (7.5)	108 (6.6)		142 (6.8)

(Continues)

TABLE 2 (Continued)

Measures	Cerebral amyloid angiopathy (CAA)[a] No ($n = 465$)	Yes ($n = 1653$)	p-value	All ($n = 2118$)
Head injury			0.35	
No	417 (92.9)	1492 (94.1)		1909 (93.8)
Yes	32 (7.1)	94 (5.9)		126 (6.2)
Memory complaints			0.14	
No	309 (66.9)	1035 (63.1)		1344 (63.9)
Yes	153 (33.1)	605 (36.9)		758 (36.1)
APOE-ε4 carrier status			**<0.001**	
APOE-ε4 non-carrier	396 (88.8)	1092 (69.9)		1488 (74.1)
APOE-ε4 carrier (homo/heterozygous)	50 (11.2)	471 (30.1)		521 (25.9)
Vision acuity			0.28	
High	418 (92.1)	1458 (90.4)		1876 (90.8)
Low	36 (7.9)	155 (9.6)		191 (9.2)
Medical conditions			0.16	
No	89 (19.1)	367 (22.2)		456 (21.5)
Yes	376 (80.9)	1286 (77.8)		1662 (78.5)
MMSE			**0.001**	
=30	117 (25.2)	343 (20.8)		460 (21.8)
25-29	302 (65.0)	1018 (61.8)		1320 (62.4)
20-25	36 (7.7)	215 (13.0)		251 (11.9)
<20	10 (2.1)	72 (4.4)		82 (3.9)

Statistical significance: The chi-squared test (for qualitative variables) and ANOVA (for quantitative variables) were used to compare the characteristics of participants with and without CAA. The statistics in bold indicate statistical significance ($p < 0.05$).
[a]Refer to Table 1, row 2.
[b]Refer to Table 1, row 4.
[c]Refer to Table 1, row 6.
[d]Refer to Table 1, row 13.

plaque at Thal phases 4&5 (OR 57.92 [25.26–132.81], $p < 0.001$) and frequent NP (OR 35.89 [17.59–73.23], $p < 0.001$) were associated with significantly higher odds of severe CAA. NFT at Braak stages V or VI (OR 25.10 [13.70–46.03], $p < 0.001$) was associated with significantly higher odds of moderate CAA. Interestingly, TDP-43 pathology was associated with CAA (moderate: OR 1.59 [1.07–2.38]; severe: OR 1.79 [1.11–2.87], all $p = 0.02$) only in the neocortical regions. In addition, mild cerebral atherosclerosis was associated with a 1.71-fold increase in the odds of severe CAA (OR 1.71 [1.03–2.86], $p = 0.04$).

3.1.2 | Stratified ORs for the ADNC-CAA association and effect modification by DLMO

ADNC increased the odds of CAA (any severity: OR 7.21 [5.57–9.33], $p < 0.001$), with the strength of the association increasing as CAA severity advanced (mild: OR 5.44 [4.12–7.19]; moderate: OR 11.69 [8.13–16.82]; severe: OR 12.34 [7.90–19.28], all $p < 0.001$) (Table 3, upper panel). The ADNC-CAA association, stratified by DLMO risk factors, is shown in the lower panel of Table 3. The OR of the ADNC-CAA association was generally higher in females, non-Caucasians, smokers, and people with a history of stroke, head injury, memory complaints, or APOE-ε4 carriers. In addition, the p-value of the LRT indicated that education was a potential effect modifier of the association between ADNC and moderate CAA (LRT $p = 0.02$). Interestingly, the stratified ORs suggested that the association increased with more years of education (≤12 years: OR 4.76 [2.24–10.11]; 13–18 years: OR 13.02 [8.05–21.06]; > 18 years: OR 20.95 [9.38–46.81], all $p < 0.001$). Smoking appeared to be a potential effect modifier for the ADNC-mild CAA association (LRT $p = 0.04$), with higher odds observed in smokers compared to non-smokers (non-smokers: OR 4.51 [3.25–6.26]; smokers: OR 8.39 [5.03–13.97], all $p < 0.001$). Moreover, diabetes was a potential effect modifier of the ADNC-CAA association (any severity/mild/moderate/severe; LRT, all $p < 0.05$), with lower odds observed in people with diabetes compared to those without. Furthermore, heart conditions (including heart attack, coronary thrombosis, coronary occlusion, or myocardial infarction) modified the ADNC-CAA association (any/mild severity: LRT $p = 0.03$), with consistently lower odds observed in people with heart conditions.

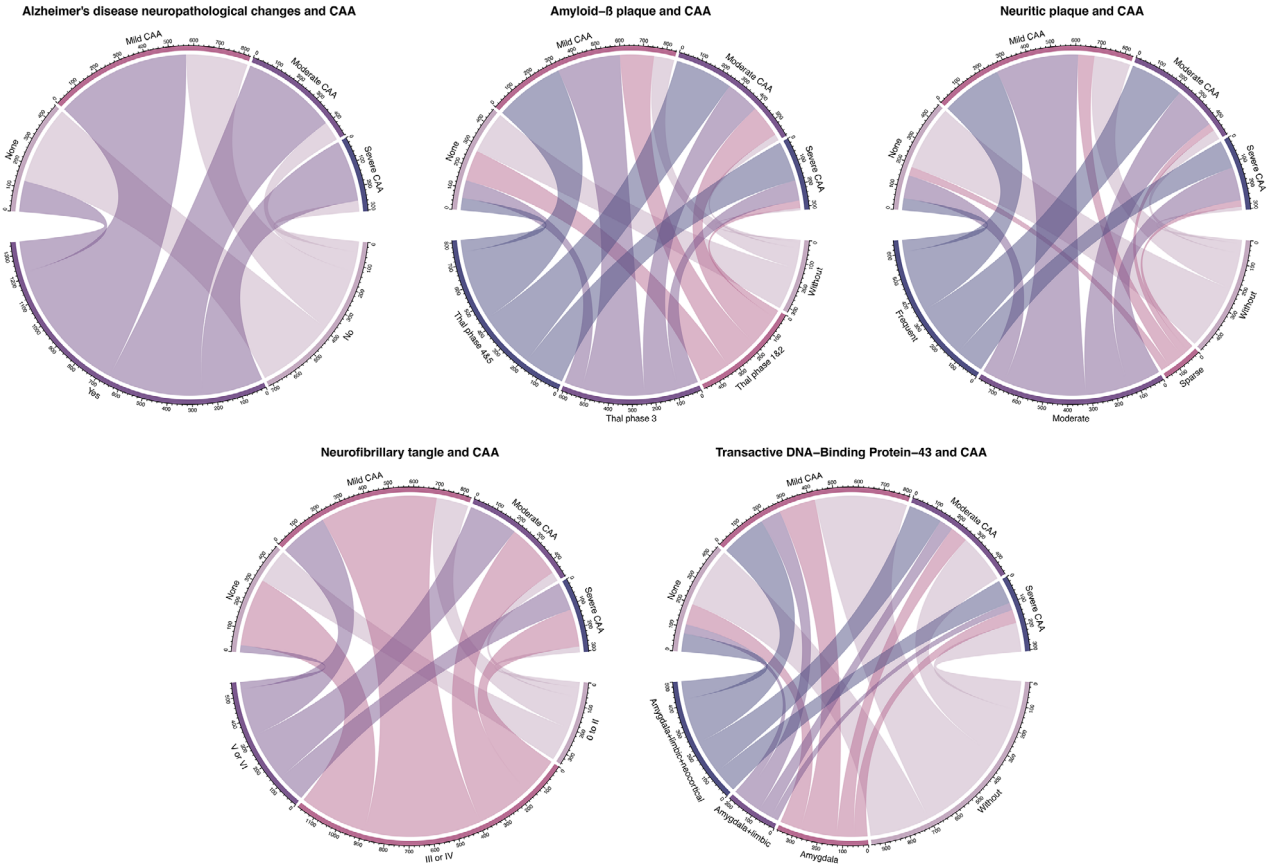

FIGURE 1 Distribution of ADNC (Aβ plaque, neuritic plaque, neurofibrillary tangle) and TDP-43 pathology across CAA severity. In each chord diagram, the upper semicircle indicates the severity of CAA (none, mild, moderate, severe), and the lower semicircle represents the severity or stages of ADNC or TDP-43 pathology. The thickness of the chords connecting the semicircles reflects the proportion of participants with corresponding levels of ADNC or TDP-43 pathology and CAA severity, with thicker chords indicating a larger proportion of participants. Aβ plaque, amyloid-beta plaque; ADNC, Alzheimer's disease neuropathologic change; CAA, cerebral amyloid angiopathy; TDP-43, transactive response DNA-binding protein 43 kDa pathology.

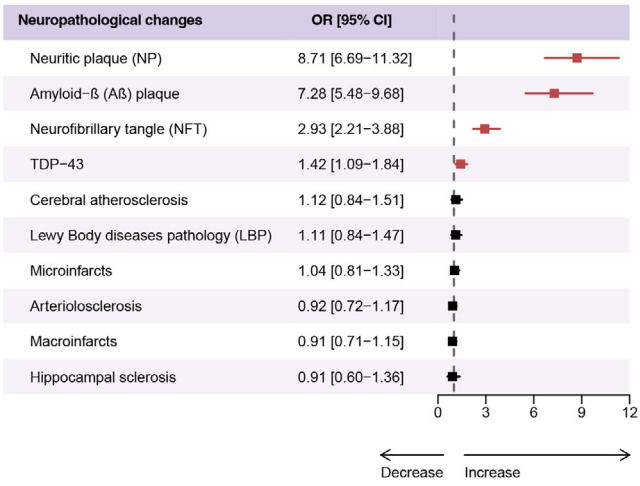

FIGURE 2 Forest plot illustrating the association between neuropathological changes and the risk of CAA. Positive associations with statistical significance are in red, and associations without statistical significance are in black. Aβ plaque, amyloid-beta plaque; LBP, Lewy body disease pathology; NFT, neurofibrillary tangle; NP, neuritic plaque; TDP-43, transactive response DNA-binding protein 43 kDa pathology.

3.1.3 | Sensitivity analysis

After further adjustment for AD-related neuropathological changes (ADNC [Aβ plaque, NP, NFT] and TDP-43 pathology), Aβ plaque and NP remained consistently and significantly associated with an increased risk of CAA across all severity levels (any severity, mild, moderate, and severe). For NFT, the Braak stages V or VI were significantly associated with an increased risk of CAA (any severity and moderate). The association between TDP-43 pathology and CAA was no longer significant after adjusting for the relevant AD-related neuropathological changes (eTable S4 and S5).

3.2 | Longitudinal analysis

3.2.1 | DLMO-CAA associations

The distribution of participants for each stratum of the DLMO risk factors is presented in Table 2, where the participants are grouped by their CAA diagnosis (no/yes). The distribution of participants for each risk factor stratum is summarized using Chord diagrams (eFigure S3),

TABLE 3 Cross-sectional association between Alzheimer's disease neuropathological change (ADNC) and the risk of cerebral amyloid angiopathy (CAA), stratified by various comorbidities and risk factors.

Adjusted odds ratio (OR) [95% CI], *P*-value regarding the association between ADNC and CAA[a]				
	Any severity of CAA	Mild CAA	Moderate CAA	Severe CAA
Alzheimer's disease neuropathological change (ADNC)[b]				
No	Reference	Reference	Reference	Reference
Yes	**7.21 [5.56–9.33], $p < 0.001$**	**5.44 [4.12–7.19], $p < 0.001$**	**11.69 [8.13–16.82], $p < 0.001$**	**12.34 [7.90–19.28], $p < 0.001$**
Adjusted odds ratio (OR) [95% CI], *P*-value regarding the association between ADNC and CAA[a] stratified by DLMO factors				
	Any severity of CAA	**Mild CAA**	**Moderate CAA**	**Severe CAA**
Sex				
LRT[c]	$P = 0.33$	$P = 0.48$	$P = 0.21$	$P = 0.37$
Female	**7.82 [5.75–10.63], $p < 0.001$**	**5.81 [4.16–8.11], $p < 0.001$**	**13.72 [8.77–21.44], $p < 0.001$**	**14.29 [8.18–24.97], $p < 0.001$**
Male	**5.95 [3.76–9.42], $p < 0.001$**	**4.70 [2.87–7.68], $p < 0.001$**	**8.35 [4.47–15.64], $p < 0.001$**	**9.37 [4.47–19.64], $p < 0.001$**
Age at baseline				
LRT[c]	$P = 0.55$	$P = 0.29$	$P = 0.91$	$P = 0.82$
<70	**10.30 [4.64–22.85], $p < 0.001$**	**7.25 [3.01–17.46], $p < 0.001$**	**16.90 [6.00–47.56], $p < 0.001$**	**19.31 [5.42–68.73], $p < 0.001$**
70-74 years	**6.51 [3.56–11.90], $p < 0.001$**	**4.26 [2.23–8.15], $p < 0.001$**	**14.49 [5.79–36.25], $p < 0.001$**	**12.38 [3.94–38.96], $p < 0.001$**
75-79 years	**5.02 [2.98–8.45], $p < 0.001$**	**3.36 [1.93–5.84], $p < 0.001$**	**8.37 [3.97–17.66], $p < 0.001$**	**15.63 [5.26–46.44], $p < 0.001$**
80-84 years	**7.18 [4.46–11.56], $p < 0.001$**	**6.25 [3.72–10.51], $p < 0.001$**	**11.20 [5.61–22.33], $p < 0.001$**	**9.27 [4.20–20.45], $p < 0.001$**
85-89 years	**9.50 [4.81–18.75], $p < 0.001$**	**8.78 [4.21–18.29], $p < 0.001$**	**12.34 [4.93–30.87], $p < 0.001$**	**9.30 [3.51–24.62], $p < 0.001$**
>89 years	**11.00 [3.65–33.16], $p < 0.001$**	**7.70 [2.36–25.16], $p < 0.001$**	**11.38 [2.79–46.35], $p < 0.001$**	**30.32 [3.07–299.52], $p < 0.001$**
Education				
LRT[c]	$P = 0.49$	$P = 0.98$	**$P = 0.02$**[d]	$P = 0.42$
≤12 years	**5.90 [3.38–10.32], $p < 0.001$**	**5.76 [3.14–10.57], $p < 0.001$**	**4.76 [2.24–10.11], $p < 0.001$**	**16.36 [5.56–48.14], $p < 0.001$**
13-18 years	**6.98 [4.99–9.77], $p < 0.001$**	**5.35 [3.72–7.68], $p < 0.001$**	**13.02 [8.05–21.06], $p < 0.001$**	**9.57 [5.39–16.99], $p < 0.001$**
>18 years	**9.37 [5.42–16.22], $p < 0.001$**	**5.42 [3.02–9.72], $p < 0.001$**	**20.95 [9.38–46.81], $p < 0.001$**	**18.30 [7.35–45.57], $p < 0.001$**

(Continues)

TABLE 3 (Continued)

Adjusted odds ratio (OR) [95% CI], *P*-value regarding the association between ADNC and CAA[a] stratified by DLMO factors				
	Any severity of CAA	Mild CAA	Moderate CAA	Severe CAA
Race				
LRT[c]	$P = 0.38$	$P = 0.53$	$P = 0.78$	$P = 0.89$
Caucasian	6.97 [5.33–9.11], $p < 0.001$	5.32 [3.99–7.08], $p < 0.001$	11.52 [7.91–16.79], $p < 0.001$	12.24 [7.71–19.41], $p < 0.001$
Non-Caucasian	10.61 [4.25–26.46], $p < 0.001$	7.56 [2.57–22.25], $p < 0.001$	13.93 [3.93–49.32], $p < 0.001$	13.87 [2.43–79.13], $P = 0.01$
Alcohol consumption				
LRT[c]	$P = 0.85$	$P = 0.59$	$P = 0.79$	$P = 0.76$
None/infrequent drinker	6.89 [5.09–9.32], $p < 0.001$	4.98 [3.60–6.89], $p < 0.001$	12.70 [8.17–19.76], $p < 0.001$	12.75 [7.49–21.70], $p < 0.001$
Occasional drinker	8.53 [3.59–20.29], $p < 0.001$	7.33 [2.74–19.61], $p < 0.001$	9.01 [3.18–25.53], $p < 0.001$	7.71 [2.04–29.16], $p < 0.001$
Frequent drinker	7.89 [4.41–14.13], $p < 0.001$	6.67 [3.56–12.49], $p < 0.001$	10.29 [4.64–22.80], $p < 0.001$	14.17 [5.13–39.11], $p < 0.001$
Smoking status				
LRT[c]	$P = 0.26$	$P = 0.04$[d]	$P = 0.64$	$P = 0.69$
No	6.54 [4.81–8.89], $p < 0.001$	4.51 [3.25–6.26], $p < 0.001$	12.45 [7.93–19.56], $p < 0.001$	11.61 [6.79–19.84], $p < 0.001$
Yes	8.99 [5.62–14.37], $p < 0.001$	8.39 [5.03–13.97], $p < 0.001$	10.38 [5.62–19.15], $p < 0.001$	14.12 [6.30–31.65], $p < 0.001$
Hypertension				
LRT[c]	$P = 0.47$	$P = 0.64$	$P = 0.33$	$P = 0.22$
No	7.95 [5.49–11.50], $p < 0.001$	5.82 [3.91–8.66], $p < 0.001$	13.94 [8.34–23.32], $p < 0.001$	16.29 [8.55–31.03], $p < 0.001$
Yes	6.58 [4.63–9.37], $p < 0.001$	5.12 [3.50–7.49], $p < 0.001$	9.81 [5.94–16.20], $p < 0.001$	9.44 [5.15–17.32], $p < 0.001$
Diabetes				
LRT[c]	$P = 0.01$[d]	$P = 0.01$[d]	$P = 0.02$[d]	$P = 0.01$[d]
No	8.42 [6.36–11.15], $p < 0.001$	6.36 [4.70–8.61], $p < 0.001$	13.99 [9.38–20.88], $p < 0.001$	15.87 [9.69–26.00], $p < 0.001$
Yes	2.82 [1.48–5.36], $p < 0.001$	2.13 [1.05–4.30], $P = 0.04$	4.04 [1.62–10.08], $P = 0.01$	2.63 [0.88–7.92], $P = 0.08$

(Continues)

TABLE 3 (Continued)

Adjusted odds ratio (OR) [95% CI], *P*-value regarding the association between ADNC and CAA[a] stratified by DLMO factors				
	Any severity of CAA	Mild CAA	Moderate CAA	Severe CAA
Heart conditions				
LRT[c]	***P* = 0.03**[d]	***P* = 0.03**[d]	*P* = 0.51	*P* = 0.42
No	7.99 [6.07–10.53], $p < 0.001$	6.09 [4.52–8.21], $p < 0.001$	12.18 [8.30–17.88], $p < 0.001$	13.18 [8.18–21.23], $p < 0.001$
Yes	3.36 [1.68–6.74], *P* = 0.001	2.52 [1.21–5.23], *P* = 0.01	8.18 [2.74–24.38], $p < 0.001$	7.68 [2.29–25.73], *P* = 0.001
Stroke				
LRT[c]	*P* = 0.98	*P* = 0.84	*P* = 0.76	*P* = 0.95
No	7.20 [5.49–9.44], $p < 0.001$	5.39 [4.02–7.22], $p < 0.001$	11.47 [7.83–16.81], $p < 0.001$	12.39 [7.77–19.78], $p < 0.001$
Yes	7.28 [3.16–16.77], $p < 0.001$	5.95 [2.44–14.52], $p < 0.001$	13.90 [4.39–44.03], $p < 0.001$	11.84 [2.78–50.35], *P* = 0.001
Cancer				
LRT[c]	*P* = 0.36	*P* = 0.67	*P* = 0.42	*P* = 0.30
No	7.85 [5.71–10.79], $p < 0.001$	5.68 [4.04–8.00], $p < 0.001$	12.94 [8.31–20.15], $p < 0.001$	14.63 [8.35–25.62], $p < 0.001$
Yes	6.13 [3.99–9.42], $p < 0.001$	5.02 [3.15–7.99], $p < 0.001$	9.48 [5.12–17.58], $p < 0.001$	9.04 [4.38–18.69], $p < 0.001$
Claudication				
LRT[c]	*P* = 0.51	*P* = 0.81	*P* = 0.43	*P* = 0.67
No	7.38 [5.64–9.65], $p < 0.001$	5.49 [4.12–7.33], $p < 0.001$	12.18 [8.34–17.78], $p < 0.001$	12.66 [7.97–20.11], $p < 0.001$
Yes	5.37 [2.16–13.35], $p < 0.001$	4.82 [1.76–13.23], *P* = 0.01	7.17 [2.05–25.01], *P* = 0.01	8.85 [1.84–42.47], *P* = 0.01
Head injury				
LRT[c]	*P* = 0.58	*P* = 0.88	*P* = 0.25	*P* = 0.78
No	7.08 [5.42–9.23], $p < 0.001$	5.41 [4.07–7.21], $p < 0.001$	11.10 [7.64–16.11], $p < 0.001$	12.14 [7.66–19.23], $p < 0.001$
Yes	9.45 [3.46–25.77], $p < 0.001$	5.91 [1.95–17.95], *P* = 0.01	29.04 [5.30–159.09], $p < 0.001$	15.73 [2.60–95.20], *P* = 0.01
Memory complaints				
LRT[c]	*P* = 0.60	*P* = 0.36	*P* = 0.20	*P* = 0.23
No	6.86 [4.90–9.45], $p < 0.001$	4.97 [3.55–6.96], $p < 0.001$	13.89 [8.80–21.92], $p < 0.001$	10.39 [6.17–17.50], $p < 0.001$
Yes	7.92 [5.10–12.30], $p < 0.001$	6.54 [4.03–10.61], $p < 0.001$	8.57 [4.75–15.47], $p < 0.001$	19.12 [7.93–46.09], $p < 0.001$

(Continues)

TABLE 3 (Continued)

Adjusted odds ratio (OR) [95% CI], *P*-value regarding the association between ADNC and CAA[a] stratified by DLMO factors				
	Any severity of CAA	Mild CAA	Moderate CAA	Severe CAA
APOE-ε4 carrier status				
LRT[c]	$P = 0.12$	$P = 0.64$	$P = 0.14$	$P = 0.10$
APOE-ε4 non-carrier	**6.65 [5.05–8.76], $p < 0.001$**	**5.31 [3.95–7.14], $p < 0.001$**	**10.33 [6.96–15.33], $p < 0.001$**	**10.15 [6.2016.61], $p < 0.001$**
APOE-ε4 carrier (homo/heterozygous)	**11.87 [5.92–23.81], $p < 0.001$**	**6.43 [3.01–13.74], $p < 0.001$**	**20.66 [8.71–49.01], $p < 0.001$**	**24.03 [9.3361.90], $p < 0.001$**
Vision acuity				
LRT[c]	$P = 0.78$	$P = 0.89$	$P = 0.82$	$P = 0.90$
High	**7.22 [5.51–9.48], $p < 0.001$**	**5.41 [4.06–7.23], $p < 0.001$**	**11.83 [8.11–17.24], $p < 0.001$**	**12.45 [7.79–19.89], $p < 0.001$**
Low	**6.30 [2.47–16.09], $p < 0.001$**	**5.82 [2.18–15.55], $p < 0.001$**	**10.10 [2.79–36.50], $p < 0.001$**	**11.31 [2.68–47.72], $P = 0.001$**
Medical conditions				
LRT[c]	$P = 0.15$	$P = 0.38$	$P = 0.05$	$P = 0.34$
No	**10.60 [5.81–19.35], $p < 0.001$**	**7.00 [3.70–13.24], $p < 0.001$**	**24.44 [10.20–58.55], $p < 0.001$**	**18.54 [6.97–49.33], $p < 0.001$**
Yes	**6.58 [4.95–8.75], $p < 0.001$**	**5.12 [3.77–6.97], $p < 0.001$**	**9.87 [6.63–14.67], $p < 0.001$**	**11.06 [6.75–18.14], $p < 0.001$**
MMSE				
LRT[c]	$P = 0.16$	$P = 0.27$	$P = 0.55$	$P = 0.42$
=30	**8.41 [5.00–14.14], $p < 0.001$**	**6.36 [3.62–11.18], $p < 0.001$**	**14.36 [6.86–30.06], $p < 0.001$**	**15.45 [6.50–36.74], $p < 0.001$**
25-30	**6.20 [4.52–8.49], $p < 0.001$**	**4.69 [3.34–6.59], $p < 0.001$**	**10.03 [6.43–15.66], $p < 0.001$**	**10.12 [5.72–17.88], $p < 0.001$**
20-25	**10.03 [4.09–24.59], $p < 0.001$**	**7.85 [2.98–20.70], $p < 0.001$**	**13.78 [4.12–46.03], $p < 0.001$**	**12.66 [3.33–48.16], $p < 0.001$**
<20	**47.20 [4.67–477.21], $p < 0.001$**	**31.16 [2.58–375.96], $p < 0.001$**	**49.78 [3.28–754.66], $p < 0.001$**	**98.62 [4.37–2228.35], $P = 0.01$**

Upper panel: the cross-sectional association between ADNC and CAA (any severity, mild, moderate or severe).
Lower panel: the cross-sectional association between ADNC and CAA (any severity, mild, moderate or severe) stratified by various factors.
Adjusted model: Controlled for demographic factors (sex, age, education, race), lifestyle factors (alcohol consumption, smoking status), comorbidities (hypertension, diabetes, heart conditions, stroke, cancer), and other risk factors (claudication, head injury, memory complaints, APOE-ε4 carrier status, vision acuity, medical conditions, MMSE).
Statistical significance: The statistics in bold indicate statistical significance ($p < 0.05$).
aRefer to Table 1, row 2
[b]The criteria rely on a combination of neurofibrillary tangles (Braak), neuritic plaque score (CERAD), and amyloid beta plaque score (Thal). The neuropathologist determines the level of AD pathology.
[c]LRT: likelihood ratio test
[d]Identified potential effect modifiers (LRT *P*-value<.05)

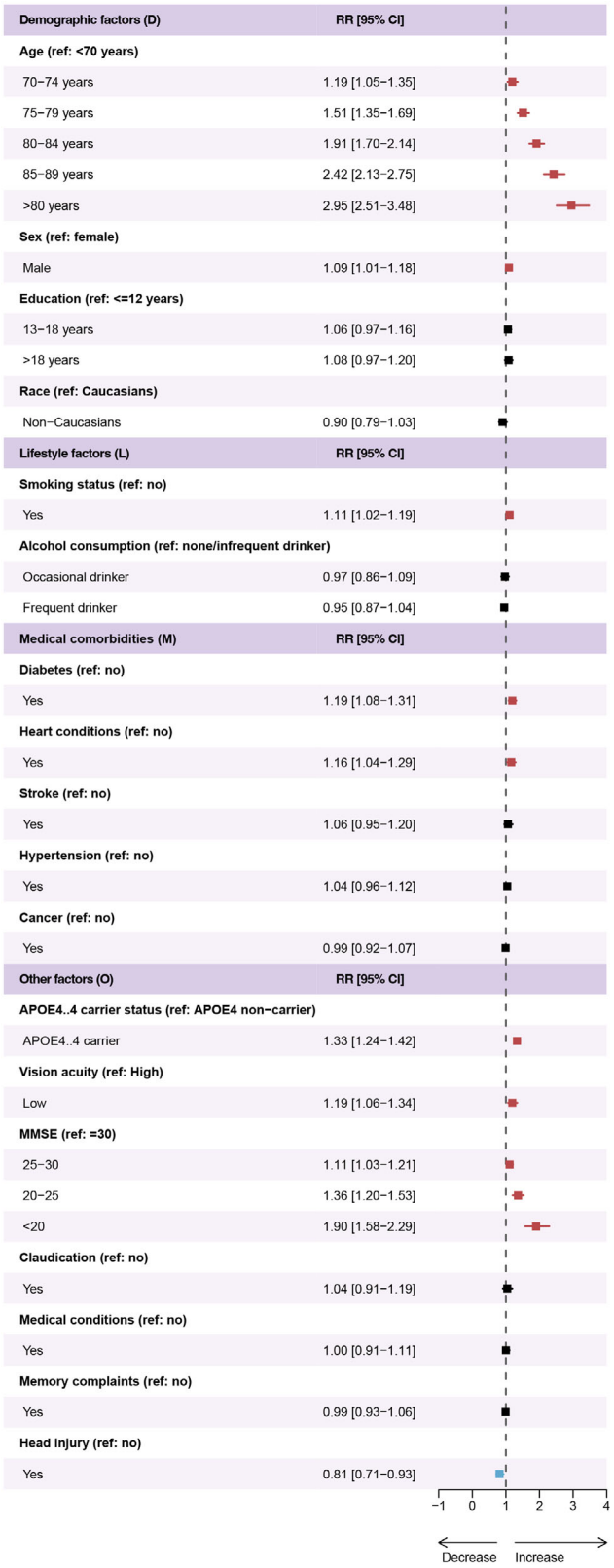

FIGURE 3 Forest plot illustrating the association between relevant risk factors and the risk of CAA. Red color indicates a positive association with statistical significance; black color indicates an association without statistical significance; blue color indicates a negative association with statistical significance. CAA, cerebral amyloid angiopathy.

with participants grouped by the CAA severity. APOE-ε4 carriers and participants with lower MMSE scores had a higher proportion of CAA (all $p < 0.05$). Interestingly, Caucasian participants and people without hypertension or diabetes also had a higher proportion of CAA (all $p < 0.05$).

After controlling for the DLMO risk factors, male sex and older age were significantly associated with a higher risk of CAA (any severity) compared to the reference groups, with the age-CAA association becoming stronger with increasing age (Figure 3, eTable S6). Smoking, medical comorbidities (diabetes/heart conditions), APOE-ε4, low vision acuity, and low MMSE scores were also associated with a higher risk of CAA. Notably, the MMSE-CAA association increased with lower MMSE scores. Unexpectedly, an inverse association was observed between head injury with loss of consciousness and CAA risk (RR 0.81 [0.71–0.93], $p = 0.01$).

When examining CAA severity separately, the DLMO-CAA associations varied across age groups (eTable S7). All age groups showed a significant association with an increased risk of CAA (mild, moderate, or severe), except for the 70–74 and 75–79 age groups, which were not associated with moderate or severe CAA. Notably, the strength of the association consistently increased with age. Significant inverse associations were observed between non-Caucasian participants or occasional alcohol consumption and mild CAA (compared to Caucasian participants or non/infrequent alcohol consumption); however, no such inverse association was found for moderate or severe CAA. Diabetes, heart conditions, and low vision acuity were positively linked only to mild CAA. APOE-ε4 carriers and those with lower MMSE scores had a higher risk of mild, moderate, and severe CAA.

3.2.2 | Stratified RRs for the DLMO-CAA association and effect modification by ADNC

ADNC serves as a potential effect modifier in the education-moderate CAA association (WT, $p = 0.04$), with stratified RRs indicating that the strength of the association increased in the ADNC group. In addition, ADNC acts as a potential effect modifier in the diabetes-CAA associations (WTs for any/mild/moderate/severe CAA, all $p < 0.05$), where the stratified RRs showed that the strength of the diabetes-CAA associations decreased in the ADNC group. Furthermore, ADNC was also found to modify the heart conditions-any/mild CAA associations (WTs, all $p < 0.05$). Detailed information is available in Table 4.

3.3 | Machine learning algorithm

Nine DLMO risk factors associated with CAA were selected for the machine learning algorithm, including sex, age, smoking, diabetes, heart conditions, stroke, APOE-ε4, visual acuity, and MMSE. In evaluating the predictive model with interval validation, the ROC-AUC was 0.63 [0.61–0.66], and the area under the precision-recall curve (PR-AUC) was 0.86 [0.84–0.88] (eFigure S4). The external validation yielded consistent results using two cohorts for training and one cohort for testing:

TABLE 4 Longitudinal association between comorbidities or risk factors and the risk of cerebral amyloid angiopathy (CAA), stratified by Alzheimer's disease neuropathological changes (ADNC).

Adjusted relative risk (RR) [95% CI], *P*-value for the association between DLMO factors and CAA[a], stratified by ADNC status								
	Any severity of CAA		Mild CAA		Moderate CAA		Severe CAA	
Measures	Without ADNC	With ADNC	Without ADNC	With ADNC	Without ADNC	With ADNC	Without ADNC	With ADNC
Sex (Ref: female)								
WT[b]	$P = 0.49$		$P = 0.83$		$P = 0.55$		$P = 0.24$	
Male	1.17 [0.98–1.40], $P = 0.08$	**1.09 [1.01–1.18], $P = 0.02$**	1.17 [0.93–1.47], $P = 0.18$	**1.14 [1.00–1.29], $P = 0.04$**	1.19 [0.72–1.95], $P = 0.49$	1.02 [0.87–1.20], $P = 0.82$	1.50 [0.82–2.76], $P = 0.19$	1.03 [0.82–1.30], $P = 0.78$
Age (Ref: <70 years)								
WT[b]	$P = 0.55$		$P = 0.40$		$P = 0.96$		$P = 0.46$	
70-74 years	1.08 [0.78–1.49], $P = 0.64$	**1.20 [1.07–1.35], $P = 0.01$**	1.28 [0.86–1.90], $P = 0.23$	1.19 [0.95–1.50], $P = 0.13$	0.76 [0.32–1.80], $P = 0.53$	1.14 [0.90–1.43], $P = 0.27$	0.59 [0.18–1.99], $P = 0.40$	1.00 [0.71–1.42], $P = 0.99$
75-79 years	**1.57 [1.18–2.09], $P = 0.01$**	**1.44 [1.29–1.60], $p < 0.001$**	**1.88 [1.31–2.69], $P = 0.001$**	**1.41 [1.16–1.73], $P = 0.001$**	1.29 [0.60–2.77], $P = 0.51$	**1.36 [1.09–1.69], $P = 0.01$**	1.00 [0.30–3.35], $P = 0.99$	1.26 [0.92–1.72], $P = 0.15$
80-84 years	**1.66 [1.23–2.24], $P = 0.001$**	**1.88 [1.69–2.09], $p < 0.001$**	**1.72 [1.17–2.55], $P = 0.01$**	**1.83 [1.50–2.24], $p < 0.001$**	1.51 [0.72–3.15], $P = 0.27$	**1.72 [1.39–2.13], $p < 0.001$**	2.13 [0.79–5.78], $P = 0.14$	**1.85 [1.37–2.50], $p < 0.001$**
85-89 years	**2.38 [1.72–3.28], $p < 0.001$**	**2.30 [2.04–2.60], $p < 0.001$**	**2.57 [1.68–3.95], $p < 0.001$**	**2.55 [2.05–3.16], $p < 0.001$**	2.17 [0.92–5.12], $P = 0.08$	**2.20 [1.72–2.82], $p < 0.001$**	**3.71 [1.37–10.07], $P = 0.01$**	**2.42 [1.72–3.40], $p < 0.001$**
>89 years	**2.50 [1.62–3.86], $p < 0.001$**	**2.91 [2.48–3.42], $p < 0.001$**	**2.87 [1.63–5.06], $p < 0.001$**	**2.97 [2.29–3.85], $p < 0.001$**	**3.27 [1.23–8.68], $P = 0.02$**	**3.48 [2.50–4.85], $p < 0.001$**	1.53 [0.21–11.29], $P = 0.68$	**3.54 [2.34–5.36], $p < 0.001$**
Education (Ref: <13 years)								
WT[b]	$P = 0.51$		$P = 0.94$		**$P = 0.04$**[c]		$P = 0.33$	
13-18 years	0.99 [0.79–1.25], $P = 0.95$	**1.10 [1.01–1.19], $P = 0.04$**	1.08 [0.80–1.46], $P = 0.62$	1.04 [0.91–1.19], $P = 0.57$	0.73 [0.44–1.23], $P = 0.24$	**1.27 [1.03–1.57], $P = 0.02$**	1.58 [0.65–3.85], $P = 0.32$	0.94 [0.76–1.17], $P = 0.60$
>18 years	0.95 [0.72–1.24], $P = 0.69$	**1.12 [1.02–1.24], $P = 0.02$**	1.06 [0.75–1.49], $P = 0.76$	1.07 [0.90–1.26], $P = 0.44$	0.53 [0.26–1.08], $P = 0.08$	**1.33 [1.06–1.67], $P = 0.01$**	1.20 [0.41–3.48], $P = 0.74$	1.16 [0.90–1.49], $P = 0.25$
Race (Ref: Caucasian)								
WT[b]	$P = 0.09$		$P = 0.07$		$P = 0.72$		$P = 0.25$	
Non-Caucasian	0.62 [0.38–1.01], $P = 0.05$	0.95 [0.84–1.07], $P = 0.39$	**0.46 [0.24–0.91], $P = 0.02$**	0.91 [0.69–1.19], $P = 0.48$	0.75 [0.31–1.78], $P = 0.51$	0.88 [0.71–1.09], $P = 0.23$	0.31 [0.04–2.21], $P = 0.24$	1.01 [0.68–1.52], $P = 0.95$
Alcohol consumption (Ref: none/infrequent)								
WT[b]	$P = 0.91$		$P = 0.71$		$P = 0.38$		$P = 0.82$	
Occasional drinker	0.93 [0.69–1.25], $P = 0.62$	0.99 [0.87–1.12], $P = 0.87$	0.69 [0.44–1.07], $P = 0.10$	0.85 [0.66–1.09], $P = 0.20$	1.75 [0.95–3.26], $P = 0.08$	1.11 [0.88–1.39], $P = 0.38$	1.25 [0.50–3.13], $P = 0.64$	0.91 [0.62–1.33], $P = 0.63$
Frequent drinker	0.93 [0.74–1.17], $P = 0.53$	0.96 [0.88–1.05], $P = 0.36$	0.86 [0.64–1.15], $P = 0.31$	0.90 [0.78–1.03], $P = 0.12$	1.07 [0.60–1.91], $P = 0.81$	1.05 [0.87–1.26], $P = 0.64$	1.01 [0.45–2.24], $P = 0.99$	0.96 [0.75–1.23], $P = 0.76$

(Continues)

TABLE 4 (Continued)

Adjusted relative risk (RR) [95% CI], *P*-value for the association between DLMO factors and CAA[a], stratified by ADNC status								
Measures	**Any severity of CAA**		**Mild CAA**		**Moderate CAA**		**Severe CAA**	
	Without ADNC	**With ADNC**	**Without ADNC**	**With ADNC**	**Without ADNC**	**With ADNC**	**Without ADNC**	**With ADNC**
Smoking status (Ref: no)								
WT[b]	$P = 0.96$		$P = 0.16$		$P = 0.23$		$P = 0.94$	
Yes	1.10 [0.91–1.34], $P = 0.32$	**1.11 [1.03–1.20], $P = 0.01$**	0.96 [0.74–1.23], $P = 0.73$	**1.16 [1.03–1.31], $P = 0.02$**	1.52 [0.95–2.43], $P = 0.08$	1.13 [0.96–1.32], $P = 0.14$	1.04 [0.54–2.02], $P = 0.90$	1.01 [0.80–1.28], $P = 0.90$
Hypertension (Ref: no)								
WT[b]	$P = 0.98$		$P = 0.90$		$P = 0.58$		$P = 0.35$	
Yes	1.05 [0.88–1.25], $P = 0.59$	1.05 [0.98–1.13], $P = 0.19$	1.09 [0.86–1.36], $P = 0.48$	1.10 [0.97–1.25], $P = 0.12$	1.04 [0.65–1.67], $P = 0.86$	0.91 [0.78–1.07], $P = 0.25$	1.25 [0.68–2.30], $P = 0.48$	0.93 [0.74–1.16], $P = 0.52$
Diabetes (Ref: no)								
WT[b]	**$P = 0.02$**[c]		**$P = 0.02$**[c]		**$P = 0.04$**[c]		**$P = 0.04$**[c]	
Yes	**1.44 [1.18–1.77], $p < 0.001$**	1.09 [0.98–1.22], $P = 0.13$	**1.55 [1.20–2.01], $P = 0.001$**	1.06 [0.88–1.28], $P = 0.52$	**1.85 [1.02–3.39], $P = 0.04$**	0.96 [0.76–1.20], $P = 0.71$	**2.17 [1.01–4.64], $P = 0.04$**	0.96 [0.66–1.37], $P = 0.81$
Heart conditions (Ref: no)								
WT[b]	**$P = 0.04$**[c]		**$P = 0.01$**[c]		$P = 0.81$		$P = 0.49$	
Yes	**1.41 [1.12–1.78], $P = 0.01$**	1.08 [0.96–1.22], $P = 0.18$	**1.68 [1.27–2.21], $p < 0.001$**	1.11 [0.93–1.33], $P = 0.25$	0.87 [0.41–1.84], $P = 0.72$	0.96 [0.72–1.29], $P = 0.79$	1.36 [0.61–3.05], $P = 0.45$	1.01 [0.76–1.35], $P = 0.93$
Stroke (Ref: no)								
WT[b]	$P = 0.74$		$P = 0.74$		$P = 0.59$		$P = 0.63$	
Yes	1.12 [0.83–1.51], $P = 0.47$	1.06 [0.94–1.19], $P = 0.35$	1.16 [0.79–1.70], $P = 0.44$	1.08 [0.90–1.30], $P = 0.41$	0.91 [0.41–2.02], $P = 0.81$	1.14 [0.89–1.45], $P = 0.31$	0.82 [0.27–2.54], $P = 0.74$	1.11 [0.74–1.66], $P = 0.62$
Cancer (Ref: no)								
WT[b]	$P = 0.73$		$P = 0.90$		$P = 0.92$		$P = 0.43$	
Yes	1.02 [0.84–1.22], $P = 0.87$	0.98 [0.91–1.06], $P = 0.62$	1.00 [0.79–1.27], $P = 0.99$	0.98 [0.87–1.11], $P = 0.78$	0.92 [0.56–1.50], $P = 0.73$	0.89 [0.76–1.05], $P = 0.17$	1.38 [0.74–2.57], $P = 0.31$	1.06 [0.85–1.34], $P = 0.59$
Claudication (Ref: no)								
WT[b]	$P = 0.73$		$P = 0.81$		$P = 0.51$		$P = 0.81$	
Yes	1.00 [0.70–1.42], $P = 0.98$	1.06 [0.93–1.22], $P = 0.38$	0.96 [0.60–1.51], $P = 0.85$	1.02 [0.81–1.27], $P = 0.89$	1.20 [0.56–2.58], $P = 0.63$	0.91 [0.68–1.23], $P = 0.56$	0.90 [0.20–4.05], $P = 0.90$	1.09 [0.74–1.60], $P = 0.66$
Head injury (Ref: no)								
WT[b]	$P = 0.63$		$P = 0.63$		$P = 0.29$		$P = 0.85$	
Yes	0.70 [0.41–1.21], $P = 0.20$	**0.81 [0.72–0.91], $p < 0.001$**	0.66 [0.34–1.32], $P = 0.24$	**0.79 [0.65–0.96], $P = 0.02$**	0.39 [0.10–1.60], $P = 0.19$	0.84 [0.66–1.06], $P = 0.14$	0.80 [0.19–3.39], $P = 0.76$	0.92 [0.66–1.27], $P = 0.61$

(Continues)

TABLE 4 (Continued)

Adjusted relative risk (RR) [95% CI], *P*-value for the association between DLMO factors and CAA[a], stratified by ADNC status								
Measures	**Any severity of CAA**		**Mild CAA**		**Moderate CAA**		**Severe CAA**	
	Without ADNC	**With ADNC**	**Without ADNC**	**With ADNC**	**Without ADNC**	**With ADNC**	**Without ADNC**	**With ADNC**
Memory complaints (Ref: no)								
WT[b]	$P = 0.19$		$P = 0.17$		$P = 0.42$		$P = 0.14$	
Yes	0.87 [0.72–1.06], $P = 0.17$	1.00 [0.94–1.07], $P = 0.99$	0.83 [0.65–1.07], $P = 0.16$	1.01 [0.91–1.13], $P = 0.85$	1.16 [0.73–1.85], $P = 0.52$	0.95 [0.83–1.09], $P = 0.50$	0.55 [0.25–1.22], $P = 0.14$	1.01 [0.84–1.22], $P = 0.92$
APOE-ε4 carrier status (Ref: non-carrier)								
WT[b]	$P = 0.41$		$P = 0.95$		$P = 0.25$		$P = 0.09$	
APOE-ε4 carrier	**1.37 [1.10–1.70], $P = 0.01$**	**1.24 [1.16–1.33], $p < 0.001$**	1.32 [0.99–1.77], $P = 0.06$	**1.34 [1.17–1.52], $p < 0.001$**	**2.14 [1.21–3.79], $P = 0.01$**	**1.52 [1.32–1.75], $p < 0.001$**	**3.06 [1.61–5.85], $P = 0.001$**	**1.72 [1.45–2.04], $p < 0.001$**
Vision acuity (Ref: high)								
WT[b]	$P = 0.33$		$P = 0.52$		$P = 0.39$		$P = 0.96$	
Low	**1.35 [1.01–1.79], $P = 0.04$**	**1.16 [1.02–1.31], $P = 0.02$**	1.39 [0.98–1.96], $P = 0.07$	**1.22 [1.01–1.47], $P = 0.04$**	1.48 [0.63–3.46], $P = 0.37$	1.00 [0.71–1.41], $P = 0.99$	1.15 [0.40–3.34], $P = 0.80$	1.18 [0.89–1.58], $P = 0.26$
Medical conditions (Ref: no)								
WT[b]	$P = 0.49$		$P = 0.86$		$P = 0.22$		$P = 0.73$	
Yes	1.06 [0.85–1.33], $P = 0.58$	0.99 [0.89–1.09], $P = 0.76$	0.95 [0.71–1.27], $P = 0.73$	0.92 [0.79–1.09], $P = 0.34$	1.65 [0.85–3.20], $P = 0.14$	1.10 [0.90–1.33], $P = 0.35$	1.01 [0.49–2.08], $P = 0.99$	0.88 [0.67–1.17], $P = 0.38$
MMSE (Ref: =30)								
WT[b]	$P = 0.16$		$P = 0.62$		$P = 0.10$		$P = 0.41$	
25-30	1.22 [0.98–1.52], $P = 0.07$	1.07 [0.99–1.16], $P = 0.07$	1.27 [0.95–1.69], $P = 0.11$	1.05 [0.93–1.20], $P = 0.43$	1.49 [0.84–2.64], $P = 0.17$	1.10 [0.93–1.29], $P = 0.28$	1.13 [0.56–2.28], $P = 0.73$	0.95 [0.76–1.18], $P = 0.64$
20-25	1.27 [0.90–1.78], $P = 0.17$	**1.34 [1.19–1.50], $p < 0.001$**	1.26 [0.79–2.00], $P = 0.33$	**1.22 [1.00–1.47], $P = 0.04$**	1.62 [0.68–3.90], $P = 0.28$	**1.43 [1.13–1.81], $P = 0.01$**	1.66 [0.58–4.79], $P = 0.35$	**1.54 [1.10–2.13], $P = 0.01$**
<20	**2.77 [1.76–4.36], $p < 0.001$**	**1.71 [1.41–2.08], $p < 0.001$**	**2.44 [1.26–4.73], $P = 0.01$**	**1.86 [1.27–2.73], $P = 0.001$**	**7.57 [2.53–22.64], $p < 0.001$**	**1.78 [1.24–2.56], $P = 0.01$**	**6.35 [1.55–25.99], $P = 0.01$**	**1.85 [1.27–2.68], $P = 0.001$**

Adjusted model: Controlled for demographic factors (sex, age, education, race), lifestyle factors (alcohol consumption, smoking status), comorbidities (hypertension, diabetes, heart conditions, stroke, cancer), and other risk factors (claudication, head injury, memory complaints, APOE-ε4 carrier status, vision acuity, medical conditions, MMSE).

Statistical significance: The statistics in bold indicate statistical significance ($p < 0.05$).

[a] Refer to Table 1, row 2.

[b] WT: Wald tests.

[c] Identified potential effect modifiers (LRT p-value < 0.05).

ROS as the test set (ROC-AUC = 0.65, PR-AUC = 0.87), MARS as the test set (ROC-AUC = 0.65, PR-AUC = 0.78), and MAP as the test set (ROC-AUC = 0.63, PR-AUC = 0.87) (eFigure S5).

4 | DISCUSSION

Our study comprehensively investigated the risk factors for CAA using data from three cohort studies of older adults. We cross-sectionally examined the neuropathology-CAA association in 2118 decedents and revealed that people with ADNC (Aβ plaques, NP, and NFT combined or separated) had significantly higher odds of CAA. This finding can be useful in that diagnostic tools assessing for Aβ may indicate CAA risk or increase index of suspicion of CAA in cases of diagnostic uncertainty or mixed pathology.[28] However, it is uncertain if this may add definitive diagnostic value in clinical practice. In addition, our study identified a novel and significant positive association between TDP-43 pathology in neocortex and moderate/severe CAA.[16,29,30] While clinically validated diagnostic imaging for TDP-43 is not yet available, future tools to assess TDP-43 could potentially be valuable in distinguishing mild CAA from moderate to severe cases. However, it is important to note that these associations were identified *post mortem* and have yet to be validated in living patients, which should be investigated in future studies. In addition, the cross-sectional ADNC-CAA association was found to be modified by education, smoking, and comorbidity (diabetes, heart conditions). Notably, the stratified ORs suggested that the strength of the ADNC-CAA association increased with more years of education (for moderate CAA) and among smokers (for mild CAA). This novel observation should also be confirmed in future studies. Interestingly, the strength of ADNC-CAA association was reduced in people with diabetes (any/mild/moderate/severe CAA) and heart conditions (any/mild CAA). The use of medications could potentially contribute to the weaken ADNC-CAA association observed for people with diabetes/heart conditions, such as metformin,[31,32] thiazolidinediones,[33,34] statins, and beta-blockers[35,36]; however, this hypothesis is yet to be confirmed and could serve as focus for the follow-up studies.

We also examined the longitudinal associations between DLMO (demographic, lifestyle, medical comorbidities, and other risk factors) and CAA in 2048 participants, an area not comprehensively explored in previous studies.[27] Consistent with previous studies, male sex, older age, APOE-ε4 genotype, and diabetes were identified as risk factors for CAA.[10,11,37,38] However, our study conflicts with a study conducted in an older Japanese cohort, reporting that the risk of CAA was not associated with diabetes mellitus.[26] Future studies exploring the impact of ethnicity on this association should be conducted to clarify this discrepancy.

We also discovered novel associations between smoking and CAA. However, it must be noted that stroke could be a potential mediator for smoking-CAA association, given smoking increases the risk of hemorrhagic stroke.[39–41] Unexpectedly, the results indicated that a history of head injury was associated with a decreased risk of CAA. However, the relatively small sample size (n = 126) may have limited the statistical power to detect the true relationship, and further studies are needed to confirm this finding. Other novel associations we identified include links between heart conditions (such as heart attack, coronary thrombosis, coronary occlusion, or myocardial infarction), lower visual acuity, and lower MMSE scores with a higher risk of CAA. The link between heart conditions and CAA is yet to be explored. The visual acuity-CAA association should be interpreted with care, due to a small sample size (n = 191). Microbleeds from CAA can contribute to cognitive impairment,[42] which could possibly be one of the mechanisms underlying the MMSE-CAA association. The importance of this topic underscores the need for further studies to confirm these findings. Furthermore, we found that the longitudinal associations between diabetes, heart conditions, and CAA risk are ADNC-dependent—specifically, the association was stronger in non-ADNC participants than in ADNC participants. This is worthwhile being explored in the future.

The sensitivity analysis indicated that the lack of a significant association between TDP-43 pathology and the risk of CAA, after adjusting for AD-related neuropathological changes (ADNC: Aβ plaque, NP, and NFT), could be attributed to a confounding effect caused by these other neuropathological factors. Aβ plaque, NP, and NFT are strongly associated with both AD and CAA, potentially overshadowing the independent contribution of TDP-43 pathology. This suggests that the initial association observed between TDP-43 and CAA may have been partially or wholly driven by its correlation with these dominant AD-related neuropathological changes. Future studies are required to investigate the precise role of TDP-43 pathology in the development of CAA. We also observed an interesting finding that 7.7% of CAA cases lack amyloid-beta plaques in the brain parenchyma, which agrees with a previous meta-analysis.[3] It is possible that a small portion of the CAA cases may originate predominantly from the vascular unit, given that amyloid-beta can be produced by vasculature.[43]

Our epidemiology analyses have several strengths. A high autopsy rate and neuropathologists being blind to clinical diagnoses during *post mortem* analysis have helped reduce selection bias. In addition, the study participants were community-dwelling older adults, making the sample more representative of the general population and encompassing a wide range of health statuses. Moreover, the clinical classification of ADNC and CAA was based on standard criteria (e.g., National Institute on Aging – Alzheimer's Association) and uniform examinations by experienced neuropathologists and clinicians, minimizing misclassification and diagnostic error. With 1653 incident CAA cases across the three studies, our findings were supported by a substantial statistical power. Furthermore, the stratification analyses enabled us to investigate the specific associations between ADNC, DLMO, and the risk of CAA across distinct variable layers, thereby minimizing potential confounding effects and identifying potential effect modifiers.

This study is not without limitations. Neuropathological data were only available for decedents who had consented to autopsy. Decline for autopsy could be due to religious reason and, therefore, lead to selection bias. The participants included in our study are predominantly Caucasians with more years of education. Given increased intracerebral hemorrhage risk has been observed in non-Caucasians,[44,45] we have attempted to study if ethnicity may impact CAA risk. However, with less than 10% of the cohort being non-Caucasian, we cannot study

this impact with confidence. This investigation using culturally, and linguistically diverse cohorts should be encouraged. In addition, the presence of medical comorbidities and other risk factors (e.g., head injury) was self-reported, which could introduce recall bias. Nevertheless, these exposures were ascertained at a time when participants were known not to have dementia and before the evaluation of neuropathological changes in the ROS/MAP/MARS studies. However, since CAA can only be definitively diagnosed through autopsy, the exact timing of CAA occurrence for each participant cannot be determined. In addition, the unavailability of AD biomarkers and brain imaging data in the present study limited our ability to assess the dynamic association between biomarkers, brain imaging changes, and CAA.

Employing our epidemiology findings, we have attempted to develop a machine learning model to predict occurrence of CAA. This model achieved a ROC-AUC of 0.63 [0.61–0.66], relying solely on baseline data (age, sex, smoking, diabetes, heart conditions, APOE, vision acuity, MMSE), which are significantly associated with CAA risk, to forecast CAA over an average of 10 years follow-up. The model shows that artificial intelligence solely using risk factors does have predictive value; however, further refinement is still required to develop a robust clinical grade model. In addition, although we have developed the model with two cohorts and test on the other cohort, these study cohorts are not completely independent. Aging and dementia cohort studies should be encouraged to collect the relevant data to advance CAA research. Future machine learning models could benefit from using longitudinal data, biomarkers, and advanced imaging data to enhance predictive performance, as well as being validated across different populations. Nevertheless, this model, informed by epidemiological evidence, has already demonstrated the potential to predict CAA based on our selected risk factors. We have a separate study by Chu et al. that provides details on the development of several more advanced models, which were built upon the identified risk factors.[46]

The current study explored the risk factors for CAA. Future studies are required to identify risk factors for the sequelae of CAA,[1] such as cerebral microbleeds, cortical superficial hemosiderosis, or lobar intracerebral hemorrhage. While identifying risk factors for CAA is important, there may be patients who develop CAA yet do not experience debilitating sequelae of CAA, for whom anti-Aβ MAB treatment could still be considered. Thus, identifying which patients are at risk of sequelae of CAA is an important follow-up for the current study.

In conclusion, investigating the associations between neuropathology, DLMO risk factors, and CAA has led to the identification of some modifiable risk factors for CAA. However, whether addressing these factors will reduce CAA risk remains to be investigated. In addition, we developed a machine learning model to predict CAA, using our identified risk factors for CAA. While external validation and optimization of the model are still needed, our study demonstrates the potential to create a CAA prediction tool informed by epidemiological findings.

AUTHOR CONTRIBUTIONS

Concept and design of the study: Liwei Ma (L.M.), Colin L Masters, Benjamin Goudey, Liang Jin, and Yijun Pan (Y.P.). Data analysis and interpretation: L.M., Yihan Wang (Y.W.), and Y.P. Drafting of the manuscript: L.M., Y.W., and Y.P. Andrew Liem Hieu Huynh, Sanka Amadoru, Scott Wrigley, and Paul Yates are clinician researchers/geriatricians who have contributed by providing clinical insight of our study. All authors critically revised the draft and contributed substantially to the final version. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts to report (None declared). Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

Data requests should be made to Rush University (radc.rush.edu). The analysis files to support the results of this manuscript can be made available upon written request to the corresponding authors, which may also be subject to approval by the Rush University.

ETHICS STATEMENT

ROS, MAP, MARS studies were approved separately by the Rush University Medical Center Institutional Review Board. Written informed consent was provided to participants who signed an Anatomical Gift Act. The current study performed secondary data analysis on de-identified data, where ethics approval is not required.

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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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