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Asymptomatic carotid artery stenosis is associated with increased Alzheimer's disease and non-Alzheimer's disease dementia risk

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ABSTRACT

Background In the absence of a cerebrovascular accident, whether asymptomatic extracranial carotid atherosclerotic disease (aECAD) affects Alzheimer's disease (AD) and non-AD dementia risk is not clear. Understanding whether aECAD is associated with an increased risk for AD is important as it is present in roughly 10% of the population over 60 and could represent a modifiable risk factor for AD and non-AD dementia.

Methods This retrospective cohort study analysed Mariner insurance claims. Enrolment criteria included patients aged 55 years or older with at least 5 years of data and no initial dementia diagnosis. Subjects with and without aECAD were evaluated for subsequent AD and non-AD dementia diagnoses. Propensity score matching was performed using confounding factors identified by logistic regression. χ^2 tests and Kaplan-Meier survival curves were used to evaluate the impact of aECAD diagnosis on AD and non-AD dementia risk over time.

Results 767 354 patients met enrolment criteria. After propensity score matching, 62 963 subjects with aECAD and 62 963 subjects without ECAD were followed through data records. The aECAD cohort exhibited an increased relative risk of 1.22 (95% CI 1.15 to 1.29, p<0.001) for AD and 1.48 (95% CI 1.38 to 1.59, p<0.001) for non-AD dementias compared with the propensity score-matched cohort without aECAD. The increased AD risk associated with aECAD was evident in patients younger than 75 years old and was less apparent in patients over 75 years of age.

Conclusions aECAD is associated with an increased risk of developing AD and non-AD dementias. These findings underscore the need for further prospective evaluation of interactions between aECAD and dementia, with potential implications for change of clinical care in both of these large patient populations.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with asymptomatic carotid disease are not clinically evaluated for or treated for dementia-related outcomes as a standard of care. Furthermore, whether carotid stenosis, in the absence of stroke, is associated with AD risk is unknown.

WHAT THIS STUDY ADDS

⇒ This study reveals that in the absence of stroke, asymptomatic carotid disease increases risk for both AD and non-AD dementia.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Outcomes from this study should prompt further prospective studies aimed at better testing and treatment of patients with asymptomatic carotid stenosis. Additionally, it underscores the importance of improved evaluation of carotid stenosis in patients at risk for AD and related dementias.

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia.[1] As of 2022, 6.55 million people in the USA had AD alone.[2] Non-Alzheimer's dementias comprise a large group of dementias that include vascular, Lewy-Body, frontotemporal and other dementias.[3] There is a growing appreciation that vascular disease and associated vascular risk factors contribute to dementia risk.[4 5]

Vascular contributions to cognitive impairment and dementia (VCID) encompass a broad group of systemic vascular processes impacting brain health.[4–6] Research in VCID has predominantly focused on cerebral small vessel disease (cSVD)[7 8] and vascular risk factors including age, hypertension (HTN), hyperlipidaemia (HLD) and smoking.[2 8–10] In contrast to cSVD, extracranial carotid atherosclerotic disease (ECAD) is characterised by large vessel atherosclerosis at the common carotid artery bifurcation and the internal carotid artery, leading to arterial stenosis.

Emboli from ECAD can cause cerebrovascular accidents, which have immediate effects on brain tissue and cognition and are associated with a well-defined long-term risk for dementia.[11] Patients with ECAD who have no recent history of stroke or transient ischaemic attack (TIA) attributed to ECAD are

considered asymptomatic. The prevalence of asymptomatic ECAD (aECAD) is approximately 7.5% for moderate ECAD (defined as 50%–70% stenosis) and 3% for severe ECAD (>70% stenosis) in individuals over 60 years of age, with higher predominance in men.[12] Current treatment for aECAD primarily focuses on managing comorbidities (eg, smoking, HTN, HLD and diabetes) and on stroke prevention.[13] However, there is no clinical evaluation or treatment goals targeting dementia outcomes. This is due to the lack of a well-established association between aECAD and dementia.

Few studies have focused on evaluating the impact of carotid disease on AD.[14–20] Of these studies, five reported a positive association between carotid disease and AD,[14–19] and one not confirming this association.[20] Key limitations of these studies include (1) most rely on small cohorts; (2) use of non-clinical indicators of carotid atherosclerosis, such as carotid intima–media thickness ratio and common carotid plaque counting; (3) they do not control for cardiovascular confounders such as HTN, smoking, diabetes and heart disease and (4) inclusion of patients with both symptomatic and asymptomatic carotid disease. These studies, including the Rotterdam study,[15] contributed significantly to the AD field by highlighting the importance of vascular disease and vascular risk factors in AD physiology. However, whether asymptomatic carotid stenosis is associated with AD and non-AD dementia risk remains unclear.

Defining the association between aECAD and AD as well as other forms of dementia is crucial considering the availability of effective treatments for aECAD that are currently not used for reducing the risk of AD and non-AD dementias. Furthermore, a deeper understanding of the cognitive effects of ECAD could inform clinical trials aimed at modifying the management of carotid disease. Cognition is a critical outcome to document in the aECAD population, as cognitive dysfunction results in increased disability, dependence, decreased medication adherence, higher healthcare costs and higher caregiving needs.[2]

This study evaluated the hypothesis that aECAD is associated with an elevated risk of AD and non-AD dementias leveraging longitudinal data with a US-based population insurance claims records.

METHODS

Data source

The Mariner database is an insurance claims dataset that serves the USA with patient populations from all US states and territories.[21] Pearl Diver is for-fee research software that facilitates interaction with commercial, state-based Medicaid, Medicare stand-alone prescription drug plan, group Medicare Advantage and individual Medicare Advantage data. The Mariner dataset contains patient demographic characteristics and numerous other data points for patients with Current Procedural Terminology, International Classification of Diseases, 9th Revision (ICD-9-CM) and ICD and Related Health Problems, 10th Revision (ICD-10-CM) codes. Mariner encompasses all diagnoses and represents 161 million patients throughout the duration of the set with claims from 2010 to April 2022.

This report follows the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

Study design and variables

Similar to previous studies,[22 23] a subset of 7 133 677 patients diagnosed with non-melanoma skin cancer was selected for medical informatic analysis from the Mariner database as this medical condition is not associated with neurodegenerative disease or cardiovascular diseases, its treatment does not require chemotherapy or surgical anaesthesia which can impact the risk of AD or non-AD dementias, and it occurs with sufficient frequency in the general population to enable robust analyses. Additionally, patients diagnosed with melanoma, the more aggressive form of skin cancer, were specifically excluded.

The outcome variable was determined by identifying the first diagnosis of AD and non-AD dementias using ICD-9-CM and ICD-10-CM codes in the patient's medical claims data. Detailed ICD procedural codes used to identify the diagnosis of AD and non-AD dementias are reported in online supplemental table 1.

For the aECAD group, patients were defined as those with three or more ICD code diagnosis claims for aECAD who did not undergo carotid endarterectomy (CEA) or carotid artery stenting (CAS) surgical interventions. The ICD procedural codes for aECAD, CEA and CAS are provided in online supplemental table 1. Conversely, the control group included subjects without any aECAD or CEA or CAS ICD procedural codes. Patients younger than 55 years old, with a history of AD, dementia, brain cancer or neurosurgery were excluded from the study (ICD codes for these conditions are provided in online supplemental table 1).

To ensure a robust population, an active enrolment criterion of a minimum of 6 months before and 5 years after the diagnosis of aECAD was required, accounting for potential factors such as patients leaving, dying or switching insurance providers (figure 1). The index dates were defined as the first record of aECAD diagnosis for the treatment group and 6 months after the first patient claim record in the database for the control group. The 6 months prior to the index date were used to calculate baseline comorbidities in both groups. A start date of 1 year after the index date was selected to survey records for AD and non-AD dementia diagnoses to focus on long-term impact on disease progression.

Statistical analysis

Statistical analyses were conducted between 12 May 2023 and 10 January 2024. Patient demographic statistics (table 1) and incidence statistics were analysed using unpaired two-tailed t-tests or χ^2 tests, as appropriate, to test the significance of the differences between

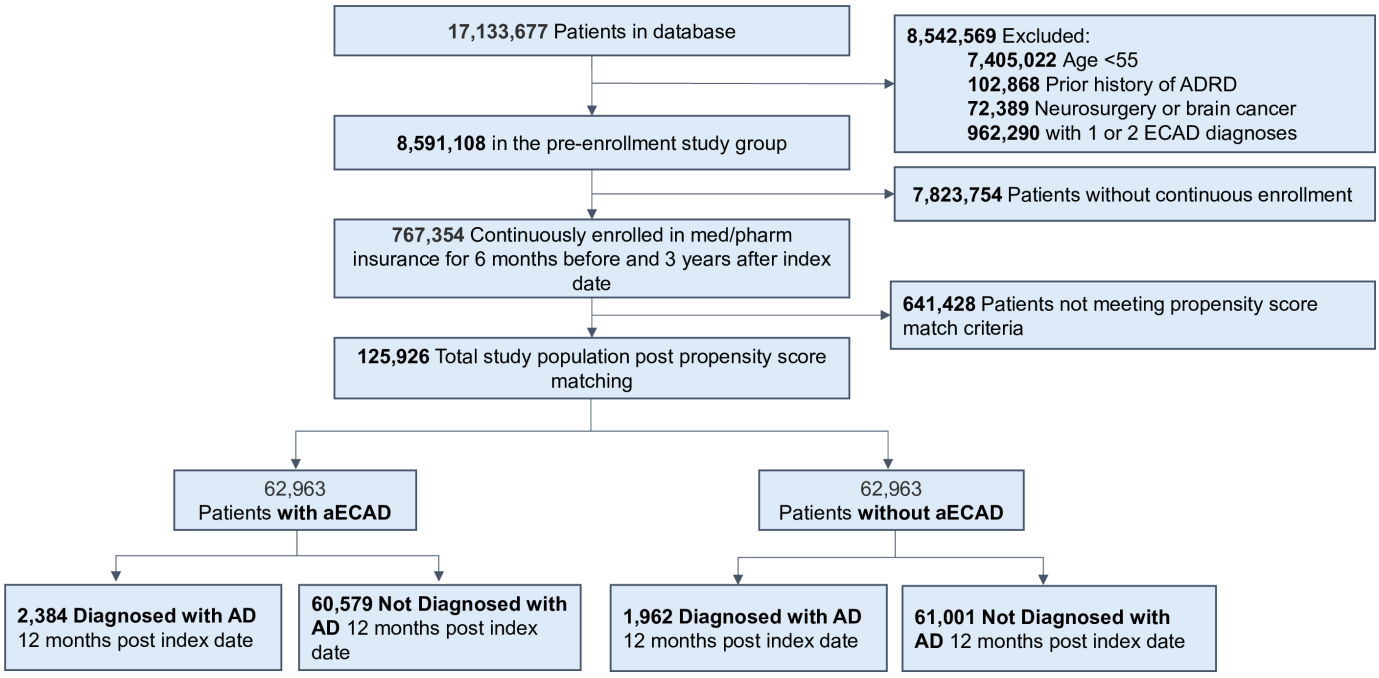


Figure 1 Study design and patient breakdown.

continuous and categorical variables. In all analyses, a two-sided p<0.05 was considered statistically significant.

A propensity score-matched population was generated by using a logistic regression to identify confounding factors for the diagnosis of aECAD status between the exposure and non-exposure groups. The resulting confounding factors included age, region, Charlson Comorbidity Index (CCI) rank, as well as variable comorbidities listed in online supplemental table 1. These factors were integrated into the matching process using a 1:1 ratio, matching patients in the aECAD group to those in the control (no aECAD) group to minimise confounding variables in the two populations. Kaplan-Meier survival curves for disease-free survival were created using the propensity score-matched population in the Bellwether-Pearl Diver interface.

Patient and public involvement

This study is a retrospective review of an insurance claims database. All data were deidentified and there was no patient involvement in the study, its design, recruitment or the outcomes. Data are publicly available with a subscription at http://www.pearldiverinc.com/.

RESULTS

Of the 17 133 677 patients in the Mariner's data subset, 767 354 met the inclusion and exclusion criteria and the claims enrolment period requirements for our study (figure 1). Of the 125 926 patients who met the propensity score matching criteria, 62 963 patients were assigned to the treatment group and 62 963 were assigned to the control group. Patients were evaluated for a diagnosis of AD or non-AD dementia 12 months after the index date (figure 1).

Demographics and comorbidities for the unadjusted populations are summarised in table 1. In the unadjusted cohort, 207 159 individuals (mean (SD) age, 67.6 (7.1) years) were diagnosed with aECAD (defined by at least three consecutive aECAD diagnosis codes), whereas 560 195 individuals (mean (SD) age, 63.7 5.0) years) did not have any diagnosis of aECAD (table 1). The majority of patient records in the study were from individuals aged 70–74 years (table 1). There were significant differences in comorbidities between patients with aECAD and those without (asthma, 1.47% vs 9.71%; chronic obstructive pulmonary disease, 23.91% vs 26.70%; chronic kidney disease 10.60% vs 15.90%; congestive heart failure, 9.15% vs 6.72%; coronary artery disease, 45.00% vs 27.16%; deep vein thrombosis, 0.18% vs 2.02%; diabetes, 37.44% vs 35.85%; HTN, 75.64% vs 70.87%; obesity, 10.35% vs 24.98%; pulmonary heart disease, 4.08% vs 6.98% and tobacco use, 14.69% vs 25.28%) (table 1).

Logistic regression analysis for potential confounders associated with aECAD identified the following confounding factors and comorbidities: age, gender, region, CCI score, asthma, chronic obstructive pulmonary disease, chronic kidney disease, congestive heart failure, coronary artery disease, deep vein thrombosis, diabetes, HTN, obesity, pulmonary heart disease and tobacco use (online supplemental table 1).

Propensity score matching was used to create groups that controlled for identified confounding factors between the aECAD and control groups. Demographic characteristics and comorbidities of propensity score-matched populations are detailed in table 1. In the matched dataset, 62 963 individuals (mean (SD) age, 67.3 (2.8) years) comprised the aECAD group and were matched with an equal number of control individuals (mean (SD) age,

Table 1 Baseline characteristics and comorbidities of patients not diagnosed and diagnosed with aECAD

	Unadjusted population			Propensity Score-matched population		
	Without aECAD	With aECAD		Without aECAD	With aECAD	
	n (%)	n (%)	P value	n (%)	n (%)	P value
Number of patients	560 195	207 159		62 963	62 963	
Age						
55–59	133 237 (23.78)	15 942 (7.70)	0.02	6447 (10.24)	6447 (10.24)	>0.99
60–64	124 978 (22.31)	25 747 (12.43)		9316 (14.80)	9316 (14.80)	
65–69	108 108 (19.30)	39 378 (19.01)		11 673 (18.54)	11 673 (18.54)	
70–74	141 479 (25.26)	86 577 (41.79)		20 499 (32.56)	20 499 (32.56)	
75–79	52 393 (9.35)	39 515 (19.07)		15 028 (23.87)	15 028 (23.87)	
Gender						
Female	320 617 (57.23)	97 644 (47.13)	0.16	33 079 (52.54)	33 079 (52.54)	>0.99
Male	239 578 (42.77)	109 515 (52.87)		29 884 (47.46)	29 884 (47.46)	
Region						
Midwest	123 222 (22.00)	42 169 (20.36)	0.03	11 858 (18.83)	11 858 (18.83)	>0.99
Northeast	138 288 (24.69)	50 789 (24.52)		14 990 (23.81)	14 990 (23.81)	
South	240 344 (42.90)	103 508 (49.97)		29 574 (46.97)	29 574 (46.97)	
Unknown	1544 (0.28)	377 (0.18)		24 (0.04)	24 (0.04)	
West	87 236 (15.57)	20 547 (9.92)		6517 (10.35)	6517 (10.35)	
Comorbidities						
Asthma	54 408 (9.71)	3055 (1.47)	<0.001	435 (0.69)	435 (0.69)	>0.99
Chronic obstructive pulmonary disease	149 548 (26.70)	49 537 (23.91)	<0.001	8513 (13.52)	8513 (13.52)	>0.99
Chronic kidney disease	89 077 (15.90)	21 967 (10.60)	<0.001	3272 (5.20)	3272 (5.20)	>0.99
Congestive heart failure	37 637 (6.72)	18 960 (9.15)	<0.001	1856 (2.95)	1856 (2.95)	>0.99
Coronary artery disease	152 144 (27.16)	93 215 (45.00)	<0.001	15 993 (25.40)	15 993 (25.40)	>0.99
Deep vein thrombosis	11 339 (2.02)	364 (0.18)	<0.001	11 (0.02)	11 (0.02)	>0.99
Diabetes	200 826 (35.85)	77 552 (37.44)	<0.001	18 529 (29.43)	18 529 (29.43)	>0.99
Hypertension	397 033 (70.87)	156 704 (75.64)	<0.001	38 264 (60.77)	38 264 (60.77)	>0.99
Obesity	139 945 (24.98)	21 440 (10.35)	<0.001	4324 (6.87)	4324 (6.87)	>0.99
Pulmonary heart disease	39 101 (6.98)	8458 (4.08)	<0.001	719 (1.14)	719 (1.14)	>0.99
Tobacco use	141 602 (25.28)	30 440 (14.69)	<0.001	6574 (10.44)	6574 (10.44)	>0.99
CCI score						
0–4	533 751 (95.28)	173 512 (83.76)	0.43	56 929 (90.42)	56 890 (90.35)	>0.99
5–10	24 606 (4.39)	26 592 (12.84)		5820 (9.24)	5855 (9.30)	
11+	1838 (0.33)	7055 (3.41)		214 (0.34)	218 (0.35)	

aECAD, asymptomatic extracranial carotid atherosclerotic disease; CCI, Charlson Comorbidity Index.

67.3 (2.8) years) without aECAD (table 1). Patient demographics and comorbidities, as well as CCI scores, did not exhibit statistically significant differences between the matched groups (table 1).

Analysis of unadjusted population data indicated that a diagnosis of aECAD was associated with a significantly higher incidence of AD compared with controls (9803 (4.51%) vs 12 814 (2.17%); relative risk (RR), 2.07; 95% CI 2.02 to 2.13; p<0.001) and a significant increased risk of developing non-AD dementia (7777 (3.58%) vs 8498 (1.44%); RR 2.49; 95% CI 2.41 to 2.56; p<0.001) (figure 2a and b). Results of the χ^2 analysis in the propensity score-matched populations indicated that aECAD diagnosis was associated with a significantly higher incidence of AD (2384 (3.79%) vs 1962 (3.12%); RR 1.22; 95% CI 1.15 to 1.29; p<0.001) and non-AD dementia (1879 (2.98%) vs 1271 (2.02%); RR 1.48; 95% CI 1.38 to 1.59; p<0.001) compared with controls (figure 2a and c).

The propensity score-matched population was used to generate Kaplan-Meier survival curves for AD-free

a

	AD	Non-AD dementia
Unadjusted Cohort		
Patients without aECAD	12,814	8,498
%	2.17%	1.44%
Patients with aECAD	9,803	7,777
%	4.51%	3.58%
Relative Risk	*2.07*	*2.49*
95%CI	2.02-2.13	2.41-2.56
p-value	*<0.001*	*<0.001*
Propensity Score-Matched Cohort		
Patients without aECAD	1,962	1,271
%	3.12%	2.02%
Patients with aECAD	*2,384*	*1,879*
%	3.79%	2.98%
Relative Risk	*1.22*	*1.48*
95%CI	1.15-1.29	1.38-1.59
p-value	*<0.0001*	*<0.0001*

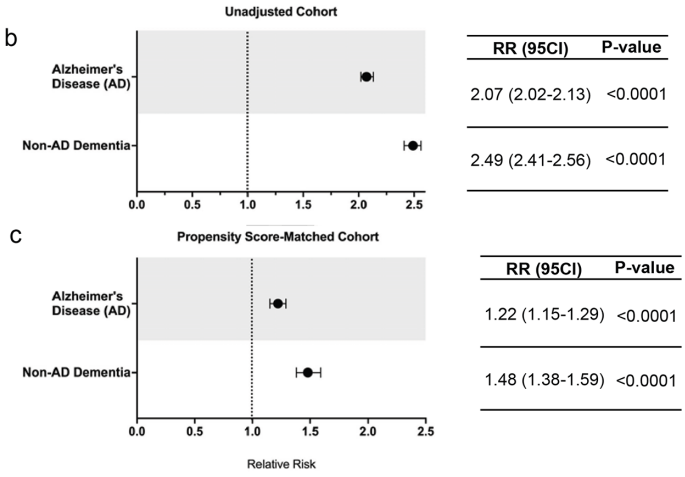
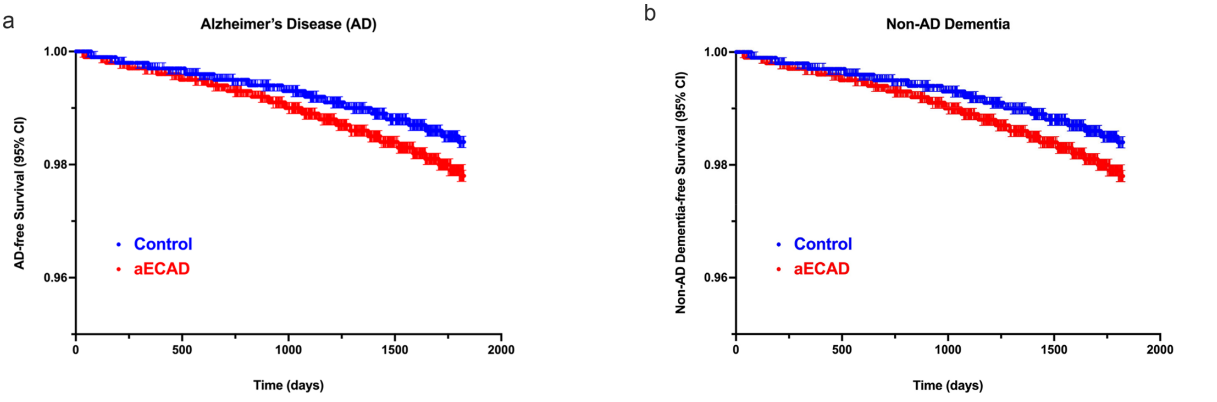


Figure 2 Relative risk (RR) of patients diagnosed with aECAD to develop AD and non-AD Dementia. (A) Statistics of the unadjusted and adjusted (propensity score-matched) cohorts. (B, C) Plots and statistics of relative risk of developing AD and non-AD dementia, respectively. aECAD was associated with a significantly increased RR for non-AD dementia compared with patients without a diagnosis of aECAD. AD, Alzheimer's disease; aECAD, asymptomatic extracranial carotid atherosclerotic disease.

survival and non-AD dementia-free survival to assess the rate and proportion of the population developing these conditions over a period of 5 years (figure 3a,b). Changes in disease incidence rates between patients diagnosed with aECAD and controls mirrored the χ^2 analysis results. aECAD diagnosis was associated with a higher incidence and faster progression to AD (figure 3a) and non-AD dementia (figure 3b) over 5 years; CIs did not overlap in the 5-year analysis and were divergent. AD-free survival over 5 years was also stratified by age (figure 4), exhibiting a more evident increased risk in patients aged 60–74 years (figure 4a–c), where the greater risk was more apparent in those aged 70–74 years (figure 4c). In contrast, patients older than 75 years of age did not exhibit a significant difference in AD risk (figure 4d).

DISCUSSION

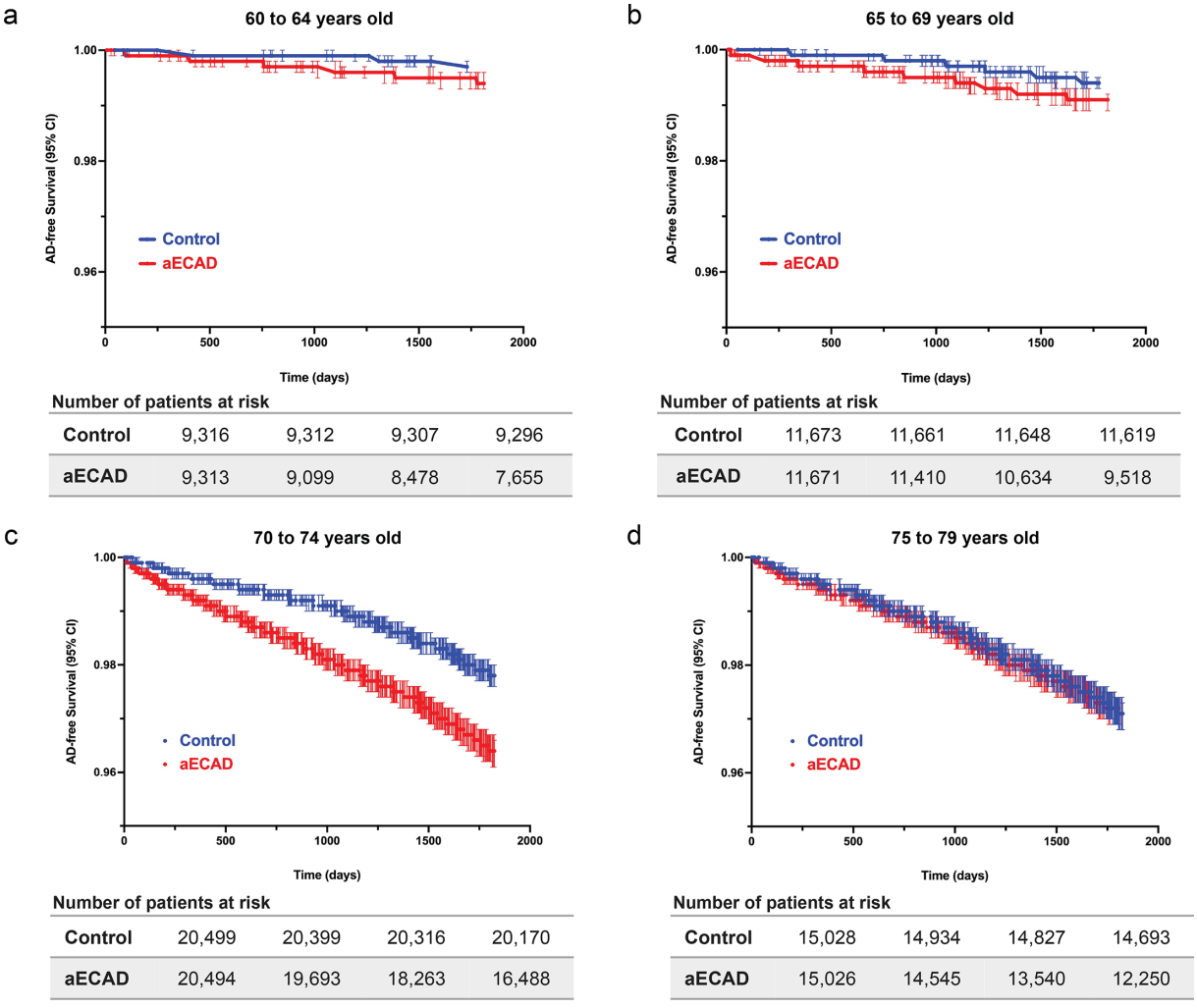
The impact of AD and non-AD dementias is growing worldwide, and its incidence is expected to triple over the next three decades.[2] Vascular diseases have emerged as crucial contributors to dementia risk.[4 5 8 24] The majority of current research related to vascular contributions to dementia focuses on cSVD and associated cardiovascular risk factors,[4–6 8] with few studies investigating the specific contribution of ECAD to dementia and none of them



Number of patients at risk				
Control	62,963	62,750	62,541	62,218
aECAD	62,963	62,675	62,353	61,933

Number of patients at risk				
Control	62,963	62,818	62,680	62,506
aECAD	62,963	62,771	62,571	62,273

Figure 3 Kaplan-Meier survival curves of AD-free survival. (A, B) Kaplan-Meier curves along with the number of patients falling in each time group for AD and non-AD dementia, respectively. aECAD, asymptomatic extracranial carotid atherosclerotic disease.



Number of patients at risk

Control	9,316	9,312	9,307	9,296
aECAD	9,313	9,099	8,478	7,655

Number of patients at risk

Control	11,673	11,661	11,648	11,619
aECAD	11,671	11,410	10,634	9,518

Number of patients at risk

Control	20,499	20,399	20,316	20,170
aECAD	20,494	19,693	18,263	16,488

Number of patients at risk

Control	15,028	14,934	14,827	14,693
aECAD	15,026	14,545	13,540	12,250

Figure 4 Kaplan-Meier survival curves of AD-free survival by age. (A–D) Kaplan-Meier curves along with the number of AD-free survival by age 60–64 (A), 65–69 (D), 70–74 (C) and 75–79 (D). Increased risk was more evident in patients from 60–74 years of age (A–C), where the greater risk was more apparent in patients aged 70–74 years (C). In contrast, patients older than 75 years of age did not exhibit a significant difference in AD risk (D). AD, Alzheimer's disease; aECAD, asymptomatic extracranial carotid atherosclerotic disease.

differentiating between asymptomatic and symptomatic ECAD.[14–19] This study addressed the limitations of prior research by using US-based Mariner insurance claims of a large clinical population of 7 133 677 individuals to evaluate the specific impact of aECAD on the risk of developing AD and non-AD dementias. This approach used clinically defined carotid stenosis as a marker of carotid atherosclerosis (overcoming limitations of indirect indicators, such as carotid intima–media thickness ratio and common carotid plaque counting) and assured the exclusion of symptomatic patients with stroke or TIA. Distinguishing between symptomatic and asymptomatic carotid disease is crucial, as stroke and TIA are independent risk factors for dementia[25 26] and, therefore, key confounders.

Propensity score matching was used to mitigate potential confounders between aECAD cohort and controls. Regression analysis identified confounding factors associated with aECAD including established aECAD risk factors, such as age, HTN, HLD, smoking, statin therapy and coronary artery disease, as well as unexpected factors, such as deep vein thrombosis, asthma and pulmonary heart disease. This strategy for identifying potential confounders promotes unbiased selection. Both the unmatched and propensity score-matched aECAD cohorts exhibited similarities to those in classic carotid studies, such as the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST trial, including high incidence of HTN and heart diseases.[27] Interestingly, we observed slightly higher rates of diabetes and lower rates of smoking in the aECAD cohorts, which likely reflect changing demographics of the USA.

Within the propensity score-matched 125 926 individuals, aECAD was associated with a 22% increased risk of developing AD and a 48% increased risk of developing non-AD dementias. Higher non-AD dementia risk compared with AD may be due to the inclusion of vascular dementia in this category. Furthermore, the matching approach indicated that aECAD was associated

with increased risk of dementia independently of general cardiovascular diseases, suggesting that distinct mechanisms related to aECAD risk impact dementia risk.

Potential mechanisms by which aECAD influences dementia pathophysiology include decreased cerebral perfusion, which is considered an early contributor to AD pathology including neurofibrillary tangle (NFT) and β-amyloid (Aβ) accumulation.[28 29] Supporting this, previous studies have shown that aECAD is associated with cerebral hypoperfusion[30] and increased NFT accumulation.[31] Additionally, we hypothesise that subclinical microembolic events, which occur in 10%–15% of patients with aECAD[32] and do not result in TIA or stroke, may contribute to endothelial dysfunction, blood–brain barrier impairment and neuroinflammation, all mechanisms that contributor to AD pathophysiology.[33] Endothelial inflammation is another mechanism that may contribute to AD risk in individuals with aECAD. Chronic endothelial inflammation, often observed in patients with aECAD,[34 35] creates a proinflammatory environment that can exacerbate vascular and neural damage. The resulting endothelial dysfunction contributes to a cycle of inflammation, oxidative stress and vascular impairment, all of which are implicated in the progression of dementia.[36]

Findings from the survival analysis indicated that the largest difference in AD risk between aECAD and non-aECAD cohorts occurred in the age group of 70–74 years (figure 4), slightly younger than the typical peak age range for AD incidence, which peaks at 80 years old.[37] This earlier peak aligns with evidence suggesting that combined vascular disease may accelerate AD onset and progression[38 39] emphasising the importance of early aECAD diagnosis and highlighting a key window for intervention that could mitigate AD risk.

Outcomes from this study have broad implications across medical disciplines.[40] Currently, aECAD evaluation and treatment do not routinely consider neurodegenerative outcomes such as AD or non-AD dementia. Our data suggest that these outcomes are relevant and that aECAD should be regularly considered as a risk factor in AD and dementia evaluation. The intervention and treatment of AD and dementia risk factors, including aECAD, could represent a new target for risk modification and contribute to delay the onset and progression of AD and dementia. Delaying AD onset by 5 years would reduce total health and long-term care spending for people with Alzheimer's by 33%.[2] This 5-year delay is also highly relevant considering that a difference between mild and moderate dementia is loss of independent living.[2]

Limitations of this study include the retrospective analysis of insurance claims, potentially excluding patients receiving service outside the database. Furthermore, insurance claims do not include indicators of carotid disease severity, therefore, the analyses reported here likely include a mixed population of subjects with both moderate and severe stenosis. Additionally, this study relied on clinical diagnoses for aECAD, AD and non-AD dementia included in the claim insurance data which may result in less reliable diagnoses than in prospective studies. To mitigate this limitation and increase the likelihood that patients have clinically relevant carotid stenosis, three consecutive diagnoses of aECAD were required for inclusion of aECAD patients in the study. Moreover, the inclusion of 62 963 patients in both propensity-matched cohorts mitigates these limitations.

Future retrospective research could confirm, validate and address the limitations of this study by using comprehensive datasets that include both patient diagnosis, medication data, laboratory values and imaging data that quantify the severity of the carotid disease. Additionally, well-designed prospective trials will be needed to confirm the role of aECAD in dementia risk.

In summary, this study evaluated whether asymptomatic carotid stenosis is associated with dementia risk using matched cohorts of a total of 125 926 patients from insurance claim records. The outcomes of this study indicated that aECAD is associated with an increased risk of AD and non-AD dementia over 5 years independent from other cardiovascular risks. As roughly 10% of the population over the age of 65 have aECAD, these are clinically relevant results and should prompt a closer evaluation of aECAD-specific effects on brain health and how aECAD-specific interventions can impact AD onset and progression.

Contributors CW is the guarantor is responsible for the overall content. Concept and design: FV, CW and EJB. Data acquisition, analysis or interpretation of data: GT-H, GB, FV, CW and EJB. Drafting of the manuscript: all authors. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: GT-H, GB, FV and EJB. Obtained funding: CW and RDB. Administrative, technical or material support: CW. Supervision: CW.

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Competing interests None declared.

Patient consent for publication Not applicable.

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Data availability statement Data are available on reasonable request.

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REFERENCES

1 Scheltens P, Blennow K, Breteler MMB, *et al*. Alzheimer's disease. *Lancet* 2016;388:505–17.
2 2022 Alzheimer's disease facts and figures. *Alzheimer's & Dementia* 2022;18:700–89.
3 Gale SA, Acar D, Daffner KR. Dementia. *Am J Med* 2018;131:1161–9.
4 Corriveau RA, Bosetti F, Emr M, *et al*. The Science of Vascular Contributions to Cognitive Impairment and Dementia (VCID): A Framework for Advancing Research Priorities in the Cerebrovascular Biology of Cognitive Decline. *Cell Mol Neurobiol* 2016;36:281–8.
5 Gladman JT, Corriveau RA, Debette S, *et al*. Vascular contributions to cognitive impairment and dementia: Research consortia that focus on etiology and treatable targets to lessen the burden of dementia worldwide. *Alzheimers Dement (N Y)* 2019;5:789–96.
6 Eisenmenger LB, Peret A, Famakin BM, *et al*. Vascular contributions to Alzheimer's disease. *Transl Res* 2023;254:41–53.
7 Inoue Y, Shue F, Bu G, *et al*. Pathophysiology and probable etiology of cerebral small vessel disease in vascular dementia and Alzheimer's disease. *Mol Neurodegener* 2023;18:46.
8 Hainsworth AH, Markus HS, Schneider JA. Cerebral Small Vessel Disease, Hypertension, and Vascular Contributions to Cognitive Impairment and Dementia. *Hypertension* 2024;81:75–86.
9 Geifman N, Brinton RD, Kennedy RE, *et al*. Evidence for benefit of statins to modify cognitive decline and risk in Alzheimer's disease. *Alzheimers Res Ther* 2017;9:10.
10 Glans I, Nägga K, Gustavsson A-M, *et al*. Associations of modifiable and non-modifiable risk factors with cognitive functions – a prospective, population-based, 17 years follow-up study of 3,229 individuals. *Alz Res Therapy* 2024;16:135.
11 Pendlebury ST, Rothwell PM, Oxford Vascular Study. Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: analysis of the population-based Oxford Vascular Study. *Lancet Neurol* 2019;18:248–58.
12 de Weerd M, Greving JP, Hedblad B, *et al*. Prevalence of Asymptomatic Carotid Artery Stenosis in the General Population. *Stroke* 2010;41:1294–7.
13 Hackam DG. Optimal Medical Management of Asymptomatic Carotid Stenosis. *Stroke* 2021;52:2191–8.
14 Hofman A, Ott A, Breteler MM, *et al*. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. *Lancet* 1997;349:151–4.
15 van Oijen M, de Jong FJ, Witteman JCM, *et al*. Atherosclerosis and risk for dementia. *Ann Neurol* 2007;61:403–10.
16 Wendell CR, Waldstein SR, Ferrucci L, *et al*. Carotid Atherosclerosis and Prospective Risk of Dementia. *Stroke* 2012;43:3319–24.
17 Silvestrini M, Gobbi B, Pasqualetti P, *et al*. Carotid atherosclerosis and cognitive decline in patients with Alzheimer's disease. *Neurobiol Aging* 2009;30:1177–83.
18 Baradaran H, Demissie S, Himali JJ, *et al*. The progression of carotid atherosclerosis and imaging markers of dementia. *Alzheimers Dement (N Y)* 2020;6:e12015.
19 Xiang J. Carotid atherosclerosis promotes the progression of Alzheimer's disease: A three-year prospective study. *Exp Ther Med* 2017;14:1321–6.
20 Carcaillon L, Plichart M, Zureik M, *et al*. Carotid plaque as a predictor of dementia in older adults: The Three-City Study. *Alzheimer's & Dementia* 2015;11:239–48.
21 PearlDiver. Healthcare research: mariner details colorado springs. 2020. Available: http://www.pearldiverinc.com/researchinfo.html [Accessed 31 Dec 2020].
22 Cortes-Flores H, Torrandell-Haro G, Brinton RD. Association between CNS-active drugs and risk of Alzheimer's and age-related neurodegenerative diseases. *Front Psychiatry* 2024;15:1358568.
23 Torrandell-Haro G, Branigan GL, Vitali F, *et al*. Statin therapy and risk of Alzheimer's and age-related neurodegenerative diseases. *Alzheimers Dement (N Y)* 2020;6:e12108.
24 Lazar RM, Wadley VG, Myers T, *et al*. Baseline Cognitive Impairment in Patients With Asymptomatic Carotid Stenosis in the CREST-2 Trial. *Stroke* 2021;52:3855–63.
25 Baradaran H, Sarrami AH, Gupta A. Asymptomatic Carotid Disease and Cognitive Impairment: What Is the Evidence? *Front Neurol* 2021;12:741500.
26 Koton S, Pike JR, Johansen M, *et al*. Association of Ischemic Stroke Incidence, Severity, and Recurrence With Dementia in the Atherosclerosis Risk in Communities Cohort Study. *JAMA Neurol* 2022;79:271.
27 Brott TG, Hobson RW 2nd, Howard G, *et al*. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med* 2010;363:11–23.
28 Wolters FJ, Zonneveld HI, Hofman A, *et al*. Cerebral Perfusion and the Risk of Dementia: A Population-Based Study. *Circulation* 2017;136:719–28.
29 Kisler K, Nelson AR, Montagne A, *et al*. Cerebral blood flow regulation and neurovascular dysfunction in Alzheimer disease. *Nat Rev Neurosci* 2017;18:419–34.
30 Khan AA, Patel J, Desikan S, *et al*. Asymptomatic carotid artery stenosis is associated with cerebral hypoperfusion. *J Vasc Surg* 2021;73:1611–21.
31 Arias JC, Edwards M, Vitali F, *et al*. Extracranial carotid atherosclerosis is associated with increased neurofibrillary tangle accumulation. *J Vasc Surg* 2022;75:223–8.
32 Markus HS, King A, Shipley M, *et al*. Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. *Lancet Neurol* 2010;9:663–71.
33 Grammas P. Neurovascular dysfunction, inflammation and endothelial activation: implications for the pathogenesis of Alzheimer's disease. *J Neuroinflammation* 2011;8:26.
34 Weinkauf CC, Concha-Moore K, Lindner JR, *et al*. Endothelial vascular cell adhesion molecule 1 is a marker for high-risk carotid plaques and target for ultrasound molecular imaging. *J Vasc Surg* 2018;68:105S–113S.
35 Gimbrone MA, García-Cardeña G. Endothelial Cell Dysfunction and the Pathobiology of Atherosclerosis. *Circ Res* 2016;118:620–36.
36 Kelleher RJ, Soiza RL. Evidence of endothelial dysfunction in the development of Alzheimer's disease: Is Alzheimer's a vascular disorder? *Am J Cardiovasc Dis* 2013;3:197–226.
37 Qiu C, Kivipelto M, von Strauss E. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. *Dialogues Clin Neurosci* 2009;11:111–28.
38 Silvestrini M, Viticchi G, Falsetti L, *et al*. The role of carotid atherosclerosis in Alzheimer's disease progression. *J Alzheimers Dis* 2011;25:719–26.
39 Fresnais D, Humble MB, Bejerot S, *et al*. The Association between Carotid Intima-Media Thickness and Cognitive Impairment: A Systematic Review and Meta-Analysis. *Dement Geriatr Cogn Disord* 2021;50:305–17.
40 Bonati LH, Jansen O, de Borst GJ, *et al*. Management of atherosclerotic extracranial carotid artery stenosis. *Lancet Neurol* 2022;21:273–83.