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RESEARCH ARTICLE

Brain artery diameters and risk of dementia and stroke

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Abstract

INTRODUCTION: We tested the association of brain artery diameters with dementia and stroke risk in three distinct population-based studies using conventional T2-weighted brain magnetic resonance imaging (MRI) images.

METHODS: We included 8420 adults > 40 years old from three longitudinal population-based studies with brain MRI scans. We estimated and meta-analyzed the hazard ratios (HRs) of the brain and carotids and basilar diameters associated with dementia and stroke.

RESULT: Overall and carotid artery diameters > 95th percentile increased the risk for dementia by 1.74 (95% confidence interval [CI], 1.13–2.68) and 1.48 (95% CI, 1.12–1.96) fold, respectively. For stroke, meta-analyses yielded HRs of 1.59 (95%

Daniel Bos and Jose Gutierrez contributed equally to this study.

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CI, 1.04–2.42) for overall arteries and 2.11 (95% CI, 1.45–3.08) for basilar artery diameters > 95th percentile.

DISCUSSION: Individuals with dilated brain arteries are at higher risk for dementia and stroke, across distinct populations. Our findings underline the potential value of T2-weighted brain MRI-based brain diameter assessment in estimating the risk of dementia and stroke.

KEYWORDS
brain artery diameter, dementia, magnetic resonance imaging, population-based science, stroke

1 | INTRODUCTION

Dementia and stroke are two of the most burdensome neurological syndromes associated with aging.[1] The etiology of both is complex and pathological vascular changes play a pivotal role in their pathogenesis.[2,3] Such vascular changes are characterized by structural and functional changes in blood vessels that lead to remodeling, usually thought of as inward remodeling due to atherosclerosis and luminal stenosis.[3] Inward remodeling can lead to changes in cerebral blood flow that may have deleterious effects on distal organs including the brain.[2] However, recent studies suggest also generalized vascular changes that are characterized by dilation and tortuosity (dolichoectasia) relate to neurological outcomes of presumed vascular origin.[4–7] In particular, these generalized dilative changes of the brain arteries have been poorly studied in large population-based studies.

An important reason for this is that in-depth investigations of dolichoectasia require arterial imaging such as magnetic resonance angiography or computerized tomography angiography, which are not standard sequences obtained in large population-based cohort studies. An alternative approach is to assess instead the cross-sectional diameters of the brain carotid and basilar arteries on magnetic resonance imaging (MRI) axial T2-weighted scans, which are routinely performed in clinical settings and large-scale epidemiological studies. Using this approach, we previously found the first evidence that elderly people with dilated brain arteries may be at a higher risk of dementia.[8] It remains unclear whether this finding can be generalized to the general population and whether dilated brain arteries also contribute to the risk of stroke. Therefore, we investigated the association of the diameters of the brain carotid and basilar arteries with the risk of dementia and stroke across three large population-based cohort studies the United States, France, and the Netherlands.

2 | METHODS

2.1 | Cohorts studied

We analyzed data from three prospective observational population-based cohorts (Table S1 in supporting information). Inclusion criteria were the availability of MRI scans to measure the brain carotid and basilar artery diameters and follow-up of fatal and non-fatal outcomes. The Northern Manhattan Study (NOMAS, from the United States) included 1290 participants aged ≥ 40 years; the Three-City Study (3C Study) included 1924 individuals aged ≥ 65 years from Dijon, France; and the Rotterdam Study (the Netherlands) included 5103 participants aged ≥ 40 years. Details of each cohort design and methods are available elsewhere.[7,9,10] The first MRI scan was considered the baseline assessment. Participants were recruited between 1989 and 2010.[10] Each study received ethical approval from the institutional review boards at their institution of origin and adhered to the principles of the Declaration of Helsinki.[11] All participants provided written informed consent. Due to data-sharing regulations, we did not pool individual-level data from these cohorts into one dataset. Instead, cohort-specific summary statistics and syntax were shared and accessible to the three cohorts.

2.2 | MRI acquisition and brain artery diameters

Brain MRI images were acquired on 1.5 T Philips Intera,[8] Magnetom,[12] or GE Healthcare[13] scanners and included T1-weighted, T2-weighted fluid-attenuated inversion recovery, T2-weighted gradient recalled echo, and proton density. On MRI axial T2-weighted scans, we identified the "black voids" (Figure 1) corresponding to the cross-sectional diameters of the ascending portion of the supraclinoid intracranial carotid artery and the basilar artery at its most proximal segment to obtain their axial diameters. The slice thickness of T2-weighted sequences was 3 mm in the NOMAS, 3.5 mm in the Three-City Study, and 1.6 mm in the Rotterdam Study. To capture variations in the arterial angle, each black void was measured in two perpendicular directions to form a cross, and the average of both measurements was used to determine the arterial diameter for each void. Brain arterial measurements were obtained by a rater trained and supervised by a vascular neurologist (J.G.) and epidemiologist (J.G., D.B.). The reproducibility among experienced readers has been reported to be good, with an intraclass correlation ranging from 0.68 to 0.77.[8]

2.3 | Ascertainment of dementia and stroke

The incidence of fatal and non-fatal end points was ascertained following standardized protocols and from appropriate sources in each cohort. All outcomes were prespecified and coded according to the International Classification of Diseases, version 10 (ICD-10). End points were incident dementia, and a composite of fatal and non-fatal strokes. Experienced physician scientists or neurologists adjudicated end points at each cohort blinded to arterial diameter measurements. Information on vital status was continuously obtained through linkage of practitioner files with the study database and regular checks of municipal records. More detailed information about the protocols for the collection of these data is described in Expanded Methods in supporting information.

In each of the separate studies, dementia was adjudicated following standardized protocols, and through a local consensus panel constituted by a multidisciplinary team that included various possible combinations of research physicians,[14,15] geriatricians,[16] neuropsychologists,[14,15] or neurologists,[14–16] as described elsewhere. Two cohorts followed a similar three-step protocol to adjudicate dementia (see Expanded Methods).[14,16] Neuropsychological batteries were applied in the three cohorts to assess memory, orientation, reasoning, auditory comprehension, and visuospatial cognitive domains. The consensus panel reviewed the cognitive, functional, and medical data collected at each visit[15,16] and/or via continuous monitoring for dementia through computerized linkage between the study database and medical records from general practitioners and regional health care institutes.[14] Clinical imaging data were collected when possible as supplemental information for the ascertainment of dementia.[14,16] In all three cohorts, dementia was ascertained in accordance with the Diagnostic and Statistical Manual of Mental Disorders, versions third revised[14,15] or fourth.[16]

Stroke definition was made by a blinded expert panel of physicians (3C Study)[17,18] or by two independent vascular neurologists unaware of the status of the patient in the study (NOMAS).[7] In the Rotterdam Study,[19] stroke cases identified during the continuous updating of the database via general practitioners or hospital records were reviewed by research physicians and verified by an experienced stroke neurologist. In all cohorts, stroke was defined, in accordance with the criteria of the World Health Organization, as a new focal neurological deficit of sudden or rapid onset and of presumed vascular origin, lasting 24 hours or more, or leading to death. Confirmed stroke cases were further classified as ischemic, hemorrhagic, or unspecified. Stroke subtypes (hemorrhagic or ischemic) were based on neuroimaging reports,[7,19] or according to the ICD-10.[17,18]

2.4 | Other measurements

Throughout interviews, physical examinations, and fasting blood sampling, we collected demographics and clinical variables including sex, ethnicity, completion of high school, self-reported ethnicity, smoking status, height in cm, office blood pressure recordings, diabetes mellitus, serum cholesterol, previous history of coronary artery disease or stroke, and use of antihypertensive and antidiabetic medications. Apolipoprotein E ε4 was obtained in the NOMAS and Rotterdam studies. In all cohorts, office hypertension was the average of two consecutive systolic and diastolic blood pressure ≥ 140/90 mmHg or use of antihypertensive medication. Hypercholesterolemia was a serum total cholesterol ≥ 240 mg/dL in the NOMAS and Rotterdam studies and ≥200 mg/dL in the 3C Study; all cohort studies additionally included the use of lipid-lowering medication to define hypercholesterolemia. Diabetes was defined as a serum fasting glucose ≥ 126 mg/dL or use of antidiabetic medication in all three cohorts.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed journal articles using PubMed and Google Scholar. Dilated brain artery diameters relate to cerebrovascular diseases but information on population-based studies is scarce. This represents a missing opportunity to expose a potential novel pathway through which arterial changes exert an effect on the brain.
2. **Interpretation**: Using prospective data from three population-based studies (8420 adults > 40 years), we documented that brain artery diameters measured on T2-weighted magnetic resonance imaging (MRI) axial scans were associated with the development of dementia and stroke, particularly, dilated brain artery diameters.
3. **Future directions**: Contrary to the clinical intuition that small arterial diameters are pathological, we present evidence that people with dilated brain arteries are at a higher risk of dementia and stroke. The study of MRI-based artery diameters measured provides an opportunity to investigate aging-related neurological pathologies beyond luminal stenosis due to arteriosclerosis.

2.5 | Statistical analysis

Baseline characteristics were reported as arithmetic mean with standard deviation for continuous variables with normal distribution, or median with interquartile ranges (IQRs) for non-normally distributed variables. Categorical data were reported as frequency and percentage (%). The arterial diameters of the carotids and basilar arteries were rank normalized to equalize the expected larger carotid arterial diameter compared to the basilar artery. We then added and averaged the three arterial measures to obtain the overall brain arterial diameter as marker of the overall status of dolichoectasia across the brain. We then categorized this continuous variable into percentiles and defined dilated arterial diameters if > 95th percentile while small arteries if < 5th percentile, and a reference group including participants with diameters between the 5th and 95th percentiles.[8] We have used this

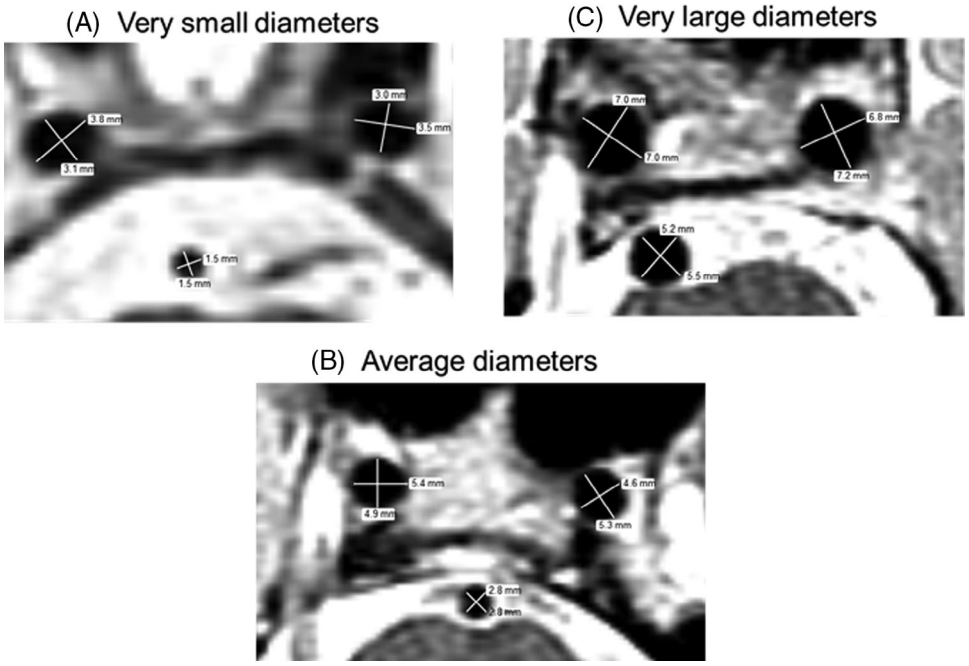

FIGURE 1 Examples of MRI axial T2-weighted measurements of brain arterial luminal diameters. The diameters are measured as cross-sectional axial voids in brain MRI T2-weighted sequences. Each artery is measured twice as observed in all panels; (A) is an example of a participant with very small diameters (below the 5th of the percentile), (B) is a case with normal average diameters, and (C) displays a subject with dilated diameters (above the 95th percentile). MRI, magnetic resonance imaging.

percentile-based approach and these cut-offs in similar analyses in the past to avoid focusing on more extreme phenotypes (usually > 2 standard deviations) while allowing for greater power.[8,20] Next, we estimated the age, sex, and head size/brain volume adjusted incidence of dementia and stroke according to the three categories of brain artery arteries. To assess the risk association, adjusted Cox regression models were performed to assess the relationship of dementia and stroke with brain artery diameter categories in each individual cohort. We expressed hazard ratios (HRs) and their 95% confidence interval (CI) for small and dilated brain artery diameters compared to the reference group. We also performed analyses separately using the averaged carotid diameters and the basilar artery continuously. We checked the proportional hazard assumption by the Kolmogorov-type supremum test. We also conducted three sets of exploratory analysis including (1) adjusting Cox proportional models accounted for total mortality as competing risk for dementia and stroke end points by using the cause-specific approach due to the etiological nature of our study,[21] (2) exploring whether setting a higher cutoff for large brain artery diameters in NOMAS similar to the cutoff noted in European cohorts could produce an effect size of similar magnitude in NOMAS as in the European cohorts, and (3) estimating the association of overall brain diameters with dementia and stroke risk in subgroup analysis based on modifiable cardiovascular risk factors (smoking, dyslipidemia, hypertension, and diabetes). For database management and statistical analysis, we used SAS software, version 9.4, maintenance level 5. Statistical significance was a two-tailed α-level of 0.05 or less. Additionally, RevMan software (5.4) was used to conduct the meta-analysis.

3 | RESULTS

3.1 | Baseline characteristics of participants

Table 1 contains the baseline characteristics of the three cohorts. The mean age ranged from 64.7 to 72.9 years, with women representing at least 57% in all three studies. NOMAS was constituted of 17.3% non-Hispanic White, 17.3% non-Hispanic Black, and 65.5% Hispanics, whereas the Rotterdam Study included only White participants (there was no documentation of race/ethnicity in the 3C Study). The median carotid artery diameters ranged from 3.7 to 4.6 mm, and the basilar ranged from 2.0 to 2.9 mm. The thresholds of brain artery diameters corresponding to the 5^{th} and 95^{th} percentiles of the rank-normalized diameters are shown in Table S2 in supporting information.

3.2 | Incidence of dementia and stroke

In NOMAS, with a median follow-up of 12.5 (IQR, 10.2–14.2) years, 158 participants developed dementia (Table S3 in supporting information) and 126 strokes. In the 3C (follow-up, 10 years; IQR, 0.5–12.0) and Rotterdam (follow-up 7.0 years; IQR, 6.1–9.4) studies, these numbers were 45/132, and 78/127, respectively. After adjusting for age, sex, and head size/brain volume, participants with dilated brain artery diameters consistently had the highest incidence rates of dementia and stroke across the three cohorts (Table 2).

TABLE 1 Baseline characteristics of participants.

Baseline characteristic s	United States NOMAS (*n* = 1280)	Europe	
		France Three-City Study (*n* = 1924)	The Netherlands Rotterdam Study (*n* = 5103)
Demographic characteristics			
Age in year, mean ± SD	70.7 ± 9.0	72.9 ± 4.1	64.7 ± 10.8
Women (%)	770 (60.7)	1157 (60.1)	2905 (56.9)
Race/ethnicity (%)			
Non-Hispanic White	219 (17.3)	–	5216 (100)
Non-Hispanic Black	219 (17.3)	–	0 (0)
Hispanic	831 (65.5)	–	0 (0)
Completed high school (%)	592 (45.9)	750 (38.9)	3558 (70.5)
Clinical characteristics			
Heighta in cm	163 (156–170)	162 (155–169)	169 (162–176)
Office hypertension, *n* (%)	996 (78.5)	1485 (77.2)	2998 (58.8)
Hypertension treatment, *n* (%)	778 (60.0)	834 (43%)	988 (19.4)
Systolic blood pressure, mean ± SD	136.0 ± 17.5	147.3 ± 22.3	140.1 ± 21.6
Diastolic blood pressure, mean ± SD	78.0 ± 9.7	84.0 ± 12.4	82.8 ± 11.1
Diabetes mellitus, *n* (%)	323 (25.4)	167 (8.8)	530 (10.4)
Hypercholesterolemia, *n* (%)	978 (81.0)	1089 (56.6)	3293 (64.5)
Smoking			
Current, *n* (%)	148 (11.7)	110 (5.7)	833 (16.7)
Past smoking, *n* (%)	517 (40.4)	633 (32.9)	2086 (41.7)
Previous history of stroke, *n* (%)	0 (0)	78 (4.1)	77 (1.5)
Previous coronary artery disease, *n* (%)	312 (24.6)	162 (8.4)	201 (3.94)
Dementia before MRI scan, *n* (%)	27 (2.1)	109 (5.7)	0 (0)
APOE ε4 carrier, *n* (%)	303 (24.8)	NA	1339 (28.2)
MRI features			
MRI enrollment period	2003–2008	1999–2001	2005–2015
Magnet strength	1.5	1.5	1.5
Axial T2-weighted brain diameters, mm			
Right carotida	3.8 (3.3–4.2)	4.6 (4.2–5.0)	4.6 (4.1–5.1)
Left carotida	3.7 (3.2–3.7)	4.5 (4.1–4.9)	4.6 (4.2–5.1)
Basilar[a]	2.0 (1.5–2.4)	2.7 (2.3–3.1)	2.9 (2.5–3.4)
Follow-up time, years[a]	12.5 (10.2–14.2)	10.0 (0.5–12.0)	7.0 (6.1–9.4)

Abbreviations: *APOE*, apolipoprotein E; cm, centimeters; IQR, interquartile range; MRI, magnetic resonance imaging; NA, not available; NOMAS, the Northern Manhattan Study; SD, standard deviation.
[a]Reported as median with interquartile range.

3.3 | Risk of dementia

In adjusted Cox proportional models (Table S4 in supporting information and Figure 2), participants with dilated brain arterial diameters had an increased risk of dementia in the 3C (HR, 4.50; 95% CI, 1.39–14.35; $P = 0.01$) and Rotterdam (HR, 2.14; 95% CI, 1.30–3.62; $P = 0.004$) studies. However, in NOMAS the risk was attenuated and not statistically significant (HR, 1.15; 95% CI, 0.79–1.68). A meta-analysis of the three cohorts confirmed an increased risk of dementia associated with dilated brain arterial diameters (HR, 1.74; 1.13–2.68; $I^2 = 44\%$; Figure 2) but not for small brain arterial diameters (HR, 1.27; 95% CI, 0.69–2.33; $I^2 = 44\%$).

Segregating the carotid arteries from the basilar artery measurements revealed that the direction of the association between dilated carotid diameters with dementia was consistent in the three cohorts (HR range 1.23 to 1.95; the overall meta-analyzed HR was 1.48, 95% CI, 1.12–1.92, $I^2 = 0\%$; Figure 2). There was a trend for higher risk of dementia among those with dilated basilar artery diameter (HR, 1.53;

TABLE 2 Age, sex, and head size–adjusted incidence rates by brain arterial diameter categories per 1000 person–year.

	United States		France		The Netherlands	
T2-weighted brain artery diameters	E/AR	NOMAS ($n = 1290$)	E/AR	Three-City Study ($n = 1924$)	E/AR	Rotterdam[a] ($n = 5103$)
Dementia						
5–95th	145/1129	19.9 (17.4–22.7)	35/1627	1.33 (0.7–2.22)	109/4593	4.25 (3.50–5.25)
<5th	6/62	23.7 (14.0–40.2)	4/93	4.7 (1.4–15.2)	3/255	1.30 (1.24–35.4)
>95th	7/61	26.5 (16.9–41.7)	6/93	5.2 (1.8–15.9)	20/255	9.70 (4.90–16.2)
Stroke						
5–95th	112/1143	9.2 (4.1–20.6)	70/1732	4.8 (2.6–4.7)	104/4593	4.00 (3.24–5.00)
<5th	6/63	7.6 (0.6–9.3)	1/69	1.6 (0.2–11.7)	5/255	1.65 (0.50–3.70)
>95th	8/63	11.8 (5.7–24.3)	7/69	4.7 (1.7–13.3)	18/255	13.5 (5.71–24.8)

Abbreviations: CI, confidence interval; E/AR, number of end points/number of participants at risk; NOMAS, Northern Manhattan Study.
[a]In the Rotterdam Study, the age–sex adjustment was done by intracranial volume instead.

95% CI, 0.97–2.42; $I^2 = 42\%$, Figure 2). None of the estimates for small brain arterial diameters were associated with dementia in each cohort or in meta-analyses.

3.4 | Risk of stroke

In adjusted Cox proportional models (Table S4), participants with dilated brain arterial diameters also had an increased risk of stroke in NOMAS (HR, 1.50; 95% CI, 1.05–2.17) and in the Rotterdam (HR, 2.03; 95% CI, 1.19–3.45) studies, but not in the 3C Study (HR, 0.86; 95% CI, 0.26–2.86). A meta-analysis of the three cohorts revealed an increased risk of stroke associated with dilated brain arterial diameters (HR, 1.59; 95% CI, 1.04–2.42; $I^2 = 44\%$) but not with small brain arterial diameters (HR, 1.21; 95% CI, 0.67–2.20; $I^2 = 44\%$; Figure 3).

Segregating the carotid arteries from the basilar artery diameters revealed that the direction of the association between dilated basilar diameters with stroke was consistent in the three cohorts (HR range 1.03–2.63; meta-analyzed HR, 2.11; 95% CI, 1.45–3.08; $I^2 = 53\%$; Figure 3).

3.5 | Exploratory analysis

We conducted three sets of exploratory analyses. First, considering total mortality as a competing risk for stroke or dementia did not change the consistency of the findings, particularly for the results pertaining to dilated basilar artery diameters (Table S5 in supporting information). Second, defining large brain arterial diameters in NOMAS using a similar cutoff as in the 3C Study showed a significantly higher risk of dementia with large brain artery diameters (HR 2.26, 95% CI, 1.01–5.09) and specifically with large carotid diameters (HR 3.02, 95% CI, 1.34–6.82) for carotid arteries (Table S6 in supporting information). Third, subgroup analysis based on modifiable cardiovascular risk factors is illustrated in Figure 4. The effect of diameters over the risk of dementia were more consistent in smokers and those without hypertension in the three cohorts.

4 | DISCUSSION

In this study including 8310 adults from three prospective population-based studies with a median follow-up over 7 years, we investigated the association of dementia and stroke with brain artery diameters measured on T2-weighted MRI axial scans in each cohort separately. We found that individuals with dilated brain arteries are at higher risk of developing dementia and stroke, across three distinct populations. The HRs obtained from the meta-analysis of dilated brain arteries associated with dementia risk ranged from 1.48 to 1.74 and for stroke risk ranged from 1.59 to 2.11.

Our findings underline the potential value of conventional T2-weighted brain MRI-based diameters assessment in studying the risk of dementia and stroke. The pathophysiological mechanisms underlying the association of small or dilated brain arteries potentially differ. As opposed to small brain arteries often caused by arteriosclerosis that reduces brain perfusion pressure,[22] dilated brain artery diameters may be exerting their pathological effects on the brain via increased blood flow states. This form of abnormal brain artery diameter is thought to reflect generalized brain dolichoectasia, which is described as a distinct non-arteriosclerotic form of poor vascular aging.[4]

Physiologically, brain outward remodeling is related to increased blood flow states. For example, during pregnancy, brain parenchyma arterioles undergo an increase in luminal diameter due to hemodynamics changes such as high blood volume.[23] In the presence of changes in systemic blood flow, the brain autoregulates its blood flow, which operates at a certain range of perfusion pressure.[24] If autoregulation fails, acutely or chronically, cerebral blood flow hemodynamics can eventually reach these arterioles and capillaries resulting in blood–brain barrier dysfunction.[24] Such blood-barrier dysfunction leads to extravasation of neurotoxic proteins associated with inflammation,

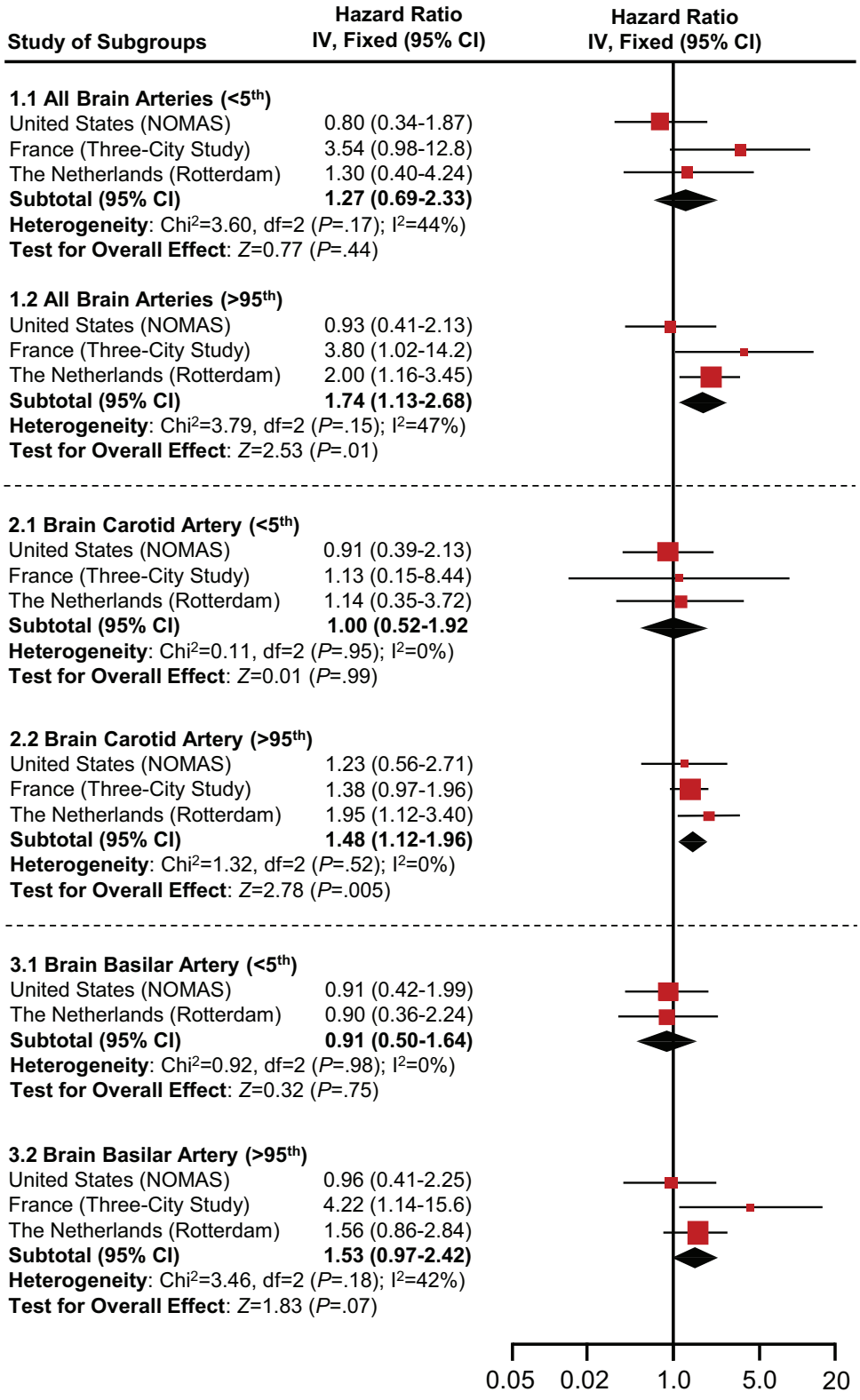

FIGURE 2 Meta-analyses of small and dilated brain arterial diameters with risk of dementia. Hazard ratios were derived from Cox proportional models adjusted by age, sex, race/ethnicity (if available), education, office systolic and diastolic blood pressure, use of antihypertensive medication, diabetes mellitus, hypercholesterolemia, smoking, prior cardiovascular diseases, brain volume, and *APOE* ε4. *APOE*, apolipoprotein; CI, confidence interval; IV, inverse variance; NOMAS, Northern Manhattan Study.

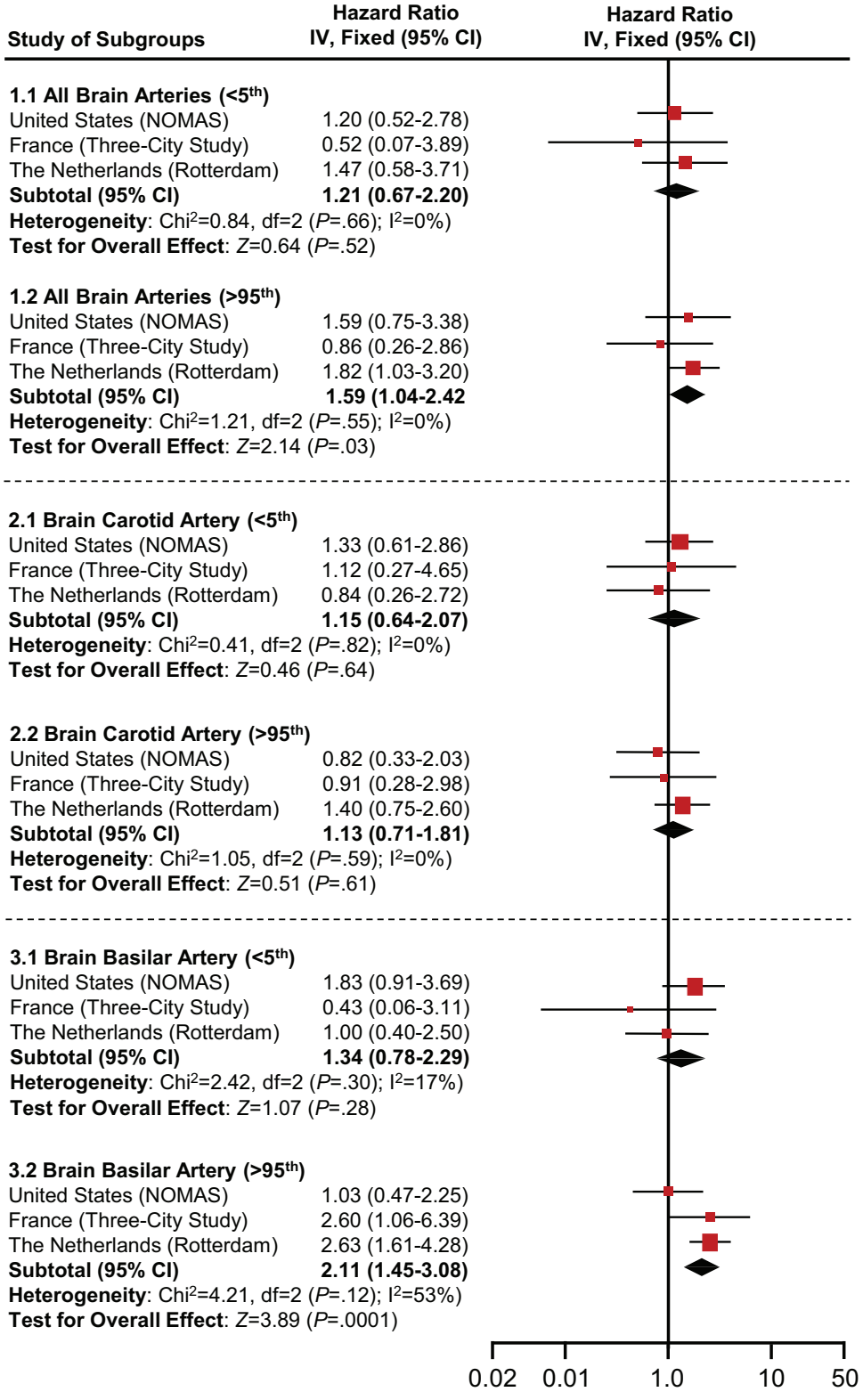

FIGURE 3 Meta-analyses of small and dilated brain arterial diameters with risk of stroke. Hazard ratios were derived from Cox proportional models adjusted by age, sex, race/ethnicity (if available), office systolic and diastolic blood pressure, use of antihypertensive medication, diabetes mellitus, hypercholesterolemia, smoking, prior cardiovascular diseases, and brain volume. CI, confidence interval; IV, inverse variance; NOMAS, Northern Manhattan Study.

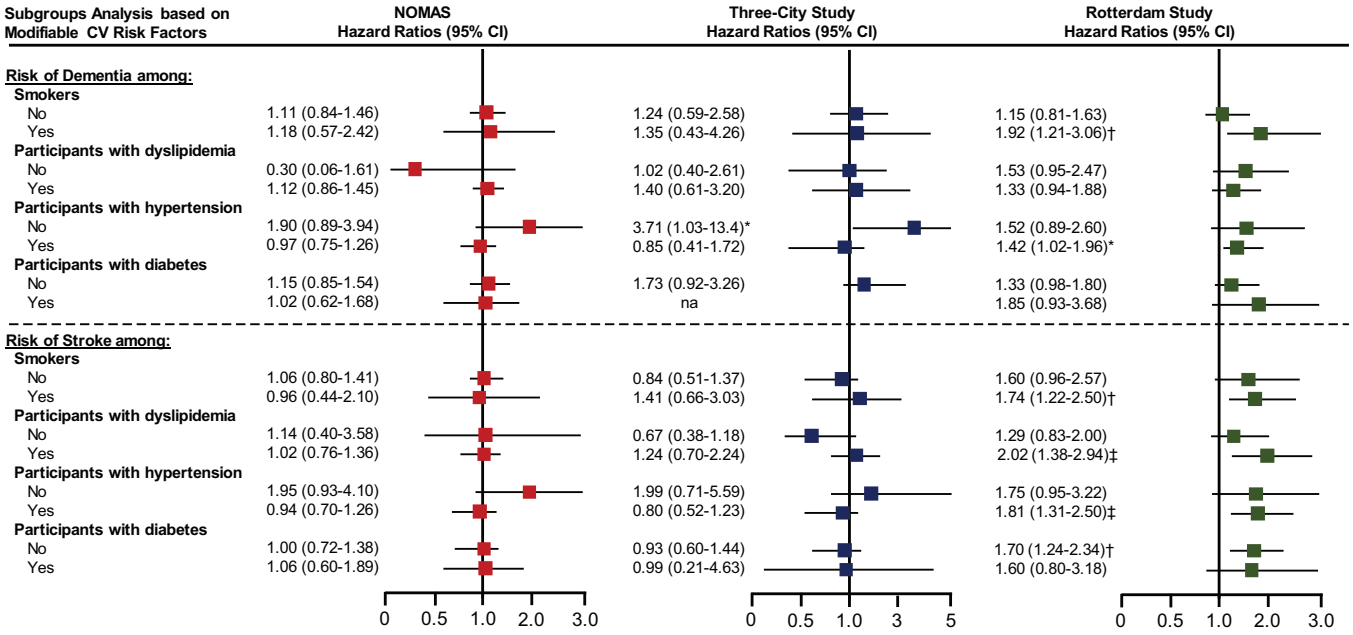

FIGURE 4 Association of dementia and stroke with brain arterial diameters according to categories of modifiable CV risk factors. Estimates were calculated for the Northern Manhattan Study (NOMAS, red squares), Three-City Study (blue squares), and the Rotterdam Study (green squares). Hazard ratios, given with 95% confidence interval, describe the relative risk of dementia incident associated with each unit increase in rank-normalized brain artery luminal diameters. Except when analyzing the corresponding vascular risk factors which were excluded from the models, hazard ratios accounted for total mortality as competing risk and by age, sex, race/ethnicity (if available), office systolic and diastolic blood pressure, use of antihypertensive medication, diabetes mellitus, hypercholesterolemia, smoking, prior cardiovascular diseases, and brain volume. For dementia, models were additionally adjusted by education achievement and *APOE* ε4. $^{*}P \leq 0.05$; $^{\dagger}P \leq 0.01$; $^{\ddagger}P \leq 0.001$. *APOE*, apolipoprotein; CI, confidence interval; CV, cardiovascular; NOMAS, Northern Manhattan Study.

oxidative stress, synaptic alterations, and disruption of amyloid beta clearance, which correlates to Alzheimer's disease (AD) pathology.[2] At the same time, synaptic alterations might exert a deleterious effect back into the neurovascular unit,[25] possibly potentiating further neurovascular degeneration. Another aspect to consider as a consequence of high blood flow is that dilated arterioles are less responsive to autoregulation.[23] Therefore, reduced contractility alongside arteriolar outward remodeling would decrease vascular resistance and raise the transmission of hydrostatic pressure to downstream microcirculation.

The outward remodeling documented in dolichoectasia might coexist with systemic arterial disease that includes the aorta, that is, arteriosclerosis of stiff type (i.e., nonspecific hardening or stiffening of arteries). The consequences of aortic stiffening on the brain circulation includes excessive penetration of pulsatile energy into the microvasculature of target organs that operate at low vascular resistance such as the brain.[26] The presence of dilated brain arteries might attenuate the low impedance to flow, which alongside increased pulsatility waves—due to aortic stiffness—may render the brain more susceptible to pulse-wave velocities.[5] Arterial stiffness might interplay with brain dilated vessels to exacerbate the mechanical brain tissue damage caused by high pulsatility waves.

The average of the three brain artery diameters as a proxy of the overall status of brain dolichoectasia was shown to associate with the risk of dementia and stroke. Understanding the impact of such risk association further benefits if the brain carotids and basilar arteries are separately studied. Dilated vessels reflecting dolichoectasia in the posterior circulation often present with dolichoectatic vessels in the anterior circulation.[4] This likely results in both circulatory circuits synergistically affecting the brain tissue due to increased blood flow albeit via different pathways. For instance, AD is the most common presentation of dementia and is characterized by hippocampal atrophy.[27] Because the vascular supply of the hippocampus largely comes from the posterior cerebral circulation and dolichoectasia affects more posterior arteries,[28] the presence of a dilated basilar artery potentially increases the risk of dementia via abnormal blood flow to the hippocampal microcirculation. In the case of stroke risk, increased and turbulent blood flow predisposes the formation of thrombi distal to the dilated anterior or posterior circulation, causing occlusion of the perforating artery. Although the anterior circulation provides ≈ 80% of the cerebral circulation while the posterior circulation provides ≈ 20%,[29] artery disease seems to trigger different mechanisms leading to dementia and stroke based on location. They are not mutually exclusive and can synergistically damage the brain.

The average brain artery diameters varied among cohorts, with participants in the NOMAS having smaller diameters compared to the European cohorts. These findings could be expected as NOMAS participants were shorter than Europeans, and height is one of the main determinants of brain diameters.[23] Testing a higher cutoff for defining "large brain arteries" in NOMAS, similar to the cutoff used in the European cohort, enhanced the effect size of the association between

brain arterial diameters and dementia in NOMAS. This suggests an absolute size threshold at which the brain parenchyma could be at risk. Further studies using various cutoffs for dolichoectasia in other populations may help us understand whether the risk of adverse neurological events is relative to the distribution of the sample or if a fixed cutoff across populations might better identify those at risk.

4.1 | Strengths and limitations

The strengths of our study included the use of three distinct multiethnic population-based cohorts, complementary to low rates of loss to follow-up and the rigorous standardized protocols that all cohorts underwent to adjudicate neurological end points. Nevertheless, our study should be interpreted within the context of its limitations. For example, using magnetic resonance angiography would decrease error compared to axial T2-weighted MRI measurements and would allow a better description of other phenotypes such as arterial curvature, length, and circle of Willis connectivity. Axial T2-based measurements, given their inherent error, might increase the risk of type II error and decrease the power to detect associations in smaller samples. Also, although the methods are simple and reproducible, the remaining errors introduced by various readers could also undermine power. Automated methods and possible 3D reconstructions of black voids in the desired anatomical segment could overcome this limitation.

5 | CONCLUSIONS

Contrary to the clinical intuition that small arterial diameters are pathological, we present evidence that people with dilated brain arteries are at a higher risk of dementia and stroke. Considering the numerous clinical and population-based studies with available axial T2-weighted MRI sequences, we expect our study would promote the investigation of brain diameters in relation to cerebrovascular outcomes and perhaps open a novel line of research into the mechanism by which dilated brain arteries can influence the risk of dementia and stroke. Using an error-prone but ubiquitous MRI sequence might offer an opportunity to investigate aspects of vascular aging, especially dilatation of blood vessels, which has been poorly investigated.

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CONFLICT OF INTEREST STATEMENT

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and none was reported. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All human subjects provided informed consent within the corresponding population-based study; however, informed consent did not include data sharing or transfer among third parties and data was analyzed in each corresponding center.

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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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