Cognitive impairment and intracranial atherosclerotic stenosis in general population

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Abstract

Objective

To investigate the association between asymptomatic intracranial atherosclerosis and cognitive impairment in the Atherosclerosis Risk in Communities (ARIC) cohort.

Methods

ARIC participants underwent high-resolution 3T magnetic resonance angiography and a neuropsychology battery and neurologic examination adjudicated by an expert panel to detect mild cognitive impairment (MCI) and dementia. We adjusted for demographic and vascular risk factors in weighted logistic regression analysis, accounting for stratified sampling design and attrition, to determine the association of intracranial atherosclerotic stenosis (ICAS) with cognitive impairment.

Results

In 1,701 participants (mean age 76 ± 5.3 , 41% men, 71% whites, 29% blacks) with adequate imaging quality and no history of stroke, MCI was identified in 578 (34%) and dementia in 79 (4.6%). In white participants, after adjustment for demographic and vascular risk factors, ICAS $\geq 50\%$ (vs no ICAS) was strongly associated with dementia (odds ratio [OR] 4.1, 95% confidence interval [CI] 1.7–10.0) and with any cognitive impairment (OR 1.7, 95% CI 1.1–2.8). In contrast, no association was found between ICAS $\geq 50\%$ and MCI or dementia in blacks, although the sample size was limited and estimates were imprecise.

Conclusion

Our results suggest that asymptomatic ICAS is independently associated with cognitive impairment and dementia in whites.

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Glossary

AD = Alzheimer disease; **ARIC** = Atherosclerosis Risk in Communities; **CES-D** = Center for Epidemiologic Studies Depression Scale; **CI** = confidence interval; **ICAS** = intracranial atherosclerotic stenosis; **MCI** = mild cognitive impairment; **MRA** = magnetic resonance angiography; **OR** = odds ratio; **WASID** = Warfarin-Aspirin Symptomatic Intracranial Disease; **WMH** = white matter hyperintensity.

The relation between cognitive impairment and intracranial atherosclerosis is increasingly recognized.^{1–4} There is growing evidence that intracranial atherosclerosis is associated with clinical and pathologic manifestations of Alzheimer disease (AD).^{5–12} Experimental^{13–18} and clinical studies^{13,19–21} support the hypothesis that cerebral ischemia contributes to AD pathology. Intracranial atherosclerotic stenosis (ICAS) may also be associated with cognitive impairment and AD by causing cerebral hypoperfusion.^{5–7,22} However, these studies were limited to small clinical case-control series^{5,6} or autopsy studies without clinical data.⁷

To study the association of ICAS with cognitive impairment, we performed a cross-sectional study using cognitive screening and high-resolution magnetic resonance angiography (MRA) in participants of the Atherosclerosis Risk in Communities (ARIC) study cohort.

Methods

Study population

The ARIC study cohort recruited 15,792 participants 45 to 64 years of age from 1987 to 1989 from 4 randomly selected US communities: Forsyth County, North Carolina; Jackson, MS; suburban Minneapolis, MN; and Washington County, Maryland. Follow-up examinations occurred in 1990 to 1992, 1993 to 1995, and 1996 to 1998. A fifth examination was conducted from 2011 to 2013. Among the 10,036 participants alive at the time of the fifth visit, 6,538 (65%) were evaluated. Among those who had no contraindications, MRA was offered to those who had received an ARIC brain MRI scan in 2004 to 2006 (offered to 573, completed in 433), those with low current cognitive test scores and large declines on the longitudinally administered tests (offered to 1,047, completed in 664),²³ and an age-stratified random sample of the remaining individuals (offered to 1,202, completed in 861). The goal was to acquire MRA scans in ≈2,000 participants.

We excluded all participants who had history of clinical strokes (n = 60) and those with a lack of cognitive status information (n = 4).

Standard protocol approvals, registrations, and patient consents

Institutional Review boards approved the study at each site, and participants provided written informed consent.

MRA protocol and image analysis

A total of 1,958 participants completed a standard MRA protocol. Details of the MRI protocol, image analysis, quality control, and reliability have been reported.²⁴ All MRI scans were performed on 3.0T Siemens scanners. High-resolution vascular sequences included a 3-dimensional time-of-flight MRA acquired in a transverse plane through the circle of Willis, centered to include the distal vertebral artery segments inferiorly and the middle cerebral artery branches superiorly. Repeat MRI scans were performed in 102 participants with a target interval of 13 weeks to establish interscan reliability. MRIs were analyzed by certified readers at the MRI reading center without knowledge of the participant characteristics. Studies with poor image quality or poor protocol adherence (n = 193) were excluded from this analysis. MRA images for the remaining participants had adequate or excellent quality for ICAS identification in the vessels of interest and were included in the current analysis.

Vessel segments analyzed included the supraclinoid and cavernous segments of the internal carotid artery, middle cerebral artery (M1–M4 segments), anterior cerebral artery (A1–A3 segments), intracranial segments of the vertebral artery, basilar artery, and posterior cerebral artery (P1–P3 segments). For each territory, the ordinal degree of narrowing was recorded for the most stenotic plaque measured on time-of-flight MRA images with criteria established in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial.²⁵ The κ statistics for agreement were 0.68 (intrareader), 0.63 (interreader), and 0.60 (interscan) for ordinal ICAS²⁴ and were similar between races. Because our objective was to study the association of ICAS with cognitive impairment, vessel segments noted to have plaque but without any measurable stenosis were not included. We identified the most stenotic segment of each vessel territory analyzed and used the severity of the most stenotic lesion in each participant to determine the association of ICAS with cognitive impairment. We made an effort to accurately classify stenosis in clinically significant and commonly used ordinal categories (no detectable stenosis, <50%, 51%–70%, 71%–99%, and occlusion).²⁶ For this analysis, we grouped ≥50% stenosis into 1 category to achieve meaningful statistical power.

Demographic and clinical risk factors

Demographic covariates included age (continuous), sex, and race (white or black). Because most of the black population was from a single study center (Jackson, MS), race was excluded when the model was adjusted for study center. Education status was classified as <12, 12, and >12 grades. Clinical

risk factors were assessed at the time of visit 5 examination and included history of cigarette smoking (current, past, or never), use of antihypertensive or cholesterol-lowering medications, body mass index (kilograms per meter squared), prevalent myocardial infarction, systolic blood pressure, plasma low-density lipoprotein cholesterol, plasma high-density lipoprotein cholesterol, and plasma triglycerides. We defined hypertension as blood pressure $\geq 140/90$ mm Hg or use of antihypertensive medications and diabetes mellitus as fasting glucose ≥ 126 mg/dL, nonfasting glucose ≥ 200 mg/dL, use of hypoglycemic medications, or self-reported physician diagnosis of diabetes mellitus. Distribution of ICAS across demographic and clinical variables has been previously reported.²⁶

Depressive symptoms were measured at visit 5 with the 11-item Center for Epidemiologic Studies Depression Scale (CES-D). The total score can range from 0 to 22. Only 3 participants had a total score ≥ 16 (cutoff for clinical depression). We used a median of 2 as the cutoff, i.e., ≤ 2 vs ≥ 3 . A sports index was calculated on the basis of the intensity (light, moderate, or heavy) and duration of leisure time activity as

a measure of physical activity.²⁷ The data from these 2 codons (130 and 176) were combined to generate APOE genotypes.²⁸

For volumetric analysis of white matter hyperintensity (WMH), leukoaraiosis voxels were automatically separated out from the CSF and normal brain on axial fluid-attenuated inversion recovery images.²⁹ Infarcts were manually identified and excluded to calculate the WMH volume. Because all patients with clinical strokes were excluded from the analysis, any infarct noted on MRI was considered a silent infarct.

Cognitive impairment

A detailed description of the cognitive assessments performed at ARIC visit 5 and the criteria used to define mild cognitive impairment (MCI) and dementia have been published.²³ Briefly, all study participants completed extensive cognitive testing, and an additional subset, including those with evidence of some cognitive impairment on the basis of Mini-Mental State Examination score and decline in 5 cognitive domains, underwent a neurologic examination and completed additional questionnaires, including the Clinical Dementia

Figure Attrition and use of sampling weights to adjust for selection bias

ARIC = Atherosclerosis Risk in Communities.

Rating interview, the Functional Activities Questionnaire (completed by an informant), the Neuropsychiatric Inventory, and the Hachinski ischemic score (completed by study staff). Using this information, a committee of neurologists and neuropsychologists reviewed the results of cognitive testing and clinical data and provided a syndromic and etiologic diagnosis based on established criteria.^{30,31} Syndromic categories included no cognitive impairment, MCI, and dementia. Etiologic categories included pure AD, all AD (AD with or without other etiologies), pure cerebrovascular disease–related dementia, and all cerebrovascular dementia (cerebrovascular dementia with or without other etiologies). In addition, standardized domain scores were calculated for the memory, language, and executive function domains. A global *z* score was created by averaging these 3 domain-specific *z* scores. These scores were then scaled so that 1 unit equaled 1 SD of that score.³²

Statistical analysis

Weights based on the inverse probability of being sampled for the MRI examination from visit 5 were applied to adjust for the stratified sampling design (figure). Because the presence of both ICAS and cognitive impairment is likely to cause attrition by reducing survival and participation among survivors, we calculated stabilized inverse survival probability weights for attrition based on demographic and vascular risk factors at visit 1 for survival up to visit 5, and we stabilized inverse participation probability weights for attrition based on demographic variables at visit 1 for participation in visit 5. The product of these 2 stabilized sampling weights and the stratified sampling design weights was used to minimize the selection bias for the analysis. These weights were used for all statistical analyses. We used logistic regression analysis with robust standard errors³³ to study the association of ICAS

($\geq 50\%$ stenosis vs no detectable stenosis) in any of the vessel segments with outcome variable classified as no cognitive impairment (reference category), any cognitive impairment (MCI or dementia), MCI only, and dementia only. For etiologic categories, no cognitive impairment was used as the reference category. Additional sensitivity analysis was performed for domain scores (continuous) as outcome with linear regression. The analysis was adjusted with confounding variables in the following models: model 1: age, sex, race, and education; model 2: model 1 plus education, body mass index, diabetes mellitus, systolic blood pressure, use of antihypertension medicine, triglycerides (milligrams per deciliter), low-density lipoprotein (milligrams per deciliter), high-density lipoprotein (milligrams per deciliter), total cholesterol, cholesterol medication, cigarette smoking, and alcohol consumption; and model 3: model 2 plus myocardial infarction.

Additional confounding variables—depressive symptoms, sports index, *APOE* polymorphisms, silent infarcts, and WMH volume—were tested by adding these variables to model 2. Because most of the black population was from a single study center (Jackson, MS), race was excluded when the model was adjusted for study center.

Results

The mean $\pm$ SD age of the 1,701 participants with adequate neuroimaging studies was 76 ± 5 years; 700 (41%) were men; 1,208 (71%) were white; 490 (29%) were black; and 3 were categorized as other races. MCI, dementia, and no cognitive impairment were diagnosed in 578 (34%), 79 (4.6%), and 1,044 (61.4%) participants, respectively.

Table 1 Unweighted prevalence of ICAS according to cognitive status: ARIC cohort

	No cognitive impairment, %	Any cognitive impairment, %	MCI, %	Dementia, %
All participants (n = 1,701)				
No ICAS	734 (70.3)	441 (67.1)	391 (67.6)	50 (63.3)
ICAS < 50%	218 (20.9)	139 (21.2)	123 (21.3)	16 (20.2)
ICAS $\geq 50\%$	92 (8.8)	77 (11.7)	64 (11.1)	13 (16.5)
Whites (n = 1,208)				
No ICAS	524 (74.5)	332 (65.7)	301 (66.4)	31 (59.6)
ICAS < 50%	127 (18.1)	114 (22.6)	103 (22.7)	11 (21.2)
ICAS $\geq 50\%$	52 (7.4)	59 (11.7)	49 (10.8)	10 (19.2)
Blacks (n = 490)				
No ICAS	209 (61.5)	108 (72)	89 (71.8)	19 (73.1)
ICAS < 50%	91 (26.8)	24 (16)	20 (16.1)	4 (15.4)
ICAS $\geq 50\%$	40 (11.8)	18 (12)	15 (12.1)	3 (11.5)

Abbreviations: ARIC = Atherosclerosis Risk in Communities; ICAS = intracranial atherosclerotic stenosis; MCI = mild cognitive impairment.

Table 1 cross-tabulates the 3 categories of cognitive status with severity of ICAS. ICAS $\geq 50\%$ was more prevalent in participants with dementia and MCI than in those with no cognitive impairment. In whites, with increasing severity of cognitive impairment (dementia, MCI, and no cognitive impairment), there was a trend toward a higher prevalence of ICAS ≥ 50 . No such trend was identified in black participants.

Results of the multivariable-adjusted analysis to study the association of ICAS with cognitive impairment are shown in table 2. Among white participants, ICAS $\geq 50\%$ was associated with dementia after adjustment for demographic and clinical variables (model 2). After inclusion of history of myocardial infarction in the model (model 3), there was a higher prevalence of ICAS $\geq 50\%$ in those with MCI, with a stronger

association in those with dementia. Among blacks, ICAS $\geq 50\%$ was not significantly associated with cognitive impairment. Additional multivariate models using study center instead of race, history of hypertension instead of use of antihypertensive medications, and use of statins instead of use of any cholesterol-lowering medications did not change the results.

The significant association of ICAS $\geq 50\%$ (vs no ICAS) with dementia (vs no cognitive impairment) noted in whites in model 2 remained unchanged after adjusted for *APOE* genotype (odds ratio [OR] 3.3, 95% confidence interval [CI] 1.3–8.5), continuous CES-D (OR 3.3, 95% CI 1.3–7.9), dichotomized CES-D (OR 3.2, 95% CI 1.3–7.7), sports index (OR 2.9, 95% CI 1.2–7.4), WMH volume (OR 3.02, 95% CI

Table 2 Association between ICAS and cognitive impairment in unadjusted and adjusted logistic regression analyses weighted for sampling design and inverse probability weights for attrition: ARIC cohort

	Model	OR (95% CI)		
		Any cognitive impairment vs no cognitive impairment	MCI vs no cognitive impairment	Dementia vs no cognitive impairment
All participants (n = 1,701)				
ICAS <50% vs no ICAS	1	0.92 (0.7–1.2)	0.94 (0.7–1.3)	0.7 (0.3–1.6)
	2	0.8 (0.6–1.1)	0.8 (0.6–1.2)	0.6 (0.2–1.5)
	3	0.8 (0.6–1.2)	0.9 (0.6–1.2)	0.6 (0.2–1.6)
ICAS ≥50% vs no ICAS	1	1.4 (0.95–2.1)	1.4 (0.9–2.1)	1.8 (0.8–3.8)
	2	1.2 (0.8–1.8)	1.1 (0.7–1.8)	1.4 (0.6–3.4)
	3	1.2 (0.8–1.9)	1.2 (0.8–1.9)	1.5 (0.6–3.8)
Whites (n = 1208)				
ICAS <50% vs no ICAS	1	1.2 (0.8–1.7)	1.2 (0.8–1.7)	1.05 (0.4–2.6)
	2	1.03 (0.7–1.5)	1.07 (0.7–1.6)	0.7 (0.2–2.4)
	3	1.05 (0.7–1.5)	1.09 (0.7–1.6)	0.8 (0.2–2.5)
ICAS ≥50% vs no ICAS	1	1.9 (1.2–3) ^a	1.7 (1.07–2.8) ^a	3.3 (1.5–7.5) ^a
	2	1.6 (0.97–2.6)	1.5 (0.9–2.5)	3.2 (1.3–7.8) ^a
	3	1.7 (1.06–2.8) ^a	1.6 (0.94–2.6)	4.1 (1.6–10.2) ^a
Blacks (n = 490)				
ICAS <50% vs no ICAS	1	0.4 (0.2–0.8) ^a	0.4 (0.2–0.9) ^a	0.4 (0.1–1.7)
	2	0.5 (0.2–0.91) ^a	0.4 (0.2–0.9) ^a	0.4 (0.1–2.6)
	3	0.4 (0.2–0.9) ^a	0.4 (0.2–0.8) ^a	0.5 (0.1–2.9)
ICAS ≥50% vs no ICAS	1	0.7 (0.3–1.5)	0.7 (0.3–1.7)	0.4 (0.1–2.2)
	2	0.5 (0.2–1.2)	0.6 (0.2–1.3)	0.3 (0–3.2)
	3	0.6 (0.2–1.3)	0.6 (0.3–1.5)	0.3 (0–3.1)

Abbreviations: ARIC = Atherosclerosis Risk in Communities; CI = confidence interval; ICAS = intracranial atherosclerotic stenosis; MCI = mild cognitive impairment; OR = odds ratio.

Model 1: age, sex, race, and education. Model 2: age, sex, race, education, body mass index, diabetes mellitus, systolic blood pressure, use of antihypertension medicine, triglycerides, low-density lipoprotein, high-density lipoprotein, total cholesterol, cholesterol medication, cigarette smoking, and alcohol consumption. Model 3: model 2 plus myocardial infarction.

^a *p* Value < 0.05.

1.2–7.4), and silent infarcts (OR 3.0, 95% CI 1.2–7.1). The results of similar analysis of MCI vs no cognitive impairment (in all participants, whites, and blacks) and dementia vs no cognitive impairment (in all participants and blacks) remained statistically nonsignificant.

Analysis for an association of syndromic cognitive impairment with ICAS $\geq 50\%$ is included in tables e-1 and e-2 (links.lww.com/WNL/A301). In white participants, there was an association between ICAS $\geq 50\%$ and all AD after adjustment for demographic risk factors (model 1), but this association was attenuated and no longer statistically significant after the addition of vascular risk factors to the model. The association between cerebrovascular disease and ICAS $\geq 50\%$ was significant in all models for whites. There was no association between any syndromic dementia diagnosis and ICAS $\geq 50\%$ in blacks. Additional sensitivity analysis with cognitive domain scores as outcome and adjusted for model 2 covariates demonstrated a significant association of ICAS $\geq 50\%$ (vs no ICAS) with memory ($\beta = -0.25$, $p < 0.05$), executive function ($\beta = -0.13$, $p < 0.05$), and global domains ($\beta = -0.20$, $p < 0.05$), but not with language domain ($\beta = -0.08$, $p > 0.05$), in whites. Similar analysis demonstrated no significant association in blacks.

Discussion

We found that white participants with ICAS $\geq 50\%$, compared to those without ICAS, had 4-times higher odds of dementia, even after adjustment for demographic and vascular risk factors.

Multiple autopsy studies have identified a higher occurrence of intracranial atherosclerosis among patients with pathologic findings of AD.^{5,7–9} Because vascular anatomy is deformed in autopsy specimens, most of the autopsy studies used measures of atherosclerotic plaque burden instead of luminal narrowing. Even though these studies were adjusted only for age, sex and *APOE* and grading of intracranial atherosclerosis severity in cadaveric studies differs from measurements in our study, the associations between severity of intracranial atherosclerosis and AD noted in these studies support our findings.

ICAS is often used as a surrogate for intracranial atherosclerosis, but atherosclerotic plaque may exist without any luminal stenosis.³⁴ Quantification of ICAS severity allows us to study the relationship between hemodynamic compromise and cognitive impairment. Some clinical studies have suggested that hypoxia may play a role in the genesis of pathologic findings of AD, including β -amyloid,^{19,20} neuritic plaques,²¹ and cortical microinfarcts.¹³ ICAS can also cause atherothrombotic embolization, and spontaneous cerebral microemboli have been shown to be associated with both vascular dementia and AD.³⁵ Other studies have followed up patients with cognitive impairment and noted cognitive decline in

those with ICAS.^{10,11} Results of these studies suggest that the association between ICAS and cognitive impairment noted in our study is causative.

One interesting finding of our study is that adjustment for vascular risk factors led to minimal change in the strong association between ICAS and dementia. Finding an association between ICAS and dementia in an analysis unadjusted for vascular risk factors, as was used in autopsy studies, is expected because vascular risk factors are associated with both dementia^{1,2} and ICAS.³ Previous studies that adjusted for vascular risk factors are limited. A case-control study of 55 participants noted an association between ICAS detected by transcranial Doppler and AD.⁶ Another study used MRA in 278 participants and noted an association between cognitive impairment and ICAS that was independent of vascular risk factors.¹² Recently, in a larger case-control study of 424 participants, ICAS was strongly associated with dementia (OR 4.7) after adjustment for vascular risk factors.⁴ This association was attenuated by WMH volume, and those investigators considered WMH a mediator between ICAS and dementia. This is in contrast to our study in which the association between ICAS and dementia remained significant even after adjustment for WMH volume. We believe this difference is the result of a larger sample size in our study, especially considering that the association between WMH and ICAS is controversial.³⁶ Identification of an association between ICAS and dementia that is independent of vascular risk factors is an important finding in that it raises the possibility that ICAS is a possible direct pathway for vascular risk factors to cause dementia.

There was a strong association of ICAS with cognitive impairment in whites in our study, but we did not identify an association in blacks. Strokes in blacks are known to be more attributable to ICAS than other etiologies.³⁷ In addition, the incidence³⁸ and prevalence³⁹ of dementia are higher in elderly blacks compared to whites. It is possible that compared to whites more blacks with ICAS had strokes and dementia and thus were unable to participate in the study. It is also possible that some of this selection bias remained unaccounted for despite our use of selection weights. One small autopsy study of 39 black and 81 white patients with AD reported results contradictory to our finding.⁴⁰ On the basis of the identification of severe intracranial atherosclerosis in 2 black participants and 2 white participants, this study concluded a higher prevalence of severe intracranial atherosclerosis in blacks than whites with AD. There was no difference in mild and moderate atherosclerosis. Considering the study design difference of the use of living participants in our study, it is possible that both studies are actually complementary. Blacks with ICAS and dementia may have shorter survival, and thus, the incidence of this association is higher in autopsies and lower in cross-sectional studies. Our sample size of black participants was also small, and an association of a smaller magnitude than what is noted in whites would not be identifiable. We adjusted for major vascular risk factors; however, these differences

between races could be the result of other unexplored factors such as cultural differences or discrimination in the health care setting.

This was a cross-sectional study, so a causative association between ICAS and cognitive impairment cannot be established from this analysis. However, ICAS secondary to dementia will be an implausible explanation of this association. Although we attempted adjustment for all potential cross-sectional confounders, the cross-sectional nature of this study cannot rule out confounding risk factors earlier in life. In addition, because of a lack of information, we may have missed some other confounders (e.g., overall dietary quality). The study was also limited by the possibility of uncontrolled selection bias. Although the ARIC cohort originally was community based, if participants with ICAS and dementia had low survival and those who survived had low participation rates in visit 5, then the OR for this association will be artifactually lowered. We noted an increase in the association between ICAS and cognitive impairment in whites after adjusting for selection bias, suggesting that there was some selection bias affecting this association before this adjustment. We probably were unable to completely eliminate the selection bias despite our selection-weighted analysis. We did not identify a significant association between ICAS $\geq 50\%$ and cognitive impairment in blacks, probably because of a smaller sample size and a lack of power. It is also possible that measurements are less reliable in blacks, and this would have contributed to the lack of significant association.

We did not measure ICAS as a continuous variable and are unable to check whether the association between ICAS and cognitive impairment is linear. Another limitation of our analysis was the use of OR as a measure of association. Because of the high prevalence of MCI, the OR would overestimate relative risk. However, the prevalence of dementia was only 4.6%, so the OR would be a good estimator of the relative risk for dementia.

We found a strong association of ICAS with dementia in whites. This finding supports a potential role of ICAS in the development of dementia. Because the association was independent of demographic and vascular risk factors, the role of ICAS in identifying the population at risk of dementia needs to be further investigated in longitudinal studies.

Author contributions

M. Fareed K. Suri: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, study supervision, obtaining funding. Jincheng Zhou: study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis, study supervision. Ye Qiao: study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, contribution of vital reagents/tools/patients,

acquisition of data, study supervision. Haitao Chu: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis. Adnan I. Qureshi: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and will give final approval. Thomas Mosley: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Rebecca F. F. Gottesman: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval. Lisa Wruck: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval. A. Richey Sharrett: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, review approval of final manuscript. Alvaro Alonso: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, study supervision. Bruce A. Wasserman: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision, obtaining funding.

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Disclosure

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Cognitive impairment and intracranial atherosclerotic stenosis in general population

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Study question

Is asymptomatic intracranial atherosclerotic stenosis (ICAS) associated with cognitive impairment?

Summary answer

ICAS is associated with cognitive impairment and dementia in Whites but not in African-Americans.

What is known and what this paper adds

Some small case-control and autopsy studies have suggested that ICAS is associated with cognitive impairment. This cross-sectional study provides evidence from a relatively large cohort supporting the hypothesized association in Whites.

Participants and setting

The study analyzed 1,701 US participants from the Atherosclerosis Risk in Communities study that was conducted from 1987 to 2013. These participants had no histories of stroke and had undergone magnetic resonance angiography (MRA) that generated usable results. The subset included 1,208 (71%) Whites and 490 (29%) African-Americans.

Design, size, and duration

The study reviewed the participants' results from 3-T MRA, a neuropsychology battery, and a neurologic examination. The ICAS percentage was calculated from the MRA results. Logistic regression analyses with adjustments for various demographic and clinical data were used to calculate odds ratios (ORs) for the primary outcomes given certain ICAS percentage ranges.

Primary outcomes

The primary outcomes were mild cognitive impairment (MCI) and dementia, as measured with the neuropsychology battery and neurologic examination.

Group for ≥50% ICAS vs 0% ICAS comparison	Adjusted OR (95% CI) for MCI	Adjusted OR (95% CI) for dementia
Whites	1.6 (0.9–2.6)	4.1 (1.6–10.2)
African-Americans	0.6 (0.3–1.5)	0.3 (0–3.1)

Main results and the role of chance

MCI was detected in 578 (34%) participants, and dementia was detected in 79 (4.6%). After various adjustments, ICAS levels of ≥50% were associated with dementia ($p < 0.05$) and not associated with MCI ($p > 0.05$) in Whites and dementia and MCI ($p > 0.05$) in African-Americans.

Bias, confounding, and other reasons for caution

The sample size for African-Americans was smaller than that for Whites. The African-American participants also predominantly came from one of 4 study centers. Various racial disparities in health may have disproportionately prevented African-Americans from participating in the study. The study's cross-sectional nature precludes the establishment of causal links.

Generalizability to other populations

The study does not provide conclusions about associations in races other than Whites and African-Americans.

Study funding/potential competing interests

This study was supported by NIH grants. Dr. Wasserman reports an ownership interest in the MRI device used in this study. Go to Neurology.org/N for full disclosures.

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.