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Midlife Smaller and Larger Infarctions, White Matter Hyperintensities, and 20-Year Cognitive Decline

A Cohort Study

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Background: Smaller (<3-mm) infarctions are associated with stroke and stroke mortality, but relationships with cognitive decline are unknown.

Objective: To characterize the relationships of smaller, larger, and both smaller and larger infarctions in middle age with 20-year cognitive decline.

Design: Longitudinal cohort study.

Setting: Two ARIC (Atherosclerosis Risk in Communities) study sites with magnetic resonance imaging data (1993 to 1995) and up to 5 cognitive assessments over 20 years.

Participants: Stroke-free participants aged 50 years or older.

Measurements: Infarctions were categorized as none, smaller only, larger only (3 to 20 mm), or both smaller and larger. Global cognitive *Z* scores were derived from 3 cognitive tests administered up to 5 times. Mixed-effects models estimated adjusted associations between infarctions and cognitive decline. Results are the average difference in standardized cognitive decline associated with infarctions versus no infarctions.

Results: Among 1884 participants (mean age, 62 years; 60% women; 50% black), 1611 (86%) had no infarctions, 50 (3%) had smaller infarctions only, 185 (10%) had larger infarctions only, and 35 (2%) had both. Participants with both smaller and larger infarctions had steeper cognitive decline by more than half an SD (difference, −0.57 SD [95% CI, −0.89 to −0.26 SD]) compared with those who had no infarctions. Amounts of cognitive decline associated with only smaller infarctions and only larger infarctions were similar and were not statistically different from that associated with no infarctions.

Limitation: Few participants had only smaller infarctions or both smaller and larger infarctions, and the data lacked counts of smaller infarctions and volumes of white matter hyperintensities.

Conclusion: The substantial cognitive decline from middle age associated with having both smaller and larger infarctions, but not larger infarctions alone, suggests that the combination of smaller and larger infarctions may escalate risk for cognitive decline later in life in stroke-free persons.

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Cerebral small vessel disease (SVD), including subclinical infarctions and white matter hyperintensities (WMHs), is common even among asymptomatic persons and begins as early as middle age (1). The prevalence of infarctions 3 mm or larger among stroke-free adults has been reported as 15% in middle age (1) and 28% later in life (2). Cerebral SVD is associated with adverse outcomes, including poorer cognition, cognitive decline, poor mobility, and stroke (2–5), although some studies have not found associations with cognitive decline. For example, WMHs were associated with cognitive decline in cognitively normal older adults in the Rotterdam Scan Study (6) but not in the CHS (Cardiovascular Health Study) (7). They were not associated with progression to mild cognitive impairment in younger participants of the Framingham Offspring Study, although they showed a borderline association with incident, amnestic mild cognitive impairment among those older than 60 years (8). However, CHS, the Austrian Stroke Prevention Study, and the Rotterdam Scan Study have demonstrated associations between WMH progression and cognitive decline (4, 9–11) and dementia risk (4, 8, 12, 13) in older age. Some of the discrepancies in findings could be explained by shorter follow-up times among mostly older populations. Another gap in knowledge is whether less obvious abnormalities in brain structure in middle age—when interventions might be more effective—compromise cognitive function later in life. The importance of assessments earlier in life is supported by findings that cognitive decline is more strongly associated with vascular risk factors measured in middle age than in late life (14).

Prior studies have shown that less severe WMHs may also adversely affect cognition (15) and that even a single infarction is associated with poor cognition (4, 16). Identifying biomarkers of microvascular processes related to subclinical cognitive outcomes was named a priority of the Alzheimer's Disease-Related Dementias Summit 2016 sponsored by the National Institute of Neurological Disorders and Stroke (17). Brain infarctions smaller than 3 mm (smaller infarctions) are candidate microvascular biomarkers that may adversely affect cognition. However, they have received considerably less attention than larger infarctions and WMHs, in part because of concerns about inaccurate classification of smaller infarctions (that is, infarctions vs. benign lesions) and lack of data linking them to clinical outcomes. Because smaller infarctions are typically not reported, our knowledge of larger infarctions may be misinformed if concomitant smaller infarctions influence their effect. However, we found no reports of studies comparing cognitive decline's relationship with smaller infarctions versus that with either

larger infarctions in the absence of smaller infarctions or with the combination of smaller and larger infarctions.

The CHS reported associations of smaller infarctions with subjective memory loss, but not with cognition, in older adults (2). However, the effects of these smaller infarctions on cognition might be seen only over time, as the aging brain becomes increasingly vulnerable to insults. Using a shared imaging protocol with CHS, the ARIC (Atherosclerosis Risk in Communities) study showed an association between these small midlife infarctions and incident stroke and stroke mortality; this relationship was amplified by coexisting large infarctions (18). The objective of this study was to examine associations of smaller-only infarctions, larger-only infarctions, coexisting smaller and larger infarctions, and WMH in middle age with cognitive decline over 20 years.

METHODS

Population

Details of the ARIC study sampling and design have been previously described (19, 20). In brief, the ARIC study recruited 15 792 men and women aged 45 to 64 years from the following 4 locations at the baseline examination (1987 to 1989): Forsyth County, North Carolina; Jackson, Mississippi (black persons only); selected suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Participants had cognitive assessments at visits 2 (1990 to 1992), 4 (1996 to 1998), and 5 (2011 to 2013). At visit 3 (1993 to 1995), the index examination for the current analysis, stroke-free participants aged 50 years or older from 2 sites (North Carolina and Mississippi) were invited to undergo brain magnetic resonance imaging (MRI) and a cognitive assessment. Of the 2892 participants who were screened for eligibility and met inclusion criteria, 1934 had the brain MRI (**Appendix Figure**, available at Annals.org). Participants with brain MRI at visit 3 were also invited to 2 ancillary studies (2003 to 2006 and 2005 to 2006) that repeated the cognitive assessments. We excluded 4 participants who reported their race as nonwhite or nonblack and 46 with prevalent stroke, leaving 1884 for this analysis. The study was approved by institutional review boards, and all participants provided informed consent.

Cerebral MRI

The MRI scanning protocol and image analysis were identical to those used in CHS (21, 22). In brief, 1.5-Tesla MRI scanners (GE or Picker) were used to obtain 5-mm, contiguous, axial images of the whole brain that were T1-, T2-, and proton density–weighted. Infarctions were defined by shape, location, absence of mass effect, and hyperintensity to gray matter on proton density–weighted and T2-weighted images to distinguish infarctions from perivascular spaces. In addition, infarctions were isodense or hypodense on T1-weighted images. Hyperintensity on spin-density images was required to distinguish small deep infarctions from dilated perivascular spaces, which were not characterized. An electronic cursor was used to record the maximum right-to-left and anterior-to-posterior dimensions of the lesion. The superior-to-inferior dimension was reported as the number of 5-mm axial sections on which the lesion appeared. Two trained readers blinded to participant information independently interpreted MRI scans. Discrepancies were resolved by consensus adjudication among 3 or more readers.

Infarctions smaller than 3 mm on right-to-left or anterior-to-posterior measurements were recorded as "less than 3 mm" (1) and categorized as absent or present. Infarctions that were at least 3 mm and up to 20 mm were classified as "larger infarctions" and dichotomized as absent or present. Infarctions were categorized as none, small only, large only, or both small and large. Staff quantified WMHs in periventricular and subcortical regions by visual comparison with 8 standard scans using a 0-to-9 scale that successively increased from no white matter changes (grade 0) to extensive, confluent changes (grade 9) and dichotomized as "present" for grades 3 and greater (22).

Cognitive Function

Each participant's cognitive function was assessed up to 5 times using the same protocol across examinations. The delayed word recall test (DWRT), the digit symbol substitution test (DSST), and the word fluency test, all derived from standard test batteries in clinical neuropsychology, were administered in a quiet room by trained examiners in a fixed order. The Mini-Mental State Examination (MMSE), a global screening measure of cognition, was administered only at the fifth examination.

The DWRT measures verbal learning and recent memory. Participants were given a list of 10 common nouns and asked to compose 2 sentences with each word to standardize elaborative processing of the words. They were asked to recall these words after a 5-minute delay (23) during which the DSST was administrated as a nonverbal distractor. The DWRT score is the number of nouns recalled (0 to 10).

The DSST assesses executive function and psychomotor speed (24, 25). Participants had 90 seconds to translate numbers to symbols using a key. The score (0 to 93) is the number of correct translations.

The word fluency test measures verbal fluency and executive function. Participants were given 60 seconds to generate words beginning with a specified letter, avoiding proper nouns; the score is the number of acceptable words generated.

The primary outcome was 20-year decline in global cognition, measured with a *Z* score. Standardizing scores for individual tests reduces measurement error and ceiling and floor effects (26, 27). At each assessment, *Z* scores for each cognitive test (DWRT, DSST, and word fluency test) were calculated, standardized to visit 2 results (the first cognitive assessment), then averaged to create a global *Z* score for each visit, as previously done in ARIC (14) and other studies (26, 28). The results describe the average 20-year change in SD units associated with the infarction category. For example, an estimate of −0.25 for the group with only larger infarctions would translate to

an adjusted average difference in standardized 20-year cognitive decline that is 0.25 SD steeper than that of the group with no infarctions.

Covariates

Participants self-reported sex, race, and education, and apolipoprotein E was assayed at the first ARIC visit. Other covariates were assessed at the index examination (visit 3) when the MRI was done. Smoking history and alcohol use were self-reported (never, former, or current). Education level was categorized as less than 12 years of education (less than high school); high school, an equivalent degree, or vocational training (high school graduate); or any college education (greater than high school). The *APOE* ε4 allele was genotyped using the TaqMan assay (Applied Biosystems). Diabetes mellitus was defined as a fasting glucose level of at least 6.99 mmol/L (126 mg/dL), a nonfasting glucose level greater than 11.10 mmol/L (200 mg/dL), a self-reported physician diagnosis, or receipt of hypoglycemic medication within the previous 2 weeks. Hypertension was defined as systolic blood pressure greater than 140 mm Hg, diastolic blood pressure greater than 90 mm Hg, or use of antihypertensive medication in the previous 2 weeks. Clinical strokes requiring hospitalization were identified through annual telephone calls, standardized interviews, and surveillance methods that used hospital record reviews and medical record abstraction; stroke cases were adjudicated by expert stroke reviewers (29).

Statistical Analysis

Mixed-effects models with random slopes and intercepts were used to examine associations between MRI measurements and cognitive function and decline. Infarctions were specified as none (reference), small only, large only, or both. The time scale was years since the index visit, and models were adjusted for the nontime-varying covariates of index age, sex, race, education, and *APOE* ε4 status. Additional adjustors were examined in sensitivity analyses. Linear splines with 2 knots were used to account for nonlinearities in cognitive change trajectories. Robust Huber–White estimates of SE were used throughout. Because participants who develop more cognitive decline and dementia are less likely to return over 20 years for testing, we did sensitivity analyses that accounted for this differential dropout. Appendixes 1 and 2 (available at Annals.org) give additional modeling details for primary and sensitivity analyses. Stata, version 14.0 (StataCorp), was used for analyses. Statistical significance was defined as $P < 0.05$.

Role of the Funding Source

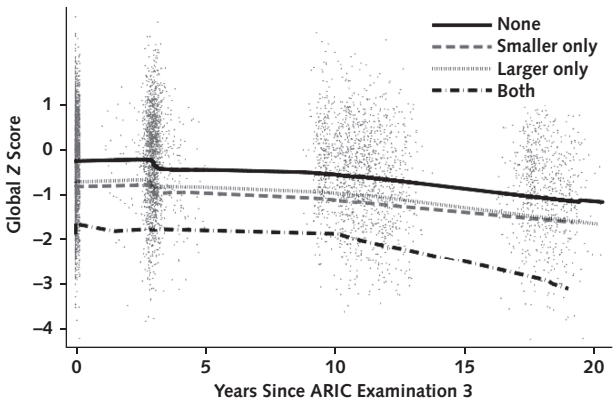
Funding sources were not involved in the design or conduct of the study; collection, management, or anal-

Table 1. Characteristics of Participants With MRI Scans at ARIC Visit 3, Overall and by Infarction Status (1993–1995)*

Characteristic	Total (*n* = 1881)	None (*n* = 1611)	Smaller Infarcts Only (*n* = 50)	Larger Infarcts Only (*n* = 185)	Both (*n* = 35)
Mean age (SD), *y*	62.4 (4.5)	62.1 (4.5)	63.5 (4.2)	64.11 (4.3)	64.3 (4.6)
Male sex, *n (%)*	748 (40)	642 (40)	20 (40)	70 (38)	16 (46)
Black race, *n (%)*	934 (50)	761 (47)	33 (66)	111 (60)	29 (83)
Education, *n (%)*					
Less than high school	508 (27)	408 (25)	19 (38)	61 (33)	20 (61)
High school or equivalent	639 (34)	558 (35)	15 (30)	58 (31)	8 (24)
Any college	731 (39)	644 (40)	16 (32)	66 (36)	5 (15)
Smoking status, *n (%)*					
Current	341 (18)	277 (17)	7 (14)	44 (24)	13 (38)
Former	693 (37)	600 (37)	15 (30)	67 (37)	11 (32)
Never	835 (45)	725 (45)	28 (56)	72 (39)	10 (29)
Alcohol drinking status, *n (%)*					
Current	705 (38)	628 (39)	11 (22)	56 (31)	10 (29)
Former	442 (24)	354 (22)	16 (32)	58 (32)	14 (41)
Never	723 (39)	621 (39)	23 (46)	69 (38)	10 (29)
Diabetes, *n (%)*	326 (18)	264 (17)	12 (24)	39 (22)	11 (32)
Mean body mass index (SD), kg/m^2	28.0 (5.2)	28.0 (5.2)	28.1 (4.2)	28.1 (5.6)	28.2 (5.0)
Mean systolic blood pressure (SD), *mm Hg*	128.2 (20.7)	126.7 (19.6)	138.3 (17.4)	136.1 (26.3)	139.1 (20.8)
Mean diastolic blood pressure (SD), *mm Hg*	72.1 (11.1)	71.7 (10.8)	74.0 (11.9)	74.5 (13.0)	75.9 (12.8)
Hypertension, *n (%)*	899 (48)	722 (45)	34 (68)	114 (63)	29 (85)
Hypertension medication, *n (%)*	801 (43)	636 (40)	27 (54)	110 (59)	28 (80)
Mean total cholesterol level (SD)					
mmol/L	5.42 (0.99)	5.43 (0.98)	5.37 (0.96)	5.41 (1.04)	5.00 (0.93)
mg/dL	209.2 (38.2)	209.6 (38.0)	207.4 (36.9)	208.7 (40.3)	193.0 (36.1)
Cholesterol medication, *n (%)*	641 (34)	507 (32)	23 (46)	87 (48)	24 (71)
APOE ε4 allele, *n (%)*	609 (33)	505 (32)	16 (34)	72 (39)	16 (47)
Mean global *Z* score (SD)	−0.29 (1.04)	−0.21 (1.02)	−0.61 (0.98)	−0.66 (1.07)	−1.60 (0.98)
Mean delayed word recall *Z* score (SD)	−0.11 (1.08)	−0.06 (1.05)	−0.27 (1.09)	−0.35 (1.15)	−1.24 (1.44)
Mean digit symbol substitution *Z* score (SD)	−0.43 (1.05)	−0.37 (1.03)	−0.74 (1.01)	−0.78 (1.05)	−1.49 (0.73)
Mean word fluency *Z* score (SD)	−0.15 (1.04)	−0.10 (1.03)	−0.45 (0.98)	−0.45 (1.06)	−0.95 (0.80)
Mean white matter hyperintensity grade (SD)†	1.41 (1.13)	1.27 (0.96)	1.60 (1.14)	2.39 (1.65)	2.57 (1.52)

ARIC = Atherosclerosis Risk in Communities; MRI = magnetic resonance imaging.
* Percentages may not sum to 100 because of rounding.
† Range, 0 to 9 (where 0 indicates no white matter and 9 indicates extensive, confluent changes).

Figure 1. Twenty-year global cognitive change, by infarction category.



ARIC = Atherosclerosis Risk in Communities.

ysis of the data; interpretation of the results; preparation, review, or approval of the manuscript; or decision to submit for publication.

RESULTS

At the index examination, participants were in late middle age on average; 60% were women, and 50% were black. Participants with infarctions were more likely to be older, self-report race as black, have lower education, and have more vascular risk factors. We observed any infarction (smaller, larger, or both) in 270 participants (14%), most of whom had large infarctions only (n = 185 [10%]). Fifty participants (3%), most of whom were black (33 of 50), had smaller infarctions only. Thirty-five participants (2%) had both smaller and larger infarctions; most of these (29 of 35) and most of participants with only larger infarctions (111 of 185) were black (Table 1). Participants who completed at least visits 3, 4, and 5 were younger; were more educated; were less likely to have diabetes, hypertension, or *APOE* ε4 genotype; had higher baseline cognitive scores and lower WMH scores; and were more likely to have no infarctions than those who died or dropped out by visit 5 (Appendix Table 1, available at Annals.org).

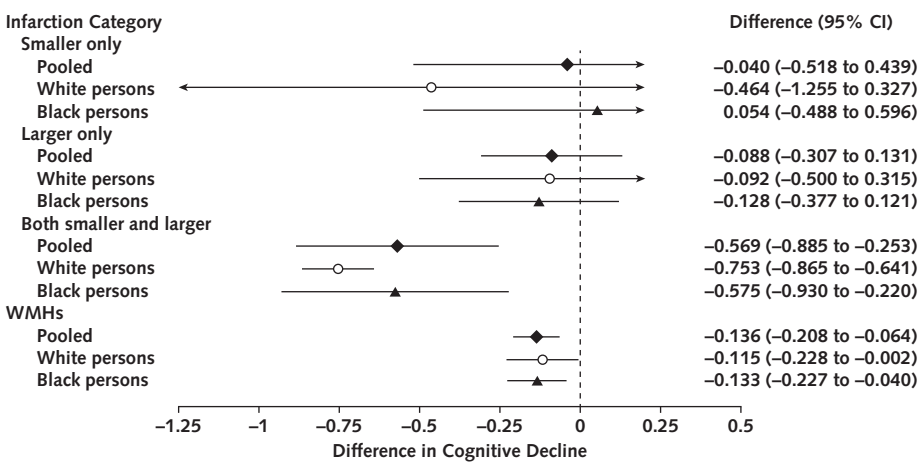
Infarctions and 20-Year Cognitive Decline

Figure 1 shows that participants with no infarctions had better cognition than those with only smaller, only larger, or both smaller and larger infarctions. Cognitive decline seemed to be similar between participants with only smaller infarctions and those with only larger infarctions. Participants with both smaller and larger infarctions had a steeper decline in standardized cognitive scores, by more than half an SD on average, than participants with no infarctions (difference, −0.57 SD [95% CI, −0.89 to −0.25 SD]). To put this in context, each additional year of age was associated with a −0.04-SD steeper cognitive decline (difference per 1 year of age, −0.042 SD [CI, −0.049 to −0.034 SD]). Thus, having both smaller and larger infarctions was akin to 13.6 years of aging. In contrast, the data did not support differences in 20-year cognitive decline in participants with only smaller infarctions (difference, 0.04 SD [CI, −0.52 to 0.44 SD]) or only larger infarctions (difference, −0.09 SD [CI, −0.31 to 0.13 SD]) versus no infarctions. We did not find strong support for differences in relationships by race, although small numbers of persons with both infarction sizes limited these analyses (Figure 2).

Infarctions and Cognitive Scores at the End of the Study (After 20 Years)

Compared with having no infarctions, having both smaller and larger infarctions was also associated with 20-year cognitive scores that were more than a full SD

Figure 2. Overall and race-stratified differences in 20-y cognitive decline, by midlife infarction category (*top*) and WMHs (*bottom*).



Reference groups are no infarctions (*top*) and no WMHs (*bottom*). WMH = white matter hyperintensity.

Table 2. Associations of Infarctions With Cognitive Decline and Final Cognitive Levels*

Infarction Category	20-Year Cognitive Decline			
	Absolute Decline (95% CI)	***P* Value**	**Relative Decline (95% CI)**	***P* Value**
None	−1.079 (−1.151 to −1.006)	<0.001	Reference	
Smaller only	−1.118 (−1.592 to −0.645)	<0.001	−0.040 (−0.518 to 0.439)	0.87
Larger only	−1.166 (−1.373 to −0.960)	<0.001	−0.088 (−0.307 to 0.131)	0.43
Both	−1.647 (−1.955 to −1.340)	<0.001	−0.569 (−0.885 to −0.253)	<0.001
	Cognition at End of Study (After 20 Years)			
	Absolute Level (95% CI)	***P* Value**	**Difference (95% CI)**	***P* Value**
None	−1.303 (−1.380 to −1.226)	<0.001	Reference	
Smaller only	−1.535 (−1.987 to −1.082)	<0.001	−0.232 (−0.691 to 0.227)	0.32
Larger only	−1.609 (−1.833 to −1.385)	<0.001	−0.306 (−0.543 to −0.069)	0.011
Both	−2.511 (−2.890 to −2.132)	<0.001	−1.208 (−1.595 to −0.821)	<0.001

* Models are adjusted for age, sex, race, education, and *APOE* ε4 genotype. Cognitive function was measured as an overall *Z* score (see Methods).

lower than the group with no infarctions (difference, −1.21 SD [CI, −1.60 to −0.82 SD]) (Table 2 and Figure 3). This effect was comparable to 30 years of aging; differences by race were not supported. Appendix Table 2 (available at Annals.org) shows infarction associations with baseline cognition, 20-year cognitive change, and cognition after 20 years.

WMH Relations to 20-Year Cognitive Decline and Cognitive Scores at the End of the Study

Compared with having little or no WMH, the presence of WMH was associated with a 0.14-SD steepening of 20-year decline in standardized cognitive scores (difference, −0.14 SD [CI, −0.21 to −0.06 SD]) (Figure 2). Race-stratified results were similar for black and white persons (Figure 2). The presence of WMH was associated with a 0.20-SD lower standardized cognitive score after 20 years (difference, −0.20 SD [CI, −0.28 to −0.12 SD]), with nondifferential results in black and white persons (Figure 3).

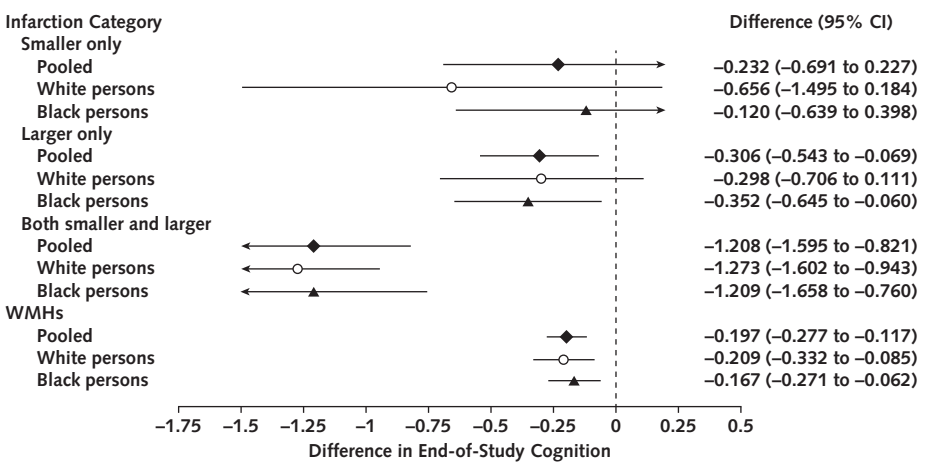
Sensitivity Analyses

In sensitivity analyses accounting for missing data and study dropout, having both smaller and larger infarctions was associated with steeper decline in standardized cognitive scores (difference, −0.63 SD [CI, −1.02 to −0.25 SD]) (Appendix Tables 3 and 4, available at Annals.org), similar to primary findings. Similar results were also found with adjustments for cardiovascular risk factors (Appendix Table 5, available at Annals.org) and restriction to lacunar infarctions (Appendix Table 6, available at Annals.org).

DISCUSSION

We report novel findings that although neither larger subclinical infarctions nor smaller infarctions in middle age were associated with 20-year cognitive decline when examined in isolation, the combination of larger and smaller infarctions was associated with cognitive decline and cognitive performance at the end of 20 years of follow-up. Specifically, the association of cognition at the end of the study with having both smaller and larger infarctions was 4 times stronger than that with having only larger infarctions and 6 times stronger than that with having only smaller infarctions. The association between having both infarction sizes

Figure 3. Overall and race-stratified differences in cognition at the end of 20 y, by midlife infarction category (*top*) and WMHs (*bottom*).



Reference groups are no infarctions (*top*) and no WMHs (*bottom*). WMH = white matter hyperintensity.

and cognitive decline was equivalent to 13 years of aging, compared with 2 years for only larger infarctions, suggesting that the combination of smaller and larger infarctions has a more detrimental effect than larger infarctions in isolation. The importance of this relationship is further exemplified by findings for MMSE scores, which were assessed at the end of the 20-year follow-up: Having both smaller and larger infarctions (vs. no infarctions) was associated with an MMSE score that was 2.7 points lower (difference, −2.66 points [CI, −5.09 to −0.23 points]), a clinically meaningful difference in MMSE scores (**Appendix Table 7**, available at Annals.org). Larger-only infarctions were not associated with MMSE score (difference, 0.01 points [CI, −0.96 to 0.98 points]), and smaller-only infarctions were associated with a 1.5 points lower MMSE score (difference, −1.47 points [CI, −2.94 to 0.009 points]). Prior studies of infarctions did not consider concomitant smaller infarctions and were likely influenced by the presence of coexisting smaller and larger infarctions. Ignoring smaller infarctions may overestimate the effects of isolated larger infarctions and underestimate those of larger infarctions that coexist with smaller infarctions; this may contribute to a lack of identification of patients at highest risk for cognitive decline.

We hypothesize that the combination of smaller and larger infarctions represents more pervasive disease processes that do not result from a dose–response process—that is, smaller arteries are not always affected before larger arteries. In this study, larger infarctions alone were more frequent than either smaller infarctions alone or a combination of smaller and larger infarctions. The mechanism underlying smaller and larger infarctions is presumed ischemia from potentially related but different processes leading to atherosclerotic and arteriolosclerotic vascular disease. Lipohyalinosis and endothelial dysfunction are favored etiologic mechanisms for smaller lesions (30), and microatheromatous disease is believed to contribute more to larger lesions (31); microinfarctions and disrupted white matter are related candidate pivotal processes (32–35) that could contribute to smaller and larger infarctions, as are other unidentified processes that damage cognitively relevant brain regions. Pathologic changes that have affected only smaller arteries or only larger arteries may represent stages in which a patient remains cognitively resilient despite underlying damage. An arterial system that is more extensively damaged may eventually surpass a threshold at which resilience is lost. In support of this hypothesis, thresholds of impaired cerebral vasomotor reactivity are predictive of short-term cognitive decline (36). Clinical thresholds of WMHs and infarctions need to be elucidated to better define at-risk populations.

This study extends existing research on markers of cerebral SVD and cognitive outcomes in several ways. Our findings suggest that smaller and larger subclinical infarctions could be markers of risk as early as middle age and before symptom onset—markers that are available with routine imaging. With no truly effective therapies to treat cognitive decline and dementia, prevention is increasingly recognized as an important means to maintain cognitive health. We also found that black persons, whose risk for dementia is 2 to 3 times that of white persons, had a higher prevalence of smaller or larger infarctions, which could contribute to racial disparities in dementia. This aligns with other studies reporting more severe cerebral SVD in older minority groups than in white persons (37). Because the midlife prevalence of infarctions was 3 times higher in black than white persons, the benefits of preventing infarctions could be substantial over time for black persons at the population level.

This research builds on studies linking structural brain changes with cognitive outcomes. Smaller infarctions in CHS were not associated with cognition cross-sectionally (2), and WMHs were not associated with cognitive decline (7); CHS may have been limited by short follow-up and an initial evaluation in late life, whereas ARIC provides data on cognitive decline over 20 years. Investigators in CHS observed associations between WMH progression and 5-year cognitive decline (9), further supporting the notion that a more severe disease process is required to see relationships in the short term. Our findings regarding WMHs are consistent with those of the Rotterdam Scan Study, which included participants aged 60 years or older—slightly older than the current ARIC subset and younger than in CHS—with an average follow-up of 5.2 years (6). In addition, WMHs have been associated with incident dementia in the Rotterdam Scan Study (13) and the Framingham Offspring Study (8) and with prevalent dementia in CHS (12) and other cohorts (8, 13), including the middle-aged, primarily white participants of the Framingham Offspring Study. They have been associated with mild cognitive impairment among Framingham Offspring participants aged 60 years or older (8) and with cognitive decline in selected populations, including persons with prevalent mild cognitive impairment (38), those with stroke (39), and older adults with minor neurologic problems (40); we now show similar findings in a cognitively normal, middle-aged, biracial population. Collectively, these studies support the importance of preserving brain health throughout adulthood for optimal cognitive outcomes in late life.

The current findings suggest that having both smaller and larger infarctions in middle age may be a sensitive indicator of risk for cognitive decline. Smaller infarctions have not been well studied, but a growing literature supports a nonbenign nature with a prevalence that increases from 3% in stroke-free, middle-aged ARIC participants to almost 8% in stroke-free, older CHS participants (2). We have previously shown that these smaller infarctions are associated with hypertension, older age, incident stroke, and stroke-related mortality (18); together with the current study, this prior research highlights the importance of elucidating subtle, subclinical changes in the aging brain that may have detrimental long-term effects.

Some limitations warrant discussion. Few participants had only smaller infarctions, and the analysis may have been underpowered to detect relationships between smaller infarctions and cognitive decline. Another limita-

tion is the lack of detailed measurements of infarction or WMH burden, such as continuous counts of smaller infarctions or quantitative measurements of WMHs. This study also lacked information on enlarged perivascular spaces, which are associated with cognition in some but not all studies (41, 42). However, the ARIC protocol was developed before guidelines for classifying vascular changes on imaging were available (43), and it specifically sought to distinguish infarctions from perivascular spaces. Lesions that met criteria for perivascular spaces were not classified as infarctions, although misclassification remains possible. Attrition over the extended follow-up could be a limitation because participants with abnormalities on MRI or poorer baseline cognition were less likely to return for follow-up visits. The expected bias from this would be to show no association; the sensitivity analyses supported this and suggested that the findings are reliable and probably conservative. Qualitative ratings of WMHs and use of a 1.5-Tesla MRI, which has limited pixel resolution and could mislabel infarctions, could be considered a limitation. More sensitive technology was not available at the time of the index examination. Misclassification would likely mislabel normal findings as infarctions and bias results to null findings. Current imaging with higher definition would be useful to confirm these results. In addition, most black persons in this study were from 1 field center and all white persons from another, which could limit generalizability. As with all observational studies, we cannot exclude residual confounding.

In summary, having only larger or only smaller infarctions was not associated with 20-year cognitive decline from middle to late life; in contrast, the combination in middle age of larger with smaller subclinical infarctions may represent more severe disease that amplifies the effects of infarctions of either size on cognitive decline and thus on cognitive function in late life. This possibility is especially important because smaller infarctions, whether isolated or in combination with larger infarctions, are typically ignored. Preventing subtle changes in the brain structure and vasculature earlier in life may reduce late-life cognitive impairment.

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Reproducible Research Statement: *Study protocol and data set:* Protocols and data for the ARIC and ARIC Brain MRI studies may be obtained by approved persons through written agreements with the ARIC Steering Committee and the research sponsor (NIH and NHLBI) (e-mail, tmosley@umc.edu). *Statistical code:* Available from Dr. Griswold (e-mail, mgriswold@umc.edu).

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Appendix 1: Technical Details of Statistical Models

Overarching Modeling Information

Outcomes, predictors, and adjustors: Our longitudinal data analyses examine relationships between cognitive function outcomes (GlobalZ: a composite cognitive "*Z* score" measure) over time (yrs: years since index cognitive examination and brain MRI [ARIC visit 3]) and the primary predictor of baseline infarction category (inf4cat; 4 levels: none, small only, large only, both small and large infarctions). Covariates used for adjustment (adj) included an indicator for male sex, baseline (visit 3) age in years, race (white or black), and educational attainment (educ; 3 levels: basic, intermediate, and advanced).

Nonlinear cognitive trajectories: To account for observed nonlinear cognitive change trajectories over time, we used linear splines $(\text{yrs} - \text{k})^+$ with knots at $k_1 = 3$ and $k_2 = 13$ years after ARIC visit 3. These knots correspond approximately to the ends of ARIC visit 4 and the ARIC Carotid MRI study, an ancillary study with cognitive assessments, and were informed by LOWESS smoothers and by minimizing Akaike information criterion over yearly calipers within the set $\{-2, -1, 0, 1, 2\}$ from the median years within visits. Main effects and interaction terms of infarction category with the linear spline terms were then used to estimate differences in the trajectories over time in the mean model specified as follows.

Mean model specification: Denoting participant (i) at time (j), all approaches used the following mean model specification for cognitive trajectories over time:

$$\begin{aligned}E(\text{GlobalZ}_{ij}) &= X\beta_{ij}\\ &= \beta_0 + \beta_1(\text{yrs}) + \beta_2(\text{yrs} - k_1)^+ + \beta_3(\text{yrs} - k_2)^+\\ &+ \beta_4\text{Small} + \beta_5\text{Small}\bullet(\text{yrs}) + \beta_6\text{Small}\bullet(\text{yrs} - k_1)^+\\ &+ \beta_7\text{Small}\bullet(\text{yrs} - k_2)^+\\ &+ \beta_8\text{Large} + \beta_9\text{Large}\bullet(\text{yrs}) + \beta_{10}\text{Large}\bullet(\text{yrs} - k_1)^+\\ &+ \beta_{11}\text{Large}\bullet(\text{yrs} - k_2)^+\\ &+ \beta_{12}\text{Both} + \beta_{13}\text{Both}\bullet(\text{yrs}) + \beta_{14}\text{Both}\bullet(\text{yrs} - k_1)^+\\ &+ \beta_{15}\text{Both}\bullet(\text{yrs} - k_2)^+\\ &+ \beta\bullet(\text{adj})\end{aligned}$$

where Small, Large, and Both are indicators for their respective infarction-burden categories (small only, large only, and both small and large infarctions) and $\beta\bullet(\text{adj})$ represents the vector of additional regression parameters and design matrix corresponding to the adjustment covariates specified earlier. Estimates of expected absolute and relative 20-year cognitive decline for each group are then constructed by appropriate linear combinations of the regression variables and linear spline terms.

Robust SEs: We used Huber–White robust SE estimates throughout our results, tables, and figures; however, we also examined model-based (nonrobust) estimates (not shown). We recommend using robust SE estimates whenever possible but recognize that this option is not available in all statistical packages and can occasionally cause convergence issues.

Generalized Linear Mixed Model (Missing at Random) Specification

Random intercepts, slopes, and their covariance were incorporated into our primary mixed model variance structure.

1. $\text{GlobalZ}_{ij}|b_i = X\beta_{ij} + b_{0i} + b_{1i}\bullet(\text{yrs}) + e_{ij}$
2. $b_{oi} \sim N(0, \tau_0^2)$; $b_{1i} \sim N(0, \tau_1^2)$; $\text{Cov}(b_{oi}, b_{1i}) = \tau_{01}$
3. $e_{ij}|b_i \sim N(0, \sigma^2)$

Robust SEs were used; additional variance structures with random intercepts only or random linear spline terms matching the fixed-effect linear spline terms were also fitted and gave similar results.

Appendix 2: Sensitivity Analysis to Missingness Using Shared Parameter Models

During follow-up, measurements on each participant may be lost because of dementia, death, or simple dropout (that is, right-censored). Appendix Table 3 summarizes the amounts of missingness and relationships with the primary predictor (infarction category) by missingness group.

Participants with any level of infarction had higher rates of dementia or death than those with no infarctions. Participants with both small and large infarctions had the highest risks; dementia incidence rates of 27 cases per 1000 person-years and death rates of 49 deaths per 1000 person-years led to hazard ratios for dementia and death of 2.9 (CI, 1.6 to 5.3; $P = 0.001$) and 2.4 (CI, 1.6 to 3.7; $P < 0.001$), respectively, compared with participants with no infarctions. Given these levels of likely informative missingness, we did sensitivity analyses to examine potential missingness effects on our primary generalized linear mixed model (GLMM) estimates (which operate under a missing at random [MAR] assumption).

Shared parameter models (SPMs) are a class of statistical "joint models" that simultaneously model repeated measurement outcomes (such as cognition over time) and survival or event outcomes (such as dementia or death). Joint models have many uses, and SPMs have been long studied in application to longitudinal missing data, where longitudinal outcomes are connected with survival or event outcomes responsible for missingness via a set of shared latent variables (for example, in the work of Vonesh and colleagues [44] and Gueorguieva and colleagues [45]).

Let $T_i = (T_i, K_i)$ be the times to dementia, death, or censoring on participant i, with K_i taking values {0 = censoring, 1 = dementia, 2 = death} and $T_{ki} = (T_i, K_i = k)$ indicating that the censoring time is due to the kth reason. Throughout, right-censoring is assumed to be independent of dementia and death, and longitudinal outcomes are assumed to be independent of the censoring events after conditioning on the shared random effects. Following Vonesh (44) and Gueorguieva (45), we used a joint SPM to extend our primary GLMM (specified in **Appendix 1**) and examine missingness effects by specifying additional related event submodels as follows.

Longitudinal GLMM submodel:

1. $\text{GlobalZ}_{ij}|b_i = X\beta_{ij} + b_{0i} + b_{1i}\bullet(\text{yrs}) + e_{ij}$
2. $b_{oi} \sim N(0, \tau_0^2)$; $b_{1i} \sim N(0, \tau_1^2)$; $\text{Cov}(b_{oi}, b_{1i}) = \tau_{01}$
3. $e_{ij}|b_i \sim N(0, \sigma^2)$

Dementia event submodel:

1. $\log\{H(T_{1i}|b_i)\} = \log\{H_0(T_{1i})\} + \alpha_{11}\text{Small} + \alpha_{12}\text{Large} + \alpha_{13}\text{Both} + \alpha_1\bullet(\text{adj}) + \rho_{10}b_{0i} + \rho_{11}b_{1i}$
2. $T_{1i}|b_i \sim \text{Weibull}$

Death event submodel:

1. $\log\{H(T_{2i}|b_i)\} = \log\{H_0(T_{2i})\} + \alpha_{21}\text{Small} + \alpha_{22}\text{Large} + \alpha_{23}\text{Both} + \alpha_2\bullet(\text{adj}) + \rho_{20}b_{0i} + \rho_{21}b_{1i}$
2. $T_{2i}|b_i \sim \text{Weibull}$

where Small, Large, and Both are again indicators for their respective infarction-burden categories (small infarctions only, large infarctions only, and both small and large infarctions) and $\alpha_1\bullet(\text{adj})$ and $\alpha_2\bullet(\text{adj})$ represent vectors of regression variables for each event submodel with the same design matrix corresponding to the adjustment covariates in the primary GLMM submodel specified previously. The random intercepts and slopes are incorporated as additional covariates in the hazard submodels, with loading factors (ρ) identifying informative censoring connections across the submodels. If, for example, participants with lower cognitive function at baseline develop dementia faster (and thus have longitudinal cognitive data that are more informatively missing because of dementia occurrence), then we would expect the loading factor in the dementia submodel (ρ_{10}) to be negative, because higher values of b_{0i} (that is, better baseline cognition) would lead to lower dementia hazards.

The joint SPM approach ties together the primary longitudinal model with potentially informative censoring events, and thus, comparing our primary GLMM (MAR) results to the joint SPM results provides an examination of potential missingness effects. As in our primary models, robust SEs were used throughout. Additional variance structures with random intercepts only or random linear spline terms matching the fixed-effect linear spline terms were also fitted and gave similar results.

Appendix Table 4 compares estimates of infarction category associations on 20-year cognitive decline from generalized estimating equation (missing completely at random), separate GLMM (MAR), and SPMs. In the ARIC data, inferences seemed to be robust toward the modeling approach; for example, having both infarction sizes was associated with more than a half SD greater cognitive decline than having no infarctions across all models and missingness assumptions (primary GLMM estimate, −0.569 SD [CI, −0.885 to −0.253 SD]; $P < 0.001$; generalized estimating equation estimate, −0.551 SD [CI, −0.907 to −0.195 SD]; $P = 0.002$; SPM estimate, −0.634 SD [CI, −1.017 to −0.250 SD]; $P < 0.001$).

Effects of missing data assumptions were apparent in estimated effect sizes, with GLMM (MAR) and generalized estimating equations (missing completely at random) producing estimates that were approximately 10% less than the corresponding SPM estimates. These effect size attenuations from nonoptimal missing data assumptions are expected given the missing data patterns discussed earlier, but the CI and inferential supports across the models are within clinically meaningful agreement for the ARIC data, suggesting that our conclusions are robust to the effects of missing data.

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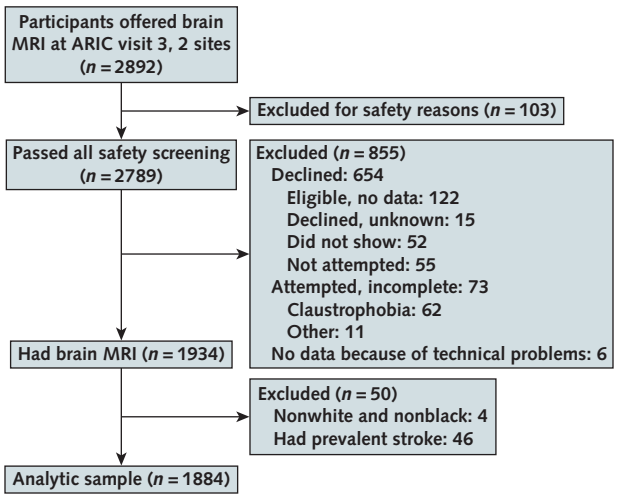
Appendix Figure. Study flow diagram.



ARIC = Atherosclerosis Risk in Communities; MRI = magnetic resonance imaging.

Appendix Table 1. Characteristics of Participants at Index Examination (Visit 3) Who Completed at Least Visits 3, 4, and 5 (Completers); Those Who Died Before Visit 5; and Those Who Dropped Out by Visit 5

Characteristic	Total (*n* = 1881)	Completers (*n* = 714)	Died (*n* = 707)	Dropped Out (*n* = 460)
Mean age (SD), *y*	62.4 (4.5)	60.9 (4.1)	63.98 (4.35)	62.2 (4.5)
Male sex, *n (%)*	748 (40)	255 (36)	339 (48)	154 (33)
Black race, *n (%)*	934 (50)	347 (49)	367 (52)	220 (48)
Education, *n (%)*				
Less than high school	508 (27)	113 (16)	261 (37)	134 (29)
High school or equivalent	639 (34)	256 (36)	226 (32)	157 (34)
Any college	731 (39)	344 (48)	220 (31)	167 (36)
Smoking status, *n (%)*				
Current	341 (18)	98 (14)	190 (27)	53 (12)
Former	693 (37)	270 (38)	257 (37)	166 (36)
Never	835 (45)	344 (48)	254 (36)	237 (52)
Alcohol drinking status, *n (%)*				
Current	705 (38)	316 (44)	234 (33)	155 (34)
Former	442 (24)	145 (20)	203 (29)	94 (21)
Never	723 (39)	251 (35)	265 (38)	207 (45)
Diabetes, *n (%)*	326 (18)	80 (11)	179 (26)	67 (15)
Mean body mass index (SD), kg/m^2	27.99 (5.21)	27.60 (4.76)	28.24 (5.58)	28.19 (5.29)
Mean systolic blood pressure (SD), *mm Hg*	128.16 (20.65)	123.88 (17.95)	133.10 (23.00)	127.25 (19.12)
Mean diastolic blood pressure (SD), *mm Hg*	72.14 (11.11)	72.12 (10.23)	72.30 (11.99)	71.92 (11.03)
Hypertension, *n (%)*	899 (48)	285 (40)	405 (58)	209 (46)
Hypertension medication, *n (%)*	801 (43)	245 (34)	370 (53)	186 (41)
Mean total cholesterol level (SD)				
mmol/L	5.42 (0.99)	5.43 (0.95)	5.35 (1.03)	5.50 (0.98)
mg/dL	209.16 (38.24)	209.74 (36.86)	206.45 (39.74)	212.42 (37.80)
Cholesterol medication, *n (%)*	641 (34)	200 (28)	299 (43)	142 (31)
APOE ε4 allele, *n (%)*	609 (33)	191 (28)	261 (38)	157 (35)
Mean global *Z* score (SD)	−0.29 (1.04)	0.01 (0.94)	−0.59 (1.06)	−0.32 (1.04)
Mean delayed word recall *Z* score (SD)	−0.11 (1.08)	0.07 (0.99)	−0.33 (1.17)	−0.05 (1.02)
Mean digit symbol substitution *Z* score (SD)	−0.43 (1.05)	−0.15 (0.99)	−0.72 (1.02)	−0.46 (1.05)
Mean word fluency *Z* score (SD)	−0.15 (1.04)	0.09 (1.03)	−0.35 (1.01)	−0.26 (1.01)
Mean white matter hyperintensity grade (SD)*	1.41 (1.13)	1.18 (0.88)	1.72 (1.32)	1.32 (1.04)
White matter hyperintensity grade >3, *n (%)*	223 (12)	45 (6)	136 (19)	42 (9)
Infarctions, *n (%)*				
None	1611 (86)	654 (92)	558 (79)	399 (87)
Smaller only	50 (3)	16 (2)	24 (3)	10 (2)
Larger only	185 (10)	39 (5)	105 (15)	41 (9)
Both	35 (2)	5 (1)	20 (3)	10 (2)

* Range, 0 to 9 (where 0 indicates no white matter and 9 indicates extensive, confluent changes).

Appendix Table 2. Associations of Infarction Category With Baseline Cognitive Function, 20-Year Cognitive Decline, and End-of-Study Cognitive Function*

Infarction Category	Baseline Cognition (ARIC Visit 3)			
	Absolute Level (95% CI)†	***P* Value**	**Difference (95% CI)**	***P* Value**
None	−0.224 (−0.261 to −0.188)	<0.001	Reference	
Smaller only	−0.417 (−0.629 to −0.204)	<0.001	−0.192 (−0.408 to 0.023)	0.080
Larger only	−0.443 (−0.569 to −0.316)	<0.001	−0.218 (−0.350 to −0.087)	0.001
Both	−0.864 (−1.156 to −0.572)	<0.001	−0.640 (−0.934 to −0.346)	<0.001
	20-Year Cognitive Decline			
	Absolute Decline (95% CI)†	***P* Value**	**Relative Decline (95% CI)**	***P* Value**
None	−1.079 (−1.151 to −1.006)	<0.001	Reference	
Smaller only	−1.118 (−1.592 to −0.645)	<0.001	−0.040 (−0.518 to 0.439)	0.87
Larger only	−1.166 (−1.373 to −0.960)	<0.001	−0.088 (−0.307 to 0.131)	0.43
Both	−1.647 (−1.955 to −1.340)	<0.001	−0.569 (−0.885 to −0.253)	<0.001
	Cognition at End of Study (After 20 Years)			
	Absolute Level (95% CI)†	***P* Value**	**Difference (95% CI)**	***P* Value**
None	−1.303 (−1.380 to −1.226)	<0.001	Reference	
Smaller only	−1.535 (−1.987 to −1.082)	<0.001	−0.232 (−0.691 to 0.227)	0.32
Larger only	−1.609 (−1.833 to −1.385)	<0.001	−0.306 (−0.543 to −0.069)	0.011
Both	−2.511 (−2.890 to −2.132)	<0.001	−1.208 (−1.595 to −0.821)	<0.001

ARIC = Atherosclerosis Risk in Communities.
* Models are adjusted for age, sex, race, education, and *APOE* ε4 genotype. Estimates and *P* values are from primary generalized linear mixed models. Cognitive function was measured as an overall *Z* score (see Methods).
† Absolute estimates use marginal standardization over adjustment variables.

Appendix Table 3. Dementia and Death Rates, by Infarction Category

Outcome and Infarction Category	Participants, *n (%)*	Person-Years, *n*	Incidence per 1000 Person-Years	Hazard Ratio (95% CI)	*P* Value
Dementia					
No infarctions	189 (12)	25 541	8.85	Reference	
Smaller only	10 (20)	715	16.78	2.1 (1.2–3.8)	0.011
Larger only	26 (14)	2369	12.24	1.5 (1.0–2.2)	0.051
Both	10 (29)	402	27.37	2.9 (1.6–5.3)	0.001
Death					
No infarctions	453 (28)	26 163	22.02	Reference	
Smaller only	18 (36)	742	32.35	1.5 (1.0–2.2)	0.055
Larger only	87 (47)	2439	43.87	2.2 (1.7–2.7)	<0.001
Both	16 (46)	425	49.41	2.4 (1.6–3.7)	<0.001

Appendix Table 4. Comparisons of Absolute and Relative 20-Year Cognitive Decline Estimates Across Infarction Burden Status From GEE (MCAR), GLMM (MAR), and SPM (MNAR) Models*

Infarction Category	MCAR: GEE				MAR: GLMM				MNAR: SPM			
	Estimated Absolute Decline (95% CI)†	*P* Value	Estimated Relative Decline (95% CI)‡	*P* Value	Estimated Absolute Decline (95% CI)†	*P* Value	Estimated Relative Decline (95% CI)‡	*P* Value	Estimated Absolute Decline (95% CI)†	*P* Value	Estimated Relative Decline (95% CI)‡	*P* Value
None (*n* = 1611)	−1.035 (−1.107 to −0.964)	<0.001	Reference		−1.079 (−1.151 to −1.006)	<0.001	Reference		−1.143 (−1.228 to −1.058)	<0.001	Reference	
Smaller only (*n* = 50)	−1.053 (−1.496 to −0.611)	<0.001	−0.018 (−0.466 to 0.430)	0.94	−1.118 (−1.592 to −0.645)	<0.001	−0.040 (−0.518 to 0.439)	0.87	−1.153 (−1.585 to −0.722)	<0.001	−0.01 (−0.442 to 0.422)	0.96
Larger only (*n* = 185)	−1.062 (−1.250 to −0.875)	<0.001	−0.027 (−0.228 to 0.174)	0.79	−1.166 (−1.373 to −0.960)	<0.001	−0.088 (−0.307 to 0.131)	0.43	−1.246 (−1.463 to −1.029)	<0.001	−0.103 (−0.32 to 0.114)	0.35
Both (*n* = 35)	−1.587 (−1.935 to −1.238)	<0.001	−0.551 (−0.907 to −0.195)	0.002	−1.647 (−1.955 to −1.340)	<0.001	−0.569 (−0.885 to −0.253)	<0.001	−1.777 (−2.167 to −1.386)	<0.001	−0.634 (−1.017 to −0.25)	<0.001

GEE = generalized estimating equation; GLMM = generalized linear mixed model; MAR = missing at random; MCAR = missing completely at random; MNAR = missing not at random; SPM = shared parameter model.

* Models are adjusted for age, sex, race, education, and *APOE* ε4 genotype. Longitudinal outcomes were standardized general cognition (*Z* scores).

† Estimated absolute 20-y cognitive decline marginalized over adjustors.

‡ Estimated, adjusted, relative 20-y cognitive decline compared with the reference group (no infarctions).

Appendix Table 5. Associations of Infarction Category With Baseline Cognitive Function, 20-Year Cognitive Decline, and End-of-Study Cognitive Function, Adjusting for Additional Cardiovascular Risk Factors*

Infarction Category	Baseline Cognition (ARIC Visit 3)			
	Absolute Level (95% CI)	***P* Value**	**Difference (95% CI)**	***P* Value**
None	−0.220 (−0.256 to −0.183)	<0.001	Reference	
Smaller only	−0.377 (−0.584 to −0.170)	<0.001	−0.157 (−0.368 to 0.054)	0.144
Larger only	−0.408 (−0.536 to −0.280)	<0.001	−0.188 (−0.321 to −0.055)	0.006
Both	−0.783 (−1.049 to −0.518)	<0.001	−0.564 (−0.831 to −0.296)	<0.001
	20-Year Cognitive Decline			
	Absolute Decline (95% CI)	***P* Value**	**Relative Decline (95% CI)**	***P* Value**
None	−1.078 (−1.152 to −1.004)	<0.001	Reference	
Smaller only	−1.121 (−1.595 to −0.647)	<0.001	−0.043 (−0.523 to 0.437)	0.86
Larger only	−1.217 (−1.442 to −0.991)	<0.001	−0.138 (−0.375 to 0.099)	0.25
Both	−1.652 (−1.973 to −1.332)	<0.001	−0.574 (−0.903 to −0.245)	0.001
	Cognition at End of Study (After 20 Years)			
	Absolute Level (95% CI)	***P* Value**	**Difference (95% CI)**	***P* Value**
None	−1.298 (−1.377 to −1.219)	<0.001	Reference	
Smaller only	−1.498 (−1.949 to −1.046)	<0.001	−0.200 (−0.659 to 0.258)	0.39
Larger only	−1.624 (−1.868 to −1.381)	<0.001	−0.327 (−0.582 to −0.071)	0.012
Both	−2.435 (−2.826 to −2.045)	<0.001	−1.138 (−1.537 to −0.739)	<0.001

ARIC = Atherosclerosis Risk in Communities.
* Models are adjusted for age, sex, race, education, *APOE* ε4 genotype, smoking status, diabetes, hypertension, body mass index, and prevalent coronary heart disease. Cognitive function was measured as an overall *Z* score (see Methods).

Appendix Table 6. Associations of Infarction Category, Limited to Lacunar Infarctions, With Baseline Cognitive Function, 20-Year Cognitive Decline, and End-of-Study Cognitive Function*

Infarction Category	Baseline Cognition (ARIC Visit 3)			
	Absolute Level (95% CI)	***P* Value**	**Difference (95% CI)**	***P* Value**
None	−0.221 (−0.258 to −0.185)	<0.001	Reference	
Smaller only	−0.415 (−0.628 to −0.203)	<0.001	−0.194 (−0.410 to 0.022)	0.078
Larger only	−0.413 (−0.547 to −0.278)	<0.001	−0.191 (−0.331 to −0.052)	0.007
Both	−0.960 (−1.253 to −0.667)	<0.001	−0.739 (−1.034 to −0.444)	<0.001
	20-Year Cognitive Decline			
	Absolute Decline (95% CI)	***P* Value**	**Relative Decline (95% CI)**	***P* Value**
None	−1.078 (−1.150 to −1.005)	<0.001	Reference	
Smaller only	−1.117 (−1.590 to −0.643)	<0.001	−0.039 (−0.518 to 0.440)	0.87
Larger only	−1.158 (−1.379 to −0.936)	<0.001	−0.080 (−0.313 to 0.153)	0.50
Both	−1.626 (−1.939 to −1.314)	<0.001	−0.548 (−0.869 to −0.228)	0.001
	Cognition at End of Study (After 20 Years)			
	Absolute Level (95% CI)	***P* Value**	**Difference (95% CI)**	***P* Value**
None	−1.299 (−1.377 to −1.222)	<0.001	Reference	
Smaller only	−1.532 (−1.985 to −1.079)	<0.001	−0.233 (−0.692 to 0.227)	0.32
Larger only	−1.570 (−1.806 to −1.334)	<0.001	−0.271 (−0.519 to −0.023)	0.032
Both	−2.587 (−2.969 to −2.204)	<0.001	−1.287 (−1.677 to −0.897)	<0.001

ARIC = Atherosclerosis Risk in Communities.
* Models are adjusted for age, sex, race, education, and *APOE* ε4 genotype. Cognitive function was measured as an overall *Z* score (see Methods).

Appendix Table 7. Cross-Temporal (Visit 3 Predictors With Visit 5 Outcomes) and Longitudinal End-of-Study Results for Global *Z* Score and Individual Raw and Standardized Cognitive Scores*

Outcome and Infarction Category	Cross-Temporal Linear Regression Results (Visit 5 Outcomes Simply Regressed on Visit 3 Predictors [MCAR])				End-of-Study (Visit 5) Results From Full Primary GLMMs (MAR)	
	Raw Outcome Result (95% CI)	*P* Value	Standardized Outcome Result (95% CI)	*P* Value	Standardized Outcome Result (95% CI)	*P* Value
Global outcomes						
No infarction	NA		Reference		Reference	
Smaller only	NA		−0.094 (−0.322 to 0.135)	0.42	−0.232 (−0.691 to 0.227)	0.32
Larger only	NA		−0.238 (−0.361 to −0.114)	<0.001	−0.306 (−0.543 to −0.069)	0.011
Both	NA		−0.687 (−0.990 to −0.384)	<0.001	−1.208 (−1.595 to −0.821)	<0.001
Delayed word recall (range, 0–10)						
No infarction	Reference		Reference		Reference	
Smaller only	−0.080 (−0.532 to 0.372)	0.73	−0.052 (−0.348 to 0.243)	0.73	−0.549 (−1.232 to 0.133)	0.115
Larger only	−0.290 (−0.533 to −0.046)	0.020	−0.151 (−0.311 to 0.010)	0.066	−0.175 (−0.521 to 0.170)	0.32
Both	−1.396 (−1.968 to −0.823)	<0.001	−0.841 (−1.229 to −0.453)	<0.001	−1.558 (−2.724 to −0.393)	0.009
Digit symbol substitution (range, 0–85)						
No infarction	Reference		Reference		Reference	
Smaller only	−0.183 (−3.171 to 2.806)	0.91	−0.016 (−0.225 to 0.193)	0.88	−0.012 (−0.281 to 0.258)	0.93
Larger only	−2.444 (−4.047 to −0.840)	0.003	−0.161 (−0.274 to −0.048)	0.005	−0.054 (−0.266 to 0.158)	0.62
Both	−5.607 (−9.419 to −1.795)	0.004	−0.321 (−0.599 to −0.044)	0.023	−0.255 (−0.873 to 0.362)	0.42
Word fluency (range, 0–76)						
No infarction	Reference		Reference		Reference	
Smaller only	−1.947 (−5.238 to 1.344)	0.25	−0.158 (−0.421 to 0.105)	0.24	−0.228 (−0.626 to 0.169)	0.26
Larger only	−3.194 (−4.975 to −1.413)	<0.001	−0.246 (−0.389 to −0.102)	0.001	−0.422 (−0.642 to −0.201)	<0.001
Both	−4.050 (−8.220 to 0.120)	0.057	−0.329 (−0.675 to 0.017)	0.062	−0.701 (−1.038 to −0.363)	<0.001
MMSE (range, 4–30)						
No infarction	Reference		NA		NA	
Smaller only	−1.467 (−2.944 to 0.009)	0.051	NA		NA	
Larger only	0.009 (−0.962 to 0.980)	0.99	NA		NA	
Both	−2.664 (−5.093 to −0.234)	0.032	NA		NA	

GLMM = generalized linear mixed model; MAR = missing at random; MCAR = missing completely at random; MMSE = Mini-Mental State Examination; NA = not applicable.
* Models are adjusted for age, sex, race, education, and *APOE* ε4 genotype.