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Associations Between Midlife Vascular Risk Factors and 25-Year Incident Dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort

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IMPORTANCE Vascular risk factors have been associated with cognitive decline. Midlife exposure to these factors may be most important in conferring late-life risk of cognitive impairment.

OBJECTIVES To examine Atherosclerosis Risk in Communities (ARIC) participants in midlife and to explore associations between midlife vascular risk factors and 25-year dementia incidence.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort investigation of the Atherosclerosis Risk in Communities (ARIC) Study was conducted from 1987-1989 through 2011-2013. The dates of this analysis were April 2015 through August 2016. The setting was ARIC field centers (Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and Minneapolis suburbs, Minnesota). The study comprised 15 744 participants (of whom 27.1% were black and 72.9% white) who were aged 44 to 66 years at baseline.

MAIN OUTCOMES AND MEASURES Demographic and vascular risk factors were measured at baseline (obesity, smoking, diabetes, prehypertension, hypertension, and hypercholesterolemia) as well as presence of the *APOE* ε4 genotype. After the baseline visit, participants had 4 additional in-person visits, for a total of 5 in-person visits, hospitalization surveillance, telephone calls, and repeated cognitive evaluations. Most recently, in 2011-2013, through the ARIC Neurocognitive Study (ARIC-NCS), participants underwent a detailed neurocognitive battery, informant interviews, and adjudicated review to define dementia cases. Additional cases were identified through the Telephone Interview for Cognitive Status–Modified or informant interview, for participants not attending the ARIC-NCS visit, or by an *International Classification of Diseases, Ninth Revision* dementia code during a hospitalization. Fully adjusted Cox proportional hazards regression was used to evaluate associations of baseline vascular and demographic risk factors with dementia.

RESULTS In total, 1516 cases of dementia (57.0% female and 34.9% black, with a mean [SD] age at visit 1 of 57.4 [5.2] years) were identified among 15 744 participants. Black race (hazard ratio [HR], 1.36; 95% CI, 1.21-1.54), older age (HR, 8.06; 95% CI, 6.69-9.72 for participants aged 60-66 years), lower educational attainment (HR, 1.61; 95% CI, 1.28-2.03 for less than a high school education), and *APOE* ε4 genotype (HR, 1.98; 95% CI, 1.78-2.21) were associated with increased risk of dementia, as were midlife smoking (HR, 1.41; 95% CI, 1.23-1.61), diabetes (HR, 1.77; 95% CI, 1.53-2.04), prehypertension (HR, 1.31; 95% CI, 1.14-1.51), and hypertension (HR, 1.39; 95% CI, 1.22-1.59). The HR for dementia for diabetes was almost as high as that for *APOE* ε4 genotype.

CONCLUSIONS AND RELEVANCE Midlife vascular risk factors are associated with increased risk of dementia in black and white ARIC Study participants. Further studies are needed to evaluate the mechanism of and opportunities for prevention of the cognitive sequelae of these risk factors in midlife.

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Supplemental content

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Vascular risk factors are increasingly recognized as important contributors to the development of dementia and thus as targets for future therapies. Midlife vascular risk factors appear to be most strongly associated with later-life cognitive decline, as supported by reports from the Atherosclerosis Risk in Communities (ARIC) Study and other cohort studies.[1-4] Vascular risk factors may cause vascular dementia, contribute to the impairment associated with Alzheimer disease (AD), or lead to AD itself[5]; midlife hypertension alone is estimated to be responsible for 425 000 additional cases of AD in the United States annually.[6]

In the above-cited and other studies of vascular risk factors and dementia, ascertainment of dementia has been limited to those participants who are able to attend an in-person evaluation (for epidemiological studies) or patients who voluntarily enroll in a memory clinic cohort, potentially leading to selection bias. Persons with dementia are more likely to be lost to follow-up or reside in nursing facilities, which may lead to ascertainment and examination of a biased sample of cases, diluting estimates of risk factor associations. While some studies use careful rigorous dementia ascertainment methods, few studies combine such ascertainment with longitudinal associations in a racially diverse population.

In this study, we examined ARIC participants in midlife, when vascular risk assessment appears to be most critical, using several methods to maximize completeness of dementia ascertainment, including information from 5 in-person visits (after the baseline visit, participants had 4 additional in-person visits), telephone calls, informant interview for living and deceased participants, and use of *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes from hospitalizations and death certificates. We hypothesized that midlife vascular risk factors (ie, obesity, smoking, diabetes, hypertension, and hypercholesterolemia) would be associated with incident dementia, with the strongest associations among black participants and persons with an *APOE* ε4 allele (OMIM 107741), the primary known genetic risk factor for AD.

Key Points

Question Do vascular risk factors measured in middle age increase risk of dementia in later life?

Findings In this cohort study of 15 744 black and white adults, midlife smoking, diabetes, prehypertension, and hypertension were associated with risk of dementia.

Meaning Potentially modifiable vascular risk factors in midlife may be associated with later-life dementia; further studies are needed to evaluate the influence of risk factor control.

Methods

Participants

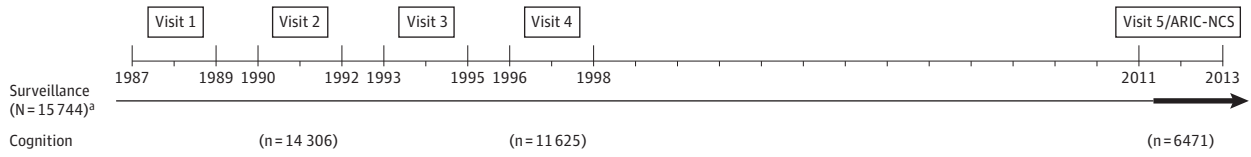
In 1987-1989, the prospective cohort ARIC Study recruited 15 792 participants aged 44 to 66 years from ARIC field centers in 4 US communities (Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and Minneapolis suburbs, Minnesota), with the goal of evaluating atherosclerosis and its risk factors.[7] The present analysis includes 15 744 participants who reported their race at baseline as black (27.1%) or white (72.9%). Since visit 1 at baseline (1987-1989), participants were seen at the following 4 additional visits: visit 2 (1990-1992), visit 3 (1993-1995), visit 4 (1996-1998), and visit 5 as part of the ARIC Neurocognitive Study (ARIC-NCS) (2011-2013) (**Figure 1**). The dates of this analysis were April 2015 through August 2016. Participants were contacted by telephone (annually and then semiannually since 2012), with hospital record abstraction and adjudication of clinical cardiovascular events, followed by informant interviews after a participant's death. The study was approved by each site's institutional review board (at The Johns Hopkins University, Wake Forest University, University of Mississippi Medical Center, and University of Minnesota), and written informed consent was signed by all participants (and proxies, when required).

Visits 2, 4, and 5 each included 3 cognitive tests (Delayed Word Recall, Word Fluency, and Digit Symbol Substitution). Visit 5 included a detailed neuropsychological assessment, representing 3 cognitive domains; participants with cognitive decline and a random sample of those without cognitive decline[8] (eMethods in the Supplement) were invited for further testing, including informant interview, with the Clinical Dementia Rating, the Functional Activities Questionnaire, and the Neuropsychiatric Inventory.

Covariates

All ARIC visits include vascular risk factor assessments, defined herein from visit 1. Sex, race (selected from several choices), date of birth, and educational attainment (less than high school, high school graduate or general equivalency diploma, or beyond high school) are self-reported. The presence

Figure 1. Chronology of Atherosclerosis Risk in Communities (ARIC) Study Visits for All Black and White Participants



ARIC-NCS indicates ARIC Neurocognitive Study.
[a]Continuous surveillance of hospitalizations and deaths; annual telephone calls from study onset through 2012, when the calls were switched to a semiannual schedule. Informant telephone interviews for dementia also began in 2013.

of diabetes (fasting glucose level ≥126 mg/dL, nonfasting glucose level ≥200 mg/dL, self-report of physician-diagnosed diabetes, or use of oral diabetes medications or insulin) was recorded (to convert glucose level to millimoles per liter, multiply by 0.0555). Also recorded was the presence of hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications [the mean of the last 2 blood pressure measurements was used]) or prehypertension (not meeting hypertension criteria, systolic blood pressure ≥120 mm Hg, and diastolic blood pressure ≥80 mm Hg). Smoking was self-reported (current, former, or never). Prevalent coronary heart disease was self-reported (yes or no), and prevalent stroke before visit 1 was self-reported, with incident strokes from visit 1 through visit 5 adjudicated by expert review by one of us (R.F.G. and a nonauthor). Body mass index was calculated as weight in kilograms divided by height in meters squared. *APOE* ε4 carriers, genotyped previously, were defined based on the number of ε4 alleles (0, 1, or 2), with 680 individuals classified as having unknown *APOE* ε4 genotype status. Plasma total cholesterol level was measured using enzymatic methods.[9,10]

Dementia

Dementia ascertainment was classified in 3 ways.[8] Level 1 includes adjudicated dementia from complete evaluation at the ARIC-NCS visit. These assessments incorporated data from longitudinal cognitive evaluations (visits 2, 4, and 5), complete neuropsychological battery at the ARIC-NCS visit (visit 5), and the informant interview, with expert classification of cognitive status[8]; computer algorithmic diagnoses generated standardized definitions of dementia, which were confirmed by these same experts (7 of us, R.F.G., M.S.A., L.H.C., G.M.M., T.H.M., B.G.W., D.S.K., and O. Selnes, PhD, a nonauthor). Level 2 includes level 1 plus (1) participants who did not attend visit 5 but were classified as having dementia based on predefined criteria[8] from the Telephone Interview for Cognitive Status-Modified (TICSm), (2) living or deceased persons classified as having dementia based on predefined criteria[8] from informant telephone interviews using a modified version of the Clinical Dementia Rating and the Functional Activities Questionnaire among a subset identified as having suspect dementia, and (3) a random sample described elsewhere.[8] Level 3, the outcome in this analysis, also includes dementia cases identified solely by surveillance based on a prior discharge hospitalization *ICD-9* or death certificate code for dementia[11,12] through the date of last participant contact up to September 1, 2013.

Statistical Analysis

Statistical software (SAS, version 9.4; SAS Institute Inc) was used for analysis. Time to onset of dementia was the primary outcome. Because participants identified via level 1 underwent complete neurocognitive assessment at a discrete time point (2011-2013), we defined dementia onset as the date of assessment; however, for Level 1 dementia cases who also had a prior dementia hospitalization, we used the hospitalization date. For participants with Level 2 or Level 3 dementia, we used the earliest date from the TICSm, informant interview, hospitalization discharge, or death certificate code, as applicable. To account for the expected lag in ascertainment of dementia identified by informant interviews, hospitalization, and death, 6 months was subtracted from these dates to yield an estimated date of onset. Participants without a dementia diagnosis (through any level) were censored at the latest date among the visit 5 assessment, TICSm, or informant interview (when available) or at the date of last participant contact up to September 1, 2013.

Primary analyses used Cox proportional hazards regression models. Because of uncertainty about the exact date of dementia onset, we also evaluated a discrete time analysis binary model with a complementary log-log link (with time divided into 5-year intervals, allowing assignment of a timeline for diagnosis, without requiring a specific date). To assess sensitivity of results to misclassification of dementia diagnoses based on discharge and death codes, we fit a logistic regression of Level 1 or Level 2 dementia (excluding those with only a hospitalization code). A further sensitivity analysis accounted for the competing risk of stroke or nondementia death with a competing risks proportional hazards model[13] in which participants with a competing event are included in the risk set for dementia at any time after the competing event but with a weight of 1 or less that reduces over time after the competing event. Finally, we conducted a sensitivity analysis that excluded participants with a stroke before visit 5.

Models included all the covariates described above in the Covariates subsection. We checked for collinearity and evaluated interactions between the primary vascular risk factors and *APOE* ε4 genotype (any vs no ε4 allele, ignoring the unknown *APOE* ε4 genotype status group), between the primary vascular risk factors and race (hypothesizing stronger associations in black participants), and between the primary vascular risk factors and sex (hypothesizing similar associations by sex). Race was specifically evaluated given prior investigations demonstrating disparities in dementia rates.[14] In addition, analyses were stratified by age at study baseline (44-54 vs 55-66 years) to determine whether associations were stronger in earlier vs later midlife. Wald χ^2 tests were used to test the significance of each interaction, and a final model was fit that included interactions with 2-sided $P < .10$. The proportional hazards assumption was checked using Martingale residuals and by fitting interactions with time.

Results

Cohort Characteristics

Of the 15 744 ARIC cohort members who self-identified as black or white, approximately 55% were female; 6471 participants attended visit 5. Participants attending visit 5 were younger and generally healthier at visit 1 than other participants (**Table 1**).

In total, 1516 cases of dementia (57.0% female and mean [SD] age, 57.4 [5.2] years at visit 1) were identified among 15 744 participants, representing 9.6% of the total evaluable sample (eTable 1 in the Supplement); 34.9% of these cases were among

Table 1. Demographic Characteristics of Atherosclerosis Risk in Communities (ARIC) Participants by Assessment Type[a]

Variable	Visit 5	TICSm	Informant Interview	Deceased	Alive With ≥1 Hospitalizations	No Death or Hospitalization	Total
No.	6471	1461	826	5337	1191	458	15 744
Median follow-up, y	23.7	24.1	22.8	15.2	24.4	23.2	23.0
Female, %	58.8	65.7	56.3	45.4	62.1	63.5	55.2
Black, %	23.8	23.8	29.7	32.0	25.9	26.6	27.1
Visit 1 age, mean (SD) y	52.1 (5.2)	53.4 (5.5)	57.1 (5.4)	56.7 (5.5)	53.9 (5.6)	52.2 (5.3)	54.2 (5.8)
Educational attainment, %							
<High school	15.2	19.2	35.2	34.0	25.5	19.7	23.9
High school graduate or GED	41.7	47.4	34.5	38.3	41.3	44.7	40.7
>High school	43.2	33.4	30.3	27.7	33.2	35.5	35.4
Visit 1 BMI, %							
Underweight	0.6	0.8	0.2	1.4	1.1	1.1	0.9
Normal	35.6	32.1	27.0	28.3	30.4	41.4	32.1
Overweight	40.2	40.3	42.1	37.7	39.9	37.5	39.4
Obese	23.7	26.8	30.6	32.6	28.6	20.0	27.5
Visit 1 smoking, %							
Current	17.9	24.3	21.8	38.0	24.6	22.9	26.2
Former	33.2	30.6	33.5	31.9	30.0	30.6	32.2
Never	48.9	45.1	44.7	30.1	45.4	46.5	41.6
APOE ε4 genotype, %							
0 Alleles	67.9	69.6	55.4	64.2	66.9	68.1	66.1
1 Allele	25.8	24.6	35.7	28.2	26.3	24.7	27.0
2 Alleles	2.1	1.6	5.1	3.0	2.6	2.0	2.6
Unknown *APOE*	4.2	4.1	3.8	4.6	4.2	5.2	4.3
Visit 1 diabetes, %	6.0	7.6	14.7	21.1	9.7	5.7	12.0
Visit 1 hypertension, %							
Normal	48.0	40.4	27.5	25.5	37.2	48.5	37.8
Prehypertension	22.7	23.7	26.7	20.8	23.3	25.3	22.5
Hypertension	29.3	35.9	45.8	53.7	39.5	26.2	39.7
Visit 1 total cholesterol, mg/dL, %							
<200	40.4	36.2	34.1	35.2	36.2	37.4	37.5
200 to <240	38.0	36.6	36.1	37.2	37.5	40.7	37.5
≥240	21.6	27.2	29.8	27.6	26.3	22.0	25.0
Visit 1 coronary heart disease, %	1.9	2.5	4.1	10.3	3.3	0.9	5.0
Visit 2 Delayed Word Recall *z* score, mean (SD)	0.17 (0.95)	0.12 (0.98)	−0.23 (0.98)	−0.26 (1.03)	−0.01 (0.99)	0.14 (0.94)	0.00 (1.00)
Visit 2 Digit Symbol Substitution *z* score, mean (SD)	0.25 (0.95)	0.12 (0.92)	−0.32 (1.01)	−0.36 (1.00)	−0.00 (0.93)	0.18 (0.93)	0.00 (1.00)
Visit 2 Word Fluency *z* score, mean (SD)	0.15 (0.98)	0.02 (0.96)	−0.11 (1.02)	−0.19 (1.02)	−0.07 (0.96)	0.05 (0.98)	0.00 (1.00)
Stroke before visit 5, %	4.1	4.2	17.4	16.0	8.6	0.4	9.1

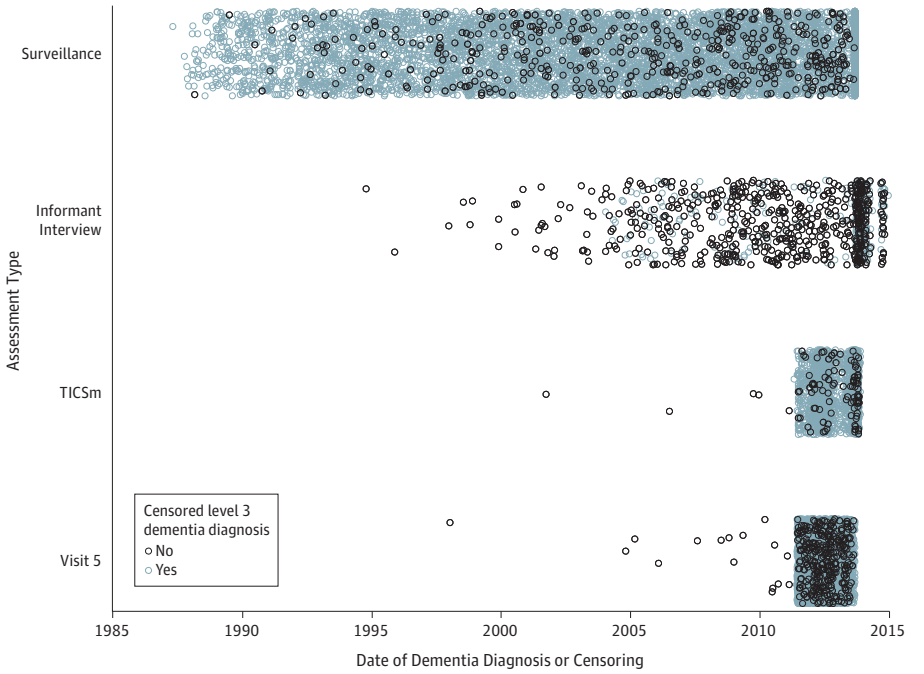
Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GED, general educational development; TICSm, Telephone Interview for Cognitive Status–Modified.

SI conversion factor: To convert cholesterol level to millimoles per liter, multiply by 0.0259.

[a] The numbers with missing data are 26 for Educational attainment, 25 for Visit 1 BMI, 16 for Visit 1 smoking, 680 for *APOE* ε4 genotype, 147 for Visit 1 diabetes, 13 for Visit 1 hypertension, 251 for Visit 1 total cholesterol, 341 for Visit 1 coronary heart disease, 1582 for Visit 2 Delayed Word Recall *z* score, 1632 for Visit 2 Digit Symbol Substitution *z* score, and 1602 for Visit 2 Word Fluency *z* score.

black participants. Because of the way cases were identified, Level 1 assessments (cases and noncases) were clustered during visit 5, with similar clustering for the TICSm and informant interviews (performed during the same period). The earliest dates were from surveillance (from hospitalization or death certificate codes or from censoring at last contact) (**Figure 2**). By design, only persons with a high suspicion of dementia were contacted for an informant interview; therefore, 69.6% of this

Figure 2. Distribution of Dates of Dementia Diagnoses



Darker circles represent dementia cases; lighter circles represent other censored cases (due to either death or dropout). TICSm indicates Telephone Interview for Cognitive Status–Modified.

group had dementia, with fewer in the other groups in whom dementia was ascertained.

Risk Factors for Dementia

Of the 15 744 participants, 15 407 (97.9%) had nonmissing data on all the covariates of interest except for *APOE* ε4 genotype. In our primary analysis, the multivariable hazard for dementia was increased in persons of black race and in those with baseline older age, lower educational attainment, current smoking, diabetes, and prehypertension and hypertension, as well as among *APOE* ε4 carriers (**Table 2**). Although, other than age, *APOE* genotype status was the strongest risk factor for subsequent risk of dementia, with a near doubling of risk for at least 1 ε4 allele, midlife diabetes neared this effect size (hazard ratio [HR], 1.77; 95% CI, 1.53-2.04). Total cholesterol level was not associated with increased hazard of dementia; in separate models, other lipid fractions were evaluated and also were not significant. Risk for dementia was minimally reduced in women compared with men.

Stratified Analyses

We evaluated our Cox proportional hazards regression models stratified in separate models by race, sex, *APOE* genotype status, and baseline age. When stratified by race (Table 2), risk for dementia associated with having at least 1 *APOE* ε4 allele was greater for whites (HR, 2.23; 95% CI, 1.96-2.54) than for blacks (HR, 1.61; 95% CI, 1.34-1.92), with a significant *APOE* ε4 genotype by race interaction (interaction $P < .01$). Midlife smoking status was also a predictor only among white participants and not among black participants, with stronger influences of age in whites compared with blacks (interaction $P < .01$ for each). Other risk factors had similar results among both races. Dementia had similar predictors in men and women (eTable 2 in the Supplement).

APOE ε4 carriers and noncarriers had similar associations between vascular risk factors and dementia (eTable 3 in the Supplement); the *APOE* ε4 genotype by race interaction was again found. No other significant interactions with *APOE* ε4 genotype were identified. With baseline age stratification (eTable 4 in the Supplement), educational attainment, current smoking, diabetes, hypertension, and total cholesterol level all showed somewhat stronger elevated risk among the younger age group (44-54 years) than among the older age group (55-66 years), but differences were significant only for educational attainment and diabetes.

Sensitivity Analyses

Because clinical strokes might mediate the influence of vascular risk factors on subsequent dementia, we repeated the analysis after excluding 1430 participants with stroke. Results in this sample were similar to those of the full cohort (eTable 5 in the Supplement). In sensitivity analyses treating stroke and death as competing risks to dementia, associations were somewhat attenuated for race, current smoking, diabetes, and hypertension, but all remained statistically significant (**Table 3**).

Findings using a complementary log-log link analysis, considering dementia cases during intervals, and using logistic regression, with exclusion of those cases identified only via hospitalization codes, showed similar results compared with our primary Cox proportional hazards regression model. These results are summarized in eTable 6 in the Supplement.

Table 2. Cox Proportional Hazards Regression Model of Time to Incident Dementia Overall and Stratified by Race

Variable	Hazard Ratio (95% CI)		
	Full Eligible Cohort (n = 15 407)[a]	Black (n = 4004)	White (n = 11 403)
Female	0.89 (0.79-0.99)	0.87 (0.72-1.06)	0.92 (0.80-1.05)
Black	1.36 (1.21-1.54)	NA	NA
Visit 1 age, y[b]			
44-49	1 [Reference]	1 [Reference]	1 [Reference]
50-54	2.04 (1.66-2.49)	2.22 (1.66-2.98)	1.98 (1.49-2.62)
55-59	3.97 (3.28-4.81)	3.53 (2.63-4.73)	4.37 (3.37-5.65)
60-66	8.06 (6.69-9.72)	6.20 (4.64-8.28)	9.54 (7.41-12.27)
Educational attainment			
<High school	1.37 (1.20-1.57)	1.61 (1.28-2.03)	1.29 (1.09-1.53)
High school graduate or GED	1.05 (0.93-1.20)	1.17 (0.90-1.53)	1.02 (0.88-1.18)
>High school	1 [Reference]	1 [Reference]	1 [Reference]
Visit 1 BMI			
Underweight	0.99 (0.53-1.87)	1.15 (0.36-3.66)	0.92 (0.43-1.97)
Normal	1 [Reference]	1 [Reference]	1 [Reference]
Overweight	1.05 (0.92-1.19)	0.95 (0.73-1.22)	1.08 (0.93-1.26)
Obese	1.14 (0.99-1.31)	0.92 (0.71-1.20)	1.22 (1.03-1.45)
Visit 1 smoking[b]			
Current	1.41 (1.23-1.61)	1.07 (0.85-1.35)	1.62 (1.37-1.92)
Former	1.00 (0.89-1.13)	0.77 (0.61-0.98)	1.13 (0.97-1.31)
Never	1 [Reference]	1 [Reference]	1 [Reference]
APOE ε4 genotype[b]			
0 Alleles	1 [Reference]	1 [Reference]	1 [Reference]
≥1 Alleles	1.98 (1.78-2.21)	1.61 (1.34-1.92)	2.23 (1.96-2.54)
Unknown *APOE*	1.18 (0.89-1.56)	1.84 (0.97-3.47)	1.11 (0.81-1.52)
Visit 1 diabetes	1.77 (1.53-2.04)	1.85 (1.50-2.29)	1.69 (1.39-2.07)
Visit 1 hypertension			
Normal	1 [Reference]	1 [Reference]	1 [Reference]
Prehypertension	1.31 (1.14-1.51)	1.17 (0.86-1.59)	1.35 (1.14-1.59)
Hypertension	1.39 (1.22-1.59)	1.36 (1.04-1.77)	1.37 (1.17-1.60)
Visit 1 total cholesterol, mg/dL			
<200	1 [Reference]	1 [Reference]	1 [Reference]
200 to <240	0.87 (0.77-0.98)	0.91 (0.74-1.13)	0.86 (0.74-1.00)
≥240	0.91 (0.80-1.04)	0.78 (0.62-0.98)	0.99 (0.84-1.16)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GED, general educational development; NA, not applicable.

SI conversion factor: To convert cholesterol level to millimoles per liter, multiply by 0.0259.

[a] Of the 15 744 participants, 15 407 (97.9%) had nonmissing data on all the covariates of interest except for APOE ε4 genotype.

[b] $P < .01$ for significance of interaction of race with each covariate ($P > \chi^2$ statistic).

Discussion

This analysis of incident dementia in a biracial community-based cohort demonstrates increased risk of dementia among persons with the following characteristics: black race, older age, lower educational attainment, current smoking, diabetes or hypertension in midlife, and the presence of at least 1 *APOE* ε4 allele. These findings support prior reports that emphasize the importance of midlife vascular risk factors in subsequent dementia,[15-18] adding new information about risk from prehypertension. In contrast to some prior investigations, the ARIC Study, which includes a large number of black and white participants, obtained detailed evaluations during midlife and extensive surveillance of dementia, comorbidities, and mortality, as well as formal assessments to diagnose dementia in those evaluated in person. Results from previous studies have also suggested higher rates of dementia in blacks[19,20] and in persons with lower educational attainment,[21-23] as supported by this study.

Although supportive of previous investigations demonstrating the importance of midlife vascular risk factors in the development of subsequent dementia, by ascertaining cases of dementia using several methods, our study adds to the existing literature by avoiding many of the biases caused by incomplete case ascertainment or use of memory clinic cohorts and by evaluating a racially diverse population over decades. Our approach allowed for inclusion of deceased participants among our cases by using hospitalization and death certificate codes for dementia and by obtaining informant interviews for deceased participants in whom suspicion for dementia was high, as well as those participants who are so

Table 3. Competing Risk Cox Proportional Hazards Regression Model of Time to Incident Dementia

Variable	Hazard Ratio (95% CI)	
	Competing Risk of Stroke (n = 15 407)[a]	Competing Risk of Stroke or Death (n = 15 407)[a]
Female	0.99 (0.88-1.12)	0.97 (0.86-1.09)
Black	1.22 (1.07-1.40)	1.24 (1.09-1.41)
Visit 1 age, y		
44-49	1 [Reference]	1 [Reference]
50-54	2.25 (1.80-2.81)	2.09 (1.70-2.58)
55-59	4.18 (3.38-5.18)	3.89 (3.18-4.75)
60-66	8.23 (6.67-10.16)	7.48 (6.14-9.12)
Educational attainment		
<High school	1.37 (1.18-1.59)	1.39 (1.20-1.60)
High school graduate or GED	1.04 (0.91-1.20)	1.03 (0.90-1.18)
>High school	1 [Reference]	1 [Reference]
Visit 1 BMI		
Underweight	0.82 (0.37-1.81)	1.07 (0.56-2.04)
Normal	1 [Reference]	1 [Reference]
Overweight	1.03 (0.89-1.18)	1.06 (0.92-1.21)
Obese	1.10 (0.95-1.29)	1.16 (0.99-1.35)
Visit 1 smoking		
Current	1.22 (1.05-1.41)	1.24 (1.07-1.43)
Former	0.96 (0.84-1.09)	0.97 (0.86-1.11)
Never	1 [Reference]	1 [Reference]
APOE ε4 genotype		
0 Alleles	1 [Reference]	1 [Reference]
≥1 Alleles	2.08 (1.86-2.34)	2.02 (1.81-2.26)
Unknown *APOE*	1.19 (0.87-1.63)	1.21 (0.90-1.64)
Visit 1 diabetes	1.35 (1.14-1.60)	1.34 (1.14-1.58)
Visit 1 hypertension		
Normal	1 [Reference]	1 [Reference]
Prehypertension	1.29 (1.11-1.50)	1.29 (1.11-1.50)
Hypertension	1.23 (1.06-1.42)	1.24 (1.08-1.43)
Visit 1 total cholesterol, mg/dL		
<200	1 [Reference]	1 [Reference]
200 to <240	0.89 (0.78-1.02)	0.88 (0.77-1.00)
≥240	0.93 (0.80-1.07)	0.93 (0.81-1.07)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GED, general educational development.

SI conversion factor: To convert cholesterol level to millimoles per liter, multiply by 0.0259.

[a] Of the 15 744 participants, 15 407 (97.9%) had nonmissing data on all the covariates of interest except for APOE ε4 genotype.

cognitively impaired that they cannot attend a clinic visit or complete neuropsychological testing. We also found some novel associations, including the higher risk for dementia associated with prehypertension in midlife.

Furthermore, we evaluated differential influences of risk factors by race. We did not detect major differences by race in the relative influence of midlife vascular risk factors on dementia incidence, other than smoking, which contradicts previous hypotheses that differences in the influence of vascular disease on cognition by race may explain racial disparities.[24] However, it is possible that risk factors are longer lasting and more prevalent among blacks than among whites; we find more hypertension in blacks than in whites, although smoking is more common in whites than in blacks in the ARIC cohort[25] and appears to also be a stronger risk factor in whites, perhaps because of their smoking more cigarettes. This difference in risk factor prevalence would affect attributable risk (ie, more dementia cases among blacks would be attributed to hypertension and diabetes) and thus would still be consistent with our race-stratified results.

The discrepancy that we observed in the influence of *APOE* ε4 genotype on dementia risk by race (an ε4 allele increases risk of dementia in both races but to a greater degree in whites vs blacks) has been noted in prior investigations, with others reporting no ε4 influence in blacks.[26,27] This result is in contrast to our group's recent findings in a subset of ARIC participants who underwent amyloid positron emission tomography, among whom the influence of *APOE* on amyloid deposition was similar in blacks and in whites.[28] Understanding the role of *APOE* in blacks is critical if future treatment or prevention studies are to identify potential candidates for AD-specific therapies on the basis of the most widely recognized risk factors, including *APOE*. Race-specific inclusion criteria may need to be considered in future treatment trials.

Participants with lower educational attainment had more dementia in this study, as reported in prior investigations.[29] These results support our group's previous hypothesis[30] that less educated participants, with lower baseline cognitive performance, would more easily and quickly fall below a threshold under which dementia might be identified, thus leading to more cases of dementia. We did not find a statistically different influence of educational attainment on dementia by sex, as reported previously.[31]

Limitations

Although attempts were made to minimize missed cases of dementia, the accuracy of review for Level 2 or Level 3 assessment was not as good as that for Level 1 cases, in whom complete in-person neuropsychological assessment with informant interview and expert review took place. Therefore, some cases found through TICSm or through informant interview may be incorrectly identified; it is even more likely that cases identified only through hospitalization codes for dementia may be incorrect or may be more frequent in individuals with a greater number of vascular comorbidities. If vascular risk factors are overrepresented in hospitalized individuals, risk factor and dementia associations might be exaggerated. However, our logistic regression sensitivity analysis that excluded hospitalized cases shows results similar to those of the primary analysis, as does the analysis that excluded interim strokes, reducing the likelihood of this type of bias. Misclassified cases, if numerous, might lead to an underestimation of associations between vascular risk factors and dementia. Furthermore, because of the limited information available through Level 2 and Level 3, we were not able to evaluate mild cognitive impairment in this complete cohort or etiology of dementia given the range of sources of information to identify dementia. We also note that our estimates of onset dates are not precise, particu-

larly without a clear date of when individuals were last known to be cognitively normal. It is likely that some participants had an onset years before a diagnosis was made; we conservatively subtracted 6 months from estimated diagnoses made via Level 2 or Level 3 and incorporated several sensitivity analyses, including a discrete time analysis that allowed for binning of dementia diagnoses into 5-year intervals. Finally, we acknowledge that, as with any observational study, our results might be susceptible to residual confounding. Some risk factors are more prevalent among persons of lower socioeconomic status, and adjustment for educational attainment is unlikely to capture that potential confounding completely. Although our models included the primary vascular risk factors and demographics together, we did not evaluate medication use, nor did we consider trajectories of risk factors during follow-up. Treatment of modifiable risk factors is likely to influence outcomes, but we did not test the role of medications in the observed associations.

We focused on midlife vascular risk factors based on prior observations, including in our group's investigations using dementia hospitalization codes,[11] that midlife status is more important than later-life status of these risk factors in subsequent brain aging. Our age-stratified analyses showed that associations tended to be stronger in individuals at earlier midlife (44-54 years), emphasizing the heightened importance of vascular risk at earlier ages. These age-stratified results also demonstrate a sufficient number of dementia cases, all of whom were younger than 80 years at the time of visit 5, to still show strong associations. Furthermore, trials focusing on treating vascular disease in late-life have been unsuccessful in reducing dementia,[32] thus underscoring the importance of identifying a period in midlife when risk is increased but dementia prevention may be possible.

Conclusions

A primary goal of the ARIC-NCS is to evaluate the role of vascular disease in subsequent development of dementia. This study points to the importance of midlife vascular risk factors, including smoking, diabetes, prehypertension, and hypertension, in later-life development of dementia and identifies disparities in dementia rates, with higher rates among blacks than among whites. Vascular risk factors are modifiable, and their association with dementia emphasizes that many cases of dementia may be prevented or delayed. Future studies need to evaluate the mechanism of this racial disparity in dementia rates and assess subclinical vascular disease (systemic and cerebrovascular) as a risk factor for dementia.

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