Smoking and white matter hyperintensity progression

The ARIC-MRI Study

Melinda C. Power, ScD
Jennifer A. Deal, PhD
A. Richey Sharrett, MD,
DrPH
Clifford R. Jack, Jr., MD
David Knopman, MD
Thomas H. Mosley, PhD
Rebecca F. Gottesman,
MD, PhD

Correspondence to
Dr. Power:
melindacpower@gmail.com

ABSTRACT

Objective: Our objective was to examine the link between smoking and smoking history, including smoking intensity and cessation, overall and by race, in a biracial prospective cohort study.

Methods: A subset of Atherosclerosis Risk in Communities Study participants ($n = 972$, 49% black) completed brain MRI scans twice (1993–1995 and 2004–2006). We defined white matter hyperintensity (WMH) progression as an increase of ≥ 2 points on the 9-point Cardiovascular Health Study scale across scans. Participants reported information on smoking behavior at the baseline MRI and at 2 prior study visits, approximately 3 and 6 years before baseline. We used adjusted logistic regression to evaluate the association between smoking variables and WMH progression in the total sample and separately by race (black and white).

Results: We found WMH progression in 23% of participants (30% of black participants, 17% of white participants). Overall, being a current smoker 6 years before baseline was associated with WMH progression. In race-stratified analyses, we found adverse associations with smoking status at multiple time points and persistent smoking in white but not in black participants. However, we found no statistical support for effect modification by race for most of these analyses. Increasing pack-years of smoking was associated with greater risk of WMH progression, while time since quitting and age at smoking initiation were not associated with WMH progression, with little indication of differences in these associations by race.

Conclusions: Our findings concur with previous studies suggesting a relationship between smoking and WMH progression, and further demonstrate a dose-dependent association.

Neurology® 2015;84:841–848

GLOSSARY

ARIC = Atherosclerosis Risk in Communities; **BMI** = body mass index; **CHD** = coronary heart disease; **CHS** = Cardiovascular Health Study; **IPAW** = inverse probability of attrition weight; **WMH** = white matter hyperintensity.

Smoking may be related to white matter hyperintensities (WMH), also called leukoaraiosis, which reflect subclinical small vessel disease, specifically white matter damage due to hypoperfusion, thrombosis of arterioles, or a leaky blood-brain barrier.^{1–3} Cross-sectional studies reporting on the association between smoking and WMH severity are mixed.^{4–11} Prospective studies of smoking and WMH progression are likely more informative. Associations with progression provide stronger evidence for a causal relation, because studies of within-person change are less susceptible to confounding, and WMH progression may be more strongly associated with clinically relevant outcomes than WMH severity.¹² The few studies reporting on smoking and WMH progression, including our own, suggest an association between current smoking and WMH progression.^{13–16} However, these studies crudely classified smoking (e.g., current/former/never). Demonstration of a dose-response relationship and declines in risk with smoking cessation would strengthen causal claims. Furthermore, prior findings in the Atherosclerosis Risk in Communities (ARIC) Study support stronger cross-sectional associations between smoking and increased WMH severity in black compared with white persons,⁹ potentially attributable to geographic, socioeconomic, or cultural differences by race.^{17,18} However, it is

Supplemental data
at Neurology.org

From the Department of Neurology, Johns Hopkins University School of Medicine (R.F.G.), and Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health (M.C.P., J.A.D., A.R.S., R.F.G.), Baltimore, MD; Departments of Radiology (C.R.J.) and Neurology (D.K.), Mayo Clinic, Rochester, MN; and Department of Medicine (T.H.M.), University of Mississippi Medical Center, Jackson.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

currently unknown whether this pattern persists for the association between smoking and WMH progression.

Our goal was to expand on prior work in ARIC, a biethnic prospective cohort study suggesting an association between baseline current smoking status and WMH progression,¹³ to assess whether smoking history, intensity, and cessation are associated with WMH progression overall and by race (black and white).

METHODS Study population. The ARIC Study is a population-based cohort of 15,792 persons, including a substantial proportion of black participants, from 4 US communities recruited in 1987–1989 (visit 1). At enrollment, participants were between the ages of 45 and 65 years. Relevant to this analysis, all participants were invited to return for in-person study visits in 1990–1992 (visit 2) and 1993–1995 (visit 3), and a subset of participants from the Forsyth County, NC, and Jackson, MS, ARIC sites completed brain MRI at visit 3 in 1993–1995 and again in 2004–2006. The choice of targeting these sites ensured the resulting sample with brain MRI included a substantial proportion of black participants; although the majority of Forsyth County participants are white, all Jackson participants, by design of the study, are black. In addition to requiring all participants to have MRI data on WMH severity at both MRI visits and complete data on smoking at visits 1–3 ($n = 1,029$), we excluded persons with confirmed clinical stroke or report of multiple sclerosis, surgery or radiation to the head, or brain tumor at any time before the 2004–2006 brain MRI ($n = 52$), as well as persons missing data on a priori-specified confounders ($n = 5$): age, sex, race, center, and education.

Standard protocol approvals, registrations, and patient consents. The institutional review boards of the academic institutions associated with each field center approved this study. All subjects provided written informed consent to participate, based on local standards at Wake Forest University School of Medicine or the University of Mississippi Medical Center.

Smoking and covariate assessment. At each study visit, we asked participants to complete questionnaires, including questions about smoking. We categorized participants as current, former, or never smokers at each visit. We also classified persons according to their pattern of smoking status across the 3 visits: (1) current smoker at all visits, (2) quit smoking between visits 1 and 3, (3) quit smoking before visit 1, (4) never smoker, and (5) other (e.g., relapsed former smokers, initiators). We computed pack-years of smoking up to the time of the baseline MRI examination, defined as number of packs per day (assuming 20 cigarettes to a pack) times the number of years of smoking for current or former smokers. Similarly, we computed the number of years between smoking cessation and the time of the baseline MRI examination among former smokers, and evaluated age at smoking initiation among ever smokers.

We used data obtained at visits 1–3 (including self-report, administrative, and physical examination data) to define our covariates. Time-invariant covariates included sex (male/female), race (black/white), study center (Forsyth County/Jackson), and education (<high school/high school, GED, or vocational

school/college, graduate, or professional school). For nonrace-stratified analyses, we combined race and center into a single variable (black in Jackson/black in Forsyth County/white in Forsyth County). We defined covariates that may vary over time at each study visit using data available from that visit, including age, body mass index (BMI) ($<25/25\text{--}29/\geq 30$ kg/m²), hypertension (yes/no), diabetes (yes/no), and prevalent coronary heart disease (CHD) (yes/no). We calculated BMI as measured weight divided by the square of measured height (kg/m²). We defined hypertension as blood pressure of $>140/90$ mm Hg or use of antihypertensive medication. We defined diabetes as self-reported diabetes diagnosis, ≥ 126 mg/dL fasting glucose, ≥ 200 mg/dL nonfasting glucose, or antidiabetic medication use. We defined prevalent CHD as self-reported myocardial infarction, coronary bypass, balloon angioplasty, or angioplasty of one or more coronary arteries at visit 1 or adjudicated disease after baseline.

WMH progression. All eligible sample participants underwent 1.5-tesla brain MRI twice, once in 1993–1995 and again in 2004–2006. Technical details are available elsewhere.^{13,19,20} For both sets of MRIs, proton density-weighted images were viewed and assigned a score of 0 to 9 according to the WMH scale developed for the Cardiovascular Health Study (CHS).^{8,9,21} Subcortical and periventricular WMH were evaluated together. The CHS scale has been shown to have good inter- and intrarater reliability in other settings.²¹ We defined WMH progression as an increase of ≥ 2 points on the CHS scale across the 2 MRI scans (completed approximately 11 years apart). This definition is more likely to capture true progression than a 1-point change and is consistent with prior work defining progression as 1 point per 4 to 6 years of follow-up.^{14–16}

Statistical analyses. For all analyses, we used adjusted logistic regression to evaluate the relationship between smoking and WMH progression in the total sample and separately by race. We ran separate models for each of our smoking variables: smoking status at each visit, smoking pattern, years since quitting, pack-years of smoking, and age at smoking initiation. We adjusted primary analyses for a core set of potential confounders, determined a priori: age, sex, race/center, and education. We updated time-varying covariates as appropriate for each analysis (i.e., visit 1 covariate values were used to adjust models of visit 1 smoking status while visit 2 covariate values were used to adjust models of visit 2 smoking status, etc.). Because we were concerned that the association between years since quitting, age at initiation, or pack-years of smoking on subsequent WMH progression may be nonlinear, we performed exploratory analyses using penalized splines to characterize the shape of the dose-response curve. These splines informed our decisions whether or not to use linear splines and choice of the knot point. We evaluated the strength of the evidence for effect modification by race using likelihood ratio tests comparing models with and without interaction terms between race and smoking variables.

We also conducted several sensitivity analyses: (1) we considered additional adjustment for other predictors of WMH that may act either as confounders or intermediates (hypertension, diabetes, prevalent CHD, and BMI), imputing missing data on any of these covariates using standard methods²²; (2) we excluded persons with potentially erroneous improvement in WMH grade of ≥ 2 points ($n = 8$) because WMH due to vascular disease would not be expected to diminish over time; (3) because we were concerned that it would be more difficult for those with high baseline WMH grades to exhibit WMH progression than those with lower baseline grades, we considered an alternate

definition of progression, requiring a change of ≥ 2 for those with a baseline grade of <3 and ≥ 1 point for those with a baseline grade of ≥ 3 ; and (4) we considered analyses weighted with inverse probability of attrition weights (IPAWs) to account for potential selection bias given loss to follow-up from the baseline to follow-up MRI. Theoretical and practical details of IPAWs are available elsewhere.^{23–25} Briefly, we computed weights for death and nondeath attrition separately (28% of attrition was due to death, while the remainder was due to dropout). These weights were multiplied together to create the final weight. Separate sets of weights were created for each analysis (e.g., evaluating smoking status at visit 1). Models to create weights included the baseline WMH score, the exposure of interest for that analysis (e.g., visit 1 smoking status), all covariates included in original or sensitivity models, self-reported health compared with others (fair/poor or good/excellent), hypercholesterolemia, and income. We considered separate analyses weighted to account for total and nondeath attrition given the controversial nature of weighting to account for attrition due to death,^{26,27} as well as analyses in which IPAWs were computed separately by race, given potential variation in predictors of attrition by race. Because all 4 versions (e.g., considering total attrition, computed with race-stratified models)

produced similar results, we present and discuss only results using IPAWs for nondeath attrition, derived from race-combined models. We report 95% confidence intervals and consider a 2-sided p value <0.05 to be statistically significant. All analyses were completed using SAS version 9.3 (SAS Institute, Cary, NC), Stata version 13.1 (StataCorp, College Station, TX), or R version 3.0.1.

RESULTS A total of 972 ARIC participants met our eligibility criteria. Compared with ARIC participants who did not have a baseline MRI and those who completed only the baseline MRI, our sample was more educated, healthier, and more likely to be never smokers (table e-1 on the *Neurology*® Web site at Neurology.org). These trends were not markedly different by race. In our sample, WMH progression was more common in black than in white participants, as was having low education, hypertension, diabetes, and obesity (table 1). We provide the details of covariate distribution by smoking status at the baseline MRI in table e-2 and the distributions of smoking

Table 1 Demographic and health-related characteristics of eligible ARIC Study participants at the time of the initial MRI (visit 3, 1993–1995)

Variable	Total (n = 972; 100%)	White (n = 491; 51%)	Black (n = 481; 49%)	p Value
WMH progression, n (%)	226 (23)	81 (17)	145 (30)	<0.001
Baseline CHS WMH score, mean $\pm$ SD	1.2 $\pm$ 0.9	1.4 $\pm$ 0.8	1.1 $\pm$ 1.0	<0.0001
Time between MRI scans, y, mean $\pm$ SD	10.6 $\pm$ 0.8	10.3 $\pm$ 0.7	10.8 $\pm$ 0.9	<0.0001
Age, y, mean $\pm$ SD	61.8 $\pm$ 4.4	62.5 $\pm$ 4.3	61.0 $\pm$ 4.4	<0.0001
Female, n (%)	595 (61)	285 (58)	310 (64)	0.04
Education, n (%)				<0.0001
<12 y	205 (21)	43 (9)	162 (34)	
12–16 y	344 (35)	227 (46)	117 (24)	
>16 y	423 (44)	221 (45)	202 (42)	
Hypertension, n (%)				<0.0001
Yes	417 (43)	143 (29)	274 (57)	
No	551 (57)	347 (71)	204 (42)	
Missing	4 (0)	1 (0)	3 (1)	
Diabetes, n (%)				<0.0001
Yes	160 (16)	50 (10)	110 (23)	
No	810 (83)	440 (90)	370 (77)	
Missing	2 (0)	1 (0)	1 (0)	
Prevalent coronary heart disease, n (%)				0.08
Yes	32 (3)	21 (4)	11 (2)	
No	922 (95)	460 (94)	462 (96)	
Missing	18 (2)	10 (2)	8 (2)	
Body mass index, kg/m ² , n (%)				<0.0001
<25	296 (30)	211 (43)	85 (18)	
25–29	405 (42)	195 (40)	210 (44)	
≥ 30	271 (28)	85 (17)	186 (39)	

Abbreviations: ARIC = Atherosclerosis Risk in Communities; CHS = Cardiovascular Health Study; WMH = white matter hyperintensity.

Table 2 Association of smoking status at each prior ARIC Study visit and smoking history with WMH progression

	All participants			White participants			Black participants		
	No. (%)	No. (%) with WMH progression	Adjusted OR ^a (95% CI)	No. (%)	No. (%) with WMH progression	Adjusted OR ^a (95% CI)	No. (%)	No. (%) with WMH progression	Adjusted OR ^a (95% CI)
Smoking status at visit 1 (1987-1989)									
Current	180 (19)	52 (29)	1.52 (1.01, 2.30)	85 (17)	22 (26)	2.37 (1.26, 4.46)	95 (20)	30 (32)	1.11 (0.65, 1.90)
Former	294 (30)	63 (21)	0.90 (0.62, 1.32)	172 (35)	27 (16)	1.05 (0.57, 1.92)	122 (25)	36 (30)	0.85 (0.52, 1.40)
Never	498 (51)	111 (22)	Ref.	234 (48)	32 (14)	Ref.	264 (55)	79 (30)	Ref.
The p value for interaction with race: 0.18									
Smoking status at visit 2 (1990-1992)									
Current	158 (16)	41 (26)	1.21 (0.78, 1.88)	74 (15)	19 (26)	2.28 (1.17, 4.42)	84 (17)	22 (26)	0.76 (0.42, 1.37)
Former	367 (38)	82 (22)	0.89 (0.62, 1.28)	201 (41)	31 (15)	0.94 (0.52, 1.70)	166 (35)	51 (31)	0.88 (0.56, 1.39)
Never	447 (46)	103 (23)	Ref.	216 (44)	31 (14)	Ref.	231 (48)	72 (31)	Ref.
The p value for interaction with race: 0.02									
Smoking status at visit 3/initial MRI (1993-1995)									
Current	135 (14)	38 (28)	1.35 (0.85, 2.14)	62 (13)	16 (26)	2.24 (1.10, 4.57)	73 (15)	22 (30)	0.96 (0.52, 1.76)
Former	406 (42)	87 (21)	0.83 (0.59, 1.19)	225 (46)	35 (16)	0.95 (0.53, 1.70)	181 (38)	52 (29)	0.78 (0.50, 1.23)
Never	431 (44)	101 (23)	Ref.	204 (42)	30 (15)	Ref.	227 (47)	71 (32)	Ref.
The p value for interaction with race: 0.19									
Smoking history									
Current smoker at all visits	115 (12)	33 (29)	1.36 (0.84, 2.22)	52 (11)	15 (29)	2.58 (1.24, 5.35)	63 (13)	18 (29)	0.86 (0.45, 1.66)
Quit smoking after visit 1	56 (6)	17 (31)	1.47 (0.78, 2.78)	27 (6)	7 (26)	1.97 (0.75, 5.21)	29 (6)	10 (34)	1.16 (0.50, 2.71)
Quit smoking before visit 1	281 (29)	61 (22)	0.84 (0.56, 1.24)	164 (33)	26 (16)	0.91 (0.48, 1.71)	117 (24)	35 (30)	0.81 (0.48, 1.35)
Never smoker	431 (44)	101 (23)	Ref.	204 (42)	30 (15)	Ref.	227 (47)	71 (31)	Ref.
Other pattern (e.g., relapsed smoker, initiator)	89 (9)	14 (16)	0.57 (0.30, 1.08)	44 (9)	3 (7)	0.41 (0.12, 1.43)	45 (9)	11 (24)	0.65 (0.30, 1.39)
The p value for interaction with race: 0.16									

Abbreviations: ARIC = Atherosclerosis Risk in Communities; CI = confidence interval; OR = odds ratio; Ref. = reference; WMH = white matter hyperintensity.

WMH progression defined as a difference in Cardiovascular Health Study score of ≥ 2 points across scans.

^a Adjusted for age, sex, race/center, and education.

characteristics in tables 2 and 3. The prevalence of current smoking declined with time. Black and white participants showed similar distributions of smoking status and smoking history, with black participants slightly less likely to be ever smokers. Nonetheless, black participants had fewer pack-years of smoking than white participants among both current and former smokers. Conversely, black former smokers typically quit smoking more recently than white former smokers.

Smoking status and smoking history. Overall, current smoking at visit 1, but not former smoking, was associated with increased risk of WMH progression relative to never smoking (table 2). Analyses of visit 2 and visit 3 smoking status showed a similar pattern, although estimates with current smoking were not statistically significant. Risk of WMH progression was elevated among always smokers or recent quitters, but the confidence intervals for all estimates included the null. Likelihood ratio tests provided statistical support for a difference in the association between smoking and WMH by race for smoking status at visit 2, but not for smoking status at visit 1 or 3, or for pattern of smoking history. In stratified analyses, current smoking at each visit and always smoking across all visits was strongly associated with WMH progression in white but not black participants (table 2).

Years since quitting, age at start of smoking, and pack-years of smoking. We were able to calculate pack-years of smoking at the time of the initial MRI for 87% of ever smokers. Consideration of the shape of the dose-response curve for pack-years using penalized

splines illustrates that the association between WMH progression and pack-years of smoking appeared log-linear for former smokers (figure, B), but not for current smokers (figure, A). Before approximately 50 pack-years of smoking, increased pack-years appears linearly associated with increased risk of WMH among current smokers, while risk diminished with pack-years beyond this point; however, these estimates at >50 pack-years were based on relatively few participants, disallowing strong conclusions. Therefore, we used a linear spline with a single knot at 50 pack-years of smoking to allow estimation of effect sizes for models considering ever or current smokers, and report associations only within the range of 0 to 50 pack-years. Among ever smokers, increasing pack-years of smoking within the range of 0 to 50 pack-years was associated with increased risk of WMH progression; separate analyses among current or former smokers also suggested increased risk with higher pack-years (table 3). We found no support for effect modification by race, and stratified analyses were similar by race. We found no association between age at smoking initiation and WMH progression among the 88% of ever smokers for whom we were able to calculate this measure (table 3). There was little statistical support for effect modification; however, in stratified analyses, results were similar among white participants, but suggestive of increased risk with older age at initiation in black participants. There was no association between years since quitting and WMH progression among the 99% of former smokers at the time of the initial MRI for whom we

Figure Adjusted log-odds of white matter hyperintensity progression and pack-years of smoking, parameterized using penalized splines

Adjusted log-odds of white matter hyperintensity progression across the range of pack-years of smoking among current (A), former (B), and ever (C) smokers at the time of the initial MRI. Rug plots demonstrate the distribution of pack-years of smoking in the sample. The log-odds at each value of pack-years of smoking are denoted by a solid black line, with gray shading indicating the 95% confidence intervals for the estimated log-odds. The association for a given difference in pack-years (e.g., 20–30) is derived through comparison of the log-odds at each of these 2 points. A straight line indicates that the association (here, the odds ratio) for a given absolute difference in pack-years is the same regardless of the actual values chosen as the starting point. A curved line suggests that that magnitude and potentially also direction of the association for a given difference in pack-years varies depending on the starting pack-years value.

Table 3 Association between white matter hyperintensity progression and a 10-unit increase in years since quitting, age at start of smoking, and pack-years of smoking

	Total			White participants			Black participants		
	n cases/n total	Median (25th, 75th percentile)	Adjusted OR ^a (95% CI) per 10-unit increase	n cases/n total	Median (25th, 75th percentile)	Adjusted OR ^a (95% CI) per 10-unit increase	n cases/n total	Median (25th, 75th percentile)	Adjusted OR ^a (95% CI) per 10-unit increase
Years since quitting	83/400	13 (6, 26)	0.90 (0.73, 1.11)	33/222	16 (6, 26)	0.81 (0.59, 1.13)	50/178	12 (6, 25)	0.98 (0.74, 1.31)
				The p value for interaction with race: 0.31					
Age at start of smoking	115/476	18 (16, 21)	1.18 (0.89, 1.55)	48/256	20 (16, 20)	0.85 (0.51, 1.40)	67/220	21 (17, 22)	1.41 (0.99, 2.02)
				The p value for interaction with race: 0.19					
Pack-years of smoking, ever smokers^b	106/473	18 (6, 34)	1.21 (1.04, 1.41)	48/269	22 (9, 38)	1.22 (0.99, 1.51)	58/204	13 (5, 28)	1.21 (0.96, 1.52)
				The p value for interaction with race: 0.48					
Pack-years of smoking, current smokers^b	34/128	29 (18, 42)	1.25 (0.89, 1.76)	15/60	36 (26, 45)	1.76 (0.93, 3.35)	19/68	22 (10, 32)	1.19 (0.75, 1.88) ^c
				The p value for interaction with race: NR ^d					
Pack-years of smoking, former smokers	72/345	14 (4, 29)	1.08 (0.96, 1.22)	33/209	17 (5, 31)	1.07 (0.93, 1.24)	39/136	9 (3, 23)	1.08 (0.87, 1.35)
				The p value for interaction with race: 0.81					

Abbreviations: CI = confidence interval; NR = not reported; OR = odds ratio.

^a Adjusted for age, sex, race/center, and education.^b Within the range of 0 to 50 pack-years of smoking.^c Estimated after excluding n = 4 participants with >50 pack-years, as opposed to the linear spline analyses used for analyses in the total sample or white participants.^d Quasi-separation of data points precluded stable estimation of the p value for interaction.

were able to calculate years since quitting. Race-stratified analyses of years since quitting were similarly null, and we found no support for effect modification by race.

Sensitivity analyses. Estimates were materially unchanged in analyses considering our alternate WMH progression definition or that excluded persons with large improvements in WMH score (data not shown). Additional adjustment for other predictors of WMH progression, including hypertension, diabetes, prevalent CHD, and BMI, and use of IPAWs to account for potential bias due to dependent censoring likewise had little impact on estimates or conclusions (table e-3).

DISCUSSION Our analyses are consistent with both our own and other published reports suggesting an adverse effect of smoking on WMH progression. Our prior study in ARIC noted suggestive, but not statistically significant, positive associations between ever vs never and current vs former/never smokers at baseline and ≥ 1 increase in WMH score in race-combined analyses.¹³ In the CHS¹⁴ and the Rotterdam Scan Study,¹⁵ whose participants are primarily white and older than 65 years, baseline current cigarette smoking was associated with WMH progression. In the Framingham Offspring Study, whose participants were also primarily white, midlife smoking behavior was associated with extensive change in WMH volume, equivalent to approximately a 1-grade difference on the CHS scale, but was not associated with WMH change when characterized as a continuous variable.¹⁶ Our study adds to this literature by demonstrating a dose-response relationship between pack-years of smoking and WMH progression. Of note, age at start of smoking was not associated with WMH progression, and if anything, suggested later age at onset was associated with increased risk. Therefore, it is unlikely that earlier start of smoking accounts for the association with pack-years. Apparent diminishing risk with increasing pack-years among current smokers with >50 pack-years is surprising, and may reflect a “healthy survivor effect”²⁸ or chance. We did not see evidence of reduced risk with increased time since quitting. Recent prior smoking may adversely affect future WMH progression, but our study may be underpowered to detect such an association given the relatively few former smokers who quit recently in our data. In support of this hypothesis, the 6% of participants who quit between visits 1 and 3 were more likely, although not significantly so, to exhibit WMH progression compared with never smokers.

In contrast to prior findings in ARIC of stronger cross-sectional associations between smoking and

increased WMH severity in black compared with white participants,⁹ we found statistical evidence to support a difference in the association by race only for smoking status at visit 2. Here, the pattern was reversed, with an association in white participants, but not black participants. In stratified analyses, similar patterns were observed for smoking status at visits 1 and 3 and for smoking history, although we lack the statistical support to conclude that these associations truly differ by race. There was no evidence to support effect modification by race for pack-years, age at initiation, or time since quitting smoking. (While we discuss differences by race, note the alternate interpretation as differences by geography, given their close link in our sample.) The suggestion of a lack of association with smoking status in black participants at visit 2 may be attributable to chance. Alternatively, it may reflect differences in smoking behavior. For example, we observed lower smoking intensity in black participants. Unmeasured characteristics (e.g., use of menthol cigarettes) may also contribute. Although it cannot be completely discounted, we found little support for the theory that these findings are attributable to differential survival and/or participation of black vs white smokers. There was no suggestion of similar differences in associations by race with pack-years, age at start of smoking, and years since quitting, and effect estimates were similar in sensitivity analyses designed to address this possibility. Similarly, while it is possible that the high prevalence of hypertension, which is strongly associated with WMH progression in black participants in ARIC,²⁰ masks any additional impact of smoking, analyses adjusting for hypertension and health factors were similar to primary analyses.

Strengths of this study include the longitudinal design, biracial sample, and data on smoking behavior beyond smoking status. However, our study has limitations. We cannot discount the possibility that the associations we observed are attributable to chance or unmeasured confounding. We were unable to assess the impact of combined smoking characteristics (e.g., pack-years by time since quitting) given the relatively small sample size of current and former smokers. Similarly, we lack data on other smoking characteristics of interest (e.g., use of menthol cigarettes). Those who underwent MRI were slightly healthier than those who did not participate and our racial groups are intractably confounded by geography, which may limit generalizability of our findings. Finally, our use of the CHS scale may be viewed as a limitation, for example, because it does not provide information on location of WMH; however, a change in CHS grade of 2 or more arguably represents true progression, and WMH progression is associated with increased risk

of clinical outcomes, including stroke and cognitive impairment.^{12,29}

Within the context of a broader literature with similar findings, our report of a dose-dependent association between pack-years of smoking and WMH progression supports the hypothesis of a causal effect of smoking on WMH progression. Therefore, it is plausible that effects of smoking on cognition, dementia, and stroke are mediated by effects on small vessel disease.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception or design of the work (Gottesman, Power) or the analysis and interpretation of the data (Deal, Gottesman, Jack, Knopman, Mosley, Power, Sharrett). Dr. Power drafted the work, and all other authors revised it critically for important intellectual content. All authors gave final approval to the version to be published and take responsibility for the conduct of the research. Dr. Melinda C. Power had access to the data and takes responsibility for the data, accuracy of the data analysis, and conduct of the research.

ACKNOWLEDGMENT

The authors thank the staff and participants of the ARIC Study for their important contributions.

STUDY FUNDING

The Atherosclerosis Risk in Communities Study is conducted as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). This work was also supported by grant R01-HL70825. Melinda C. Power is supported by NIA (T32 AG027668). The study funders and sponsors had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript.

DISCLOSURE

M. Power is supported by NIH T32 AG027668 and reports no disclosures. J. Deal and A. Richey Sharrett report no disclosures relevant to the manuscript. C. Jack, Jr., has provided consulting services for Janssen Research & Development LLC, serves on scientific advisory boards for Janssen AI and Eli Lilly & Company, and receives research support from the NIH/NIA (R01-AG011378, U01-HL096917, U01-AG024904, R01 AG041851, R01 AG37551, R01AG043392, U01-AG06786) and the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Foundation. D. Knopman serves as Deputy Editor for *Neurology*[®]; served on a Data Safety Monitoring Board for Lilly Pharmaceuticals; will serve on a Data Safety Monitoring Board for Lundbeck Pharmaceuticals and for the DIAN study; served as a consultant to TauRx Pharmaceuticals, is an investigator in clinical trials sponsored by TauRx Pharmaceuticals; and receives research support from the NIH. T. Mosley and R. Gottesman report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received June 2, 2014. Accepted in final form November 4, 2014.

REFERENCES

1. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 2013;12:822–838.
2. Schmidt R, Scheltens P, Erkinjuntti T, et al. White matter lesion progression: a surrogate endpoint for trials in cerebral small-vessel disease. *Neurology* 2004;63:139–144.
3. Zeevi N, Pachter J, McCullough LD, Wolfson L, Kuchel GA. The blood-brain barrier: geriatric relevance

of a critical brain-body interface. *J Am Geriatr Soc* 2010; 58:1749–1757.

4. Bots ML, Breteler MMB, Hofman A, et al. Cerebral white matter lesions and atherosclerosis in the Rotterdam Study. *Lancet* 1993;341:1232–1237.
5. van Swieten JC, Kappelle LJ, Algra A, van Latum JC, Koudstaal PJ, van Gijn J. Hypodensity of the cerebral white matter in patients with transient ischemic attack or minor stroke: influence on the rate of subsequent stroke. Dutch TIA Trial Study Group. *Ann Neurol* 1992;32:177–183.
6. Murray AD, Staff RT, Shenkin SD, Deary IJ, Starr JM, Whalley LJ. Brain white matter hyperintensities: relative importance of vascular risk factors in nondemented elderly people. *Radiology* 2005;237:251–257.
7. Jeerakathil T, Wolf PA, Beiser A, et al. Stroke risk profile predicts white matter hyperintensity volume: the Framingham Study. *Stroke* 2004;35:1857–1861.
8. Longstreth WT, Manolio TA, Arnold A, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people: the Cardiovascular Health Study. *Stroke* 1996;27:1274–1282.
9. Liao D, Cooper L, Cai J, et al. The prevalence and severity of white matter lesions, their relationship with age, ethnicity, gender, and cardiovascular disease risk factors: the ARIC Study. *Neuroepidemiology* 1997;16:149–162.
10. Fukuda H, Kitani M. Cigarette smoking is correlated with the periventricular hyperintensity grade on brain magnetic resonance imaging. *Stroke* 1996;27:645–649.
11. Kim S, Yun CH, Lee SY, Choi KH, Kim M, Park HK. Age-dependent association between cigarette smoking on white matter hyperintensities. *Neurol Sci* 2012;33:45–51.
12. Silbert LC, Howieson DB, Dodge H, Kaye JA. Cognitive impairment risk: white matter hyperintensity progression matters. *Neurology* 2009;73:120–125.
13. Knopman DS, Penman AD, Catellier DJ, et al. Vascular risk factors and longitudinal changes on brain MRI: the ARIC Study. *Neurology* 2011;76:1879–1885.
14. Longstreth WT, Arnold AM, Beauchamp NJ, et al. Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke* 2005;36:56–61.
15. van Dijk EJ, Prins ND, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MMB. Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam Scan Study. *Stroke* 2008;39:2712–2719.
16. Debette S, Seshadri S, Beiser A, et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology* 2011;77:461–468.
17. Andoh J, Verhulst S, Ganesh M, Hopkins-Price P, Edson B, Sood A. Sex- and race-related differences among smokers using a national helpline are not explained by socioeconomic status. *J Natl Med Assoc* 2008;100:200–207.
18. Kiefe CI, Williams OD, Lewis CE, Allison JJ, Sekar P, Wagenknecht LE. Ten-year changes in smoking among young adults: are racial differences explained by socioeconomic factors in the CARDIA Study? *Am J Public Health* 2001;91:213–218.
19. Mosley TH Jr, Knopman DS, Catellier DJ, et al. Cerebral MRI findings and cognitive functioning: the Atherosclerosis Risk in Communities Study. *Neurology* 2005;64:2056–2062.
20. Gottesman RF, Coresh J, Catellier DJ, et al. Blood pressure and white-matter disease progression in a biethnic cohort: Atherosclerosis Risk in Communities (ARIC) Study. *Stroke* 2010;41:3–8.
21. Manolio TA, Kronmal RA, Burke GL, et al. Magnetic resonance abnormalities and cardiovascular disease in older adults: the Cardiovascular Health Study. *Stroke* 1994;25:318–327.
22. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;30:377–399.
23. Hernan MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology* 2000;11:561–570.
24. Power MC, Tchetgen EJ, Sparrow D, Schwartz J, Weisskopf MG. Blood pressure and cognition: factors that may account for their inconsistent association. *Epidemiology* 2013;24:886–893.
25. Weuve J, Tchetgen Tchetgen EJ, Glymour MM, et al. Accounting for bias due to selective attrition: the example of smoking and cognitive decline. *Epidemiology* 2012;23:119–128.
26. Tchetgen Tchetgen EJ, Glymour MM, Shpitser I, Weuve J. To weight or not to weight? On the relation between inverse-probability weighting and stratification for truncation by death. *Epidemiology* 2012;23:132–137.
27. Chaix B, Evans D, Merlo J, Suzuki E. Weighting up the dead and missing: reflections on inverse-probability weighting and principle stratification to address truncation by death. *Epidemiology* 2012;23:129–131.
28. Shah D. Healthy worker effect phenomenon. *Indian J Occup Environ Med* 2009;13:77–79.
29. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ* 2010;341:c3666.