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Relationship of Cigarette Smoking and Time of Quitting with Incident Dementia and Cognitive Decline

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Abstract

Importance: Understanding how dementia risk is impacted by timing of smoking cessation has public health implications for prevention efforts.

Objective: Investigate the relationship of cigarette smoking and cessation with dementia risk and cognitive decline in the Atherosclerosis Risk in Communities (ARIC) Study.

Design and Setting: Begun in 1987–1989, ARIC is an ongoing prospective cohort study conducted in 4 US communities.

Participants: 13002 men and women (25% African American) aged 52–75 years.

Main Outcome and Measures: All-cause dementia was defined using standardized algorithms incorporating longitudinal cognitive data, proxy report and hospital and death certificate dementia

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Author Contributions:

All authors gave final approval of the manuscript.

JAD: Designed and conceptualized study; analyzed the data; drafted the manuscript for intellectual content

MCP: Conceptualized the study; Interpreted the data; revised the manuscript for intellectual content

PP: Interpreted the data; Revised the manuscript for intellectual content

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codes. Cognitive decline was measured using a composite cognitive score created from 3 tests measured at 2 time points (1996–1998 and 2011–2013). Smoking and cessation status were defined by self-report using data from 1987–1989 (visit 1) and 1996–1998 (visit 4). Incident dementia risk and differences in cognitive change by smoking status were estimated with Cox proportional hazards and linear regression models, respectively. To address smoking-related attrition, cognitive scores were imputed for living participants with incomplete cognitive testing.

Results: The proportion of never, former and current smokers was 44%, 41% and 14%; 79% of former smokers quit 9 years prior to baseline. A total of 1347 participants developed dementia. After adjustment, compared to never smoking, the hazard ratio for all-cause dementia for current smoking was 1.33 (95% CI: 1.12, 1.59), and for recent quitting (<9 years prior to baseline) was 1.24 (95% CI: 1.01, 1.52). Quitting 9 years prior to baseline was not associated with dementia. We found no differences in rates of cognitive decline by smoking status.

Conclusions and Relevance: Although quitting at any time suggested benefit, dementia risk depended on time since smoking cessation. Our study highlights the importance of early midlife cessation to decrease dementia risk.

Keywords

smoking; cessation; cognitive decline; dementia

Cigarette smoking, even in low doses,¹ increases risk for vascular disease² and stroke,^{3,4} providing a strong biological rationale for a relationship between smoking and dementia and cognitive decline. Current smoking is a modifiable cause of dementia^{5,6} and cognitive decline,^{7,8} although studies of the impact of smoking cessation, particularly timing of cessation, on dementia risk are lacking.^{9,10} Observational data supporting an association with current smoking and dementia is generally consistent,⁵ however evidence for an association between current smoking and cognitive decline is less so.^{11,12} In many studies, the extent of the contribution of smoking to dementia and cognitive decline may be underestimated given methodological limitations, including selective loss of susceptible smokers due to death or dropout from a study over time,^{10,13,14} particularly if participants are required to attend clinic visits during follow-up in order to have cognition measured.

We used data from the Atherosclerosis Risk in Communities (ARIC) Study, a large, prospective cohort, to estimate the association of midlife cigarette smoking status and time since smoking cessation on subsequent 12-year risk for dementia and cognitive decline using methods to address informative attrition.

METHODS

Study population

ARIC is a population-based study of 15792 predominantly white or black adults aged 45–64 years in 1987–89 randomly sampled from 4 US communities: Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi (all black participants); and suburbs of Minneapolis, Minnesota.¹⁵ Informed consent was obtained from all participants

at each visit. Study procedures were approved by the Institutional Review Board for each field center.

ARIC participants were seen for 4 clinic visits ~3 years apart from 1987–89 to 1996–98, with a 15-year gap between visits 4 (1996–98) and 5 (2011–13). Given this design, baseline for this study was defined as visit 4 (1996–98) in order to capture smoking patterns in midlife. For both the smoking-dementia and the smoking-cognitive decline analyses, participants were excluded if race was other than black or white (N=48), or if non-white from Minneapolis or Washington County field sites (N=55).

For the smoking-dementia analysis, participants were excluded if they had a dementia diagnosis (N=213) or censor date (N=2422) on or before the time origin for the study, or were missing smoking status (N=52), yielding an analytic sample of 13002.

For the smoking-cognitive decline analysis, participants with incomplete cognitive data at the first ARIC testing occasion (visit 2, N=2429) were excluded in order to aid in the imputation of missing cognitive scores at later visits. Participants were also excluded if they were missing cognitive test scores at both visit 4 (1996–98) and 5 (2011–13) (N=1923), as were participants missing education (N=15), resulting in an analytic sample of 11322.

Dementia diagnosis

Dementia was ascertained for all participants including those who died or were lost to follow-up.^{16,17} For participants who attended visit 5 (2011–13), diagnosis used standardized algorithms incorporating longitudinal cognitive data and a neuropsychological battery administered at that visit, with algorithmic diagnoses confirmed by expert panel review. Diagnoses for participants who did not attend visit 5 were based on a Modified Telephone Interview for Cognitive Status-Modified (TICS) interview with the participant, on modified Clinical Dementia Rating (CDR) interviews with informants, or on hospital or death certificate dementia codes alone.^{16,17} Active surveillance for dementia was through Sept 1, 2013. For diagnoses ascertained by codes, the date of dementia onset was set 6 months prior to death or hospitalization.

Cognitive decline

Three cognitive tests were administered in 1996–98 (visit 4) and 2011–13 (visit 5): **Delayed Word Recall** (memory), **Word Fluency** (language) and the **Digit Symbol Substitution** (executive function/attention). Scores at each testing occasion were standardized as z-scores and then scaled to the mean and SD on first testing (1996–98). The primary measure for inference was a more reliable **Composite Cognitive Score** at each visit, which was created by averaging the three test-specific z-scores at that visit, and scaling to the SD of the composite score in 1996–98.^{18,19} Secondary analyses modeled cognitive change for each individual cognitive test. Cognitive change from visits 4–5 was calculated by subtracting the z-score at visit 4 from that at visit 5.

Cigarette smoking

Self-reported cigarette smoking status was obtained at each visit (never, former, current) and during annual follow-up telephone calls (“Do you now smoke cigarettes?”) beginning in 1998. For the primary analysis, we defined smoking status using data from visit 4 (1996–98), or for those participants who did not attend visit 4, from an annual phone call within 6 months of the mean visit 4 date (N=857). Using smoking data from visit 1 (1987–89), former smokers at visit 4 were categorized as having quit 9 years earlier if they also reported former smoking at visit 1, because 9 years was the average difference between visits 1 and 4 (Figure 1). Former smokers at visit 4 who were current smokers at visit 1 were categorized as having quit more recently (<9 years prior to baseline).

Additional covariates

Demographic information was collected at visit 1 (1987–89), including age, sex, race and education (<high school, high school or equivalent, or >high school). Covariates measured at baseline (1996–98) included body mass index (kg/m²); pre-hypertension, defined in persons not taking antihypertensive medication as diastolic blood pressure (DBP) 80–89 mmHg or systolic blood pressure (SBP) 120–139 mmHg; hypertension, defined as DBP ≥90 mmHg, SBP ≥140 mmHg, or antihypertensive medication use; diabetes defined as fasting blood glucose level ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, self-reported physician-diagnosed diabetes, or use of diabetes medication; and prevalent stroke, defined as self-reported history of stroke diagnosed by a physician at visit 1 and adjudicated stroke through visit 4. Chronic obstructive pulmonary disease (COPD) was defined as self-reported physician-diagnosed bronchitis or emphysema. Self-reported health compared to other persons of the same age (excellent, good, fair, or poor) was collected at each annual follow-up call beginning in 1989.

Statistical analysis

Baseline covariate distributions by smoking status were compared using the Pearson chi-square test for categorical values and the Kruskal-Wallis test for continuous variables.

Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals of incident dementia by smoking status; ties were handled using the Efron method. The proportional hazards assumption was verified by assessing correlation between scaled Schoenfeld residuals and transformed survival times.²⁰ Because poor health related to smoking may influence quitting but may also be related to subsequent dementia risk, the time origin for the dementia analysis was defined as 5 years post-baseline. The timing of this lag was varied in sensitivity analyses (1 year, N=13984; 8 years, N=12118; and 10 years, N=11416). Analyses were adjusted for age (linear and quadratic terms), sex, education, a combination variable of race and study site, BMI, diabetes and hypertension. Adjustment factors were chosen a priori based on known relationships with both exposure and outcome. Because BMI, diabetes hypertension could possibly result from smoking, and therefore mediate the association between smoking and dementia/cognitive decline, models that adjust only for demographic variables are also presented. To account for smoking cessation that may be related to poor health due to smoking, we additionally adjusted for a composite variable of COPD, CHD, or ever self-reporting poor or fair health prior to

baseline, and alternatively, we restricted the analysis to participants with self-reported good or excellent health, no CHD and no COPD. We also explored for potential smoking and sex, and smoking and race interactions, by including interaction terms in the models.

Missing covariate data were imputed using multiple imputation using chained equations (MICE) with 10 sets of imputations.²¹ The imputation model included all covariates in the final, fully-adjusted model, as well as apolipoprotein ε4 genotype, cognitive function and history of stroke.

Two sensitivity analyses were conducted. To address possible bias in ascertaining cases using only hospital codes, we censored individuals after a hospitalization for comorbidities related to cigarette smoking, including cerebrovascular (ICD-9 430–438) or ischemic heart disease (410–414). Also, because current smokers had lower cognitive scores at baseline, they may have been more likely than non-smokers to be diagnosed with dementia assessed at a single point in time (the hospital visit) if that assessment did not include accurate knowledge of prior cognitive performance. To address this possible diagnostic bias, we adjusted for midlife cognitive test scores (visit 2, 1990–92).

Given the strong association of current smoking with mortality, and to aid in the interpretation of the estimated cause-specific hazards of the relationship between smoking and dementia, we conducted a secondary competing risks analysis of smoking and non-dementia deaths using Cox proportional hazards models, treating dementia prior to death as a censoring event.²²

Linear regression was used to model the association between smoking status and cognitive change from 1996–98 to 2011–13. Analyses were adjusted for age (linear and quadratic terms), sex, education, a combination variable of race and study site, BMI, history of stroke, diabetes, hypertension and COPD.

Because attrition was strongly related both to smoking status and to cognitive performance, to address potential selection bias for the smoking-cognitive decline analysis, we used MICE to impute missing covariate and cognitive scores. Cognitive scores were imputed at the median follow-up time for participants who were alive at the time of the visit, but did not complete cognitive testing. MICE models included all covariates in the fully-adjusted final model, as well as apolipoprotein ε4 genotype, the TICS,²³ suspect dementia status,²¹ and CDR²⁴. This method has been described and validated in this cohort.²¹

Analyses were conducted in Stata 15 (StataCorp. 2013. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LP).

RESULTS

Compared to participants included in the analysis, excluded participants were older (66 vs. 63 years); more likely to be black (34% vs. 25%), male (54% vs. 43%), an ever smoker (61% vs. 56%) and to die during follow-up (86% vs. 20%); and more likely to have less than a high school education (36% vs. 21%), diabetes (58% vs. 19%), hypertension (83% vs. 51%), and chronic obstructive pulmonary disease (28% vs. 9%) (Supplementary Table S1).

Of 13002 participants, 5784 (44%), 5346 (41%) and 1872 (14%) were never, former and current cigarette smokers at baseline (visit 4), respectively (Table 1). 70% of never smokers were female compared to 46% of ever smokers. Most former smokers (79%) quit 9 years prior to baseline. Current smokers and former smokers who quit recently (<9 years prior to baseline) were more likely to have less than a high school education (30% and 26%, respectively, vs. 19% for never smokers) and to have COPD (15% and 14% respectively, vs. 6% for never smokers). Consistent with the hypothesis that health concerns may be associated with cessation, compared to participants who recently quit (<9 years prior to baseline), a somewhat lower proportion of current smokers had hypertension (50% vs. 52%) and diabetes (17% vs. 23%); current smokers also had a lower BMI (27 ± 5 vs 29 ± 6 kg/m²). 20% of participants died during follow-up; current smokers (32%) and former smokers who quit recently (29%) were more likely to die than participants who were never smokers (15%) or who quit 9 years prior to baseline (20%) (Table 1).

1347 (10%) participants developed dementia during follow-up (Table 2, Model 3). After full adjustment, recent quitting and current smoking were both associated with increased risk of all-cause dementia. In models using imputed covariate data, the hazard ratio (HR) comparing recent quitting to never smoking was 1.24 [95% Confidence Interval (CI): 1.01, 1.52] and comparing current to never smokers was 1.33 (95% CI: 1.12, 1.59) (Table 2, Model 3, Figure 2). In analyses restricted to participants with complete covariate data (Model 2), estimates were similar in magnitude. To account for smoking cessation related to poor health due to smoking, we adjusted for COPD, CHD and self-reported health. Estimates in these models were attenuated slightly (Model 4). When the analysis was restricted to participants without CHD and COPD who self-reported good or excellent health (Model 5), compared to never smokers, participants who quit recently had 1.34 times the hazard of developing dementia (95% CI: 0.91, 1.99) and current smokers had 1.40 times the hazard (95% CI: 1.02, 1.92) of developing dementia. Estimates were similar when the time of the lag between smoking status and start of dementia follow-up was varied (Supplementary Table S2). Interaction terms for race and sex were not statistically significant.

In a sensitivity analysis that censored participants following a hospitalization for cerebrovascular or ischemic heart disease, the HR for incident dementia associated with recent quitting was 1.51 (95% CI: 1.05, 2.16) and with current smoking, 1.27 (95% CI: 0.92, 1.75) (Table 2, Model 6). When models were adjusted for midlife cognition (1990–92), the relationship between recent quitting (vs. never smoking) and current smoking (vs. never smoking) was 1.23 (95% CI: 1.00, 1.51) and 1.27 (95% CI: 1.07, 1.52), respectively (Table 2, Model 7).

17% (N=2266) of participants died during follow-up. In the competing risks analysis, compared to never smoking, the HR for mortality for quitting 9 years prior to baseline was 1.18 (95% CI: 1.06, 1.33), for more recent quitting was 1.96 (95% CI: 1.72, 2.24), and for current smoking was 2.61 (95% CI: 2.35, 2.93) (Supplementary Table S3, Model 2).

In analyses restricted to participants with complete data (N=5434), rates of 15-year global cognitive decline did not differ by smoking status (Table 3, Available case). Estimated

absolute rates of change were greater in models accounting for informatively missing cognitive data (N=11322) in all exposure groups, but differences between groups remained small and non-significant (Table 3, Imputation model). Results were similar and also not statistically significant for each cognitive test (Supplementary Table S4).

DISCUSSION

In 13002 men and women (aged 52–75 years, 25% African American), current cigarette smoking and recent cessation (<9 years) were associated with increased risk of all-cause dementia over 12 years in a dose-dependent manner: 33% and 24%, respectively. There was no increased dementia risk in persons who quit ≥9 years prior to when smoking was measured (at a mean age of 54 years). Associations with quitting were robust to adjustment for diagnoses of CHD, COPD and self-reported poor or fair health. We did not find that the smoking-dementia association varied by sex or race but may have been underpowered to detect these associations.

Our findings are consistent with previous studies showing a ~30% increase in all-cause dementia risk in older adults associated with current smoking.^{12,25,26} Meta-analyses of longitudinal studies suggest a stronger association with probable Alzheimer's disease than for other dementias –a 40–80% increase in risk,^{5,12,26} and it has been estimated that 5–14% of Alzheimer's disease worldwide may be attributable to smoking.^{5,27} Current smoking may also be associated with vascular dementia.²⁶ However, findings from individual studies often are not statistically significant,²⁵ and are often based on a small number of clinically diagnosed vascular dementia cases, a condition which is generally underdiagnosed.²⁸ It is a limitation of our study that etiologic diagnoses were not assigned for all dementia cases, and that we cannot stratify by etiologic subtype.

Most studies fail to show a relationship between former smoking and increased dementia risk,^{25,26} and a very limited number of longitudinal studies have investigated the impact of smoking cessation on dementia risk. In 46,140 men aged 60 years or older in the Korean National Health Insurance System - National Health Screening Cohort, nonsmokers and participants who quit four or more years prior to baseline had a 19% and 14% decreased risk of Alzheimer's disease over 8 years, respectively, and a 29% and 32% decreased risk of vascular dementia, respectively.²⁹ In our study, we found that risk depended on time since smoking cessation. When assessed at a mean of 63 years, recent quitters had a 24% increased dementia risk compared to never smokers, but those who had quit ≥9 years prior to baseline had the same risk of dementia as never smokers, although we did find an 18% increase in mortality for that group. Our study adds to the literature by explicitly testing the relationship between time since quitting and incident dementia.

Smoking is related to hypertension, cardiovascular disease, stroke, incidence and progression of cerebrovascular small vessel lesions, including white matter hyperintensities,^{30–32} and possibly increased number of neuritic plaques on autopsy.³³ A recent systematic review also concluded that cigarette smoking is associated with Alzheimer's disease specifically, potentially through increased cerebral oxidative stress.³⁴ Because most of the studies included in that review primarily relied on clinical diagnoses of Alzheimer's disease,

concomitant cerebrovascular pathology could potentially help to explain the association. However, the authors also conducted a study showing that a history of smoking was associated with increased cortical amyloid deposition compared to never smoking in 263 cognitively normal older adults.³⁴

Although interventional studies of smoking cessation on dementia risk are limited,¹⁰ cardiovascular and cerebrovascular risk is known to decrease rapidly with cessation.³⁵ Cessation seems also to be related to diminishing dementia risk over time, which may help to explain the general lack of an association with former smoking in the literature, particularly when smoking history is assessed in late life (i.e., at a greater time since quitting for former smokers). Our study highlights the importance of early midlife cessation to decrease dementia risk.

For participants who attended visit 5 (2011–13), dementia diagnosis incorporated longitudinal cognitive data. However, only 45% of participants attended visit 5 and importantly, death rates differed by smoking status – 32% of current smokers died compared to only 15% of never smokers. Therefore, for participants who did not attend visit 5, auxiliary cognitive information (TICS, CDR) and community-wide hospital and death certificate surveillance were used to ascertain dementia cases. Although the availability of multiple sources of data and the ability to assign dementia diagnoses for all participants - not just those who survived to visit 5 - is a strength of our study, it should be acknowledged that a potential limitation is that the auxiliary cognitive information (TICS, hospital and death certificate codes) is likely an insensitive measure of dementia diagnosis. There may also be a few false-positive hospital codes.¹⁶ Additionally, another possible limitation of our study is that the use of hospitalization codes might overestimate the association between smoking and dementia, simply because smokers are more likely to have the opportunity to be hospitalized,³⁶ and therefore to be diagnosed. Associations were robust to censoring following a hospitalization for ischemic heart disease or cerebrovascular disease, however. Additionally, because current smokers had lower cognitive scores at baseline, they may have been more likely than non-smokers to be diagnosed with dementia at a single (hospital) visit (i.e., a diagnostic bias). However, when we adjusted for midlife cognition (1990–92), although attenuated by ~20%, estimates remained significant. Diagnostic bias could therefore account for a proportion of the risk associated with smoking. Alternatively, smoking-dementia association may be due in part to some cognitive deficits related to smoking already present at study baseline.

To investigate the etiologic association between smoking and dementia, our primary analysis estimated the cause-specific hazard of dementia prior to death by smoking status. However, our estimate cannot be interpreted as the predicted risk of dementia over time, because whether dementia occurs depends both on the risk for dementia as well as for competing events, including death. To aid in the interpretation of our findings, therefore, we conducted a secondary analysis to estimate the cause-specific hazard of death without dementia.²² Associations were stronger than the estimated associations for the dementia analysis, suggesting that that differential survival by smoking status may have had a substantial impact on the time smokers were at-risk for dementia compared to non-smokers.

Contrary to our hypothesis, we found no relationship between smoking and cognitive decline. Cognitive decline is associated with death and dropout, and attrition is also strongly associated with smoking. We therefore expected that available-case analyses would underestimate associations with decline (although not for dementia, as we believe our ascertainment is likely to be nearly complete). When multiple imputation was used to address selection bias due to informative attrition, absolute rates of cognitive decline were greater than in available-case analyses. However, we again found no difference between rates of change by smoking status. MICE imputation strengthened effect estimates of cognitive decline for other exposures in this cohort (e.g., diabetes,¹⁹ retinal signs³⁷), yet did not for smoking in this analysis. One possible explanation of this finding is that smoking is analogous to education. Some factors, such as education, are related to dementia risk, but not with rates of cognitive decline.³⁸ Education is strongly related to pre-morbid cognitive ability; thus, even in the absence of an effect on cognitive decline, persons with lower pre-morbid cognitive ability likely reach the threshold for dementia earlier than those with higher pre-morbid cognitive ability. Given the social and cultural concomitants of smoking, it may also be strongly related to premorbid ability. However, when we adjusted for baseline global cognition, we found little attenuation of the relationship between smoking and dementia. A second explanation for this finding could be that MICE methods were insufficient given the strong association of current smoking with attrition. Current smokers who survived had better cognitive health than smokers who died, so that the imputation, which is necessarily based on living, observed cases, may have underestimated the attrition bias.²¹ This concern may help explain mixed findings in other studies,^{11, 39, 40} and is supported by a study that found rates of cognitive decline to be strengthened using inverse probably of attrition weighting.¹³

This study documented a dose-dependent association between cigarette smoking assessed at a mean age 63 years (range 52 to 75) and greater 12-year risk of incident dementia in a biracial cohort of 13002 men and women from four US communities. Although quitting at any time may be beneficial – risk in recent quitters was reduced by 24% compared to current smokers – quitting early in midlife may be especially beneficial, as the risk in persons who quit at least 9 years earlier did not differ from the risk in never smokers. Although there is consensus that smoking cessation is beneficial for brain health, there is a lack of evidence as to when cessation should occur in order to minimize dementia risk. Our findings support current recommendations for smoking cessation for dementia prevention, and inform clinical practice and public health messaging about the importance of early smoking cessation to reduce dementia risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Study design of the Atherosclerosis Risk in Communities (ARIC) Study, 1987–89 to 2011–13

* N=11,656 participants attended Visit 4. Missing smoking values at visit 4 were completed using self-report smoking status from annual follow-up phone calls

Figure 2. Hazard Ratios and 95% Confidence Intervals (CIs) of Dementia (2001–2013) by Smoking Status (1996–98), Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study, N=13002

Adjusted for age (years), age² (years²), sex, education, race*center interaction, BMI, diabetes, hypertensive status; time-varying covariates measured in 1996–98.

Table 1.

Participant Characteristics by Smoking Status (visit 4, 1996–98), Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study^a

	Total Cohort (N=13002)	Smoking Status				P-value ^b
		Never (N=5784)	Former (N=5898)		Current (N=1872)	
			Quit 9 years ago (N=4235)	Quit < 9 years ago (N=1111)		
Age (years), mean (SD)	63.0 (5.7)	63.1 (5.7)	63.6 (5.7)	62.9 (5.4)	61.7 (5.4)	<0.0001
Black race, N(%)	3304 (25)	1659 (29)	783 (18)	312 (28)	550 (29)	<0.0001
Female, N(%)	7427 (57)	4071 (70)	1697 (40)	622 (56)	1037 (55)	<0.0001
Education, N(%)						
< High school	2773 (21)	1111 (19)	819 (19)	292 (26)	551 (30)	
High school or equivalent	5364 (41)	2440 (42)	1676 (40)	478 (43)	770 (41)	<0.0001
> High school	4847 (37)	2224 (39)	1736 (41)	340 (31)	547 (29)	
BMI (kg/m ²)	28.8 (5.9)	29.2 (5.8)	30.0 (5.3)	29.2 (5.6)	27.0 (5.2)	<0.0001
Diabetes, N(%)	2111 (19)	945 (19)	718 (19)	204 (23)	244 (17)	0.007
Hypertensive Status, N(%)						
Normotensive	5315 (45)	2391 (44)	1719 (44)	431 (44)	774 (49)	
Prehypertension	429 (4)	180 (3)	183 (5)	42 (4)	24 (2)	<0.0001
Hypertension	6085 (51)	2805 (52)	1987 (51)	509 (52)	784 (50)	
COPD, N(%)	928 (9)	294 (6)	303 (8)	123 (14)	208 (15)	<0.0001
1 <i>APOE</i> ε4 allele	3837 (31)	1686 (30)	1216 (30)	355 (33)	580 (32)	0.081
Follow-up Status, N(%)						
Died during follow-up	2644 (20)	878 (15)	855 (20)	320 (29)	591 (32)	
Living, did not attend Visit 5	4492 (35)	2021 (35)	1412 (33)	381 (34)	678 (36)	<0.0001
Attended Visit 5	5866 (45)	2885 (50)	1968 (46)	410 (37)	603 (32)	

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; *APOE*, apolipoprotein^aRestricted to participants with complete covariate data. Analysis includes imputed exposure data: education, N=18; diabetes, N=1892; hypertension, N=1173; *APOE* ε4, N=435^bP-values from Kruskal-Wallis test (continuous variables) or Pearson's chi2 test (categorical variables)

Table 2.

Multivariable-adjusted Hazard Ratios and 95% Confidence Intervals (CIs) of Dementia (2001–2013) by Smoking Status (1996–98), Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study, N=13002

			Smoking Status			
			Never	Former		Current
				Quit 9 years ago	Quit < 9 years ago	
Primary Analysis	MODEL 1	N _{dementia} / N _{total}	501 / 4893	363 / 3564	80 / 857	127 / 1362
		HR (95% CI)	Ref	1.05 (0.91, 1.20)	1.18 (0.93, 1.49)	1.37 (1.12, 1.67)
		P-value	--	0.535	0.183	0.002
		N _{dementia} / N _{total}	501 / 4893	363 / 3564	80 / 857	127 / 1362
		HR (95% CI)	Ref	1.05 (0.91, 1.21)	1.19 (0.94, 1.51)	1.40 (1.15, 1.72)
	MODEL 2	P-value	--	0.486	0.148	0.001
		N _{dementia} / N _{total}	632 / 5784	432 / 4235	112 / 1111	171 / 1872
		HR (95% CI)	Ref	1.01 (0.88, 1.14)	1.24 (1.01, 1.52)	1.33 (1.12, 1.59)
	MODEL 3	P-value	--	0.938	0.037	0.001
		N _{dementia} / N _{total}	632 / 5784	432 / 4235	112 / 1111	171 / 1872
		HR (95% CI)	Ref	0.99 (0.87, 1.13)	1.19 (0.97, 1.46)	1.29 (1.08, 1.54)
	MODEL 4	P-value	--	0.908	0.089	0.005
		N _{dementia} / N _{total}	212 / 2816	167 / 1996	29 / 392	49 / 654
		HR (95% CI)	Ref	1.13 (0.91, 1.39)	1.34 (0.91, 1.99)	1.40 (1.02, 1.92)
	MODEL 5	P-value	--	0.271	0.139	0.039
		N _{dementia} / N _{total}	186 / 3500	124 / 2373	37 / 603	52 / 1126
		HR (95% CI)	Ref	1.06 (0.84, 1.35)	1.51 (1.05, 2.16)	1.27 (0.92, 1.75)
Sensitivity Analyses	MODEL 6 Ascertainment Bias	P-value	--	0.625	0.026	0.143
		N _{dementia} / N _{total}	632 / 5784	432 / 4235	112 / 1111	171 / 1872
		HR (95% CI)	Ref	1.00 (0.88, 1.14)	1.23 (1.00, 1.51)	1.27 (1.07, 1.52)
	MODEL 7 Diagnostic Bias	P-value	--	0.958	0.045	0.008

Model 1, N=10676. Available case (restricted to participants with complete data). Adjusted for demographic factors, including age (years), age² (years²), sex, education, and race*center interaction.

Model 2, N=10676, Available case (restricted to participants with complete data). Adjusted for Model 1 covariates as well as BMI, diabetes, hypertensive status; time-varying covariates measured in 1996–98.

Model 3, N=13002, Imputation model. Adjusted for Model 2 covariates. Model includes imputed covariate data (BMI, N=2196; diabetes, N=1892; hypertension, 24N=1173; and COPD, N=2178).

Model 4, N=13002, Imputation model. Adjusted for Model 2 covariates plus a composite variable of ever reporting fair or poor health prior to visit 4, presence of COPD or CHD at visit 4. Model includes imputed covariate data.

Model 5, N=5858, Imputation model. Restricted to participants with good health (did not ever self-report fair or poor health prior to baseline, did not have COPD or CHD at visit 4). Adjusted for Model 2 covariates. Model includes imputed covariate data.

Model 6, Ascertainment bias, N=7602. Participants censored following a hospitalization with an ischemic heart disease or cerebrovascular disease code. Adjusted for Model 2 covariates. Model includes imputed covariate data.

Model 7, Diagnostic bias, N=13002, Adjusted for Model 2 covariates and for Visit 2 cognition. Model includes imputed covariate data.

Table 3.

Multivariable-adjusted^a Estimates and Differences in Estimates in the 15-Year Rates of Cognitive Change in Global Function (1996–98 to 2011–13) by Smoking Status (1996–98), Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study, N=11322

Smoking Status	AVAILABLE CASE (N=5434)		IMPUTATION MODEL (N=11322)	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Average Rates of Change over Time by Smoking Status Category				
Never (N=5763)	-0.563 (-0.646, -0.480)	<0.0001	-0.704 (-0.815, -0.592)	<0.0001
Former (N=5809)	Quit 9 years ago (N=4356)	<0.0001	-0.699 (-0.802, -0.596)	<0.0001
	Quit < 9 years ago (N=1128)	<0.0001	-0.723 (-0.853, -0.594)	<0.0001
Current (N=1853)	-0.613 (-0.708, -0.520)	<0.0001	-0.746 (-0.867, -0.626)	<0.0001
Difference in Average Rates of Change over Time Compared to Never Smoking				
Difference comparing Former (Quit 9 years ago) to Never	-0.032 (-0.076, 0.011)	0.144	0.005 (-0.040, 0.050)	0.826
Difference comparing Former (Quit < 9 years ago) to Never	-0.015 (-0.091, 0.061)	0.698	-0.020 (-0.106, 0.067)	0.650
Difference comparing Current to Never	-0.050 (-0.117, 0.016)	0.139	-0.043 (-0.129, 0.043)	0.318

Available case, Analysis includes only participants with complete data, N=5434; includes only participants with available covariate data

Imputation model, Analysis with imputed values for missing cognitive outcome and covariate data, N=11322. Imputed covariate data includes BMI, N=1883; history of stroke, N=1869; diabetes, N=1499; hypertension, N=1899; and COPD, N=1830.

ARIC visit 4 and visit 5 global z-scores were imputed for participants with an observed Visit 2 global z-score who were missing a global z-score at visit 4 or 5 (but not at both visits) but who were alive at the start of data collection for the visit.

^aAdjusted for age (years), age² (years²), sex, education, race*center, BMI, history of stroke, diabetes, hypertension, and COPD; all time-varying covariates measured in 1996–98.