ORIGINAL ARTICLE

Smoking Behaviors and Arterial Stiffness Measured by Pulse Wave Velocity in Older Adults: The Atherosclerosis Risk in Communities (ARIC) Study

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BACKGROUND
Though smoking is strongly associated with peripheral vascular disease and arteriosclerosis, smoking's association with arterial stiffness has been inconsistent and mostly limited to a single arterial segment. We examined the relationship between smoking behaviors with arterial stiffness in multiple arterial segments among community dwelling older adults.

METHODS
The cross-sectional relationship between smoking behavior with carotid-femoral (cfPWV) and femoral-ankle pulse wave velocity (faPWV) was examined in 5,002 men and women, separately, of the Atherosclerosis Risk in Communities (ARIC) cohort study. Brachial-ankle PWV was also assessed and presented in Supplementary Material. Heckman selection models were used to control for selective attrition and death in the ARIC cohort.

RESULTS
In women, faPWV was lower in current smokers compared to never smokers (−66.0 cm/s; 95% confidence interval (95% CI): −94.6, −37.4), and was 1.0 cm/s lower (95% CI: −1.8, −0.2) for every additional year a woman smoked, after adjustment for confounders. Among women, cfPWV was not associated with smoking status or cigarette pack-years. Additionally, no associations of smoking status and cigarette pack-years with PWV were observed among men. Years since smoking cessation was not associated with PWV in either gender.

CONCLUSION
Both smoking status and cumulative smoking exposure were associated with lower peripheral arterial stiffness among women, but not among men. We did not observe an association between central arterial stiffness and smoking status in either gender. The profound and well-documented adverse effects of cigarette smoking on the vasculature may not include a sustained stiffening of the arteries measured at older age.

Keywords: arterial stiffness; arteriosclerosis; blood pressure; central and peripheral arterial stiffness; health behavior; hypertension; smoking; smoking cessation; subclinical cardiovascular disease.

doi:10.1093/ajh/hpv189

Cigarette smoking is among the most prominent, preventable causes of cardiovascular disease[1] and smoking cessation is related to reduction in cardiovascular disease risk.[2] Smoking is associated with factors that adversely affect arterial elastic properties, such as systemic and vascular inflammation,[1] endothelial function,[3] tissue uptake of smoke particles,[4] and damage to the extracellular matrix[5] that are putatively related to arterial stiffness. Arterial stiffening is a progressive arteriosclerotic process that occurs during the course of aging and exposure to cardiovascular disease risk factors. Arterial stiffness and associated properties can be measured noninvasively and reproducibly by pulse wave velocity (PWV), with higher values signifying stiffer arteries.

Cigarette smoking causes arteries to become less distensible acutely.[6–11] Reported long-term effects of smoking on arterial stiffness, however, are inconsistent, and whether long-term smoking cessation is associated with a reduction in arterial stiffness has not been well established.[12–14] Also, the effects of intensity and duration of smoking on arterial stiffness are unknown. The findings of the association of smoking behaviors with carotid-femoral PWV (cfPWV), the reference standard measure of aortic stiffness, have been inconsistent.[6,14–18] Previous studies that included brachial-ankle PWV (baPWV), a composite measure of central and peripheral arterial stiffness,[10,13] are difficult to interpret given the structural and hemodynamic differences of the arterial territories subsumed in baPWV.[19,20] The relationship

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Initially submitted August 26, 2015; date of first revision October 12, 2015; accepted for publication November 11, 2015; online publication December 10, 2015.

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between smoking behaviors and femoral-ankle PWV (faPWV), a measure of peripheral arterial stiffness, has not been explored.

The aim of this study was to examine the association of smoking behaviors, including smoking status, intensity, and duration of smoking over the lifetime, and years since smoking cessation with segment specific arterial stiffness measured by cfPWV and faPWV in older adults.

METHODS

Study population

The Atherosclerosis Risk in Communities (ARIC) Study is an ongoing prospective cohort study of cardiovascular disease and atherosclerosis.[21] Recruitment occurred during 1987–1989 and included 15,792 Caucasian and African American participants aged 45–64 years from 4 US communities: Forsyth County, North Carolina; Jackson, Mississippi; Washington County, Maryland; and Minneapolis, Minnesota. Standardized physical examinations and interviewer-administered questionnaires were conducted at baseline. Follow-up examinations occurred approximately 3 years apart until visit 4 (1996–1998). The visit 5 examination was conducted from 2011 to 2013. Participants were asked to fast (no food or drink, with the exception of water) beginning 8 hours prior to their visit and to abstain from tobacco products, vigorous physical activity, and caffeine in the morning of the exam. Participants were followed-up annually through telephone interviews and review of hospitalization and vital status records. Institutional Review Boards at each participating institution approved the study and all participants provided written informed consent at each examination.

Smoking behaviors

Primary exposures included cigarette smoking status at ARIC visit 5, cumulative cigarette pack-years, and years since smoking cessation. Smoking behavior was obtained by interview at each of the 5 study visits and by annual telephone interviews beginning the 11th year from baseline. Participants were categorized into current, former, and never smokers. For ever smokers, age at smoking initiation and cigarettes per day were determined at baseline. Additionally, age when a participant stopped smoking cigarettes was collected for former smokers. To calculate pack-years of smoking, average cigarettes per day were collected at ARIC visits 1–4 and years of cigarette smoking were calculated using age at initiation of smoking subtracted from the participant's age at the visit or as the time between the previous and current visit. At each visit, pack-years were calculated as the average number of reported cigarettes smoked per day multiplied by the years of smoking divided by 20 (the number of cigarettes in a standard pack). The area under the continuous pack-year curve was calculated using the trapezoid rule. Pack-years were classified into 5 categories (<10, 10–19, 20–29, 30–39, and ≥40 pack-years). In the lung cancer and smoking literature, duration of cigarette smoking has a stronger effect on disease outcomes compared to intensity of smoking; therefore, we assessed the association of total number of years smoked and average cigarettes per day of cigarette smoking separately with PWV.[22] Years since smoking cessation were determined for former smokers. Current smokers at baseline with inconsistent smoking status during follow-up were classified as continuous smokers (e.g., former smoker at visit 2 but current smoker at later visits). Participants who reported never smoking and those with missing date of smoking initiation were not included in smoking cessation analyses.

Pulse wave velocity

Technicians measured cfPWV, baPWV, and faPWV following a standardized protocol with the automated waveform analyzer VP-1000 Plus (Omron, Kyoto, Japan) after participants were supine for 5–10 minutes at study visit 5.[23] Carotid and femoral arterial pressure waveforms were acquired for 30 seconds by application tonometry sensors attached on the left common carotid artery (via neck collar) and left common femoral artery (via elastic tape around the hip). Bilateral brachial and posterior-tibial arterial pressure waveforms were detected over 10 seconds by extremity cuffs connected to a plethysmographic and an oscillometric pressure sensor wrapped on both arms and ankles. PWV measures were simultaneously measured twice; the average of the 2 was used for analyses. PWV was calculated as the path length between 2 arterial sites divided by the time delay between the foot of the respective waveforms. Distance for cfPWV was measured with a segmometer (Rosscraft, Surray, Canada), and calculated as the distance between the suprasternal notch to carotid minus the carotid to femoral distance. Distances for baPWV and faPWV were automatically calculated by the VP-1000 Plus using height-based formulas. Repeat visits were conducted for a subset of participants at each field center (n = 79; mean age 75.7 years; 46 females) approximately 4–8 weeks later.[24] The intra-class correlations and 95% confidence intervals (95% CI) were 0.70 (0.59, 0.81) for cfPWV, 0.84 (0.78, 0.90) for baPWV, and 0.69 (0.59, 0.79) for faPWV.

Results for baPWV were presented in Supplementary Material due to the nature of baPWV as a composite measure of PWV.

Covariates

Educational attainment was assessed with questionnaires at the ARIC baseline visit and dichotomized as less or more than high school. At the visit 5 examination, level of physical activity was assessed using the sport index of the Baecke Questionnaire.[25] We calculated minutes per week of moderate to vigorous physical activity and classified participants into gender-specific quartiles. Three sitting blood pressure measurements were taken after a 5-minute rest with an oscillometric automated sphygmomanometer (Omron HEM-907 XL, Schaumburg, IL); the last 2 measurements were averaged. Pulse pressure was calculated as systolic (SBP)–diastolic blood pressure (DBP). Hypertension was defined as SBP ≥ 140, DBP ≥ 90, or antihypertensive medication use at visit 5. Mean arterial

blood pressure was calculated as [2/3(DBP) ± 1/3(SBP)]. Height was measured to the nearest centimeter and body weight to the nearest 0.1 kg. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Blood was drawn after an 8-hour fasting period with both glucose and plasma total cholesterol measured centrally by standard enzymatic methods. Diabetes was defined as a hemoglobin A1c value ≥6.5%, using medication for diabetes, or self-reported diabetes at visit 5. Peripheral artery disease was defined as a hospitalization with one of the following International Classification of Disease, 9th Edition Clinical Modification codes present in the claim: 440.21–440.24, 443.9, 707.10–707.19, 785.4, 84.10–84.19, 84.91, 39.25, 39.29, 38.08, 38.16, 38.18, 38.38, 38.48–38.49, 39.50, 39.56–39.58, and 39.90 or a right or left ankle brachial index value of <0.9. Ankle brachial index was measured concurrently with cfPWV, faPWV, and baPWV and calculated as the average of ankle systolic blood pressure divided by the higher of the left or right arm systolic blood pressure.

Overall, 5,683 ARIC participants with PWV measured at visit 5 were considered for the present study. Because of numbers insufficient for stratified analyses, participants were excluded if they reported ethnicity other than African American or Caucasian. PWV measurements 3 SDs from the mean, participants with a body mass index >40 kg/m^2, a major arrhythmia on the 12-led electrocardiogram (Minnesota code 8-1-2, 8-1-3, 8-3-1, and 8-3-2), self-reported aortic revascularization surgery, abdominal aortic aneurysm (maximal diameter ≥5 cm), aortic stenosis, moderate or greater aortic regurgitation, and missing values of respective PWV or exposure variables (N = 681) were excluded. We also excluded participants with peripheral revascularization when assessing the associations between smoking behaviors and faPWV. Associations were evaluated in 5,002 individuals.

Statistical analysis

Continuous data were expressed as mean ± SD and categorical data as percentages for descriptive characteristics. Multivariable linear regression was used to estimate associations between smoking status, smoking intensity and duration, and years since smoking cessation with PWV. Covariates were assessed for inclusion by directed acyclic graph evaluation and from the literature. Models were stratified by gender (P < 0.1 for interaction) and adjusted for age, body mass index, a quadratic term for body mass index, heart rate, race, hypertension, diabetes, physical activity, peripheral artery disease, and mean arterial blood pressure.

At the time of the visit 5 examination, 33% (n = 5,275) of participants had died and 38% (n = 3,979) of those alive did not attend the examination. Thus, attrition and selection biases are of concern when using ARIC data since healthier participants would have the greatest influence on associations when analyses are restricted to visit 5. We used Heckman selection models to account for this informative missingness.[26,27] The Heckman selection model is a joint model that allows for a 2-stage estimation of the following submodels: the probability of nonattendance at visit 5 due to either death or dropout and the exposure–outcome association accounting for probability of nonattendance. We first examined the association of several sociodemographic, clinical, and social risk factors with nonattendance to identify predictors of both death and dropout. Age, education, race-center, self-rated health, income, and functional status were identified as significant predictors of nonattendance and used to estimate the probability of not attending visit 5. This estimated probability of nonattendance at visit 5 was subsequently included as an explanatory variable for the exposure–outcome association. All results presented are adjusted for selective attrition due to death or dropout. Similar Heckman-type selection models have been used and validated in other epidemiologic studies to account for selection biases.[28]

Estimates are presented as the predicted mean difference in PWV (β) and their associated 95% CI. Statistical analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC) with 2-sided P < 0.05.

RESULTS

Participant characteristics

Current smokers at visit 5 were younger and a higher proportion of African Americans were current smokers compared to never and former smokers (Table 1). Current smokers were more likely to be normal weight and have peripheral artery disease compared to never and former smokers. Current smokers had a higher average of cigarette pack-years and total years smoked compared to former smokers.

Smoking status and pulse wave velocity

In women, compared to never smokers, faPWV was 14.2 cm/s (95% CI: −27.0, −1.4) lower in former smokers and 60.1 cm/s (95% CI: −87.7, −32.5) lower in current smokers (Table 2). Smoking status at visit 5 was not associated with cfPWV in women and there were no associations between smoking status and PWV in men.

Cigarette pack-years and pulse wave velocity

Because there did not appear to be a linear association between cigarette pack-years and PWV, cigarette pack-years were categorized and disjoint indicator terms were used. Linear regression models yielded no association between cigarette pack-years and cfPWV (Table 3). For women, faPWV was lower in former and current smokers who smoked 10 pack-years or greater compared to never smokers. Cigarette pack-years were not associated with PWV in men.

Cigarettes per day, cigarette smoke-years and pulse wave velocity

Average cigarettes smoked per day were not associated with PWV (Supplementary Table 3). However, cigarette smoke-years were associated with lower faPWV in women (Supplementary Table 4). The predicted faPWV was 0.9 cm/s (95% CI: −1.7, −0.1) lower for every additional year a woman smoked. Cigarette smoke-years were not associated with PWV in men.

Table 1. Descriptive characteristics of ARIC participants by gender and smoking status (*N* = 5,002)

	Women				Men			
		Smoking status				Smoking status		
	Overall	Never	Former	Current	Overall	Never	Former	Current
Characteristics	*N* = 2,914	*N* = 1,414	*N* = 1,326	*N* = 174	*N* = 2,088	*N* = 598	*N* = 1,363	*N* = 127
African American (%)	679 (23.3)	345 (24.4)	286 (21.6)	48 (27.6)	349 (16.7)	85 (14.2)	233 (17.1)	31 (24.4)
Body mass index (kg/m^2)								
≤25	880 (30.2)	409 (28.9)	389 (29.3)	82 (47.1)	484 (23.2)	140 (23.4)	298 (21.9)	46 (36.2)
25-<30	1,114 (38.2)	563 (39.8)	498 (37.6)	53 (30.5)	952 (45.6)	295 (49.3)	607 (44.5)	50 (39.4)
≥30	920 (31.6)	442 (31.3)	439 (33.1)	39 (22.4)	652 (31.2)	163 (27.3)	458 (33.6)	31 (24.4)
Less than high school education (%)								
Diabetes mellitus[a] (%)	739 (25.5)	366 (26.0)	337 (25.6)	36 (20.8)	602 (28.9)	148 (24.8)	418 (30.8)	36 (28.4)
Hypertension[b] (%)	2,131 (73.6)	1,047 (74.4)	347 (73.6)	116 (67.8)	1,472 (71.5)	397(67.4)	990 (73.5)	85 (68.6)
Peripheral artery disease[c]	266 (9.1)	100 (7.1)	136 (10.3)	30 (17.2)	212 (10.2)	31 (5.2)	150 (11.0)	31 (24.4)
Age (years)	75.2±5.0	75.7±5.1	74.9±4.9	73.2±4.2	75.7±5.1	75.6±5.1	75.9±5.1	73.9±4.4
Moderate to vigorous physical activity (minutes per week)	152.5 (165.1)	151.04 (164.7)	155.8 (166.3)	139.8 (158.6)	215.3 (193.7)	219.0 (191.2)	218.5 (196.3)	164.3 (170.0)
Systolic blood pressure (mm Hg)	131.2±18.2	131.8±18.4	131.0±18.1	128.4±17.4	128.6±16.8	128.4±16.5	128.6±16.7	129.0±19.3
Diastolic blood pressure (mm Hg)	66.3±10.3	66.2±10.1	66.7±10.5	65.3±9.7	66.5±10.6	67.3±10.6	66.2±10.4	65.3±11.8
Heart rate (bpm)	63.0±10.3	63.2±9.9	62.8±9.8	63.2±8.9	60.5±10.0	59.9±9.7	60.6±10.1	62.3±10.3
Pulse pressure (mm Hg)	64.9±15.0	65.6±15.0	64.4±15.0	63.1±14.1	62.1±13.3	61.1±12.7	62.4±13.4	63.7±14.1
Mean arterial blood pressure[d]	88.0±11.4	88.1±11.4	88.1±11.5	86.3±11.0	87.2±11.4	87.7±11.4	87.0±11.2	86.6±13.1
Total cholesterol (mmol/l)	5.0±1.0	5.0±1.0	5.0±1.1	4.8±0.9	4.3±1.0	4.4±1.1	4.3±1.0	4.4±0.9
HDL cholesterol (mmol/l)	1.5±0.4	1.5±0.3	1.5±0.4	1.5±0.3	1.2±0.3	1.2±0.3	1.2±0.3	1.2±0.3
LDL cholesterol (mmol/l)	2.9±0.9	2.9±0.9	2.8±0.9	2.7±0.7	2.5±0.9	2.6±0.9	2.5±0.8	2.5±0.7
Fasting glucose (mmol/l)	6.1±1.4	6.1±1.4	6.1±1.4	5.8±1.1	6.4±1.6	6.3±1.4	6.5±1.6	6.5±2.2
Triglycerides (mmol/l)	1.4±0.7	1.4±0.7	1.4±0.7	1.4±0.7	1.4±0.8	1.4±0.7	1.4±0.8	1.5±1.0
Average cigarettes per day[e]	14.5±10.1	—	14.2±10.1	17.0±9.7	21.1±11.9	—	21.0±12.0	22.0±11.3
Years smoked cigarettes[e]	27.2±13.4	—	25.9±13.3	37.1±9.9	26.7±13.7	—	25.5±13.3	40.0±10.1
Cigarette pack-years [f]	22.2±15.4	—	20.6±18.5	33.5±20.8	31.0±24.6	—	29.5±23.7	47.3±28.6
Years since smoking cessation[g]	27.2±15.4	—	27.2±15.4	—	31.3±14.4	—	31.3±15.4	—
cfPWV (cm/s)	1,143±300	1,156±306	1,134±290	1104±319	1180±309	1168±301	1186±310	1171±333
baPWV (cm/s)	1,731±317	1,755±315	1,721±318	1612±288	1737±319	1745±303	1737±322	1693±359
faPWV (cm/s)	1,099±180	1,111±176	1,092±182	1044±184	1095±183	1108±172	1092±185	1072±208

Data are percentages or mean ± SD.

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; HDL, high-density lipoprotein; LDL, low-density lipoprotein; cfPWV, carotid-femoral pulse wave velocity; baPWV, brachial-ankle pulse wave velocity; faPWV, femoral-ankle pulse wave velocity.

[a]Diabetes was defined as hemoglobin A1c value ≥6.5%, using medication for diabetes, or self-report diagnosis of diabetes at visit 5.

[b]Hypertension was defined as systolic blood pressure ≥140, diastolic blood pressure ≥90, or on medication for high blood pressure at study visit 5.

[c]Peripheral artery disease was defined as a hospitalization with one of the following International Classification of Disease, 9th Edition Clinical Modification codes: 440.21–440.24, 443.9, 707.10–707.19, 785.4, 84.10–84.19, 84.91, 39.25, 39.29, 38.08, 38.16, 38.18, 38.38, 38.48–38.49, 39.50, 39.56–39.58, and 39.90 or a right or left ankle brachial index value of <0.9.

[d]Mean arterial blood pressure calculated as 2/3(diastolic blood pressure) + 1/3(systolic blood pressure).

[e]Average cigarettes per day and years smoked cigarettes evaluated in current and former smokers.

[f]Pack-years calculated as the product of the average number of cigarettes smoked per day and years smoked, divided by 20.

[g]Years since smoking cessation evaluated in former smokers.

Years since smoking cessation and pulse wave velocity

In addition to covariates and attrition, years since smoking cessation and PWV models were adjusted for total cigarette smoke-years. No associations were detected between years since smoking cessation and PWV (Table 4, Supplementary Table 5).

DISCUSSION

Chronic smoking is inversely associated with peripheral arterial stiffness measured by faPWV in older women, but not in men. Similarly, cigarette pack-years were inversely associated with faPWV in women. When the components of

Table 2. Adjusted regression coefficients and 95% confidence intervals for the associations between smoking status and pulse wave velocity by gender

		cfPWV (cm/s)				faPWV (cm/s)			
Gender	**Smoking status**	***N***	**β**	**(95% CI)**	***P***	***N***	**β**	**(95% CI)**	***P***
Women									
	Never	1,325	ref			1,306	ref		
	Former	1,198	−9.2	−30.2, 11.8	0.4	1,182	−14.2	−27.0, −1.4	0.02
	Current	160	−18.2	−63.0, 26.6	0.4	154	−60.1	−87.7, −32.5	<0.0001
Men									
	Never	540	ref			533	ref		
	Former	1,196	5.7	−22.8, 34.2	0.7	1,180	−1.2	−15.7, 18.0	0.9
	Current	115	−13.4	−70.5, 43.8	0.6	114	−1.2	−32.7, 35.0	0.9

Models adjusted for age, body mass index, quadratic term for body mass index, heart rate, race, hypertension, diabetes status, physical activity, peripheral artery disease, mean arterial blood pressure, and attrition.

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; 95% CI, 95% confidence interval; cfPWV, carotid-femoral pulse wave velocity; faPWV, femoral-ankle pulse wave velocity.

Table 3. Adjusted regression coefficients and 95% confidence intervals for the associations between cigarette pack-years of smoking and pulse wave velocity by gender

	cfPWV (cm/s)				faPWV (cm/s)			
Gender pack-years	***N***	**β**	**(95% CI)**	***P***	***N***	**β**	**(95% CI)**	***P***
Women								
Never smokers	1,325	ref			1,306	ref		
<10	383	−17.6	−47.9, 12.6	0.3	375	−6.4	−24.9, 12.2	0.5
10–19	252	16.6	−16.5, 52.7	0.4	247	−28.6	−50.7, −6.5	0.01
20–29	163	−4.3	−47.6, 39.1	0.8	161	−40.1	−66.6, −13.6	0.01
30–39	143	−47.2	−93.6, −0.9	0.04	139	−19.1	−47.6, −13.6	0.003
≥40	178	−40.3	−83.0, 2.5	0.07	177	−53.9	−80.0, −27.9	<0.0001
Men								
Never smokers	540	ref			533	ref		
<10	236	−18.7	−61.4, 24.0	0.4	234	5.5	−19.9, 30.8	0.7
10–19	252	−18.7	−60.4, 23.0	0.4	251	1.8	−22.9, 26.6	0.9
20–29	186	21.0	−25.3, 67.2	0.4	182	−17.4	−45.1, 10.2	0.2
30–39	165	44.1	−4.4, 92.6	0.07	162	−6.9	−35.8, 22.0	0.6
≥40	312	17.1	−22.7, 56.9	0.4	308	3.6	−20.1, 27.3	0.6

Models adjusted for age, body mass index, quadratic term for body mass index, heart rate, race, hypertension, diabetes status, physical activity, peripheral artery disease, mean arterial blood pressure, and attrition.

Abbreviations: 95% CI, 95% confidence interval; cfPWV, carotid-femoral pulse wave velocity; faPWV, femoral-ankle pulse wave velocity.

pack-years (intensity and duration of smoking) were evaluated separately, cigarette smoke-years, not cigarettes per day, were associated with faPWV in women. When considering an individual's cigarette smoking experience over their lifetime, no associations between years since smoking cessation and PWV measures were observed.

The effect of chronic smoking on endothelial function is detrimental.[29] Reports on the effect of smoking on arterial stiffening in older populations is limited and inconsistent in healthy, young, and middle-aged populations.[30] In younger populations, smokers have higher central stiffness and lower central distensibility compared to nonsmokers,[4,6,11,14–16,31,32] whereas there is support for greater distensibility among those who smoke,[9,33] and others report little difference in aortic stiffness by smoking status,[7,15] consistent with our findings.

Little evidence exists on the association between intensity and duration of cigarette smoking with arterial stiffening. To our knowledge, the present study is the first to assess the association of pack-years of cigarette smoking and peripheral arterial stiffness measured by faPWV. Cigarette pack-years is positively related to carotid stiffness measured by

Table 4. Adjusted regression coefficients and 95% confidence intervals for the association between years since smoking cessation and pulse wave velocity by gender

	cfPWV (cm/s)				faPWV (cm/s)			
Gender	***N***	**β**	**(95% CI)**	***P***	***N***	**β**	**(95% CI)**	***P***
Women	945	0.2	−1.9, 2.3	0.8	931	0.7	−0.6, 2.0	0.3
Men	987	−0.3	−3.0, 2.3	0.8	975	−0.5	−2.1, 1.1	0.5

Models adjusted for age, body mass index, quadratic term for body mass index, heart rate, race, hypertension, diabetes status, physical activity, peripheral artery disease, mean arterial blood pressure, cigarette pack-years of smoking, and attrition.

Abbreviations: 95% CI, 95% confidence interval; cfPWV, carotid-femoral pulse wave velocity; faPWV, femoral-ankle pulse wave velocity.

augmentation and stiffness indices.[34,35] Smoking history quantified by pack-years is not sufficient because effects of smoking cigarettes is modest for the first decade, but substantial after several decades, leading to sharp increases in the effect estimates with age in continuous smokers.[22] Therefore, we assessed the association of smoking duration and smoking intensity with PWV measures separately, i.e., the time exposed to cigarettes regardless of the amount smoked, and the average number of cigarettes consumed per day, to evaluate the drivers of a relationship between cigarette pack-years and PWV. Although there was an association between duration of smoking and PWV, but no association of cigarette pack-years with PWV in women, substantial missingness of average cigarettes per day and years smoked cigarettes data for ARIC participants may have biased estimates. However, women and men with missing data were similar to those who reported cigarettes per day and years smoked (data not shown).

The lack of an association between years since smoking cessation and PWV is consistent with other observations.[12,14] However, never and former smokers had more similar PWV measures compared to never and current smokers, suggesting a possible association. We did not observe a difference in arterial stiffness between never and former smokers, consistent with other studies that have shown improvements in endothelial function following smoking cessation.[14,18,36] These observations, coupled with previous work, are consistent with improvement in endothelial function in the first few months after smoking cessation.[3,37]

We found no relationship between smoking status and cfPWV, although power constraints might have limited our ability to detect small PWV differences between former and never smokers. Given our study size and measurement properties, our study had 80% power to detect a difference of 32 cm/s in cfPWV between never smokers and those who ever smoked. Additionally, attrition of the ARIC cohort is associated with cigarette smoking. For example, 42% of women and 56% of men who identified as current smokers compared to 23% of women and 29% of men who identified as never smokers at ARIC visit 1 were deceased by 2011. Thus, it is plausible that cohort members who attended ARIC visit 5 represent a healthier population that could be more resilient to the effects of cigarette smoking. However, Heckman selection modeling accounts for this informative missingness. A limitation of the Heckman selection model is that it relies on model specification; thus, we may not have controlled for attrition appropriately if relevant predictors were excluded from our model. Lastly, although smoking behavior was assessed repeatedly during the 25–27 years of follow-up predating the PWV measurement at visit 5, the cross-sectional nature of these analyses prevented us from relating temporal changes in smoking behavior to changes in arterial stiffness over time.

Among the documented mechanisms at the tissue level, smoking compromises vessel wall structure and its mechanical properties through activation of matrix metalloproteinases (MMPs).[38] MMPs digest components of the extracellular matrix and basement membrane during development, tissue maintenance and repair, and remodeling. Activation of MMPs has major structural and physiological consequences since dysregulation of the MMP system contributes to a broad spectrum of diseases, including atherosclerosis. Tobacco smoke extract induces damage to the extracellular matrix. Macrophages exposed to tobacco smoke extract experience a sequence of events that culminates in apoptosis of macrophages and the release of small membrane-bound vesicles, specifically MMP-14, that break down collagen and gelatin, degrading the local matrix and thus the hemodynamic properties of the arterial wall.

Chronic smoking also causes sustained activation of the sympathetic nervous system that induces sympathetically mediated vasoconstriction, promoting arterial wall remodeling that more likely affects the peripheral, muscular vasculature.[39] It is remarkable that the association between smoking and peripheral arterial stiffness has attracted little attention, judging by the paucity of published reports, beyond an indication that smoking may not affect peripheral vascular stiffness as measured by the peripheral augmentation index.[40] In contrast, our study suggests that peripheral arteries of women who smoke are more distensible than those of never smokers, suggesting that the effects of smoking on large arteries should be assessed with consideration of specific arterial segments.

Because most research on PWV was conducted in younger populations, we have little basis for the interpretation of our results on smoking cessation and PWV in older adults. It is conceivable that PWV measured in older adults is not sensitive to the functional and structural changes that occur following smoking cessation in middle adulthood. Alternatively, although smoking cessation interrupts the repeated acute effects of cigarette smoking on the vasculature, our results in older adults suggest that damage accrued to the arterial extracellular matrix may not be reversible.

The present study among older adults revealed that women who smoked have lower peripheral arterial stiffness measured by faPWV compared to never smokers. In particular, women who reported higher intensity and duration of smoking, notably if greater than 20 pack-years, have lower faPWV compared to never smokers. The profound and well-documented adverse effects of cigarette smoking on the vasculature may not include a sustained stiffening of the arteries measured at older age.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at *American Journal of Hypertension* (http://ajh.oxfordjournals.org).

ACKNOWLEDGMENTS

The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C) with the ARIC carotid MRI examination funded by U01HL075572-01. The authors thank the staff and participants of the ARIC study for their important contributions. R.C. was supported by the National Heart, Lung, and Blood Institute GRS Diversity Supplement (HHSN268201100007C).

DISCLOSURE

The authors declared no conflict of interest.

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