ORIGINAL RESEARCH

Longitudinal Effects of Cigarette Smoking and Smoking Cessation on Aortic Wave Reflections, Pulse Wave Velocity, and Carotid Artery Distensibility

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***Background*—**We evaluated the effects of smoking and smoking cessation on aortic wave reflections (augmentation index), aortic pulse wave velocity, and carotid artery distensibility and stiffness (distensibility coefficient, Young's elastic modulus).

***Methods and Results*—**Current smokers underwent carotid, radial, and femoral artery tonometry and carotid ultrasound at baseline and 3 years after a quit attempt. Baseline associations of smoking heaviness markers (exhaled carbon monoxide and cigarettes smoked/d) and effects of smoking cessation at year 3 on changes in arterial measures were assessed using multivariable linear regression models. The 1417 smokers (54% female) were mean (SD) 49.3 (11.6) years old and smoked 17.2 (8.3) cigarettes/d (exhaled carbon monoxide 14.7 [8.2] parts per million). Arterial measures were associated more strongly with age, blood pressure (BP), and waist circumference than with smoking heaviness markers. Augmentation index was associated independently with carbon monoxide (P=0.004). Pulse wave velocity, distensibility coefficient, and Young's elastic modulus had small, inconsistent associations with smoking heaviness markers. At year 3, augmentation index improved with smoking cessation (P=0.006) despite more weight gain (2.54 vs 0.36 kg, P<0.001) and insulin resistance (P=0.001) among abstainers, but distensibility coefficient decreased (P=0.004). Changes in arterial measures were related more strongly to changes in BP than smoking cessation.

***Conclusions*—**Arterial wave reflection and stiffness measures were associated more strongly with age, BP, and waist circumference than smoking heaviness. Smoking cessation was associated with weight gain and increased insulin resistance. Changes in arterial measures were predicted by changes in BP, highlighting the need to address weight gain and BP changes during a quit attempt. **(*J Am Heart Assoc*. 2019;8:e013939. DOI: 10.1161/JAHA.119.013939.)**

Key Words: arterial stiffness • blood pressure • smoking

Cigarette smoking contributes to ≈480 000 deaths per year in the United States; >20% of all cardiovascular disease (CVD)–related deaths in the United States are attributable to smoking.[1–3] Smoking cessation reduces risk of mortality, future adverse CVD events, and improves several measures of cardiovascular health.[4–8] The cardiovascular effects of smoking include reduced aerobic fitness, endothelial dysfunction, platelet activation and thrombosis, chronic inflammation, sympathetic nervous system activation, and coronary artery vasoconstriction.[3] Several of these physiological parameters improve following smoking cessation, despite the weight gain that may accompany successful abstinence from cigarette use.[9–11]

Smoking cigarettes also reduces arterial distensibility and increases arterial stiffness,[12–22] which has been identified as an independent predictor of CVD.[23,24] Adverse changes in arterial distensibility and stiffness measures with cigarette smoking may be dose dependent; however, even light smoking (<5 cigarettes per day) and secondhand smoke exposure worsen arterial distensibility.[22,25–27] The effects of smoking cessation on arterial distensibility and stiffness are less clear. Some studies showed improvements in arterial distensibility and stiffness measures with cessation,[16,28–30] though others have not.[31,32] These studies were limited by small sample sizes, short-term follow-up, and cross-sectional study designs; they also did not carefully consider the role of longitudinal weight gain and changes in blood pressure that

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Clinical Perspective

What Is New?

- Among current smokers, aortic wave reflections were associated independently with exhaled carbon monoxide, but these reflections and stiffness measures were associated more strongly with age, blood pressure, and waist circumference than smoking heaviness markers.
- After 3 years, aortic wave reflections improved with smoking cessation, despite more weight gain and insulin resistance; however, carotid artery distensibility worsened.

What Are the Clinical Implications?

- Changes in arterial measures with smoking cessation were predicted by changes in blood pressure, highlighting the need to address weight gain and blood pressure changes among smokers making a quit attempt.

may accompany smoking cessation.[12–14,17,20–22,26,29,30,33–36] Furthermore, these studies may have yielded different results because they used several different arterial measures that reflect different arterial beds and different manifestations of arterial distensibility and stiffening, including aortic wave reflections and velocity.[12–14,23,25–28,33,34] Characterizing the effects of smoking cessation on aortic wave reflections, pulse wave velocity, and carotid artery distensibility and stiffness measures is an important step for elucidating the mechanisms of cardiovascular risk reduction related to smoking cessation.

We performed the first large, comprehensive, longitudinal study to evaluate the effects of smoking and smoking cessation on aortic wave reflections (aortic augmentation index [AIx]), aortic pulse wave velocity (PWV), and carotid artery distensibility and stiffness measures (distensibility coefficient and Young's elastic modulus [YEM]) in a large, longitudinal cohort of smokers making a quit attempt who were followed for 3 years.

Material and Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participants

We analyzed baseline and year 3 follow-up data from the WSHS-2 (Wisconsin Smokers Health Study 2), a longitudinal study with 2 components: a randomized, open-label comparative effectiveness trial that evaluated the efficacy of 3 different pharmacotherapies for smoking cessation, and a long-term health study of the effects of smoking and smoking cessation on CVD risk.[37] Participants were smokers recruited from the Madison and Milwaukee areas. Some participants had previously participated in the WSHS-1[38] and others were newly recruited. Primary inclusion criteria for the WSHS-2 effectiveness trial were as follows: age ≥18 years old, smoking ≥5 cigarettes per day (cpd), exhaled carbon monoxide (CO) value ≥5 parts per million, and desire to quit smoking.[37] Relevant exclusion criteria were as follows: end-stage renal disease; untreated hypertension, heart attack, congestive heart failure or diabetes mellitus hospitalization within the last year; using other forms of tobacco more than twice in the past week; and exclusionary incidental findings from baseline health assessments such as carotid stenosis, advanced heart block, or stress-induced ischemia.[37] This study was approved by the institutional review board at the University of Wisconsin School of Medicine and Public Health.

Study Procedures

All participants were screened for eligibility and provided written informed consent. At the baseline and year 3 visits, various health markers were recorded including heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), weight (to calculate body mass index), waist circumference, height, and current medication use. Fasting laboratory tests at both visits included a lipid panel, blood glucose, and hemoglobin A_1C. Homeostasis model of insulin-resistance (HOMA-IR) was calculated.[39] Smoking burden was measured by patient-reported cpd and confirmed via exhaled CO. Smoking abstinence was defined as patient-reported point-prevalence abstinence for the 7 days before the year 3 visit, which was biochemically confirmed via exhaled CO (≤5 parts per million). Arterial measures were obtained at baseline and at the year 3 visit after an 8-hour fast as below.

Aortic Wave Reflections

After a 10-minute supine rest period, brachial artery blood pressures were obtained by oscillometric sphygmomanometry using a Dynamap Pro-400 (DINAMAP, GE Medical Systems, Milwaukee, WI). Radial artery tonometry was performed using the SphymoCor Px System (AtCor Medical Inc., Itasca, IL). After generation of 11 s of quality radial artery waveforms, this software used a transfer function to estimate the central aortic pressure from the radial pressure. Derived aortic waveforms were calibrated using the peripheral diastolic and mean blood pressures. AIx, which measures the amplitude of pulse wave reflection with greater pulse wave augmentation in stiffer arteries, was calculated.[40] In our laboratory, reproducibility of blinded repeated AIx measurements was excellent (interclass correlation coefficient=0.90 [95% CI 0.85–0.93]).[41]

Carotid-Femoral PWV

Carotid and femoral artery tonometry were used to calculate PWV. PWV measures the speed at which a pulse wave travels through the circulatory system, with higher values indicating stiffer arteries.[42] While subjects were supine, 3 electrodes were placed to obtain an electrocardiographic signal with a high-amplitude R-wave. The location of a strong right carotid pulse was palpated and the distance between the suprasternal notch and the palpated carotid pulse was recorded. The location of a strong right femoral pulse was palpated and the measured distance to the suprasternal notch was recorded. Applanation tonometry of the carotid artery followed by the femoral artery was performed using the SphymoCor Px System (AtCor Medical Inc., Itasca, IL). Only waveforms with ≥80% detectable upstrokes and SD of ≤10% of the derived PWV were saved. PWV was calculated from the average of 2 high-quality measurements. In our laboratory, reproducibility of blinded repeated PWV measurements was excellent (interclass correlation coefficient=0.91 [95% CI 0.70–0.98]).[41]

Common Carotid Artery Distensibility

Longitudinal B-mode ultrasound images were obtained of the distal segment of the right common carotid artery using a high-resolution linear array transducer (L10-5) with a cardiovascular ultrasound system (CV70; Siemens Medical Solutions, Mountain View, CA). Simultaneous ECG was used to capture 3-beat loops. Systolic and diastolic artery diameter measurements of the distal 1 cm of the common carotid artery were made manually from 3 consecutive cardiac cycles using Access Point Web (version 8.0, Freeland Systems, Alpharetta, GA).

The carotid artery distensibility coefficient (DC, mm $Hg^{-1} \times 10^3$) was calculated as:

$$DC = \frac{(Ds^2 - Dd^2)}{\Delta p \cdot Dd^2}$$

Ds represents the internal arterial diameter at peak systole, Dd represents the internal diameter at end-diastole, and Δp represents the difference between the systolic and diastolic measurements (pulse pressure). DC represents a change in artery diameter throughout the cardiac cycle for a given change in blood pressure, with higher values in more distensible and lower values in stiffer arteries.[43,44]

YEM (mm Hg) of the carotid artery was calculated as:

$$YEM = \left(\frac{Dd/h}{DC}\right)$$

Dd is the arterial diameter at end-diastole, h is the arterial wall thickness at end-diastole (external carotid artery diameter minus internal carotid artery diameter). YEM describes artery stiffness per centimeter of wall thickness, with higher values indicating stiffer arteries.[43–45] YEM and DC are inversely related; thus increased arterial stiffness corresponds to a lower DC and a higher YEM.[42,44] For reproducibility analyses, we blindly remeasured DC and YEM from 24 WSHS-2 participants. Reproducibility was excellent: for DC, interclass correlation coefficient=0.88 (95% CI 0.77–0.94); for YEM, interclass correlation coefficient=0.89 (95% CI 0.76–0.95).

Statistical Analysis

Analyses were performed using SPSS software (version 25.0; IBM Corp, Armonk, NY). Descriptive statistics were used to evaluate baseline participant characteristics. We expected smoking heaviness (cpd, CO) to adversely influence arterial measures (higher AIx, higher PWV, lower DC, higher YEM) and evaluated those relations and the relations between arterial measures and traditional cardiovascular disease risk factors (age, sex, race, body mass index, waist circumference, heart rate, SBP, DBP, lipids, HOMA-IR) using Pearson and point-biserial correlations. We used the Benjamini-Hochberg procedure to evaluate the 21 predictors for each outcome. To characterize the independent associations of these factors, we created separate hierarchical linear regression models to determine the influence of smoking heaviness on each arterial measure (AIx, PWV, DC, YEM) after adjustment for traditional CVD risk factors and use of antihypertensive, lipid-lowering, and antiglycemic medications. Pack-years of smoking was not considered as a marker of smoking heaviness for this analysis because it is so strongly correlated with cigarettes smoked per day (r=0.80, P<0.0001) and age (r=0.56, P<0.0001). Models of AIx also controlled for heart rate.[46]

Independent samples t tests and χ^2 tests were used to evaluate differences between continuing smokers and successful abstainers at year 3, as well as year 3 returners and nonreturners. We expected that smoking cessation would lead to improvements in arterial measures, independently of changes in CVD risk factors that may have occurred over 3 years. Separate hierarchical linear regression models were used to evaluate changes in arterial measures based on smoking status, with each year 3 arterial measure as the outcome and the baseline arterial measure as a predictor. The regression models were then adjusted for age, sex, race, and changes in waist circumference, total cholesterol, high-density lipoprotein cholesterol, SBP, DBP, and HOMA-IR in order to examine the relative importance of these variables in predicting changes in arterial measures after a quit attempt. The sensitivity of these models to the effects of antihypertensive, lipid-lowering, and antiglycemic medications at baseline and in year 3 also was evaluated. To further explore the

possibility of differential effects by key participant characteristics, we used regression models to determine whether baseline smoking heaviness (cpd, CO), age (median split), sex, and race (white/nonwhite) moderated the effect of year 3 status on each year 3 arterial measure using a moderator*year 3 smoking status term.

Results

Baseline Participant Characteristics

Baseline characteristics of all participants are shown in Table 1. There were 1417 smokers in this study. They were 54.0% female, 66.5% white, and were mean (SD) 49.3 (11.6) years old with a smoking heaviness of 17.2 (8.3) cpd and an exhaled CO of 14.7 (8.2) parts per million.

Table 1. Baseline Participant Characteristics (N=1417)

	Mean (SD)	Range
Age, y	49.3 (11.6)	18–90
Sex (% female)	54.0	
Race		
White, %	66.5	
Nonwhite, %	33.5	
Cigarettes smoked/d	17.2 (8.3)	5–75
Exhaled carbon monoxide, ppm	14.7 (8.2)	4–67
Weight, kg	85.7 (20.6)	42–181
Body mass index, kg/m^2	29.4 (6.5)	16–56
Waist circumference, cm	98.3 (15.9)	48–153
Heart rate, bpm	65.5 (10.3)	41–106
Systolic blood pressure, mm Hg	126.5 (17.1)	79–197
Diastolic blood pressure, mm Hg	76.0 (10.1)	53–117
Pulse pressure, mm Hg	50.5 (15.4)	12.5–115
Total cholesterol, mg/dL	192.7 (41.0)	84–452
High-density lipoprotein cholesterol, mg/dL	50.3 (17.4)	19–149
Low-density lipoprotein cholesterol, mg/dL	114.4 (34.7)	17–302
Triglycerides, mg/dL	142.1 (130.4)	30–2774
Hemoglobin A_1C, %	5.9 (1.0)	4–14.4
HOMA-IR	3.1 (3.5)	0–39.1
Medication use, %		
Antihypertensive	28.8	
Lipid-lowering	17.5	
Antiglycemic medications	7.8	

HOMA-IR indicates homeostasis model of insulin resistance.

Baseline Associations of CVD Risk Factors and Smoking Heaviness with Arterial Measures

AIx correlated significantly with age (r=0.52, P<0.001), sex (female=0, male=1; r=−0.31, P<0.001), race (white=1, nonwhite=2; r=0.09, P=0.001), SBP (r=0.24, P<0.001), and DBP (r=0.23, P<0.001), but no other traditional CVD risk factors. AIx did not correlate significantly with cpd or CO; however, in models that adjusted for age and other CVD risk factors, AIx was independently associated with CO (standardized beta=0.054 [SE 0.027], P=0.004). PWV correlated significantly with age (r=0.48, P<0.001), sex (r=0.07, P<0.001), race (r=0.08, P=0.005), SBP (r=0.50, P<0.001), DBP (r=0.38, P<0.001), and waist circumference (r=0.28, P<0.001). PWV correlated weakly with cpd (r=0.06, P=0.03) and inversely with exhaled CO (r=−0.06, P=0.03), but these associations no longer were significant using the Benjamini-Hochberg correction or after adjusting for age.

DC correlated significantly and inversely with age (r=−0.42, P<0.001), sex (r=−0.15, P<0.001), race (r=−0.17, P<0.001), SBP (r=−0.49, P<0.001), DBP (r=−0.34, P<0.001), and waist circumference (r=−0.27, P<0.001). DC had a weak correlation with CO (r=0.11, P<0.001); however, this association no longer was significant after adjusting for blood pressure (P=0.290). DC was not significantly correlated with cpd. YEM correlated significantly with age (r=0.19, P<0.001), sex (r=0.11, P<0.001), race (r=0.08, P=0.003), SBP (r=0.37, P<0.001), DBP (r=0.27, P<0.001), and waist circumference (r=0.13, P<0.001). YEM also had a weak, inverse correlation with CO (r=−0.08, P=0.002) that no longer was statistically significant after adjusting for blood pressure. The unexpected directionality of the weak correlations between DC and YEM with CO levels likely was related to their stronger inverse relationships with waist circumference and HOMA-IR, which were more strongly associated with DC and YEM than CO (data not shown).

Characteristics of Participants at Year 3

The 848 participants who completed year 3 follow-up are described in Table 2, including mean changes from baseline. There were some differences among people who attended the year 3 visit, compared with those who did not; they were older (mean age 50.0 [11.3] vs 48.2 [11.9] years old; P=0.003), had lower SBPs (125.6 [16.9] vs 127.9 [17.5] mm Hg, P=0.018), lower heart rate (64.8 [10.1] vs 66.5 [10.4] bpm, P=0.002), and were more commonly on lipid-lowering medication (19.3% vs. 14.8%) at baseline. No other significant differences in predictor variables were identified (Table S1).

Compared with continuing smokers (N=636), successful abstainers (N=212) were more likely to be white (82.1% vs 59.0%, P<0.001) with a similar percent female (56% vs 54%, P=0.58). Baseline SBPs and DBPs and pulse pressures were

Table 2. Participant Characteristics at Year 3 and Changes from Baseline

	All (N=848)		Smokers (N=636)		Abstainers (N=212)	
	Year 3 Mean (SD)	Mean Change From Baseline (SD)	Year 3 Mean (SD)	Mean Change From Baseline (SD)	Year 3 Mean (SD)	Mean Change From Baseline (SD)
Age, y	53.2 (11.3)	3.1 (0.4)	53.0 (11.0)	3.1 (0.4)	53.9 (12.0)	3.2 (0.4)
Sex (% female)	54.2		53.6		56.1	
Race (% white)	64.7		59.0		82.1	
Cigarettes/d	10.9 (8.0)	−6.2 (8.8)	10.8 (8.0)	−6.2 (8.8)	0	−16.8 (7.2)
Carbon monoxide, ppm	9.8 (8.6)	−4.6 (9.6)	12.5 (8.5)	−1.9 (8.5)	2.0 (0.9)	−12.7 (7.9)
Weight, kg	87.2 (21.2)	2.0 (8.4)	85.7 (20.3)	0.8 (7.9)	91.5 (23.3)	5.6 (8.9)
Body mass index, kg/m^2	30.0 (7.0)	0.7 (2.9)	29.5 (6.7)	0.3 (2.8)	31.2 (7.5)	1.9 (3.2)
Waist circumference, cm	101.6 (16.1)	3.1 (8.5)	100.9 (15.6)	1.9 (8.6)	103.6 (17.5)	6.4 (7.4)
Heart rate, bpm	66.2 (11.2)	1.7 (9.1)	66.5 (11.1)	2.0 (9.3)	65.5 (11.4)	0.8 (8.4)
Systolic blood pressure, mm Hg	129.3 (17.4)	4.0 (15.1)	129.0 (17.8)	3.4 (15.6)	130.0 (16.3)	5.9 (13.5)
Diastolic blood pressure, mm Hg	77.0 (10.0)	1.5 (8.3)	77.2 (10.3)	1.5 (8.3)	76.2 (9.0)	1.4 (8.3)
Pulse pressure, mm Hg	52.3 (15.1)	2.5 (13.7)	51.8 (14.9)	1.9 (14.1)	53.8 (15.6)	4.4 (12.4)
Total cholesterol, mg/dL	190.8 (41.5)	−1.6 (38.5)	188.8 (41.0)	−2.9 (39.1)	196.6 (42.5)	2.4 (36.7)
High-density lipoprotein cholesterol, mg/dL	54.1 (18.5)	3.9 (12.0)	53.9 (18.3)	3.2 (12.4)	54.6 (19.0)	5.9 (10.5)
Low-density lipoprotein cholesterol, mg/dL	109.1 (37.0)	−4.9 (33.1)	108.0 (36.9)	−5.2 (33.6)	112.5 (37.0)	−3.9 (31.7)
Triglycerides, mg/dL	142.9 (129.5)	0.7 (135.2)	137.8 (109.0)	−3.9 (125.8)	157.6 (176.2)	14.2 (159.2)
Hemoglobin A_1C, %	6.0 (1.0)	0.1 (0.7)	6.0 (1.0)	0.1 (0.7)	6.0 (0.8)	0.1 (0.5)
HOMA-IR	3.9 (4.4)	0.7 (3.6)	3.6 (4.1)	0.5 (3.8)	4.8 (5.2)	1.6 (3.2)
Medication use, %						
Antihypertensive	38.2	7.8	39.0	6.6	35.8	9.7
Lipid-lowering	25.0	5.7	25.2	5.7	24.5	5.6
Antiglycemic medications	11.1	2.6	11.8	2.7	9.0	2.4

HOMA-IR indicates homeostasis model of insulin resistance.

similar. Of those abstinent at year 3, 69% also had been abstinent at year 1; of those who smoked at year 3, 95% were smoking at year 1. Successful abstainers gained more weight (5.6 [8.9] vs 0.8 [7.9] kg, $P<0.001$), had a significantly larger change (year 3-baseline) in waist circumference (6.4 [7.4] vs 1.9 [8.6] cm; $P=0.001$), high-density lipoprotein cholesterol (5.9 [10.5] vs 3.2 [12.4] mg/dL; $P=0.005$), and HOMA-IR (1.6 [3.2] vs 0.5 [3.8] mg/dL; $P<0.001$) compared with continuing smokers. Abstainers had a greater increase in SBP (5.9 [13.5] vs 3.3 [15.6] mm Hg; $P=0.084$) and pulse pressure (4.4 [12.4] vs 1.9 [14.1] mm Hg, $P=0.03$), but not DBP. After year 3, the percentage of continuing smokers on antihypertensive medications increased to 39%, but decreased to 36% among successful abstainers. Also, use of antihypertensive medication increased, especially among continuing smokers (74 new users vs 28 new users) so SBP, DBP, and pulse pressure were similar among continuing smokers and eventual abstainers. However, weight gain correlated significantly with increases in HOMA-IR ($r=0.29$, $P<0.001$) and SBP ($r=0.08$, $P=0.022$) in all participants at year 3. Among continual smokers, weight gain also correlated inversely with DBP ($r=-0.10$, $P=0.017$).

Changes in Arterial Measures at Year 3 Related to Smoking Cessation Group

Changes in arterial measures among abstainers and continuing smokers at year 3 are shown in Table 3. In hierarchical linear regression models of year 3 arterial measures adjusted for the baseline arterial measure (but not other covariates), year 3 AIx was less in abstainers ($P=0.006$) than in continuing smokers. Year 3 DC was lower in abstainers than in smokers ($P=0.004$). Neither year 3 PWV nor YEM were significantly impacted by smoking status.

To better understand the factors that influenced changes in arterial measures 3 years after the quit attempt, we examined the impact of year 3 smoking status on year 3 arterial stiffness measures after accounting for baseline arterial measures, age, sex, race, and changes in CVD risk factors (waist circumference,

Table 3. Changes in Arterial Measures From Baseline to Year 3

	Baseline (N=1417)	Year 3 (N=848)	Year 3 Smokers (N=636)			Year 3 Abstainers (N=212)			*P* Value*
			Baseline	Year 3	Δ	Baseline	Year 3	Δ	
AIx, %	27.5 (12.3)	28.9 (10.8)	28.4 (11.9)	29.4 (10.5)	1.0 (7.9)	26.8 (11.5)	27.3 (11.4)	0.2 (6.9)	0.006
PWV, m/s	7.2 (1.7)	7.4 (1.9)	7.2 (1.7)	7.5 (2.0)	0.3 (1.5)	7.1 (1.5)	7.2 (1.5)	0.2 (1.2)	0.239
DC, mm $Hg^{-1}\times10^3$	4.2 (1.9)	3.6 (1.6)	4.3 (2.0)	3.7 (1.7)	−0.6 (1.7)	4.3 (1.8)	3.4 (1.6)	−1.0 (1.6)	0.004
YEM, mm Hg	1339.1 (823.6)	1458.7 (1022.9)	1312.2 (848.9)	1430.4 (945.6)	120.7 (908.8)	1296.4 (700.2)	1545.2 (1228.3)	270.6 (1304.1)	0.074

All values are means (SDs). AIx indicates aortic augmentation index; DC, carotid distensibility coefficient; PWV, carotid-femoral pulse wave velocity; YEM, carotid Young's elastic modulus. **P* value for group effect in hierarchical linear regression model of year 3 arterial measures, adjusted for baseline arterial measure.

heart rate, SBP, DBP, total cholesterol, high-density lipoprotein cholesterol, and HOMA-IR) (Tables 4 through 7). Year 3 AIx was related independently and inversely to changes in heart rate and SBP, positively to changes in DBP, and was greater in women, but no longer was related to smoking status. Year 3 PWV was related to age and changes in SBP, but not smoking status. Year 3 DC was related to changes in SBP, but no longer smoking status. Year 3 YEM was related to changes in SBP but not year 3 smoking status. Adjusting for antihypertensive, lipid-lowering, and antiglycemic medication use at year 3 did not have a major effect on the findings for arterial measures at year 3.

Neither age (median split at 50 years old), sex, race (white vs nonwhite), nor either baseline smoking heaviness measure (cpd, exhaled CO) moderated the effect of year 3 smoking status on AIx or DC (Table S2). Sex weakly moderated the effect of year 3 smoking status on PWV (β=−0.52 m/s, SE=0.25, standardized β=−0.14, *P*=0.04). Age moderated the effect of year 3 smoking status on YEM (β=463.0 mm Hg, SE=153.6, standardized β=0.361, *P*=0.003). Baseline exhaled CO also moderated the effect of year 3 smoking status on YEM (β=19.1 mm Hg, SE=9.3, standardized β=0.136, *P*=0.037).

Discussion

The harmful effects of smoking and the numerous benefits of smoking cessation are well-established. However, the effects of smoking cessation on arterial distensibility, stiffness, and wave reflections are unclear. Prior studies evaluating the longitudinal effects of smoking cessation on arterial stiffness and wave reflections were limited by small sample size, short-term follow-up, cross-sectional study designs, and incomplete arterial stiffness assessment, yielding widely varying effect sizes and conclusions.[12–14,17,20–22,26,29,30,33–36] This is the first large, comprehensive, longitudinal study to evaluate the effects of smoking and smoking cessation on aortic wave reflections (which reflect global arterial stiffness), aortic PWV (which reflects regional arterial stiffness), and carotid artery distensibility and stiffness (which reflect local arterial stiffness) in a contemporary cohort of smokers making a quit attempt.

When examining associations among those smoking at baseline, we observed a weak association between exhaled CO levels and AIx. Unlike a previous study that identified a dose-dependent association of AIx with smoking heaviness, as measured by cpd,[22] we did not find an association between cpd and AIx. We did not find any associations between smoking heaviness and PWV, DC, or YEM. AIx was associated with other traditional CVD risk factors such as age, SBP, DBP, and heart rate, as described previously.[24,40] Similarly, PWV, DC, and YEM were most strongly and consistently associated with increasing age, blood pressures, and waist circumference. Overall, among current smokers, age, blood pressures, and central adiposity were much more strongly associated with arterial measures than was smoking heaviness. These

Table 4. Predictors of Arterial Measures at Year 3: Augmentation Index

	Standardized *B*	SE	*P* Value
Δ Heart rate	−0.32	0.043	<0.001
Sex	−0.17	0.979	0.001
Δ Systolic blood pressure	−0.12	0.034	0.022
Δ Diastolic blood pressure	0.12	0.063	0.016
Year 3 smoking status	0.03	1.026	0.484

All data are from hierarchical linear regression models, adjusted for baseline augmentation index, where sex was coded as female=0, male=1, and year 3 smoking status was coded as abstainers=0, continuing smokers=1. Δ=year 3—baseline value.

Table 5. Predictors of Arterial Measures at Year 3: Pulse Wave Velocity

	Standardized *B*	SE	*P* Value
Age	0.31	0.02	<0.001
Δ Diastolic blood pressure	0.16	0.02	0.028
Smoking status	0.13	0.30	0.053

All data are from hierarchical linear regression models, adjusted for baseline pulse wave velocity, where year 3 smoking status was coded as abstainers=0, continuing smokers=1. Δ=year 3—baseline value.

Table 6. Predictors of Arterial Measures at Year 3: Distensibility Coefficient

	Standardized *B*	SE	*P* Value
Δ Systolic blood pressure	−0.31	<0.001	<0.001
Smoking status	0.11	<0.001	0.067

All data are from hierarchical linear regression models, adjusted for baseline distensibility coefficient, where year 3 smoking status was coded as abstainers=0, continuing smokers=1. Δ=year 3—baseline value.

findings emphasize that the effects of smoking cigarettes on arterial injury are multifactorial and may not even be related to arterial stiffness.

After 3 years, successful abstainers had significantly greater weight gain and greater increases in waist circumference, insulin resistance, and pulse pressure compared with continuing smokers, consistent with prior studies demonstrating that weight gain after successful smoking cessation can lead to comorbidities such as hypertension and disorders of glucose metabolism.[47–49] Despite weight gain, abstainers in our study still experienced improvements in AIx but not PWV. Prior studies have described similar findings, with significant improvements in AIx, but not PWV.[29,50] However, changes in AIx after 3 years were influenced more by changes in blood pressure and changes in heart rate than by abstinence, consistent with our cross-sectional observation that nonsmoking risk factors more powerfully influence AIx than smoking heaviness. In this study, more women quit smoking compared with men. Women also experienced less of an increase in AIx over time compared with men, which likely contributed to lower AIx values among abstainers. Heart rate went up in both groups, but less among abstainers compared with continuing smokers, possibly because of a decrease in autonomic activity with smoking cessation.[51,52] Abstainers tended to have greater increases in SBP compared with continuing smokers; however, this may be because of more use of antihypertensive medication among continuing smokers. The effects of smoking cessation on blood pressure are complicated and seem to be affected by baseline blood pressures, degree of weight gain, and changes in antihypertensive medications.[53]

Successful abstainers had worse measures of carotid DC and YEM than continuing smokers. In a small study, smoking cessation did not improve carotid DC or intima-media thickness.[31] As we have noted previously, this may be because of greater weight gain and its attendant increases in blood pressure and insulin resistance among abstainers.[49,54] Our multivariable models suggest that worsening DC and YEM are most strongly related to increases in SBP and possibly insulin resistance for YEM. Carotid artery systolic and diastolic diameters did not differ between successful abstainers and continuing smokers and were not related to weight gain (data not shown). Weight gain, insulin resistance, and increases in blood pressure among successful abstainers may mitigate some of the beneficial arterial effects of smoking cessation such as improvements in arterial endothelial function.[10]

Table 7. Predictors of Arterial Measures at Year 3: Young's Elastic Modulus

	Standardized *B*	SE	*P* Value
Δ Systolic blood pressure	0.19	4.0	0.012
Δ HOMA-IR	0.14	10.9	0.050
Smoking status	−0.05	120.3	0.474

All data are from hierarchical linear regression models, adjusted for baseline Young's Elastic Modulus, where year 3 smoking status was coded as abstainers=0, continuing smokers=1. Δ=year 3—baseline value. HOMA-IR indicates homeostasis model of insulin resistance.

Limitations

As commonly seen in smoking cessation studies, ≈40% of participants did not return for their year 3 follow-up visits. This is consistent with dropout rates in other recent smoking cessation pharmacotherapy trials.[9–11,55] Those who completed the year 3 follow-up visit were more likely to be older and white with higher systolic blood pressures at baseline than those who did not. They also used more antihypertensive medications. We used exhaled CO as a quantitative measure of smoking heaviness. Serum cotinine may be a more accurate marker. We had to use CO levels because it is a biomarker that would not be affected by the nicotine from nicotine replacement therapy during the treatment phase of this study; at year 3 no participants were using nicotine replacement therapy.[11,37] All of our participants were smokers at baseline, so we do not have a nonsmoking control group with whom to compare the changes. Although the effects of other risk factors on arterial stiffness measures in nonsmokers have been well described in the medical literature,[18,24,42,44,45,56] we cannot exclude the influence of unknown confounders, especially changes in diet. Indeed, this study was not designed to evaluate causes of weight gain after smoking cessation; because we did not obtain food records from participants, we could not assess the effects of changes in dietary composition. This was the longest prospective study of the effects of smoking cessation on changes in arterial wave reflection and stiffness measures we are aware of; however, our follow-up duration of 3 years may not have been long enough to detect changes; indeed, a decade or more may be needed.[44,57] Finally, the generalized transfer function to derive central aortic wave forms for calculating AIx may have differential error between sexes and people with impaired glucose metabolism.[58,59]

Conclusions

In a large cohort of contemporary smokers, aortic AIx was independently associated with exhaled CO, a measure of smoking heaviness. However, arterial wave reflection and stiffness measures were associated more strongly with age, blood pressure, and waist circumference than smoking heaviness. Smoking cessation was associated with weight gain, increased insulin resistance, and increased pulse pressure. Changes in arterial wave reflections and stiffness were predicted by changes in blood pressure, highlighting the need to address weight gain and blood pressure changes among smokers making a quit attempt.

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Disclosures

None.

References

1. Ezzati M, Henley SJ, Thun MJ, Lopez AD. Role of smoking in global and regional cardiovascular mortality. *Circulation*. 2005;112:489–497.
2. Centers for Disease Control and Prevention (US). Smoking & tobacco use. Fast facts. Available at: https://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/index.htm. Accessed October 31, 2019.
3. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. Centers for Disease Control and Prevention (US). Services USDoHaH. The Health consequences of smoking-50 years of progress: A report of the surgeon general. 2014.
4. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. *BMJ*. 1994;309:901–911.
5. Gordon T, Kannel WB, McGee D, Dawber TR. Death and coronary attacks in men after giving up cigarette smoking. A report from the Framingham study. *Lancet*. 1974;2:1345–1348.
6. Johansson S, Bergstrand R, Pennert K, Ulvenstam G, Vedin A, Wedel H, Wilhelmsson C, Wilhelmsen L, Aberg A. Cessation of smoking after myocardial infarction in women. Effects on mortality and reinfarctions. *Am J Epidemiol*. 1985;121:823–831.
7. Lightwood JM, Glantz SA. Short-term economic and health benefits of smoking cessation: myocardial infarction and stroke. *Circulation*. 1997;96:1089–1096.
8. Sato I, Nishida M, Okita K, Nishijima H, Kojima S, Matsumura N, Yasuda H. Beneficial effect of stopping smoking on future cardiac events in male smokers with previous myocardial infarction. *Jpn Circ J*. 1992;56:217222.
9. Asthana A, Piper ME, McBride PE, Ward A, Fiore MC, Baker TB, Stein JH. Long-term effects of smoking and smoking cessation on exercise stress testing: three-year outcomes from a randomized clinical trial. *Am Heart J*. 2012;163:81–87.e81.
10. Johnson HM, Gossett LK, Piper ME, Aeschlimann SE, Korcarz CE, Baker TB, Fiore MC, Stein JH. Effects of smoking and smoking cessation on endothelial function: 1-year outcomes from a randomized clinical trial. *J Am Coll Cardiol*. 2010;55:1988–1995.
11. King CC, Piper ME, Gepner AD, Fiore MC, Baker TB, Stein JH. Longitudinal impact of smoking and smoking cessation on inflammatory markers of cardiovascular disease risk. *Arterioscler Thromb Vasc Biol*. 2017;37:374–379.
12. Argacha JF, Adamopoulos D, Gujic M, Fontaine D, Amyai N, Berkenboom G, van de Borne P. Acute effects of passive smoking on peripheral vascular function. *Hypertension*. 2008;51:1506–1511.
13. Failla M, Grappiolo A, Carugo S, Calchera I, Giannattasio C, Mancia G. Effects of cigarette smoking on carotid and radial artery distensibility. *J Hypertens*. 1997;15:1659–1664.
14. Kubozono T, Miyata M, Ueyama K, Hamasaki S, Kusano K, Kubozono O, Tei C. Acute and chronic effects of smoking on arterial stiffness. *Circ J*. 2011;75:698–702.
15. Levenson J, Simon AC, Cambien F, Beretti C. (Effect of smoking on blood viscosity and arterial rigidity in normal and hypertensive subjects [Article in French]). *Arch Mal Coeur Vaiss*. 1987;80:794–798.
16. Li H, Srinivasan SR, Berenson GS. Comparison of the measures of pulsatile arterial function between asymptomatic younger adult smokers and former smokers: the Bogalusa Heart Study. *Am J Hypertens*. 2006;19:897–901.
17. Mahmud A, Feely J. Effect of smoking on arterial stiffness and pulse pressure amplification. *Hypertension*. 2003;41:183–187.
18. Malayeri AA, Natori S, Bahrami H, Bertoni AG, Kronmal R, Lima JA, Bluemke DA. Relation of aortic wall thickness and distensibility to cardiovascular risk factors (from the Multi-Ethnic Study of Atherosclerosis [MESA]). *Am J Cardiol*. 2008;102:491–496.
19. Markus MR, Stritzke J, Baumeister SE, Siewert U, Baulmann J, Hannemann A, Schipf S, Meisinger C, Dörr M, Felix SB, Keil U, Völzke H, Hense HW, Schunkert H; MONICA/KORA Augsburg Cohort Study. Effects of smoking on arterial distensibility, central aortic pressures and left ventricular mass. *Int J Cardiol*. 2013;168:2593–2601.
20. Sassalos K, Vlachopoulos C, Alexopoulos N, Gialernios T, Aznaouridis K, Stefanadis C. The acute and chronic effect of cigarette smoking on the elastic properties of the ascending aorta in healthy male subjects. *Hellenic J Cardiol*. 2006;47:263–268.
21. Stefanadis C, Vlachopoulos C, Tsiamis E, Diamantopoulos L, Toutouzas K, Giatrakos N, Vaina S, Tsekoura D, Toutouzas P. Unfavorable effects of passive smoking on aortic function in men. *Ann Intern Med*. 1998;128:426–434.
22. Tsuru T, Adachi H, Enomoto M, Fukami A, Kumagai E, Nakamura S, Nohara Y, Kono S, Nakao E, Sakaue A, Morikawa N, Fukumoto Y. Augmentation index (AI) in a dose-response relationship with smoking habits in males: the Tanushimaru study. *Medicine (Baltimore)*. 2016;95:e5368.
23. Choudhary MK, Eräranta A, Tikkakoski AJ, Bouquin H, Hautaniemi EJ, Kähönen M, Sipilä K, Mustonen J, Pörsti I. Effect of present versus previous smoking on non-invasive haemodynamics. *Sci Rep*. 2018;8:13643.
24. Janner JH, Godtfredsen NS, Ladelund S, Vestbo J, Prescott E. The association between aortic augmentation index and cardiovascular risk factors in a large unselected population. *J Hum Hypertens*. 2012;26:476–484.
25. Barnoya J, Glantz SA. Cardiovascular effects of secondhand smoke: nearly as large as smoking. *Circulation*. 2005;111:2684–2698.
26. Ciftci O, Gunday M, Caliskan M, Gullu H, Guven A, Muderrisoglu H. Light cigarette smoking and vascular function. *Acta Cardiol*. 2013;68:255–261.
27. Kallio K, Jokinen E, Hämäläinen M, Saarinen M, Volanen I, Kaitosaari T, Viikari J, Rönnemaa T, Simell O, Raitakari OT. Decreased aortic elasticity in healthy 11-year old children exposed to tobacco smoke. *Pediatrics*. 2009;123:e267–e273.
28. Bassareo PP, Fanos V, Crisafulli A, Mercuro G. Daily assessment of arterial distensibility in a pediatric population before and after smoking cessation. *Clinics (Sao Paulo)*. 2014;69:219–224.
29. Polonia J, Barbosa L, Silva JA, Rosas M. Improvement of aortic reflection wave responses 6 months after stopping smoking: a prospective study. *Blood Press Monit*. 2009;14:69–75.
30. Takami T, Saito Y. Effects of smoking cessation on central blood pressure and arterial stiffness. *Vasc Health Risk Manag*. 2011;7:633–638.
31. van den Berkmortel FW, Wollersheim H, van Langen H, Smilde TJ, den Arend J, Thien T. Two years of smoking cessation does not reduce arterial wall thickness and stiffness. *Neth J Med*. 2004;62:235–241.
32. Kim S, Lee SJ, Kim YH, Kim JS, Lim SY, Kim SH, Ahn JC, Song WH, Jee SH, Park CG. Irreversible effects of long-term chronic smoking on arterial stiffness: an analysis focusing on ex-smokers among otherwise healthy middle-aged men. *Clin Exp Hypertens*. 2018;1–8.
33. Camplain R, Meyer ML, Tanaka H, Palta P, Agarwal SK, Aguilar D, Butler KR, Heiss G. Smoking behaviors and arterial stiffness measured by pulse wave velocity in older adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Hypertens*. 2016;29:1268–1275.

34. Kool MJ, Hoeks AP, Struijker Boudier HA, Reneman RS, Van Bortel LM. Short- and longterm effects of smoking on arterial wall properties in habitual smokers. *J Am Coll Cardiol*. 1993;22:1881–1886.
35. Lemogoum D, Van Bortel L, Leeman M, Degaute JP, van de Borne P. Ethnic differences in arterial stiffness and wave reflections after cigarette smoking. *J Hypertens*. 2006;24:683–689.
36. Yu-Jie W, Hui-Liang L, Bing L, Lu Z, Zhi-Geng J. Impact of smoking and smoking cessation on arterial stiffness in healthy participants. *Angiology*. 2013;64:273–280.
37. Baker TB, Piper ME, Stein JH, Smith SS, Bolt DM, Fraser DL, Fiore MC. Effects of nicotine patch vs varenicline vs combination nicotine replacement therapy on smoking cessation at 26 weeks: a randomized clinical trial. *JAMA*. 2016;315:371–379.
38. Piper ME, Smith SS, Schlam TR, Fiore MC, Jorenby DE, Fraser D, Baker TB. A randomized placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies. *Arch Gen Psychiatry*. 2009;66:1253–1262.
39. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28:412–419.
40. Janner JH, Godtfredsen NS, Ladelund S, Vestbo J, Prescott E. Aortic augmentation index: reference values in a large unselected population by means of the SphygmoCor device. *Am J Hypertens*. 2010;23:180–185.
41. Gepner AD, Ramamurthy R, Krueger DC, Korcarz CE, Binkley N, Stein JH. A prospective randomized controlled trial of the effects of vitamin D supplementation on cardiovascular disease risk. *PLoS One*. 2012;7:e36617.
42. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27:2588–2605.
43. Gamble G, Zorn J, Sanders G, MacMahon S, Sharpe N. Estimation of arterial stiffness, compliance, and distensibility from M-mode ultrasound measurements of the common carotid artery. *Stroke*. 1994;25:11–16.
44. Gepner AD, Korcarz CE, Colangelo LA, Hom EK, Tattersall MC, Astor BC, Kaufman JD, Liu K, Stein JH. Longitudinal effects of a decade of aging on carotid artery stiffness: the multiethnic study of atherosclerosis. *Stroke*. 2014;45:4853.
45. O'Rourke M. Arterial stiffness, systolic blood pressure, and logical treatment of arterial hypertension. *Hypertension*. 1990;15:339–347.
46. Stoner L, Faulkner J, Lowe A, Lambrick MD, Young MJ, Love R, Rowlands SD. Should the augmentation index be normalized to heart rate? *J Atheroscler Thromb*. 2014;21:11–16.
47. Bush T, Lovejoy JC, Deprey M, Carpenter KM. The effect of tobacco cessation on weight gain, obesity, and diabetes risk. *Obesity (Silver Spring)*. 2016;24:1834–1841.
48. Li G, Wang H, Wang K, Wang W, Dong F, Qian Y, Gong H, Hui C, Xu G, Li Y, Pan L, Zhang B, Shan G. The association between smoking and blood pressure in men: a cross-sectional study. *BMC Public Health*. 2017;17:797.
49. Stein JH, Asthana A, Smith SS, Piper ME, Loh WY, Fiore MC, Baker TB. Smoking cessation and the risk of diabetes mellitus and impaired fasting glucose: three-year outcomes after a quit attempt. *PLoS One*. 2014;9:e98278.
50. Rehill N, Beck CR, Yeo KR, Yeo WW. The effect of chronic tobacco smoking on arterial stiffness. *Br J Clin Pharmacol*. 2006;61:767–773.
51. Persico AM. Persistent decrease in heart rate after smoking cessation: a 1-year follow-up study. *Psychopharmacology*. 1992;106:397–400.
52. Yotsukura M, Koide Y, Fujii K, Tomono Y, Katayama A, Ando H, Suzuki J, Ishikawa K. Heart rate variability during the first month of smoking cessation. *Am Heart J*. 1998;135:1004–1009.
53. Lee DH, Ha MH, Kim JR, Jacobs DR Jr. Effects of smoking cessation on changes in blood pressure and incidence of hypertension: a 4-year follow-up study. *Hypertension*. 2001;37:194–198.
54. Johnson HM, Piper ME, Baker TB, Fiore MC, Stein JH. Effects of smoking and cessation on subclinical arterial disease: a substudy of a randomized controlled trial. *PLoS One*. 2012;7:e35332.
55. Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, Watsky EJ, Gong J, Williams KE, Reeves KR; Varenicline Phase 3 Study Group. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296:47–55.
56. Giltay EJ, Lambert J, Elbers JM, Gooren LJ, Asscheman H, Stehouwer CD. Arterial compliance and distensibility are modulated by body composition in both men and women but by insulin sensitivity only in women. *Diabetologia*. 1999;42:214–221.
57. Jatoi NA, Jerrard-Dunne P, Feely J, Mahmud A. Impact of smoking and smoking cessation on arterial stiffness and aortic wave reflection in hypertension. *Hypertension*. 2007;49:981–985.
58. Hope SA, Tay DB, Meredith IT, Cameron JD. Comparison of generalized and gender-specific transfer functions for the derivation of aortic waveforms. *Am J Physiol Heart Circ Physiol*. 2002;283:H1150–H1156.
59. Lehmann ED. Where is the evidence that radial artery tonometry can be used with a generalised transfer function to accurately and non-invasively predict central aortic blood pressure? *J Hum Hypertens*. 2001;15:145–146.

SUPPLEMENTAL MATERIAL

Table S1. Comparisons of Baseline Values from Participants that Completed versus Participants that did not Complete the Year 3 Visit.

	Completed Year 3 (N=848)	Did not complete Year 3 (N=569)		
Baseline variables	Mean (SD)	Mean (SD)	Test statistic (t-test or χ^2)	p-value
Age (years)	50.0 (11.3)	48.2 (11.9)	-2.93	0.003
Sex (% female)	54.2	53.6	0.06	0.81
Race (% white)	64.7	69.2	3.10	0.08
Cigarettes per day	16.9 (8.1)	17.7 (8.5)	1.75	0.08
Carbon monoxide (ppm)	14.5 (8.2)	15.2 (8.3)	1.59	0.11
Weight (kg)	85.5 (20.3)	86.1 (21.0)	0.56	0.58
Body-mass index (kg/m^2)	29.4 (6.5)	29.4 (6.5)	-0.11	0.92
Waist circumference (cm)	98.4 (15.6)	98.2 (16.2)	-0.27	0.79
Systolic blood pressure (mmHg)	125.6 (16.9)	127.9 (17.5)	2.39	0.02
Diastolic blood pressure (mmHg)	75.7 (9.9)	76.4 (10.3)	1.28	0.20
Pulse pressure (mmHg)	49.9 (15.1)	51.4 (15.8)	1.82	0.07
Heart rate (bpm)	64.8 (10.1)	66.5 (10.4)	3.08	0.002
Total cholesterol (mg/dL)	192.4 (40.7)	193.1 (41.5)	0.33	0.74
High-density lipoprotein cholesterol (mg/dL)	50.3 (17.7)	50.2 (17.1)	-0.11	0.92
Low-density lipoprotein cholesterol (mg/dL)	114.2 (34.3)	114.6 (35.2)	0.24	0.81
Triglycerides (mg/dL)	141.6 (120.1)	142.9 (144.6)	0.19	0.85
Hemoglobin A_1C (%)	5.9 (0.9)	5.9 (1.1)	-.14	0.89
HOMA-IR	3.1 (3.8)	3.1 (3.2)	-.37	0.71
Medication use (%)				
Antihypertensive	30.4	26.4	2.74	0.10
Lipid-lowering	19.3	14.8	4.94	0.03
Anti-glycemic	8.5	6.9	1.26	0.26

SD = standard deviation; HOMA-IR = homeostasis model of insulin resistance

Table S2. Changes in Year 3 Arterial Measures by Smoking Status by Age, Sex, and Race Groups.

Changes in Arterial Measures from Baseline to Year 3 by Age (median split; ≤50 vs ≥51 years old)

		Baseline (N=1417)	Year 3 (N=848)	Year 3 Smokers (N=636)			Year 3 Abstainers (N=212)		
				Baseline	Year 3	Δ	Baseline	Year 3	Δ
AIx (%)	Younger	22.2 (12.6)	24.6 (10.7)	22.9 (12.3)	25.2 (10.4)	2.1 (8.3)	22.3 (12.1)	22.7 (11.6)	0.3 (6.2)
	Older	32.3 (9.7)	32.2 (9.6)	32.7 (9.6)	32.7 (9.4)	0.1 (7.5)	30.2 (9.7)	30.6 (10.1)	0.2 (7.5)
PWV (m/s)	Younger	6.5 (1.2)	6.7 (1.4)	6.5 (1.2)	6.8 (1.5)	0.3 (1.2)	6.4 (1.6)	6.5 (1.2)	0.3 (1.1)
	Older	7.7 (1.8)	8.0 (2.0)	7.7 (1.8)	8.0 (2.1)	0.3 (1.7)	7.6 (1.6)	7.7 (1.5)	0.2 (1.3)
DC ($mmHg^{-1}$ x10^3)	Younger	4.8 (2.0)	4.1 (1.7)	4.9 (2.0)	4.2 (1.7)	-0.7 (1.8)	5.2 (1.9)	3.9 (1.8)	-1.3 (1.8)
	Older	3.7 (1.7)	3.2 (1.5)	3.8 (1.8)	3.2 (1.6)	-0.6 (1.6)	3.6 (1.5)	3.0 (1.2)	-0.7 (1.4)
YEM (mmHg)	Younger	1227.6 (659.5)	1326.6 (1008.2)	1160.6 (675.5)	1238.0 (638.0)	70.7 (625.2)	1110.9 (545.5)	1604.0 (1687.3)	492.8 (1728.1)
	Older	1430.5 (902.9)	1560.3 (1027.7)	1394.3 (903.7)	1574.5 (1109.3)	188.9 (1024.1)	1442.1 (775.4)	1518.0 (734.9)	112.7 (845.1)

Changes in Arterial Measures from Baseline to Year 3 by Sex

		Baseline (N=1417)	Year 3 (N=848)	Year 3 Smokers (N=636)			Year 3 Abstainers (N=212)		
				Baseline	Year 3	Δ	Baseline	Year 3	Δ
AIx (%)	Men	23.4 (12.2)	25.7 (10.4)	24.7 (11.5)	26.3 (10.0)	1.4 (8.3)	22.6 (10.8)	23.7 (11.3)	1.1 (6.9)
	Women	31.0 (11.2)	31.6 (10.3)	31.6 (11.3)	32.1 (10.2)	0.6 (7.6)	30.2 (10.9)	30.2 (10.6)	-0.5 (7.0)
PWV (m/s)	Men	7.3 (1.7)	7.5 (1.8)	7.3 (1.6)	7.5 (1.8)	0.3 (1.5)	7.2 (1.5)	7.5 (1.5)	0.5 (1.3)

	Women	7.0 (1.6)	7.4 (1.9)	7.2 (1.8)	7.5 (2.1)	0.4 (1.5)	7.0 (1.6)	6.9 (1.4)	0.04 (1.2)
DC ($mmHg^{-1}$ $x10^3$)	Men	3.9 (1.7)	3.4 (1.5)	4.0 (1.8)	3.5 (1.6)	-0.5 (1.6)	3.9 (1.4)	3.0 (1.1)	-0.9 (1.2)
	Women	4.5 (2.0)	3.7 (1.7)	4.5 (2.1)	3.8 (1.7)	-0.7 (1.8)	4.6 (2.1)	3.7 (1.8)	-1.0 (1.9)
YEM (mmHg)	Men	1435.9 (870.2)	1528.9 (998.7)	1404.5 (900.6)	1515.8 (1074.8)	111.1 (1020.5)	1334.3 (583.2)	1571.4 (701.1)	242.1 (746.6)
	Women	1256.5 (772.6)	1399.4 (1040.4)	1232.1 (794.1)	1356.6 (812.1)	129.0 (800.2)	1266.4 (781.6)	1524.6 (1520.9)	293.0 (1616.4)

Changes in Arterial Measures from Baseline to Year 3 by Race/Ethnicity (White vs. Non-White)

		Baseline (N=1417)	**Year 3 (N=848)**	**Year 3 Smokers (N=636)**			**Year 3 Abstainers (N=212)**		
				Baseline	**Year 3**	**Δ**	**Baseline**	**Year 3**	**Δ**
AIx (%)	White	26.7 (12.4)	28.5 (10.6)	27.6 (11.8)	29.1 (10.3)	1.4 (7.6)	26.3 (11.5)	27.1 (11.3)	0.6 (6.5)
	Non-white	29.0 (11.9)	29.6 (11.0)	29.6 (11.9)	29.9 (10.8)	0.3 (8.3)	29.2 (11.3)	28.0 (11.9)	-1.4 (8.6)
PWV (m/s)	White	7.1 (1.6)	7.3 (1.8)	7.1 (1.6)	7.4 (1.9)	0.3 (1.4)	7.0 (1.6)	7.1 (1.5)	0.2 (1.2)
	Non-white	7.3 (1.7)	7.7 (2.0)	7.4 (1.8)	7.8 (2.1)	0.3 (1.6)	7.5 (1.3)	7.6 (1.4)	0.3 (1.5)
DC ($mmHg^{-1}$ $x10^3$)	White	4.4 (1.9)	3.8 (1.7)	4.6 (2.1)	4.0 (1.7)	-0.6 (1.9)	4.4 (1.8)	3.5 (1.6)	-0.9 (1.5)
	Non-white	3.8 (1.7)	3.1 (1.5)	3.8 (1.7)	3.1 (1.5)	-0.7 (1.5)	3.9 (2.1)	2.8 (1.4)	-1.2 (2.0)
YEM (mmHg)	White	1292.4 (793.8)	1336.9 (759.0)	1252.9 (850.1)	1290.4 (768.6)	35.5 (886.9)	1266.4 (622.3)	1439.8 (729.2)	183.3 (758.7)
	Non-white	1433.3 (873.7)	1686.5 (1360.7)	1399.1 (841.3)	1636.7 (1128.7)	247.1 (927.8)	1438.0 (988.2)	2034.1 (2426.3)	687.1 (2650.9)