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FULL RESEARCH PAPER
Smoking

Cross-sectional and longitudinal associations of smoking behaviour with central arterial haemodynamic measures: the Framingham Heart Study

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Aims To assess the cross-sectional and longitudinal associations of smoking behaviour with central arterial haemodynamic measures in samples of the Framingham Heart Study.

Methods and results In 6597 participants [3606 (55%) women, 51.5% never smoked, 34.8% formerly quit, 4.3% recently quit, and 9.3% currently smoking], we assessed relations of smoking behaviour with central arterial measures using multivariable linear regression models. In cross-sectional models, central arterial measures were different across smoking behaviour groups. Particularly, augmentation index (AI) was higher among participants who formerly quit smoking (least squares mean ± standard error = 14.1 ± 0.4%; $P < 0.001$) and were currently smoking (18.1 ± 0.5%; $P < 0.001$) compared with participants who never smoked (12.6 ± 0.3%). Among participants currently smoking, higher cigarettes per day [$B = 1.41$; 95% confidence interval (CI), 0.47–2.34] were associated with higher AI. Among participants who had quit smoking, higher pack-years were associated with higher AI ($B = 0.85$; 95% CI, 0.60–1.14) and central pulse pressure ($B = 0.84$; 95% CI, 0.46–1.21). Using restricted cubic splines, we observed a negative linear association for AI, but non-linear associations for characteristic impedance and central pulse pressure, with higher time since quit (all $P < 0.001$). Additionally, we observed non-linear patterns of central arterial measures with smoking cessation by smoking burden (<20 vs. ≥20 pack-years). In longitudinal models, we observed higher increases in AI among participants who persistently quit (4.62 ± 0.41%; $P < 0.001$) and persistently smoked (5.48 ± 0.70%; $P = 0.002$) compared with participants who never smoked (3.45 ± 0.37%).

Conclusion Central arterial measures are sensitive to differences and changes in smoking behaviour. Longer cessation may revert central arterial measures to levels observed with lower smoking exposure.

Lay summary Smoking duration and intensity are known to contribute to cardiovascular disease. We assessed cross-sectional and longitudinal associations of smoking behaviour with measures of large (central) arterial function in the Framingham Heart Study.

- In a 'snapshot' at a single point in time (cross-sectional study), those who had quit smoking for a long time and those who were currently smoking had a higher augmentation index compared with those who never smoked. Participants who

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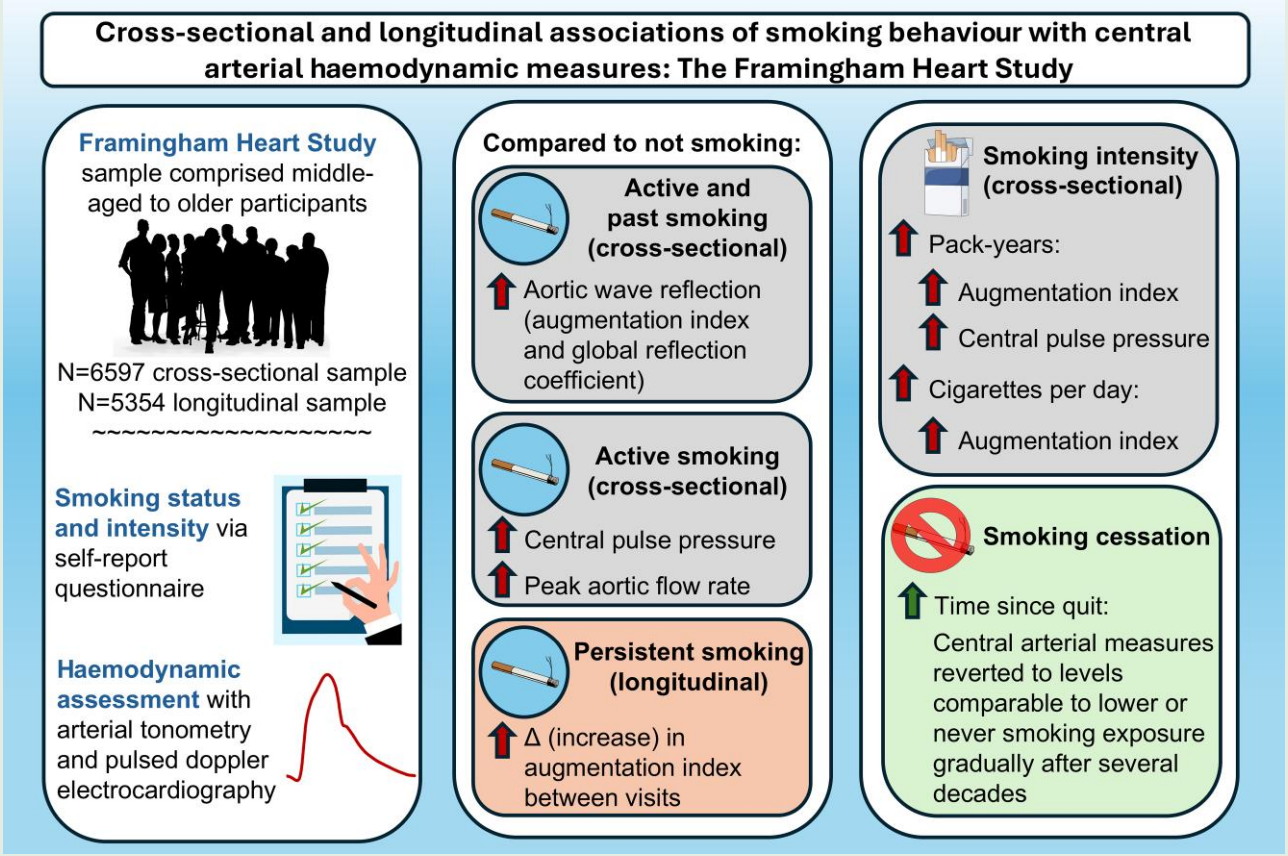
were currently smoking also had higher central pulse pressure, global reflection coefficient, and peak aortic flow rate compared with those who never smoked. A greater overall burden of cigarette smoking was linked to a higher augmentation index and central pulse pressure. The putative impact of quitting smoking on large (central) arterial function weakened the longer participants had quit. Over time (longitudinal study), the augmentation index increased more in participants who kept smoking or had quit for a long time compared with those who never smoked.

- Central arterial haemodynamic measures are influenced by smoking status and intensity and changes in smoking behaviour. Longer smoking cessation may restore large (central) arterial measures to levels close to those in individuals with lower smoking exposure.

Graphical Abstract



Keywords Vascular biology • Smoking • Lifestyle • Vascular hemodynamics • Epidemiology

Introduction

Cigarette smoking is a major modifiable risk factor for cardiovascular disease (CVD) and annually contributes to ~6 million deaths worldwide and nearly half a million deaths in the United States.[1,2] Smoking duration and intensity are known to contribute to the toxicologic burden of CVD and increase disease risk. For example, smoking contributes to a range of cardiovascular consequences, including endothelial dysfunction and inflammation, as well as conditions such as coronary artery disease, myocardial infarction, heart failure, stroke, aneurysms, and peripheral vascular disease.[3] Conversely, smoking cessation is associated with a reduction of morbidity and mortality and improvement to cardiovascular health.[4] For example, a prior Framingham Heart Study (FHS) investigation showed that in persons with heavy smoking burden, smoking cessation was associated with a lower risk of CVD within 5 years compared with persons who were actively smoking.[4] Measures of vascular central haemodynamics and aortic stiffness are pre-clinical predictors of CVD events.[5,6] Several cross-sectional studies have shown inconsistent associations of smoking status and intensity with vascular haemodynamic measures that contribute to CVD that were assessed in various vascular beds. Additionally, the impact of changes in smoking behaviours on central arterial haemodynamic measures has yet to be elucidated in well-characterized cohorts with longitudinal tracking of smoking status and comprehensive vascular haemodynamics. Thus, the putative effects of continuous and changing smoking behaviour (intensity, cessation, and relapse) on central arterial haemodynamics are not defined. We aimed to assess the cross-sectional and longitudinal associations of smoking behaviour with measures of central arterial haemodynamics in samples of the FHS.

Methods

Study sample

The study samples were drawn from the FHS Offspring, New Offspring Spouses, Generation 3, Omni 1, and Omni 2 cohorts. Participants who attended examinations when both smoking data and measures of vascular function were reliably collected for the index examination visit and a follow-up visit were eligible for this investigation [examinations 8 (2005–08) and 9 (2011–14) for offspring; examinations 2 (2008–11) and 3 (2016–19) for New Offspring Spouses, Generation 3, and Omni 2; and examinations 3 (2007–08) and 4 (2011–14) for Omni 1]. About 7119 participants were eligible for this investigation at the index examination visit. We excluded 522 due to missing data or a quit history of <1 year (among participants who reported quitting) to censor for unsuccessful quit attempts and relapses. Three participants with inconsistent self-reported smoking behaviour were classified among those with missing smoking data. At follow-up, 1243 participants were further excluded due to loss to follow-up, death, or missing smoking data. All protocols were approved by the Boston University Medical Center's Institutional Review Board, and all participants provided written informed consent.

Smoking status and intensity

At each examination, participants were categorized by smoking status based on their responses to a self-report questionnaire. We defined currently smoking as smoking regularly within 12 months of each respective examination. We defined smoking cessation (or quitting) behaviour for participants who (i) responded 'no' when asked if they smoke cigarettes regularly in the last year; (ii) responded 'no' when asked if they were currently smoking (as of 1 month ago); (iii) indicated current or regular smoking at a prior visit; and (iv) provided an age if they have stopped smoking completely. To better capture the effects of smoking cessation, we further categorized participants by their quit history as recently quit (participants who reported regular cigarette use at prior visits but had quit by the index examination visit) and formerly quit (participants who reported no regular cigarette use at or before the visit prior to the index examination visit) based on responses given for the questionnaire. We defined 'never smoked' when participants reported never having smoked. Participants who were currently smoking and those who quit were asked their age when they started smoking, cigarettes smoked per day when smoking, or when they smoked, and age at quitting (if smoking ceased). For these questions, we assessed smoking duration, cumulative pack-years, and years since quitting. Using the same questionnaire, we assessed change in smoking status between the two exam cycles for longitudinal analyses.

Haemodynamic assessment with arterial tonometry

Haemodynamic assessment with arterial tonometry and pulsed Doppler electrocardiography was performed as previously described.[5] We obtained non-invasive arterial tonometry with simultaneous electrocardiography from supine participants for the brachial, radial, femoral, and carotid arteries using a custom tonometer. During the tonometric assessment of the carotid artery, we performed pulsed Doppler of the left ventricular outflow tract to assess aortic flow. We digitized and transferred tonometric data and Doppler electrocardiography data to a core laboratory (Cardiovascular Engineering, Inc., Norwood, MA, USA) for blinded analyses. We signal-averaged and synchronized tonometry waveforms using the electrocardiographic R-wave and then calculated mean arterial pressure as the integral of the signal-averaged brachial pressure tonometry waveform.[5] We estimated pulse wave velocities from tonometry waveforms and body surface measurements that adjusted for parallel transmission in the aortic arch and brachiocephalic artery as previously described.[7] We calculated the carotid-femoral pulse wave velocity (CFPWV), carotid–brachial pulse wave velocity, and carotid–radial pulse wave velocity as the ratios of the adjusted transit distance and the pulse transit time difference between the carotid and the femoral, brachial, and radial sites, respectively. We calculated the pulse wave velocity ratio as the CFPWV divided by the carotid–brachial pulse wave velocity. We calculated central pulse pressure as the difference between carotid systolic and diastolic blood pressures. We defined forward pressure wave amplitude as the difference between pressure at the foot and at the peak of the forward pressure waveform by performing time domain wave separation analysis using central pressure and flow.[8] The global reflection coefficient was defined as backward wave amplitude divided by forward pressure wave amplitude. We calculated the augmentation index as the fraction of central pulse pressure attributable to late systolic pressure. Characteristic impedance was calculated in the time domain as the ratio of the pressure increase and the flow increase during the time interval between flow onset and 95% of peak flow.[8]

Clinical evaluation and covariates

Medical history was acquired, and a physical examination was performed routinely at each examination visit. Age, sex, use of antihypertensive and hyperlipidaemia medications, and CVD history were assessed through questionnaires. Height (metres) and weight (kilograms) were assessed during the examination. Body mass index was calculated as weight in kilograms divided by height in metres squared. Heart rate and blood pressures were assessed during tonometry. We estimated glomerular filtration rate (eGFR) via the calculation equation without considering race using creatinine.[9] Serum cholesterol levels were measured from fasting blood tests. Criteria for diabetes were a fasting glucose level of ≥126 mg/dL (7.0 mmol/L) or treatment with insulin or an oral hypoglycaemic agent.

Statistical analysis

We tabulated characteristics for the study sample. CFPWV was inverted to limit heteroscedasticity, then multiplied by −1000 to convert units to ms/m and rectify the directionality of associations with aortic stiffness. We selected covariates a priori as follows: age, age^2, sex, cohort, body mass index, heart rate, mean arterial pressure, total to HDL cholesterol ratio, triglycerides, prevalent CVD, lipid-lowering medication use, hypertension treatment, and prevalent diabetes. The triglycerides variable was natural logarithmically transformed to normalize its skewed distribution. We present a directed acyclic graph of our causal framework in *Figure 1A*. To maximize sample sizes, we excluded participants missing individual tonometry measures on an analysis-by-analysis basis.

In cross-sectional analyses, we used multivariable linear regression models to relate smoking status (currently smoking, formerly quit, recently quit, and never smoked) with central arterial haemodynamic measures. The never smoked group was the reference group. We estimated least squares means based on regression models with central arterial haemodynamic measures as dependent variables and smoking status groups as independent variables, adjusting for the above-mentioned covariates. We further adjusted the cross-sectional models for eGFR. In secondary analyses, we used multivariable linear regression models to relate smoking status with eGFR and peripheral arterial haemodynamic measures. To assess the association of smoking intensity among participants who ever smoked, we used multivariable linear regression models to relate cigarettes per day (among participants who were currently smoking) and pack-years (among participants who had quit smoking) with central arterial measures. We estimated multivariable-adjusted non-linear relations of time since quit with central arterial measures using restricted cubic splines. We further assessed the putative interaction of smoking burden and time since quit by stratifying the spline analyses by cumulative smoking burden (<20 vs. ≥20 pack-years).

For longitudinal analyses, we calculated change from the index examination visit to the follow-up exam in central arterial measures for each of the groups as follows: persistently never smoked, persistently quit, recently quit, and persistently smoking. Participants in a change in smoking status group with a low sample size were excluded from the analysis. We assessed the association of changes in central arterial measures with smoking status in the longitudinal sample using multivariable linear regression adjusted for the aforementioned covariates and central arterial haemodynamic values at the index examination visit. We estimated least squares means based on regression models with change in vascular measures as dependent variables

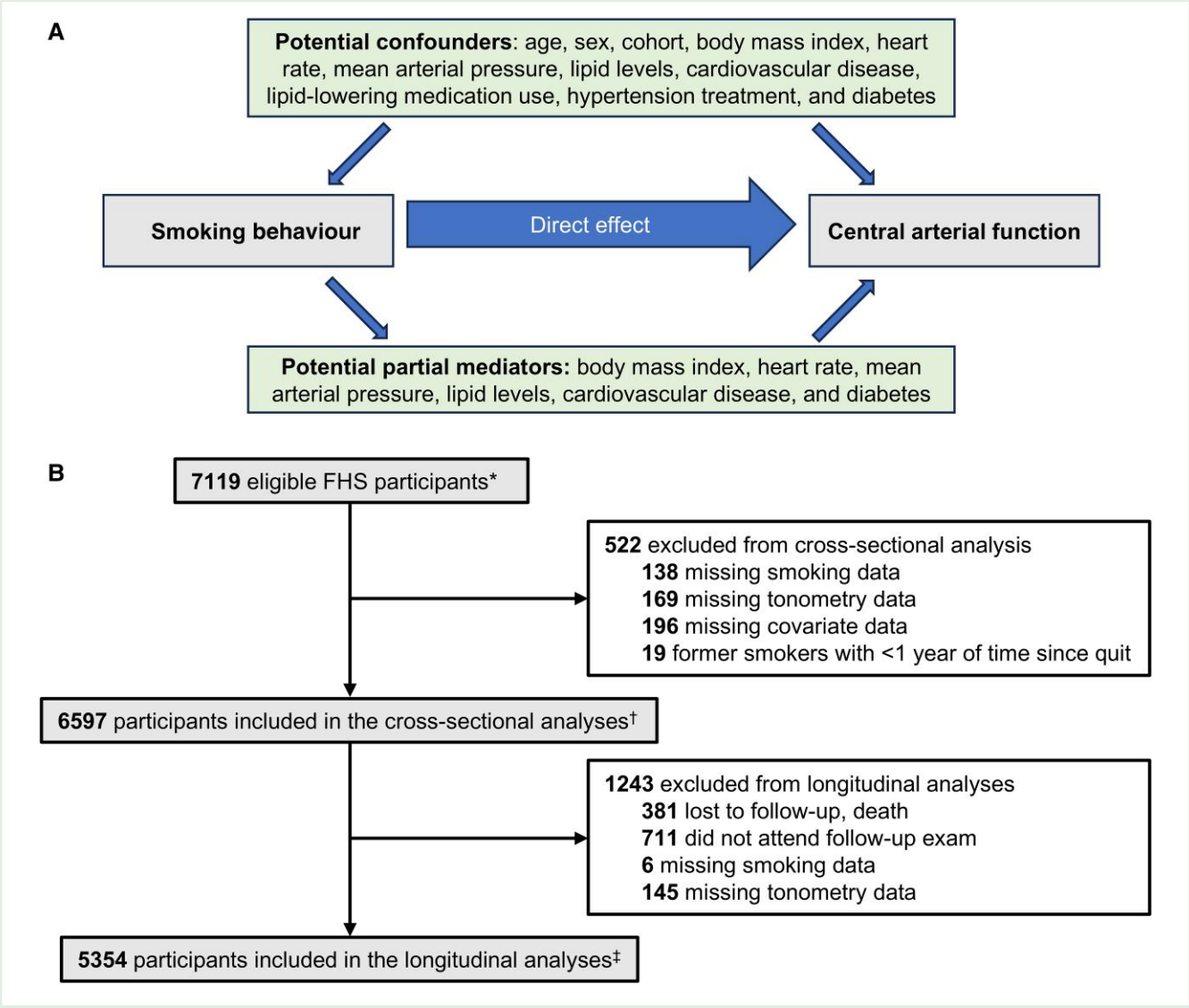


Figure 1 Causal framework and sample selection for the analyses. We present (*A*) a directed-acyclic graph of our causal framework and (*B*) a flow diagram of the Framingham Heart Study cohorts comprising the analytic samples. *3021 Offspring participants at Exam 8; 68 New Offspring Spouses participants at Exam 2; 3411 Generation 3 participants at Exam 2; 298 Omni 1 participants at Exam 3; and 321 Omni 2 participants at Exam 2. †2644 Offspring participants at Exam 8; 63 New Offspring Spouses participants at Exam 2; 3292 Generation 3 participants at Exam 2; 283 Omni 1 participants at Exam 3; and 315 Omni 2 participants at Exam 2. ‡2009 Offspring participants (Exams 8–9); 44 New Offspring Spouses participants (Exams 2–3); 2799 Generation 3 participants (Exams 2–3); 231 Omni 1 participants (Exams 3–4); and 271 Omni 2 participants (Exams 2–3). The mean follow-up time (longitudinal analysis) for the sample was 7.0 ± 1.2 years. The follow-up times for each cohort were as follows: Offspring, 5.8 ± 0.5 years; New Offspring Spouses, 7.4 ± 0.7 years; Generation 3, 7.9 ± 0.7 years; Omni 1, 5.0 ± 0.5 years; and Omni 2, 7.1 ± 0.6 years.

and smoking status groups as independent variables, adjusting for the above-mentioned covariates. We further adjusted the longitudinal models for eGFR at the index visit. In secondary analyses, we used multivariable linear regression models to relate changes in smoking status with changes in eGFR between visits. All analyses were performed with SAS version 9.4 for Windows (SAS Institute, Cary, NC, USA). Bonferroni-adjusted, two-sided *P*-values were used to assess statistical significance.

Results

We included 6597 participants [3606 (55%) women] in the analyses. The mean follow-up time (longitudinal analysis) for the sample was 7.0 ± 1.2 years (range: 3.6–10.8 years). A flow diagram for the analysis samples is presented in *Figure 1B*, and clinical characteristics and arterial haemodynamic measures of the study participants stratified by smoking category at the index examination visit are presented in *Table 1* and Supplementary material online, *Table S1*, respectively. Participants with a shorter quit history (recently quit) had a median time since quit of 3.2 years, and participants with a longer quit history (formerly quit) had a median time since quit of 23.1 years.

We present comparisons of least squares means estimates of central arterial haemodynamic measures according to smoking status at the index examination visit in *Figure 2*. Compared with participants who never smoked, participants who formerly quit and were currently smoking had

Table 1 Clinical characteristics at the index examination visit

Variable	Overall $n = 6597$	Never smoked $n = 3399$	Formerly quit $n = 2299$	Recently quit $n = 284$	Currently smoking $n = 615$
Age, years	55.3 ± 13.1	52.7 ± 13.2	60.4 ± 12.0	52.2 ± 12.3	52.2 ± 11.6
Women, *n* (%)	3606 (55)	1888 (56)	1246 (54)	153 (54)	319 (52)
Body mass index, kg/m^2	28.0 ± 5.6	27.8 ± 5.6	28.4 ± 5.4	29.4 ± 5.7	27.6 ± 6.0
Heart rate, b.p.m.	63 ± 10	62 ± 10	62 ± 10	64 ± 10	66 ± 10
Mean arterial pressure, mmHg	92 ± 13	91 ± 13	94 ± 12	92 ± 13	91 ± 12
Total-to-HDL cholesterol ratio	3.4 ± 1.1	3.4 ± 1.1	3.4 ± 1.0	3.6 ± 1.2	3.7 ± 1.3
Triglycerides, mg/dL	97 [70, 136]	94 [68, 131]	98 [72, 137]	106 [74, 159]	104 [76, 147]
Prevalent CVD disease, *n* (%)	557 (8)	174 (5)	288 (13)	36 (13)	59 (10)
Lipid-lowering medications, *n* (%)	1825 (28)	765 (23)	833 (36)	77 (27)	150 (24)
Prevalent hypertension, *n* (%)	2502 (38)[a]	1106 (33)	1096 (48)	102 (36)	198 (32)
Hypertension treatment, *n* (%)	2046 (31)	899 (26)	918 (40)	78 (28)	151 (25)
Prevalent diabetes, *n* (%)	600 (9)	250 (7)	276 (12)	29 (10)	45 (7)
Age of smoking initiation, years	17.7 ± 3.8[b]	—	17.7 ± 3.7	18.0 ± 4.2	17.3 ± 4.0
Smoking duration, years	21.0 ± 13.5[b]	—	17.1 ± 11.5	26.9 ± 13.5	32.9 ± 12.7
Cumulative pack-years, years	20.7 ± 20.3[b]	—	17.6 ± 18.3	22.0 ± 22.7	31.7 ± 22.4
Years since quitting	22.5 ± 12.3[c]	—	24.8 ± 11.1	4.2 ± 3.3	—
Cigarettes per day, *n*	13.5 ± 9.4[d]	—	—	—	13.5 ± 9.4

Values are mean ± standard deviation, number (%), or median [25th and 75th percentile].
CVD, cardiovascular disease; HDL, high-density lipoprotein.
[a] $n = 6595$.
[b] n ranges from 3058 to 3195.
[c] $n = 2582$.
[d] $n = 612$.

a higher augmentation index. Participants who formerly quit had a higher mean global reflection coefficient, and participants who were currently smoking had a higher mean central pulse pressure, global reflection coefficient, and peak aortic flow rate compared with those who never smoked. We observed no significant cross-sectional differences for other central vascular measures by smoking status. We present comparisons of least squares means estimates of eGFR according to smoking status at the index examination visit in Supplementary material online, *Figure S1A*. Compared with participants who never smoked, participants who had recently quit and currently smoke had higher eGFR at the index examination visit. However, the cross-sectional associations of central arterial haemodynamic measures with smoking status were similar, regardless of adjustment for eGFR (see Supplementary material online, *Figure S2*). We present comparisons of least squares means estimates of peripheral arterial haemodynamic measures according to smoking status at the index examination visit in Supplementary material online, *Table S2*. Compared with participants who never smoked, participants who were currently smoking had lower carotid–brachial pulse wave velocity. We observed no significant cross-sectional differences for other peripheral vascular measures by smoking status.

We present multivariable cross-sectional associations of central arterial haemodynamic measures with surrogates of smoking intensity in *Table 2*. Among participants who were currently smoking, higher cigarettes per day [estimated $B = 1.41$; 95% confidence interval (CI), 0.47–2.34; $P = 0.003$] was associated with higher augmentation index but was not associated with other central arterial measures. Among participants who had quit smoking, higher pack-years was associated with higher augmentation index (est. $B = 0.85$; 95% CI, 0.60–1.14) and central pulse pressure (est. $B = 0.84$; 95% CI, 0.46–1.21) but was not associated with other central arterial measures. *Figure 3* depicts multivariable-adjusted restricted cubic spline plots of the relations of time since quit with select central arterial haemodynamic measures. We observed a steep, linear negative association for augmentation index ($P < 0.001$) with higher time since quit. However, we observed distinct non-linear associations of time since quit with characteristic impedance ($P < 0.001$) and central pulse pressure ($P < 0.001$). Among participants with shorter quit histories, characteristic impedance was similar, but we observed progressively higher characteristic impedance after 25 years of smoking cessation. Among participants with shorter quit histories, central pulse pressure was progressively lower until after 25 years of smoking cessation when central pulse pressure was progressively higher among those with longer quit histories. We observed effect modification by smoking burden for the relations of time since quit with central arterial haemodynamic measures (see Supplementary material online, *Figure S3*). Generally, higher smoking burden was significantly related to higher aortic stiffness and central pressure pulsatility across the spectrum of quit history. Differences between high and low smoking burdens for augmentation index were attenuated whereas differences for characteristic impedance were exacerbated with greater time since quit.

We present a comparison of least squares means estimates of the longitudinal change in central arterial haemodynamic measures between two examination visits by smoking behaviour in *Figure 4*. We excluded participants who exhibited a change in smoking status with low sample sizes (never smoked to quit, never smoked to currently smoking, and quit to currently smoking). We present the observed (unadjusted) values of central arterial haemodynamic measures between two visits for the longitudinal sample in Supplementary material online, *Table S3*. Compared with participants who persistently never smoked, participants who persistently quit and persistently smoked had higher increases in augmentation index. We did not observe differences in longitudinal changes for other

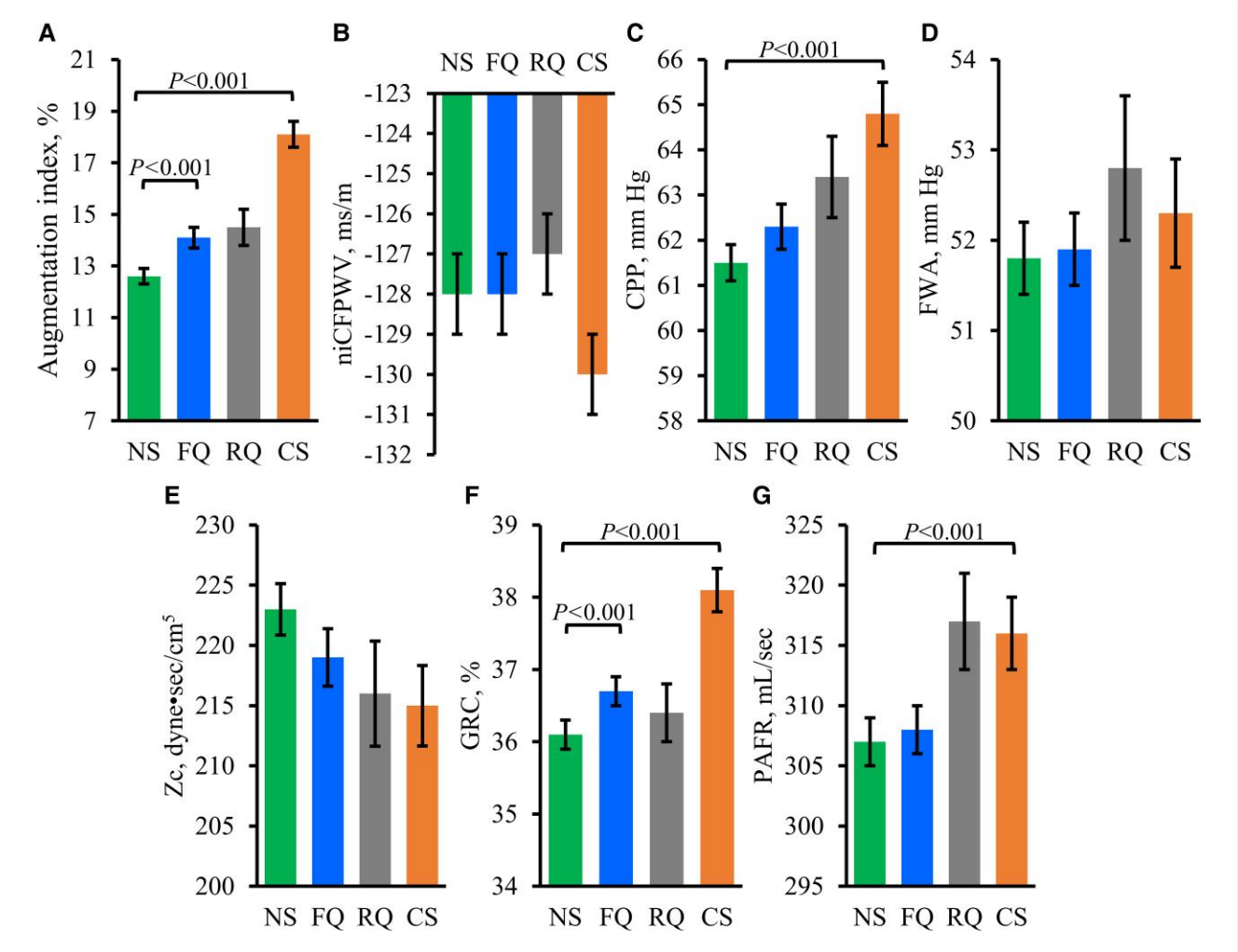


Figure 2 Estimated least squares means of central arterial haemodynamic measures according to smoking status at the index examination visit. We present a comparison of least squares means estimates ± standard deviations of (*A*) augmentation index, (*B*) negative inverse carotid–femoral pulse wave velocity, (*C*), central pulse pressure, (*D*) forward pressure wave, (*E*) characteristic impedance, (*F*) global reflection coefficient, and (*G*) peak aortic flow rate, at the index visit. Participants who formerly quit (blue), recently quit (grey), and were currently smoking (orange) are compared with participants who never smoked (green). Bonferroni-adjusted *P*-values ($P = 0.05/21 = 0.0024$) were used to assess the significance of associations. Only comparisons with *P*-values below the Bonferroni-adjusted significance threshold are indicated. Multivariable models adjusted for age, age^2, sex, cohort, body mass index, tonometry heart rate, mean arterial pressure, total to HDL cholesterol ratio, triglycerides, prevalent cardiovascular disease, lipid-lowering medication use, hypertension treatment, and prevalent diabetes. CPP, central pulse pressure; CS, currently smoking; FQ, formerly quit; FWA, forward wave amplitude; GRC, global reflection coefficient; NS, never smoked; niCFPWV, negative inverse carotid-femoral pulse wave velocity; PAFR, peak aortic flow rate, RQ, recently quit; Zc, characteristic impedance.

haemodynamic measures across smoking behaviour groups. Participants who recently quit smoking showed a more pronounced longitudinal decrease in eGFR compared to those who persistently never smoked (see Supplementary material online, *Figure S1*B). However, the longitudinal associations of changes in central arterial haemodynamic measures with smoking behaviour were similar, regardless of adjustment for eGFR (see Supplementary material online, *Figure S4*).

Discussion

We investigated the cross-sectional and longitudinal relations of smoking behaviour and intensity with measures of central arterial haemodynamics in two generations of the community-based FHS. In cross-sectional models, participants who formerly quit and were currently smoking had a higher augmentation index compared to participants who never smoked. Compared with participants who never smoked, participants who currently smoked had higher mean central pulse pressure, global reflection coefficient, and peak aortic flow rate. Higher smoking intensity (cigarettes per day and pack-years) was associated with higher augmentation index and central pulse pressure. The association of smoking cessation (time since quit) with augmentation index, characteristic impedance, and central pulse pressure diminished among participants with longer duration of smoking cessation. However, we observed distinct patterns of central vascular measures with smoking cessation by smoking burden (<20 vs. ≥20 pack-years).

Table 2 Multivariable cross-sectional associations of central arterial haemodynamic measures with smoking intensity at the index examination visit

Outcome variable	Cigarettes per day[a]		Pack-years[b]	
	Est. B (95% CI)	*P*	Est. B (95% CI)	*P*
Augmentation index, %	1.41 (0.47, 2.34)	0.003	0.85 (0.60, 1.14)	<0.001
niCFPWV, ms/m	0.18 (−1.44, 1.79)	0.83	0.59 (0.06, 1.13)	0.03
Central pulse pressure, mm Hg	0.38 (−0.75, 1.51)	0.51	0.84 (0.46, 1.21)	<0.001
Forward pressure wave, mm Hg	0.20 (−0.80, 1.20)	0.70	0.33 (0.00, 0.66)	0.06
Characteristic impedance, dyne·s/cm^5	−1.33 (−6.89, 4.22)	0.64	−0.90 (−2.85, 1.04)	0.36
Global reflection coefficient, %	0.06 (−0.44, 0.56)	0.81	0.15 (−0.01, 0.32)	0.06
Peak aortic flow rate, mL/s	3.52 (−1.48, 8.52)	0.17	1.37 (−0.24, 2.98)	0.09

Regression estimates (*B*) in native units followed by the 95% confidence interval and *P*-values. Bonferroni-adjusted *P*-values ($P = 0.05/14 = 0.0036$) were used to assess significance of associations. All continuous outcome variables expressed as change per standard deviation of the independent variables. All models were adjusted for age, age^2 sex, cohort, body mass index, tonometry heart rate, mean arterial pressure, total to high-density lipoprotein cholesterol ratio, triglycerides, prevalent cardiovascular disease, lipid-lowering medication use, hypertension treatment, and prevalent diabetes.

niCFPWV, negative inverse carotid–femoral pulse wave velocity.

[a]Assessed among participants who were currently smoking.

[b]Assessed among participants who had quit smoking; models were further adjusted for time since quit.

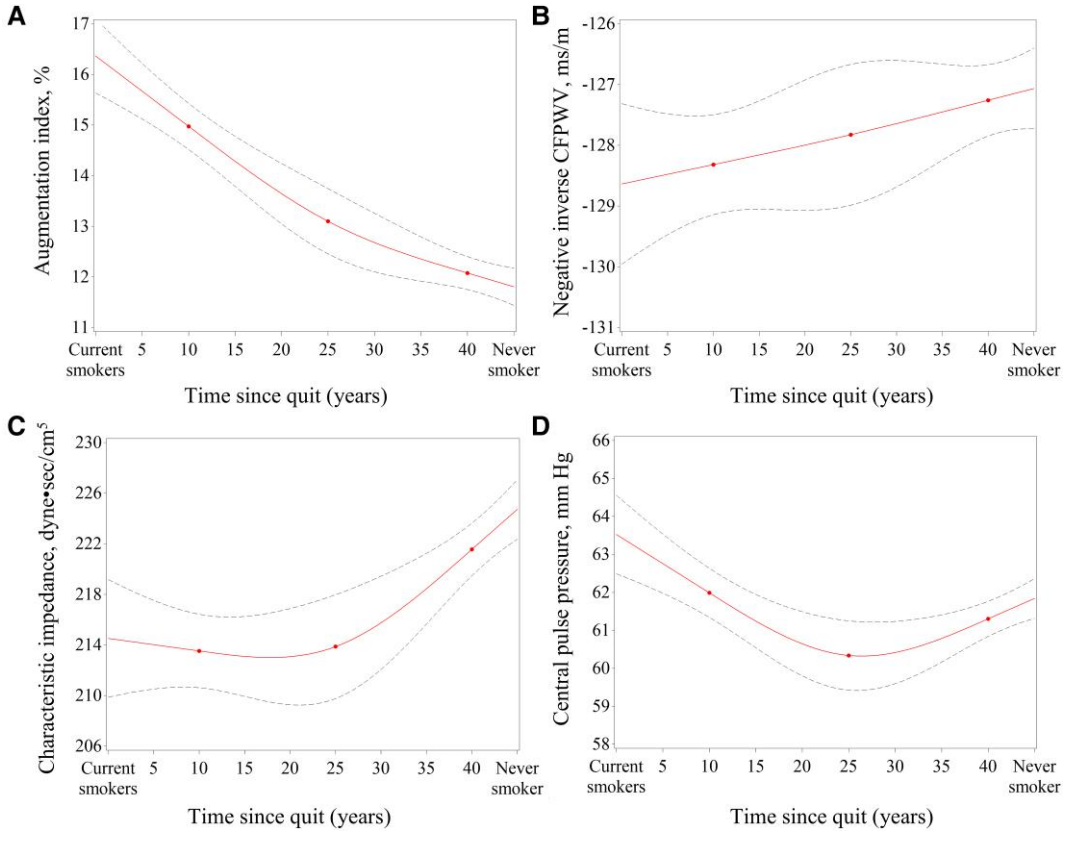


Figure 3 Multivariable-adjusted splines illustrate the associations of time since quit with central arterial haemodynamic measures. Restricted cubic splines (red solid lines) with 95% confidence intervals (black dotted lines) derived from associating time since quit with (*A*) augmentation index, (*B*) negative inverse carotid-femoral pulse wave velocity, (*C*) characteristic impedance, and (*D*) central pulse pressure. The *x*-axis ranges from currently smoking (minimum) to never smoked (maximum), capturing the distribution of participants based on their time since smoking cessation. We placed knots at the 25th, 50th, and 100th percentiles of the distribution of time since quit. All models were adjusted for age, age^2, sex, cohort, body mass index, heart rate, mean arterial pressure, total to HDL cholesterol ratio, triglycerides, prevalent cardiovascular disease, lipid-lowering medication use, hypertension treatment, and prevalent diabetes. *P* for overall association is <0.001 for augmentation index; 0.07 for negative inverse carotid–femoral pulse wave velocity; <0.001 for characteristic impedance; and <0.001 for central pulse pressure. *P* for non-linearity is 0.08 for augmentation index; 0.93 for negative inverse carotid–femoral pulse wave velocity; and 0.02 for characteristic impedance; and <0.001 for central pulse pressure.

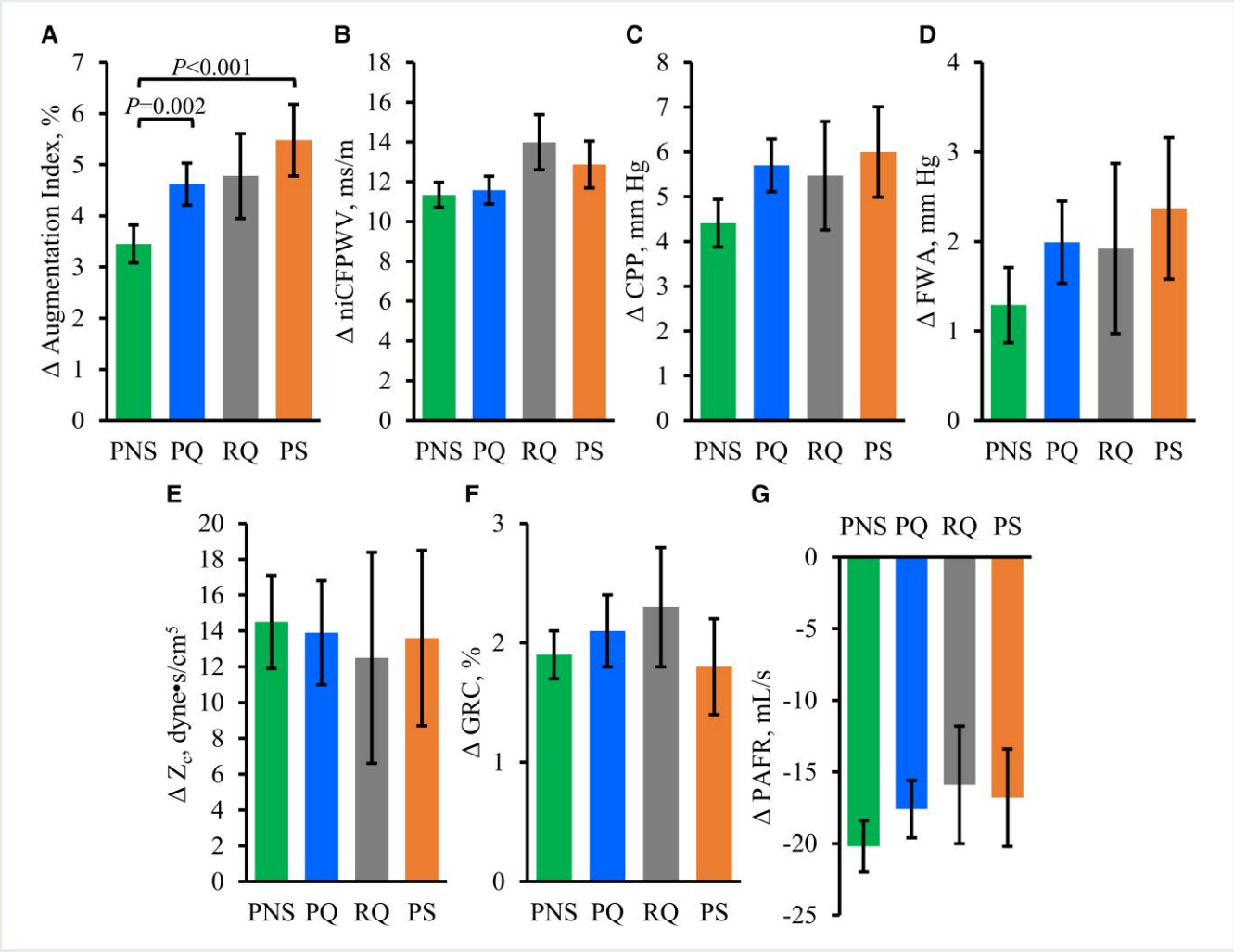


Figure 4 Longitudinal change (Δ) in central arterial haemodynamic measures between two examination visits by smoking behaviour. We present a comparison of least squares means estimates ± standard errors of the longitudinal change in (*A*) augmentation index, (*B*) negative inverse carotid–femoral pulse wave velocity, (*C*), central pulse pressure, (*D*) forward pressure wave, (*E*) characteristic impedance, (*F*) global reflection coefficient, and (*G*) peak aortic flow rate, between two examinations. Participants who had persistently quit (blue), recently quit (grey), and were persistently smoking (orange) are compared with participants who persistently never smoked (green). Bonferroni-adjusted *P*-values ($P = 0.05/21 = 0.0024$) were used to assess the significance of associations. Only comparisons with *P*-values below the Bonferroni-adjusted significance threshold are indicated. Multivariable models adjusted for age, age^2, sex, cohort, body mass index, tonometry heart rate, mean arterial pressure, total to HDL cholesterol ratio, triglycerides, prevalent cardiovascular disease, lipid-lowering medication use, hypertension treatment, prevalent diabetes, and vascular measures at the index examination visit. Participants with a change in smoking status of never smoked to quit, never smoked to currently smoking, and quit to currently smoking were excluded from the analysis due to low statistical power to resolve differences. CPP, central pulse pressure; FWA, forward pressure wave; GRC, global reflection coefficient; niCFPWV, negative inverse carotid-femoral pulse wave velocity; PAFR, peak aortic flow rate, PNS, persistently never smoked, PQ, persistently quit; PS, persistently smoking; RQ, recently quit; Zc, characteristic impedance.

Between exam visits, the augmentation index increased more among participants who were persistently smoking and who had persistently quit smoking compared with participants who had never smoked. Central arterial haemodynamic measures, particularly indices related to central wave reflection and pressure augmentation, are sensitive to smoking status and intensity and changes in smoking behaviour. Longer smoking cessation may partially restore central arterial measures to levels akin to those observed in individuals with lower smoking exposure.

Previous studies examining the acute and chronic effects of smoking on arterial stiffening are controversial and mixed; however, many studies consistently suggest that chronic changes in arterial haemodynamics substantially affect peripheral vessels.[10–15] In a recent Gutenberg Health Cohort Study, researchers observed that smoking status and smoking intensity were positively associated with peripheral arterial stiffness and wave reflection (assessed by digital photoplethysmography and digital plethysmography, respectively) in the community.[12] Our data suggest that higher levels of central wave reflection substantially contribute to the aortic haemodynamic physiologic state in the setting of current, chronic smoking. These findings align with previous research conducted within a young, healthy sample by Mahmud and Feely,[13] who reported a higher aortic augmentation index in participants who were actively,

chronically smoking compared with non-smoking participants. Additionally, higher smoking intensity was associated with a higher central augmentation index indicating a potential dose–response relation of smoking with wave reflection. In healthy, young arteries, there is a progressive increase in arterial stiffness from the highly elastic aorta to the smaller resistance arteries, which creates an impedance mismatch and partial reflection of the forward pressure wave.[16] We had hypothesized that smoking may increase the peripheral arterial stiffness relative to central aortic stiffness, thereby shifting reflecting sites more proximal to the heart. Higher impedance mismatch would increase wave reflection and contribute to higher levels of wave reflection (higher augmentation index and global reflection coefficient), as reflecting sites shift more proximal to the heart among participants who ever smoked compared with participants who never smoked. However, in secondary analyses of muscular and peripheral arterial haemodynamics (see Supplementary material online, *Table S2*), we observed lower carotid–brachial pulse wave velocity among participants who were currently smoking compared with participants who never smoked. These results suggest that smoking-related differences in central-to-peripheral arterial impedance gradient were not the underlying factor behind our observations. Furthermore, both the cross-sectional and longitudinal analyses with and without adjustment with eGFR are nearly identical (see Supplementary material online, *Figures S2* and *S4*). Since further adjustment for eGFR did not meaningfully change the results, smoking-related differences in kidney function do not appear to drive the associations in this relatively healthy sample.

Smoking is known to affect vascular function and may contribute to differences and longitudinal changes in central arterial haemodynamics across smoking behaviours. Smoking-induced reactive oxygen species production leads to oxidative stress and contributes to endothelial dysfunction,[17] which impairs vascular tone.[10,11] A hallmark of endothelial dysfunction is lower nitric oxide bioavailability, a characteristic of healthy individuals who smoke.[18] Endothelial dysfunction impairs regulation of small arteries, which can increase wave reflections from peripheral sites.[19] Our study suggests that among individuals who smoke, wave reflections return to the central aorta more prominently, raising the central pressure augmentation without significantly affecting central aortic stiffness. Kelly *et al.*[20] showed that aortic augmentation index, but not aortic pulse wave velocity, is sensitive to vasoactive drugs, which suggests that dysregulation of vascular tone affects wave reflection independently of aortic stiffness. We observed no differences in aortic stiffness and no to modest differences in peripheral arterial stiffness across smoking behaviour groups. It is plausible that smoking-associated differences in vascular tone regulation (in the absence of major differences in arterial stiffness) are a contributor to a higher augmentation index.[21] For example, differential dysregulation of small arterial tone may promote the relatively higher augmentation index (and its increase over time) in participants who have smoked compared to participants who never smoked. While this explanation is not yet fully established, multiple studies have shown that vascular endothelium-dependent relaxation and downstream microvascular function are impaired in individuals who smoke.[17,22,23] Nonetheless, the differences and changes to measures of small and microvascular arterial function due to chronic smoking and changes in smoking behaviours warrant further investigation. In the current study, quitting smoking appears to gradually reduce the impact of smoking on central wave reflection, suggesting that the harmful effects of smoking may be partially reversible with longer time since quitting. Our findings indicate that the potential effects of smoking cessation on vascular measures differ between individuals with higher (≥20 pack-years) and lower smoking burdens. Specifically, smoking cessation was associated with a greater reduction in augmentation index and a greater increase in characteristic impedance and CFPWV among those with a higher smoking burden. These data suggest that overall smoking burden, along with duration of smoking cessation, may be complementary factors in reducing the risk of adverse outcomes among those who quit smoking. Yet, the residual effects of past smoking may persist, especially with shorter durations since quitting. This concept is underscored in the current longitudinal analysis, which showed that participants who consistently quit smoking still experienced a higher increase in central augmentation index than those who had never smoked, although the increase was less than that of individuals who continued to smoke.

Compared with central haemodynamic measures, we observed little variation in peripheral arterial measures by smoking behaviour groups, which suggests that the chronic effects of smoking may be more pronounced in central arteries. Augmentation index is a measure of the pressure effects of the reflected wave, which are influenced by a complex interplay of timing, amplitude, and the left ventricular response to the reflected wave. The high flow state we previously documented in smokers would theoretically tend to lower augmentation index values.[23] Despite this, we observed a positive association of current smoking with a higher augmentation index, even in the absence of an effect on CFPWV, suggesting that smoking may be influencing reflecting sites upstream of the resistance vessels or impacting left ventricular structure, function, or preload. Smoking status and smoking intensity may contribute to elevated aortic pressure pulsatility. In a clinical sample, Mahmud and Feely[13] observed that smoking acutely increased both brachial and central blood pressure, augmentation index, and aortic pulse wave velocity, whereas aortic systolic blood pressure and augmentation index were higher in participants who chronically smoked compared to participants who did not smoke. Acute nicotine exposure increases heart rate, cardiac contractility, and blood pressure,[24] which have non-complementary effects on the timing and amplitude of reflected wave and subsequent effects on augmentation index. In the current study, we observed higher central wave reflection and augmented central pulse pressure among participants who currently smoked compared with participants who never smoked. Similar to the augmentation index, the association of smoking with central pulse pressure also demonstrated a dose-response relation. Taken together, higher pressure pulsatility and the earlier arrival of central wave reflection during systole (instead of diastole) may impair coronary perfusion.[25] Higher central pulse pressure increases afterload and may alter cardiac geometry maladaptively as concentric remodelling for individuals who smoke.[26,27] Similar to the current study, Markus *et al.*[15] observed in two separate cohorts that participants who were currently smoking had higher mean central systolic blood pressure, augmentation index, and left ventricular mass compared with participants who did not smoke. Additionally, in their longitudinal analyses, participants who were currently smoking showed a significant increase in left ventricular mass index, with both an increase in left ventricular wall thickness and end-diastolic diameter, whereas, left ventricular end-diastolic diameter decreased among participants who did not smoke, consistent with ageing-associated concentric remodelling.[15] Leigh *et al.*[9] observed that higher smoking burden was associated with higher left ventricular mass, worse diastolic function (higher E/e' ratio), and altered LV geometry (higher relative wall thickness). A concentrically remodelled left ventricle can more effectively augment pressure in the presence of a given reflected wave. Furthermore, it causes the reflected wave to be re-reflected as pressure into the aorta, both of which contribute to a higher augmentation index and central pressure. Our study reveals that quitting smoking may reduce the putative effect of smoking on central pulse pressure in a non-linear pattern, so, similar to wave reflection,

the higher haemodynamic burden from smoking might be partially reversed over time. Further studies that assess the mechanisms of smoking and smoking cessation on vascular dysfunction and CVD pathogenesis and prevention of CVD events are warranted.

Despite differences in other central arterial haemodynamic measures, aortic stiffness was similar in participants who never smoked compared with participants who ever smoked in our sample, as indicated by no significant differences in the CFPWV among smoking behaviour groups. This observation is consistent with prior work in assessing differences in chronic smoking.[28,29] However, our observations are in contrast with other studies that assessed aortic stiffness via MRI or ultrasound methods.[14,30] For example, in the Multi-Ethnic Study of Atherosclerosis Study, researchers observed higher aortic stiffness (assessed via MRI) among participants who were currently smoking compared with participants who had quit smoking and had never smoked.[14] Assessing aortic stiffness with MRI involves calculating the change in aortic cross-sectional area with pulsatile blood flow and normalizing this by the brachial pulse pressure. This method does not directly measure the pulse wave in the aorta (like arterial tonometry), which may contribute to differences between the MRI investigations and the current study. Additionally, areas of aortic calcification can interfere with the accuracy of MRI measurements, and errors in blood pressure measurements can significantly affect the aortic distensibility calculation, particularly when brachial pressures are used to estimate aortic pulse pressure.[31,32]

Although epidemiologic studies have shown that higher pulse pressure is associated with lower aortic root diameter,[33] smoking is associated with higher aortic diameter.[34] A recent mechanistic study in mice revealed significant interactions between nicotine exposure and hypertension on aortic diameter and cross-sectional area, consistent with eccentric remodelling.[35] The transition from concentric to eccentric remodelling may reflect the ongoing adaptation of the aorta to fluctuating and evolving physiological demands and stressors due to smoking. The higher cross-sectional area in individuals who chronically smoke is consistent with our observation of higher peak aortic flow rates in currently smoking participants compared with participants who never smoked. Additionally, we observed a significant non-linear association of time since quitting smoking and characteristic impedance, suggesting a threshold effect after about 25 years. While CFPWV shows limited sensitivity to changes in aortic diameter, characteristic impedance demonstrates a high degree of sensitivity to variations in the aortic diameter.[36] Rather than attributing our observations to smoking-related microvascular damage or changes in peripheral vascular tone, we posit an alternative hypothesis. Specifically, lower characteristic impedance from aortic root dilation and left ventricular concentric remodelling may contribute to the elevated central wave reflection, pulse pressure, and aortic flows observed in participants who actively smoke. The remodelled heart generates a higher incident forward wave into a more compliant aorta, adapted to accommodate increased left ventricular outflow. However, this greater compliance makes the aorta more susceptible to the return of the reflected wave, resulting in pressure augmentation and, consequently, higher pulse pressure, augmentation index, and reflection coefficient values. Thus, although measures of aortic stiffness trend towards more favourable levels among individuals who actively smoke or have previously smoked, this vascular response in this context is maladaptive. Compared with participants who did not smoke, participants who were currently smoking tended to have lower CFPWV and characteristic impedance (*Figure 2*; $P = 0.049$ and 0.006, respectively). However, these differences did not reach statistical significance due to correction for multiple comparisons (Bonferroni-adjusted $\alpha = 0.0024$). Yet, the observed trend towards lower values for characteristic impedance and CFPWV may be a consequence of smoking-induced aortic remodelling (i.e. lumen dilation and weakening or loss of aortic wall integrity) with biological significance. Despite appearing to improve aortic stiffness measures, smoking-related aortic remodelling may be pathological and may contribute to thoracic or abdominal aortic aneurysms, atherosclerosis, and other CVD events. In the current study, smoking cessation marks a return of central haemodynamic measures to physiological values closer to participants who never smoked. Smoking also increases blood viscosity,[37] which raises characteristic impedance. However, blood viscosity has a limited direct effect on characteristic impedance, which is dominated by inertial rather than viscous effects.[38] Additionally, Shimada *et al.*[39] reported that blood viscosity was markedly reduced in only a few months after smoking cessation. Given that we observed differences in characteristic impedance only after an extended period of smoking cessation, it appears that the probable recovery of characteristic impedance may be attributed to changes in aortic structure rather than to restoration of blood viscosity. However, future observational and animal experimental research is needed to provide further insight into the effect of smoking and smoking cessation on central arterial haemodynamics and vascular remodelling.

Limitations

Our study has limitations that should be considered. Although we were able to establish a temporal relation in our longitudinal analyses, the observational nature of the study limits causal inference. The gold standard for establishing causality is randomized, blinded placebo-controlled trials, but studying smoking exposures as a randomized study in humans would be unethical. Additionally, we cannot dismiss the possibility of residual confounding by unknown or unmeasured factors. Some of the covariates in our models may partially mediate the relations of smoking behaviour with vascular function. As a result, adjusting for these variables may have led to an underestimation of the observed associations; however, the reported associations are likely more conservative estimates of the true effect. We used self-reported smoking data, and cotinine levels or expiratory carbon monoxide levels were not measured in FHS, preventing us from validating smoking behaviours, which may lead to misclassification of participants who underreport or inaccurately report their smoking behaviours. In particular, time since quitting and the amount of smoking may be misclassified. We did not account for e-cigarettes, cigars, and hookah (waterpipe or shisha) or cannabis use; therefore, our study may underestimate the total tobacco and smoking exposure of the participants. In the longitudinal analyses, participants with a change in smoking status of never smoked to quit ($n = 3$), never smoked to currently smoking ($n = 5$), and quit to currently smoking ($n = 41$) were excluded from the analysis due to low statistical power to resolve differences. Although our sample includes participants of the Omni 1 and Omni 2 cohorts from under-represented racial and ethnic groups, most participants were White individuals of European ancestry; therefore, our findings may not be generalizable to other ethnic or racial groups. Similarly, our sample comprised middle-aged to older participants, so our findings may not be generalizable to younger individuals.

Conclusions

We examined the cross-sectional and longitudinal relations of smoking behaviour and intensity with central arterial haemodynamic measures

in middle-aged to older participants of the FHS. Our results suggest that smoking is associated with increases in relative wave reflection, aortic pressure pulsatility, and aortic flow, with associations more pronounced among those who are currently smoking and have smoked compared with those who never smoked, with higher levels among those with greater smoking intensity. However, longer smoking cessation may be associated with reduced relations over time, indicating a potential restoration of vascular function towards levels observed in individuals who never smoked. Relative wave reflection notably was associated with continuing to smoke or quitting compared with those who never smoked after one exam cycle, emphasizing the association of smoking and cessation on central arterial function in a relatively short time. Our study underscores the connection between smoking and cessation on central arterial haemodynamics, highlighting the sensitivity of vascular function to smoking behaviours and intensity.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contribution

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Conflict of interest: G.F.M. is the owner of Cardiovascular Engineering, Inc., a company that designs and manufactures devices that measure vascular stiffness. The company uses these devices in clinical trials that evaluate the effects of diseases and interventions on vascular stiffness. G.F.M. also serves as a consultant to and receives grants and honoraria from Novartis, Merck, Bayer, Servier, Philips, and deCODE genetics. The remaining authors have no disclosures to report.

Data availability

Our study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. The data underlying this article will be shared upon request. The procedures for requesting data from the Framingham Heart Study can be found at: https://www.framinghamheartstudy.org/.

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