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Cigarette Smoking, Smoking Cessation, and Long-Term Risk of 3 Major Atherosclerotic Diseases

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ABSTRACT

BACKGROUND Public statements about the effect of smoking on cardiovascular disease are predominantly based on investigations of coronary heart disease (CHD) and stroke, although smoking is recognized as a strong risk factor for peripheral artery disease (PAD). No study has comprehensively compared the long-term association of cigarette smoking and its cessation with the incidence of 3 major atherosclerotic diseases (PAD, CHD, and stroke).

OBJECTIVES The aim of this study was to quantify the long-term association of cigarette smoking and its cessation with the incidence of the 3 outcomes.

METHODS A total of 13,355 participants aged 45 to 64 years in the ARIC (Atherosclerosis Risk In Communities) study without PAD, CHD, or stroke at baseline (1987 to 1989) were included. The associations of smoking parameters (pack-years, duration, intensity, and cessation) with incident PAD were quantified and contrasted with CHD and stroke using Cox models.

RESULTS Over a median follow-up of 26 years, there were 492 PAD cases, 1,798 CHD cases, and 1,106 stroke cases. A dose-response relationship was identified between pack-years of smoking and 3 outcomes, with the strongest results for PAD. The pattern was consistent when investigating duration and intensity separately. A longer period of smoking cessation was consistently related to lower risk of PAD, CHD, and stroke, but a significantly elevated risk persisted up to 30 years following smoking cessation for PAD and up to 20 years for CHD.

CONCLUSIONS All smoking measures showed significant associations with 3 major atherosclerotic diseases, with the strongest effect size for incident PAD. The risk due to smoking lasted up to 30 years for PAD and 20 years for CHD. Our results further highlight the importance of smoking prevention and early smoking cessation, and indicate the need for public statements to take PAD into account when acknowledging the impact of smoking on overall cardiovascular health.
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Cigarette smoking is a major modifiable risk factor for cardiovascular disease (CVD) (1). Public statements and reports about the effect of smoking cessation on CVD are predominantly based on investigations of coronary heart disease (CHD) and stroke. For example, the 2004 Surgeon General's report concluded that the excess risk of CHD caused by smoking was reduced to that of

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never-smokers 15 years after smoking cessation (1); the Heart Disease and Stroke Statistics—2018 Update concluded that the CVD risk would return to the level of nonsmokers after ~10 years of cessation (2).

However, these public statements may underestimate the effect of smoking on CVD, because smoking is recognized as a particularly strong risk factor for peripheral artery disease (PAD) (3). Despite this recognition, to our knowledge, there have been only a few prospective studies directly comparing PAD and CHD as complications of current smoking status (4,5). Importantly, none of these studies examined other key smoking measures (pack-years, duration, intensity, and smoking cessation), and only one of them also assessed stroke simultaneously (4). Thus, a comprehensive study is needed for us to better understand the contribution of smoking to these 3 major atherosclerotic diseases.

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Although a number of studies have reported a positive association between smoking and PAD (4–21), these previous studies have important limitations as well. Specifically, most of these studies were cross-sectional (6–15,21) and susceptible to biases introduced by cessation of smoking after a diagnosis of PAD. There have been a few prospective studies exploring the association of smoking and PAD, but they have some caveats, such as an inclusion of only women (16) or men (17), a simple categorization of smoking status (current, former, or never [4,18,20]), short follow-up time of ≤5 years (5), or limited information about duration of smoking cessation (19).

To fill in the aforementioned knowledge gaps, the objective of this study was to quantify the long-term association of cigarette smoking and its cessation with the incidence of the 3 major atherosclerotic diseases using data from the ARIC (Atherosclerosis Risk In Communities) Study with follow-up for nearly 3 decades. We a priori hypothesized that all representative smoking measures would be more strongly associated with incident PAD than incident CHD and stroke, and the impact of smoking after its cessation would last longer for PAD than CHD and stroke.

METHODS

STUDY POPULATION. The ARIC study enrolled 15,792 participants age 45 to 64 years from 4 U.S. communities. The first clinic examinations (visit 1) took place from 1987 to 1989, with 3 short-term clinic visits (visits 2 to 4) approximately every 3 years (1990 to 1992, 1993 to 1995, and 1996 to 1998, respectively) and subsequent visits 5 and 6 during 2011 to 2013 and 2016 to 2017, respectively (22). Phone interviews were conducted annually from visit 1 to 2011 (smoking status was added from 1999), and semi-annually thereafter. For this analysis, we excluded participants whose race/ethnicity was recorded as other than white or black (n = 48); who had prevalent PAD (ankle-brachial index ≤0.9 [23], self-reported intermittent claudication based on Rose questionnaire, or a history of leg artery revascularization) at baseline (n = 746); who had prevalent CHD (electrocardiogram evidence of myocardial infarction at visit 1 or self-reported history of physician-diagnosed myocardial infarction or prior coronary reperfusion procedure [24]) or stroke (self-reported) at baseline (n = 916); or who had missing variables of interest (n = 727) (Online Figure 1). The final sample included 13,355 participants. The comparison of the baseline characteristics between the included population and the excluded because of missing data population was shown in Online Table 1.

MEASUREMENT OF SMOKING. Smoking status (current, former, never smoker), age smoking started, age smoking stopped, duration, and intensity were assessed by interview at baseline. Smoking duration at baseline was calculated based on participants' response to the following questions: "how old were you when you first started regular cigarette smoking," "age stopped smoking cigarettes," and "how many years did you not smoke cigarettes during the years that you have smoked." For current smokers, we calculated smoking duration as age at baseline minus age first started regular cigarette smoking minus years not smoking cigarettes (when applicable). For former smokers, smoking duration was calculated as age stopped smoking cigarettes minus age first started regular cigarette smoking minus years not smoking cigarettes. At the baseline visit, participants were also asked to specify how many cigarettes/day they usually smoked on the average of the entire time they smoked. This information was used to categorize the smoking intensity (packs/day) (25) among current and former smokers. Then, pack-years of smoking were calculated as the average number of cigarettes/day divided by 20 (converting to packs per day) times duration of smoking in years.

Years since cessation in former smokers at baseline were calculated as baseline age minus the recalled age of cessation. Because smoking status (current, former, never smoker) was also examined at 4 subsequent clinic visits and the annual/semi-annual phone interview, we were able to define smoking cessation as a time-varying exposure for over 2

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CHD = coronary heart disease

CVD = cardiovascular disease

eGFR = estimated glomerular filtration rate

PAD = peripheral artery disease

decades. Specifically, if the former smoker (at baseline or during follow-up) responded negatively to the question "do you now smoke cigarettes," years since cessation was accumulated for 1 more year. If current smokers transitioned to noncurrent smokers, the midpoint of these time points of data collection was assigned as the time of cessation. When never or former smokers transitioned to current smokers, they were categorized as current smokers until a subsequent visit or phone interview they reported noncurrent smoking. At clinic visit 1 to 4, current smokers were asked to specify the number of cigarettes/day they smoked at that moment; thus, we were able to adjust for time-varying smoking intensity when analyzing time-varying smoking cessation.

COVARIATES. Age, sex, race, educational level (completed college or more, high school to less than college, and less than high school) and alcohol use were self-reported. Body mass index (BMI) was calculated as body weight (kilograms) over height (meters) squared. Systolic and diastolic blood pressure was measured 3 times after 5 min of rest using a random-zero sphygmomanometer, and the average of the second and third readings was recorded. Total cholesterol and high-density lipoprotein cholesterol were determined using enzymatic methods. Physical activity was categorized from 1 (least active) to 5 (most active) according to sports during leisure time using a modified Baecke questionnaire (26). Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation (27). Medication use over the prior 2 weeks was verified by reviewing medication containers. Diabetes mellitus was defined as a fasting glucose ≥7.0 mmol/l, nonfasting glucose ≥11.1 mmol/l, self-reported physician diagnosis, or use of glucose-lowering medications.

OUTCOMES. The ARIC investigators conduct continuous, comprehensive surveillance for hospitalizations and deaths in the 4 communities (28–30). Based on previous published data (31–33), incident PAD was defined as hospitalizations with the International Classification of Diseases-9th Revision codes (listed in Online Table 2).

CHD events were adjudicated and defined as definite or probable myocardial infarction or fatal CHD (24). Stroke was adjudicated, and we included definite or probable ischemic and hemorrhagic stroke cases (28,30). Participants were followed until a cardiovascular outcome of interest, date of death, date of the last contact, or September 30, 2015, whichever came first. If >1 type of cardiovascular outcome happened in the same person, we included them in each relevant atherosclerotic type.

STATISTICAL ANALYSES. Baseline characteristics of the study population were compared according to smoking status (current, former, never) at baseline. Cox regression models were used to quantify the associations between smoking measures (pack-years of smoking, duration, intensity [packs/day], and cessation) and incident PAD, CHD, and stroke. Based on the distribution, pack-years were largely evenly categorized as <10, 10 to <25, 25 to <40, and ≥40 pack-years among current and former smokers. Duration of smoking was largely evenly categorized as <20 and ≥20 years among former smokers, and <35 and ≥35 years among current smokers. Intensity of smoking was categorized as <1 and ≥1 pack/day among former and current smokers. Age smoking started was categorized as <16, 16 to 17, 18 to 19, an ≥20 years. Age smoking stopped was categorized as <31, 31 to 39, 40 to 47, and ≥48 years. We also modeled the pack-years as spline terms with knots at 10, 20, 40 and 60. Years since cessation in former smokers (<5, 5 to <10, 10 to <20, 20 to <30, and ≥30 years) were explored as a time-varying variable, with each participant contributing person-time and events to separate time bins. We also modeled the years since quitting continuously as spline terms with knots at 10, 20, 30, and 40 years.

We constructed 2 models. Model 1 was adjusted for age, race, sex, education, BMI, total and high-density lipoprotein cholesterols, drinking status, physical activity, systolic and diastolic blood pressure, blood pressure-lowering medication use, cholesterol-lowering medication use, eGFR, and diabetes. Never-smoker was used as the reference group in general. However, for the analysis of smoking cessation, according to the 1990 Surgeon General's report (34), we also performed the analysis with current smokers as the reference category. For this specific analysis, we added smoking intensity in model 2, following the Surgeon General's report (34). Time-varying covariates were used for the analysis of smoking cessation whenever available. In the case of missing data, we carried forward the relevant data from a prior visit or phone interview until any different information was available subsequently.

The proportional hazards assumption was verified using log-log plots. We used the likelihood ratio test to test for interaction by key demographic and clinical factors (e.g., age, sex, race, alcohol use, hypertension, and diabetes) at baseline. Seemingly unrelated estimation was used to formally compare hazard ratios (HRs) for PAD, CHD, and stroke (35). Given the

TABLE 1 Baseline Characteristics by Smoking Status at Baseline

	Overall (N = 13,355)	Current Smokers (n = 3,323)	Former Smokers (n = 4,185)	Never Smokers (n = 5,847)	p Value
Age, yrs	53.9 ± 5.7	53.2 ± 5.6	54.5 ± 5.7	53.9 ± 5.8	<0.001
Female	7,505 (56.2)	1,776 (53.4)	1,657 (39.6)	4,072 (69.6)	<0.001
Black	3,377 (25.3)	953 (28.7)	768 (18.4)	1,656 (28.3)	<0.001
Body mass index, kg/m^2	27.6 ± 5.3	26.4 ± 5.0	27.9 ± 5.0	28.1 ± 5.6	<0.001
Education level					
Basic	2,921 (21.9)	956 (28.8)	835 (20.0)	1,330 (19.3)	<0.001
Intermediate	5,522 (41.4)	1,422 (42.8)	1,648 (39.4)	2,452 (41.9)	0.006
Advanced	4,912 (36.8)	945 (28.4)	1,702 (40.7)	2,265 (38.7)	<0.001
Physical activity	2.4 ± 0.8	2.3 ± 0.8	2.6 ± 0.8	2.4 ± 0.8	<0.001
Current drinker	7,603 (56.9)	2,158 (64.9)	2,734 (65.3)	2,711 (46.4)	<0.001
Systolic blood pressure, mm Hg	120.7 ± 18.3	118.9 ± 19.4	120.9 ± 17.1	121.6 ± 18.4	<0.001
Diastolic blood pressure, mm Hg	73.7 ± 11.1	72.0 ± 11.9	74.1 ± 10.5	74.3 ± 10.9	<0.001
Total cholesterol, mmol/l	5.5 ± 1.1	5.5 ± 1.1	5.5 ± 1.0	5.6 ± 1.1	0.052
HDL cholesterol, mmol/l	1.3 ± 0.4	1.3 ± 0.5	1.3 ± 0.4	1.4 ± 0.4	<0.001
eGFR, ml/min	102.9 ± 15.2	106.1 ± 14.6	100.5 ± 14.6	102.8 ± 15.7	<0.001
Antihypertensive medication	3,669 (27.5)	815 (24.5)	1,122 (26.8)	1,732 (29.6)	<0.001
Cholesterol-lowering medication	340 (2.5)	61 (1.8)	125 (3.0)	154 (2.6)	0.006
Diabetes	1,420 (10.6)	300 (9.0)	433 (10.3)	687 (11.7)	<0.001

Values are mean ± SD or n (%).
eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein.

potential effect of the competing risk of death, we conducted sensitivity analysis using Fine and Gray's proportional subhazards models (36).

All statistical analyses were conducted using Stata SE, version 14 (Stata Corp, College Station, Texas), and a p value <0.05 was considered statistically significant.

RESULTS

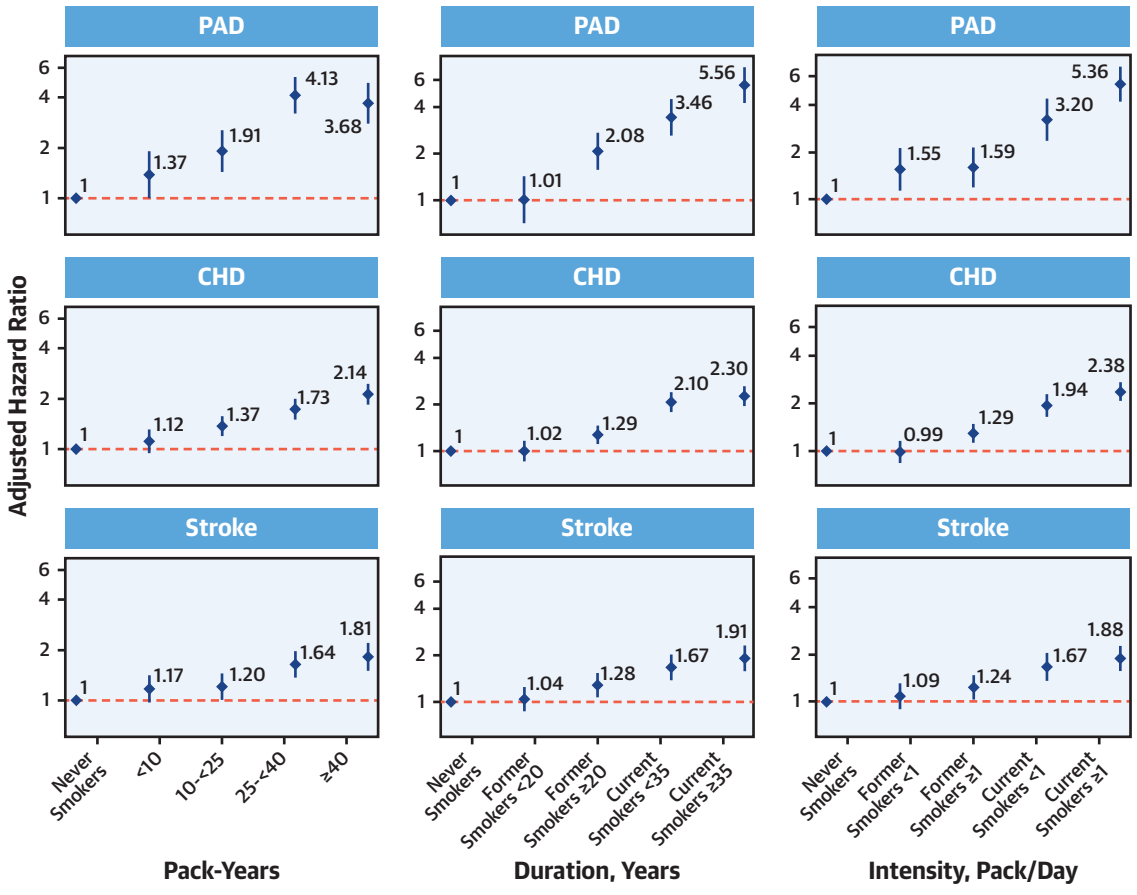
BASELINE CHARACTERISTICS. Among 13,355 participants, there were 3,323 (25%) current smokers, 4,185 (31%) former smokers, and 5,847 (44%) never smokers. Compared with never smokers, current smokers were more likely to be younger, male, black race, less educated, less physically active, and a current drinker (**Table 1**). Current smokers had a lower BMI and blood pressure and a lower prevalence of diabetes compared with never smokers. Former smokers tended to show properties intermediate between never and current smokers for most factors except the oldest mean age, lowest proportion of female and blacks, highest physical activity, lowest eGFR, and highest prevalence of cholesterol-lowering medication use.

SMOKING AND THE RISK OF ATHEROSCLEROTIC DISEASES. Over a median follow-up of 26.0 years, there were 492 cases of PAD, 1,798 CHD cases, and 1,106 stroke cases. Pack-years of smoking showed a graded association with PAD after adjusting for potential confounders (**Figure 1**). Compared with never smokers, those who smoked for ≥40 pack-years had ~4-fold increased risk for PAD, whereas the corresponding HR was 2.1 for CHD and 1.8 for stroke. Based on seemingly unrelated estimation, the association of pack-years was significantly greater for PAD than for CHD and stroke (p value for difference <0.001) (Online Table 3). Similar patterns were seen in competing risk models (Online Table 4). When we modeled pack-years of smoking as a continuous variable, the HR for the 3 outcomes increased monotonically between 0 and 40 pack-years and plateaued above this range (Online Figure 2).

The associations of pack-years with PAD were largely consistent in subgroups. A significant interaction was seen for diabetic status, with a stronger association of pack-years with PAD among those without diabetes compared with diabetes (Online Figure 3). For CHD, the association was stronger among younger participants (age ≤55 years), women, and those without diabetes compared to their counterparts (Online Figure 3). Nonetheless, except CHD in diabetes, higher pack-years were significantly associated with higher risk of these atherosclerotic diseases in all subgroups tested.

Stronger associations for PAD over CHD and stroke were consistently seen when we analyzed smoking duration and intensity separately (**Figure 1**). For

FIGURE 1 Adjusted Hazard Ratio for PAD, CHD, and Stroke by Categories of Pack-Years, Duration, and Intensity at Baseline



Model was adjusted for age (years), race (black, white), sex (male, female), education level, body mass index, total cholesterol, high-density lipoprotein cholesterol, drinking status, physical activity, systolic blood pressure, diastolic blood pressure, blood pressure–lowering medication use, cholesterol-lowering medication use, estimated glomerular filtration rate, and diabetes. CHD = coronary heart disease; PAD = peripheral artery disease.

example, current smokers with ≥35 years of smoking duration showed HRs of 5.56 (95% confidence interval [CI]: 4.26 to 7.26) for PAD, 2.30 (95% CI: 1.98 to 2.66) for CHD, and 1.91 (95% CI: 1.57 to 2.31) for stroke compared with never smokers. Similarly, current smokers of ≥1 pack/day (higher intensity) demonstrated HRs of 5.36 (95% CI: 4.16 to 6.91) for PAD, 2.38 (95% CI: 2.08 to 2.73) for CHD, and 1.88 (95% CI: 1.57 to 2.26) for stroke. Again, all associations were strongest for PAD (p value for difference <0.02) (Online Table 3), and similar results were observed in competing risk models (Online Table 4).

The majority of ever smokers started smoking before or at age 20 years. Compared to never smokers, regardless of initiation age, ever smokers had significantly higher risk of all atherosclerotic diseases (Online Table 5). We observed a statistically significant trend between younger initiation and higher risk for CHD (p for trend <0.001) and borderline trend for stroke (p = 0.064). Although there was no evident pattern between smoking initiation age and PAD risk, at any given initiation age, the HR was higher for PAD than CHD or stroke. Quitting smoking at a younger age was associated with a lower risk of the 3 outcomes compared with current smokers (especially in Model 1 in Online Table 6). The results were most evident for PAD (p for trend <0.001 vs. >0.7 for CHD and stroke in Model 2 in Online Table 6).

SMOKING CESSATION AND THE RISK OF ATHEROSCLEROTIC DISEASES. A longer period of smoking cessation showed a lower risk of all atherosclerotic diseases (Table 2). We observed a lower risk for PAD, CHD, and stroke within 5 years of cessation, although

TABLE 2 Adjusted Hazard Ratios (95% CIs) for PAD, CHD, and Stroke by Years Since Cessation as a Time-Varying Variable (Current Smokers as the Reference Group) (N = 13,355)

		Years Since Cessation in Former Smokers					
	Current Smokers	<5 Years	5 to <10 Years	10 to <20 Years	20 to <30 Years	≥30 Years	Never Smokers
PAD							
Events/person-yrs	124/42,319	57/16,601	29/14,226	58/25,400	42/24,590	58/34,465	124/128,780
Model 1	1.00 (reference)	0.73 (0.53–1.00)	**0.43 (0.28–0.64)**	**0.44 (0.32–0.61)**	**0.34 (0.24–0.49)**	**0.22 (0.16–0.31)**	**0.20 (0.15–0.26)**
Model 2	1.00 (reference)	0.75 (0.54–1.03)	**0.43 (0.29–0.65)**	**0.44 (0.32–0.60)**	**0.33 (0.23–0.47)**	**0.22 (0.16–0.31)**	**0.23 (0.17–0.31)**
CHD							
Events/person-yrs	377/41,210	145/15,767	110/13,460	168/24,319	129/23,820	259/32,846	610/125,486
Model 1	1.00 (reference)	**0.77 (0.63–0.93)**	**0.71 (0.57–0.88)**	**0.56 (0.47–0.68)**	**0.43 (0.35–0.53)**	**0.47 (0.39–0.56)**	**0.44 (0.38–0.50)**
Model 2	1.00 (reference)	**0.78 (0.64–0.95)**	**0.71 (0.58–0.89)**	**0.56 (0.46–0.67)**	**0.43 (0.35–0.53)**	**0.47 (0.40–0.56)**	**0.49 (0.41–0.57)**
Stroke							
Events/person-yrs	195/42,035	69/16,426	54/14,017	108/25,038	94/24,240	152/33,757	434/126,807
Model 1	1.00 (reference)	**0.65 (0.49–0.86)**	**0.61 (0.45–0.82)**	**0.64 (0.50–0.82)**	**0.58 (0.45–0.75)**	**0.49 (0.39–0.62)**	**0.50 (0.42–0.61)**
Model 2	1.00 (reference)	**0.67 (0.51–0.88)**	**0.62 (0.45–0.84)**	**0.64 (0.50–0.81)**	**0.57 (0.45–0.74)**	**0.49 (0.39–0.62)**	**0.58 (0.47–0.72)**

Model 1 was adjusted for age (years), race (black, white), sex (male, female), education level, body mass index, total cholesterol, high-density lipoprotein cholesterol, drinking status, physical activity, systolic blood pressure, diastolic blood pressure, blood pressure–lowering medication use, cholesterol-lowering medication use, estimated glomerular filtration rate, and diabetes. Model 2 was adjusted for all variables in model 1 and smoking intensity (packs/day). **Bold** indicates statistical significance.

CHD = coronary heart disease; CI = confidence interval; PAD = peripheral artery disease.

the results for PAD were borderline significant, likely due to the smaller number of events. For any period of smoking cessation >5 years, the risk was lowest for PAD. For example, compared with current smokers, smoking cessation for 5 to <10 years had an HR of 0.43 (95% CI: 0.28 to 0.64) for PAD, 0.71 (95% CI: 0.57 to 0.88) for CHD, and 0.61 (95% CI: 0.45 to 0.82) for stroke (Model 1 in Table 2). Long-term smoking cessation (≥30 years) showed an HR of 0.22 (95% CI: 0.16 to 0.31) for PAD, 0.47 (95% CI: 0.39 to 0.56) for CHD, and 0.49 (95% CI: 0.39 to 0.62) for stroke. After further adjusting for smoking intensity, the associations were slightly attenuated (Model 2 in Table 2). Competing risk models demonstrated similar patterns (Online Table 7). When we modeled years since cessation as a continuous variable, on average, 1-year cessation was significantly associated with 4% lower risk of PAD (HR: 0.96; 95% CI: 0.96 to 0.97), 2% lower risk for CHD (HR: 0.98; 95% CI: 0.98 to 0.99), and 1% lower risk for stroke (HR: 0.99; 95% CI: 0.98 to 0.99) (Online Figure 4).

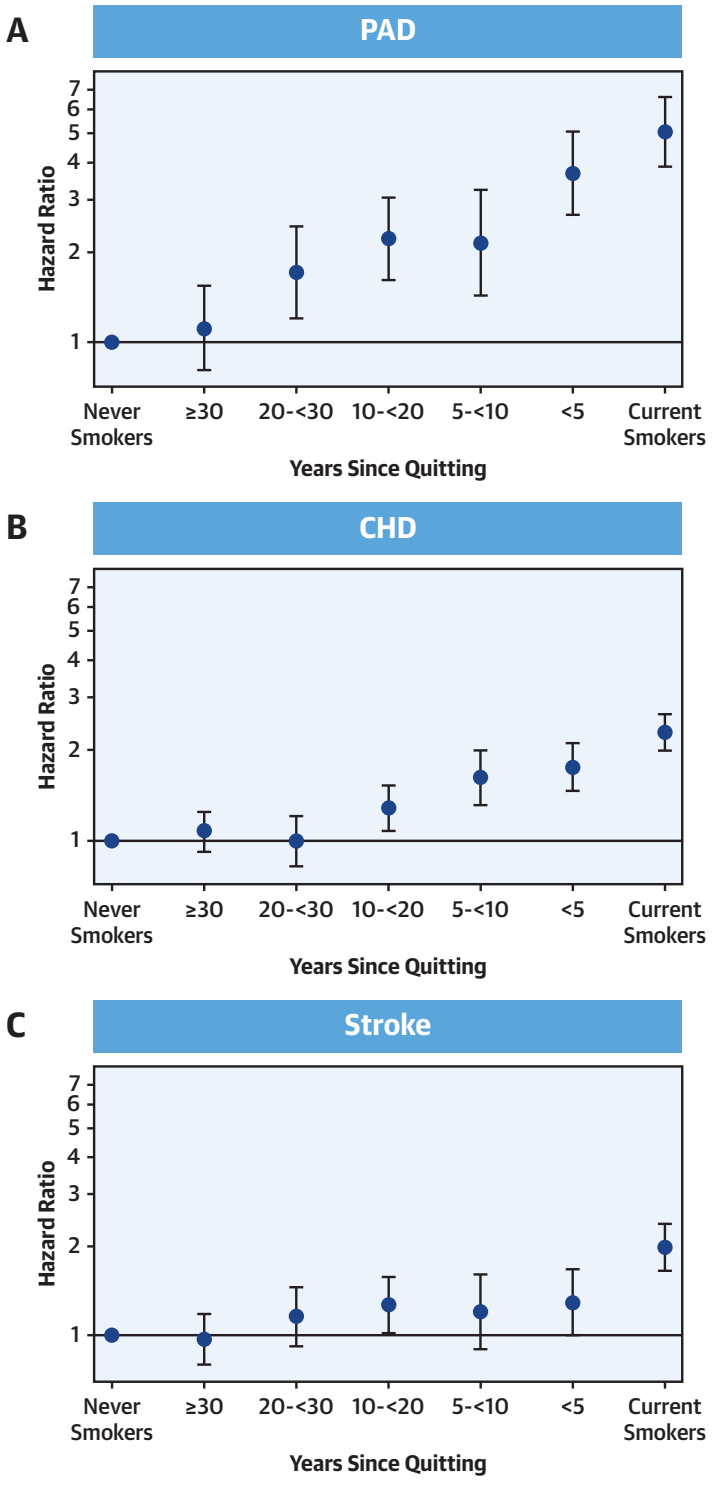
When we used never smokers as a reference group, only smoking cessation for ≥30 years had a similar risk of PAD as never smoking (Figure 2A), and smoking cessation for a period of 20 to <30 years was still associated with elevated HR: 1.71 (95% CI: 1.20 to 2.44). For CHD, the risk was equivalent between never smoking and smoking cessation over 20 years, and the HR for smoking cessation 10 to <20 years was 1.29 (95% CI: 1.08 to 1.53) (Figure 2B). For stroke, although a significant association was observed with smoking cessation 10 to <20 years (HR: 1.27; 95% CI: 1.02 to 1.57), overall, the HR was relatively low even in smoking cessation <5 years (HR: 1.29; 95% CI: 1.00 to 1.67) (Figure 2C).

DISCUSSION

In this community-based cohort with nearly 3 decades of follow-up, all smoking measures examined (pack-years, duration, intensity) demonstrated considerably stronger associations with PAD compared with CHD or stroke (Central Illustration). Smoking cessation was associated with the greatest risk reduction for PAD among these atherosclerotic diseases. Compared with current smokers, those with smoking cessation for 5 to <10 years showed an HR of ~0.4 for PAD and 0.6 to 0.7 for CHD and stroke. Nonetheless, with never smokers as a reference, significantly elevated risk was observed up to 30 years for PAD and 20 years for CHD.

Although numerous studies have evaluated the effect of smoking on atherosclerotic diseases, there are several unique aspects of our study. First, this is the first prospective study to comprehensively examine the association of several smoking measures with 3 major atherosclerotic diseases in a single study population. Second, we were able to update the smoking status during follow-up and analyze smoking cessation as a time-varying exposure. Third, we also rigorously updated the information of potential confounders. Fourth, our outcomes were ascertained from hospitalization records, and thus, the analyses were less

FIGURE 2 Adjusted Hazard Ratio for PAD, CHD, and Stroke by Years Since Cessation as a Time-Varying Variable



(A) PAD, **(B)** CHD, and **(C)** stroke. The model is the same as in Figure 1. Abbreviations as in Figure 1.

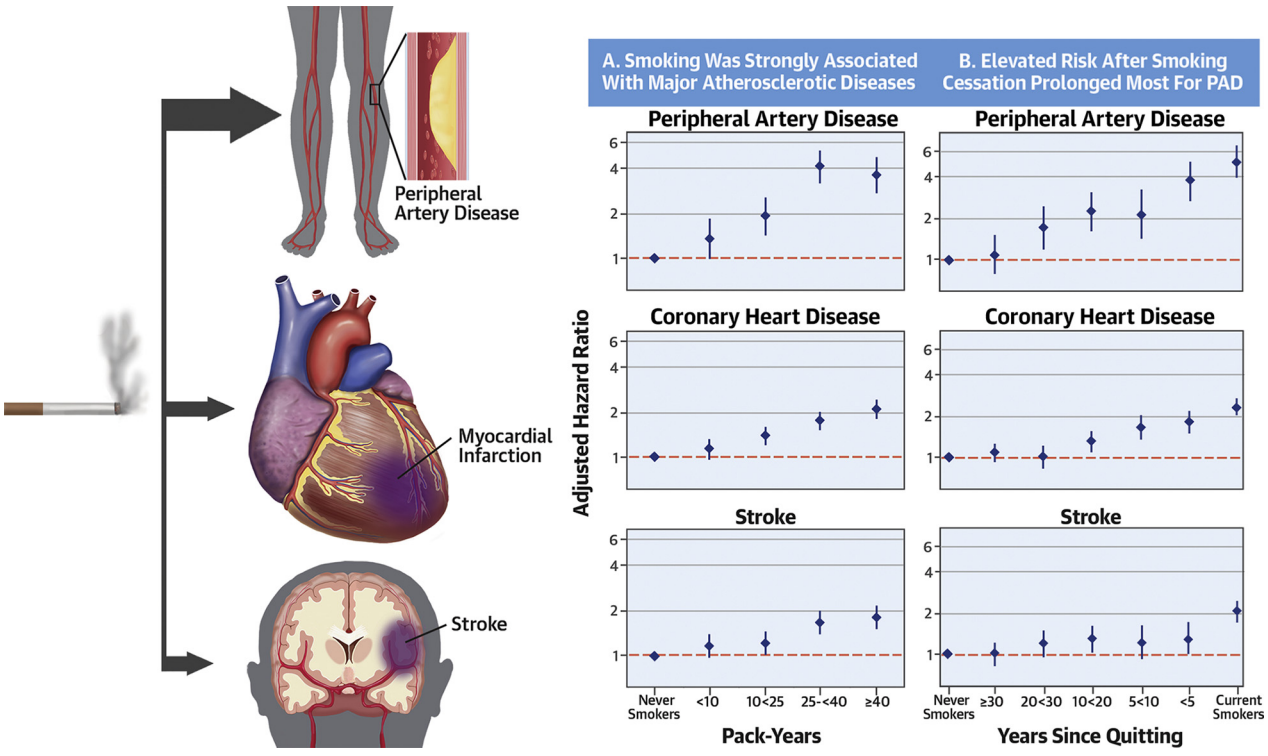
susceptible to bias associated with attrition. Finally, we were able to examine the long-term association of smoking cessation with PAD, CHD, and stroke over 30 years.

Although we observed a plateau over pack-years >40 for all 3 CVDs, a general dose-response relationship supports an etiological contribution of smoking to atherosclerosis. Indeed, there are a number of plausible mechanisms. Smoking is known to cause vascular constriction; influence several cardiovascular risk factors, such as blood pressure, lipid metabolism, and the coagulation system (5,6); and contain a number of atherothrombogenic compounds (37). Recent studies have shown that smokers had a greater extent and severity of coronary plaques and CHD by computed tomographic angiography compared with never smokers (38,39). However, the reason that smoking affects the lower-extremity peripheral arteries more than the coronary and cerebral arteries is uncertain. One possible explanation is the different anatomy and hemodynamics of the peripheral arteries in the legs compared with the coronary and cerebral arteries (14,40). Regarding the plateau, it is possible that there may be a ceiling for these mechanisms to damage arterial wall and selective mortality/attrition among those most heavily exposed. Also, we need to acknowledge that the sample size in the highest pack-years group was somewhat limited in our study.

Smoking cessation was associated with a substantially lower risk of PAD in our study, with 80% lower risk after cessation for ≥30 years compared with current smokers. However, from another point of view, with never smokers as a reference category, the elevated risk of PAD was sustained up to 30 years after smoking cessation. The Women's Health Study (16) and the Health Professionals Follow-up Study (17) reported similar results with a significantly higher risk of PAD in women and men who quit for ≥20 years. Nonetheless, our study uniquely subdivided the cessation duration ≥20 years and found that the risk of PAD became indistinguishable to never smokers after quitting for more than 30 years. Of note, regarding the time for the excess risk of CHD to be eliminated, our result of 20 years is similar to a landmark study from the Nurse's Health Study (41).

Our study confirms the long-sustained risk of atherosclerotic diseases after smoking cessation. However, the mechanisms behind this observation are not fully elucidated (16,17,41). Some adverse effects of smoking, such as pro-thrombotic state and endothelial dysfunction, are quickly reversible after smoking cessation (40,42,43). Conversely, structural

CENTRAL ILLUSTRATION **Smoking Is Associated With Higher Risk of Peripheral Artery Disease Compared With Coronary Heart Disease and Stroke and Longer Residual Risk of Peripheral Artery Disease After Cessation**



Ding, N. et al. J Am Coll Cardiol. 2019;74(4):498–507.

(Left) The **width and length of the arrows** represent the strength of association of smoking and its cessation with the outcomes, respectively. **(Right)** The **left column** of the plot **(A)** shows the adjusted hazard ratio of peripheral artery disease (PAD), coronary heart disease (CHD), and stroke by pack-years at baseline. The **right column** of the plot **(B)** shows the adjusted hazard ratio of PAD, CHD, and stroke by time-varying years since quitting. The model was adjusted for age (years), race (black, white), sex (male, female), education level, body mass index, total cholesterol, high-density lipoprotein cholesterol, drinking status, physical activity, systolic blood pressure, diastolic blood pressure, blood pressure–lowering medication use, cholesterol-lowering medication use, estimated glomerular filtration rate, and diabetes.

vascular changes such as atherosclerosis as a consequence of smoking do not readily regress. Indeed, a registry demonstrated a similar extent and severity of coronary atherosclerosis between current and former smokers (38). Also, the progression of atherosclerosis was greater among former smokers than never smokers (44,45). Thus, it is reasonable for former smokers to develop clinical manifestations of atherosclerotic disease earlier than never smokers. These aspects may explain why the contribution of smoking sustains longer after its cessation for PAD than CHD and stroke, because it is known that atherosclerosis itself is key for the development of the majority of PAD cases, whereas thrombosis, in addition to atherosclerosis, plays an important role in CHD and stroke (46).

Our results have important public health implications. It is important to recognize that the risk of the atherosclerotic diseases started to decline after smoking cessation in a short timeframe of <5 years, which would be encouraging to persons attempting or considering quitting smoking. In addition, a clear dose-response relationship between the length of smoking cessation and lower risk of atherosclerotic diseases may encourage individuals with short-term smoking cessation to maintain cessation. More importantly, the evidently elevated risk of 3 major atherosclerotic diseases according to any smoking measures further highlights the importance of smoking prevention. Indeed, the risk of PAD sustained even after maintaining cessation up to 30 years. Given that nearly all first use of cigarettes

occurs by 18 to 26 years of age, efforts to reduce smoking initiation should continue to target adolescents and younger adults. In this context, it would be important to make them aware that smoking initiation at their age may influence vascular health in their 40s and 50s. Last, although public statements about the relationship between smoking cessation and CVD are predominantly based on investigations of CHD and stroke, the uniquely strong association between smoking and PAD should be taken into account as well.

STUDY LIMITATIONS. First, as is true in many epidemiological studies, potential measurement errors might exist in the assessment of smoking status because the information is self-reported. Second, there might be misclassification of time-varying exposures and covariates, because we carried forward prior data in the case of missing updated information. Third, the ascertainment of PAD was based on hospitalization with PAD diagnosis or leg revascularization, and thus, mild PAD cases were likely to be missed. Nonetheless, this may be optimal for the present study aiming to compare PAD with CHD and stroke requiring hospitalization. Finally, we were not able to eliminate the possibility of residual confounding.

CONCLUSIONS

All smoking measures tested in our study were strongly associated with a long-term risk of 3 major atherosclerotic diseases, but the association was especially strong for PAD. Of note, the elevated risk of incident PAD was prolonged even up to 30 years after smoking cessation. Our study provides evidence for an anti-smoking campaign to continue to advocate smoking prevention and cessation. Although public statements about smoking and CVD have been focusing on CHD and stroke, our results indicate the need to take account of PAD as well for comprehensively acknowledging the effect of smoking on overall cardiovascular health.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The quantity, duration, and intensity of cigarette smoking are all more strongly associated with PAD than with CHD or stroke. The risk of all 3 forms of atherosclerotic disease declines <5 years after smoking cessation, but the elevated risk of incident PAD persists up to 30 years after smoking cessation.

TRANSLATIONAL OUTLOOK: Novel strategies are needed to enhance public education about the effect of smoking on PAD and target populations at greatest risk.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.