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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 impact 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 three major atherosclerotic diseases (PAD, CHD, and stroke).

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

METHODS—13,355 participants aged 45–64 years in the Atherosclerosis Risk in Communities (ARIC) study without PAD, CHD, or stroke at baseline (1987–89) were included. We quantified the associations of smoking parameters (pack-years, duration, intensity, and cessation) with incident PAD and contrasted them 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 three outcomes, with the strongest results for PAD. The pattern was consistent when investigating duration and intensity separately. A longer period of smoking cessation was

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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 or stroke.

CONCLUSIONS—All smoking measures showed significant associations with three 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 for appropriately acknowledging the impact of smoking on overall cardiovascular health.

Condensed abstract:

In 13,355 ARIC participants, we quantified the associations of smoking parameters (pack-years, duration, intensity, and cessation) with incident PAD, CHD and stroke using Cox models. Over a median follow-up of 26 years, all smoking measures showed significant associations with three outcomes, with the strongest effect size for 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 cessation, and indicate the need for public statements to take PAD into account for appropriately acknowledging the impact of smoking on overall cardiovascular health.

Short tweet summary:

Impact of smoking lasting for 30 years for #PAD (leg vascular disease) An ARIC study found smoking more strongly related to PAD than #CHD and #stroke

Keywords

cigarette smoking; smoking cessation; peripheral artery disease; coronary heart disease; stroke

Introduction

Cigarette smoking is a major modifiable risk factor for cardiovascular disease (CVD) (1). Public statements and reports about the impact 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 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 impact of smoking on CVD since 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 three major atherosclerotic diseases.

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 the aforementioned knowledge gaps, the objectives of this study were to quantify the long-term association of cigarette smoking and its cessation with the incidence of the three major atherosclerotic diseases using data from the Atherosclerosis Risk in Communities (ARIC) Study with follow-up for nearly three 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 aged 45–64 years from four U.S. communities. The first clinic examinations (visit 1) took place from 1987 to 1989, with three short-term clinic visits (visits 2–4) approximately every three years (1990–92, 1993–95, and 1996–98, respectively) and subsequent visits 5 and 6 during 2011–13 and 2016–17, respectively (22). Phone interviews were conducted annually from visit 1 to 2008–2011, and semiannually 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 started smoking, age stopped smoking, 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 they usually smoked per day 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 per 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. Since smoking status (current, former, never smoker) was also examined at subsequent four clinic visits and annual phone interview after 1999, we were able to define smoking cessation as a time-varying exposure for over 2 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 wa s accumulated for one more year. If current smokers transitioned to non-current 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 non-current smoking. At clinic visit 1–4, current smokers were asked to specify the number of cigarettes they smoked per day at that moment, thus we were able to adjust for time-varying smoking intensity when analyzing time-varying smoking cessation.

Covariates

Age, gender, 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 blood pressure (SBP) and diastolic blood pressure (DBP) was measured three times after five minutes of rest using a random-zero sphygmomanometer, and the average of the second and third readings was recorded. Total cholesterol and high-density lipoprotein (HDL) cholesterol were determined using enzymatic methods. Physical activity was categorized from 1 (least active) to 5 (most active) as according to sports during leisure time using 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 two weeks was verified by reviewing medication containers. Diabetes mellitus was defined as a fasting glucose ≥7.0 mmol/L, non-fasting glucose ≥11.1 mmol/L, self-reported physician diagnosis, or use of glucose-lowering medications.

Outcomes

ARIC investigators conduct continuous, comprehensive surveillance for hospitalizations and deaths in the four communities (28–30). Based on previous literature (31–33), incident PAD was defined as hospitalizations with the following International Classification of Diseases, ninth version (ICD-9) codes, (Online Table 2 for detail).

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 [pack/day], and cessation) and incident PAD, CHD, and stroke. Based on the distribution, pack-years was largely evenly categorized as <10, 10-<25, 25-<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 started smoking was categorized as <16, 16–17, 18–19, ≥20. Age stopped smoking was categorized as <31, 31–39, 40–47, ≥48. 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-<10, 10-<20, 20-<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.

We constructed 2 models. Model 1 was adjusted for age, race, sex, education, BMI, total and HDL cholesterols, drinking status, physical activity, SBP, DBP, 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 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 potential impact of the competing risk of death, we conducted sensitivity analysis using Fine and Gray's proportional sub-hazards 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 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 three outcomes increased monotonically between 0–40 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 non-diabetes compared with diabetes (Online Figure 3). For CHD, the association was stronger among younger participants (age ≤55), female, 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 example, current smokers with ≥35 years of smoking duration showed HRs of 5.56 (95% CI 4.26–7.26) for PAD, 2.30 (1.98–2.66) for CHD, and 1.92 (1.58–2.33) for stroke compared to never smokers. Similarly, current smokers with ≥1 pack/day (higher intensity) demonstrated a HR of 5.36 (4.16–6.91) for PAD, 2.37 (2.07–2.72) for CHD, and 1.88 (1.57–2.26) for stroke. Again, all associations were strongest for PAD (p 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 the age of 20. 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 lower risk of the three 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 five years of cessation although the results for PAD were borderline significant, likely owing to the smaller number of events. For any period of smoking cessation greater than five years, the risk was lowest for PAD. For example, compared to current smokers, smoking cessation for 5-<10 years had a HR of 0.43 (0.28–0.64) for PAD, 0.71 (0.57–0.88) for CHD, and 0.61 (0.45–0.82) for stroke (Model 1 in Table 2). Long-term smoking cessation (≥30 years) showed a HR of 0.22 (0.16–0.31) for PAD, 0.44 (0.38–0.56) for CHD, and 0.49 (0.39–0.62) 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, one year cessation was significantly associated with 4% lower risk of PAD (HR 0.96 [0.96, 0.97]), 2% lower risk for CHD (HR 0.98 [0.98, 0.99]), and 1% lower risk for stroke (HR 0.99 [0.98, 0.99]) (Online Figure 4).

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

Discussion

In this community-based cohort with nearly three decades of follow-up, all smoking measures examined (pack-years, duration, intensity) demonstrated considerably stronger associations with PAD compared to 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 5–9 years showed a HR of ~0.4 for PAD and 0.6–0.7 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 impact of smoking on atherosclerotic diseases, there are several unique aspects of our study. First, this is the first prospective study to comprehensively examine the impact of several smoking measures on three 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 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 greater than 40 for all three cardiovascular diseases, 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 coronary artery disease by computed tomographic angiography compared with never smokers (38,39). However, the reasons 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.

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 female and male who quitted ≥20 years, respectively. 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 vascular changes like atherosclerosis as a consequence of smoking do not readily regress. Indeed, a registry demonstrated 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 manifest 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 since 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 less than five 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 three major atherosclerotic diseases according to any smoking measures further highlights the importance of smoking prevention. Indeed, the risk of PAD sustained even after maintained cessation up to 30 years. Given that nearly all first use of cigarettes occurs by 18–26 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 in their age may influence vascular health at their 40s and 50s. Lastly, although public statements about the smoking cessation and CVD relationship are predominantly based on investigations of CHD and stroke, those statements should take account of the uniquely strong smoking-PAD association as well.

There are several limitations of our study. 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 since 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

In conclusion, all smoking measures tested in our study were strongly associated with a long-term risk of three major atherosclerotic diseases, but the association was especially strong for PAD. Of note, the elevated risk of incident PAD prolonged even up to 30 years after smoking cessation. Our study provides evidence for 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 impact of smoking on overall cardiovascular health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations list:

BMI	body mass index
CHD	coronary heart disease
CVD	cardiovascular disease
DBP	diastolic blood pressure
eGFR	estimated glomerular filtration rate
HDL	high-density lipoprotein
PAD	peripheral artery disease
SBP	systolic blood pressure

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CLINICAL PERSPECTIVES

Competency in Medical Knowledge:

The quantity, duration and intensity of cigarette smoking are all more strongly associated with peripheral artery disease (PAD) than with coronary artery disease 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 of ≤30 years after smoking cessation.

Translational Outlook:

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

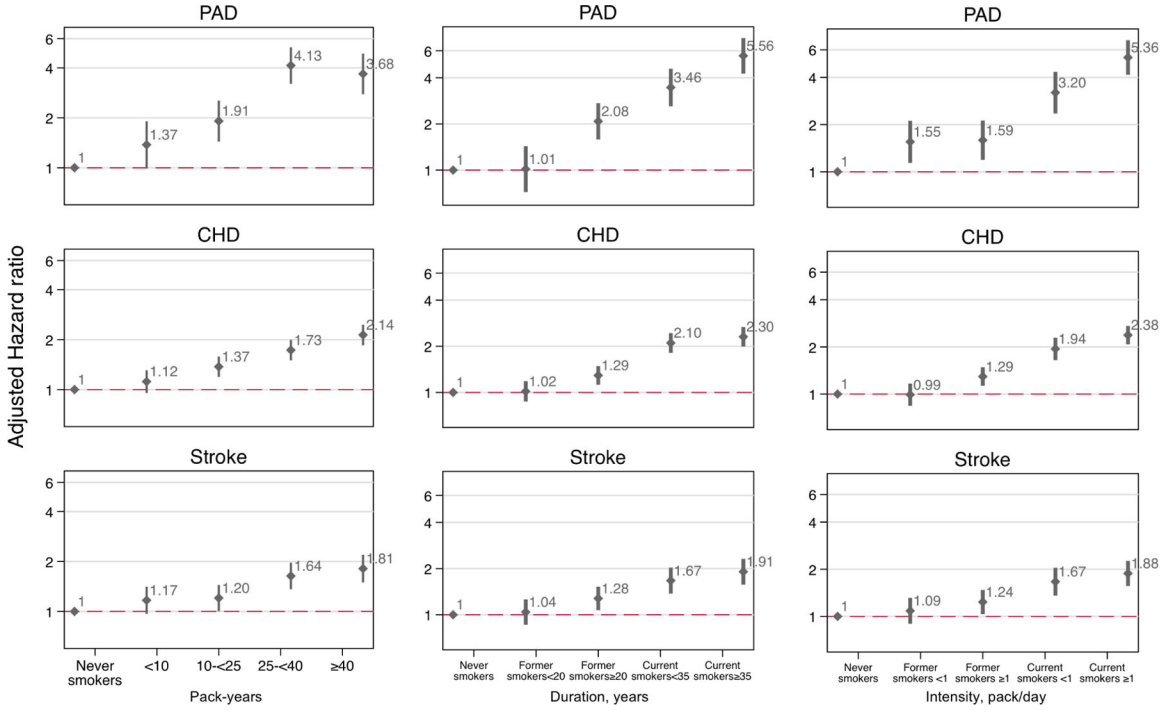


Figure 1. Adjusted* hazard ratio for PAD, CHD and stroke by categories of pack-years, duration and intensity at baseline.

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.

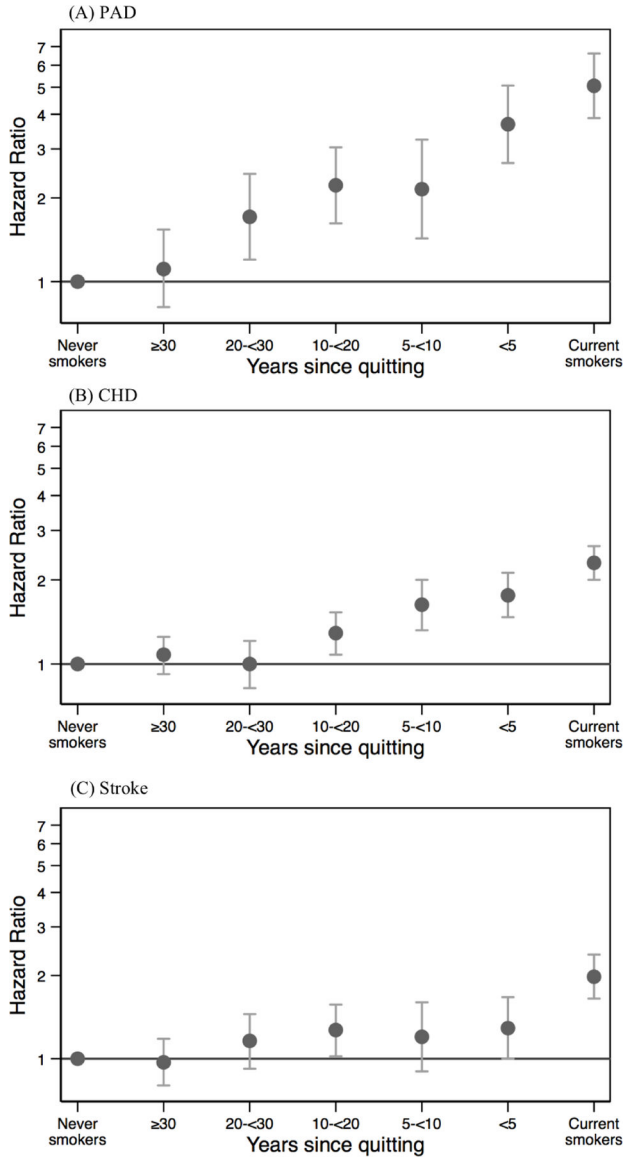
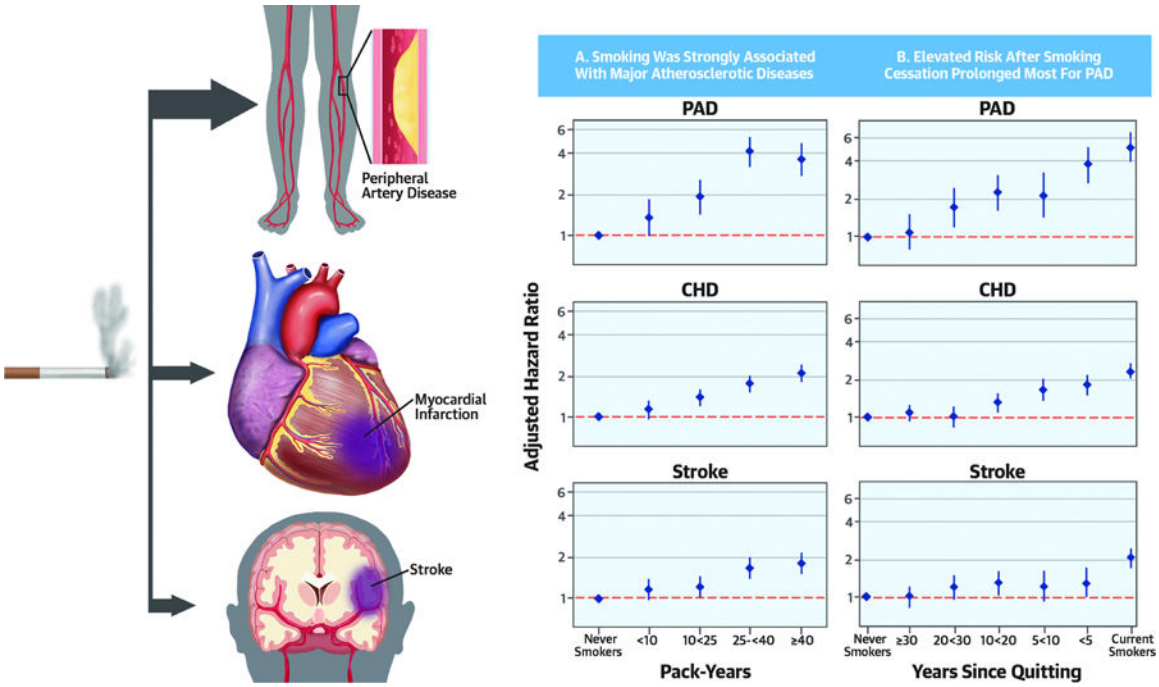


Figure 2. Adjusted hazard ratio for (A) PAD, (B) CHD, (C) stroke by years since cessation as a time-varying variable.

Model same as Figure 1. CHD = coronary heart disease; PAD = peripheral artery disease.



Central Illustration. Smoking is associated with higher risk of PAD compared with CHD and stroke and longer residual risk of PAD after cessation.

The width and length of the arrows represent the strength of association between smoking and the outcomes. The left column of plot showed the adjusted hazard ratio of PAD, CHD and stroke by pack-years at baseline. The right column of plot showed the adjusted hazard ratio of PAD, CHD and stroke by time-varying years since quitting. 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.

Table 1.

Baseline Characteristics by Smoking Status at Baseline (N=13,355)

Characteristic	Overall	Current smokers	Former smokers	Never smokers	P-values
Total N	13,355	3,323	4,185	5,847	
Age, years	53.9 (5.7)	53.2 (5.6)	54.5 (5.7)	53.9 (5.8)	<0.001
Females, No. (%)	7,505 (56.2)	1,776 (53.4)	1,657 (39.6)	4,072 (69.6)	<0.001
Black, No. (%)	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, No. (%)					
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, No (%)	7,603 (56.9)	2,158 (64.9)	2,734 (65.3)	2,711 (46.4)	<0.001
Systolic blood pressure, mmHg	120.7 (18.3)	118.9 (19.4)	120.9 (17.1)	121.6 (18.4)	<0.001
Diastolic blood pressure, mmHg	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, No. (%)	3,669 (27.5)	815 (24.5)	1,122 (26.8)	1,732 (29.6)	<0.001
Cholesterol-lowering medication, No. (%)	340 (2.5)	61 (1.8)	125 (3.0)	154 (2.6)	0.006
Diabetes, No. (%)	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.

Table 2.

Adjusted hazard ratio (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)

	Current smokers	Years since cessation in former smokers					Never smokers
		<5 years	5-<10 years	10-<20 years	20-<30 years	≥30 years	
PAD							
Events/person-years	124/42319	57/16601	29/14226	58/25400	42/24590	58/34465	124/128780
Model 1	1 (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 (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-years	377/41210	145/15767	110/13460	168/24319	129/23820	259/32846	610/125486
Model 1	1 (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 (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-years	195/42035	69/16426	54/14017	108/25038	94/24240	152/33757	434/126807
Model 1	1 (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 (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). CHD = coronary heart disease; PAD = peripheral artery disease