

Associations Between Conventional Cardiovascular Risk Factors and Risk of Peripheral Artery Disease in Men

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PERIPHERAL ARTERY DISEASE (PAD) is a distinct atherosclerotic syndrome marked by stenosis or occlusion of the arteries, particularly of the lower extremities. PAD affects 8 to 10 million individuals in the United States,^{1,2} and is associated with reduced functional capacity^{3,4} and increased risk for cardiovascular morbidity and mortality.⁵⁻⁷ Despite its widespread prevalence and negative associations with quality of life, morbidity, and mortality, PAD remains underdiagnosed and undertreated.^{2,8,9}

Preventable or treatable risk factors for PAD are generally thought to mirror other forms of cardiovascular disease and include cigarette smoking, type 2 diabetes, and clinically elevated levels of blood pressure and cholesterol, which are the main therapeutic targets in clinical and prevention guidelines.^{10,11} However, their respective associations with risk of PAD and the extent to which they are jointly associated with the incidence of PAD are

Context Previous studies have examined the associations of individual clinical risk factors with risk of peripheral artery disease (PAD), but the combined effects of these risk factors are largely unknown.

Objective To estimate the degree to which the 4 conventional cardiovascular risk factors of smoking, hypertension, hypercholesterolemia, and type 2 diabetes are associated with the risk of PAD among men.

Design, Setting, and Participants Prospective study of 44 985 men in the United States without a history of cardiovascular disease at baseline in 1986; participants in the Health Professionals Follow-up Study were followed up for 25 years until January 2011. The presence of risk factors was updated biennially during follow-up.

Main Outcome Measure Clinically significant PAD defined as limb amputation or revascularization, angiogram reporting vascular obstruction of 50% or greater, ankle-brachial index of less than 0.90, or physician-diagnosed PAD.

Results During a median follow-up of 24.2 years (interquartile range, 20.8-24.7 years), there were 537 cases of incident PAD. Each risk factor was significantly and independently associated with a higher risk of PAD after adjustment for the other 3 risk factors and confounders. The age-adjusted incidence rates were 9 (95% CI, 6-14) cases/100 000 person-years (n=19 incident cases) for 0 risk factors, 23 (95% CI, 18-28) cases/100 000 person-years (n=99 incident cases) for 1 risk factor, 47 (95% CI, 39-56) cases/100 000 person-years (n=176 incident cases) for 2 risk factors, 92 (95% CI, 76-111) cases/100 000 person-years (n=180 incident cases) for 3 risk factors, and 186 (95% CI, 141-246) cases/100 000 person-years (n=63 incident cases) for 4 risk factors. The multivariable-adjusted hazard ratio for each additional risk factor was 2.06 (95% CI, 1.88-2.26). Men without any of the 4 risk factors had a hazard ratio of PAD of 0.23 (95% CI, 0.14-0.36) compared with all other men in the cohort. In 96% of PAD cases (95% CI, 94%-98%), at least 1 of the 4 risk factors was present at the time of PAD diagnosis. The population-attributable risk associated with these 4 risk factors was 75% (95% CI, 64%-87%). The absolute incidence of PAD among men with all 4 risk factors was 3.5/1000 person-years.

Conclusion Among men in this cohort, smoking, hypertension, hypercholesterolemia, and type 2 diabetes account for the majority of risk associated with development of clinically significant PAD.

JAMA. 2012;308(16):1660-1667

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and questions on p 1696.

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not well established. Furthermore, despite the ongoing identification of novel risk factors for PAD,^{12,13} this disease may have a less prominent component of thrombosis than does ischemic stroke or myocardial infarction (MI),^{14,15} raising the possibility that traditional atherosclerotic risk factors may be even more important in this form of cardiovascular disease.

To estimate the individual and cumulative associations of 4 conventional and preventable risk factors with risk of PAD and their associated population-attributable risk (PAR), we studied a large, well-characterized, prospective sample of US men with more than 2 decades of follow-up.

METHODS

Participants

The Health Professionals Follow-up Study is a prospective investigation of 51 529 US male health professionals aged 40 to 75 years at baseline in 1986 who returned a mailed questionnaire about disease history, including an item that specifically queried intermittent claudication and lifestyle factors.¹⁶ Questionnaires were mailed biennially to update information on newly diagnosed disease and potential risk factors. We excluded men with missing data on age, height, or family history, or those diagnosed with cardiovascular disease (MI, stroke, coronary artery bypass graft surgery, coronary angioplasty, and intermittent claudication) at baseline. All participants provided written informed consent, and the Harvard School of Public Health human subjects and the Beth Israel Deaconess Medical Center committee review boards approved the study protocol.

Assessment of Medical History, Anthropometric Data, and Lifestyle Factors

Smoking status and self-report of physician-diagnosed hypertension, hypercholesterolemia, and type 2 diabetes were assessed at baseline and updated biennially thereafter. At baseline, participants also reported past smoking, time since quitting, and the average

number of cigarettes smoked per day. Pack-years were calculated as years of smoking multiplied by the average number of packs smoked per day and updated biennially. The validity of self-reported hypertension has been confirmed with medical record review in a sample of Health Professionals Follow-up Study participants.¹⁷ Likewise, self-reported total cholesterol levels have been shown to highly correlate with measured values.¹⁸

Self-reported type 2 diabetes has been confirmed by a validated supplementary questionnaire detailing symptoms, diagnostic laboratory test results, and diabetes treatment as described previously,¹⁹ and has been demonstrated to be highly accurate compared with medical record reviews in a validation study.²⁰ Durations of hypertension, hypercholesterolemia, and type 2 diabetes were calculated as years from clinical diagnosis to the return of the most recent questionnaire. Weight, physical activity, and medication use were assessed biennially and alcohol consumption every 4 years, using validated questionnaires.²¹⁻²⁴ Height, geographical region of residence, and parental history of MI at age 60 years or younger were obtained from the baseline questionnaire. Body mass index (BMI) was calculated using height at baseline and updated weight.

Case Ascertainment

If a participant reported PAD of the lower extremity during follow-up, we requested permission to review all relevant medical records to confirm the diagnosis and the date of occurrence. Confirmed PAD cases required at least 1 of the following in the medical record: a report of revascularization (or amputation) for atherosclerotic peripheral artery occlusion in a lower limb, angiogram reporting obstruction of 50% or greater of at least 1 limb artery with ipsilateral symptoms, ankle-brachial index of less than 0.90 at rest, or a physician's diagnosis of PAD.

Data Analyses

Each participant contributed person-time from the return of the 1986 ques-

tionnaire to the date of diagnosis of PAD, death, date of last questionnaire return, or end of follow-up (January 2011), whichever came first. We used Cox proportional hazards models with time-dependent covariates to calculate hazard ratios (HRs) and 95% confidence intervals. The assumption of proportional hazards was checked and met for each Cox model. Once a participant reported a positive history of ever smoking (past or current), hypertension, hypercholesterolemia, or diabetes, he was considered to have a positive history throughout follow-up. Analyses that defined hypertension and hypercholesterolemia based on either a physician's diagnosis or a patient's medication use (thiazides, β -blockers, calcium channel blockers, and angiotensin-converting enzyme or angiotensin II receptor antagonists for hypertension, and statins and other cholesterol-lowering agents for hypercholesterolemia) yielded similar results.

We used ever rather than current smoking to ensure that the 4 risk factors were broadly comparable in terms of increased risk. This enabled us to sum the total number of risk factors to create a score (range, 0-4). We also developed a weighted risk score to account for the magnitude of risk observed with each risk factor.

We explored whether there were statistical interactions between the 4 binary risk factors by comparing the -2 log likelihood of a nested model with and without all possible 2-, 3-, and 4-way interaction terms. We found no overall evidence of interaction ($\chi^2_{11}=11.0$, $P=.45$) and none of the individual interactions were statistically significant.

We examined the associations between individual risk factors and risk of PAD in several ways. We evaluated the risk of former smoking using 4 categories (quit for ≥ 20 , 10- <20 , 5- <10 , or <5 years) and intensity of current smoking using 3 categories (1-14, 15-24, and ≥ 25 cigarettes/d). We investigated the dose-response relationship between cumulative lifelong smoking exposure and incident PAD by evaluating pack-years of

Table 1. Characteristics of Men in the Health Professional Follow-up Study (n = 43 243)^a

	No. of Clinical Risk Factors in 1986				
	0 (n = 15 293)	1 (n = 20 047)	2 (n = 6571)	3 (n = 1245)	4 (n = 87)
Age, mean (SD), y	51.6 (9.4)	54.3 (9.5)	57.6 (9.3)	59.2 (8.6)	59.3 (7.9)
Ever smoker, No. (%)	0	15 566 (77.6)	5764 (87.7)	1202 (96.5)	87 (100)
Type 2 diabetes, No. (%)	0	219 (1.1)	501 (7.6)	320 (25.7)	87 (100)
Hypertension, No. (%)	0	2912 (14.5)	4679 (71.2)	1159 (93.1)	87 (100)
Hypercholesterolemia, No. (%)	0	1351 (6.7)	2198 (35.5)	1018 (81.8)	87 (100)
Body mass index, mean (SD) ^b	25.0 (3.1)	25.5 (3.2)	26.2 (3.6)	26.7 (4.3)	27.5 (4.1)
Height, mean (SD), in	70.2 (2.8)	70.2 (2.7)	70.0 (2.8)	69.8 (2.9)	70.0 (2.4)
Physical activity, median (IQR), METs/wk	13.4 (4.4-30.8)	11.3 (3.8-27.1)	10.2 (3.3-24.3)	8.4 (1.1-21.0)	7.8 (1.9-17.9)
Aspirin use >2 times/wk, No. (%)	3504 (22.9)	5812 (29.0)	2259 (34.4)	463 (37.2)	42 (48.3)
Parental history of MI at age ≤ 60 y, No. (%)	1685 (11.0)	2375 (11.8)	917 (14.0)	187 (15.0)	14 (16.1)
Alcohol consumption, median (IQR), g/d	3.1 (0-11.1)	7.4 (1.1-16.8)	8.1 (1.1-19.7)	8.4 (1.1-21.0)	3.9 (0-17.3)

Abbreviations: IQR, interquartile range; MET, metabolic equivalent; MI, myocardial infarction.

^aThe biannual follow-up in this study allowed a staggered entry of participants with missing data in 1986 that were acquired later during follow-up so the total number of men in this table differs from the total number of men in the analysis (n=45 985).^bCalculated as weight in kilograms divided by height in meters squared.

smoking (0, <10, 10-24, 25-44, 45-64, or ≥65 pack-years).

Similarly, we modeled duration of type 2 diabetes, hypercholesterolemia, and hypertension in relation to PAD risk in 3 categories (0, ≤5, 6-15, or >15 years); we have previously shown a positive association of diabetes duration with PAD in this cohort.²⁵ We also examined the number of antihypertensive medication classes used as a marker of severity.

To determine the independent associations of these risk factors, we adjusted for age (continuous), height (quintiles), aspirin intake of 2 or more per week, parental history of MI before age 60 years, geographical region (West, Midwest, South, and Northeast), BMI (<20, 20-22.9, 23-24.9, 25-29.9, and >30; calculated as weight in kilograms divided by height in meters squared), physical activity level (quintiles), and alcohol consumption (0, 0.1-4.9, 5.0-29.9, and ≥30.0 g/d) in the multivariable models. If covariate data were missing at a given time point, the last observation was carried forward for that cycle.

If data were still missing, contributions of person-time were skipped during follow-up for that specific period; participants with missing data on covariates at baseline could enter the cohort during follow-up if they had complete data on later questionnaires. We

obtained similar results if we used missing indicators for covariates and with a single imputation model using the Markov Chain Monte Carlo method. We tested for linear trend in 2 ways: for all 4 factors simultaneously, we treated the number of risk factors as a continuous variable; and for individual risk factors (eg, for duration of hypertension), we used the median of each category as a continuous variable.

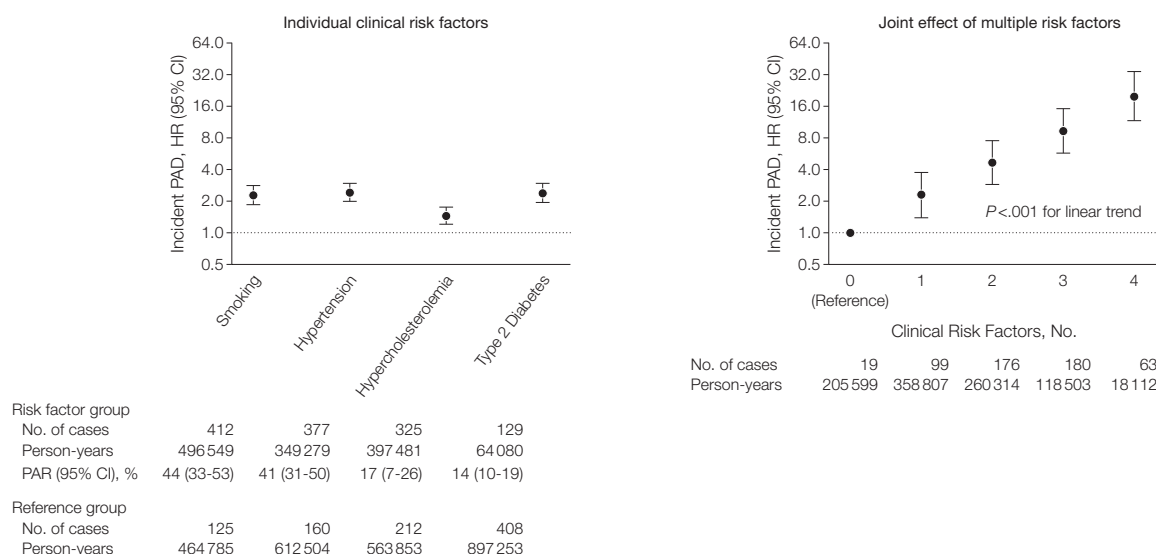
We calculated the multivariable-partial PAR percentage with its 95% confidence interval to integrate the prevalence and relative risk associated with each risk factor or set of risk factors.²⁶ To calculate the PAR percentage, we estimated the prevalence of combinations of each risk factor and the relative risk from multivariable-pooled logistic regression models,²⁷ using a counting process data structure.²⁸ In this approach, each 2-year interval for each participant was treated as an independent observation, and all observations were pooled into a single sample. Because smoking (both current and former) is a strong risk factor for PAD, we also assessed the effect of the other 3 risk factors among never smokers.

Statistical analyses were conducted using SAS software version 9.2 (SAS Institute Inc). All *P* values are 2-sided and a *P* value of less than .05 is considered statistically significant.

RESULTS

We excluded 3817 men with diagnosed cardiovascular disease at baseline and 2727 men with missing data on confounders at baseline who did not provide this information during follow-up, leaving 44 985 participants for the analyses. During a median follow-up of 24.2 years (interquartile range, 20.8-24.7 years; 961 333 person-years), we documented 537 cases of incident PAD. TABLE 1 shows the baseline characteristics of the cohort according to the number of clinical risk factors. Men with more risk factors were older, had a higher BMI, were less physically active, and were more likely to report aspirin use and a family history of MI.

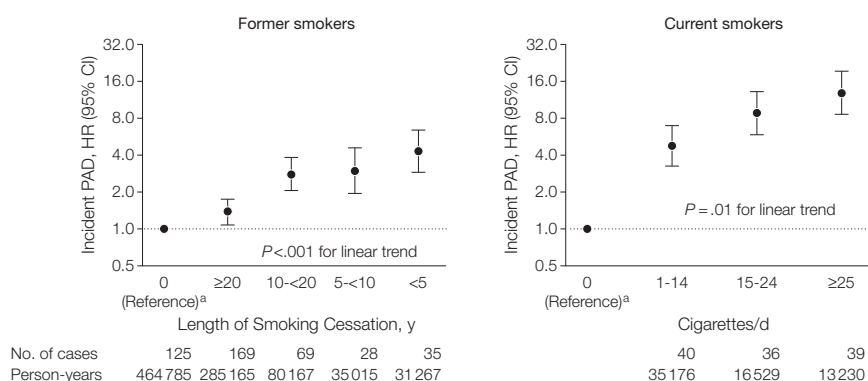
Ever smoking or having a history of hypertension, hypercholesterolemia, or type 2 diabetes were all independently and significantly associated with a higher risk of PAD after multivariable adjustment (FIGURE 1). The differences in age-adjusted incidence of PAD per 100 000 person-years were 33 cases for ever smoking, 43 cases for hypertension, 21 cases for hypercholesterolemia, and 67 cases for diabetes. The age-adjusted incidence rates were 9 (95% CI, 6-14) cases/100 000 person-years (n=19 incident cases) for 0 risk factors, 23 (95% CI, 18-28) cases/100 000 person-years (n=99 incident cases) for 1 risk factor, 47 (95% CI, 39-56) cases/100 000

Figure 1. Incident Peripheral Artery Disease (PAD) According to Individual and Joint Clinical Risk Factors

The hazard ratios (HRs) were adjusted for age, height, aspirin use, parental history of myocardial infarction at age 60 years or younger, geographical region, body mass index, physical activity, alcohol consumption, and each of the other 3 clinical risk factors. The reference group for each of the individual risk factors was the remainder of the cohort without the individual risk factor. The population attributable risk (PAR) percentages for each individual risk factor were calculated using pooled logistic regression models and were adjusted for the same factors mentioned above. The linear trend for the joint risk factors was obtained by treating the number of risk factors as a continuous variable.

person-years ($n=176$ incident cases) for 2 risk factors, 92 (95% CI, 76-111) cases/100 000 person-years ($n=180$ incident cases) for 3 risk factors, and 186 (95% CI, 141-246) cases/100 000 person-years ($n=63$ incident cases) for 4 risk factors. The absolute and age-adjusted incidence of PAD were 3.5/1000 person-years and 1.9/1000 person-years, respectively, among participants with all 4 risk factors. The multivariable-adjusted HR for each additional risk factor was 2.06 (95% CI, 1.88-2.26) compared with the group free of risk factors ($P<.001$ for linear trend). Similar results were obtained when men aged 80 years or older were censored to minimize the effects of extreme age.

The 4 risk factors were not statistically identical ($P<.001$). Therefore, we alternatively created a weighted score that subtracted 1 from each multivariable-adjusted HR in Figure 1 and summed the values. When this weighted score was transformed to the original 4-point scale and analyzed as a continuous variable, the multivariable-adjusted HR associated with a 1-point increase in weighted score was 2.07 (95% CI, 1.89-2.26).

Figure 2. Incident Peripheral Artery Disease (PAD) According to Smoking Status

The hazard ratios (HRs) were adjusted for age, height, history of type 2 diabetes, hypertension, hypercholesterolemia, aspirin use, parental history of myocardial infarction at age 60 years or younger, geographical region, body mass index, physical activity, and alcohol consumption. Linear trends are based only on former and current smokers, respectively, and are tested by treating the median of each category as a continuous variable.

^aThe reference group was never smokers.

Risk of PAD was strongly and dose dependently associated with current smoking compared with men who never smoked; there was a multivariable-adjusted HR of 12.89 (95% CI, 8.59-19.34) among the heaviest smokers compared with men who have never smoked (FIGURE 2). Duration of smoking cessation was also strongly associated with risk of PAD ($P<.001$ for lin-

ear trend), with progressively lower risk associated with greater duration since cessation. Even men who quit smoking more than 20 years in the past had a significantly higher risk compared with men who never smoked (HR, 1.39; 95% CI, 1.10-1.76). Compared with all former smokers, the HR for incident PAD among all current smokers was 3.81 (95% CI, 3.00-4.84). There was a

strong dose-response relationship between pack-years of smoking and risk of PAD ($P < .001$ for linear trend; FIGURE 3).

FIGURE 4 displays the association between duration of hypertension, hypercholesterolemia, and type 2 diabetes and risk of PAD. Regardless of duration category, all men with a risk factor had higher risks of developing PAD compared with men without risk factors. Risk of PAD tended to increase with duration of both type 2 diabetes ($P < .001$ for linear trend) and hypercholesterolemia ($P = .05$ for linear trend), although duration of hyperten-

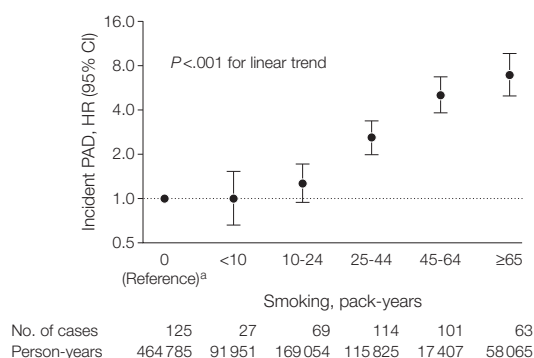
sion did not clearly modify risk. Among men with a positive history of hypertension, risk of PAD was higher among men who reported use of 1 antihypertensive drug (HR, 1.40; 95% CI, 1.09-1.78) or 2 or more antihypertensive drugs (HR, 2.07; 95% CI, 1.55-2.78) compared with men with hypertension who did not report current use of antihypertensive drugs.

TABLE 2 provides the PAR percentages associated with combinations of 2, 3, or all 4 clinical risk factors. The PAR associated with these 4 risk factors was 75% (95% CI, 61%-84%). The PAR increased slightly to 78% (95% CI, 66%-

86%) when we did not adjust for potentially modifiable variables (ie, BMI, physical activity level, aspirin use, and alcohol consumption). Men who did not have any of the 4 risk factors had a HR of 0.23 (95% CI, 0.14-0.36) compared with all other men in the cohort. In addition, the proportion of cases with at least 1 risk factor at the time of PAD diagnosis was 96% (95% CI, 94%-98%).

Given the strong relationship between both current and past smoking and risk of PAD, we explored the association of the remaining 3 clinical risk factors separately among never smokers. Among never smokers, the adjusted HRs for PAD were 2.55 (95% CI, 1.60-4.06) for type 2 diabetes, 1.84 (95% CI, 1.23-2.76) for hypertension, and 1.80 (95% CI, 1.20-2.72) for hypercholesterolemia. Never smokers with no other risk factors (44.6% of all never smokers) had a relative risk of 0.37 (95% CI, 0.23-0.62) compared with all other never smokers in this cohort. Among never smokers, the PAR associated with the 3 remaining clinical risk factors was 53% (95% CI, 29%-71%).

Figure 3. Incident Peripheral Artery Disease (PAD) According to Pack-Years of Smoking



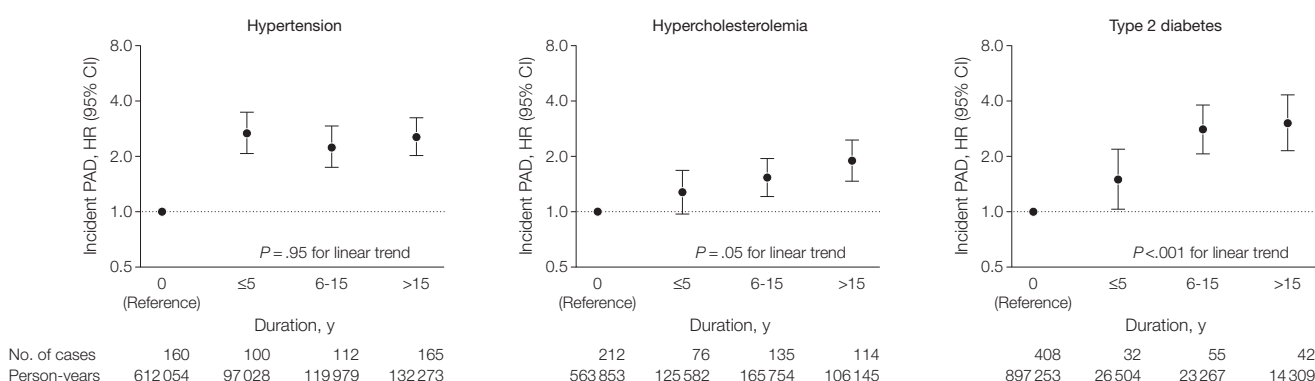
The hazard ratios (HRs) were adjusted for age, height, history of type 2 diabetes, hypertension, hypercholesterolemia, aspirin use, parental history of myocardial infarction at age 60 years or younger, geographical region, body mass index, physical activity, and alcohol consumption. Data on pack-years of smoking were missing for 6.0% of person-years during follow-up. Linear trends are based only on former and current smokers, respectively, and are tested by treating the median of each category as a continuous variable.

^aThe reference group was never smokers.

COMMENT

In this large prospective cohort study of men, the combination of the 4 clinical risk factors of smoking, hyperten-

Figure 4. Incident Peripheral Artery Disease (PAD) According to Duration of Hypertension, Hypercholesterolemia, and Diabetes



The hazard ratios (HRs) were adjusted for age, height, smoking status, history of diabetes, hypertension, hypercholesterolemia, aspirin use, parental history of myocardial infarction at age 60 years or younger, geographical region, body mass index, physical activity, and alcohol consumption. Linear trends are based only on participants with the disease and are tested by using the median of each duration category as a continuous variable. The reference group for each of the individual risk factors was the remainder of the cohort without the individual risk factor.

sion, hypercholesterolemia, and type 2 diabetes was strongly and independently associated with risk of confirmed and clinically significant PAD. Duration of diabetes and hypercholesterolemia, severity of hypertension, and cumulative intensity of smoking all demonstrated graded relationships with risk. Participants without these 4 traditional risk factors had an HR of 0.23 for developing PAD compared with all other men.

The overall incidence of PAD was low in this cohort (537 events among 44 985 participants, or an incidence of 1%). This low incidence of PAD is likely related to the definition of a new PAD diagnosis. Most people with PAD will never require lower-extremity revascularization or even undergo angiography. In addition, previous studies showed that PAD is frequently underdiagnosed.^{2,8,9} Thus, our findings regarding risk factors for PAD are generalizable to people with clinically significant PAD diagnosed in a medical practice setting. In addition, the absolute risk of our PAD outcome was low. Among individuals with 1 risk factor, the absolute inci-

dence of PAD was 0.28/1000 person-years. Even among individuals with all 4 risk factors, the absolute incidence of PAD was 3.5/1000 person-years, likely because of the definition used for the PAD outcome.

All of the 4 risk factors appeared to confer increased risk within short periods following recognition and, in the case of smoking, associated risk remained elevated even 20 years after cessation. At the same time, the joint effect of multiple risk factors combined was independent and graded, with no evidence that these risk factors became less important among those already at high risk. Further study is needed to determine whether aggressive risk factor modification in patients with multiple atherosclerotic risk factors can reduce the incidence of clinically severe PAD. Among patients with PAD, intense risk factor modification in the form of correcting blood pressure,²⁹ optimizing control of diabetes,³⁰ and normalizing low-density lipoprotein cholesterol levels³¹ is associated with lower morbidity and mortality. Nevertheless, lowering low-density lipoprotein cholesterol, for in-

stance, does not necessarily improve functional capacity, such as calf muscle perfusion or exercise performance among patients with PAD, and impairment of quality of life associated with the disease remains.³² Unfortunately, millions of US adults with prevalent but undiagnosed PAD do not receive secondary prevention therapies.²

Taken together, these 4 risk factors had a PAR of 75% for incident PAD, roughly comparable with the PAR seen for other cardiovascular diseases,^{33,34} and for cardiovascular and noncardiovascular mortality.³⁵ Despite this similarity, there are distinct and important differences between their relationships with PAD and other forms of cardiovascular disease. For example, at least 1 of these risk factors is present in 80% of patients with coronary heart disease (CHD)³⁴ compared with more than 95% of cases of severe PAD.

Similarly, active smoking is 2 to 3 times more strongly associated with PAD than with CHD,³⁶ and elevated risk among former smokers does not appear to return to baseline, in contrast to our findings on both CHD³⁷ and stroke.³⁸ Although risk remained el-

Table 2. Peripheral Artery Disease (PAD) by Combinations of Clinical Risk Factors^a

		Exposed Group, No. (%)		Unexposed Group, No. (%)		HR (95% CI) ^b	PAR (95% CI), % ^c
		Person-Years	PAD Cases	Person-Years	PAD Cases		
2 Risk factors							
Hypercholesterolemia and type 2 diabetes		421 803 (44)	361 (67)	539 530 (56)	176 (33)	2.08 (1.71-2.52)	28 (18-37)
Hypertension and hypercholesterolemia		550 313 (57)	449 (84)	411 020 (43)	88 (16)	2.61 (2.05-3.32)	48 (37-58)
Hypertension and type 2 diabetes		370 415 (39)	403 (75)	590 918 (61)	134 (25)	3.28 (2.67-4.03)	50 (41-58)
Smoking and type 2 diabetes		522 607 (54)	441 (82)	438 729 (46)	96 (18)	2.91 (2.32-3.65)	53 (42-61)
Smoking and hypercholesterolemia		680 275 (71)	490 (91)	281 058 (29)	47 (9)	3.00 (2.21-4.07)	57 (44-68)
Smoking and hypertension		652 259 (68)	491 (91)	309 074 (32)	46 (9)	3.29 (2.42-4.48)	60 (47-71)
3 Risk factors							
Hypertension, hypercholesterolemia, and type 2 diabetes		561 786 (58)	461 (86)	399 547 (42)	76 (14)	2.92 (2.26-3.76)	56 (46-64)
Smoking, hypercholesterolemia, and type 2 diabetes		690 551 (72)	498 (93)	270 782 (28)	39 (7)	3.40 (2.44-4.73)	63 (50-73)
Smoking, hypertension, and hypercholesterolemia		750 808 (78)	513 (96)	210 524 (22)	24 (4)	3.59 (2.37-5.44)	67 (52-78)
Smoking, hypertension, and type 2 diabetes		660 985 (69)	501 (93)	300 348 (31)	36 (7)	4.08 (2.89-5.76)	70 (58-78)
4 risk factors							
Smoking, hypertension, hypercholesterolemia, and type 2 diabetes		755 734 (79)	518 (96)	205 599 (21)	19 (4)	4.37 (2.75-6.94)	75 (61-84)

Abbreviations: HR, hazard ratio; PAR, population attributable risk.

^aThere were 961 333 person-years in the cohort and 537 cases of PAD.

^bThe HRs compare individuals exposed to a specified combination of clinical risk factors with all unexposed individuals (reference group) in this population. The HRs (95% CIs) were estimated from Cox proportional hazard models and adjusted for age, height, regular aspirin use, parental history of myocardial infarction at age 60 years or younger, geographical region, body mass index (calculated as weight in kilograms divided by height in meters squared), physical activity, and alcohol consumption, and each of the other clinical risk factors not included in the exposed group.

^cThe PAR was calculated using pooled logistic regression models and was adjusted for age, period, height, regular aspirin use, parental history of myocardial infarction at age 60 years or younger, geographical region, body mass index, physical activity, and alcohol consumption.

evated among former smokers, it was nearly 3-fold higher among current smokers, emphasizing that smoking cessation is never too late because it is associated with lower risk of cardiovascular disease morbidity and mortality even among individuals with diagnosed PAD.³⁹

Our findings also highlight the importance of hypertension as a major risk factor for PAD, with a PAR of more than 40%. Among men with hypertension, the number of different antihypertensive medications used (as a proxy for hypertension severity) was also associated with risk of PAD. We have previously reported the importance of healthy lifestyle practices in prevention of CHD among men with hypertension,⁴⁰ and our current findings support the need for lifestyle measures to prevent hypertension and reduce its severity when possible.

The 4 risk factors were not of equal magnitude in their association with PAD risk. We found a somewhat lower increase in risk of PAD associated with hypercholesterolemia compared with the other 3 risk factors. This may reflect the importance of effective treatment for hypercholesterolemia. While treatment for hypertension does not appear to fully reduce its associated risk for CHD,⁴¹ statin therapy treats hypercholesterolemia extremely effectively, essentially eliminating its associated risk.⁴² It is also possible that hypercholesterolemia is simply less important in the arterial beds that characterize PAD. A similar phenomenon has been observed for stroke compared with CHD.⁴³

The strengths of our study include its prospective design, large sample size, long-term and updated follow-up, validated questionnaires to assess large numbers of potential confounders, homogeneity in sex and profession, and many clinically confirmed end points.

Nevertheless, several potential limitations warrant clarification. First, we used symptomatic PAD as our outcome. Subclinical or asymptomatic PAD, which may have otherwise been detected by abnormal pulse examination or ankle-brachial index, may have

been missed, similar to how individuals with asymptomatic carotid stenosis or silent stroke are missed in studies of clinical stroke. If true, our results represent only the most severe manifestations of a much more common problem, although these risk factors also appear to increase the risk of subclinical PAD.⁴⁴ Moreover, end points included in this analysis were confirmed by medical records, reducing the likelihood of false-positive cases albeit at the risk of a falsely low incidence rate. Perhaps most importantly, this definition (similar to that used in most large cohort studies) captures clinically meaningful cases and a level of disease severity that is of unequivocal importance to both patients and physicians.

To account for missing data on confounding variables that were updated biennially during follow-up, we imputed missing data by carrying values of the last questionnaire forward. This method was best suited to our biennial assessment of risk factors and the large number of observations and variables in our database. Given our study design, this method of imputation is likely to closely represent the multiple imputation method. However, the multiple imputation method may have lead to a less biased estimate.

Smoking status and physician-diagnosed diabetes, hypertension, and hypercholesterolemia were self-reported. While generally valid and clearly associated with risk, these self-reported measures may underestimate the risk if nondifferential misclassification is present. We also evaluated duration of risk factors but not detailed measures of severity, which may be important for the relationships of blood pressure⁴⁵ and diabetes³⁰ with risk of PAD. Nevertheless, the simplicity of binary cut points of clinically elevated levels may help provide discrete guidance for patients in the clinical setting.

The cohort included mainly white men, and our findings may not be generalizable to other groups, although we have no reason to suspect that standard risk factors are any less impor-

tant in other populations. In addition, as with any observational study, unmeasured or residual confounding may be present despite the substantial number of potentially confounding factors for which we adjusted. For example, these risk factors co-occur with elevations in inflammatory and hemostatic biomarkers, although they appear to represent independent statistical factors.⁴⁶

In conclusion, in this well-characterized cohort of US men followed up for longer than 2 decades, smoking, hypertension, hypercholesterolemia, and type 2 diabetes each demonstrated strong, graded, and independent associations with risk of clinically significant PAD.

Author Contributions: Dr Joosten had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Joosten, Pai, Mukamal.

Acquisition of data: Pai, Rimm, Mukamal.

Analysis and interpretation of data: Joosten, Pai, Bertoia, Rimm, Spiegelman, Mittleman, Mukamal.

Drafting of the manuscript: Joosten.

Critical revision of the manuscript for important intellectual content: Joosten, Pai, Bertoia, Rimm, Spiegelman, Mittleman, Mukamal.

Statistical analysis: Joosten, Bertoia, Spiegelman, Mittleman.

Obtained funding: Pai, Mukamal.

Administrative, technical, or material support: Joosten, Pai.

Study supervision: Rimm, Mukamal.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Mittleman reported institutional grant support from the National Heart, Lung, and Blood Institute; and receiving or having institutional grants pending from the National Institutes of Health, the Environmental Protection Agency, and Health Effects Institute. Dr Mukamal reported institutional grant support from the National Heart, Lung, and Blood Institute and the National Institutes of Health; and institutional support in the form of active and placebo capsules provided from the Martek Corporation to Harvard Medical School for a trial of docosahexaenoic acid for periodontitis. No other author reported disclosures.

Funding/Support: This work was supported by National Institutes of Health grants R01 HL091874, HL35464, and CA55075.

Role of the Sponsor: The National Institutes of Health had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Additional Contributions: We thank Lydia Liu, MSc (Department of Nutrition of the Harvard School of Public Health), for statistical and programming assistance; Ms Liu did not receive additional compensation for her contribution above her normal salary from Harvard.

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