

Risk Factors for Mortality Among Those with Peripheral Arterial Disease

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OBJECTIVE

- To characterize risk factors for cardiovascular and all-cause mortality among those with peripheral arterial disease using a nationally representative survey of US adults.

BACKGROUND

- Rates of peripheral arterial disease (PAD), a leading cause of atherosclerotic cardiovascular morbidity, continue to increase.
- Traditional cardiovascular risk factors are implicated in the development of PAD, yet the extent to which such risk factors correlate with mortality in such patients remains insufficiently assessed.

METHODS

- Data from the 1999-2004 National Health and Nutrition Examination Survey (NHANES) waves were used.
- Mortality status was determined from a probabilistic record match of the National Death Index conducted by the National Center for Health Statistics. Deaths from any cause and from cardiovascular disease (i.e., *International Classification of Diseases, 10th Revision* codes I00 to I99) were examined. Follow-up duration was calculated from the date of interview to either the date of death or to December 31, 2011.
- Individuals ≥ 40 years old, weighed < 400 pounds, and who did not have bilateral amputation were asked to participate in an ankle-brachial index (ABI) examination. The ABI was calculated automatically (Parks Mini-Laboratory IV, Model 3100) by dividing the systolic blood pressure at the ankle by the brachial artery systolic blood pressure. Limb pressure was measured twice among those aged 40 to 59 years old and once in those 60 years of age and older. PAD was defined as an ABI ≤ 0.90 in either leg.
- Demographic variables included age, sex, ethnicity, and smoking status. Comorbidities included previously recognized personal history of cardiovascular disease, diabetes mellitus, hypertension, and hyperlipidemia. Comorbidities were assessed either by respondent self-report or through laboratory data.
- Physical activity was assessed by responses to whether respondents had participated in moderate (e.g., brisk walking, bicycling for pleasure, golf, dancing) or vigorous (e.g., running, lap swimming) exercise for at least 10 minutes in the past 30 days.
- Individuals were classified as taking statins, antihypertensive medicines, angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) medications, and antiplatelet agents using a standardized interview procedure.
- To account for NHANES's complex study design including oversampling, survey non-response, and post-stratification, analyses were weighted as per Centers for Disease Control and Prevention recommendations. Standard errors were calculated by Taylor series linearization to account for clustering of responses.
- To account for missing data, five multiply imputed datasets were analyzed using an expectation-maximization with bootstrapping algorithm, with results combined by standard rules.
- For both all-cause and cardiovascular mortality, multivariable Cox proportional-hazards models were employed, stratified by medication utilization to ensure proportionality of hazards, which were assessed by inspection of Schoenfeld residuals.

RESULTS

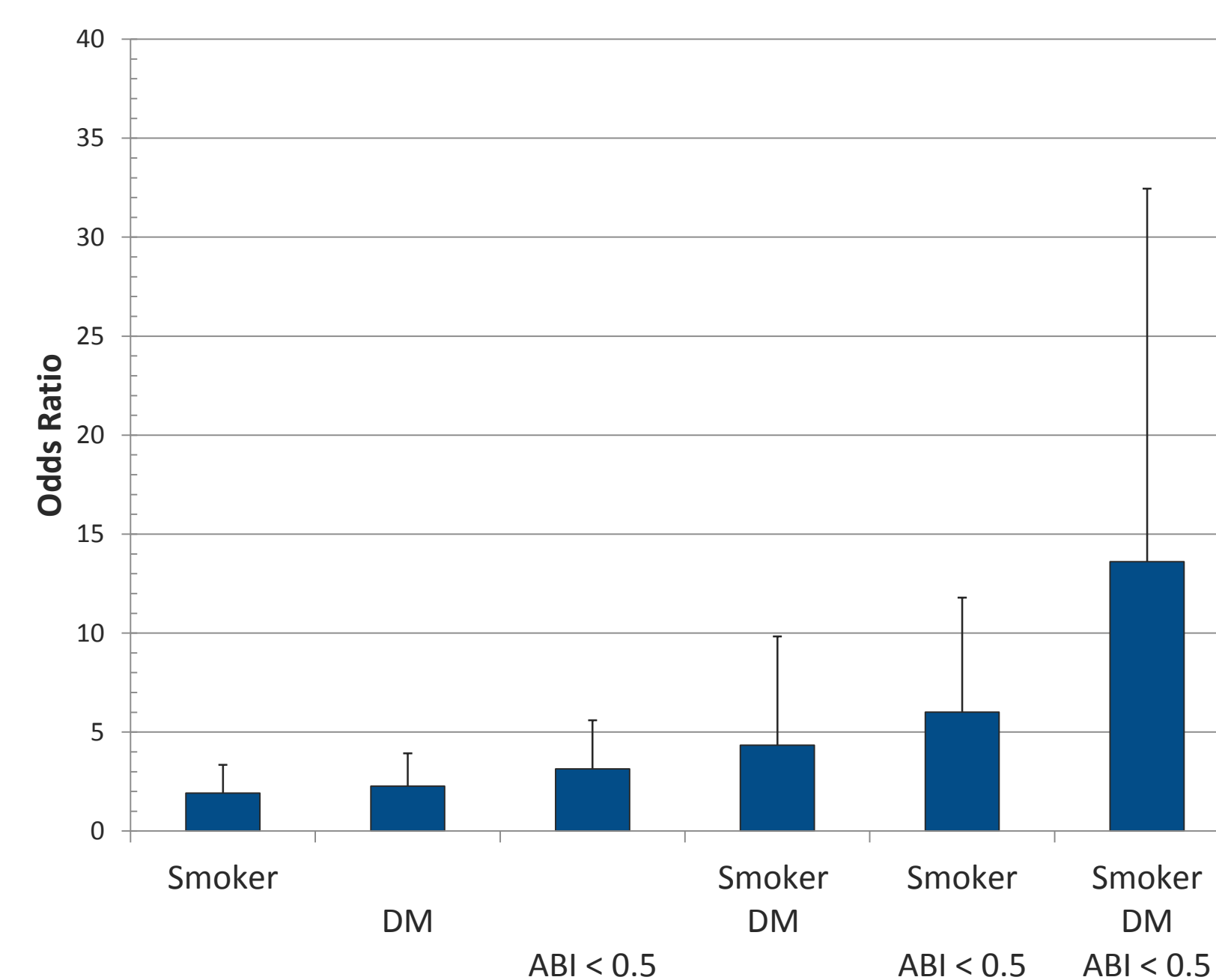
- 7571 adults aged ≥ 40 and above underwent ABI measurement, of which 647 were found to have PAD.
- Individuals were followed for a median 7.8 years (interquartile range [IQR], 4.8–9.7 years; mean, 7.2 years). During that time, there were 336 (51.9%) deaths, of which 79 (12.2%) were attributable to cardiovascular causes. Missing data were minimal (e.g., 6.3% for hs-CRP, 3.3% for BMI).
- Compared to never smokers, current smokers (hazard ratio [HR] 2.45; 95% confidence interval [CI], 1.62–3.71) and former smokers (HR 1.62; 95% CI, 1.14–2.29) with PAD had higher rates of death. Also associated with increased rates of cardiovascular death were: an ABI < 0.5 (HR 3.14; 95% CI, 1.44–6.85, compared to those with ABI 0.7-0.9), diabetes mellitus (HR 2.27; 95% CI, 1.09–4.70) and a systolic blood pressure > 160 mmHg (HR 4.75; 95% CI, 1.09–21.8, compared to the lowest-risk second quartile). Moderate or vigorous physical activity ≥ 10 minutes monthly was associated with lower death rates (HR 0.63; 95% CI, 0.44–0.91). Neither C-reactive protein nor body-mass index was associated with mortality.

TABLE 1. BASELINE CHARACTERISTICS (N=647)

Characteristic	Overall*
Age—yr	67.8(0.7)
Male sex—%	41.6(2.5)
Race, non-Hispanic white—%	78.1(2.1)
Recognized cardiovascular disease—%†	30.4(2.5)
Diabetes mellitus—%	25.1(2.5)
Hypertension—%	76.6(2.4)
Systolic blood pressure—mmHg	141(1.3)
Smoking (current)—%	22.2(1.6)
Body mass index—kg/m ²	28.5(0.3)
Total cholesterol—mg/dL	210.2(2.7)
High density cholesterol—mg/dL	51.9(1.0)
Physical activity—%§	42.1(2.7)
Statin use—%	30.5(2.5)
Anti-platelet use—%	8.1(1.4)
ACEI/ARB use—%	24.5(1.7)
Anti-hypertensive medication—%	35.5(2.8)
Ankle-brachial index	0.77(0.007)
High-sensitivity C-reactive protein—mg/L	7.1(0.7)

* Values shown are means or percentages with standard errors in parentheses.
 † Recognized cardiovascular disease includes prior diagnosis of coronary heart disease, angina pectoris, myocardial infarction, or cerebrovascular disease.
 § Physical activity includes moderate or vigorous exercise at least 10 minutes in duration during the past 30 days.

FIGURE. RISK OF MULTIPLE COMORBIDITIES ON CARDIOVASCULAR MORTALITY AMONG THOSE WITH PAD.



The figure demonstrates the relationship between increasing cardiovascular risk factor burden and cardiovascular mortality among those with PAD. The combination of current smoking, diabetes, and low ankle-brachial index increased the risk of cardiovascular death thirteen-fold.

TABLE 2. HAZARD RATIOS FROM COX PROPORTIONAL HAZARD MODELS EXAMINING ALL-CAUSE AND CARDIOVASCULAR MORTALITY AMONG INDIVIDUALS WITH PAD.

	All-Cause Mortality		Cardiovascular Mortality	
	Age and Gender Adjusted	Fully Adjusted Model*	Age and Gender Adjusted	Fully Adjusted Model*
Ankle-brachial index				
≤ 0.50	2.15(1.39-3.33)	1.43(0.87-2.35)	4.61(1.88-11.3)	3.14(1.44-6.85)
0.50-0.69	1.11(0.83-1.48)	0.91(0.70-1.20)	1.34(0.64-2.81)	0.91(0.44-1.86)
0.70-0.90	Ref.	Ref.	Ref.	Ref.
Smoking status				
Never	Ref.	Ref.	Ref.	Ref.
Former	1.54(1.08-2.19)	1.62(1.14-2.29)	2.21(1.01-4.90)	2.44(1.35-4.41)
Current	2.37(1.60-3.50)	2.45(1.62-3.71)	2.29(1.08-4.85)	1.91(0.90-4.05)
Physical activity†				
No	Ref.	Ref.	Ref.	Ref.
Yes	0.64(0.46-0.89)	0.63(0.44-0.91)	0.39(0.20-0.77)	0.41(0.20-0.82)
BMI—kg/m²				
≤ 25	Ref.	Ref.	Ref.	Ref.
25-29	0.91(0.62-1.33)	0.91(0.62-1.34)	1.27(0.64-2.49)	1.12(0.61-2.08)
≥ 30	0.93(0.58-1.49)	0.94(0.59-1.54)	1.09(0.51-2.32)	0.88(0.40-1.92)
Diabetes				
No	Ref.	Ref.	Ref.	Ref.
Yes	1.37(1.00-1.89)	1.29(0.92-1.80)	1.77(0.90-3.49)	2.27(1.09-4.70)
Systolic blood pressure—mmHg				
≤ 127	Ref.	Ref.	Ref.	Ref.
127-140	1.10(0.68-1.76)	1.07(0.64-1.81)	1.81(0.75-4.36)	2.32(0.77-6.98)
141-160	1.37(0.88-2.13)	1.49(0.94-2.39)	0.95(0.31-2.88)	1.30(0.30-5.66)
≥ 160	1.43(0.90-2.28)	1.51(0.92-2.47)	2.70(0.92-7.92)	4.75(1.09-21.8)
Non-HDL				
≤ 130 mg/dL	Ref.	Ref.	Ref.	Ref.
> 130 mg/dL	1.08(0.79-1.48)	1.18(0.76-1.84)	1.11(0.67-1.83)	1.85(0.94-3.64)
log_e hs-CRP				
≤ 1.0	Ref.	Ref.	Ref.	Ref.
> 1.0	1.16(1.00-1.34)	1.09(0.94-1.27)	0.98(0.70-1.37)	0.89(0.69-1.15)

* Estimates are derived from Cox proportional hazards model stratified for use of statins, antihypertensive medicines, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker medications, and antiplatelet agents. Models adjusted for the listed variables and age, sex, race, and history of cardiovascular disease.
 † Physical activity includes moderate or vigorous exercise at least 10 minutes in duration during the past 30 days.

LIMITATIONS

- The study is observational in nature and residual confounding might remain. Sample size limitations may have hampered our ability to detect true underlying relationships. Many data are based on participant self-report, which could also bias results.

CONCLUSIONS

- Among those with PAD, tobacco use was associated with increased risk, and physical activity associated with decreased risk, of all-cause and cardiovascular death.
- A low ankle-brachial index, diabetes, and uncontrolled blood pressure were also predictive of increased cardiovascular mortality.
- These findings underscore the importance not only of tobacco cessation but physical activity for patients with PAD, extending results of recent clinical trials and prior observational data to a likely long-term mortality benefit from exercise in those with PAD.