

Published in final edited form as:

*Eur J Prev Cardiol*. 2014 June ; 21(6): 704–711. doi:10.1177/2047487312452968.

# Peripheral arterial disease, prevalence and cumulative risk factor profile analysis

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## Abstract

**Background—**The primary aim of the present study was to determine the cumulative effect of a set of peripheral artery disease (PAD) risk factors among age, gender and race/ethnicity groups in the United States.

**Methods—**We examined data from a nationally representative sample of the US population (National Health and Nutrition Examination Survey [NHANES], 1999–2004). A total of 7058 subjects 40 years or older that completed the interview, medical examination and had ankle–brachial index (ABI) measurements were included in this study.

**Results—**The age- and sex-standardized prevalence of PAD was 4.6 % (standard error [SE] 0.3%).The highest prevalence of PAD was observed among elderly, non-Hispanic Blacks and women. In a multivariable age-, gender- and race/ethnicity-adjusted model hypertension, diabetes, chronic kidney disease, and smoking were retained as PAD risk factors ($p \leq 0.05$ for each). The odds of PAD increased with each additional risk factor present from a non-significant 1.5-fold increase (O.R 1.5, 95% confidence interval [CI] 0.9–2.6) in the presence of one risk factor, to more than ten-fold (OR 10.2, 95% CI 6.4–16.3) in the presence of three or more risk factors. In stratified analysis, non-Hispanic Blacks (OR 14.7, 95% CI 2.1–104.1) and women (OR 18.6, 95% CI 7.1–48.7) were particularly sensitive to this cumulative effect.

**Conclusion—**In a large nationally representative sample, an aggregate set of risk factors that included diabetes mellitus, chronic kidney disease, hypertension and smoking significantly increase the likelihood of prevalent PAD. A cumulative risk factor analysis highlights important



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susceptibility differences among different population groups and provides additional evidence to redefine screening strategies in PAD.

### Keywords

Peripheral arterial disease; risk assessment; traditional cardiovascular risk factors; NHANES

## Introduction

Peripheral artery disease (PAD) is a strong independent predictor of cardiovascular mortality and all-cause mortality.[1] The excess risk of cardiovascular disease is similar between subjects with symptomatic and asymptomatic PAD.[2] Risk factors for PAD of the lower extremities are similar to markers of atherosclerosis in the coronary and other vascular territories. However, the dynamic changes in the prevalence of risk factors in the general population makes imperative to determine a clinical profile associated with prevalent PAD that reflects age, gender and racial/ethnic differences at a population-based level.

The primary aim of the present analysis was to determine the cumulative effect of established risk factors on the prevalence of PAD across distinctive demographic groups. We also sought to estimate prevalence of PAD in high-risk groups in a sample that reflects the general population demographic distribution without the selection and survival biases often found in more convenient samples.

## Material and methods

### Study population

The National Health and Nutrition Examination Survey (NHANES) is an ongoing, cross-sectional survey of the civilian, non-institutionalized population in the United States. The 1999–2004 NHANES data collection and laboratory procedures were reviewed and approved by the National Center for Health Statistics (NCHS) Institutional Review Board (IRB). Informed consent was obtained from all subjects. For the purpose of this study we combined data from the survey years (1999–2004) in which the ankle–brachial index (ABI) is currently available. A total of 7058 subjects 40 years or greater who completed the interview and medical examination sections, had the brachial pressure, ankle pressures, serum creatinine, total cholesterol and blood glucose measured, and responded all relevant questions were included.

### Study parameters

**ABI measurement—**A defined protocol was used to measure ABI in NHANES 1999–2002 and 2003–2004.[3,4] Briefly, an 8MHz Doppler device (Parks Minilaboratory IV, model 3100, Parks Medical Electronics) was used to measure the right brachial artery systolic blood pressure (left if a medical condition precluded measurement) and posterior tibial arteries. For individuals 40–59 years old, ankle pressures were measured twice and once for individuals 60 years or older. The ABI for each leg was calculated as the mean systolic blood pressure in the ankle pressures divided by the mean brachial pressure. Participants

with bilateral amputation or weight above 400 pounds were excluded from the ABI measurement procedures. PAD was defined as an ABI value <0.9 on either leg.[5]

**Laboratory analysis—**An automated chemical analyzer (Beckman Syncrom LX20 (Beckman Coulter, Fullerton, Ca) was used to determine serum creatinine. Values from the 1999–2000 examination dataset were corrected as suggested in the laboratory documentation files due to a change in assay with subsequent data. A Hitachi 704 analyzer was used to measure fasting lipids. Fasting glucose was measured using a hexokinase method.

**Covariates—**Participants self-reported their age, race/ethnicity and gender. Hypertension was defined if a subject had a systolic blood pressure 140 mmHg and/or diastolic blood pressure ≥90 mmHg, a self-reported prescription use for hypertension or a self-reported physician diagnosis of hypertension. Hypercholesterolemia was defined if a subject reported use of cholesterol lower prescription, a self-reported physician diagnosis of hyperlipidemia or if the total serum cholesterol level was ≥240 mg/dl. The presence of diabetes was determined if a subject had any of the following: a fasting glucose ≥126 mg/dl, a non-fasting glucose ≥200 mg/dl, self-reported a physician diagnosis of diabetes or use of oral hypoglycemic medications or insulin. Each subject had the estimated glomerular filtration rate (eGFR) calculated based on the abbreviated Modification of Diet in Renal disease Study equation: $175\times (\text{serum creatinine in mg/dl})^{-1.154} \times (\text{age in years})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if non-Hispanic Black})$.[6] Chronic kidney disease (CKD) was categorized based on eGFR ≤60 ml/min.1.73 $m^2$. Smoking status was categorized using a self-reported questionnaire. If subjects had a positive response to the question ‘Do you now smoke cigarettes?’ they were labeled as ‘current smokers’. Subjects who answered no were labeled as ‘former smokers’ if they answer positively to the question ‘Have you smoked at least 100 cigarettes in your life?’. If they never smoked in their lifetime they were labeled as ‘never smokers’. Obesity was defined by the presence of a body mass index (BMI) of 30 or higher.

## Statistical analysis

The NHANES is a complex, multi-stage probability survey in which African-Americans, Mexican-Americans, and subjects 60 years and older were over sampled. A 6-year weight variable was calculated following the NHANES analytic and reporting guidelines.[7] Age-gender standardized prevalence was calculated based on the most recent (2007) U.S. Census Bureau, current population report.[8] PAD prevalence difference across population groups were estimated using the Rao–Scott chi-squared test. In order to determine the predictors that are associated with PAD, we first developed a multivariate logistic regression model that included traditional cardiovascular risk factors (obesity, hypertension, diabetes, kidney disease, smoking and hypercholesterolemia) using the NHANES 1999–2002 dataset. We next used a backward model selection approach to remove non-significant risk factors until all risk factors were significant ($p \leq 0.05$). We then used the significant risk factors to define the number of risk factors for each respondent. The odds of PAD were determined for each age, gender and race/ethnicity stratum based on the number of risk factors. The 2003–2004 NHANES dataset was used as an independent population sample to replicate all of the logistic regression models using the simplified set of risk factors as predictors. All

descriptive and statistical analyses were performed on SAS 9.2 using the proper commands to account for the complex sampling design. Domain statement was used in all analysis to ensure the correctness of variance estimates. All *p*-values presented are two-tailed; $p \leq 0.05$ was considered statistically significant.

## Results

A total of 7058 subjects aged ≥40 years with an ABI measurement and the rest of covariates measured were included in this study. Age- and gender-standardized prevalence of PAD was 4.64% (standard error [SE] 0.29%). Table 1 presents selected baseline demographic groups and clinical characteristics. A substantially higher prevalence of PAD was observed in older patients. The overall prevalence of PAD ranged from 1.43% (SE 0.29%) in individuals aged 40–49 to 16.62% (SE 1.09%) in individuals aged ≥70 years. Significant differences in the prevalence of PAD were also observed across race/ethnic groups. Non-Hispanic Blacks had a higher prevalence of PAD (7.46% [SE 0.79%]) than non-Hispanic Whites (4.66% [SE 0.32%]), whereas the lower prevalence of PAD was observed in Mexican-Americans (3.11% [SE 0.62%]). Among traditional cardiovascular risk factors, the highest prevalence of PAD was observed among diabetics (9.57% [SE 1.31%]) and subjects with CKD (eGFR < 60) (15.33 % [SE 1.81%]). No difference in the prevalence of PAD was noted between lean, overweight and obese participants.

Subsequent stratified analysis based on race and gender with the presence of other cardiovascular comorbidities revealed population groups with a high prevalence of PAD. The highest prevalence of PAD was observed in non-Hispanic Black women 70 years or older (25.3% [SE 4.4%]), non-Hispanic Black women with CKD (21.7% [SE 4.6%]) and Mexican-American men 70 years or older (20.85% [SE 3.78%]). Age greater than 70 was a consistent determinant of high PAD prevalence in both males and females and among all racial/ethnic groups (Table 2).

A total of 4705 participants in the NHANES 1999–2002 dataset had assessment of ABI and information on all clinical risk factors. In a multivariable model adjusted for age, gender and race/ethnicity only hypertension, diabetes, CKD, smoking and hypercholesterolemia were retained as significant PAD risk factors ($p \leq 0.05$ for each). Obesity was not significantly associated with PAD (Table 3). Hypercholesterolemia (odds ratio [OR] 1.4, 95% confidence interval [CI] 1.0–1.8), hypertension (1.4, 95% CI 1.0–2.2) and diabetes (OR 1.5, 95% CI 1.0–2.3) conferred a modest and equivalent increase in the likelihood of PAD. CKD and former smokers were associated with a two-fold increase, whereas current smokers (OR 4.1, 95% CI 3.1–5.4) had the highest likelihood of PAD.

A simplified scoring system was devised to better understand the impact of concomitant and additive presence of cardiovascular disease (CVD) risk factors using only risk factors retained in the multivariate model (hypertension, diabetes, kidney disease, hypercholesterolemia and smoking). An incremental trend in the odds of PAD was noted proportional to the presence of CVD risk factors. The additive presence of risk factors dramatically increased the odds of PAD (Table 4). In the overall sample in 1999–2002, for each additional risk factor present the odds of PAD nearly doubled ($p$ for trend <0.001). The

presence of three or more risk factors increased the odds of PAD more than ten-fold (OR 10.2, 95% CI 6.4–16.3) (Figure 1). A subgroup analysis was performed to determine whether groups based on age, gender and race/ethnicity were particularly sensitive to this cumulative effect. Females in particular were highly susceptible to aggregate effect of more than one risk factor, their odds of PAD were nearly triple in the presence of two and three or more risk factors compared with females with no risk factors, respectively (two risk factors OR 6.9 [95% CI 3.2–14.8]; three or more risk factors OR 18.6 [95% CI 7.1–48.7]) (Figure 2).

We then used the NHANES 2003–2004 ($n$ = 2347) as a control population to replicate results and validate our score system analysis. The additive presence of each additional risk factor approximately doubled the odds of PAD (Figure 3) and the findings were similar in all subgroups.

## Discussion

We examined the utility of a set of traditional cardiovascular risk factors to predict risk for PAD in a sample representative of the United States population. Our analysis is consistent with previously published reports[9] and provides new insights on the aggregate role that traditional cardiovascular risk factors have in identifying patients at risk for PAD. After adjusting for age, race and gender we noted that diabetes, hypertension, smoking, hypercholesterolemia and kidney dysfunction were retained as the main predictors of PAD. A sensitivity analysis revealed that an aggregate simplified score based on these predictors dramatically increased the likelihood of PAD among different groups stratified by age, gender and race/ethnicity. Females and non-Hispanic Blacks were particularly susceptible to this clustering of risk factors.

Smoking is a determinant risk factor of PAD among all groups. However, a higher prevalence of current smokers among women and non-Hispanic Blacks may explain the excess risk of PAD observed in these populations. Consistent from findings of other large population studies smoking, even for a short time, increases the risk of PAD in women.[10] Conen et al. in a large prospective study of 20, 366 women found that women who smoke even fewer than 15 cigarettes per day had a 12 fold increase in PAD risk and the risk decreased with smoking cessation.[11] This finding highlights the importance of increasing the awareness of PAD in women and targeting smoking cessation campaigns to populations at risk as one the single most important measures to decrease the prevalence of PAD.[11] Other benefits associated with smoking cessation in PAD are a reduced rate of disease progression, regression and a reduced risk of critical limb ischemia requiring revascularization.[12,13] We acknowledge selection and recall bias when addressing smoking status as a health risk factor in NHANES and other large population-based studies. However, the definition used for the present study has been used and validated in other studies to be a reliable predictor of cardiovascular risk.

CKD is a well-known risk factor for PAD and others forms of advance vascular disease.[14,15] PAD subjects with CKD are known to have increased morbidity, higher rates of amputation and revascularization failure, and increased risk of cardiovascular mortality.[16] We noted that

the presence of CKD appears to be a particularly important risk factor for PAD among women from all racial/ethnic groups. This finding is consistent with results from the prospective Heart and Estrogen/Progestin Replacement Study (HERS) in which renal insufficiency was independently associated with future PAD among postmenopausal women.[16]

The modest association of hypercholesterolemia, hypertension and diabetes with PAD after adjusting for age, gender and race/ethnicity in the general population is consistent with prior reports.[13] Diabetes is also a major modifier of PAD natural history; diabetics are known to have a higher prevalence of functionally limiting claudication, an increase incidence of amputation and acute cardiovascular events.[17–19] In PAD, the degree of hypertension is linked to the severity of disease and it is an important therapeutic target to reduce cardiovascular mortality in the presence of PAD.[20] In addition, blood pressure therapy has been associated with improvements in claudication symptoms and blood flow distal to the stenosis. This effect appears to be specifically linked to angiotensin-converting enzyme inhibitors.[21]

We found a weak association between PAD and hypercholesterolemia when compared with other risk factors. A finding also noted in other European and North-American population-based studies. In the Get ABI study no association was noted between multiple lipid parameters and PAD.[22] In a prospective analysis of 27,935 US female health professionals, no significant association between PAD and total cholesterol (TC), LDL-c (low-density lipoprotein cholesterol) or non-HDL-c (non-high-density lipoprotein cholesterol) was found. However, a modest risk of PAD was attributed to a low high-density lipoprotein cholesterol (HDL-c) and an increased TC: HDL-c ratio.[23] Interestingly, there is strong evidence from prospective clinical trials that lipid lower medications, in particular satins, improve clinical and cardiovascular outcomes in subjects with PAD.[24–26] A recent meta-analysis demonstrated that the benefit of statins appear to be related to functional improvement even if no apparent changes in the ABI are noted.[27]

The strength of our study relies on the nature of the NHANES standardized protocols. This is a large survey sampling that follows complex, multistage and stratified procedures to provide data representing the US population. Our results are novel in providing quantitative evidence of the aggregate effect that traditional cardiovascular risk factors have on PAD prevalence. Focusing on specific PAD risk prediction tools using traditional, non-traditional and novel risk factors[28–30] will not only facilitate the discovery of specific PAD therapeutic interventions but may also contribute to decreasing the excess cardiovascular mortality and disparities in the implementation of preventive measures observed in persons with PAD.[31] Our study also has important limitations to consider. First, the cross-sectional design does not allow us to make causal inferences or to establish the prospective value of the risk stratification performed. Second, although the ABI is regarded as a primary screening and severity assessment tool for PAD in persons at risk, we acknowledge the presence of ascertainment bias as the ABI is only an indirect measurement of luminal stenosis.[13] Finally, we acknowledge that a non-compressible artery artifact due to underlying vascular calcification could cause the ABI to underestimate flow limiting arterial disease of the lower extremity in diabetics and patients with CKD. In NHANES, as in other large

epidemiological databases, direct imaging analysis is not available thus we are unable to provide a reliable estimate of atherosclerosis disease of the lower extremities in the setting of normal or high ABI or the impact on the risk profile analysis we performed.

In summary, a sample representative of the US population was used to develop a novel and simple PAD risk factor score based on the presence of diabetes mellitus, CKD, hypertension, hypercholesterolemia and smoking history. An elevated PAD risk score dramatically increased the likelihood of identifying subjects with PAD (ABI < 0.9). Women and non-Hispanic Blacks were particularly sensitive to the aggregate effect of multiple risk factors. A cumulative factor analysis approach allows for the quantification of risk in different populations groups and provides additional evidence to expand the limited PAD screening strategies advocated by health policy agencies.[32,33]

## Acknowledgments

**Funding**

This work was supported by a NHLBI-K12 Research Career Development Award (grant number RFA-HL-05-002; PI ERM) to LHE, EF and JSB.

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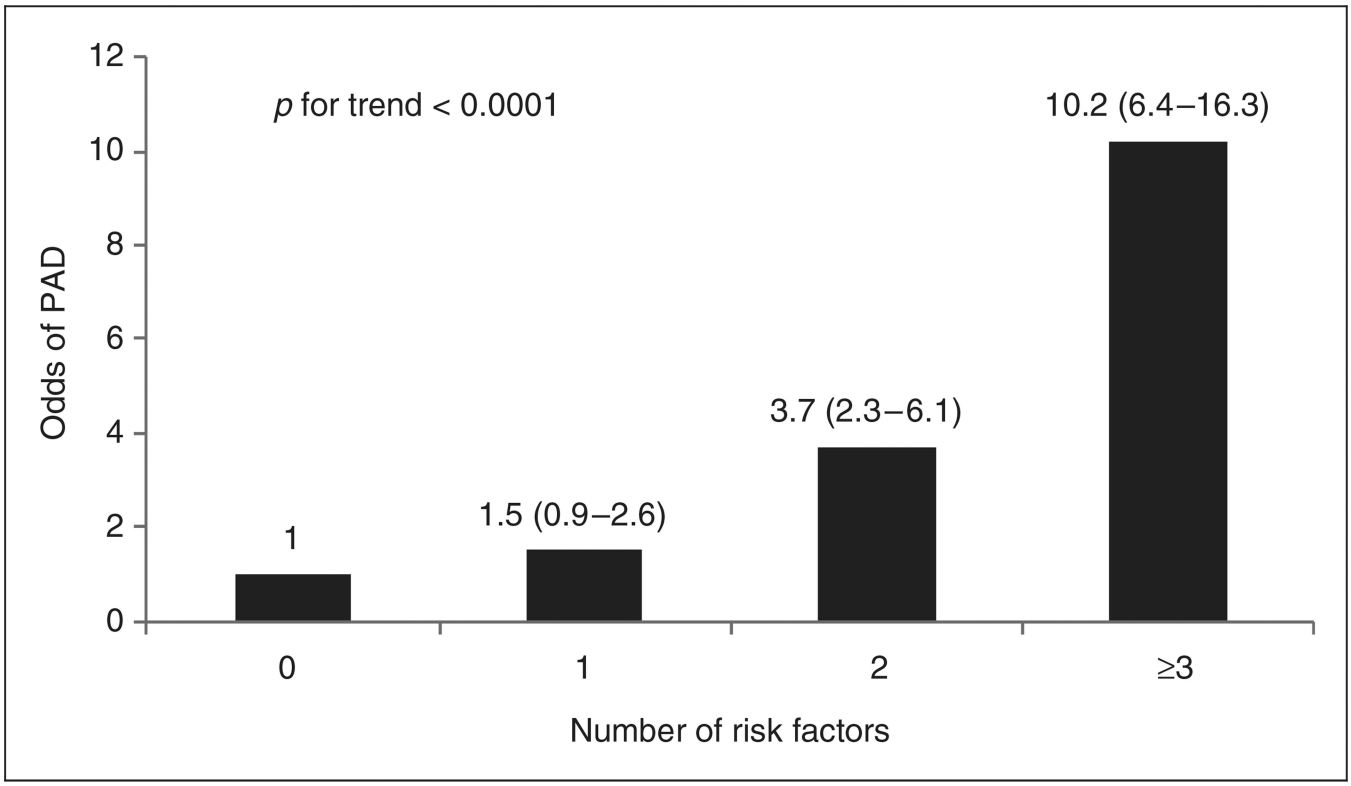


**Figure 1.**

Relative odds of peripheral arterial disease (PAD) based on the number of clinical risk factors (NHANES 1999–2002). Odds ratios (95% confidence intervals) and trend probabilities of PAD based on an increased number of cardiovascular risk factors (hypertension, diabetes, hypercholesterolemia, current smoking and chronic kidney disease [estimated glomerular filtration rate ≤60]) are presented.

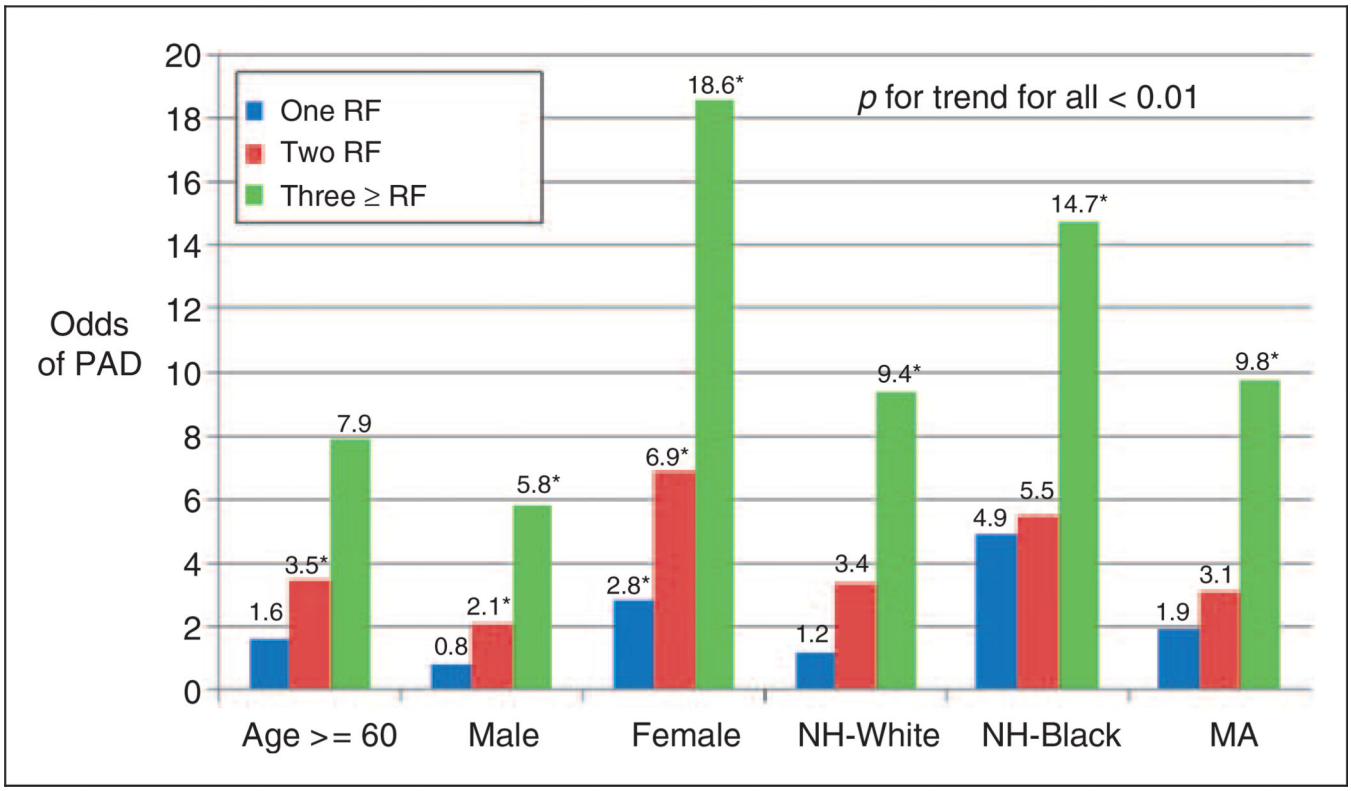


**Figure 2.**

Subgroup analysis of the relative odds of peripheral arterial disease (PAD) based on the number of clinical risk factors (NHANES 1999–2004). Odds ratios and trend probabilities of PAD among age, gender, race/ethnicity groups based on an increased number of cardiovascular risk factors (hypertension, diabetes, hypercholesterolemia, current smoking and chronic kidney disease [estimated glomerular filtration rate ≤60]) are presented. NH, non-Hispanic; MA, Mexican-American. *Significant associations $p \leq 0.05$.

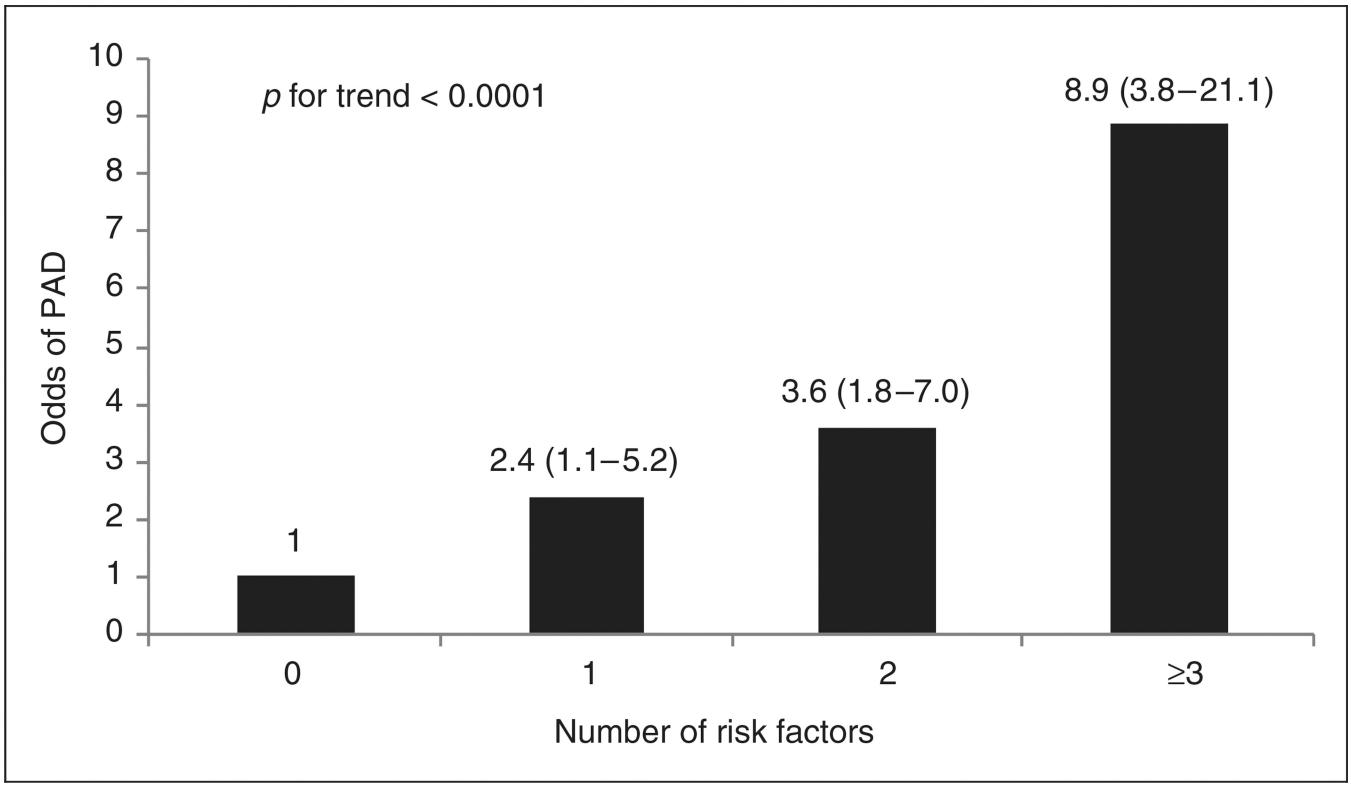


**Figure 3.**

Relative odds of peripheral arterial disease (PAD) based on the number of clinical risk factors (NHANES 2003–2004). Odds ratio (95% confidence intervals) and trend probability of PAD based on an increased number of cardiovascular risk factors (hypertension, diabetes, hypercholesterolemia, current smoking and chronic kidney disease [estimated glomerular filtration rate ≤60]).

## Table 1

Age- and gender-standardized PAD prevalence in the US among adults 40 or older, NHANES 1999–2004.

| ***n* = 7058** | **Prevalence of PAD, % (SE)** | ***p*-value** |
|---|---|---|
| Overall | 4.64 (0.29) | |
| Age groups | | <0.01 |
| 40–49 | 1.43 (0.29) | |
| 50–59 | 3.41 (0.58) | |
| 60–69 | 7.77 (0.77) | |
| ≥70 | 16.62 (1.09) | |
| Gender | | <0.01 |
| Male | 3.54 (0.38) | |
| Female | 5.57 (0.46) | |
| Race/ethnicity | | <0.01 |
| Non–Hispanic White | 4.66 (0.32) | |
| Non-Hispanic Black | 7.46 (0.79) | |
| Mexican-American | 3.11 (0.62) | |
| Other | 2.06 (0.53) | |
| BMI | | 0.20 |
| <25 | 4.63 (0.55) | |
| 25–30 | 4.09 (0.35) | |
| >30 | 5.29 (0.58) | |
| Smoking | | <0.01 |
| Never | 3.73 (0.40) | |
| Current | 5.44 (0.49) | |
| Former | 5.46 (0.55) | |
| Diabetes | | <0.01 |
| Yes | 9.57 (1.31) | |
| No | 4.00 (0.28) | |
| Hypertension | | <0.01 |
| Yes | 7.61 (0.63) | |
| No | 2.33 (0.26) | |
| Kidney function | | <0.01 |
| eGFR >90 | 2.99 (0.41) | |
| eGFR 60–90 | 3.77 (0.29) | |
| eGFR <60 | 15.33 (1.81) | |
| Hypercholesterolemia | | <0.01 |
| Yes | 5.56 (0.41) | |
| No | 3.73 (0.34) | |

Age- and sex-standardized prevalence of peripheral arterial disease (PAD, ABI <0.9) and standard error (SE). Differences across groups were estimated using the Rao–Scott chi-squared test; ABI, ankle–brachial index; eGFR, estimated glomerular filtration rate; BMI, body mass index.

**Table 2**

Peripheral artery disease prevalence among high-risk groups based on gender and race/ethnicity Stratum.

| | | NH-White | | NH-Black | | Mexican American | |
|---|---|---|---|---|---|---|---|
| **Gender** | **Race/ethnicity** | ***n*** | **PAD, % (S.E)** | ***n*** | **PAD, % (SE)** | ***n*** | **PAD, % (SE)** |
| Men | Age >70 years | 671 | 15.13 (1.46) | 109 | 19.43 (3.26) | 154 | 20.85 (3.78) |
| | Diabetes | 302 | 10.97 (2.15) | 146 | 18.75 (2.77) | 189 | 6.40 (1.83) |
| | Current Smoker | 382 | 7.15 (1.04) | 198 | 10.77 (2.44) | 180 | 2.76 (0.90) |
| | CKD | 345 | 14.85 (2.28) | 61 | 18.57 (5.55) | 46 | 10.27 (4.10) |
| | Hypertension | 1037 | 7.94 (0.84) | 378 | 9.26 (1.23) | 354 | 7.33 (2.02) |
| | Hypercholesterolemia | 1073 | 5.69 (0.72) | 260 | 9.85 (1.75) | 368 | 3.39 (1.03) |
| Female | Age >70 years | 603 | 16.81 (1.61) | 109 | 25.33 (4.43) | 134 | 19.97 (3.08) |
| | Diabetes | 208 | 12.89 (2.73) | 136 | 12.77 (2.65) | 170 | 7.43 (1.93) |
| | Current Smoker | 312 | 7.02 (1.25) | 122 | 8.91 (2.46) | 90 | 2.43 (1.23) |
| | CKD | 389 | 16.63 (2.44) | 66 | 21.74 (4.61) | 64 | 18.84 (4.05) |
| | Hypertension | 1027 | 9.68 (1.03) | 420 | 12.01 (1.71) | 385 | 6.84 (1.18) |
| | Hypercholesterolemia | 1016 | 8.06 (0.82) | 298 | 10.20 (2.02) | 380 | 6.52 (1.34) |

Gender and race/ethnicity stratified prevalence of peripheral arterial disease (PAD, ABI <0.9) and standard error (SE) among individuals at risk for cardiovascular disease; ABI, ankle–brachial index; CKD, chronic kidney disease; NH, non-Hispanic.

## Table 3

Odds of peripheral arterial disease, NHANES 1999–2002.

| | OR | 95%, CI | | *p*-value |
|---|---|---|---|---|
| Diabetes | 1.5 | 1.0 | 2.3 | 0.04 |
| Hypertension | 1.5 | 0.9 | 2.2 | 0.05 |
| Current smoker | 4.1 | 3.1 | 5.4 | <0.01 |
| Former smoker | 1.8 | 1.3 | 2.5 | <0.01 |
| Chronic kidney disease (eGFR < 60) | 2.0 | 1.4 | 2.7 | <0.01 |
| Hypercholesterolemia | 1.3 | 1.0 | 1.8 | 0.03 |
| Obesity (BMI > 30) | 1.0 | 0.7 | 1.4 | 0.58 |

Odds ratio (ORs) and 95% confidence interval Wald limits (95 %, CI) were calculated using a multivariate logistic regression model adjusting for age, sex and race/ethnicity; eGFR, estimated glomerular filtration rate; BMI, body mass index.

**Table 4**

Odds ratio of PAD by number of clinical risk factors according to age, gender, and race/ethnicity, NHANES 1999–2002.

| | | Number of risk factors | | | | |
|---|---|---|---|---|---|---|
| | ***N*** | **0** | **1** | **2** | **≥3** | ***p* for trend** |
| Overall Population | 4705 | Ref | 1.5 (0.9–2.6) | 3.7 (2.3–6.1) | 10.2 (6.4–16.3) | <0.01 |
| Age <60 years | 2350 | Ref | 1.0 (0.5–2.0) | 1.6 (0.7–3.4) | 4.4 (1.8–10.6) | <0.01 |
| ≥60 years | 2355 | Ref | 1.6 (0.6–4.3) | 3.5 (1.6–7.7) | 7.9 (3.8–16.1) | <0.01 |
| Male | 2403 | Ref | 0.8 (0.4–1.8) | 2.1 (1.1–3.9) | 5.8 (3.7–9.3) | <0.01 |
| Female | 2302 | Ref | 2.8 (1.1–7.0) | 6.9 (3.2–14.8) | 18.6 (7.1–48.7) | <0.01 |
| Non-Hispanic White | 2510 | Ref | 1.2 (0.6–2.3) | 3.4 (1.9–6.0) | 9.4 (5.6–15.9) | <0.01 |
| Non-Hispanic Black | 822 | Ref | 4.9 (0.6–39.0) | 5.5 (0.8–38.6) | 14.7 (2.1–104.1) | <0.01 |
| Mexican American | 1057 | Ref | 1.9 (0.4–7.9) | 3.1 (0.7–13.3) | 9.8 (2.0–47.2) | <0.01 |

Odds ratios (ORs) and 95% confidence interval (CIs) of peripheral arterial disease (PAD) were estimated using an age-, gender- and race/ethnicity-adjusted model in the overall population using the number of risk factors as the main predictor. Stratified unadjusted analysis was performed to evaluate the odds of PAD among different age, gender and race/ethnicity groups.