Family History of Peripheral Artery Disease Is Associated With Prevalence and Severity of Peripheral Artery Disease

The San Diego Population Study

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Objectives

The purpose of this study was to determine the association of family history of peripheral artery disease (PAD) with PAD prevalence and severity.

Background

PAD is a significant public health problem. Shared genetic and environmental factors may play an important role in the development of PAD. However, family history of PAD has not been investigated adequately.

Methods

The San Diego Population Study enrolled 2,404 ethnically diverse men and women 29 to 91 years of age who attended a baseline visit from 1994 through 1998 to assess PAD and venous disease. Ankle brachial index measurement was performed at the baseline clinic examination, and family history of PAD was obtained via questionnaire. Family history of PAD was defined primarily as having any first-degree relative with PAD. Prevalent PAD was defined as ankle brachial index \( \geq 0.90 \), and severe prevalent PAD was defined as ankle brachial index \( \leq 0.70 \), with both definitions also including any previous leg revascularization. Logistic regression was used to evaluate the association of family history of PAD with prevalent PAD.

Results

The mean age was 59 ± 11 years, 66% were women, and 58% were Caucasian, with 42% representing other racial or ethnic groups. Prevalence of PAD was 3.6%, and severe prevalent PAD was 1.9%. In fully adjusted models, family history of PAD was associated with a 1.83-fold higher odds of PAD (95% confidence interval: 1.03 to 3.26, \( p = 0.04 \)), an association that was stronger for severe prevalent PAD (odds ratio: 2.42, 95% confidence interval: 1.13 to 5.23, \( p = 0.02 \)).

Conclusions

Family history of PAD is independently strongly associated with PAD prevalence and severity. This indicates a role for genetic factors or other shared environmental factors, or both, contributing to PAD.

Peripheral artery disease (PAD) is a significant public health issue, with approximately 8.5 million Americans currently affected (1). PAD is associated with an increased risk of cardiovascular events and mortality (2–5). Morbidities resulting from PAD, including functional decline, intermittent claudication, critical leg ischemia, and amputation, severely affect quality of life (6–9). PAD prevalence differs by racial and ethnic group, with African Americans having the highest prevalence (10). Several studies have evaluated potential explanatory factors for this higher prevalence in African Americans and consistently have concluded that it cannot be explained entirely by differences in traditional or novel cardiovascular disease (CVD) risk factors (1,11–14). This result may indicate that genetic factors are important in the development of PAD.

Genes, environment, and the interaction of these factors likely play a role in the development of PAD. However, few genetic variants have been associated consistently with PAD (15). Familial aggregation also is likely an important factor...
in determining PAD susceptibility (16); however, the association of family history of PAD with prevalent PAD largely is unknown. To our knowledge, only 2 small studies have previously examined this association, but only evaluated premature-onset PAD (\leq 49 years of age), and both were conducted in samples consisting almost exclusively of individuals of European descent (17,18).

Thus, we examined the association of family history of PAD with prevalent PAD in a large, ethnically diverse cohort of men and women 29 to 91 years of age who were participants in the San Diego Population Study. Additionally, we examined the association of family history of PAD with prevalent CVD and family history of CVD with prevalent PAD in this cohort.

**Methods**

**Study participants.** The San Diego Population Study enrolled an ethnically diverse group of men and women who were current or former employees of the University of California, San Diego, and their significant others who were invited to participate between 1994 and 1998 in a study of PAD and venous diseases. Briefly, participants were chosen randomly within age, sex, and ethnicity strata. Age strata were 29 to 49 years (primarily 40 to 49 years), 50 to 59 years, 60 to 69 years, and 70 to 91 years (primarily 70 to 79 years). Women and ethnic minorities (African American, Hispanic, Asian) were oversampled to have adequate power for hypotheses involving these groups. Additionally, a small number of volunteers and their significant others (n = 193) heard about the study, asked to participate, and were enrolled. The final sample included persons of all levels of education and occupation and included working, unemployed, and retired persons. Further details of the study have been published elsewhere (13,19,20).

For all study procedures, participants provided signed, informed consent after a detailed introduction and description of the study. The study received approval from the Committee on Investigations Involving Human Subjects at the University of California, San Diego.

**Family history of PAD.** Family history of PAD was obtained via interviewer-administered questionnaire prior to the ankle brachial index (ABI) measurements. The family history questionnaire was ascertained by study personnel who were not performing the ABI measurement and who were blinded to the vascular examination results. Participants were asked specifically to exclude foster or adoptive family members and were asked about PAD history of all first-degree relatives, including mother, father, brothers, sisters, sons, and daughters. The exact sequence of questions was as follows for parental history: “Has your father or mother ever had any of the following?” and then, “Trouble with arterial circulation in the legs (peripheral arterial disease) including bypass surgery in the legs and/or amputation?” These questions were repeated for brothers, sisters, sons, and daughters. This questionnaire has not been validated previously for family history of PAD, which would involve contact of parents, brothers, sisters, sons, or daughters, and/or obtaining medical records of these family members with regard to PAD. All questions regarding family history of PAD can be found in the Online Appendix. Family history of CVD also was assessed similarly via questionnaire and included questions regarding history of heart attack, stroke, angina, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, and carotid endarterectomy of first-degree relatives.

**ABI measurement.** Systolic blood pressure was measured in both arms with the participant in a supine position. Continuous-wave Doppler ultrasound was used to measure systolic blood pressure twice in the posterior tibial artery; in the rare event that there was no obtainable signal in the posterior tibial artery, the dorsalis pedis was used. The ABI was calculated as average systolic blood pressure in the posterior tibial artery (or dorsalis pedis) divided by the higher of the systolic blood pressure in the 2 arms. For these analyses, the worst ABI was used and was defined as the minimum ABI value of the left and right leg. The higher arm systolic blood pressure was used because of previous studies showing a strong association between PAD and subclavian stenosis (21).

**Covariates.** Age, sex, and race or ethnicity were determined via questionnaire. Diabetes was defined as self-report or use of antidiabetic medications or insulin. Current and past cigarette smoking habits were ascertained via questionnaire, and pack-years of smoking was calculated as the average number of cigarettes smoked per day over all the years cigarettes were smoked divided by 20, multiplied by the total number of years cigarettes were smoked. Smoking also was defined as ever having smoked versus never having smoked. Hypertension was defined as a systolic pressure of 140 mm Hg or more or a diastolic pressure of 90 mm Hg or more, or use of antihypertensive medications. Height (in centimeters) and weight (in kilograms) were measured, and the body mass index was calculated as weight in kilograms divided by height in meters squared. A blood sample was drawn, and total and high-density lipoprotein (HDL) cholesterol were measured with standardized laboratory assays (Beckman Coulter analyzer, Beckman Coulter, Inc., Carlsbad, California). Dyslipidemia was defined as a ratio of total cholesterol to HDL cholesterol of more than 5.0 or use of hyperlipidemic medications (22).

**Statistical analysis.** Univariate associations were assessed using the t test, chi-square test, or Wilcoxon rank sum test. Because pack-years of smoking was a skewed variable, the difference between the PAD and non-PAD groups was assessed using a Wilcoxon rank sum test. All other continuous variables (i.e., HDL cholesterol and systolic blood
pressure) were distributed normally, and thus differences between the PAD and non-PAD groups for these variables were assessed using a t test.

To examine the multivariate association of family history of PAD with prevalent PAD, staged logistic regression models were used, adding in adjustment variables for potential confounders and mediators. Family history of PAD was defined 3 ways: 1) any family history of PAD (including any first-degree relative); 2) parental history of PAD (either parent); and 3) number of first-degree relatives with PAD as a continuous variable. Prevalent PAD was defined as ABI of 0.90 or less or leg revascularization, and severe prevalent PAD was defined as ABI of 0.70 or less or leg revascularization.

To compare associations of family history of PAD and family history of CVD with prevalent PAD and prevalent CVD outcomes, we defined family history of CVD or PAD separately as any parental history. Prevalent CVD was defined as any previous myocardial infarction, stroke, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft. Staged logistic regression models also were used for this analysis.

SAS software version 9.1.3 (SAS Institute, Cary, North Carolina) was used for all analyses, and p < 0.05 was considered statistically significant.

Results

Participant characteristics. A total of 2,376 participants had complete ABI and family history data and had an ABI of 1.4 or less in both legs. Overall, the mean age was 59 ± 11 years, and 66% were women, 58% were Caucasian, 14% were African American, 15% were Hispanic, and 14% were other races or ethnicities. There were 87 cases of prevalent PAD, defined as ABI of 0.90 or less or leg revascularization, and 44 cases of severe prevalent PAD, defined as ABI of 0.70 or less or leg revascularization. PAD prevalence differed significantly by sex and ethnic group and was significantly higher in men and African Americans (Table 1).

Participants with prevalent PAD had significantly higher systolic blood pressure, total cholesterol, and pack-years of smoking and were more likely ever to have been smokers. Those with prevalent PAD also were more likely to have dyslipidemia, hypertension, diabetes, and CVD. Participants with PAD were somewhat more likely to have any family history of PAD (p = 0.06), but did not differ significantly with regard to parental history of PAD or parental history of CVD or with regard to the distribution of the number of first-degree relatives with PAD.

Associations of family history of PAD with PAD prevalence and severity. In the fully adjusted analysis shown in Table 2, any family history of PAD, defined as any first-degree relative with PAD, was significantly associated with higher odds of PAD (odds ratio [OR]: 1.83, 95% confidence interval [CI]: 1.03 to 3.26, p = 0.04). Parental history of PAD, defined as either mother or father with PAD, similarly was associated with higher odds of PAD (Table 2). Both any family history of PAD and parental history of PAD were associated strongly with severe prevalent PAD, with approximately 2.4-fold higher odds of severe PAD for any family history and 2.9-fold higher odds for parental history of PAD (Table 2). Defining smoking in pack-years instead of ever smoking or using HDL and total cholesterol instead of dyslipidemia did not change the results.

There were no statistically significant interactions of sex (p = 0.15), race or ethnicity (p = 0.86), body mass index (p = 0.20), pack-years of smoking (p = 0.41), or ever smoking (p = 0.95) with any family history of PAD for prevalent PAD. There was, however, a marginally significant interaction of family history with diabetes (p = 0.06) such that among those with no diabetes, any family history of PAD was associated significantly with a 6.42-fold higher odds of prevalent PAD (95% CI: 3.35 to 12.35, p = 0.001), whereas among those with diabetes, any family history of PAD was not associated significantly with prevalent PAD (OR: 1.67, 95% CI: 0.46 to 6.03, p = 0.44).

Because participants with prevalent PAD who had undergone a leg revascularization procedure would have been aware of this at the time of the examination interview,
which could have caused recall bias, we performed a sensitivity analysis excluding the 10 participants with prevalent PAD who had undergone revascularization procedures. Results were very similar—for example, any family history of PAD was associated with 1.91-fold higher odds of prevalent PAD (95% CI: 1.07 to 3.40, p = 0.04) and with a 2.64-fold higher odds of severe prevalent PAD (95% CI: 1.34 to 4.31, p = 0.0008).

Number of relatives with PAD was associated only marginally with prevalent PAD. Each increase in the number of relatives with PAD (i.e., 0 to 1, 1 to 2, 2 to 3) was associated with a 1.51-fold greater odds of prevalent PAD (95% CI: 0.95 to 2.42, p = 0.08). The number of relatives with PAD, however, was associated significantly with severe prevalent PAD (OR: 1.91, 95% CI: 1.07 to 3.36, p = 0.04) and parental history of PAD was associated significantly with prevalent CVD and severe prevalent PAD. Moreover, this study demonstrated that family history of PAD is associated more strongly with prevalent CVD than with prevalent PAD. The number of first-degree relatives with PAD is associated marginally with higher odds of prevalent PAD and is associated significantly with higher odds of severe prevalent PAD. Moreover, this study demonstrated that family history of PAD is associated more strongly with prevalent CVD than with prevalent PAD, suggesting some specificity of the type of family history.

Results of the present study indicate that a significant genetic component exists for PAD. Studies have shown that ABI, a major criterion for PAD diagnosis, is moderately heritable, in the range of 0.20 to 0.50 (23–25), but to date, results of candidate gene studies and genome-wide association studies for ABI or PAD have been mixed, and/or not well replicated (15,26). Preliminary evidence suggests that genes in the inflammatory pathways, the renin-angiotensin

### Table 2

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<thead>
<tr>
<th>Any Family History*</th>
<th>Parents Only*</th>
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<tr>
<td><strong>OR (95% CI)</strong></td>
<td><strong>OR (95% CI)</strong></td>
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<td><strong>p Value</strong></td>
<td><strong>p Value</strong></td>
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<td>Prevalent PAD†</td>
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<td>Unadjusted</td>
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<tr>
<td>+ Demographics‡</td>
<td>1.63 (0.97-2.75)</td>
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<td>0.07</td>
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<tr>
<td>+ Lifestyle/comorbidities§</td>
<td>1.90 (1.01-3.26)</td>
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<td></td>
<td>0.02</td>
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<tr>
<td>+ SBP, DBP, dyslipidemia</td>
<td>1.77 (1.00-3.11)</td>
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<td>Severe prevalent PAD†</td>
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<tr>
<td>Unadjusted</td>
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<tr>
<td>+ Demographics‡</td>
<td>2.18 (1.11-4.28)</td>
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<tr>
<td>+ Lifestyle/comorbidities§</td>
<td>2.39 (1.14-5.01)</td>
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<td></td>
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<tr>
<td>+ SBP, DBP, dyslipidemia</td>
<td>2.42 (1.13-5.23)</td>
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*Any family history is any first-degree relative with PAD (mother, father, brothers, sisters, sons, daughters); parents only is either mother or father having PAD. †PAD is ABI ≤ 0.90 or leg revascularization; severe prevalent PAD is ABI ≤ 0.70 or leg revascularization. ‡Age, sex, and race or ethnicity. §Adding body mass index, ever smoker, diabetes, hypertension.

### Table 3

| Association of Number of First-Degree Relatives With PAD and Prevalent PAD* |
|---------------------------|----------------------------|----------------------------|
| **OR (95% CI)**          | **p Value**                     |
| **Prevalent PAD†**       | **Severe Prevalent PAD†** |
| Unadjusted               | 1.37 (0.90-2.09)               | 1.70 (1.02-2.82) |
| + Demographics‡           | 1.47 (0.96-1.12)               | 1.84 (1.10-3.06) |
| + Lifestyle/comorbidities§ | 1.48 (0.93-2.36)               | 1.91 (1.08-3.40) |
| + SBP, DBP, dyslipidemia | 1.51 (0.95-2.42)               | 1.91 (1.07-3.40) |

*Number of first-degree relatives modeled as a continuous variable. †Prevalent PAD is ABI ≤ 0.90 or leg revascularization; severe prevalent PAD is ABI ≤ 0.70 or leg revascularization. ‡Age, sex, and race or ethnicity. §Adding body mass index, ever smoker, diabetes, hypertension. Abbreviations as in Tables 1 and 2.
pathway, and genes important in nicotine metabolism and dependence are important determinants of PAD or ABI (27–30), although it is unclear the extent to which these associations may be mediated through smoking status or pack-years of smoking. Previous studies also have suggested interactions of inflammatory or nicotine dependence genes with smoking and diabetes, 2 of the major risk factors for PAD (27,29). In addition to the association of the 9p21 locus with PAD (31), 9q33 also has been implicated recently, with higher odds for both abdominal aortic aneurysm and PAD (32).

It also is likely true that a complex interplay of genetic and environmental factors, including smoking, diabetes, obesity, diet, sex, and racial or ethnic group, lead to the development of PAD, although we did not find any indication of interaction of any family history of PAD and ever smoking, pack-years of smoking, sex, or race or ethnicity for prevalent PAD in the current study. This is likely because of the limited power to detect interactions with the relatively modest number of prevalent PAD cases within each subgroup in this study. We did find a marginally significant interaction between any family history of PAD and diabetes such that family history was associated with much higher odds of prevalent PAD among those without diabetes as compared with those with diabetes. This may indicate that the set of genetic variants involved in diabetes could be distinct from those involved in PAD; however, these results should be interpreted with caution given the wide confidence intervals.

Only 2 studies previously have examined the association of family history of PAD with PAD or symptomatic CVD (17,18). One study found that participants with a sibling with premature PAD had 3-fold higher odds of PAD (17). A second study found that first-degree relatives of individuals with premature PAD had higher odds of early onset CVD events than relatives of healthy participants (18). However, these studies were in small, family-based samples almost exclusively of European descent, only studied premature onset PAD (age ≤49 years), or concentrated on CVD events as an outcome. Results of the current study are consistent with those of Valentine et al. (17). Our study extends the literature by showing the association of family history of PAD with both prevalent PAD and CVD concurrently, confirming the relationship in a multiethnic and much larger community-living sample.

Our study suggests that having a parental history of CVD does not significantly increase the odds of PAD, nor does having a parental history of PAD significantly increase the
odds of CVD. These results are not consistent with those of Valentine et al. (18), who found that first-degree relatives of individuals with premature PAD had higher odds of early onset CVD events than relatives of healthy participants; however, the present study was not restricted to premature PAD cases. Our differing results could be the result of a lack of specificity of family history of CVD for PAD or vice versa. They also could be the result of the heterogeneity inherent in complex chronic diseases such as CVD and PAD or the genetic heterogeneity in these diseases. In this regard, traditional risk factors do not entirely overlap for PAD and CVD; some traditional risk factors such as smoking and diabetes are stronger for PAD than CVD (2). Genetic risk factors also do not seem to overlap entirely or to be consistent findings in all studies of PAD and CVD, suggesting that some genetic factors exclusive to PAD may exist. One study did find 9p21, a well-replicated locus for congenital heart disease and myocardial infarction (33), to be associated significantly with PAD and ABI after accounting for myocardial infarction (31). However, in another study, 9p21 was associated only marginally with clinical PAD (34), and after accounting for congenital heart disease, the association was no longer marginally significant.

**Study strengths and limitations.** The San Diego Population Study is a population-based cohort of ethnically diverse men and women with a large age range and was designed specifically to study PAD. Careful ABI measurement was performed by trained vascular technicians, and ascertainment of other traditional risk factors was standard and complete. The current study also did not restrict the definition of PAD to premature PAD only, but sought to examine whether family history of PAD was important factors despite age at onset and despite severity of PAD. The study also has important limitations. Family history of PAD and CVD was obtained via an interview-administered questionnaire, which can result in misclassification, but this likely would result in bias toward the null hypothesis. However, information on family history was obtained before the ABI measurement to avoid recall bias. Results are from an actively employed and retired population, and so may not generalize fully to the overall population.

**Conclusions**

We found that family history of PAD was associated significantly with PAD, but not with CVD. To date, significant genetic risk factors for PAD are ORs generally in the range of 1.1 to 1.3. Currently, familial aggregation seems to be the most strongly associated genetic risk factor for PAD, with an OR similar in magnitude to those of smoking, hypertension, and diabetes, all of which range from 2- to 4-fold greater odds for PAD (2). This finding also suggests that asking about family history of PAD specifically (rather than CVD) may be more useful to identify individuals at risk for PAD. Based on these findings, future studies are warranted to identify genetic loci, gene or environment interactions, or a combination thereof that may contribute to development of PAD.

**Acknowledgments**

The authors thank the participants of the San Diego Population Study for their cooperation.

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**REFERENCES**


Key Words: ankle brachial index • family history • peripheral artery disease.

APPENDIX

For all questions regarding family history of PAD, please see the online version of this article.