Risk factors for chronic venous disease: The San Diego Population Study

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Background: The etiology of chronic venous disease in the lower limbs is unclear, and very limited data are available on potential risk factors from representative population studies.

Methods: Participants in the San Diego Population Study, a free-living adult population randomly selected from age, sex, and ethnic strata, were systematically assessed for risk factors for venous disease. Categorization of normal, moderate, and severe disease was determined hierarchically through clinical examination and ultrasonography imaging by trained vascular technologists, who also performed anthropometric measures. An interviewer administered a questionnaire and an examination assessed potential risk factors for venous disease suggested by previous reports.

Results: In multivariable models, moderate venous disease was independently related to age, a family history of venous disease, previous hernia surgery, and normotension in both sexes. In men, current walking, the absence of cardiovascular disease, and not moving after sitting were also predictive. Additional predictors in women were weight, number of births, oophorectomy, flat feet, and not sitting. For severe disease, age, family history of venous disease, waist circumference, and flat feet were predictive in both sexes. In men, occupation as a laborer, cigarette smoking, and normotension were also independently associated with severe venous disease. Additional significant and independent predictors in women were hours standing, history of leg injury, number of births, and cardiovascular disease, but African American ethnicity was protective. Multiple other postulated risk factors for venous disease were not significant in multivariable analysis in this population.

Conclusions: Although some risk factors for venous disease such as age, family history of venous disease, and findings suggestive of ligamentous laxity (hernia surgery, flat feet) are immutable, others can be modified, such as weight, physical activity, and cigarette smoking. Overall, these data provide modest support for the potential of behavioral risk-factor modification to prevent chronic venous disease. (J Vasc Surg 2007;46:331-7.)

Abnormalities of the veins in the lower limbs are responsible for significant and widespread morbidity. The prevalence of venous disease increases with age, and an aging world population is likely to result in an increase in venous disease. The etiology of chronic venous disease is poorly understood, however, and some results are contradictory. A recent review showed that there are many hypotheses pertaining to the development of varicose veins, chronic venous insufficiency (CVI), and venous ulcers, which has been the most frequently explored in previous studies, but it is less common than other manifestations.

In the San Diego Population Study (SDPS), we systematically examined the relationship of a wide variety of potential risk factors to both visible and functional venous disease. The risk factors considered included family history, connective tissue laxity, previous lower limb trauma, factors related to cardiovascular disease (CVD), positional factors, physical measures, smoking, constipation, fiber intake, and hormonal factors. This is a report of our findings.

MATERIALS AND METHODS

Population. The population for this study was randomly selected from current and retired employees of the University of California, San Diego (UCSD). Random selection was made within strata defined by age, sex, and ethnicity. The categories of 40 to 49 years, 50 to 59 years, 60 to 69 years, and 70 to 79 years defined the age strata. Women were over-selected to allow additional power for certain female-specific hypotheses. Ethnic minorities—Hispanics, African Americans, and Asians—were over-selected to allow statistical power for contrasts by ethnicity. The spouse or significant other of each randomly selected participant was also invited to participate in the study. Some volunteers (n = 199) who had heard about the study and who asked to participate were enrolled. By selecting individuals from all levels of education and occupation, and both working and retired, we were able to study a broad-based population sample.

For all study procedures, participants provided signed informed consent after a detailed introduction to the study. The study was approved by the Committee on Investigations Involving Human Subjects of UCSD.

Registered vascular technologists were trained and monitored for each component of the study visit. Particular attention was given to close adherence to the study proto-
col, which specifically defined the criteria for each of the venous conditions. Details of the protocol have been published.\textsuperscript{52}

**Disease classification.** In previous reports from the SDPS, we separately characterized each leg of each participant by four categories of visible disease: normal, telangiectasis or spider veins, varicose veins, or trophic changes; and by three categories determined by duplex ultrasound evaluation: normal, superficial functional disease, or deep functional disease.\textsuperscript{52} Because of the large number of risk factors evaluated, for simplicity, each leg for this report was classified in three overall, mutually exclusive, hierarchical categories: normal, moderate, or severe disease, as described:

**Normal.** Subjects without varicose veins, without trophic changes (lipodermatosclerosis, hyperpigmentation, healed ulcer, or active ulcer upon visual inspection) and without insufficiency or obstruction of either the deep or superficial systems on inspection with duplex ultrasound were classified as “normal.” This corresponds with C0 or C1 with Pn in the revised CEAP classification.\textsuperscript{53}

**Moderate venous disease.** Subjects with varicose veins or reticular varices in the absence of trophic changes upon visual inspection, or with either insufficiency or obstruction of the superficial system or the perforating veins but not in the deep system by duplex ultrasound imaging, were classified as having moderate disease. Limbs with a history of vein stripping in the absence of severe disease were classified as moderate. This corresponds with C2 or As or Ap in the revised CEAP classification.\textsuperscript{53}

**Severe venous disease.** Subjects with trophic changes upon visual inspection or insufficiency or obstruction in the deep system by duplex ultrasound imaging were classified as having severe disease for this report. This corresponds with C4 or C5 or C6 or Ad in the revised CEAP classification.\textsuperscript{53}

**Risk factors.** At the study visit, trained interviewers followed a standardized protocol to obtain information on demographics, lifestyle, and personal and family medical history. The vascular technologists assessed anthropometric measures.

**Ethnicity and occupation.** Subjects self-defined their race/ethnicity as: “White, not Hispanic,” “Hispanic/Chicano,” “African American,” “Asian/Pacific Islander,” “Native American,” or “Other.” The subject’s current occupation (or last occupation, if retired) was classified by the interviewer as “professional,” “technical/administrative/managerial,” “clerical/skilled,” “semi-skilled,” or “laborer.”

**Personal habits.** Subjects estimated hours spent lying down, sitting, walking, and standing, currently and as adults. Subjects answered whether when sitting for long periods they regularly got up to move around currently and as adults. History of wearing constrictive clothing, including girdles, corsets, abdominal braces, and exercise attire was assessed. Subjects rated their level of physical activity relative to persons their own age. Subjects estimated how often they engaged in vigorous activity (with increased heart rate) for at least 20 minutes weekly. Smoking history, including current and average daily cigarette intake and years smoked was assessed. Standardized self-administered dietary assessment forms were analyzed by the Fred Hutchinson Cancer Research Center, Seattle, Washington.\textsuperscript{54}

**Health history.** Subjects’ cardiovascular health history, history of high blood pressure and diabetes were ascertained. Questions about immobility and bowel activity were asked. Side-specific determination was made of any serious lower limb injuries. Subjects’ history of hernia surgery, diverticulosis, diverticulitis, and non-lower limb vein abnormalities was assessed. Women were asked about their reproductive history. Subjects self-reported whether they had hypermobile joints and flat feet.

**Family history.** Family history (all first-degree relatives) of telangiectasis, varicose veins, blood clots in lower limb veins, phlebitis, venous ulcer, pulmonary embolism, or other venous problems was assessed.

**Anthropometrics.** The subjects’ height, weight, heart rate, waist, and hip circumferences were measured. Blood pressures were measured in the right arm after the subject had been sitting quietly for 5 minutes. The standing foot-arch height was visually ranked as flat, small, or normal/high.

**Quality control.** In a standardized fashion, interviewers were trained to administer the questionnaire protocol, and the vascular technologists were trained in the physical examination and duplex ultrasound imaging protocol, with periodic assessment for quality control. The reliability data have been published.\textsuperscript{55} Range checks were conducted of all numeric variables entered in the Access database (Microsoft, Redmond, Wash). A 2% random sample was further checked against the chart, and outliers for each individual variable were also systematically checked against the chart.

**Statistical analysis.** All analyses were conducted using the SAS 8.1 software (SAS Institute, Cary, NC). Age-adjusted univariate analyses and all multivariable analyses used logistic regression. Multivariable analyses used entry criteria of $P < .3$ and removal criteria of $P > .1$ for forward step-wise logistic regression to develop the final models. Age and indicator variables for ethnicity were included in all models.

**RESULTS**

The study population consisted of 854 men and 1580 women with mean ($\pm$ standard deviation) ages of 60.1 $\pm$ 11.4 years and 58.8 $\pm$ 11.4 years, respectively. The ethnic distribution was approximately 60% non-Hispanic White (NHW), 15% Hispanic, 13% African American, and 12% Asian. We have previously published the relationship of venous disease by sex, age, and ethnicity in the study population.\textsuperscript{52} Table I summarizes the sex-specific percent-age distributions of moderate and severe disease in the SDPS by age and ethnicity. Both moderate and severe venous disease increased with age. Women had nearly twice the rate of moderate disease as men did, but men had higher rates of severe disease. The disease distribution was
significantly different for men and women \((\chi^2 P < .0001)\). Hispanic subjects had the highest rates of moderate, and NHW subjects had the highest rates of severe disease.

Table II summarizes the distribution of risk factors by venous disease category—normal, moderate, or severe—and by sex. These variables were selected from a long list of potential risk factors because each showed univariate relationships with moderate or severe venous disease. Thus, they were included in the multivariable logistic regression models discussed in the next section. Variables that showed no univariate associations included multiple dietary factors such as fiber intake, bowel habits, and gastrointestinal problems; regular physical activity, and constrictive clothing.

**MULTIVARIABLE MODELS**

**Moderate disease.** The four variables of age, family history of venous disease, previous hernia surgery, and hypertension were highly significant for moderate disease in men and women in multivariable analysis (Table III). The respective odds ratios (OR) were 1.59 in men and 1.43 in women for age (per decade); 2.87 and 2.34 for family history, 1.85 and 1.81 for hernia surgery; but hypertension showed an inverse relationship, with ORs of 0.58 and 0.64, respectively. All the confidence intervals for these associations excluded the null hypothesis. Although moderate disease, compared with NHW, was greater in Hispanic subjects and less in African American and Asian subjects, none of these associations reached statistical significance.

**Table II.** Distribution of risk factors in men and women by moderate and severe venous disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (n = 824)</th>
<th>Women (n = 1570)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NL</td>
<td>MOD</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>82.1</td>
<td>82.8</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>96.1</td>
<td>96.1</td>
</tr>
<tr>
<td>Current cigarettes/d</td>
<td>0.7</td>
<td>0.9</td>
</tr>
<tr>
<td>DBP, mm/Hg</td>
<td>79.0</td>
<td>77.7</td>
</tr>
<tr>
<td>Current walking, hrs</td>
<td>4.6</td>
<td>5.4</td>
</tr>
<tr>
<td>Current standing, hrs</td>
<td>3.4</td>
<td>3.1</td>
</tr>
<tr>
<td>Adult sitting, hrs</td>
<td>7.6</td>
<td>7.1</td>
</tr>
<tr>
<td>History of CVD, %</td>
<td>12.0</td>
<td>3.7</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>36.4</td>
<td>28.0</td>
</tr>
<tr>
<td>Hernia surgery, %</td>
<td>15.7</td>
<td>29.9</td>
</tr>
<tr>
<td>Flat feet, %</td>
<td>13.0</td>
<td>15.9</td>
</tr>
<tr>
<td>Flat arch, %</td>
<td>10.2</td>
<td>9.5</td>
</tr>
<tr>
<td>Small arch, %</td>
<td>27.9</td>
<td>26.7</td>
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<tr>
<td>Family history venous disease, %</td>
<td>42.6</td>
<td>63.6</td>
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<tr>
<td>Leg injury, %</td>
<td>26.3</td>
<td>28.0</td>
</tr>
<tr>
<td>Current movement after sitting, %</td>
<td>96.0</td>
<td>92.5</td>
</tr>
<tr>
<td>Laborer, %</td>
<td>2.3</td>
<td>2.8</td>
</tr>
<tr>
<td>Births (n)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Oophorectomy, %</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

NL, Normal; MOD, moderate; SEV, severe; CVD, cardiovascular disease; DBP, blood pressure; NA, not applicable.
hour), 0.92; weight (per 10 kg), 1.32; number of births (per birth), 1.14; waist circumference (per 10 cm), 0.83; previous oophorectomy, 1.37; and flat feet, 1.39.

Severe venous disease. The three variables of age, family history of venous disease, and waist circumference were highly significant for severe disease in both men and women in multivariable analysis (Table IV). The ORs in men and women, respectively, were 1.41 and 1.43 for age; 2.13 and 1.92 for family history; and 1.37 and 1.24 for waist circumference. The only significant association for ethnicity was a reduced OR of severe disease in African American women (0.44). The data for African American men were also suggestive (0.63), but the confidence interval included one.

Additional significant predictors in men, in order of statistical significance by OR, were occupation as a laborer, 3.24; diastolic blood pressure (per 10 mm/Hg), 0.80; current cigarettes per day (per 20 cigarettes), 2.24; and flat feet, 1.63. Additional predictors in women, in order of statistical significance by OR, were flat (3.28) or small (1.84) foot arch; current standing (per hour), 1.14; previous leg injury, 1.67; number of births (per birth), 1.14; and history of CVD, 2.02.

DISCUSSION
Age, sex, and ethnicity were important risk factors for venous disease in this study, as in most previous studies.1,2 Our results confirm that older age is a risk factor for venous
disease. They also showed no significant ethnic differences for moderate disease, but severe disease may be less common in African American women.

Family history was a risk factor for both moderate and severe disease. Many studies have found an association with family history and venous disease, although not all. As other researchers have pointed out, biased recall could have influenced this finding. Nevertheless, family history by subject recall was a very strong risk factor for venous disease in our study. In addition, Table II shows that subjects without venous disease reported high rates of a family history of venous disease.

Connective tissue laxity, as manifested by previous hernia surgery or findings of flat feet, was a consistent risk factor for both moderate and severe disease. The association of increasing laxity in connective tissue with venous disease corroborated previous research. It is possible that previous hernia surgery may have been a marker for previous hospitalization and immobility, however, immobility was not significantly associated with venous disease in our data.

Lower limb injury was a risk factor in women for severe disease. This finding corresponds with the results of Bermudez et al, who noted that insufficiency in the deep veins was increased in limbs that had experienced trauma compared with limbs that had not. A case-control study similarly found serious lower limb trauma to be a risk factor for CVI; however, an earlier study found no difference in CVI for injured vs uninjured limbs.

Factors related to CVD, specifically hypertension, previous CVD, and higher diastolic blood pressure, were associated with less moderate disease for men and women and with less severe disease for men. Conversely, a history of CVD was strongly associated with severe disease in women. Although some studies have found a relationship between atherosclerosis and venous disease, others have not. The reason for any protective effect of atherosclerosis on moderate or severe venous disease is not readily apparent, although relative arterial insufficiency, venous vasoconstriction, and microthrombosis could conceivably be involved.

Positional factors such as walking, standing, and sitting showed variable associations with venous disease. In women, increased time standing was positively associated with more severe disease, and increased sitting time was inversely associated with moderate disease. For men, increased daily walking was associated with moderate disease, and men who worked as laborers were more likely to have severe disease than those in occupations that typically require more desk time.

Regular movement when sitting for long periods was related to lower rates of moderate disease in men. Fowkes et al similarly found that sitting was associated with lower rates of venous insufficiency for women but not for men. They also found that walking was a risk factor for women with venous insufficiency when age-adjusted, but less so when multiply adjusted, and that walking was related to lessened risk of venous insufficiency in men.

Our data indicate that standing was a strong risk factor for severe venous disease in women. This is concordant with a number of studies and contrasts with others. Our finding that moving about if sitting for long periods of time was related to lower rates of moderate disease for men concurs with the hydrostatic model of venous disease. That is, although sitting and lying are generally more protective than walking or standing, some pooling of blood is still possible during the former activities. Moving about could activate the venous pump and prevent such pooling.

Physical measures were risk factors for women with both severe and moderate disease and for men with severe disease. Weight and waist circumference are both measures of adiposity. A number of studies have found an association of obesity with venous disease. Sisto et al found a relationship in both men and women with varicose veins, Widmer et al and Abramson et al both found an association for women, and Beaglehole et al found an association for men. Our finding of increased waist circumference in both sexes with severe disease was consistent with the Scott et al finding that obesity was associated with CVI and by the Mota-Capitao et al finding that weight was an independent risk factor for CVI in multivariable analysis.

In contrast, Coughlin et al and Fowkes et al both found that obesity was not a factor in venous insufficiency among women, and Fowkes et al extended this finding to men as well. Other studies have also found no association between obesity and venous disease. The Edinburgh group however, also found that for men and women combined, persons with more segments with reflux had higher body mass indices than those with fewer or no segments involved.

Hormonal factors in women, number of births, and oophorectomy were related to moderate or severe venous disease, or both. Gourgou et al and Laurikka et al found an increasing varicose vein prevalence with increasing numbers of births. Coughlin et al found that multiparity was associated with varicose veins in pregnant women, as did Sisto et al, Malfeti et al, and Sohn et al. Some studies have found that the changes occur with only one pregnancy. In Guberan et al and Lee et al, pregnancy was no longer a risk factor once the data had been age-adjusted. In two studies, Sparey et al and evaluated women with and without varicose veins at the beginning of pregnancy. Although neither group presented with new varicose veins during pregnancy, both had dilation of veins during pregnancy, and in women without varicose veins, the diameter had not returned to baseline size by 6 weeks postpartum.

Smoking was associated with increased rates of severe disease for men. One study has shown that varicose veins were associated with higher numbers of cigarettes smoked per day, but to our knowledge, our study is the first to report a sex-specific association of smoking limited to severe venous disease.
Constrictive clothing, immobility, exercise, constipation, and dietary fiber were not risk factors for moderate or severe disease in multivariable models. Multiple questions addressed each of these five categories of potential risk factors, but none were statistically significant in multivariable analysis. Thus, despite biologic plausibility for such factors and some earlier reports, we were unable to confirm the importance of such factors in peripheral chronic venous disease in this large population-based study.

Study limitations. Study limitations of these results include the cross-sectional study design, where correlations do not necessarily imply causation. In addition, some of the risk factors reviewed were self-reported, and no formal validation was done of the subjects’ responses. A specific concern in this area was the strong and independent association of a family history of venous disease for both men and women and for both moderate and severe disease, which could reflect recall bias to some extent. However, about half the participants with normal veins reported a family history of venous disease, so such reporting was common in those with and without venous disease.

CONCLUSION

This comprehensive cross-sectional study of venous disease helps to clarify the contributions of a variety of risk factors to moderate and severe venous disease. Our data indicate that age, family history, and ligamentous laxity were the strongest and most consistent risk factors for venous disease. None of these conditions is amenable to intervention, and thus, these findings have little implication for disease prevention. Factors related to CVD were generally associated with lower rates of venous disease.

A number of behavioral and environmental factors did show significant relationships, however. Among volitional factors important findings were central adiposity, positional factors such as hours spent standing or sitting, cigarette smoking, and parity in women, and all but the latter variable are reasonably subject to intervention. In addition, prevention of or intervention on obesity and cigarette smoking would help prevent conditions such as CVD and cancer. In women (but not men) we confirmed the importance of a previous lower limb injury for severe disease. These data provide modest support for the potential of behavioral risk-factor modification to prevent chronic venous disease. Incidence studies would provide greater understanding of the role of risk factors in the development and progression of moderate and severe venous disease.

AUTHOR CONTRIBUTIONS
Conception and design: MC, JD, AF
Analysis and interpretation: MC, JD, JB, RL, AF
Data collection: MC, RL, AF
Writing the article: MC, JD
Critical revision of the article: MC, JD, JB, RL, AF
Final approval of the article: MC, JD, JB, RL, AF
Statistical analysis: MC, JD
Obtained funding: MC
Overall responsibility: MC

REFERENCES