Peripheral arterial disease, gender, and depression in the Heart and Soul Study

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Background: **Despite the high prevalence of peripheral arterial disease (PAD) in women, risk factors for PAD in women are not well understood.**
Methods: **Gender-specific risk factors for PAD were examined in a prospective cohort study of 1024 patients (184 women and 840 men) with stable coronary artery disease who were recruited between 2000 and 2002. Logistic regression models were used to evaluate associations between traditional and nontraditional risk factors and PAD in men and women.**
Results: **PAD was found in 11% of women and in 13% of men. Women with PAD had a similar prevalence of traditional risk factors (hypertension, hyperlipidemia, and smoking) compared with women without PAD and were significantly more likely to suffer from depression than women without PAD. Men with PAD were more likely to have hypertension, diabetes mellitus, a history of smoking, a worse lipid profile, and higher levels of inflammatory biomarkers than men without PAD. A multivariate model showed depression was the strongest independent factor associated with PAD in women, whereas smoking and elevated fibrinogen were independently associated with PAD in men.**
Conclusions: **The current findings suggest there are gender differences in risk factors for the development of PAD. Further research is needed to understand the role of depression in PAD. (J Vasc Surg 2014;■:1-8.)**

Peripheral arterial disease (PAD) is a significant cause of morbidity and mortality and has recently been recognized as a global pandemic.[1] PAD is under-recognized and under-treated in women, even though there appears to be an increasing population burden of PAD in women.[2,3] In fact, in the 2010 United States Census, the prevalence of PAD was higher in women than in men.[4] Despite the high prevalence of PAD in women, women are under-represented in contemporary PAD studies,[5,6] and risk factors for PAD in women have not been extensively studied. In view of this, the American Heart Association issued a scientific statement calling for further research to study PAD in women.[4]

Traditional cardiovascular disease (CVD) risk factors are more prevalent in men with PAD than in women with PAD,[7,8] suggesting that other risk factors might be involved in the pathophysiology of PAD in women. That women are at increased risk for depression[9-11] compared with men is well known, and we recently demonstrated that depression was a strong and independent risk factor for PAD.[12] Others have shown that among patients with PAD, those with depression have worse functional outcomes, greater need for revascularization, and have poorer quality of life outcomes and a higher risk for adverse events after revascularization.[13-16] Research has also indicated that women with PAD aged <65 years are particularly vulnerable to experiencing depressive symptoms and that these symptoms seem to be accompanied with high rates of smoking.[17]

The associations between depression and psychosocial factors with PAD have not been extensively investigated.

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A better understanding of patients' psychosocial profiles might identify risk factors that can be addressed to mitigate patients' depressive symptoms and their cardiovascular risk. The Heart and Soul Study was designed to study the association between psychologic disorders and cardiovascular events, including PAD, in outpatients with stable coronary artery disease (CAD). In this study, we investigated the gender-specific prevalence of traditional CVD, psychologic, and social risk factors for PAD. We hypothesized that women with PAD would have a different risk factor profile, including psychosocial factors, compared with men with PAD.

METHODS

Study population. The Heart and Soul Study was designed to study the association between psychologic disorders and cardiovascular events in outpatients with stable CAD. Detailed methods have been previously described.[18] Briefly, the investigators performed a prospective cohort study of 1024 subjects with known coronary heart disease (CHD) who were recruited between 2000 and 2002 and followed up for 10 years.

At the baseline examination, participants completed a structured diagnostic interview for depression, an extensive questionnaire, electrocardiogram, 6-minute walk test, and full exercise treadmill testing with stress echocardiography. Participants were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications. Participants also completed 24-hour ambulatory Holter monitoring to determine heart rate variability and collected 24-hour urine for measurement of creatinine, free cortisol, and catecholamines. Fasting blood was drawn, and samples of serum, plasma, DNA, and 24-hour urine were stored in a specimen biorepository at −80°C.

After 5 years of follow-up, 667 participants (>80% of survivors) completed a repeat examination that included a structured diagnostic interview for depression, questionnaire, electrocardiogram, exercise treadmill test, fasting blood draw, and 24-hour urine collection. Participants were also contacted annually to inquire about cardiovascular events, which were confirmed by review of medical records. Follow-up information was available for >99% of the study participants.

With regards to inclusion criteria, the investigators used administrative databases to identify outpatients with documented CAD at two Department of Veterans Affairs Medical Centers (San Francisco VA Medical Center and the VA Palo Alto Health Care System), one university medical center (University of California, San Francisco), and nine public health clinics in the Community Health Network of San Francisco. Patients were eligible to participate if they had known CHD documented by at least one of the following: a history of myocardial infarction (MI), angiographic evidence of at least 50% stenosis in one or more coronary vessels, prior evidence of inducible ischemia by treadmill or nuclear testing, or a history of coronary revascularization.

Related to exclusion criteria, 15,438 patients with CHD were identified from administrative databases and mailed an invitation to participate. Of the 2495 patients who returned a form indicating that they would be interested in participating, 505 could not be reached by telephone, and 370 were excluded because they had a history of MI in the prior 6 months (treadmill test contraindicated), deemed themselves unable to walk 1 block (treadmill test not useful), or were planning to move out of the local area within 2 years (unavailable for follow-up). Of the 1620 patients who were confirmed eligible, 596 declined to participate, and 1024 (63%) enrolled.

Between September 11, 2000, and December 20, 2002, 1024 participants were enrolled and were followed up for a mean 7.2 ± 2.6 (standard deviation) years. Of those, 134 were found to have PAD (21 women and 113 men), defined by self-report of this diagnosis on entering the study in 84 (men, 8%; women, 9%); by diagnosis by a physician during hospitalization in 56 (men, 6%; women, 4%); by ultrasound imaging or angiographically demonstrated obstruction or ulcerated plaque (>50% of diameter or >75% of x-sectional area) of the iliac arteries or below in 40 (men, 4%; women, 3%); by surgery, angioplasty, or thrombolysis for PAD in 40 (men, 4%; women, 2%); or by exertional leg pain relieved by rest in 23 (men, 2%; women, 2%).

Study measurements. All participants completed a baseline examination that included an interview, fasting venous blood sample collection, a standardized medical history questionnaire, echocardiography, exercise treadmill testing, 24-hour ambulatory Holter monitoring, and a 24-hour urine collection. Age, sex, race, education level, and medical history were determined by self-report questionnaire. Height and weight were measured by a standardized protocol, with body mass index calculated as weight (kg)/height (m^2). Participants were instructed to bring their medication bottles to their enrollment visit, and study personnel recorded all current medications. Medications were categorized using Epocrates Rx (Epocrates Inc, San Mateo, Calif). None of the data presented >5% missing variables. Questionnaires were reported as missing if ≥30% of the individual items were missing. Otherwise, the total score was divided by the proportion answered to account for missing data. The appropriate Institutional Review Boards approved the protocol, and all participants provided written informed consent for participation in the study.

Blood samples. Fasting blood samples were obtained during the morning of the enrollment visit. Levels of high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) were determined from plasma and serum samples. These biomarkers were chosen because of their association with disease severity in PAD.[19-22] Levels of hsCRP were measured using the Integra assay (Roche, Indianapolis, Ind) or (owing to a change at the laboratory) the Extended Range assay (Beckman Coulter Ireland Inc, Galway, Ireland). Prior testing demonstrated high correlation of these two methods.[23] We used the Quantikine

HS IL-6 immunoassay (R&D Systems Minneapolis, Minn) to determine the concentration of IL-6 and the Human Serum Adipokine Panel B LINCOplex Kit (Linco Research Inc, St. Charles, Mo) to measure TNF-α. Low-density and high-density lipoprotein cholesterol levels were measured from fasting venous blood samples at baseline.

Behavioral and lifestyle factors. A history of smoking was determined by self-report questionnaire. Alcohol use was evaluated with the validated Alcohol Use Disorders Identification Test Alcohol Consumption Questions (AUDIT-C) questionnaire.[24] To assess medication adherence, participants were asked, "In the past month, how often did you take your medications as the doctor prescribed?" Possible responses were "all of the time (100%)," "nearly all of the time (90%)," "most of the time (75%)," "about half the time (50%)," or "less than half the time (≤50%)." We defined medication nonadherence as taking prescribed medications ≤75% of the time.[25]

To assess physical activity, the participants were asked, "Which of the following statements best describes how physically active you have been during the past month, that is, done activities such as 15 to 20 minutes of brisk walking, swimming, general conditioning, or recreational sports?" Participants chose one of the following six categories: not at all active, a little active (1-2 times per month), fairly active (3-4 times per month), quite active (1-2 times per week), very active (3-4 times per week), or extremely active (≥5 times per week). Participants who reported that they were not at all or a little active were considered physically inactive. Self-report has been shown to be a reliable, valid, and accurate method of assessing physical activity.[26,27]

Mental health factors. Depressive symptoms were assessed with the validated nine-item Patient Health Questionnaire (PHQ-9).[28] The PHQ-9, which provides a dichotomous measure of depressive symptoms based on a score of ≥10, has a sensitivity of 88% and a specificity of 88% for major depressive disorders[29] and has been used for diagnosis purposes in patients with PAD.[15] Anxiety symptoms were assessed by the Hospital Anxiety and Depression Scale (HADS).[30] The HADS questionnaire score ranges from 0 to 21, with higher scores representing higher levels of anxiety. A score of ≥8 on the anxiety subscale has a sensitivity and specificity of ∼80% as a case finder for anxiety disorders.[31]

Statistical analysis. Differences in baseline characteristics by gender were evaluated with *t*-tests for continuous variables and χ^2 tests for categoric variables (no variables had >4% missing data). We log-transformed covariates with severely right-skewed distributions (inflammatory biomarkers). Logistic regression models were used to calculate odds ratios (ORs) and confidence intervals (CIs). Variables included in the multivariate models were based on an a priori determination of significance at <.10 based on univariate models, in addition to age and activity status. To help interpret negative findings, CIs were assessed in addition to *P* values for logistic regression estimates. A wide CI generally fails to rule out substantial effects in at least one direction for negative findings, whereas a narrow CI increases the certainty about nonsignificant findings.[32] Statistical analyses were performed using Stata/SE 12 software (StataCorp LP, College Station, Tex).

RESULTS

PAD was present in 21 women (11%) and 113 men (13%). Women with PAD had a similar prevalence of hypertension, diabetes mellitus, and history of MI compared with women without PAD (Table I). There were no significant differences in the use of aspirin, angiotensin-converting enzyme inhibitors, or statins between the two groups. Women with and without PAD were equally likely to be smokers, and their lipid profiles did not differ significantly. Women with PAD were significantly more likely to suffer from depression ($P = .01$) or have a history of alcoholism ($P = .01$) compared with women without PAD.

Men with PAD, compared with men without PAD, were more likely to have hypertension, diabetes mellitus, a history of alcoholism, and past coronary revascularization (Table II). Men with PAD were also more likely to have a history of smoking and had lower levels of high-density lipoprotein cholesterol and higher levels of inflammatory biomarkers (hsCRP, IL-6, TNF-α, and fibrinogen) compared with men without PAD.

A univariate analysis demonstrated that diastolic blood pressure ($P = .07$), glucose ($P = .08$), a history of alcoholism ($P = .006$), and depression ($P = .01$) were associated with PAD. In a multivariate analysis, depressive symptoms had the strongest relationship to PAD in women ($P = .03$; Table III).

A univariate analysis demonstrated that hypertension ($P = .02$), diabetes mellitus ($P = .01$), hsCRP ($P < .0001$), fibrinogen ($P < .0001$), high-density lipoprotein cholesterol ($P = .01$), smoking ($P = .02$), physical activity ($P = .08$), and depressive symptoms ($P = .09$) were associated with PAD in men. In the multivariate analysis (Table IV), fibrinogen ($P = .05$) and a history of smoking ($P = .03$) remained independently associated with PAD in men.

DISCUSSION

That traditional CVD risk factors are strongly associated with the development and progression of PAD is well known; however, few studies have examined PAD risk factors separately by gender. In our study, we found traditional risk factors were similar in prevalence in women with and without PAD, but these traditional risk factors were more prevalent in men with PAD than in men without PAD. This suggests that other risk factors might contribute to PAD in women. In women, depression was the strongest risk factor for PAD.

The Multi-Ethnic Study of Atherosclerosis (MESA) of 1932 participants free of four traditional CVD risk factors (smoking, diabetes, hypertension, and dyslipidemia) found there was still a significant association between female gender and lower ankle-brachial index.[8] In a cohort of >15,000 participants, women who had never smoked

Table I. Characteristics of women with and without peripheral arterial disease (*PAD*)

Characteristics[a]	*Women with PAD (n = 21)*	*Women without PAD (n = 163)*	P
Traditional risk factors			
Age, years	67 ± 12	64 ± 11	.21
Caucasian	11 (52)	80 (49)	.78
BMI, kg/m^2	28 ± 7	30 ± 6	.39
Waist-to-hip ratio	0.88± 0.06	0.88 ±0.07	.86
Comorbidities and cardiac disease severity			
Hypertension	16 (76)	120 (74)	.80
History of MI	11 (55)	72 (45)	.38
Past coronary revascularization	9 (43)	72 (44)	.89
LVEF, %	64 ± 7	64 ± 8	.93
CHF	5 (24)	28 (17)	.46
Treadmill score, METs	6 ± 3	7 ± 3	.23
Diabetes mellitus	7 (33)	44 (27)	.54
Arthritis	15 (71)	100 (62)	.49
Systolic blood pressure, mm Hg	139 ± 21	137 ± 22	.82
Diastolic blood pressure, mm Hg	71 ± 11	76 ± 11	.07
Medications			
Aspirin	13 (62)	115 (71)	.42
ACE inhibitor	8 (38)	76 (47)	.46
β-blocker	8 (38)	87 (53)	.19
Statin	10 (48)	89 (55)	.55
Antidepressant	5 (24)	40 (25)	.94
Traditional risk factors, inflammation, and metabolic factors			
History of smoking	12 (57)	90 (55)	.87
Cholesterol, mg/dL			
Total	196 ± 52	191 ± 48	.65
LDL	114 ± 9	111 ± 41	.78
HDL	53 ± 17	53 ± 17	.94
Hemoglobin A_{1c}, %	6 ± 1	6 ± 1	.48
Glucose, mg/dL	132 ± 55	116 ± 36	.07
Log hsCRP, mg/L	0.7 ±1.3	1.1 ± 1.3	.22
Log IL-6, pg/mL	1.0 ± 0.6	0.9 ± 0.8	.31
Log TNF-α, pg/mL	1.4 ± 1.1	1.2 ± 0.8	.52
Log fibrinogen, mg/dL	6.0 ± 0.2	6.0 ± 0.2	.35
Psychosocial and behavioral risk factors			
Depression by PHQ-9 score	10 (48)	37 (23)	.01
Current PTSD	1 (5)	22 (14)	.26
History of general anxiety disorder	5 (24)	30 (18)	.55
Anxiety score	7 ± 3	7 ± 4	.88
Married	3 (14)	45 (28)	.19
Poor social support	16 (76)	113 (69)	.52
Physically active	14 (67)	86 (53)	.24
Adherent to medication	17 (81)	139 (87)	.41
History of alcoholism	3 (14)	8 (5)	.01
Regular alcohol use	4 (19)	25 (16)	.68

ACE, Angiotensin-converting enzyme; *BMI,* body mass index; *CHF,* congestive heart failure; *HDL,* high-density lipoprotein; *hsCRP,* high-sensitivity C-reactive protein; *IL-6,* interleukin 6; *LDL,* low-density lipoprotein; *LVEF,* left ventricular ejection fraction; *METS,* metabolic equivalents; *MI,* myocardial infarction; *PHQ,* Patient Health Questionnaire; *PTSD,* post-traumatic stress disorder; *TNF-α,* tumor necrosis factor-α.

[a]Continuous data are shown as mean ± standard deviation and categoric data as number (%).

were more likely to develop PAD compared with male never-smokers, even after adjustment for age, low-density lipoprotein cholesterol, hypertension, and diabetes.[33] In our study, depression was more common in women with PAD compared with those without PAD. It is possible that women and men have a different set of risk factors for PAD and that depression or other psychosocial factors might be more important in women. These risk factors are not commonly evaluated in PAD studies, and further research is needed to better clarify these associations.

The reason for a very close relationship between depression and PAD in women is therefore unclear. Prior research suggests that women with PAD aged <65 years are particularly vulnerable to experiencing depressive symptoms.[17] The authors postulated that this may be secondary to differential social roles and demands women face, care responsibilities for their families, combining work and home responsibilities, lower income and job inequality, as well as being a single parent.[17] Women in their study were not asked specifically why they were depressed.

Some other angles may be considered in terms of etiologic relevance. One is the association between depression and chronic diseases. Huang et al[34] recently assessed the pooled risks of depression in elderly patients with chronic

Table II. Characteristics of men with or without peripheral arterial disease (*PAD*)

Characteristics[a]	*Men with PAD (n = 113)*	*Men without PAD (n = 727)*	P
Traditional risk factors			
Age, years	68 ± 10	67 ± 11	.91
Caucasian	75 (66)	449 (62)	.36
BMI, kg/m^2	28 ± 5	28 ± 5	.99
Waist-to-hip ratio	0.98 ± 0.06	0.97 ± 0.07	.20
Comorbidities and cardiac disease severity			
Hypertension	90 (80)	497 (69)	.02
History of MI	68 (60)	396 (55)	.28
Past coronary revascularization	81 (72)	440 (61)	.03
LVEF, %	60 ± 10	61 ± 10	.43
CHF	38 (34)	108 (15)	<.0001
Treadmill score, METs	6 ± 3	8 ± 3	.0003
Diabetes mellitus	40 (35)	174 (24)	.01
Arthritis	64 (57)	377 (52)	.53
Systolic blood pressure, mm Hg	134 ± 23	132 ± 20	.31
Diastolic blood pressure, mm Hg	73 ± 13	75 ± 11	.29
Medications			
Aspirin	96 (85)	568 (78)	.10
ACE inhibitor	68 (60)	372 (51)	.07
β-blocker	74 (65)	424 (58)	.15
Statin	82 (73)	476 (65)	.14
Antidepressant	22 (19)	121 (17)	.46
Traditional risk factors, inflammation and metabolic factors			
History of smoking	92 (81)	515 (71)	.02
Cholesterol, mg/dL			
Total	171 ± 39	176 ± 41	.26
LDL	100 ± 30	103 ± 32	.27
HDL	41 ± 12	45 ± 13	.01
Hemoglobin A_{1c}, %	6 ± 1	6 ± 1	.48
Glucose, mg/dL	132 ± 55	116 ± 36	.07
Log hsCRP, mg/L	1.1±1.3	0.6 ± 1.3	.0005
Log IL-6, pg/mL	1.3 ± 0.7	0.9 ± 0.7	<.00001
Log TNF-α, pg/mL	1.4 ± 0.9	1.2 ± 0.9	.008
Log fibrinogen, mg/dL	6.0 ± 0.2	5.9 ± 0.2	.0001
Psychosocial and behavioral risk factors			
Depression by PHQ-9 score	27 (24)	125 (17)	.09
Current PTSD	10 (9)	62 (9)	.92
History of general anxiety disorder	12 (11)	60 (8)	.41
Anxiety score	5 ± 6	5 ± 4	.22
Married	51 (45)	337 (47)	.78
Poor social support	68 (60)	496 (68)	.08
Physically active	67 (60)	482 (66)	.17
Adherent to medication	106 (95)	670 (93)	.45
History of alcoholism	26 (23)	96 (13)	.02
Regular alcohol use	28 (25)	236 (33)	.10

ACE, Angiotensin-converting enzyme; *BMI,* body mass index; *CHF,* congestive heart failure; *HDL,* high-density lipoprotein; *hsCRP,* high-sensitivity C-reactive protein; *LDL,* low-density lipoprotein; *IL-6,* interleukin 6; *LVEF,* left ventricular ejection fraction; *METS,* metabolic equivalents; *MI,* myocardial infarction; *PHQ,* Patient Health Questionnaire; *PTSD,* post-traumatic stress disorder; *TNF-α,* tumor necrosis factor-α.
[a]Continuous data are shown as mean ± standard deviation and categoric data as number (%).

diseases. Their analysis demonstrated that several chronic disorders increase the risk of depression; for example, stroke (OR, 1.98; 95% CI, 1.33-2.62), poor hearing (OR, 1.71; 95% CI, 1.28-2.27), poor vision (OR, 1.94; 95% CI, 1.68-2.25), arthritis (OR, 2.27; 95% CI, 1.35-3.82), hypertension (OR, 1.25; 95% CI, 1.04-1.50), cardiac disease (OR, 1.67; 95% CI, 1.37-2.04), chronic lung disease (OR, 2.13; 95% CI, 1.23-3.71), diabetes (OR, 1.81; 95% CI, 1.29-2.54), gastrointestinal disease (OR, 1.95; 95% CI, 0.80-4.70), and kidney disease (OR, 2.22; 95% CI, 1.31-3.77). Interestingly, from the present study and our previous work, we can state that a close association exists between depression and PAD, one that appears even tighter in females. Adjustment for chronic conditions did not alter our conclusions with regards to the association between depression and PAD, suggesting an independent association between the two diseases.

We and others have demonstrated that depression is a risk factor for PAD.[12,35,36] In addition to increasing the risk of PAD, depression also appears to impact the functional status and symptoms of patients with PAD, leading to more dramatic annual declines in functional performance,[13] reduced walking distance,[14] and reduced quality of life benefit after revascularization.[15] The findings from

Table III. Independent risk factors for peripheral arterial disease (PAD) in women using a multivariate model[a]

Risk factors	*OR*	*95% CI*	P
Age	1.04	0.99-1.10	.10
Diastolic blood pressure	0.97	0.93-1.02	.30
Blood glucose	1.01	1.00-1.02	.05
Physically activity	1.21	0.88-1.66	.23
History of alcoholism	1.30	1.00-1.68	.05
Depression	3.26	1.09-9.77	.03

CI, Confidence interval; *OR*, odds ratio.
[a]Variables included in the multivariate models were based on an a priori determination of significance at <.10 based on univariate models, in addition to age.

Table IV. Independent risk factors for peripheral arterial disease (PAD) in men using a multivariate model[a]

Risk factors	*OR*	*95% CI*	P
Age	1.01	0.99-1.03	.33
Hypertension	1.54	0.92-2.57	.10
Diabetes mellitus	1.36	0.86-2.16	.19
hsCRP	1.14	0.86-1.50	.36
Fibrinogen	1.30	1.00-1.70	.05
HDL cholesterol	0.80	0.63-1.01	.07
History of smoking	1.46	1.05-2.04	.03
Physical activity	1.00	0.88-1.15	.92
Depression	1.43	0.84-2.43	.19

CI, Confidence interval; *HDL*, high-density lipoprotein; *hsCRP*, high-sensitivity C-reactive protein; *OR*, odds ratio.
[a]Variables included in the multivariate models were based on an a priori determination of significance at <.10 based on univariate models, in addition to age. Continuous predictors (log CRP, log fibrinogen, and HDL) were entered per standard deviation.

this study add to a growing body of literature on the behavioral and psychosocial risk factors in the development of CVDs. Although not specifically evaluated in patients with PAD, social support has been linked to adverse cardiovascular outcomes in other populations.[37] Patients at risk or with an atherothrombotic disorder who lived alone were at higher risk of cardiovascular death than those who lived with someone.[38] In a recent review, low "functional support" increased cardiac and all-cause mortality.[39] General stress, work-related stress, and the feeling of "lack of control" are among other psychosocial risk factors now recognized as potential risk factors for CVDs.[40] Overall, it is possible that psychosocial risk factors affect CVDs and influence the development of PAD.

The direction of the association between depression and PAD therefore remains poorly understood. From the results of the present study, we can conclude that an association between these two diseases is present. It is quite plausible that patients experiencing functional impairment secondary to PAD develop depression that contributes to worsening health behaviors and increased inflammation. Findings from our previous study, however, also suggest that patients with depressive symptoms are more likely to experience PAD when followed up prospectively.[12] Hence, a few explanations are possible:

1. depression in itself leads to an increase in modifiable risk factors, such as smoking and physical inactivity, and subsequently, to an increased risk of PAD,
2. patients with PAD are more depressed because of their disease and functional impairment,
3. these two hypotheses lead to a vicious circle tightly linking depression, PAD, and unhealthy behaviors.

At the present time and based on the findings of this study, these hypotheses remain speculative.

The findings of this study have important implications for clinical practice. Depression may play an important role in the pathophysiology of PAD. That depressive symptoms could potentially not only affect the development of disease but also hinder treatment benefits and rehabilitation is also possible. Although previous studies have demonstrated a clear association between depression and CVD, whether pharmacologic treatment of depression can improve cardiovascular outcomes, particularly those related to PAD, is still unclear. Future studies should focus on the effects of treatment of depression on the progression and outcomes of patients with PAD.

Our study findings must be interpreted in light of several limitations. The first major limitation is that this was a secondary analysis with a limited number of patients (especially women) and, subsequently, limited power to detect differences. The small sample size and low proportion of women (<20%) limits our ability to detect sex-specific differences. It is also possible that a type II statistical error was introduced in our sample when we assessed the association between men and PAD, limiting our ability to detect a significant difference. Because of these limitations, the study should be considered as a pilot and hypothesis-generating study. Furthermore, because the aim of the Heart and Soul Study was to measure risks of development of cardiac diseases, it is possible that selection bias was introduced in the study, further limiting interpretation of results in the context of PAD.

Second, because the primary objective was to assess the effect of psychologic factors in patients with CAD, several PAD measures are missing, including the ankle-brachial index. This further limits the inferences that can be made from our results and the assessment of PAD-specific measures. In addition, the Heart and Soul Study includes mostly urban men with existing heart disease, which may limit the generalizability of our results.

CONCLUSIONS

In this study of outpatients with stable CAD, traditional CVD risk factors were associated with PAD in men. Depression was significantly more common in women with PAD compared with those without PAD. Given the heavy burden of PAD in women, our findings highlight the importance of continuing investigations in the field of gender differences in PAD, with a particular focus on mental health. Depression, particularly in women,

should become an important consideration to the clinician with regards to its association with CVDs.

AUTHOR CONTRIBUTIONS

Conception and design: MG, BC, JH
Analysis and interpretation: MG, BC, KS, MW, JH, EV
Data collection: MW
Writing the article: MG
Critical revision of the article: BC, KS, MW, JH, EV
Final approval of the article: MG, BC, KS, MW, JH, EV
Statistical analysis: MG, EV
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Overall responsibility: MG

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