ORIGINAL RESEARCH

Relationship Between Depressive Symptoms and Health Status in Peripheral Artery Disease: Role of Sex Differences

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BACKGROUND: The association of depressive symptoms with health status in peripheral artery disease (PAD) is understudied. No reports of differential impact on women have been described.

METHODS AND RESULTS: The PORTRAIT (Patient-Centered Outcomes Related to Treatment Practices in Peripheral Artery Disease Investigating Trajectories) registry enrolled 1243 patients from vascular specialty clinics with new or worsening PAD symptoms. Depressive symptoms were assessed at baseline and 3 months using the 8-Item Patient Health Questionnaire (score ≥10 indicating clinically relevant depressive symptoms). Disease-specific and generic health status were measured by Peripheral Artery Questionnaire and EQ-5D Visual Analogue Scale at baseline and 3, 6, and 12 months. An adjusted general linear model for repeated measures was constructed for baseline and 3-, 6-, and 12-month health status outcomes by depressive symptoms at baseline. Differences by sex were tested with interaction effects. The mean age was 67.6±9.4 years with 38% (n=470) women. More women than men (21.1% versus 12.9%; $P<0.001$) presented with severe depressive symptoms. In the adjusted model, patients with depressive symptoms had worse health status at each time point (all $P<0.0001$). Results were similar for EQ-5D Visual Analogue Scale scores. The magnitude in 1-year change in health status scores did not differ by sex. Depressive symptoms explained 19% of the association between sex differences in 1-year Peripheral Artery Questionnaire summary scores.

CONCLUSIONS: Women with PAD have a high burden of depressive symptoms. Depressive symptoms were associated with a strikingly worse disease-specific health status recovery path over the year following PAD diagnosis in men and women. Developing and testing interventions to address depressive symptoms in PAD are urgently needed.

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Key Words: depressive symptoms ■ health status ■ peripheral artery disease ■ sex differences

Peripheral artery disease (PAD) remains a significant health problem,[1] affecting >200 million people worldwide[2] and >8 million people >40 years of age in the United States alone.[3,4] In patients with multiple atherosclerotic risk factors, including smoking and diabetes mellitus,[5] the prevalence of PAD can be as high as 30%.[6] PAD is associated with a high risk of cardiovascular mortality and morbidity,[7,8] with a disproportionate high risk of cardiovascular events compared with coronary artery disease and cerebrovascular disease.[9] From a societal perspective, PAD is a costly disease. Total annual costs associated with PAD-related hospitalizations in the United States are estimated to be in excess of $21 billion,[10] which will continue to increase as the population ages.

The disability associated with PAD is significant. PAD may present itself as excruciating pain while walking and may impact patients' mobility and

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CLINICAL PERSPECTIVE

What Is New?
- Patients with peripheral artery disease, and especially women, who experience depressive symptoms have worse 1-year peripheral artery disease–specific health status outcomes, with large differences compared with those who do not experience such symptoms.

What Are the Clinical Implications?
- Depressive symptoms in chronic disease populations, such as peripheral artery disease, should be a continuous focus of multidisciplinary treatment so as to ensure quality peripheral artery disease care and optimize health status outcomes.

Nonstandard Abbreviations and Acronyms

ABI	ankle-brachial index
GLM	general linear model
PAD	peripheral artery disease
PAQ	Peripheral Artery Questionnaire
PHQ-8	8-Item Patient Health Questionnaire
PORTRAIT	Patient-Centered Outcomes Related to Treatment Practices in Peripheral Artery Disease Investigating Trajectories
VAS	Visual Analogue Scale

functioning, as well as their health status and quality of life. Although PAD presents itself at least as commonly in women as in men,[11–14] women's experiences of the disease burden may be worse than that of men's, as expressed by greater functional impairment,[15] worse health-related quality of life,[16] and poorer outcomes after lower extremity revascularization procedures.[17,18] Women diagnosed with cardiovascular disease are also at a much higher risk of presenting with depressive symptoms compared with men.[19] The manifestation of depressive symptoms is independently associated with higher cardiac and all-cause mortality, rehospitalization, and worse functional status, including angina and quality of life after myocardial infarction.[20–23] Depressive symptoms are also more common in women with PAD than in men with PAD.[24,25] Although depressive symptoms are known to be associated with a more dramatic annual decline in functional performance,[26] reduced walking distance,[27] less quality-of-life benefit after revascularization,[28] and an increased risk of death/major adverse cardiovascular events, coronary heart disease, and contralateral PAD events,[29] it is unclear as to what extent depressive symptoms may be associated with a worse health status recovery profile in patients with PAD, and whether women are affected differently than men.

To address this gap in knowledge, we sought to (1) determine the prevalence of depressive symptoms and their treatment; (2) compare the trajectory of 1-year PAD-specific health status following a new or worsening PAD diagnosis as a function of depressive symptoms; and (3) explore sex differences in both the prevalence and health status impact of depressive symptoms among patients with PAD. We hypothesized that women with PAD have a higher burden of depressive symptoms compared with men with PAD, both at baseline and in the year following a new or worsening PAD diagnosis, and that depressive symptoms would be associated with worse health status outcomes over time. Establishing PAD-specific health status recovery profiles as a function of depressive symptoms can underscore the importance of this comorbidity, especially in women, and stimulate new research into ways to address this problem in a more holistic approach to PAD care.

METHODS

Data requests for the PORTRAIT study can be submitted to the corresponding author. Because of the sensitive nature of the data collected for this study, requests to access a deidentified data set from qualified researchers trained in human subject confidentiality protocols may be considered on an individual basis by contacting the corresponding author or by contacting the PORTRAIT (Patient-Centered Outcomes Related to Treatment Practices in Peripheral Artery Disease Investigating Trajectories) registry group on the website.[30]

Patients included in this study were enrolled from the PORTRAIT registry,[30] for which the methods have previously been described. Briefly, it is an international, prospective, observational study designed to address gaps in knowledge about the quality of care and health status outcomes of patients with PAD. Between June 2011 and December 2015, 1275 patients with a new diagnosis of PAD or those with an exacerbation of symptoms presenting to 16 vascular specialty clinics were enrolled. Of these 16 vascular specialty clinics, 10 were from the United States, 5 were from The Netherlands, and 1 was from Australia. Patients from The Netherlands and Australia were included in this study as PAD has become a global health problem with high morbidity and mortality.[31] Integrating data from these countries allows us to determine country/region-based variations in disease

characteristics, treatment patterns, and outcomes and help improve practices. Patients with a Doppler resting ankle-brachial index (ABI) ≤0.90 or a significant decrease in postexercise ankle pressure of ≥20 mmHg were enrolled in the study. Other inclusion criteria included (1) patients aged ≥18 years; (2) new-onset or recent exacerbation of exertional leg symptoms, regardless of whether symptoms were typical (buttock, thigh, hip, or calf pain; numbness or discomfort inhibiting the patient's ability to walk distances) or atypical. To classify patients' symptoms as atypical or typical, the coordinators were instructed to abstract this from patients' medical records and as described by their treating physician. Patients with a noncompressible ABI ≥1.30, those who underwent a lower-limb revascularization procedure in the past year (angioplasty, bypass surgery, atherectomy, or endarterectomy) for the ipsilateral leg relative to where the patient was currently having symptoms, patients with a current episode of critical limb ischemia (ischemic rest pain, ulceration, or gangrene; Fontaine III or IV; or Rutherford category 4–6), patients who could not speak English, Spanish, or Dutch, and patients with hearing impairment or current imprisonment were excluded. Approval from the institutional review board of each participating site was obtained, and participants provided informed consent for all study procedures and interviews. All patients provided consent to have their medical data abstracted from their electronic medical records. A 2-step process was designed to obtain medical record information from outside the enrolling facility: (1) during follow-up, patients were asked whether they obtained care outside of the enrolling facility; and (2) if patients indicated they obtained outside care, their medical record information was requested per the patient's consent that was obtained on enrollment.

Data Collection and Study Definitions

Information on patients' baseline characteristics was obtained by trained personnel using medical chart abstraction as well as in-person interviews during the first visit and before initiation of treatment. On enrollment, detailed information was obtained through chart abstraction on demographics, cardiac risk factors, comorbidities, disease severity from diagnostic tests, and baseline treatment (medications, cardiovascular risk management strategies, and referrals). Follow-up assessments were conducted by a centralized call center at 3, 6, and 12 months using standardized interviews. Information on the primary PAD treatment strategy was determined at 3 months as either noninvasive (medical therapy, including pharmacologic treatment and smoking cessation counseling) or invasive treatment (including

either surgical or endovascular intervention). Primary PAD treatment information from all US sites was adjudicated by a central committee; from non-US sites, patient-reported information was used.

Assessment of Depressive Symptoms

Depressive symptoms were assessed using the 8-Item Patient Health Questionnaire (PHQ-8),[32] an 8-item depression scale that has been established as a valid screening tool to screen for a major depressive disorder, as well as to quantify the frequency of depressive symptoms experienced in the past 2 weeks.[33] Scores range from 0 to 27, with a higher score indicating a higher level of depressive symptoms, and a score ≥10 has 88% sensitivity and specificity to detect major depression. The severity of depressive symptoms has been described using the following categories: "no" depressive symptoms if PHQ-8 scores are <5, mild depressive symptoms for PHQ-8 scores ≥5 and ≤9, and moderate/severe depressive symptoms for scores ≥10.[34]

Assessment of Outcomes

Health status was measured using the disease-specific Peripheral Artery Questionnaire (PAQ) and the generic EQ-5D Visual Analogue Scale (VAS) instrument. The PAQ[35] is a 20-item, validated, PAD-specific, multidimensional health status instrument that measures 6 health status domains relevant to patients with PAD: physical function, symptoms, symptom stability, social limitations, treatment satisfaction, and quality of life. A summary score is calculated as the average of the physical limitation, symptoms, quality of life, and social functioning scores. Scores range from 0 to 100 points, with higher scores indicating better functioning.

The EQ-5D[36] is a standardized generic measure of health status that provides a simple measure of health status for clinical assessment. The questionnaire consists of 2 parts: a descriptive section (EQ-5D index score) and a VAS (EQ-5D VAS score). We used the EQ-5D VAS score to assess patients' overall health. The 20-cm VAS ranges from the worst (a score of 0) to the best (a score of 100) imaginable health state, with higher scores indicating better health status.

Other Variables

Depression treatment information was derived from patients' medical records. Information about counseling and/or pharmacologic treatment was abstracted from patients' medical records at the time of their enrollment (up to 1 month after enrollment).

Statistical Analysis

Patients' baseline characteristics were compared by sex using χ^2 tests or the Fisher exact test for categorical

variables and Student t tests for continuous variables. Categorical variables were organized as frequencies and percentages, and continuous variables were summarized as means and SDs or medians and interquartile ranges. For the covariates considered in the model, missingness was minimal, with only 1.5% of patients who had missing information for 1 covariate and only 1 patient who had missing information for 3 covariates. The highest number of covariate missingness was for "high school education" (n=10) and "avoiding care because of cost" (n=8); 98% of the total cohort had no missing covariate information. Given the minimal level of missingness, complete case analysis was used for our analyses.

Mean PHQ-8 depressive symptoms, as well as the dichotomous prevalence of clinically relevant depressive symptoms (PHQ-8 score ≥10), were summarized by sex at each time point.

General linear models (GLMs) for repeated measures, with a random effect for site, were used to study baseline and 3-, 6-, and 12-month health status outcomes by the presence of clinically relevant depressive symptoms (PHQ-8 ≥10 at baseline versus PHQ-8 score <10). We tested the 2-way interactions between time×sex, time×depressive symptoms, and depressive symptoms×sex as well as the 3-way interaction between sex×depressive symptoms×time. GLMs were created both for the PAQ summary and EQ-5D VAS scores over time. We selected the following covariates for multivariable modeling: age, country, White race, avoiding care because of cost, high school education, ABI, exacerbation of symptoms, bilateral disease, smoking, history of diabetes mellitus, coronary artery disease, and sleep apnea. Consistent with prior work, these covariates were chosen as these were previously identified as most explanatory for patients' health status outcomes (PAQ summary scores) in the PORTRAIT registry.[37] Estimates for health status differences by depressive symptom groups were presented as mean estimates, and depressive symptom group differences over time were summarized as least square means.

For descriptive purposes, and by ways of sensitivity analysis, we compared health status outcomes by severity of depression (no, mild, or moderate-severe), and performed post hoc testing. In addition, for the modeling, we performed 2 sensitivity analyses. First, we examined the degree to which depressive symptoms explained sex differences in disease-specific health status (PAQ summary score). We ran the fully adjusted GLM without depressive symptoms or interaction terms, containing only the main effect for sex. We then replicated the analysis while adding depressive symptoms to the model to examine the difference in estimates for the main sex effect. Second, we explored the potential effect of nonresponse bias.

Baseline characteristics of those with and without complete follow-up were compared. Characteristics with a >10% standardized difference were added as covariates to the original GLM to determine if the estimated effects were different.

A 2-sided $P<0.05$ was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

In terms of participation rate, of a total of 1636 patients screened, 1243 were enrolled in the study. Follow-up rates were 92% at 3 months, 88% at 6 months, and 87% at 12 months. With respect to those enrolled versus not enrolled in the study, there were no significant differences between the 2 groups in terms of age, sex, race, and insurance. Baseline characteristics of the total cohort (n=1243) stratified by sex and depressive symptoms (PHQ-8 ≥10) are shown in Tables 1 and 2. The mean age was 67.6±9.4 years, and 38% (n=470) were women. A total of 52.6% (n=654) had new-onset PAD symptoms, whereas 47.4% (n=589) had an exacerbation of symptoms at the time of enrollment.

At enrollment, there was no significant difference in age between women and men for the overall cohort (68.0±9.9 versus 67.3±9.2 years; $P=0.23$). Women were less likely to be married, less likely to be employed, and more likely than men to avoid care because of cost. Women were more likely to be sedentary during leisure time and were less likely to engage in moderate to strenuous exercise compared with their male counterparts. Compared with men, women had lower mean ABI values and were more likely to present with atypical symptoms and to present with bilateral symptoms. Cardiovascular risk management strategies were not different by sex, except for higher rates of unsupervised exercise therapy among women. There were no differences in the rates of invasive treatment at 3 months (either surgical or endovascular) by sex (Table 1).

In the overall cohort (n=1243), a total of 199 patients (16.0%) had moderate-severe depressive (PHQ-8 ≥10) symptoms on presentation, with rates being much higher in women than in men (21.1% versus 12.9%; $P<0.001$) at presentation. Mean PHQ-8 scores were 5.6±5.3 in women versus 4.2±4.8 in men at baseline (Table 1).

After stratification by sex and clinically relevant depressive symptoms (PHQ-8 ≥10), mean PHQ-8 scores among those with depressive symptoms were similar between men and women (14.2±3.7 versus 14.1±3.7). Of those with clinically relevant depressive symptoms, almost half of women and one third of men were on some form of depression treatment. A complete

Table 1. Baseline Patient Characteristics, Stratified by Sex

Characteristics	Women (n=470 [38%])	Men (n=773 [62%])	Total (n=1243)	*P* Value
Demographics and socioeconomic status				
Age, y				
Mean±SD	68.0±9.9	67.3±9.2	67.6±9.4	0.23
Median (IQR)	68.0 (61.0–75.0)	67.0 (61.0–73.0)	68.0 (61.0–74.0)	
Race				<0.001
White	206 (63.0)	353 (78.8)	559 (72.1)	
Black	106 (32.4)	75 (16.7)	181 (23.4)	
Other	15 (4.6)	20 (4.5)	35 (4.5)	
Country				<0.001
United States	327 (69.6)	448 (58.0)	775 (62.3)	
The Netherlands	117 (24.9)	257 (33.2)	374 (30.1)	
Australia	26 (5.5)	68 (8.8)	94 (7.6)	
Health insurance	466 (99.1)	770 (99.6)	1236 (99.4)	0.44
Education, high school or above	312 (66.8)	539 (70.4)	851 (69.0)	0.19
Married	208 (44.4)	524 (68.1)	732 (59.2)	<0.001
Working for pay	82 (17.5)	211 (27.4)	293 (23.6)	<0.001
Avoid care because of cost	78 (16.8)	96 (12.5)	174 (14.1)	0.035
Activity during leisure time				
Sedentary	240 (51.6)	258 (34.2)	498 (40.8)	<0.001
Mild	146 (31.4)	257 (34.0)	403 (33.0)	
Moderate	79 (17.0)	240 (31.8)	319 (26.1)	
Risk factors and comorbidities				
Smoking status				
Never	79 (16.8)	53 (6.9)	132 (10.6)	<0.001
Former	213 (45.4)	435 (56.3)	648 (52.2)	
Current	177 (37.7)	284 (36.8)	461 (37.1)	
CAD	162 (34.5)	324 (41.9)	486 (39.1)	0.009
Dyslipidemia	381 (81.1)	606 (78.4)	987 (79.4)	0.26
Hypertension	404 (86.0)	589 (76.2)	993 (79.9)	<0.001
Diabetes mellitus	168 (35.7)	247 (32.0)	415 (33.4)	0.17
Congestive heart failure	42 (8.9)	81 (10.5)	123 (9.9)	0.38
Chronic kidney disease	59 (12.6)	79 (10.2)	138 (11.1)	0.20
Chronic back pain	72 (15.3)	97 (12.5)	169 (13.6)	0.17
Sleep apnea	32 (6.8)	68 (8.8)	100 (8.0)	0.21
PAD treatment history				
Amputation	3 (0.6)	13 (1.7)	16 (1.3)	0.11
PAD bypass	27 (5.7)	72 (9.3)	99 (8.0)	0.024
PAD endarterectomy	13 (2.8)	24 (3.1)	37 (3.0)	0.73
PAD atherectomy	11 (2.3)	20 (2.6)	31 (2.5)	0.79
PAD angioplasty	94 (20.0)	153 (19.8)	247 (19.9)	0.93
Cilostazol	28 (6.0)	48 (6.2)	76 (6.1)	0.85
Antiplatelet therapy	323 (69.0)	518 (67.4)	841 (68.0)	0.54
Statin	320 (68.4)	546 (71.0)	866 (70.0)	0.33
PAD characteristics on presentation				
Symptoms				
New onset	244 (51.9)	410 (53.0)	654 (52.6)	0.70
Exacerbation of symptoms	226 (48.1)	363 (47.0)	589 (47.4)	

Table 1. Continued

Characteristics	Women (n=470 [38%])	Men (n=773 [62%])	Total (n=1243)	P Value
ABI				
Mean±SD	0.65±0.18	0.67±0.19	0.67±0.19	0.045
Rutherford category				
Mild claudication	95 (20.7)	187 (24.5)	282 (23.1)	0.21
Moderate claudication	239 (52.1)	362 (47.4)	601 (49.1)	
Severe claudication	125 (27.2)	215 (28.1)	340 (27.8)	
Duration of pain, mo				
<1	10 (2.5)	20 (3.0)	30 (2.8)	0.38
1–6	129 (31.7)	191 (28.9)	320 (29.9)	
7–12	78 (19.2)	110 (16.6)	188 (17.6)	
>12	190 (46.7)	341 (51.5)	531 (49.7)	
Atypical PAD symptoms	75 (17.2)	88 (12.3)	163 (14.2)	0.020
Bilateral disease	264 (56.2)	364 (47.1)	628 (50.5)	0.001
Lesion site				
Proximal	130 (27.8)	217 (28.3)	347 (28.1)	0.55
Distal	149 (31.9)	223 (29.1)	372 (30.1)	
Both	188 (40.3)	327 (42.6)	515 (41.7)	
PAD treatment after enrollment				
Cilostazol	62 (13.2)	85 (11.1)	147 (11.9)	0.25
Antiplatelet therapy	368 (78.6)	583 (75.8)	951 (76.9)	0.25
Statin	370 (79.1)	629 (81.8)	999 (80.8)	0.24
Smoking cessation physician advice	153 (71.2)	231 (64.9)	384 (67.3)	0.12
Unsupervised PAD exercise therapy	200 (42.6)	249 (32.2)	449 (36.1)	<0.001
Supervised PAD exercise therapy	95 (20.2)	177 (22.9)	272 (21.9)	0.27
Invasive treatment	82 (19.9)	141 (20.1)	223 (20.0)	0.94
Surgical treatment	6 (1.5)	23 (3.3)	29 (2.6)	0.07
Endovascular treatment	78 (18.9)	122 (17.4)	200 (18.0)	0.51
Depression severity and treatment at baseline				
PHQ-8 score severity (baseline)				
None (PHQ-8 <5)	257 (54.7)	510 (66.0)	767 (61.7)	
Mild (5 ≥ PHQ-8 ≤ 9)	114 (24.3)	163 (21.1)	277 (22.3)	<0.001
Moderate/severe (PHQ-8 ≥10)	99 (21.1)	100 (12.9)	199 (16.0)	
PHQ-8 depression score, mean±SD	5.6±5.3	4.2±4.8	4.7±5.0	<0.001
Baseline depression treatments				
None	331 (70.4)	660 (85.4)	991 (79.7)	0.001
Pharmacologic treatment	79 (16.8)	71 (9.2)	150 (12.1)	
Counseling	13 (2.8)	12 (1.6)	25 (2.0)	
Both	47 (10.0)	30 (3.9)	77 (6.2)	
Antidepressant use at baseline				
SSRI	72	46	118	<0.001
SNRI	25	12	37	<0.001
TCA	17	14	31	0.06
Atypical agents	31	29	60	0.03
Miscellaneous				
Perphenazine	0	1	1	1.00

Continuous variables were compared using the Student t test. Categorical variables were compared using the χ^2 or the Fisher exact test (health insurance). Values are listed as number (percentage), unless otherwise described. ABI indicates ankle-brachial index; CAD, coronary artery disease; IQR, interquartile range; PAD, peripheral artery disease; PHQ-8, 8-Item Patient Health Questionnaire; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin receptor inhibitor; and TCA, tricyclic antidepressant.

Table 2. Baseline Patient Characteristics, Stratified by Sex and Clinically Relevant Depressive Symptoms (PHQ-8 ≥10)

| | Women | | | Men | | |
| | PHQ-8 ≥10 | PHQ-8 <10 | | PHQ-8 ≥10 | PHQ-8 <10 | |
Characteristics	(n=99)	(n=371)	*P* Value	(n=100)	(n=673)	*P* Value
Demographics and socioeconomic status						
Age, y						
Mean±SD	63.0±9.9	69.3±9.5	<0.001	63.3±8.9	67.9±9.0	<0.001
Race*						
White	47 (63.5)	159 (62.8)		50 (76.9)	303 (79.1)	
Black	19 (25.7)	87 (34.4)	0.013	8 (12.3)	67 (17.5)	0.031
Other	8 (10.8)	7 (2.8)		7 (10.8)	13 (3.4)	
Country						
United States	74 (74.7)	253 (68.2)		65 (65.0)	383 (56.9)	
The Netherlands	15 (15.2)	102 (27.5)	0.006	23 (23.0)	234 (34.8)	0.05
Australia	10 (10.1)	16 (4.3)		12 (12.0)	56 (8.3)	
Health insurance*	95 (96.0)	371 (100.0)	0.001	100 (100.0)	670 (99.6)	1.000
Education, high school or above	59 (60.8)	253 (68.4)	0.16	67 (67.7)	472 (70.8)	0.53
Married	34 (34.7)	174 (47.0)	0.028	56 (56.6)	468 (69.9)	0.008
Working for pay	14 (14.3)	68 (18.4)	0.34	20 (20.0)	191 (28.5)	0.08
Avoid care because of cost	31 (32.0)	47 (12.8)	<0.001	23 (23.0)	73 (10.9)	<0.001
Activity during leisure time						
Sedentary	64 (65.3)	176 (48.0)		62 (63.3)	196 (29.8)	
Mild	23 (23.5)	123 (33.5)	0.008	19 (19.4)	238 (36.2)	<0.001
Moderate	11 (11.2)	68 (18.5)		17 (17.3)	223 (33.9)	
Risk factors and comorbidities						
Smoking status*						
Never	13 (13.3)	66 (17.8)	0.004	7 (7.0)	46 (6.8)	0.11
Former	34 (34.7)	179 (48.2)		47 (47.0)	388 (57.7)	
Current	51 (52.0)	126 (34.0)		46 (46.0)	238 (35.4)	
CAD	43 (43.4)	119 (32.1)	0.034	48 (48.0)	276 (41.0)	0.19
Dyslipidemia	82 (82.8)	299 (80.6)	0.61	74 (74.0)	532 (79.0)	0.25
Hypertension	85 (85.9)	319 (86.0)	0.97	77 (77.0)	512 (76.1)	0.84
Diabetes mellitus	47 (47.5)	121 (32.6)	0.006	34 (34.0)	213 (31.6)	0.64
Congestive heart failure	9 (9.1)	33 (8.9)	0.95	16 (16.0)	65 (9.7)	0.05
Chronic kidney disease	14 (14.1)	45 (12.1)	0.59	8 (8.0)	71 (10.5)	0.43
Chronic back pain	17 (17.2)	55 (14.8)	0.56	20 (20.0)	77 (11.4)	0.015
Sleep apnea	11 (11.1)	21 (5.7)	0.05	13 (13.0)	55 (8.2)	0.11
PAD treatment history						
Amputation*	1 (1.0)	2 (0.5)	0.51	3 (3.0)	10 (1.5)	0.23
PAD bypass	10 (10.1)	17 (4.6)	0.036	12 (12.0)	60 (8.9)	0.32
PAD endarterectomy*	2 (2.0)	11 (3.0)	1.00	3 (3.0)	21 (3.1)	1.00
PAD angioplasty	24 (24.2)	70 (18.9)	0.23	19 (19.0)	134 (19.9)	0.83
Cilostazol	5 (5.1)	23 (6.2)	0.66	6 (6.1)	42 (6.3)	0.94
Antiplatelet therapy	75 (75.8)	248 (67.2)	0.10	70 (70.7)	448 (66.9)	0.45
Statin	67 (67.7)	253 (68.6)	0.87	65 (65.7)	481 (71.8)	0.21
PAD characteristics on presentation						
Symptoms						
New onset	53 (53.5)	191 (51.5)		50 (50.0)	360 (53.5)	
Exacerbation	46 (46.5)	180 (48.5)	0.72	50 (50.0)	313 (46.5)	0.51

(Continued)

Table 2. Continued

Characteristics	Women			Men		
	PHQ-8 ≥10	PHQ-8 <10		PHQ-8 ≥10	PHQ-8 <10	
	(n=99)	(n=371)	P Value	(n=100)	(n=673)	P Value
ABI						
Mean±SD	0.68±0.20	0.64±0.18	0.06	0.68±0.20	0.67±0.19	0.88
Rutherford category			0.57			0.001
Mild claudication	20 (20.8)	75 (20.7)		18 (18.0)	169 (25.5)	
Moderate claudication	46 (47.9)	193 (53.2)		39 (39.0)	323 (48.6)	
Severe claudication	30 (31.3)	95 (26.2)		43 (43.0)	172 (25.9)	
Duration of pain, mo*						
<1	3 (3.7)	7 (2.1)		1 (1.2)	19 (3.3)	
1–6	21 (25.9)	108 (33.1)		15 (17.9)	176 (30.4)	
7–12	18 (22.2)	60 (18.4)	0.47	21 (25.0)	89 (15.4)	0.023
>12	39 (48.1)	151 (46.3)		47 (56.0)	294 (50.9)	
Symptoms						
Typical	69 (77.5)	291 (84.1)		83 (84.7)	543 (88.1)	
Atypical	20 (22.5)	55 (15.9)	0.14	15 (15.3)	73 (11.9)	0.33
Bilateral disease	48 (48.5)	216 (58.2)	0.08	55 (55.0)	309 (45.9)	0.09
Lesion site						
Proximal	29 (29.6)	101 (27.4)		32 (32.3)	185 (27.7)	
Distal	19 (19.4)	130 (35.2)		25 (25.3)	198 (29.6)	
Both	50 (51.0)	138 (37.4)	0.007	42 (42.4)	285 (42.7)	0.54
PAD treatment after enrollment						
Cilostazol	6 (6.1)	56 (15.2)	0.017	8 (8.1)	77 (11.5)	0.31
Antiplatelet therapy	80 (80.8)	288 (78.0)	0.55	79 (79.8)	504 (75.2)	0.32
Statin	74 (74.7)	296 (80.2)	0.23	75 (75.8)	554 (82.7)	0.10
Smoking cessation advice (among smokers)	47 (88.7)	106 (65.4)	0.001	40 (80.0)	191 (62.4)	0.015
Unsupervised PAD exercise therapy	31 (31.3)	169 (45.6)	0.010	31 (31.0)	218 (32.4)	0.78
Supervised PAD exercise therapy	20 (20.2)	75 (20.2)	1.00	19 (19.0)	158 (23.5)	0.32
Invasive treatment	16 (19.8)	66 (19.9)	0.97	22 (25.3)	119 (19.3)	0.20
Surgical treatment	0 (0.0)	6 (1.8)	0.60	5 (5.7)	18 (2.9)	0.19
Endovascular treatment	16 (19.8)	62 (18.7)	0.83	18 (20.7)	104 (16.9)	0.38
Depression severity and treatment at baseline						
PHQ-8 depression score, mean±SD	14.2±3.7	3.4±2.7	<0.001	14.1±3.7	2.7±2.7	<0.001
Baseline antidepression treatments						
None	54 (54.5)	277 (74.7)	0.001	66 (66.0)	594 (88.3)	<0.001
Pharmacologic	24 (24.2)	55 (58.5)		17 (17.0)	54 (8.0)	
Counseling	4 (4.0)	9 (9.6)		3 (3.0)	9 (1.3)	
Both	17 (17.2)	30 (31.9)		14 (14.0)	16 (2.4)	

Values are listed as number (percentage), unless otherwise described. ABI indicates ankle-brachial index; CAD, coronary artery disease; PAD, peripheral artery disease; and PHQ-8, 8-Item Patient Health Questionnaire.

*Includes all covariates used in modeling by PHQ-8 ≥10. Covariates include age, country, White race, avoiding care because of cost, high school education, exacerbation of symptoms, bilateral disease, smoking, history of diabetes mellitus, coronary artery disease, sleep apnea, and ABI. Continuous variables were compared using the Student t test. Categorical variables were compared using the χ^2 or the Fisher exact test (race, health insurance, smoking status, amputation, PAD endarterectomy, and duration of pain).

breakdown of the types of depression treatment by sex and depressive symptom status for this cohort is provided in Table 2. In both men and women, patients with depressive symptoms were more likely to be younger, avoid care because of cost, and be sedentary compared with their respective counterparts without depressive symptoms; both men and women with depressive symptoms were less likely to be married compared with those without such symptoms (Table 2).

Unadjusted mean PAQ health status scores by baseline depressive symptoms and by sex are presented in Table 3. Both men and women with depressive symptoms (PHQ-8 ≥10 at baseline) had consistently lower unadjusted PAQ health status scores than those without significant depressive symptoms (mean differences ranging between 17.8 and 26.9) for the overall group. In women with and without depressive symptoms, mean differences ranged between 17.8 and 24.2, which were similar to the differences in men (mean differences ranged between 18.9 and 26.9). Women with depressive symptoms had lower PAQ summary scores compared with men with depressive symptoms, albeit only reaching statistical significance at 12 months (P=0.038). For the EQ-5D VAS scores, mean differences between patients with and without depressive symptoms ranged between 12.3 and 13.1 for women and between 14.3 and 19.5 for men and were also similar, except for the baseline levels (difference in scores for men with and without depressive symptoms was greater than for women with and without depressive symptoms [Table 3]).

For the repeated measures model, we first tested the 3-way interaction between sex×depressive symptoms×time, evaluating whether the magnitude of health status changes over time differed by sex. This interaction term was nonsignificant (P=0.39), suggesting no differences in the sex-associated disparities over time. In the final adjusted repeated measures model, the 2-way interaction between time and sex as well as time and depressive symptoms remained significant. The 2-way interaction between sex×depression was not significant

(P=0.58). Patients with depressive symptoms at the time of their PAD presentation consistently had lower PAQ health status scores at each time point compared with scores at baseline (adjusted mean score, 25.4 [Interquartile range: 21.3–29.4] versus 46.7 [Interquartile range: 43.6–49.9]; P<0.0001) and at 12 months of follow-up (adjusted mean score, 50.0 [Interquartile range: 45.3–54.6] versus 66.1 [Interquartile range: 62.8–69.5]; P<0.0001), amounting to differences between groups ranging from 16.3 to 21.4 (Figure). In this model, the interaction between depressive symptoms and time was also significant (P<0.0001), indicating that improvement in health status score trajectories over time lagged behind in those with depressive symptoms versus those who did not experience such symptoms. For the model with EQ-5D VAS scores over time, results largely mirrored the PAQ results (Figure).

As part of the descriptive sensitivity analyses, we looked at both PAQ summary scores and EQ-5D VAS over time by severity of depressive symptoms over time (no depressive symptoms, PHQ-8 score <5; mild depressive symptoms, PHQ-8 score ≤5–≤9; moderate-severe depressive symptoms, PHQ-8 score ≥10) (Tables S1 through S3). In a post hoc analysis, women with moderate-severe depressive symptoms had statistically significant lower PAQ summary scores compared with all other groups, except for men whose depressive symptoms were also moderate-severe (P=0.088). This was similar at 3 and 6 months. At 1 year, women with moderate-severe depressive symptoms had statistically lower PAQ summary scores at all time points. For the mean EQ-5D VAS levels, women with moderate-severe

Table 3. Unadjusted Mean PAQ and EQ-5D VAS Scores in Patients With and Without Depressive Symptoms at Baseline and 3, 6, and 12 Months, Stratified by Sex

| Variable | PHQ-8 Score ≥10 (Baseline) | | | | | | P Value* |
| | Women | | | Men | | | |
	Yes (n=99)	No (n=371)	Mean Differences	Yes (n=100)	No (n=673)	Mean Differences	
PAQ summary score, mean±SD							
Baseline	24.7±16.8	48.9±19.7	24.2	29.2±19.5	56.1±19.3	26.9	0.09
3 mo	45.9±27.5	66.6±23.9	20.7	51.2±28.6	71.7±21.7	20.5	0.22
6 mo	52.7±26.8	70.5±24.4	17.8	53.1±25.7	73.7±22.1	20.6	0.93
12 mo	47.0±28.2	68.7±24.8	21.7	56.6±28.0	75.5±22.7	18.9	0.038
EQ-5D VAS, mean±SD							
Baseline	55.7±21.9	68.0±18.7	12.3	49.7±19.8	69.2±17.3	19.5	0.047
3 mo	58.5±19.9	70.8±18.9	12.3	53.8±23.1	72.8±15.6	19	0.16
6 mo	60.4±21.3	73.2±17.2	12.8	57.2±22.2	71.5±16.4	14.3	0.37
12 mo	58.5±19.5	71.6±17.9	13.1	58.1±18.9	72.5±16.1	14.4	0.89

Continuous variables were compared using Student t test. PAQ indicates Peripheral Artery Questionnaire; PHQ-8, 8-Item Patient Health Questionnaire; and VAS, Visual Analogue Scale.

*P values for differences in PAQ summary and EQ-5D VAS scores between women and men with depressive symptoms (PHQ-8 ≥10).
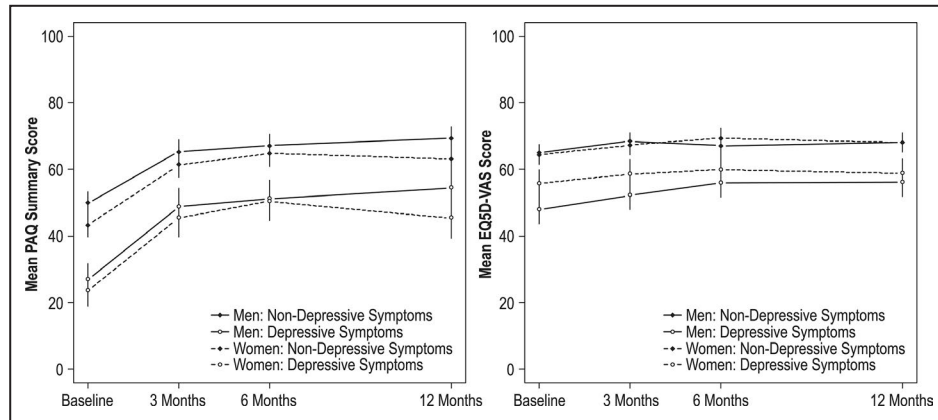
Figure. Adjusted mean Peripheral Artery Questionnaire (PAQ) summary and EQ-5D Visual Analogue Scale (VAS) scores at baseline and 3, 6, and 12 months for patients with (8-Item Patient Health Questionnaire [PHQ-8] score ≥10) and without (PHQ-8 score <10) baseline depressive symptoms.

Covariates in the model included age, country, race, avoiding care because of cost, high school education, ankle-brachial index, exacerbation of symptoms, bilateral disease, smoking, history of diabetes mellitus, coronary artery disease, and sleep apnea.

depressive symptoms had lower scores compared with all other groups, but no differences were noted for men whose depressive symptoms were moderate-severe at 3 and 12 months or for men with mild symptoms at 6 months (Table S4).

For the sensitivity analysis as it relates to our GLM modeling, we examined the association between sex and health status outcomes over time, without including depressive symptoms in the fully adjusted GLM. In that model, women scored an average of 6.4 points lower than men (women versus men, −6.4; 95% CI, −8.5 to −4.3; $P<0.0001$). After adding depressive symptoms to the adjusted model, this difference decreased to 5.2 points in the adjusted model (women versus men, −5.2; 95% CI, −7.2 to −3.3; $P<0.0001$). Depressive symptoms explained 19% ([6.4−5.2]/6.4) of the difference in outcomes between the 2 sexes.

To assess for nonresponse bias, we performed a second sensitivity analysis, comparing those with complete follow-up with those without complete follow-up. Large differences (standardized difference >10%) between the 2 groups, which were not already adjusted for in the main analyses, were duration of pain, lesion site, Rutherford category, history of chronic kidney disease, and history of amputation (Table S5). Addition of these covariates to the main analyses yielded similar results for both PAQ summary scores and EQ-5D VAS at baseline and 3, 6, and 12 months (Figure and Figure S1).

DISCUSSION

Our study demonstrates that a disproportionately higher percentage of women are affected by depressive symptoms when they seek specialty care for new or worsening PAD symptoms, with rates almost twice that observed in men. Experiencing clinically significant depressive symptoms is associated with enormous gaps in their 1-year health status recovery patterns compared with health status levels that are typically seen in their nondepressed counterparts, up to twice the magnitude that is defined as a minimally clinically important difference (Poghni, Peri-Okonny, MD, unpublished data, 2019), leaving patients with depressive symptoms at a disadvantaged position to optimally benefit from the PAD treatments that are offered to them. Although the effect size for the association between depressive symptoms and health status changes over time did not differ by sex, women are disproportionately affected given the increased prevalence of depressive symptoms observed in women. Depressive symptoms also explained about a fifth of the variation seen in health status differences by sex documented in the year following a PAD diagnosis.

Our study provides a unique perspective; it prospectively followed up patients who were dealing with new or recurrent symptoms of PAD and were actively seeking specialty care. This similar time point of identification in the clinical pathway for PAD allowed us to prospectively reconstruct the 1-year health status trajectory in men and women by patients' depressive symptoms at the time of seeking PAD care. Also notable is that our patients were included before they were assigned to treatment, and regardless of whether they underwent invasive versus noninvasive management of their disease, which is different from most other available PAD databases.[38,39]

Despite the enormous patient and economic burden associated with both depression[40] and PAD,[10,41] we are just starting to understand the potential impact of how mental health concerns may complicate PAD treatment and outcomes. Although it has been demonstrated in coronary artery disease that depressive symptoms are disproportionately present in women compared with men, and that these symptoms are linked with adverse clinical and health status outcomes,[19,42–44] the association between depressive symptoms and PAD-specific health status outcomes and how this may differ by sex have not been studied in PAD.

Various reasons for an increased depressive symptom burden in women with cardiovascular disease have been studied. Of the factors studied, socioeconomic factors may partially explain as to why women may experience this increased vulnerability.[45,46] In support of this, we found that less than half of the overall female cohort as well as only one third of those with clinically relevant depressive symptoms were married, and more women than men avoided care because of cost. It is unknown whether any biological sex differences specific to PAD explain some of the differences observed. We did demonstrate in our study that women had lower ABIs, indicating more advanced disease as well as bilateral disease. We did not find any evidence for differential PAD treatment patterns or quality of PAD care by sex. A bias toward undertreatment of depressive symptoms in the context of PAD specialty care was present as only a third of patients were receiving care and/or follow-up for their depressive symptoms, with the lowest treatment rates for men.

Having a depressed mood has potentially major implications for the success of patients' PAD rehabilitation process and their PAD functioning over time. Depressive symptoms marked a suboptimal PAD recovery pathway, with differences as large as 16 to 21 points on the PAQ summary scale 1 year following active PAD treatment, differences that are almost twice the minimally clinically important difference, as defined from the patients' perspective. To put these findings further in perspective: in the CLEVER (Supervised Exercise, Stent Revascularization, or Medical Therapy for Claudication Due to Aortoiliac Peripheral Artery Disease: A Randomized Clinical Trial),[47] differences at 18 months between patients treated with optimal medical therapy only versus those who underwent peripheral stenting were 24 points on the PAQ summary scale; and for optimal medical therapy versus supervised exercise therapy, 13 points. Such large discrepancies in PAD health status outcomes related to patients' depressive mood demand for more proactive PAD care that can detect and support patients in need, so as to allow them to be successful in managing their PAD.

Although the magnitude of the effect on health status changes over time for depressive symptoms in men and women was not different, women had a higher prevalence of symptoms and higher mean depressive symptom scores at all time periods. Sex differences in PAD-specific health status were also partially explained by depressive symptoms (19%). Whether this has implications for patients' long-term PAD outcomes needs to be further established, including intervention studies that would include and test depression interventions as a way to maximize PAD rehabilitation outcomes. Preliminary studies have shown that depression is associated with an adverse PAD prognosis as well as with an increased risk of experiencing adverse cardiovascular events.[29,48,49] In a recent study, depression was independently associated with an elevated risk of amputation, with an even higher risk in those who were not treated with antidepressents.[50] Whether the higher rates of depressive symptoms contribute to more advanced disease,[51] lower physical functioning,[52] and poorer outcomes after lower-extremity revascularization[17,18] and higher in-hospital mortality[51] in women remains to be seen. Multidirectional relationships between depressive symptoms and cardiovascular outcomes have been described before in cardiovascular disease, but to a much lesser extent in PAD.[53] Previous studies were cross-sectional, were small sampled, or did not focus on sex differences. In coronary artery disease, sex differences in quality of care, biological differences, and differences in disease manifestations, as well as interrelatedness with women's psychosocial profiles, and subsequent clinical outcomes have been well described,[54] but these associations have yet to be fully studied and understood in PAD.

Future work needs to explore whether these same mechanisms explain women's increased vulnerability to depressive symptoms in PAD. It is also important to increase the knowledge and awareness of vascular specialists who treat patients with PAD, such that they know that women have a higher prevalence of depressive symptoms from an epidemiological standpoint such that they could be referred for further depression evaluation and treatment as part of an integrated care vision that maximized patients' outcomes.

Our study must be interpreted in the light of several potential limitations. Our study cohort included patients seen at vascular specialty clinics, and our findings may not be representative of the general PAD population who may not have access to specialty clinics. For this study, we focused on depressive symptoms, and we acknowledge that there are a myriad of mental health concerns, as well as other unmeasured psychosocial and clinical factors, that may be intertwined with depressive symptoms, or that may have also impacted patients' health status.

In summary, our findings indicate that the burden of depressive symptoms in PAD is substantial, and patients affected by them, especially women, have distinctly worse PAD-specific health status after receiving PAD specialty care. Effect sizes were large and carried over at each follow-up point in the year after seeking PAD treatment. There is a need to explore mechanisms of this increased vulnerability in women. These have been extensively described in other atherosclerotic diseases (eg, exposure to psychosocial stressors and socioeconomic factors), like acute myocardial infarction.[54] The problem is not limited to women alone; among men, too, patients who are dealing with depressive symptoms have worse PAD health outcomes over time. Depressive symptoms in older, chronic disease populations, such as PAD, should be a continuous focus of its multidisciplinary treatment so as to ensure quality PAD care and optimize outcomes. In conclusion, depression warrants screening and treatment in its own right, but especially so in PAD, it is imperative to pay attention to this problem.

ARTICLE INFORMATION

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Disclosures

Supplementary Materials

Tables S1–S5
Figure S1

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Supplemental Material

Table S1. **Health Status Outcomes (PAQ summary scores and EQ-5D VAS) by Severity of Depressive Symptoms at Baseline, 3, 6 and 12 months for the Entire Cohort.**

| | PHQ-8 Depressive Symptoms Severity (Mean±SD) | | |
	None n=767	Mild n=277	Moderate-Severe n=199
*PAQ Summary (Baseline)	57.4 ± 18.8	42.9 ± 18.3	26.9 ± 18.3
PAQ Summary (3 Months)	72.5 ± 21.6	62.5 ± 23.6	48.7 ± 28.1
PAQ Summary (6 Months)	75.1 ± 21.7	65.4 ± 24.9	52.9 ± 26.1
PAQ Summary (12 Months)	75.8 ± 22.2	65.4 ± 26.0	51.9 ± 28.4
EQ5D VAS (Baseline)	71.2 ± 17.1	62.1 ± 18.0	52.8 ± 21.0
EQ5D VAS (3 Months)	74.4 ± 16.0	65.4 ± 17.5	56.1 ± 21.7
EQ5D VAS (6 Months)	74.1 ± 15.7	66.2 ± 17.9	58.8 ± 21.8
EQ5D VAS (12 Months)	74.7 ± 15.4	65.0 ± 18.3	58.3 ± 19.1

Depressive Symptom Severity was defined as; No Depressive Symptoms (PHQ-8 score < 5); Mild Depressive Symptoms (PHQ-8 score ≥ 5 and ≤ 9); Moderate-Severe (PHQ-8 score ≥ 10).

PAQ, Peripheral Artery Questionnaire; PHQ-8, 8-item Patient Health Questionnaire; VAS, Visual Analogue Scale.

* P-values for the overall comparisons and for pairwise comparisons between "None" and "Mild" depressive symptoms were derived (all p-vales <0.001)

Table S2. Health Status Outcomes (PAQ summary scores and EQ-5D) by severity of depressive symptoms at baseline, 3, 6 and 12 months for women.

	PHQ-8 Depressive Symptoms Severity (Mean±SD)		
	None n= 257	Mild n= 114	Moderate-Severe n= 99
*PAQ: Summary (Baseline)	53.0 ± 19.4	39.5 ± 17.1	24.7 ± 16.8
PAQ: Summary (3 Months)	69.9 ± 23.0	58.8 ± 24.3	45.9 ± 27.5
PAQ: Summary (6 Months)	73.7 ± 22.7	62.7 ± 26.8	52.7 ± 26.8
PAQ: Summary (12 Months)	71.5 ± 23.8	62.1 ± 26.0	47.0 ± 28.2
EQ5D VAS (Baseline)	70.8 ± 18.1	61.8 ± 18.7	55.7 ± 21.9
EQ5D VAS (3 Months)	73.1 ± 18.4	65.4 ± 19.1	58.5 ± 19.9
EQ5D VAS (6 Months)	74.8 ± 16.2	69.1 ± 18.7	60.4 ± 21.3
EQ5D VAS (12 Months)	74.9 ± 16.1	63.9 ± 19.5	58.5 ± 19.5

Depressive Symptom Severity was defined as; No Depressive Symptoms (PHQ-8 score < 5);

Mild Depressive Symptoms (PHQ-8 score ≥ 5 and ≤ 9); Moderate-Severe (PHQ-8 score ≥ 10)

*P-values for the overall comparisons and for pairwise comparisons between "None" and "Mild"

depressive symptoms were derived (all p-values <0.001).

Continuous variables compared using Linear Trend test.

Categorical variables compared using Mantel-Haenszel Trend test.

PAQ, Peripheral Artery Questionnaire; PHQ-8, 8-Item Patient Health Questionnaire; VAS,

Visual Analogue Scale.

Table S3. **Health Status Outcomes (PAQ summary scores and EQ-5D VAS) by severity of depressive symptoms at baseline, 3, 6 and 12 months for men.**

	PHQ-8 Depressive Symptoms Severity (Mean±SD)		
	None n=510	Mild n=163	Moderate-Severe n=100
*PAQ Summary (Baseline)	59.6 ± 18.1	45.4 ± 18.9	29.2 ± 19.5
PAQ Summary (3 Months)	73.8 ± 20.9	65.0 ± 22.9	51.2 ± 28.6
PAQ Summary (6 Months)	75.8 ± 21.3	67.1 ± 23.6	53.1 ± 25.7
PAQ Summary (12 Months)	77.9 ± 21.0	67.7 ± 25.9	56.6 ± 28.0
EQ5D VAS (Baseline)	71.5 ± 16.6	62.4 ± 17.5	49.7 ± 19.8
EQ5D VAS (3 Months)	75.1 ± 14.6	65.3 ± 16.5	53.8 ± 23.1
EQ5D VAS (6 Months)	73.8 ± 15.5	64.3 ± 17.1	57.2 ± 22.2
EQ5D VAS (12 Months)	74.6 ± 15.0	65.8 ± 17.6	58.1 ± 18.9

Depressive Symptom Severity was defined as; No Depressive Symptoms (PHQ-8 score < 5); Mild Depressive Symptoms (PHQ-8 score ≥ 5 and ≤ 9); Moderate-Severe (PHQ-8 score ≥ 10).

Continuous variables compared using Linear Trend test.

Categorical variables compared using Mantel-Haenszel Trend test.

PHQ-8, 8-Item, Patient Health Questionnaire; SD, Standard Deviation; PAQ, Peripheral Artery Questionnaire; VAS, Visual Analogue Scale.

*P-values for the overall comparisons and for pairwise comparisons between "None" and "Mild" depressive symptoms were derived (all p-vales <0.001).

Table S4. Post Hoc Testing for Comparisons of Differences in Mean Health Status Scores (PAQ summary scores and EQ-5D VAS) and Standard Deviations By Sex and Severity of Depressive Symptoms at baseline, 3, 6 and 12 months.

	PAQ Summary Mean Differences (SE)	P-value	EQ-5D VAS Mean Differences ± SD	P-value
Baseline				
Men (severe)	4.45 (2.61)	0.088	-6.05 (2.61)	0.020
Men (mild)	20.67 (2.35)	<0.0001	6.64 (2.33)	0.0045
Men (none)	34.87 (2.02)	< 0.0001	15.70 (2.01)	<0.0001
Women (mild)	14.77 (2.53)	<0.0001	6.09 (2.51)	0.015
Women (none)	28.32 (2.18)	< 0.0001	15.07 (2.16)	<0.0001
3 Months				
Men (severe)	5.30 (3.51)	0.13	-4.69 (2.64)	0.07
Men (mild)	19.03 (3.16)	<0.0001	6.81 (2.39)	0.004
Men (none)	27.88 (2.75)	<0.0001	16.60 (2.07)	<0.0001
Women (mild)	12.82 (3.44)	0.0002	6.84 (2.60)	0.0087
Women (none)	23.93 (2.95)	<0.0001	14.55 (2.22)	<0.0001
6 Months				
Men (severe)	0.37 (3.69)	0.92	-3.15 (2.77)	0.26
Men (mild)	14.38 (3.27)	<0.0001	-3.89 (2.45)	0.11

	PAQ Summary Mean Differences (SE)	P-value	EQ-5D VAS Mean Differences ± SD	P-value
Men (none)	23.14 (2.86)	<0.0001	13.39 (2.14)	<0.0001
Women (mild)	10.06 (3.58)	0.005	8.73 (2.69)	0.0012
Women (none)	21.04 (3.06)	<0.0001	14.46 (2.29)	<0.0001
12 Months				
Men (severe)	9.59 (3.89)	0.013	-0.41 (2.74)	0.88
Men (mild)	20.66 (3.44)	<0.0001	7.35 (2.42)	0.0024
Men (none)	30.91 (3.01)	<0.0001	16.12 (2.11)	<0.0001
Women (mild)	15.12 (3.72)	<0.0001	5.39 (2.61)	0.039
Women (none)	24.44 (3.22)	<0.0001	16.44 (2.26)	<0.0001

Depressive Symptom Severity was defined as; No Depressive Symptoms (PHQ-8 score < 5); Mild Depressive Symptoms (PHQ-8 score ≥ 5 and ≤ 9); Moderate-Severe (PHQ-8 score ≥ 10). The reference category was women with severe depressive symptoms for all comparisons.

PHQ-8, 8-Item Patient Health Questionnaire; PAQ, Peripheral Artery Questionnaire; VAS, Visual Analogue Scale; SD, Standard Error.

Table S5. Baseline Characteristics for Those With Complete and Incomplete Follow-Up.

	Follow-up		Total	p-value	Std. Diff %
	Complete n=980	Incomplete n=263	n=1243		
Age, years Mean±SD	67.8± 9.2	66.8 ±10.3	67.6 ±9.4	0.107	10.8
Race: White	821 (83.8)	198 (75.3)	1019 (82.0)	0.001	21.2
Country					
(1) United States	592 (60.4)	183 (69.6)	775 (62.3)		
(2) Netherlands	311 (31.7)	63 (24.0)	374 (30.1)		
(3) Australia	77 (7.9)	17 (6.5)	94 (7.6)	0.023	19.4
Health Insurance	974(994)	262(99.6)	1236(99.4)	1.000	3.3
Education High School or above	677 (69.5)	174 (67.2)	851 (69.0)	0.471	5.0
Married	580 (59.5)	152 (58.0)	732 (59.2)	0.666	3.0
Working for pay	236 (24.2)	57 (21.8)	293 (23.6)	0.416	5.7
Avoid care due to cost	128 (13.2)	46 (17.6)	174 (14.1)	0.069	12.2
Smoke status					
(1) Never	104 (10.6)	28 (10.7)	132 (10.6)		
(2) Former	526 (53.7)	122 (46.6)	648 (52.2)		
(3) Current	349 (35.6)	112 (42.7)	461 (37.1)	0.089	15.2

Duration of pain					
(1) < 1 Month	21 (2.5)	9 (4.0)	30 (2.8)		
(2) 1 - 6 Months	249 (29.5)	71 (31.4)	320 (29.9)		
(3) 7 - 12 Months	153 (18.1)	35 (15.5)	188 (17.6)		
(4) >12 Months	420 (49.8)	111 (49.1)	531 (49.7)	0.501	11.1
ABI					
Mean±SD	0.67 ±0.19	0.66 ±0.19	0.67 ±0.19	0.805	1.7
Symptoms					
(1) New-onset	519 (53.0)	135 (51.3)	654 (52.6)		
(2) Exacerbation	461 (47.0)	128 (48.7)	589 (47.4)	0.638	3.3
Lesion Site					
(1) Proximal	270 (27.7)	77 (29.5)	347 (28.1)		
(2) Distal	277 (28.5)	95 (36.4)	372 (30.1)		
(3) Both	426 (43.8)	89 (34.1)	515 (41.7)	0.010	21.2
Function: Symptomatic leg					
(1) Right leg	242 (24.7)	62 (23.6)	304 (24.5)		
(2) Left leg	252 (25.7)	59 (22.4)	311 (25.0)		
(3) Both legs	486 (49.6)	142 (54.0)	628 (50.5)	0.407	9.4
Function: Rutherford category					
(1) Mild claudication	215 (22.2)	67 (26.3)	282 (23.1)		
(2) Moderate claudication	478 (49.4)	123 (48.2)	601 (49.1)		
(3) Severe claudication	275 (28.4)	65 (25.5)	340 (27.8)	0.346	10.1

|					
CAD	381 (38.9)	105 (39.9)	486 (39.1)	0.757	2.1
Amputation	8 (0.8)	8 (3.0)	16 (1.3)	0.009	16.2
Dyslipidemia	779 (79.5)	208 (79.1)	987 (79.4)	0.886	1.0
Hypertension	788 (80.4)	205 (77.9)	993 (79.9)	0.376	6.1
Diabetes	319 (32.6)	96 (36.5)	415 (33.4)	0.227	8.3
Chronic kidney disease	99 (10.1)	39 (14.8)	138 (11.1)	0.030	14.3
Chronic back pain	136 (13.9)	33 (12.5)	169 (13.6)	0.576	3.9
Sleep apnea	82 (8.4)	18 (6.8)	100 (8.0)	0.419	5.7
PHQ-8 Depression Score Mean±SD	4.3 ±4.6	6.2 ±6.0	4.7± 5.0	<0.001	34.6
PAQ Summary Score Mean±SD	50.3 ±21.5	45.5 ±22.6	49.3 ±21.8	0.001	21.8
EQ-5D VAS Mean±SD	67.2± 18.7	62.7±20.9	66.2 ±19.3	0.001	22.6

Continuous variables were compared using the Student's T-test.

Categorical variables were compared using the Chi-square or Fisher's exact test (Health insurance and Amputation)

SD, Standard Deviation; Std. Diff, Standardized Difference; ABI, Ankle Brachial Index; CAD, Coronary Artery Disease; PHQ-8, 8-item Patient Health Questionnaire; PAQ, Peripheral Artery Questionnaire; VAS, Visual Analogue Scale.

Figure S1. **Sensitivity Plots Showing Differences in PAQ summary scores (A) and EQ-5D VAS (B) after additional adjustment for co-variates with a > 10% standardized difference between those with complete versus incomplete follow-up.**

A.
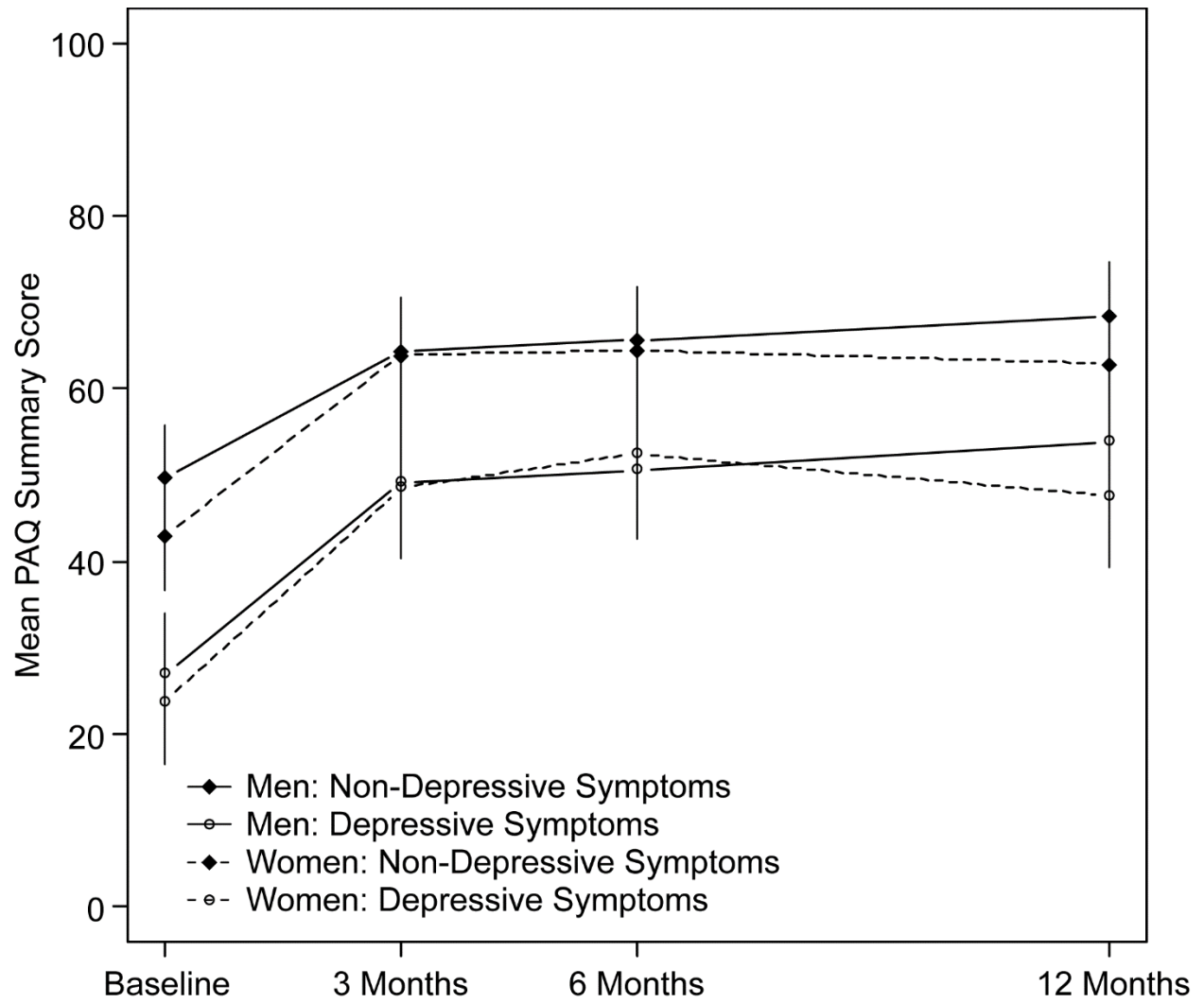
B.
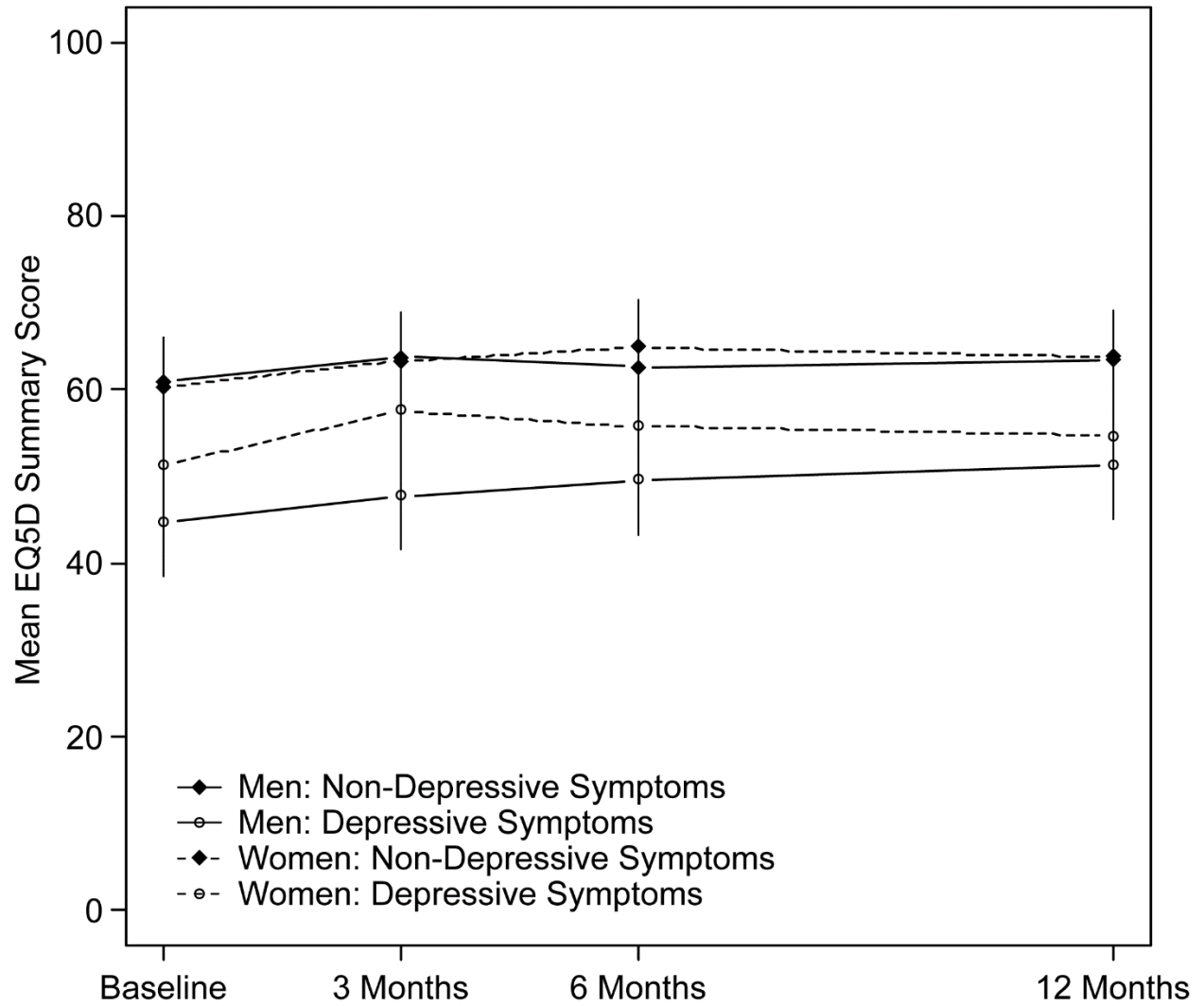
These co-variates included duration of pain, lesion site, Rutherford category, history of chronic kidney disease and history of amputation. Abbreviations: PAQ, Peripheral Artery Questionnaire; VAS: Visual Analogue Scale.