

Research report

Depressive symptoms in peripheral arterial disease: A follow-up study on prevalence, stability, and risk factors

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Abstract

Background: Depressive symptoms are associated with poor prognosis in coronary artery disease, but there is a paucity of research on these symptoms in peripheral arterial disease (PAD). We examined the clinical correlates and 18-month course of depressive symptoms in PAD patients.

Methods: 166 patients with symptomatic lower-extremity PAD (39% women; *M* age=64.9 ± 10 years) completed the 10-item Center for Epidemiological Studies Depression scale. A score ≥4 indicates clinically relevant depressive symptoms. Depressive symptoms were re-assessed at 6, 12, and 18 months follow-up. Ankle-brachial index (ABI) and treadmill walking distance were used to assess PAD severity.

Results: At baseline, depressive symptoms (CES-D ≥4) were present in 16% of the patients. Depressed patients performed worse regarding pain free ($p=0.003$) and maximum ($p=0.005$) walking distance. After adjusting for age, sex, education, ABI, psychotropic medication use, cardiovascular risk factors, and comorbidity, depressive symptoms remained stable in initially depressed patients. Using mixed modelling, three subgroups were identified in the total sample. The majority of PAD patients did not have depressive symptoms (58%), but there were two groups who persistently experienced either subclinical (27%) or clinically manifest (15%) depressive symptoms.

Limitations: Only baseline data of ABI and treadmill walking performance were available.

Conclusions: Depressive symptomatology was present in a substantial number of PAD patients, tended to be stable, and was associated with reduced walking distance. These apparently evident results are overlooked thus far in this patient group and deserve further attention in research and clinical care.

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Keywords: PAD; Intermittent claudication; Depression; Depressive symptoms; Walking distance

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1. Introduction

Lower-extremity peripheral arterial disease (PAD) occurs as a result of arterial narrowing that restricts blood flow to the lower limbs and is an important indicator for the presence of systemic atherosclerotic disease that leads to an increased risk of cardiovascular morbidity and mortality (Belch et al., 2003; Meru et al., 2006). Manifestations of PAD include (i) asymptomatic arterial insufficiency, (ii) symptomatic disease presenting as intermittent claudication (IC), and (iii) critical leg ischemia (Belch et al., 2003). PAD requires antiplatelet therapy (Belch et al., 2003) and aggressive risk factor modification, such as addressing smoking cessation, and treating associated conditions, like hyperlipidemia and hypertension (De Backer et al., 2004). In addition to traditional risk factors, there is increasing evidence that psychological risk factors such as major depression and even subclinical depressive symptoms are important determinants of prognosis in patients with ischemic heart disease (Vaccarino et al., 2001) and other vascular diseases, e.g. stroke and vascular dementia, especially in the elderly (Thomas et al., 2004). Plausible mechanisms by which depression may lead to worse prognosis are raised cortisol levels, platelet and clotting changes, reduced heart rate variability, and unhealthy lifestyle choices (Thomas et al., 2004). There is a vast literature that demonstrates that the relationship between depression and vascular disease should be understood as bi-directional. Depression predisposes to later vascular disease and may worsen pre-existing disease; moreover, vascular disease may lead to or aggravate depressive symptoms (Thomas et al., 2004). Recent findings in myocardial infarction patients (Kaptein et al., 2006) and in older adults suggest that course (i.e., increase of depressive symptoms, persistence) rather than baseline levels of depression seem to matter in terms of cardiovascular prognosis and mortality (Geerlings et al., 2002). In contrast to the literature found in old age, coronary heart disease, stroke, and vascular dementia, little is known about the presence and course of depressive symptoms and their possible role for health status and prognosis in PAD.

Preliminary evidence suggests that depressive symptoms may be common among patients with PAD (Cherr et al., 2007; McDermott et al., 2003) and may be associated with functional impairment (McDermott et al., 2003), worse patency rates (Cherr et al., 2007), and poor quality of life (Aquarius et al., 2007). However, longitudinal research on the prevalence and course of depressive symptoms in PAD is lacking (Cherr et al., 2007). Studying the course of depressive symptomatology,

together with its clinical correlates, may unravel the range of mood problems in PAD, possibly associated with the burden of lower-extremity PAD. Therefore, the aim of the present study was (i) to examine the 18-month course of clinically relevant depressive symptoms in relation to important clinical correlates in PAD patients and (ii) to identify distinctly different trajectories of depressive symptoms within the continuum of depressive scores rather than concentrating on trajectories based on baseline depressive scores alone using a mixed modelling procedure.

2. Methods

2.1. Patients

Between September 2001 and March 2004, 251 patients with IC, a common form of PAD, presented at the vascular outpatient clinic of the department of surgery of the St. Elisabeth Hospital in Tilburg, the Netherlands. Inclusion criteria were IC diagnosis, which was defined as pain occurring during exertion when blood flow velocity increases across a stenotic lesion in the legs, and an abnormal resting Ankle–Brachial Index (ABI) (<0.90) or an abnormal post-exercise ABI (ABI decrease of 15–20% after exercise) (Norgren et al., 2007). An ABI value of <0.90 is 95% sensitive to detect PAD (Belch et al., 2003). Patients received the advice to start exercise training and to quit smoking. No supervised exercise training programs were used.

Exclusion criteria were cognitive impairment, the presence of severe psychopathological (e.g. psychosis, suicidal ideation) or invalidating somatic comorbidities (e.g. cancer), participation in another study, and insufficient knowledge of the Dutch language. Of 251 patients with PAD, eight (3%) were excluded due to cognitive impairment ($n=4$), recent myocardial infarction ($n=1$), visual problems ($n=1$), influenza ($n=1$), and participation in another study ($n=1$). Of the remaining patients, 195 (80%) agreed to participate. Four patients (2%) did not complete the baseline measurement of depressive symptoms and 25 (13%) patients had two or more assessment points that were lacking [deceased ($n=8$), hospitalized ($n=2$), refused follow-up ($n=15$)], leaving 166 patients (39% women; M age = 64.9 ± 10.0 years). No significant differences were present between the patients who refused further follow-up ($n=15$) and the total sample, except for maximum walking distance (M drop-outs = 388.5 m vs. M total sample = 196.2 m, $p < 0.0001$). The study was approved by the local ethics committee. The study was conducted conform to the Helsinki Declaration and all

participants signed informed consent. All 166 PAD patients completed a measure of depressive symptoms at baseline and six, 12, and 18 months follow-up.

2.2. Measures

2.2.1. Disease severity

Resting ABI and pain free (PFWD) and maximum walking distance (MWD) were determined in all patients at baseline as indices of PAD severity. The ABI is defined as the ratio of the ankle systolic blood pressure to the brachial systolic blood pressure and has a normal resting value of about 1.0 to 1.5 (Heald et al., 2006). The ABI is sensitive to identify patients with PAD and is an important predictor of future cardiovascular events (Heald et al., 2006). A handheld Doppler device (Imexlab 9000; Imex Medical Systems Inc, Golden Colorado) was utilised to obtain systolic pressures in the right and left brachial and posterior tibial and dorsalis arteries. The ABI was calculated by dividing the highest of posterior tibial and dorsalis pedis ankle pressures in each leg by the highest brachial pressure. The ABI at rest was measured while the patient was lying in the supine position. The lowest leg ABI was used in the analysis. PFWD and MWD were determined by means of a treadmill exercise test; during this test, patients had to walk 3.5 km/h on a 5% incline, with a maximum of 1000 m (Breek et al., 2002). A decrease in ABI of 15%–20% after exercise is diagnostic of PAD (Norgren et al., 2007). Mild and moderate/severe claudication was defined using the Fontaine Stages IIa and IIb (Norgren et al., 2007).

2.2.2. Cardiovascular risk factors and comorbidity

In the present study, diabetes mellitus, smoking, hypertension, hyperlipidemia, and cardiac, carotid, renal, and pulmonary status were measured at baseline in all patients according to the Society for Vascular Surgery/North American chapter of the International Society for Cardiovascular Surgery (SVS/ISCVS) recommended standards (Rutherford et al., 1997) (Appendix A). Because of its known association with depressive symptoms (Kronish et al., 2006), information about smoking abstinence at baseline was documented by patients' medical records. The presence of back, knee or hip symptoms, unrelated to vascular disease (e.g. knee or hip arthrosis) was documented from patients' medical files because these symptoms are important for patient-based outcomes in patients with intermittent claudication (Breek et al., 2002). In addition to age and educational level, information about marital status was obtained from the participants.

2.2.3. Depressive symptoms

Depressive symptoms were measured using a Dutch version of the Center for Epidemiological Studies Depression Scale (CES-D); the CES-D was originally developed to assess the present levels of depressive symptoms in the general population (Radloff, 1977). In this questionnaire, the focus is on the affective component, the depressive mood (Radloff, 1977). The CES-D questionnaire is widely used and easy to administer, especially in older adults (Irwin et al., 1999). In the present study, a simplified and abbreviated version of the original CES-D – the Boston 10-item form – was used (Kohout et al., 1993). This version was developed to reduce response burden and consists of 10 dichotomous response options. Patients were asked to indicate (yes or no) if they had experienced each symptom “much of the time during the past week” (Kohout et al., 1993). The CES-D 10-item version has good reliability (Cronbach's $\alpha=.88$) and shows an excellent sensitivity (97%) to detect major depression according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria (American Psychiatric Association, 1994). The Cronbach's α in the present study also proved to be good ($\alpha=.83$). A cut-off score ≥ 4 indicates clinically relevant depressive symptoms without losing specificity and sensitivity; using this cut-off score, the sensitivity and specificity for the diagnosis of major depression in persons 60 years and older was 100% and 92% respectively (Cheng and Chan, 2005). Test–retest reliability of the CES-D 10-item version is high (Pearson $r=0.83$) (Irwin et al., 1999).

2.2.4. Medication

Participants listed their psychotropic medication use at baseline because of their possible interactions with the cardiovascular system and their known effects on depressive mood (Roose and Miyazaki, 2005). All reported medications were reviewed and classified according to their psychotropic function. Use of psychotropic medication was conceptualized as the intake of benzodiazepines or other anxiolytics, selective serotonin reuptake inhibitors, and tricyclic antidepressants. Because of persistent concerns that exist regarding the adverse neuropsychological side effects (e.g. depression) that may be caused by beta-blockers, beta-blocker therapy was also documented by patients at baseline (van Melle et al., 2006).

2.3. Statistical analyses

Baseline characteristics of participants were examined stratifying by baseline presence of clinically relevant

depressive symptoms (cut-off ≥ 4). ABI, PFW, and MWD were used as continuous variables and cardiovascular risk factors and use of psychotropic medication were analyzed as binary variables. We recoded the variables of Appendix A into absence of the risk factor (= 0) and all the other values (mild, moderate, severe) into presence of the risk factor (= 1). Chi-square tests and Student's t-tests were used to check for significant univariate differences.

Using the CES-D cut-off score of ≥ 4 to indicate clinically relevant depressive symptoms, two groups (baseline depressive symptoms vs. no depressive symptoms) were compared with regard to their mean depression scores during 18 months follow-up. Analysis of covariance (ANCOVA) with repeated measures were used for this purpose, adjusting for age, sex, educational level, ABI, psychotropic medication use, beta-blocker use, smoking abstinence, comorbidity, and cardiovascular risk factors. These analyses were done using SPSS for windows, version 14.0.1.

To identify subgroups with distinctly different trajectories of depressive symptoms within the whole continuum of depressive scores over an 18-month time period, SAS procedure TRAJ was used. TRAJ combines hierarchical modelling and latent growth curve modelling and fits a mixture model to identify groups of individuals following similar patterns of behaviour over time (Jones et al., 2001). To determine the optimal number of trajectories, the Bayesian Information Criterion (BIC) was used, with a higher BIC indicating a better fit. In addition, associations between group membership and covariates were determined. Multinomial logistic regression was used to determine the group characteristics of the derived trajectories.

3. Results

3.1. Clinical correlates of baseline depressive symptoms

Depressive symptoms (cut-off score ≥ 4 on the CES-D scale) were present in 16% ($n=26$) of the patients at baseline. Stratifying baseline characteristics of participants by depressive symptoms (Table 1), yielded significant differences with regard to PFW (M Depressive Symptoms Group=73.6 m vs. M No Depressive Symptoms Group=124.7 m, $p=0.003$) and MWD (M Depressive Symptoms Group=258.4 m vs. M No Depressive Symptoms Group=412.4 m, $p=0.005$). Patients who experienced depressive symptoms had shorter PFW and MWD than their non-depressed counterparts. To find out whether the relationship between depressive symptoms and walking performance remained significant after statistically controlling for confounding

Table 1

Baseline characteristics stratified by the presence of clinically relevant depressive symptoms*

	Ces-D<4 (N=140)	CES-D \geq 4 (N=26)	p-value
Mean age, years (SD)	64.9 (10.0)	64.8 (10.1)	0.959
Females, %	37.9	46.2	0.426
Low educational level, %	72.1	84.6	0.182
Having no partner, %	30.7	57.7	0.008
Mean ABI (SD)	0.61 (0.15)	0.64 (0.14)	0.439
Mean PFW (SD)	124.7 (159.9)	73.6 (48.9)	0.003
Mean MWD (SD)	412.4 (348.5)	258.4 (212.9)	0.005
Moderate/severe claudication, %	47.1	53.8	0.528
Diabetes mellitus, %	17.9	26.9	0.282
Current smoking, %	52.1	61.5	0.378
Smoking abstinence, %	33.1	24.0	0.374
Hypertension, %	45.0	50.0	0.638
Hyperlipidemia, %	48.6	53.8	0.621
Cardiac risk factor, %	29.3	19.2	0.293
Carotid risk factor, %	10.0	15.4	0.417
Renal disease, %	2.9	3.8	0.786
Pulmonary disease, %	6.4	7.7	0.812
Back symptoms, %	12.1	15.4	0.648
Hip or knee symptoms, %	9.3	7.7	0.795
Psychotropic medication use, %	5.0	30.8	<0.0001
Beta blocker use, %	22.1	30.8	0.341

*Data are presented as %, unless otherwise specified. CES-D = Center for Epidemiological Studies Depression Scale; SD = standard deviation; ABI = ankle brachial index; PFW = pain free walking distance (m); MWD = maximum walking distance (m).

factors, ANCOVA was applied. Using ANCOVA, the association between depressive symptoms and MWD remained significant ($p=0.032$) and showed a trend for PFW ($p=0.129$) after controlling for confounding factors which may impair lower-extremity functioning (ABI, sex, diabetes, back symptoms) (McDermott et al., 2005) (Fig. 1). ABI did not differ between patients with and without baseline depressive symptoms.

Patients with depressive symptoms more often had no partner (57.7% in Depressive Symptoms Group vs. 30.7% in No Depressive symptoms Group, $p=0.008$) and used more psychotropic medication (30.8% in Depressive Symptoms Group vs. 5.0% in No Depressive symptoms Group, $p<0.0001$) than their non-depressed counterparts.

3.2. 18-month course of clinically relevant depressive symptoms

A one-way repeated measures ANCOVA was conducted to compare mean CES-D scores at baseline, 6 months, 12, and 18 months of patients with baseline depressive symptoms (using the cut-off ≥ 4) vs. non-

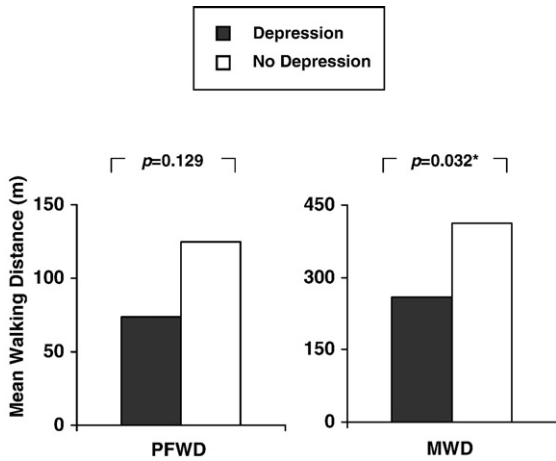


Fig. 1. Mean pain free walking distance (PFWD) and maximum walking distance (MWD) for PAD patients, stratified by baseline depressive symptoms (cut-off score ≥ 4 on CES-D Scale), adjusted for ABI, sex, diabetes, and back symptoms.

depressed patients. Depression scores of patients with baseline depressive symptoms significantly differed as compared with their non-depressed counterparts (Between-subjects effect: $F=65.4, p<0.0001$). There was no main-effect of time ($F=0.76, p=0.517$). Despite a slight decrease in severity of depressive symptoms over time in the baseline Depressive Symptoms Group ($M=5.2 \pm 1.0$ SD at baseline, $M=4.4 \pm 2.0$ SD at 6 months, $M=5.0 \pm 1.9$ SD at 12 months, and $M=4.5 \pm 2.2$ SD at 18-months, F time * baseline depression = 3.4, $p=0.03$),

most patients who were having depressive symptoms at baseline had depressed feelings at all time points. In contrast, patients who were not experiencing depressive symptoms at baseline ($M=0.9 \pm 1.0$ SD), did not have clinically relevant depressive symptoms at 6 months ($M=1.4 \pm 1.7$ SD), 12 months ($M=1.3 \pm 1.8$ SD), and 18 months ($M=1.2 \pm 1.7$ SD).

3.3. Trajectories of depressive symptoms: subclinical and clinical depressive symptoms subgroups

Using SAS procedure TRAJ, three relevant patient subgroups with regard to depressive symptoms were identified in the whole data distribution of depressive scores during follow-up. The level of depressive symptoms over time was rather stable for all identified subgroups of PAD patients (Fig. 2). The majority of the patients did not experience depressive symptoms ($n=96, 58\%$), with a predicted mean CES-D score of 0.43 (95%CI: 0.41–0.45). The level of depressive symptoms of the second group ($n=45, 27\%$ of the patients) was higher compared to the first group with a mean CES-D score of 2.64 (95%CI: 1.89–3.53), and was therefore classified as patients with subclinical depressive symptoms. Clinically relevant CES-D scores were observed in group three ($n=25, 15\%$ of the patients). This group had a predicted mean CES-D score of 5.75 (95%CI: 5.13–6.37). Accordingly, these patients were classified as experiencing depressive symptoms.

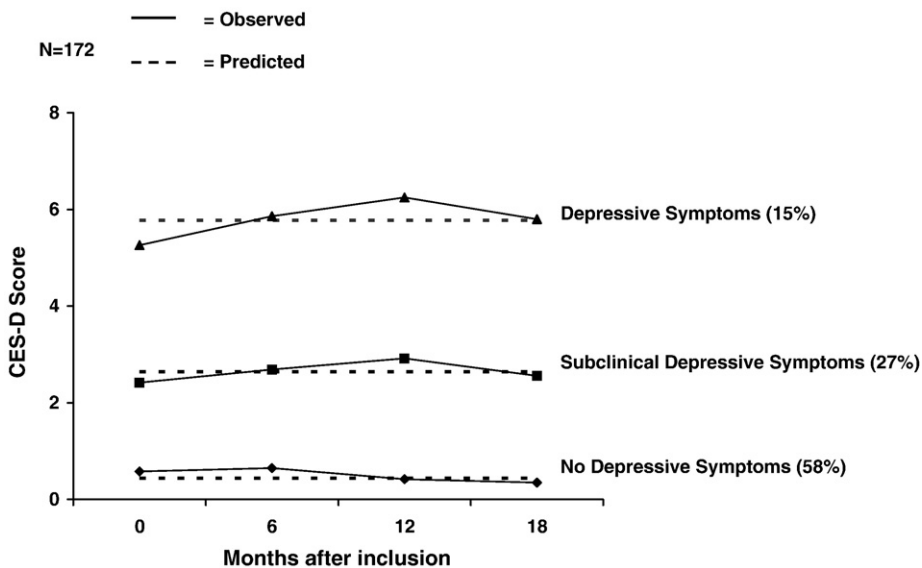


Fig. 2. Trajectories of depressive symptoms in PAD patients. The solid lines represent the observed trajectories, whereas the dashed lines represent the predicted trajectories.

Univariate associates of depressive symptoms trajectories are presented in log odds, using the non-depressed group as reference category; patients with Subclinical Depressive Symptoms were more likely to be female ($lo=1.23$; $p=0.005$) and to have a shorter PFWD ($lo=-.49$; $p=0.02$), shorter MWD ($lo=-.77$; $p<0.001$). Moreover, the Subclinical Depressive Symptoms Group more often had no partner ($lo=0.90$; $p=0.04$), had hyperlipidemia ($lo=0.86$; $p=0.05$), failed to quit smoking ($lo=-4.45$; $p=0.02$), and tended to have hypertension ($lo=0.77$; $p=0.07$). Furthermore, patients in the Depressive Symptoms Group were also more likely to have no partner ($lo=1.21$; $p=0.02$) and to have shorter MWD ($lo=-0.47$; $p=0.05$), and PFWD ($lo=-0.40$; $p=0.08$). In addition, these patients reported an increased intake of psychotropic medication ($lo=2.52$; $p=0.003$) and tobacco ($lo=1.39$; $p=0.02$) and were more likely to report back symptoms ($lo=1.22$; $p=0.05$).

4. Discussion

The present study showed that prevalence of depressive symptoms in PAD patients is high. When presenting themselves for a first visit at the vascular outpatient clinic, 16% of patients reported clinically relevant depressive symptoms ($CES-D \geq 4$). This finding is in accordance with previous findings (Cherr et al., 2007; McDermott et al., 2003). But most important, depressive symptoms in PAD tended to be stable during a follow-up period of 18 months. Future research regarding the stability of depressive symptomatology is needed to elaborate on these findings and to grasp the possible effect of chronic depressive symptoms on long-term outcomes. Cherr et al. (2007) already indicated that the presence of depression was associated with worse patency rates and recurrent leg symptoms after lower-extremity revascularization. We can only guess what the impact of chronic depressive symptomatology would be on prognosis in PAD.

Depressed PAD patients performed worse on the treadmill exercise test; i.e., they had a significantly shorter PFWD and MWD; this association remained significant for MWD and showed a trend for PFWD, after adjusting for ABI, back symptoms, hip or knee symptoms, impaired pulmonary status, and the presence of a cardiac risk factor. In contrast, ABI did not differ between patients with and without depressive symptoms. Depressive symptomatology may have impaired treadmill exercise test performances in PAD patients with depressive mood, potentially affecting the reliability of the treadmill walking test in this particular subset of patients. Lavoie et al. (2004) found evidence for this hypothesis in myocardial ischemia patients with depressive symptomatology who underwent

exercise stress tests. On the other hand, worse performance on the treadmill exercise test may be indicative for poor daily functioning and more functional decline (McDermott et al., 2006). Daily functioning, and more specifically walking behaviour seems to be of vital importance to help reduce the cardiovascular complications and mortality, even in populations with severe limitations (Smith et al., 2007). Of note, decreased walking performance at baseline predicted less accelerometer-measured physical activity and mortality in PAD at 57-month follow-up (Garg et al., 2006).

PAD patients with depressive symptoms tend to use more psychotropic medication and they were also less likely to have a partner. These results are in line with previous studies; sociodemographic variables, such as marital status, appear to be concomitant risk factors for depressive symptoms (Osborn et al., 2003). Furthermore, direct favorable effects on depressive symptoms were found for having a partner in various chronic diseases (Havranek et al., 2004). In addition, higher psychotropic medication consumption is understandably associated with presence of psychiatric symptoms and disorders. Although it was not our main purpose to evaluate the effect of psychotropic medication use, it was interesting to see that only 30.8% of the clinically depressed patients used psychotropic medication and that controlling for, among other clinical risk factors, psychotropic medication use, did not impact the stable course of depressive symptoms. Because only a small number of patients had psychotropic medication, caution is needed in drawing conclusions, but it is certainly worthwhile to consider psychotropic medication use and the appropriateness of the prescribed medication in future studies with PAD patients.

Depressive symptoms remained stable when using the recommended threshold of ≥ 4 for caseness (Cheng and Chan, 2005); stratifying by baseline CES-D depressive symptoms and controlling for cardiovascular risk factors, patients who experienced clinically relevant depressive symptoms at baseline, were also having these depressive feelings at 6, 12, and 18 months. In other words, depressive symptoms seemed to persist up to 18 months of follow-up; the chronicity of depressive symptomatology is also found in post-myocardial infarction patients and in old age and seems to be associated with worsening functional disability (Grace et al., 2005; Lenze et al., 2005; Penninx et al., 2000).

When the whole continuum of depressive symptom scores was analyzed, a more differentiated clinical picture appeared. The majority of PAD patients (58%) did not have depressive symptoms during 18 months follow-up, while 15% persistently had clinically relevant

depressive symptoms. Moreover, one third of PAD patients chronically experienced subclinical depressive symptoms. All these trajectories were stable during follow-up. These persistent trajectories of depressive symptoms might point towards the possible shared vascular pathophysiology underlying depression and PAD (Thomas et al., 2004). The term ‘vascular depression’ refers to a range of late-life depressive syndromes due to a variety of possible vascular mechanisms, e.g. thromboembolism, that leads to cerebral ischemia in key circuitry underpinning depressive symptomatology, such as frontal–subcortical circuits and the hippocampus (Thomas et al., 2004). There is some evidence that a poor cardiovascular risk profile is associated with more depressive symptomatology (Lyness et al., 2000; Van den Berg et al., 2001), which is in line with the present findings of our study. Patients with stable subclinical and clinical depressive symptoms had more cardiovascular risk factors as compared with the non-depressed group. Correlates for the Depressive Symptoms group were shorter PFW and MWD, having no partner, current smoking, having back symptoms, and psychotropic medication use. PAD patients experiencing subclinical depressive symptoms more often had no partner, failed to quit smoking, tended to be female, and had worse treadmill walking performance compared with their counterparts who did not have depressive feelings. In addition, they were more likely to suffer from hypertension and hyperlipidemia. The association between the aforementioned clinical correlates and depressive symptoms might also be interpreted against the findings that depressive symptoms are associated with poor adherence to recommended behaviour and lifestyle changes (Kronish et al., 2006), which may in turn contribute to adverse outcomes in depressed patients with PAD.

This study has some limitations. First, depressive symptoms were assessed by means of a self-report questionnaire and consequently, no diagnosis of a major depressive disorder could be established. Therefore, the use of diagnostic interviews should be incorporated in future research. Second, although ABI and treadmill walking performance were assessed at baseline, no longitudinal data of these measures were available. So, future studies are warranted to show the long-term clinical consequences of our findings with regard to disease severity and adverse medical outcomes. Third, patients with more than two assessment points lacking were left out of the analyses. Although patients who refused further follow-up did not differ much regarding baseline characteristics, we cannot rule out the possibility that this might have influenced our results. Last, only

three substantial subgroups with stable trajectories could be discerned with the mixed modelling procedure in this study. That means that there were not much individuals in the current sample that developed significantly lower or higher scores during follow-up. Studying the course of depressive symptoms in larger samples of PAD patients in the future, would provide opportunities to look at groups of patients with changing depression scores and to concentrate on the predictors of these changes.

This study adds to growing data that prevalence of depressive symptoms is high in patients with PAD and that these symptoms are associated with walking performance. The new finding in this study refers to the chronicity of depressive symptoms in this patient group.

Given the chronicity and extent of depressive symptomatology in the subgroups of patients that experienced either depressive symptoms or subclinical depressive symptoms, and given the association we found between some important clinical correlates of PAD, further consideration of the impact of depressive symptoms on prognosis in PAD is needed in research and clinical practice.

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Conflicts of interest

No conflict declared.

Appendix A. Society for Vascular Surgery/International Society for Cardiovascular Surgery (North American Chapter) grading system for cardiovascular risk factors and comorbidity (Rutherford et al., 1997)¹

0	no risk factor
1	mild
2	moderate
3	severe

Diabetes mellitus: 0, none; 1, adult onset, controlled by diet or oral agents; 2, adult onset, insulin controlled; 3, juvenile onset.

¹ We dichotomized the cardiovascular risk factors in our analyses into absence of the risk factor (=0) and all the other values (mild, moderate, severe) into presence of the risk factor (=1).

Tobacco use: 0, none or none for last 10 years; 1, none current, but smoked in last 10 years; 2, current (includes abstinence for less than 1 year), less than one pack per day; 3, current, more than 1 pack per day.

Hypertension: 0, diastolic usually lower than 90 mm Hg; 1, controlled with a single drug; 2, controlled with two drugs; 3, requires more than two drugs or is uncontrolled.

Hyperlipidemia: 0, cholesterol (low-density lipoprotein and total) and triglyceride levels within normal limits for age; 1, readily controllable by diet; 2, requires strict dietary control; 3, same as mild, but severe enough to require dietary and drug control.

Cardiac status: 0, asymptomatic with normal electrocardiogram; 1, asymptomatic but with remote myocardial infarction by electrocardiogram, or fixed defect on dipyridamole thallium or similar scan; 2, any one of the following: stable angina, no angina (but significant reversible perfusion defect on dipyridamole thallium scan), significant silent ischemia ($\geq 1\%$ of the time) on Holter monitoring, ejection fraction 25% to 45%, controlled ectopy or asymptomatic arrhythmia, or history of congestive heart failure that is now well compensated; 3, any one of the following: unstable angina, symptomatic or poorly controlled ectopy/arrhythmia (chronic/recurrent), poorly compensated or recurrent congestive heart failure, ejection fraction less than 25%, or myocardial infarction within 6 months.

Carotid disease: 0, no symptoms and no evidence of disease; 1, asymptomatic but with evidence of disease determined by duplex scan or other accepted non-invasive test or arteriogram; 2, transient or temporary stroke; 3, completed stroke with permanent neurological deficit or acute stroke.

Renal status: (refers to stable levels, not transient decreases or increases in response to intravenous medication, hydration, or contrast media): 0, no known renal disease, normal serum creatinine level; 1, moderately increased creatinine level, as high as 2.4 mg/dL; 2, creatinine level of 2.5 to 5.9 mg/dL; 3, creatinine level greater than 6.0 mg/dL or on dialysis or with kidney transplant.

Pulmonary status: 0, asymptomatic, normal chest x-ray film, pulmonary function tests within 20% of predicted; 1, asymptomatic or mild dyspnea on exertion, mild chronic parenchymal X-ray changes, pulmonary function tests 65% to 80% of predicted; 2, between 1 and 3; 3, vital capacity less than 1.85 L, forced expiratory volume in 1 s less than 1.2 L or less than 35% of predicted, maximal voluntary ventilation less than 50% of predicted, P_{CO_2} greater than 45 mm Hg,

supplemental oxygen use medically necessary, or pulmonary hypertension.

References

- American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders. In: Association AP (Ed.), American Psychiatric Association, Washington, DC.
- Aquarius, A.E., Denollet, J., Hamming, J.F., Van Berge Henegouwen, D.P., De Vries, J., 2007. Type-D personality and ankle brachial index as predictors of impaired quality of life and depressive symptoms in peripheral arterial disease. *Arch. Surg.* 142, 662–667.
- Belch, J.J., Topol, E.J., Agnelli, G., Bertrand, M., Califf, R.M., Clement, D.L., Creager, M.A., Easton, J.D., Gavin III, J.R., Greenland, P., Hankey, G., Hanrath, P., Hirsch, A.T., Meyer, J., Smith, S.C., Sullivan, F., Weber, M.A., 2003. Critical issues in peripheral arterial disease detection and management: a call to action. *Arch. Intern. Med.* 163, 884–892.
- Breek, J.C., Hamming, J.F., De Vries, J., van Berge Henegouwen, D.P., van Heck, G.L., 2002. The impact of walking impairment, cardiovascular risk factors, and comorbidity on quality of life in patients with intermittent claudication. *J. Vasc. Surg.* 36, 94–99.
- Cheng, S.T., Chan, A.C., 2005. The Center for Epidemiologic Studies Depression Scale in older Chinese: thresholds for long and short forms. *Int. J. Geriatr. Psychiatry* 20, 465–470.
- Cherr, G.S., Wang, J., Zimmerman, P.M., Dosluoglu, H.H., 2007. Depression is associated with worse patency and recurrent leg symptoms after lower extremity revascularization. *J. Vasc. Surg.* 45, 744–750.
- De Backer, G., Ambrosioni, E., Borch-Johnsen, K., Brotons, C., Cifkova, R., Dallongeville, J., Ebrahim, S., Faergeman, O., Graham, I., Mancia, G., Cats, V.M., Orth-Gomer, K., Perk, J., Pyorala, K., Rodicio, J.L., Sans, S., Sansoy, V., Sechtem, U., Silber, S., Thomsen, T., Wood, D., 2004. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of eight societies and by invited experts). *Atherosclerosis* 173, 381–391.
- Garg, P.K., Tian, L., Criqui, M.H., Liu, K., Ferrucci, L., Guralnik, J.M., Tan, J., McDermott, M.M., 2006. Physical activity during daily life and mortality in patients with peripheral arterial disease. *Circulation* 114, 242–248.
- Geerlings, S.W., Beekman, A.T., Deeg, D.J., Twisk, J.W., Van Tilburg, W., 2002. Duration and severity of depression predict mortality in older adults in the community. *Psychol. Med.* 32, 609–618.
- Grace, S.L., Abbey, S.E., Pinto, R., Shnek, Z.M., Irvine, J., Stewart, D.E., 2005. Longitudinal course of depressive symptomatology after a cardiac event: effects of gender and cardiac rehabilitation. *Psychosom. Med.* 67, 52–58.
- Havranek, E.P., Spertus, J.A., Masoudi, F.A., Jones, P.G., Rumsfeld, J.S., 2004. Predictors of the onset of depressive symptoms in patients with heart failure. *J. Am. Coll. Cardiol.* 44, 2333–2338.
- Heald, C.L., Fowkes, F.G., Murray, G.D., Price, J.F., 2006. Risk of mortality and cardiovascular disease associated with the ankle-brachial index: systematic review. *Atherosclerosis* 189, 61–69.
- Irwin, M., Artin, K.H., Oxman, M.N., 1999. Screening for depression in the older adult: criterion validity of the 10-item Center for Epidemiological Studies Depression Scale (CES-D). *Arch. Intern. Med.* 159, 1701–1704.

- Jones, B., Nagin, D., Roeder, K., 2001. A SAS procedure based on mixture models for estimating developmental trajectories. *Sociol. Methods Res.* 29, 374–393.
- Kaptein, K.I., de Jonge, P., van den Brink, R.H., Korf, J., 2006. Course of depressive symptoms after myocardial infarction and cardiac prognosis: a latent class analysis. *Psychosom. Med.* 68, 662–668.
- Kohout, F.J., Berkman, L.F., Evans, D.A., Cornoni-Huntley, J., 1993. Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index. *J. Aging Health* 5, 179–193.
- Kronish, I.M., Rieckmann, N., Halm, E.A., Shimbo, D., Vorchheimer, D., Haas, D.C., Davidson, K.W., 2006. Persistent depression affects adherence to secondary prevention behaviors after acute coronary syndromes. *J. Gen. Intern. Med.* 21, 1178–1183.
- Lavoie, K.L., Fleet, R.P., Lesperance, F., Arsenault, A., Laurin, C., Frasure-Smith, N., Bacon, S.L., 2004. Are exercise stress tests appropriate for assessing myocardial ischemia in patients with major depressive disorder? *Am. Heart J.* 148, 621–627.
- Lenze, E.J., Schulz, R., Martire, L.M., Zdaniuk, B., Glass, T., Kop, W.J., Jackson, S.A., Reynolds III, C.F., 2005. The course of functional decline in older people with persistently elevated depressive symptoms: longitudinal findings from the Cardiovascular Health Study. *J. Am. Geriatr. Soc.* 53, 569–575.
- Lyness, J.M., King, D.A., Conwell, Y., Cox, C., Caine, E.D., 2000. Cerebrovascular risk factors and 1-year depression outcome in older primary care patients. *Am. J. Psychiatry* 157, 1499–1501.
- McDermott, M.M., Greenland, P., Guralnik, J.M., Liu, K., Criqui, M.H., Pearce, W.H., Chan, C., Schneider, J., Sharma, L., Taylor, L.M., Arseven, A., Quann, M., Celic, L., 2003. Depressive symptoms and lower extremity functioning in men and women with peripheral arterial disease. *J. Gen. Intern. Med.* 18, 461–467.
- McDermott, M.M., Guralnik, J.M., Ferrucci, L., Criqui, M.H., Greenland, P., Tian, L., Liu, K., Tan, J., 2005. Functional decline in lower-extremity peripheral arterial disease: associations with comorbidity, gender, and race. *J. Vasc. Surg.* 42, 1131–1137.
- McDermott, M.M., Liu, K., Ferrucci, L., Criqui, M.H., Greenland, P., Guralnik, J.M., Tian, L., Schneider, J.R., Pearce, W.H., Tan, J., Martin, G.J., 2006. Physical performance in peripheral arterial disease: a slower rate of decline in patients who walk more. *Ann. Intern. Med.* 144, 10–20.
- Meru, A.V., Mitra, S., Thyagarajan, B., Chugh, A., 2006. Intermittent claudication: an overview. *Atherosclerosis* 187, 221–237.
- Norgren, L., Hiatt, W.R., Dormandy, J.A., Nehler, M.R., Harris, K.A., Fowkes, F.G., TASC II Working Group, 2007. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J. Vasc. Surg.* 45, 5–67 (S).
- Osborn, D.P., Fletcher, A.E., Smeeth, L., Stirling, S., Bulpitt, C.J., Breeze, E., Ng, E.S., Nunes, M., Jones, D., Tulloch, A., 2003. Factors associated with depression in a representative sample of 14217 people aged 75 and over in the United Kingdom: results from the MRC trial of assessment and management of older people in the community. *Int. J. Geriatr. Psychiatry* 18, 623–630.
- Penninx, B.W., Deeg, D.J., van Eijk, J.T., Beekman, A.T., Guralnik, J.M., 2000. Changes in depression and physical decline in older adults: a longitudinal perspective. *J. Affect. Disord.* 61, 1–12.
- Radloff, L., 1977. The CES-D scale: a self-report depression scale for research in the general population. *Appl. Psychol. Meas.* 1, 385–401.
- Roose, S.P., Miyazaki, M., 2005. Pharmacologic treatment of depression in patients with heart disease. *Psychosom. Med.* 67 (Suppl 1), S54–S57.
- Rutherford, R.B., Baker, J.D., Ernst, C., Johnston, K.W., Porter, J.M., Ahn, S., Jones, D.N., 1997. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J. Vasc. Surg.* 26, 517–538.
- Smith, T.C., Wingard, D.L., Smith, B., Kritiz-Silverstein, D., Barrett-Connor, E., 2007. Walking decreased risk of cardiovascular disease mortality in older adults with diabetes. *J. Clin. Epidemiol.* 60, 309–317.
- Thomas, A.J., Kalaria, R.N., O'Brien, J.T., 2004. Depression and vascular disease: what is the relationship? *J. Affect. Disord.* 79, 81–95.
- Vaccarino, V., Kasl, S.V., Abramson, J., Krumholz, H.M., 2001. Depressive symptoms and risk of functional decline and death in patients with heart failure. *J. Am. Coll. Cardiol.* 38, 199–205.
- Van den Berg, M.D., Oldehinkel, A.J., Bouhuys, A.L., Brilman, E.I., Beekman, A.T., Ormel, J., 2001. Depression in later life: three etiologically different subgroups. *J. Affect. Disord.* 65, 19–26.
- van Melle, J.P., Verbeek, D.E., van den Berg, M.P., Ormel, J., van der Linde, M.R., de Jonge, P., 2006. Beta-blockers and depression after myocardial infarction: a multicenter prospective study. *J. Am. Coll. Cardiol.* 48, 2209–2214.