

Association of Depression with Walking in People with Peripheral Artery Disease: A Post-Hoc Analysis of the BIP Trial

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Aims: This post-hoc analysis from the Behavioural Intervention by allied health professionals to promote Physical activity (BIP) trial examined the relationship between depression and step count and walking capacity over two years in people with peripheral artery disease (PAD).

Methods: BIP included participants with walking impairment due to PAD followed up at 4, 12 and 24 months to measure step count over 7 days using an accelerometer and six-minute walking distance. The relationships between depression at entry with step count and walking distance during follow-up were assessed using linear mixed effects models.

Results: At entry, 29 (14.5%) of the 200 participants had depression being treated with anti-depressant medication. Participants diagnosed with depression were more likely to be female (13 of 29, 44.8%) than those not diagnosed with depression (43 of 171, 25.1%). Over 24 months follow-up, daily step count progressively decreased in participants with depression (mean [SD] 4406 (2266) at entry to 3888 (2555) at 24 months) as compared to no change in participants without depression (mean (SD) 5271 (2526) at entry compared to 5120 (2446) at 24 months), inter-group difference $p = 0.010$. No significant difference in change in six-minute walking distance over 2 years was found between participants with and those without depression.

Conclusion: Depression is associated with greater decline in self-regulated walking in patients with PAD. Effective treatments for depression are needed which help promote physical activity in people with PAD.

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Key words: Peripheral artery disease, Depression, Walking

Introduction

Peripheral artery disease (PAD) has been estimated to have a prevalence of approximately 5% in 50 year olds rising to about 20% in 80 year olds¹.

Both PAD and ageing are important causes of functional decline and given the high prevalence of PAD in older adults, treatments effective at facilitating independent living are a social and economic priority^{2,3}. Interviews with people with PAD show that

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maintaining their independence is their primary goal^{4, 5}. Current guidelines focus on treating PAD by medical management and exercise therapy with selective use of surgical revascularization but the outcomes and applicability of these established therapies are imperfect⁶. New effective management models are needed to treat PAD. These include new models of care incorporating management of modifiable risk factors using combinations of drug therapies, lifestyle modification and physical and mental rehabilitation^{7, 8}.

Depression is as a risk factor for PAD which is receiving increased recognition as a treatment target^{9, 10}. In a recent cohort with PAD, 11% of participants had a current diagnosis of depression¹¹. The American Heart Association released a scientific statement highlighting the need for investigation of the impact of mental health disorders in patients with PAD¹⁰. Past studies suggest that patients with PAD who have symptoms of depression are at greater risk of functional decline and mortality^{12, 13}. It is however currently unclear if people with PAD who are receiving pharmacological treatment for depression undertake less walking and if they have increased functional decline. It is possible that treatment of depression might limit its effect on walking and functional decline in people with PAD.

The aim of this study was to assess the relationship between pharmacologically treated depression and step count and walking capacity over a 2 year follow-up amongst participants of the brief Behavioural Intervention by allied health professionals to promote Physical activity (BIP) trial^{14, 15}.

Methods

Design

The current study included participants from BIP, a parallel, randomised, multi-centre, controlled trial which found a brief counselling intervention did not significantly increase physical activity or walking capacity of people with PAD¹⁵. Participants allocated to the intervention, however, had a significant improvement in quality of life associated with a reduced risk of major adverse cardiovascular events¹⁵. Ethics approval was obtained prior to commencement (HREC/14/QRBW/60). All participants provided written informed consent. The trial was prospectively registered in June 2014 (Australian New Zealand Clinical Trials Registry: ACTRN12614000592640). This analysis aimed to test if the participants with a diagnosis of pharmacologically treated depression at the time of recruitment had increased decline in step count and walking capacity as compared to people without such a diagnosis. The STROBE reporting

guidelines were followed¹⁶.

Participants

BIP included participants with symptomatic PAD able to walk without assistance who were not currently taking part in an exercise program¹⁵. Patients with ischemic rest pain, ulceration or gangrene were excluded. Participants were recruited from hospital vascular departments in Brisbane, Sydney and Townsville, Australia.

Diagnosis and Treatment of Depression, Other Risk Factors and Medications

At entry, all participants had a face-to-face interview and clinical assessments. This included a review of the medical records of the participants. Participants with a current diagnosis of depression were noted and treatment by anti-depressant medication (i.e. selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors) recorded. Other risk factors collected included age, sex, smoking history, past diagnosis of diabetes, coronary heart disease (CHD), stroke and chronic lung disease, previous revascularisation surgery and other medications using published definitions^{17, 18}. Body mass index (BMI), ankle brachial index (ABI) and serum blood markers were measured as previously described^{17, 18}.

Physical Activity, Function and Walking Assessments

Level of physical activity was assessed objectively using an activPAL3™ accelerometer (PAL Technologies Ltd, Glasgow, United Kingdom), which has been reported to be reliable in the assessment of step count in people with PAD¹⁹. The activPAL3™ unit was attached to the right thigh of each participant for seven days at entry, 4, 12 and 24 months. Data records were uploaded and checked to ensure a seven-day recording for all participants and recording was redone if this was not the case²⁰. Activity was reported as mean step count per day. Physical activity was also assessed at entry with the self-administered International Physical Activity Questionnaire (IPAQ) which has questions designed to collect time spent undertaking moderate and vigorous physical activity and time walking and time sitting¹⁸. Walking capacity was assessed by a 6-minute walking test at entry, 4, 12 and 24 months. Participants were asked to walk up and down a 30-metre hallway for 6 minutes and encouraged to complete as many laps as possible using a standard protocol^{18, 21}. The distance walked was measured using a trundle wheel. Using this protocol the distance recorded during repeat tests was highly reproducible as previously reported (intraclass

correlation coefficient = 0.970, 95% confidence intervals 0.950 to 0.981, for tests repeated one week apart in 173 patients)²²). Function was also assessed at entry using the short physical performance battery (SPPB) examination involved three objective tests of lower body function: A test of standing balance, a timed four meter walk and five timed repetitive chair stands, as previously described²⁰.

Quality of Life

Disease-specific quality of life was assessed at entry, 4, 12 and 24 months using the Intermittent Claudication Questionnaire (ICQ) and Peripheral Artery Disease Quality of Life (PADQOL) questionnaire^{23, 24}. These assessments were chosen due to their excellent test-retest repeatability, construct validity and responsiveness to change in PAD^{17, 23, 24}. The 16-item ICQ focuses on the effect of leg pain and activity limitations on quality of life. ICQ scores were summed and transformed to a final score between 0 (worst possible quality of life) and 100 (best possible quality of life)¹⁷. Five themes of PADQOL were assessed including social relationships and interactions, self-concept and feelings, symptoms and limitations in physical functioning, fear and uncertainty and positive adaptation known as factors 1 to 5, respectively¹⁷. Scores for individual questions were weighted as originally described, with higher scores indicating better quality of life²⁴. The generic quality of life assessment short form-36 (SF-36) was also assessed at entry, 4, 12 and 24 months and transformed to physical and mental health summary components¹⁸.

Study Size

The sample size for BIP was determined by that required to test the hypothesis that the counselling intervention improved step count at 4 months, as previously described¹⁵.

Data Analysis

To test the hypothesis that patients with pharmacologically treated depression had reduced step count and walking capacity compared to those without this diagnosis step count and walking distance at entry were compared between participants in both groups using Mann Whitney *U* test. Risk factors at entry were compared between groups using Chi-squared for nominal data and Mann Whitney *U* test for continuous data. Nominal data were presented as numbers and percentages and compared between groups using chi-squared tests. Changes in step count and walking distance over 24 months were compared between groups of participants with or without a diagnosis of depression using random slope, random

intercept linear mixed effects (LMEs) models. In unadjusted models, prescription of antidepressant medication was treated as a fixed effect. Adjusted models included female sex and chronic lung disease as additional fixed effects since these were different in patients with and without depression at baseline ($p \leq 0.1$). In all models patients and time were treated as random effects, and the interaction of time with depression diagnosis was used as the test statistic. Model fit was assessed based on the distribution of standardised residuals and qq-norm plots, highlighting the need to log-transform step count to conform to model assumptions. Diagnostic plots highlighted the presence of outliers (residuals lying >3 standard deviations away from the mean of model residuals) for both daily step count and six-minute walk test distance. Given the potential for outliers to skew model estimates, outcomes from analyses excluding these outliers are reported here. All analyses were performed using the Statistical Package for Social Sciences (SPSS) version 25.0 (IBM SPSS Inc., Chicago, Illinois, USA) and R using the nlme package to conduct LME analyses. *P* values <0.05 were considered statistically significant throughout.

Results

Association of the Diagnosis of Pharmacologically Treated Depression with Risk Factors at Entry

Twenty nine (14.5%) of the 200 participants in the BIP trial had a current diagnosis of depression at entry. All 29 participants were receiving treatment with anti-depressant medications, including selective serotonin reuptake inhibitors (17 patients; escitalopram 7, sertraline 4, citalopram 3, fluoxetine 2, paroxetine 1), serotonin-norepinephrine reuptake inhibitors (4 patients; duloxetine 3, venlafaxine 1), tricyclic anti-depressants (4 patients; amitriptyline 2, dosulepin 1, clomipramine 1), atypical anti-depressants (2 patients; mirtazapine 2) and monoamine oxidase inhibitors (2 patients; moclobemide 2). Participants receiving treatment for depression were significantly more likely to be female (13 of 29, 45%) than those without this diagnosis (43 of 171, 25%) (Table 1). Other risk factors including age, current smoking, history of coronary heart disease or stroke, ABI, serum lipids, C-reactive protein, estimated glomerular filtration rate and neutrophil lymphocyte ratio, were not significantly different between participants treated for depression and other patients (Table 1).

Association of the Diagnosis of Pharmacologically Treated Depression with Quality of Life at Entry

Scores for the disease-specific quality of life instruments were not significantly different between patients with treated depression and other participants (Table 1). At entry, scores for the SF-36 mental health, but not physical, component summary were significantly lower in participants with treated depression than those without (Table 1).

Relationship between the Diagnosis of Pharmacologically Treated Depression and Physical Activity and Walking Capacity at Entry

At entry, daily step count, six-minute walk distance and SPPB score were lower but not significantly different for participants with treated depression compared to other participants (Table 1). According to the IPAQ participants with treated depression performed a mean of only 1.0 (standard deviation, SD, 3.4) hours of moderate or vigorous physical activity per week, significantly less than the mean of 3.6 (SD 7.3) hours for other participants, $p = 0.027$ (Table 1). Weekly walking time and daily sitting time were reported to be not significantly different in participants with and without treated depression (Table 1).

Relationship between the Diagnosis of Pharmacologically Treated Depression and Physical Activity and Walking Capacity during Follow-Up

Objectively measured daily step counts and six-minute walk distance were consistently lower in participants with treated depression compared to those without depression (Table 2). Cross-sectional analyses identified statistically significant inter-group differences in daily step count at 12 and 24 months but not at 4 months. Change in daily step count across the two-year follow up period was significantly lower for participants with pharmacologically treated depression than those without. Over 24 months follow-up, daily step count progressively decreased in participants with depression (mean [SD] 4406 (2266) at entry to 3888 (2555) at 24 months) as compared to no change in participants without depression (mean (SD) 5271 (2526) at entry compared to 5120 (2446) at 24 months), inter-group difference $p = 0.011$ (Table 2). This difference remained significant after adjusting for female sex and diagnosis of chronic lung disease, which were risk factors that were different between groups at baseline at $p \leq 0.1$ (see Table 2). Participants receiving pharmacological treatment for depression exhibited significantly lower six-minute walk test distances at 4 and 12 months than those without depression, however no longitudinal

significant differences between the groups in change in walking distance over 24 months were observed upon unadjusted and adjusted LME analyses (Table 2).

Discussion

The main finding from this study was that patients with PAD who were also diagnosed with depression at entry had a significant reduction in objectively measured daily step count over two years as compared to those without a diagnosis of depression. This was despite these patients being prescribed anti-depressant medications. Other studies have reported that patients with PAD with depression had a significantly faster decline in six-minute walking distance^{13, 25}, but this was not identified in the current study. This appears to be the first study to identify the association of depression with a reduction in objectively measured daily steps over time. Prior research has suggested that a decrease in physical activity over time is associated with an increase in symptoms of depression²⁶. These findings suggest a critical bidirectional link between depression and walking in people with PAD, which may only be partly addressed by pharmacological anti-depressant therapies. Past research suggests that depression increases the risk of PAD by contributing to increased risk factors⁹. Furthermore, PAD causes pain and reduced activity worsening depression¹². Exercise is known to reduce symptoms of depression and thus exercise therapy could have significant benefits for patients with PAD who are depressed¹⁰.

Numerous studies have shown that depression is common in patients with PAD and about twice as common as in healthy controls^{10-12, 27, 28}. In the current study, 15% of participants were diagnosed with depression and receiving anti-depressant medication at entry. As in other studies, depression was over-represented in female participants²⁸. Participants who had been diagnosed with depression reported undertaking a third of the weekly hours of vigorous or moderate activity of those who were not depressed at entry. This was despite there being no significant difference in ABI or six-minute walk distance between depressed and non-depressed participants at entry. At 4 and 24 months follow-up, depressed participants had significantly shorter six-minute walking distance as compared to participants who were not diagnosed with depression at entry, although overall there was no significant association between decline in six-minute walking distance and depression. Similarly at 12 and 24 months follow-up, objectively measured daily step counts were

Table 1. Baseline characteristics of participants who did and did not have a diagnosis of treated depression

Risk factor	Depression		P value
	Yes	No	
Number	29	171	
Age	69.9 (7.6)	69.0 (9.5)	0.582
Female	13 (44.8)	43 (25.1)	0.029
Male	16 (55.2)	128 (74.9)	
Diabetes	11 (37.9)	55 (32.2)	0.541
Current smoking	10 (34.5)	56 (32.7)	0.854
Hypertension	25 (86.2)	132 (77.2)	0.275
Past stroke	2 (6.9)	24 (14.0)	0.291
Coronary heart disease	17 (58.6)	76 (44.4)	0.157
Chronic lung disease	12 (41.4)	43 (25.1)	0.070
Previous lower limb revascularisation	12 (41.4)	68 (39.8)	0.870
Anti-platelet prescribed	27 (93.1)	145 (84.8)	0.233
Statin prescribed	27 (93.1)	145 (84.8)	0.233
BMI	28.0 (5.2)	28.6 (5.6)	0.608
WHR	0.97 (0.09)	0.99 (0.09)	0.213
Neutrophil lymphocyte ratio*	2.4 (1.3)	2.2 (0.9)	0.656
C-reactive protein [#]	4.3 (6.5)	5.5 (12.8)	0.645
Total cholesterol	4.19 (0.87)	4.20 (1.11)	0.644
Triglyceride	1.66 (1.02)	1.70 (1.07)	0.924
LDL [‡]	2.13 (0.75)	2.25 (0.97)	0.923
HDL [‡]	1.29 (0.41)	1.21 (0.37)	0.313
Estimated glomerular filtration rate	75.6 (18.6)	73.8 (17.6)	0.600
Left ABI	0.74 (0.23)	0.76 (0.21)	0.537
Right ABI	0.83 (0.31)	0.78 (0.26)	0.325
SPPB score	8.9 (2.1)	9.6 (1.9)	0.089
Daily steps [†]	4406 (2266)	5271 (2526)	0.063
6MWT distance	355.4 (119.3)	375.0 (93.5)	0.191
Weekly moderate or vigorous activity (hours) [¥]	1.0 (3.4)	3.6 (7.3)	0.027
Weekly walking (hours) [¥]	2.1 (2.7)	3.3 (6.1)	0.387
Daily sitting time (hours) [¥]	5.3 (4.3)	4.5 (4.3)	0.246
ICQ percent	69.6 (16.9)	72.6 (14.3)	0.378
PADQOL Factor 1	21.2 (7.7)	23.4 (7.0)	0.121
PADQOL Factor 2	17.2 (6.6)	19.5 (5.5)	0.059
PADQOL Factor 3	12.5 (5.6)	13.2 (5.0)	0.286
PADQOL Factor 4	9.0 (3.1)	9.1 (3.2)	0.817
PADQOL Factor 5	17.6 (3.3)	17.8 (2.8)	0.923
SF-36 physical component summary	34.8 (9.4)	35.4 (9.2)	0.549
SF-36 mental health component summary	45.4 (14.3)	52.7 (10.6)	0.009

Shown are number (percentage) or mean (standard deviation) of variables at baseline for participants who did or did not have a prior diagnosis of depression. Nominal and continuous data were analysed by chi-squared and Mann Whitney *U* tests, respectively. BMI: Body mass index; SPPB: Short physical performance battery; ABI: Ankle brachial index; LDL: Low density lipoprotein; HDL: High density lipoprotein; 6MWT: Six-minute walk distance in meters; CHD: Coronary heart disease; COPD: Chronic obstructive airways disease; PADQOL: Peripheral Artery Disease Quality of Life; SPPB: Short performance battery. The PADQOL consists of five factors: 1. Social relationships and interactions; 2. Self-concept and feelings; 3. Symptoms and limitations in physical functioning; 4. Fear and uncertainty; and 5. Positive adaptation. ICQ: Intermittent Claudication Questionnaire (percentage of maximum possible score). Missing data from 3[†], 5[¥], 15^{||}, 20[‡], 21[#] and 28* participants. Units for lipids mMol/L, blood pressure mmHg, age years, BMI Kg/m², C-reactive protein mg/L, Estimated glomerular filtration rate mL/min/1.73 m². Hours of moderate and vigorous physical activity or walking or sitting estimated with the International Physical Activity Questionnaire.

Table 2. Association of treated depression with physical activity and walking distance at entry and follow-up

Risk factor	Depression		<i>P</i> value*	LME estimates (inter-group differences over time)			
	Yes (<i>n</i> = 29)	No (<i>n</i> = 191)		Unadjusted		Adjusted	
			Estimate (95% CI)		<i>P</i> -value		Estimate (95% CI) <i>P</i> -value
Daily steps							
Entry	4406 (2266)	5271 (2526) [2]	0.063	-0.018	0.011 [#]	-0.018	0.010 [#]
4 months	4483 (2090) [4]	5577 (2764) [21]	0.070	(-0.032, -0.004) [#]		(-0.032, -0.004) [#]	
12 months	3942 (2156) [8]	5399 (2650) [32]	0.021				
24 months	3888 (2555) [11]	5120 (2446) [46]	0.037				
6MWT distance (metres)							
Entry	355.4 (119.3)	375.0 (93.5) [2]	0.191	-0.7	0.201	-0.9	0.119
4 months	328.1 (74.1) [6]	371.5 (104.5) [22]	0.037	(-1.9, 0.4)		(-2.0, 0.2)	
12 months	344.8 (77.1) [9]	371.8 (106.4) [36]	0.183				
24 months	298.3 (92.7) [12]	370.7 (105.0) [49]	0.008				

Shown are mean and standard deviation. Numbers in square brackets denote number of missing variables for that data point. **P*-values calculated using the Mann-Whitney *U*-test. LME: linear mixed effects. Adjusted models incorporate female sex and a diagnosis of COPD as additional fixed effects. Estimates, 95% confidence intervals and *p*-values refer to the performance of patients prescribed antidepressant medication relative to those who are not, during follow-up based on the interaction of time and group (expressed as a per-month value). Reported LME data detail estimates, 95% confidence intervals and *p*-values from models excluding outliers (residuals lying > 3 standard deviations from mean of model residuals).

[#] Step count data were log-transformed to meet LME model assumptions, thus reported numbers are log transformed.

significantly less in depressed compared to non-depressed participants. The findings suggest that depression contributes to PAD patients undertaking less self-directed activity. Previous studies in other populations, such as young adults, suggest that the negative relationship between depression and physical activity relates to the effects of depression on psychosocial determinants such as self-esteem, self-concept, self-efficacy, energy perception and pain tolerance²⁹). The lack of significance difference between depressed and non-depressed patients in decline in six-minute walking distance might be reflective of the small sample size given that only 29 participants were receiving treatment for depression. It could also reflect that depression mainly influences voluntary activity as opposed to walking capacity.

Reduced walking activity in patients with PAD who are depressed has been suggested to contribute to the excess rate of adverse events in these people¹²). This highlights the importance of effectively treating depression in PAD patients. In the current study greater decline in physical activity was found in participants with depression despite these patients receiving anti-depressants. This is in keeping with the findings of an observational study of more than 150,000 US Veterans which found that pharmacologically treated depression was associated with an increased risk of mortality and amputation compared to no depression, although the risk ratio was reduced

compared to untreated depression³⁰). These findings suggest that further research is needed to understand how best to treat depression in patients with PAD. In a recent exploratory analysis of the BIP randomised trial a counselling intervention aimed to increase physical activity was found to reduce markers of anxiety and depression and associated with a reduction in the risk of cardiovascular events¹⁴). It is possible that treatments specifically designed for the factors contributing to depression in people with PAD will reduce the high risk of adverse events in these patients.

This study has a number of strengths and weaknesses. Strengths include the prospective design and careful data collection as part of a clinical trial. Weaknesses include the small sample size, focus on pharmacological treatment, recruitment being limited to Australia and the observational nature of the study. Given these weaknesses findings may not be generalizable to other populations.

In conclusion this study suggested depression when treated with conventional anti-depression medication, is associated with reduction in physical activity over time. Treatments are needed to effectively improve physical activity in people with PAD who are depressed.

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Conflicts of Interest

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