



BMJ Open Impact of prestroke physical activity and citalopram treatment on poststroke depressive symptoms: a secondary analysis of data from the TALOS randomised controlled trial in Denmark

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ABSTRACT

Objectives To investigate the association between prestroke physical activity and depressive symptoms up to 6 months after stroke and examine if citalopram treatment modified the association.

Design A secondary analysis of data from the multicentre randomised controlled trial The Efficacy of Citalopram Treatment in Acute Ischemic Stroke (TALOS).

Setting and participants TALOS was conducted at multiple stroke centres in Denmark from 2013 to 2016. It enrolled 642 non-depressed patients with first-ever acute ischaemic stroke. Patients were eligible for this study if a prestroke physical activity level was assessed by the Physical Activity Scale for the Elderly (PASE).

Interventions All patients were randomised to citalopram or placebo for 6 months.

Outcomes Depressive symptoms 1 and 6 months after stroke measured on the Major Depression Inventory (MDI) ranging from 0 to 50.

Results A total of 625 patients were included. Median (IQR) age was 69 (60–77) years, 410 (65.6%) were men, 309 (49.4 %) received citalopram and median (IQR) prestroke PASE score was 132.5 (76–197). Higher prestroke PASE quartile, compared with the lowest PASE quartile, was associated with fewer depressive symptoms both after 1 month (mean difference third quartile –2.3 (–4.2, –0.5), $p=0.013$, mean difference fourth quartile –2.4 (–4.3, –0.5), $p=0.015$) and 6 months after stroke (mean difference third quartile –3.3 (–5.5, –1.2), $p=0.002$, mean difference fourth quartile –2.8 (–5.2, –0.3), $p=0.027$). There was no interaction between citalopram treatment and prestroke PASE score on poststroke MDI scores ($p=0.86$).

Conclusions A higher prestroke physical activity level was associated with fewer depressive symptoms 1 and 6 months after stroke. Citalopram treatment did not seem to modify this association.

Trial registration numbers NCT01937182 (ClinicalTrials.gov) and 2013-002253-30 (EUDRACT).

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The study data came from a large well-conducted multicentre randomised controlled trial, assuring standardised collection of data.
- ⇒ The study design assured reliable data on antidepressant therapy use in a cohort of stroke patients.
- ⇒ The study was exploratory, posing a risk for residual confounding.

INTRODUCTION

Stroke is a leading cause of disability and mortality worldwide.¹ Poststroke depression (PSD) is a common consequence of stroke and affects approximately one in three stroke survivors.² Patients suffering from PSD have lower quality of life and increased mortality and disability.^{3–5} Focus on prevention and treatment of PSD has therefore become a vital aspect of stroke care.⁶

Physical activity (PA) provides numerous health benefits. Regular PA can reduce mortality and risk of cardiovascular disease and stroke.⁷ Similarly, regular PA may reduce the risk of depression.^{8–9} Among stroke patients, PA may not only serve as primary prevention. A high prestroke PA level has been associated with reduced stroke severity and may also result in fewer poststroke complications.^{10,11} However, the preventive effect of PA on PSD is less studied. Research has mainly focused on PA performed after stroke and suggest that high poststroke PA can reduce risk of PSD.¹² So far, only one study has examined the association between prestroke PA and poststroke depressive symptoms.¹³ The potentially preventive role of prestroke PA thus remains unclear. Antidepressant therapy, for example, with citalopram, may be another

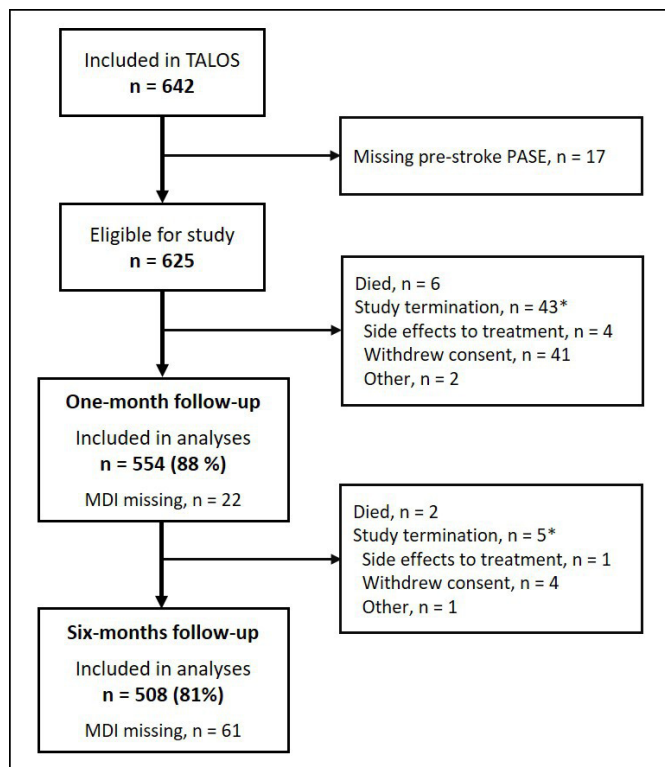


Figure 1 Flow chart of study patients. *One or more reasons for study termination could apply. MDI, Major Depression Inventory; PASE, Physical Activity Scale for the Elderly; TALOS: the efficacy of citalopram Treatment in Acute Ischaemic Stroke.

preventive measure against PSD.^{14 15} Studies of major depressive disorder have proposed a synergistic effect of PA and antidepressant therapy. However, such an effect has not yet been studied in a stroke population.

We aimed to study if higher prestroke PA was associated with fewer poststroke depressive symptoms and if an association was modified by citalopram treatment.

METHODS

Study population

This was a secondary analysis of data from The Efficacy of Citalopram Treatment in Acute Stroke (TALOS) study. TALOS was a multicentre, double-blinded, placebo-controlled, randomised trial of the effect of citalopram on functional outcome and risk of recurrent stroke, myocardial infarction and death in patients with acute ischaemic stroke (AIS).^{16 17} It was conducted in Denmark from 2013 to 2016 and enrolled consecutive patients with first-ever AIS. Adults admitted within 7 days from symptom onset were eligible. Exclusion criteria were antidepressant treatment or indication hereof, known dementia or neurodegenerative disease, contraindications for antidepressant treatment, pregnancy, breast feeding, drug or alcohol abuse, fatal stroke or severe comorbidities causing short remaining life expectancy.

Patients were randomly assigned to either placebo or citalopram in a dosage of 20 mg (10 mg when ≥ 65 years

of age or reduced liver or kidney function) once daily for 6 months. Patients were followed for 6 months with clinical follow-up visits 1 and 6 months after stroke.¹⁶ Patients or their proxy provided written informed consent before enrolment.

The TALOS study was registered under the clinicaltrials.gov unique identifier: NCT01937182 and EUDRACT number: 2013-002253-30. The conduct and safety were reviewed by an independent safety monitoring board.

PA level

Self-reported prestroke PA level was assessed by the validated questionnaire Physical Activity Scale for the Elderly (PASE). The PASE asks responders to report PA performed in the past 7 days. It combines information on leisure time, household and occupational activity to provide a total PA score. Leisure time activity is divided into six levels; for each level, it reports the PA frequency (days/week) and duration (hours/day). Household activities are divided into light and heavy housework, home repair, yard work, gardening and caring for others. Occupational activity includes paid or voluntary work, duration (hours/week) and the PA level involved. The PASE score is the sum of time spent in each activity multiplied by the item's weight the metabolic equivalent of the task. It ranges from 0 to 793 with a higher score indicating a higher PA level.^{18 19} We used the PASE to assess prestroke PA by asking patients to report PA performed 7 days prior to stroke admission. The PASE was completed by the patients or their next of kin.

Depressive symptoms

The Major Depression Inventory (MDI) was used to assess poststroke depressive symptoms at 1-month and 6-month follow-up. The MDI is a validated 10-item questionnaire covering the depressive symptoms of the International Classification of Diseases, 10th revision (ICD-10), as well as the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV).^{20 21} The items are rated on a six-point scale from 'not present at all' to 'present all the time', which corresponds to 0–5 points. Points are added to a total score ranging from 0 to 50, with a higher score indicating greater severity of depressive symptoms. The MDI was completed by the patients, not by their next of kin.

In the TALOS study, patients developing symptoms of clinical depression had dosage of their project medication doubled. If they were still considered clinically depressed at a physician's reassessment 2 weeks later, they were switched to open-label antidepressant therapy and excluded from further study activities. In the present study, those patients were included and assigned an MDI score of 21 corresponding to mild depression.²²

Statistical analyses

Prestroke PASE score was divided into quartiles. Univariable and multivariable linear regression models were used to evaluate the associations between prestroke

Table 1 Baseline characteristics of study patients overall and by prestroke PASE score quartile

	Overall n=625	PASE score quartiles			
		First n=157	Second n=156	Third n=156	Fourth n=156
PASE score, median (IQR), range	132.5 (76, 197)	<76	76–132.5	132.5–197	≥197
Study treatment, n (%)					
Citalopram	309 (49%)	75 (48%)	78 (50%)	79 (51%)	77 (49%)
Placebo	316 (51%)	82 (52%)	78 (50%)	77 (49%)	79 (51%)
Female, n (%)	215 (34%)	72 (46%)	61 (39%)	54 (35%)	28 (18%)
Age, median (IQR)	69 (60, 77)	76 (67, 82)	72 (66, 78)	66 (57, 74)	60 (53, 69)
Cohabitation, n (%)	409 (65%)	75 (48%)	107 (69%)	108 (69%)	119 (76%)
History of smoking, n (%)	195 (32%)	37 (24%)	48 (31%)	56 (36%)	54 (36%)
Missing	17	5	3	2	7
Diabetes, n (%)	71 (11%)	22 (14%)	19 (12%)	16 (10%)	14 (9.2%)
Missing	7	2	1	1	3
Hypertension, n (%)	325 (52%)	97 (62%)	93 (60%)	75 (48%)	60 (39%)
Missing	5	1	0	1	3
Atrial fibrillation, n (%)	102 (17%)	33 (21%)	30 (19%)	21 (14%)	18 (12%)
Missing	7	2	1	1	3
Prior MI, n (%)	52 (8.4%)	10 (6.5%)	20 (13%)	11 (7.2%)	11 (7.2%)
Missing	9	2	0	3	4
Prior transient ischaemic attack, n (%)	16 (2.6%)	3 (2.0%)	5 (3.2%)	5 (3.2%)	3 (2.0%)
Missing	9	4	0	1	4
PAD, n (%)	25 (4.1%)	10 (6.6%)	7 (4.5%)	5 (3.3%)	3 (2.0%)
Missing	14	6	1	3	4
Admission NIHSS, median (IQR)	3 (2, 6)	3 (2, 7)	3 (2, 6)	4 (2, 6)	3 (1, 5)
Missing	12	4	2	2	4
Reperfusion, n (%)	237 (38%)	51 (32%)	62 (40%)	57 (37%)	67 (43%)
Follow-up time, days, median (IQR)	180 (161, 185)	177 (99, 184)	180 (148, 184)	181 (172, 186)	180 (167, 186)

MI, myocardial infarction; NIHSS, National Institute of Health Stroke Scale; PAD, peripheral arterial disease; PASE, Physical Activity Scale for the Elderly; TIA, transient ischaemic attack.

PASE quartiles and MDI scores at 1-month and 6-month follow-up. Observations registered after 38 days were considered 6-month observations. In the multivariable regressions, all available covariates were included. Binary variables (yes/no) included in the analyses were citalopram treatment, female sex, cohabitant status, hypertension, diabetes, atrial fibrillation, peripheral vascular disease, history of myocardial infarction, transient ischaemic attack, smoking status and reperfusion therapy. Continuous variables included in the analyses were age and admission National Institute of Health Stroke Scale (NIHSS) score. NIHSS assesses stroke severity on a numerical scale ranging from 0 to 42 with a higher score indicating greater stroke severity.

Interaction between prestroke PASE score and citalopram treatment on poststroke MDI score was evaluated by a Wald test obtained from the multivariable linear regression models. Two sensitivity analyses were performed: the first excluded patients, who required open-label antidepressant therapy, while the second excluded patients,

who had not participated in the completion of the PASE. The sensitivity analyses were performed by repeating the regression models as described. As an exploratory analysis, univariable and multivariable linear regressions were performed to evaluate the associations between prestroke PA and admission NIHSS score. Results are presented as mean differences with a 95% CI. In addition, natural cubic spline models with knots at the PASE score quartiles were used to evaluate the relationship between prestroke PASE score as a continuous variable and poststroke MDI score. All analyses were performed in R V.4.2.1.²³

Patient and public involvement

No patients or members of the public were involved in the design, conduct, reporting or dissemination plans of the study.

Table 2 Linear regression models of the associations between prestroke PASE quartiles, other baseline characteristics and mean MDI score differences 1 and 6 months after stroke

	One-month MDI scores				Six-month MDI scores				
	Unadjusted		Adjusted		Unadjusted		Adjusted		
	Mean differences (95% CI)	P value	Mean differences (95% CI)	P value	Mean differences (95% CI)	P value	Mean differences (95% CI)	P value	
Prestroke PASE score†									
First quartile	Ref	–	Ref	–	Ref	–	Ref	–	–
Second quartile	–0.6 (–2.7, 1.5)	0.580	–0.04 (–2.2, 2.1)	0.971	–1.9 (–4.2, 0.3)	0.093	–1.4 (–3.8, 0.9)	0.227	
Third quartile	–2.3 (–4.2, –0.4)	0.017	–2.3 (–4.2, –0.5)	0.013	–3.3 (–5.4, –1.3)	0.002	–3.3 (–5.5, –1.2)	0.002	
Fourth quartile	–3.0 (–4.7, –1.4)	<0.001	–2.4 (–4.3, –0.5)	0.015	–3.2 (–5.4, –1.1)	0.003	–2.8 (–5.2, –0.3)	0.027	
Study treatment									
Placebo	Ref	–	Ref	–	Ref	–	Ref	–	–
Citalopram	0.6 (–0.7, 1.9)	0.360	0.9 (–0.4, 2.2)	0.196	–0.6 (–2.0, 0.8)	0.398	–1.4 (–3.8, 0.9)	0.227	
Sex									
Male	Ref	–	Ref	–	Ref	–	Ref	–	–
Female	1.4 (–0.02, 2.8)	0.053	1.6 (0.2, 3.1)	0.028	2.4 (0.8, 3.9)	0.004	2.3 (0.6, 4.0)	0.009	
Age, per year increase	0.003 (–0.1, 0.1)	0.903	–0.1 (–0.1, 0.002)	0.059	0.01 (–0.1, 0.1)	0.779	–0.06 (–0.1, 0.01)	0.107	
Cohabitation status									
Living alone	Ref	–	Ref	–	Ref	–	Ref	–	–
Cohabitant	–0.001 (–1.4, 1.4)	0.998	0.4 (–1.1, 1.8)	0.622	–1.2 (–2.7, 0.4)	0.148	–0.4 (–2.0, 1.3)	0.661	
Smoking status									
Never smoker	Ref	–	Ref	–	Ref	–	Ref	–	–
History of smoking	–0.9 (–2.3, 0.5)	0.200	–0.9 (–2.2, 0.5)	0.197	0.01 (–1.5, 1.5)	0.988	0.3 (–1.2, 1.8)	0.725	
Medical history‡									
Diabetes	0.9 (–1.1, 3.0)	0.363	1.0 (–1.0, 3.0)	0.311	–0.3 (–2.4, 1.7)	0.741	–0.5 (–2.6, 1.5)	0.599	
Hypertension	1.4 (0.1, 2.7)	0.036	0.6 (–0.7, 2.0)	0.345	1.4 (–0.05, 2.8)	0.058	0.6 (–0.9, 2.1)	0.443	
Atrial fibrillation	–1.0 (–2.7, 0.7)	0.227	–1.2 (–2.8, 0.4)	0.144	–0.1 (–2.1, 1.9)	0.927	–0.7 (–2.6, 1.3)	0.503	
Previous MI	2.5 (–0.5, 5.5)	0.101	2.1 (–1.0, 5.2)	0.176	1.5 (–1.2, 4.1)	0.273	2.3 (–0.7, 5.3)	0.134	
Previous TIA	2.2 (–4.2, 8.5)	0.507	2.0 (–4.3, 8.3)	0.527	–4.5 (–6.4, –2.5)	<0.001	–4.4 (–6.4, –2.4)	<0.001	
PVD	3.3 (–1.5, 8.1)	0.179	4.1 (–1.4, 9.6)	0.143	2.1 (–1.5, 5.8)	0.251	1.4 (–2.8, 5.5)	0.514	
Admission NIHSS score, per point increase	0.2 (0.03, 0.3)	0.017	0.2 (0.03, 0.3)	0.022	0.2 (0.04, 0.4)	0.014	0.2 (0.01, 0.4)	0.038	
Reperfusion treatment									
No	Ref	–	Ref	–	Ref	–	Ref	–	–
Yes	0.2 (–1.2, 1.5)	0.825	–0.2 (–1.6, 1.3)	0.836	–0.04 (–1.5, 1.4)	0.961	–0.4 (–1.9, 1.1)	0.590	

*Adjusted for citalopram treatment, sex, age, cohabitation, history of smoking, diabetes, hypertension, atrial fibrillation, myocardial infarction, transient ischaemic attack, peripheral vascular disease, admission NIHSS score and reperfusion treatment.

†All prestroke PASE score quartiles are compared to the lowest quartile (1st quartile).

‡For all medical history variables, the reference groups are patients who do not have the condition.

MDI, major depression inventory; MI, myocardial infarction; NIHSS, National Institute of Health Stroke Scale; PASE, Physical Activity Scale for the Elderly; PVD, peripheral vascular disease; TIA, transient ischaemic attack.

RESULTS

Participants

Of the 642 patients included in the TALOS study, 625 (97.4%) had a pre-stroke PASE score registered and were eligible for inclusion (figure 1). The prestroke PASE questionnaire was completed at a median of 2 (1–3) days after symptom onset. A total of 564 (90%) patients completed the PASE themselves either solely by themselves or with writing assistance (online supplemental table 1). An MDI

score was available for 554 (88%) patients at 1-month follow-up and 508 (81%) at 6-month follow-up (figure 1). In total, 18 patients were assigned an MDI score of 21 because they required open-label antidepressant treatment; 9 (1.6%) at 1-month follow-up and 9 (1.8%) at 6-month follow-up.

Baseline characteristics of study participants are summarised in table 1. Median age was 69 (60–77) years, 215 (34%) were women, median prestroke PASE score

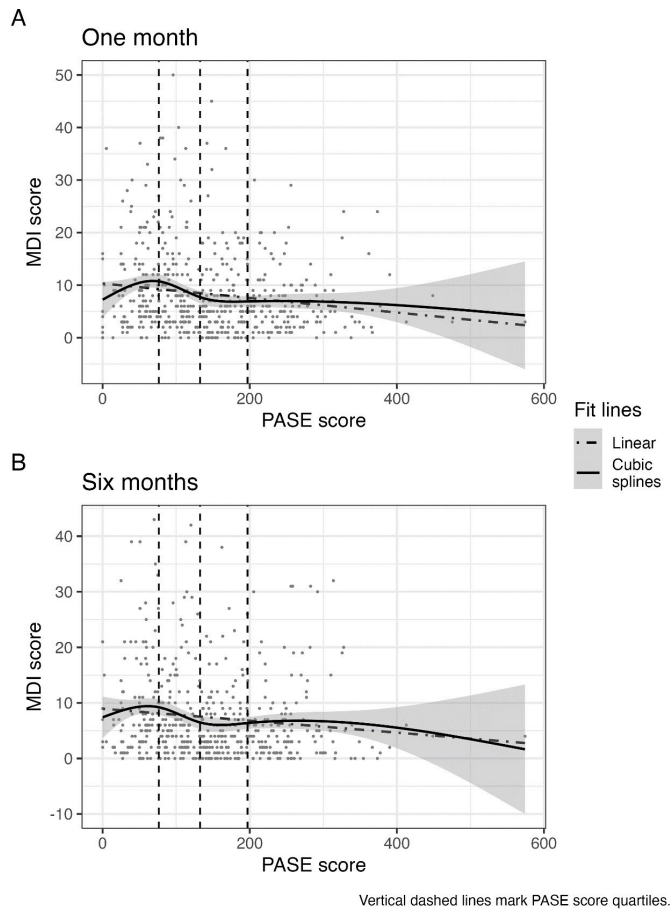


Figure 2 Plots of the cubic spline analyses of the associations between prestroke PASE score and MDI scores at 1-month and 6-month follow-up. (A) One-month observations. (B) Six-month observations. The vertical dashed lines mark the splines defined by quartiles of the prestroke PASE score. The fully drawn line marks the cubic spline regression line with a grey shaded area marking the 95% CI. The dashed black line marks the linear regression line. MDI, major depression inventory; PASE, Physical Activity Scale for the Elderly.

was 132.5 (76–197) and median NIHSS score was 3 (2–6). Baseline characteristics compared between the PASE quartiles showed that those with a high prestroke PA level were younger and more often men, and they were less likely to live alone or to suffer from hypertension, atrial fibrillation or peripheral vascular disease compared with patients with lower prestroke PA level (table 1).

Outcomes: poststroke depressive symptoms

One month after stroke, overall median (IQR) MDI score was 6 (3–11), while the median MDI scores in the PASE quartiles were 7 (4–14) in the first, 6 (3–12) in the second, 5 (2–11) in the third and 5 (3–9) in the fourth quartile. Six months after stroke, overall median (IQR) MDI score was 5 (2–10), and in the PASE quartiles, the median scores were 6 (3–12) in the first, 5 (2–10) in the second, 4 (2–9) in the third and 4 (1–7) in the fourth quartile.

Higher prestroke PASE score (third and fourth PASE quartile compared with the first) was associated with lower MDI scores 1 month after stroke (table 2) in both unadjusted analyses (mean difference third quartile -2.3 (-4.2 to -0.4), $p=0.017$, mean difference fourth quartile -3.0 (-4.7 to -1.4), $p<0.001$) and multivariable analyses (mean difference third quartile -2.3 (-4.2 to -0.5), $p=0.013$, mean difference fourth quartile -2.4 (-4.3 to -0.5), $p=0.015$) after adjusting for citalopram treatment, sex, age, cohabitation, smoking, diabetes, hypertension, atrial fibrillation, myocardial infarction, transient ischaemic attack, peripheral vascular disease, as well as admission NIHSS score and reperfusion treatment. At 6-month follow-up, higher prestroke PASE score was associated with lower MDI scores in both unadjusted analysis (mean difference third quartile -3.3 (-5.4 to -1.3), $p=0.002$, mean difference fourth quartile -3.2 (-5.3 to -1.1), $p=0.003$), and after baseline covariate adjustment (mean difference third quartile -3.3 (-5.5 to -1.2), $p=0.002$, mean difference fourth quartile -2.8 (-5.2 to -0.3), $p=0.027$) (table 2). There was no association between citalopram treatment and MDI score neither 1 nor 6 months after stroke (table 2). An interaction analysis showed no significant interaction between a high prestroke PASE score and citalopram treatment on MDI scores at neither 1-month ($p=0.94$) nor 6-month follow-up ($p=0.86$). Sensitivity analyses showed similar results as those of the main analyses. Both the analysis excluding patients who required open-label antidepressant therapy (online supplemental table 2) and the analysis excluding patients who had not participated in the completion of the PASE (online supplemental table 3) showed that a higher prestroke PASE score (third and fourth PASE quartile compared with the first) was associated with lower MDI scores at 1 month and 6 months after stroke.

Higher NIHSS score was associated with higher MDI scores at both 1-month and 6-month follow-up in multivariable analyses (table 2). An exploratory analysis showed an association between higher prestroke PASE score (fourth PASE quartile compared with the first) and lower admission NIHSS score after adjusting for baseline covariates (mean difference -1.3 (-2.6 to -0.03), $p=0.045$) (online supplemental table 4).

The cubic spline analyses (figure 2) showed that MDI scores at both 1-month and 6-month follow-up decreased with increasing prestroke PASE scores. MDI score differences were most evident between the lowest and highest PASE score halves. For the very lowest PASE scores, MDI scores might increase with increasing PASE scores. The linear regression lines were covered by the spline analyses CIs, thus the linear model could be a reasonable approximation of the relationship between prestroke PASE score and poststroke MDI score (figure 2).

DISCUSSION

In this study of non-depressed patients with acute ischaemic stroke, we found that those with a high PA level



before stroke had fewer depressive symptoms 1 and 6 months after stroke. Our results did not indicate that citalopram treatment modified the association between prestroke PA and poststroke depressive symptoms.

The role of PA on PSD symptoms is only studied to a limited extent. Studies have mainly focused on post-stroke exercise and showed both positive and neutral effects.^{12 24–26} To our knowledge, only one other study has examined the role of prestroke PA. In a post hoc analysis, Bovim *et al*¹³ found that higher prestroke PA was associated with fewer depressive symptoms 3 months after stroke. However, the study did not supply information on depressive symptoms at inclusion neither on use of antidepressant treatment during the study. In addition to confirming the potential preventive role of prestroke PA, our study offers knowledge about the yet unstudied role of prestroke PA and selective serotonin reuptake inhibitors (SSRIs) treatment in combination. In clinical studies, SSRI therapy for non-depressed stroke patients has been shown to reduce PSD risk.^{14 15} Furthermore, a synergistic effect between PA and SSRI has been proposed to reduce depressive symptoms among patients suffering from major depressive disorder.^{27 28} However, in this population of non-depressed stroke patients, we could not show such a modifying effect of citalopram treatment.

Prestroke PA may reduce poststroke depressive symptoms through several mechanisms. Prestroke PA may induce neuroprotection through beneficial effects on vascular risk factors²⁹ or it may reduce inflammation, stimulate cerebral angiogenesis and maintain the blood–brain barrier after stroke.^{30 31} Moreover, in clinical studies, higher prestroke PA has been associated with reduced stroke severity, infarct size and growth and improved functional outcome.^{10 11 32} As stroke severity and post-stroke disability are potential risk factors for PSD,^{4 33} higher prestroke PA might reduce risk of PSD mediated by these factors. We did find that higher prestroke PA was associated with lower admission NIHSS score and that higher admission NIHSS was associated with higher MDI scores up to 6 months after stroke. This indicates that the association between higher prestroke PA and fewer post-stroke depressive symptoms may be partly explained by lower stroke severity.

The main strength of our study is that the data are based on a large well-conducted randomised controlled trial, which assured compliance to treatment and standardised collection of outcome data.¹⁷ However, since analyses are exploratory, we cannot rule out residual confounding by factors such as history of depression or educational level. Another limitation was that TALOS excluded patients, who developed symptoms of clinical depression. As a conservative estimate, they were assigned an MDI score of 21, which corresponds to the threshold score for mild depression. Furthermore, sensitivity analyses without these patients showed similar results as the main analyses.

Though PASE only assesses PA 1 week prior to completion, it has been shown to be a valid measure of overall PA and to correlate to general physical capacity.^{19 34}

Furthermore, by only assessing PA performed in the past 7 days, the PASE may reduce risk of recall bias. However, in this population, the recent stroke may affect the ability to recall prestroke PA. Ten per cent of study patients had the PASE completed by their next of kin, which could introduce bias. However, the sensitivity analysis without these patients showed similar results as the main analyses.

Patients included in the study suffered from mild to moderate stroke symptoms, making the results less generalisable to patients suffering from severe strokes. Finally, since the study only enrolled non-depressed patients, it does not allow us to draw any conclusions on the effect of citalopram treatment in a clinical setting where treatment is initiated in patients with an established treatment indication.

CONCLUSION

Among non-depressed patients with minor to moderate ischaemic strokes, a high prestroke PA level was associated with fewer depressive symptoms up to 6 months after stroke. Citalopram treatment did not seem to modify this association. Our findings suggest that the association between higher prestroke PA and fewer poststroke depressive symptoms may be partly explained by lower stroke severity.

Contributors GA, SPJ and JKM conceived the study. All authors contributed to the study design and analysis plan. AGD, GA and JKM contributed to data collection. AGD was responsible for data analysis, and all authors contributed to data interpretation. SV drafted the manuscript. All authors contributed to critical revision and final approval of the manuscript. SV and JKM accepts full responsibility for the finished work and the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The TALOS study and subsequent analyses were approved by the local institutional review board and the Committees on Health Research Ethics (1-10-72-183-13). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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REFERENCES

- Feigin VL, Stark BA, Johnson CO. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet Neurol* 2021;20:795–820.
- Hackett ML, Pickles K. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. *Int J Stroke* 2014;9:1017–25.
- Cai W, Mueller C, Li Y-J, et al. Post stroke depression and risk of stroke recurrence and mortality: a systematic review and meta-analysis. *Ageing Res Rev* 2019;50:102–9.
- Ayerbe L, Ayis S, Wolfe CDA, et al. Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. *Br J Psychiatry* 2013;202:14–21.
- Kutlubaev MA, Hackett ML. Part II: predictors of depression after stroke and impact of depression on stroke outcome: an updated systematic review of observational studies. *Int J Stroke* 2014;9:1026–36.
- Towfighi A, Ovbiagele B, El Hussein N, et al. Poststroke depression: a scientific statement for healthcare professionals from the American heart association/american stroke association. *Stroke* 2017;48:e30–43.
- Kraus WE, Powell KE, Haskell WL, et al. Physical activity, all-cause and cardiovascular mortality, and cardiovascular disease. *Med Sci Sports Exerc* 2019;51:1270–81.
- Schuch FB, Vancampfort D, Firth J, et al. Physical activity and incident depression: a meta-analysis of prospective cohort studies. *Am J Psychiatry* 2018;175:631–48.
- Harvey SB, Øverland S, Hatch SL, et al. Exercise and the prevention of depression: results of the HUNT cohort study. *Am J Psychiatry* 2018;175:28–36.
- Krarup L-H, Truelsen T, Gluud C, et al. Prestroke physical activity is associated with severity and long-term outcome from first-ever stroke. *Neurology* 2008;71:1313–8.
- Ricciardi AC, López-Cancio E, Pérez de la Ossa N, et al. Prestroke physical activity is associated with good functional outcome and arterial recanalization after stroke due to a large vessel occlusion. *Cerebrovasc Dis* 2014;37:304–11.
- Eng JJ, Reime B. Exercise for depressive symptoms in stroke patients: a systematic review and meta-analysis. *Clin Rehabil* 2014;28:731–9.
- Bovim MR, Indredavik B, Hokstad A, et al. Relationship between pre-stroke physical activity and symptoms of post-stroke anxiety and depression: an observational study. *J Rehabil Med* 2019;51:755–60.
- Salter KL, Foley NC, Zhu L, et al. Prevention of poststroke depression: does prophylactic pharmacotherapy work? *J Stroke Cerebrovasc Dis* 2013;22:1243–51.
- Robinson RG, Jorge RE, Moser DJ, et al. Escitalopram and problem-solving therapy for prevention of poststroke depression: a randomized controlled trial. *JAMA* 2008;299:2391–400.
- Kraglund KL, Mortensen JK, Grove EL, et al. TALOS: a multicenter, randomized, double-blind, placebo-controlled trial to test the effects of citalopram in patients with acute stroke. *Int J Stroke* 2015;10:985–7.
- Kraglund KL, Mortensen JK, Damsbo AG, et al. Neuroregeneration and vascular protection by citalopram in acute ischemic stroke (TALOS). *Stroke* 2018;49:2568–76.
- Washburn RA, Smith KW, Jette AM, et al. The physical activity scale for the elderly (PASE): development and evaluation. *J Clin Epidemiol* 1993;46:153–62.
- Washburn RA, McAuley E, Katula J, et al. The physical activity scale for the elderly (PASE): evidence for validity. *J Clin Epidemiol* 1999;52:643–51.
- Bech P, Rasmussen NA, Olsen LR, et al. The sensitivity and specificity of the major depression inventory, using the present state examination as the index of diagnostic validity. *J Affect Disord* 2001;66:159–64.
- Olsen LR, Jensen DV, Noerholm V, et al. The internal and external validity of the major depression inventory in measuring severity of depressive states. *Psychol Med* 2003;33:351–6.
- Bech P, Timmerby N, Martiny K, et al. Psychometric evaluation of the major depression inventory (MDI) as depression severity scale using the lead (longitudinal expert assessment of all data) as index of validity. *BMC Psychiatry* 2015;15:190.
- R Core Team. R: A language and environment for statistical computing. 2021. Available: <https://www.r-project.org/>
- Lai S-M, Studenski S, Richards L, et al. Therapeutic exercise and depressive symptoms after stroke. *J Am Geriatr Soc* 2006;54:240–7.
- Ryan T, Enderby P, Rigby AS. A randomized controlled trial to evaluate intensity of community-based rehabilitation provision following stroke or hip fracture in old age. *Clin Rehabil* 2006;20:123–31.
- Mead GE, Greig CA, Cunningham I, et al. Stroke: a randomized trial of exercise or relaxation. *J Am Geriatr Soc* 2007;55:892–9.
- Guerrera CS, Furneri G, Grasso M, et al. Antidepressant drugs and physical activity: a possible synergism in the treatment of major depression? *Front Psychol* 2020;11:857.
- Belvederi Murri M, Amore M, Menchetti M, et al. Physical exercise for late-life major depression. *Br J Psychiatry* 2015;207:235–42.
- García-Cabo C, López-Cancio E. Exercise and stroke. *Adv Exp Med Biol* 2020;1228:195–203.
- Pin-Barre C, Laurin J. Physical exercise as a diagnostic, rehabilitation, and preventive tool: influence on neuroplasticity and motor recovery after stroke. *Neural Plast* 2015;2015:608581.
- Hafez S, Eid Z, Alabasi S, et al. Mechanisms of preconditioning exercise-induced neurovascular protection in stroke. *J Stroke* 2021;23:312–26.
- Blauenfeldt RA, Hougaard KD, Mouridsen K, et al. High prestroke physical activity is associated with reduced infarct growth in acute ischemic stroke patients treated with intravenous TPA and randomized to remote ischemic preconditioning. *Cerebrovasc Dis* 2017;44:88–95.
- Mortensen JK, Johnsen SP, Andersen G. Prescription and predictors of post-stroke antidepressant treatment: a population-based study. *Acta Neurol Scand* 2018;138:235–44.
- Sattler MC, Jaunig J, Tösch C, et al. Current evidence of measurement properties of physical activity questionnaires for older adults: an updated systematic review. *Sports Med* 2020;50:1271–315.

Supplementary Table 1. Baseline characteristics of study patients overall and by PASE questionnaire respondent

	PASE questionnaire respondent		
	Overall	Next of kin	Patient
N	625	61 (10%)	564 (90%)
PASE score quartile, n (%)			
1st	157 (25%)	15 (25%)	142 (25%)
2nd	156 (25%)	18 (30%)	138 (24%)
3rd	156 (25%)	14 (23%)	142 (25%)
4th	156 (25%)	14 (23%)	142 (25%)
Study treatment, n (%)			
Citalopram	309 (49%)	31 (51%)	278 (49%)
Placebo	316 (51%)	30 (49%)	286 (51%)
Female, n (%)	215 (34%)	27 (44%)	188 (33%)
Age, median (IQR)	69 (60, 77)	70 (63, 77)	69 (59, 77)
Cohabitation, n (%)	409 (65%)	38 (62%)	371 (66%)
History of smoking, n (%)	195 (32%)	24 (41%)	171 (31%)
Missing	17	2	15
Diabetes, n (%)	71 (11%)	6 (9.8%)	65 (12%)
Missing	7	0	7
Hypertension, n (%)	325 (52%)	32 (52%)	293 (52%)
Missing	5	0	5
Atrial Fibrillation, n (%)	102 (17%)	15 (25%)	87 (16%)
Missing	7	1	6
Prior MI, n (%)	52 (8.4%)	7 (12%)	45 (8.1%)
Missing	9	1	8
Prior TIA, n (%)	16 (2.6%)	2 (3.3%)	14 (2.5%)
Missing	9	0	9
PAD, n (%)	25 (4.1%)	4 (6.6%)	21 (3.8%)
Missing	14	0	14
Baseline NIHSS, median (IQR)	3 (2, 6)	11 (4, 18.5)	3 (2, 5)
Missing	12	2	10

Reperfusion, n(%)	237 (38%)	33 (54%)	204 (36%)
Follow-up time, days, median (IQR)	180 (161, 185)	175 (40, 183)	180 (167, 185)

PASE: Physical Activity Scale for the Elderly, MI: myocardial infarction, PAD: peripheral arterial disease, NIHSS: National Institute of Health Stroke Scale, IQR: interquartile range

Supplementary Table 2: Linear regression models of the associations between pre-stroke PASE quartiles, other baseline parameters and mean MDI-score differences one and six months after stroke. A sensitivity analysis without patients requiring open-label antidepressant therapy

	One month MDI scores				Six month MDI scores			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*	
	Mean differences (95% CI)	p-value	Mean differences (95% CI)	p-value	Mean differences (95% CI)	p-value	Mean differences (95% CI)	p-value
Pre-stroke PASE score†								
1 st quartile	Ref	-	Ref	-	Ref	-	Ref	-
2 nd quartile	-0.6 (-2.7, 1.5)	0.566	-0.1 (-2.2, 2.1)	0.954	-1.4 (-3.7, 0.9)	0.220	-1.2 (-3.5, 1.2)	0.335
3 rd quartile	-1.9 (-3.8, -0.1)	0.043	-2.0 (-3.8, -0.2)	0.034	-2.8 (-4.9, -0.8)	0.008	-3.0 (-5.1, -0.9)	0.006
4 th quartile	-2.8 (-4.4, -1.1)	0.001	-2.1 (-4.0, -0.2)	0.029	-2.7 (-4.9, -0.6)	0.014	-2.4 (-4.8, -0.03)	0.048
Study treatment								
Placebo	Ref	-	Ref	-	Ref	-	Ref	-
Citalopram	0.7 (-0.6, 2.1)	0.264	1.1 (-0.2, 2.4)	0.112	-0.6 (-2.0, 0.8)	0.419	-0.4 (-1.8, 1.0)	0.558
Sex								
Male	Ref	-	Ref	-	Ref	-	Ref	-
Female	1.3 (-0.1, 2.7)	0.065	1.7 (0.2, 3.2)	0.022	2.4 (0.8, 4.0)	0.003	2.1 (0.4, 3.9)	0.014
Age, per year increase	-0.001 (-0.1, 0.1)	0.964	-0.1 (-0.1, 0.01)	0.071	0.01 (-0.1, 0.1)	0.874	-0.1 (-0.1, 0.01)	0.105
Cohabitation status								
Living alone	Ref	-	Ref	-	Ref	-	Ref	-
Cohabitant	-0.01 (-1.4, 1.4)	0.986	0.3 (-1.2, 1.7)	0.705	-1.3 (-2.9, 0.3)	0.103	-0.7 (-2.4, 0.9)	0.364
Smoking status								
Never smoker	Ref	-	Ref	-	Ref	-	Ref	-
History of smoking	-1.0 (-2.3, 0.4)	0.171	-0.9 (-2.2, 0.4)	0.175	-0.1 (-1.6, 1.4)	0.892	0.2 (-1.3, 1.7)	0.812

Medical history‡								
Diabetes	0.7 (-1.3, 2.8)	0.470	0.8 (-1.2, 2.8)	0.434	-0.7 (-2.6, 1.3)	0.491	-1.1 (-3.0, 0.9)	0.271
Hypertension	1.5 (0.2, 2.8)	0.026	0.7 (-0.6, 2.1)	0.273	1.3 (-0.1, 2.7)	0.060	0.8 (-0.7, 2.3)	0.310
Atrial fibrillation	-1.2 (-2.8, 0.5)	0.168	-1.0 (-2.6, 0.6)	0.215	-0.3 (-2.2, 1.7)	0.792	-0.8 (-2.7, 1.1)	0.395
Previous MI	2.5 (-0.5, 5.6)	0.107	2.0 (-1.1, 5.1)	0.200	1.0 (-1.6, 3.7)	0.441	2.4 (-0.6, 5.3)	0.121
Previous TIA	2.4 (-4.0, 8.7)	0.464	2.2 (-4.0, 8.5)	0.484	-4.2 (-6.2, -2.3)	<0.001	-4.3 (-6.4, -2.2)	<0.001
PVD	3.5 (-1.3, 8.3)	0.151	4.3 (-1.2, 9.8)	0.128	1.8 (-1.8, 5.4)	0.335	1.6 (-2.5, 5.6)	0.455
Admission NIHSS score, per point increase	0.1 (-0.04, 0.2)	0.168	0.1 (-0.03, 0.3)	0.106	0.2 (0.03, 0.4)	0.023	0.2 (-0.01, 0.4)	0.064
Reperfusion treatment								
No	Ref	-	Ref	-	Ref	-	Ref	-
Yes	-0.1 (-1.4, 1.2)	0.874	-0.2 (-1.7, 1.2)	0.731	0.1 (-1.3, 1.6)	0.860	-0.2 (-1.7, 1.2)	0.746

MDI: Major depression inventory, CI: confidence interval, PASE: Physical Activity Scale for the Elderly, MI: myocardial infarction, TIA: transient ischemic attack, PVD: peripheral vascular disease, NIHSS: National Institute of Health Stroke Scale

* Adjusted for citalopram treatment, sex, age, cohabitation, history of smoking, diabetes, hypertension, atrial fibrillation, myocardial infarction, transient ischemic attack, peripheral vascular disease, admission NIHSS score, and reperfusion treatment

† All pre-stroke PASE score quartiles are compared to the highest quartile (1st quartile)

‡ For all medical history variables the reference groups are patients who do not have the condition

Supplementary Table 3: Linear regression models of the associations between pre-stroke PASE quartiles, other baseline parameters and mean MDI-score differences one and six months after stroke. A sensitivity analysis without patients who did not participate in the completion of the PASE

	One month MDI scores				Six month MDI scores			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*	
	Mean differences (95% CI)	p-value	Mean differences (95% CI)	p-value	Mean differences (95% CI)	p-value	Mean differences (95% CI)	p-value
Pre-stroke PASE score†								
1 st quartile	Ref	-	Ref	-	Ref	-	Ref	-
2 nd quartile	-0.9 (-3.1, 1.4)	0.439	-0.4 (-2.7, 2.0)	0.761	-1.7 (-4.0, 0.6)	0.138	-1.4 (-3.8, 1.0)	0.248
3 rd quartile	-2.7 (-4.7, -0.8)	0.006	-2.7 (-4.6, -0.8)	0.005	-3.5 (-5.6, -1.4)	0.001	-3.7 (-5.9, -1.4)	0.001
4 th quartile	-2.9 (-4.6, -1.1)	0.002	-2.1 (-4.2, -0.1)	0.039	-3.0 (-5.2, -0.8)	0.009	-2.6 (-5.2, -0.1)	0.041
Study treatment								
Placebo	Ref	-	Ref	-	Ref	-	Ref	-
Citalopram	0.6 (-0.8, 2.0)	0.406	0.9 (-0.5, 2.3)	0.202	-0.7 (-2.2, 0.7)	0.324	-0.7 (-2.2, 0.7)	0.326
Sex								
Male	Ref	-	Ref	-	Ref	-	Ref	-
Female	1.0 (-0.5, 2.5)	0.177	1.3 (-0.2, 2.8)	0.100	2.1 (0.5, 3.7)	0.012	2.0 (0.3, 3.8)	0.023
Age, per year increase	0.01 (-0.05, 0.06)	0.867	-0.05 (-0.12, 0.01)	0.103	0.004 (-0.06, 0.07)	0.895	-0.06 (-0.12, 0.01)	0.115
Cohabitation status								
Living alone	Ref	-	Ref	-	Ref	-	Ref	-
Cohabitant	-0.2 (-1.7, 1.2)	0.741	-0.1 (-1.7, 1.5)	0.917	-1.0 (-2.6, 0.7)	0.248	-0.3 (-2.0, 1.4)	0.713
Smoking status								
Never smoker	Ref	-	Ref	-	Ref	-	Ref	-
History of smoking	-1.3 (-2.8, 0.1)	0.072	-1.2 (-2.6, 0.3)	0.109	-0.6 (-2.1, 0.9)	0.435	-0.3 (-1.8, 1.3)	0.736

Medical history‡								
Diabetes	0.5 (-1.6, 2.6)	0.627	0.5 (-1.6, 2.5)	0.666	-0.1 (-2.2, 2.0)	0.893	-0.7 (-2.7, 1.4)	0.523
Hypertension	1.5 (0.1, 2.8)	0.038	0.8 (-0.6, 2.2)	0.267	1.4 (0.0, 2.9)	0.050	0.8 (-0.8, 2.3)	0.319
Atrial fibrillation	-0.9 (-2.7, 0.8)	0.302	-0.9 (-2.6, 0.8)	0.307	-0.8 (-2.6, 1.0)	0.402	-1.2 (-3.0, 0.6)	0.188
Previous MI	2.6 (-0.8, 6.1)	0.137	1.9 (-1.6, 5.4)	0.278	1.3 (-1.6, 4.2)	0.390	2.4 (-0.9, 5.7)	0.160
Previous TIA	1.6 (-5.7, 8.9)	0.671	1.8 (-5.5, 9.0)	0.629	-5.3 (-6.8, -3.8)	< 0.001	-5.2 (-6.7, -3.6)	<0.001
PVD	3.3 (-2.2, 8.7)	0.239	4.2 (-2.0, 10.3)	0.182	0.7 (-3.3, 4.8)	0.719	0.6 (-4.0, 5.2)	0.799
Admission NIHSS score, per point increase	0.2 (0.0, 0.4)	0.027	0.2 (0.0, 0.4)	0.023	0.2 (0.0, 0.4)	0.076	0.2 (0.0, 0.5)	0.097
Reperfusion treatment								
No	Ref	-	Ref	-	Ref	-	Ref	-
Yes	0.0 (-1.4, 1.4)	0.986	-0.3 (-1.8, 1.3)	0.723	-0.1 (-1.6, 1.4)	0.88	-0.5 (-2.1, 1.0)	0.504

MDI: Major depression inventory, CI: confidence interval, PASE: Physical Activity Scale for the Elderly, MI: myocardial infarction, TIA: transient ischemic attack, PVD: peripheral vascular disease, NIHSS: National Institute of Health Stroke Scale

* Adjusted for citalopram treatment, sex, age, cohabitation, history of smoking, diabetes, hypertension, atrial fibrillation, myocardial infarction, transient ischemic attack, peripheral vascular disease, admission NIHSS score, and reperfusion treatment

† All pre-stroke PASE score quartiles are compared to the highest quartile (1st quartile)

‡ For all medical history variables the reference groups are patients who do not have the condition

Supplementary Table 4: Linear regression models of the association between pre-stroke PASE quartiles, other baseline parameters and admission NIHSS score.

	Unadjusted		Adjusted*	
	Mean differences (95% CI)	p-value	Mean differences (95% CI)	p-value
Pre-stroke PASE score[†]				
1st quartile	Ref	-	Ref	-
2nd quartile	-0.4 (-1.6, 0.8)	0.544	-0.2 (-1.5, 1.0)	0.701
3rd quartile	-0.5 (-1.7, 0.7)	0.434	-0.2 (-1.5, 1.1)	0.769
4th quartile	-1.6 (-2.7, -0.5)	0.006	-1.3 (-2.6, -0.03)	0.045
Sex				
Male	Ref	-	Ref	-
Female	1.3 (0.4, 2.2)	0.005	1.0 (0.03, 2.0)	0.043
Age, per year increase	0.04 (0.004, 0.1)	0.029	0.01 (-0.03, 0.05)	0.534
Cohabitation status				
Living alone	Ref	-	Ref	-
Cohabitant	0.03 (-0.8, 0.9)	0.952	0.4 (-0.5, 1.3)	0.383
Smoking status				
Never smoker	Ref	-	Ref	-
History of smoking	0.3 (-0.6, 1.1)	0.557	-0.01 (-0.9, 0.9)	0.991
Medical history[‡]				
Diabetes	-0.2 (-1.5, 1.0)	0.696	0.05 (-1.3, 1.4)	0.942
Hypertension	-0.5 (-1.3, 0.3)	0.234	-0.9 (-1.8, -0.04)	0.041
Atrial fibrillation	2.3 (1.0, 3.6)	0.001	2.1 (0.8, 3.5)	0.002
Previous MI	-0.03 (-1.5, 1.4)	0.965	0.4 (-1.1, 1.9)	0.605
Previous TIA	-1.7 (-2.9, -0.5)	0.005	-1.5 (-2.5, -0.5)	0.002
PVD	-0.1 (-2.1, 1.9)	0.940	-1.5 (-3.4, 0.4)	0.127

NIHSS: National Institute of Health Stroke Scale, PASE: Physical Activity Scale for the Elderly, CI: confidence interval, MI: myocardial infarction, TIA: transient ischemic attack, PVD: peripheral vascular disease

* Adjusted for sex, age, cohabitant status, history of smoking, diabetes, hypertension, atrial fibrillation, myocardial infarction, transient ischemic attack, and peripheral vascular disease

† All pre-stroke PASE score quartiles are compared to the highest quartile (1st quartile)

‡ For all medical history variables the reference groups are patients who do not have the condition