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Habitual physical activity levels predict treatment outcomes in depressed adults: a prospective cohort study.

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ABSTRACT

Objective: Exercise is an efficacious stand-alone therapy for mild-to-moderate depression, but little is known about the influence of physical activity levels on responses to depression treatment. This study aimed to prospectively assess the association between self-reported habitual physical activity levels and depression severity following a 12-week intervention.

Method: 629 adults (75% women; aged 18-71 years) with mild-to-moderate depression were recruited from primary care centers across Sweden and treated for 12 weeks. The interventions included internet-based cognitive behavioural therapy (ICBT) and 'usual care' (CBT or supportive counseling). One third of all participants were taking anti-depressant medication. The primary outcome was the change in depression severity assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS). Habitual physical activity levels were self-rated and based on the estimated frequency, duration and intensity of total physical activity, including planned exercise, 'during a typical week'. Prospective associations were explored using linear regression models (percentage change) with 95% confidence intervals (CI's).

Results: Following adjustment for relevant covariates, high levels of habitual physical activity were associated with larger relative reductions in depression severity compared to low physical activity (β=-9.19, 95% CI=-18.46,-0.09, $p=0.052$) and moderate physical activity (β=-10.81, 95% CI=-21.09,-0.53, $P<0.05$), respectively.

Conclusion: Adults who routinely engage in high levels of physical activity respond more favorably to CBT-focused depression treatments than adults who engage in low-to-moderate levels of activity. The optimal level of physical activity associated with reductions in depression severity corresponds to consensus recommendations for maximizing general health. One limitation is the use of self-reported physical activity data.

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INTRODUCTION

Depression is a debilitating illness that tends to be recurrent. Evidence-based treatment continues to grow, but successful treatment and maintenance of treatment response remains limited [1]. Thus, there is a continued need for research into behavioural and biological factors that predict successful treatment response in order to facilitate the development of efficacious treatment strategies.

To date, the effects of physical activity on depression have largely been explored using intervention studies, where changes in depression severity have been assessed before and after a prescribed exercise intervention [2]. Three Cochrane reviews have each concluded that exercise is moderately more effective than a control intervention for reducing symptoms of depression (standardised mean difference from 35 trials = -0·62) [3-5]. Exercise, however, is only one subtype of physical activity, involving planned, repetitive movement, purposefully engaged in to improve fitness and/or health [6]. Physical activity has a broader definition, and includes all forms of daily movement that result in energy expenditure above resting levels [6]. Importantly, these non-exercise activities contribute a much larger proportion to overall energy expenditure than planned exercise does on a daily basis [7]. Indeed, the need to promote *both* exercise and physical activity in this population is high due to the heightened physical comorbidities associated with the disorder, including metabolic syndrome [8] and diabetes [9], which ultimately increase the risk of premature mortality [10].

Previous longitudinal research has examined associations between physical activity and depression primarily in non-clinical samples [11-14]. Indeed, a systematic review of 30 prospective studies by Mammon and Faulkner (2013) reported that baseline physical activity was negatively associated with the risk of subsequent depression in 25 out of 30 non-clinical studies [15]. The authors also concluded that any level of physical activity might be protective, with even light activities (e.g. walking) associated with improvement. This review provides useful information about the relationship between physical activity and the *onset* of depressive illness in otherwise healthy individuals. However, an equally important question – one that has not yet been addressed - is whether different levels of habitual physical activity influence the *response* to depression treatment.

We examined longitudinal relationships of self-reported habitual physical activity levels with depression severity in adults following a 12-week intervention involving either internet-based

cognitive behavioural therapy (ICBT), or 'usual care' administered by a physician (CBT with a psychologist, or supportive counseling). We also investigated the influence of meeting consensus physical activity recommendations for general health; and, possible gender-related effects.

METHOD

Study design

Data originate from the 'Regassa' study, a randomized controlled trial (RCT) conducted in primary care centres across Sweden to assess the long-term effectiveness of three 12-week interventions for mild-to-moderate depression in adults: exercise, internet-based cognitive behavioural therapy (ICBT) and treatment as usual. The RCT methodology and interim findings were published previously [16]. The present study includes data from the ICBT and usual care participants only and uses a prospective design with two assessment points: baseline and 3-month follow-up (post-treatment). The ethical review board at the Karolinska Institutet approved the study (Dnr 2010/1779-31/4). All patients provided written informed consent prior to participation. The trial protocol is registered with German Clinical Trial Register (DRKS study ID: DRKS00008745).

Patient recruitment

Patients were recruited via primary health care facilities located in six county councils in Sweden (Stockholm, Skåne, Västra Götaland, Kronoberg, Blekinge and Västmanland). The selection of regions was deliberate and helped ensure that the sample included participants from different locations varying in population size and composition. Together, these counties represent 60% of the Swedish population. Patients aged ≥18 years who scored >9 on the Patient Health Questionnaire (PHQ-9) were invited to participate in the trial. Recruitment began in February 2011 and the last participants finished the 12-week treatment in March 2013. Exclusion criteria were: a severe somatic illness, a primary alcohol or drug use disorder or a psychiatric diagnosis that required specialist treatment (e.g. psychosis). Potentially eligible patients were referred by their primary health care provider. Upon referral, trained research assistants obtained written informed consent, formally assessed trial eligibility by conducting a standardized diagnostic interview (described below), and administered outcome questionnaires. This assessment constituted the baseline evaluation. The randomization and blinding procedure is described elsewhere [16].

Follow-up assessment

All patients were contacted by a research assistant at post-treatment to attend a follow-up interview at their local health care clinic. During the interviews, participants completed the

Montgomery-Åsberg Depression Rating Scale (MADRS-clinician rated) and repeated the baseline questionnaires (described below). Those who did not return a completed follow-up questionnaire were contacted on at least two separate occasions with a reminder. 'Hard to reach' participants were contacted by phone after work hours and on weekends where necessary.

Measures

Screening

The Patient Health Questionnaire (PHQ-9) assessed the presence of depression during the past two weeks [17]. The Mini International Neuropsychiatric Interview (MINI) [18] assessed psychiatric disorders based on the *DSM-IV*.

Primary outcome – depression severity

Depression severity was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS, clinician rated)[19] Ten symptoms are rated: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic and suicidal thoughts. Total scores range between 0-60. Snaith et al [20] propose a severity categorisation based on the following ranges: 35-60=severe, 20-34=moderate, 7-19=mild, and 0-6=remission.

Exposure variable – self-reported habitual physical activity

We adopted a questionnaire and score conversion method to assess habitual physical activity previously used in a nationwide lifestyle study in Sweden [21]. The questionnaire was developed by the Swedish School of Sport and Health Science (GIH:Gymnastik och Idrottshögskolan). At baseline, participants were asked to estimate their total frequency and duration of physical activity on a 'typical week' across three categories: 'low' intensity (slow walking or equivalent); 'moderate' intensity (brisk walking or equivalent), and 'high' intensity (any movement that induces sweating and breathlessness), for both summer and winter. Five frequency-duration response options were coded for the first two intensity levels: never, once per week (≥20 minutes), a few times per week (≥1 hour), every day (≥2 hours), and every day (≥ 4 hours). The high intensity category included six frequency-duration options: never, once per week (≥20 minutes), twice per week (1-2 hours), a few times per week (3-4 hours), a few times per week (5-10 hours), and every day (10 hours or more). To quantify the estimated level of physical activity (that is, the combined frequency, duration and intensity), each response alternative was converted to a total physical activity score using the following point conversion; for low activity (0, 0.66, 2, 4, and 8 points); moderate activity (0, 2, 6, 12, and 24 points); and high activity (0, 4, 16, 40, 60, and 120 points). The final physical

activity score was then obtained by summing the activity scores for each frequency-duration-intensity, averaged for summer and winter. Total scores range from 0 (no activity) to 152 (the highest activity level possible). A score of ≥21 is equivalent to the minimum physical activity level recommended for general health by the American College of Sports Medicine (ACSM) and the World Health Organization [22, 23]. Participants who scored <21 were considered to be 'physically inactive'. Scores ≥42 are equivalent to the activity level recommended by the ACSM and WHO to achieve additional health benefits in adults [23], and were categorized as 'highly active'. Score ranges for inactivity, moderate activity and high physical activity were 0-20, 21-41, and 42-152, respectively. A summary of the scoring system for the physical activity scale is presented in Figure 1. The scale has been validated in a separate (unpublished) study using objective measures of physical activity; further details are available in the journal's supplement.

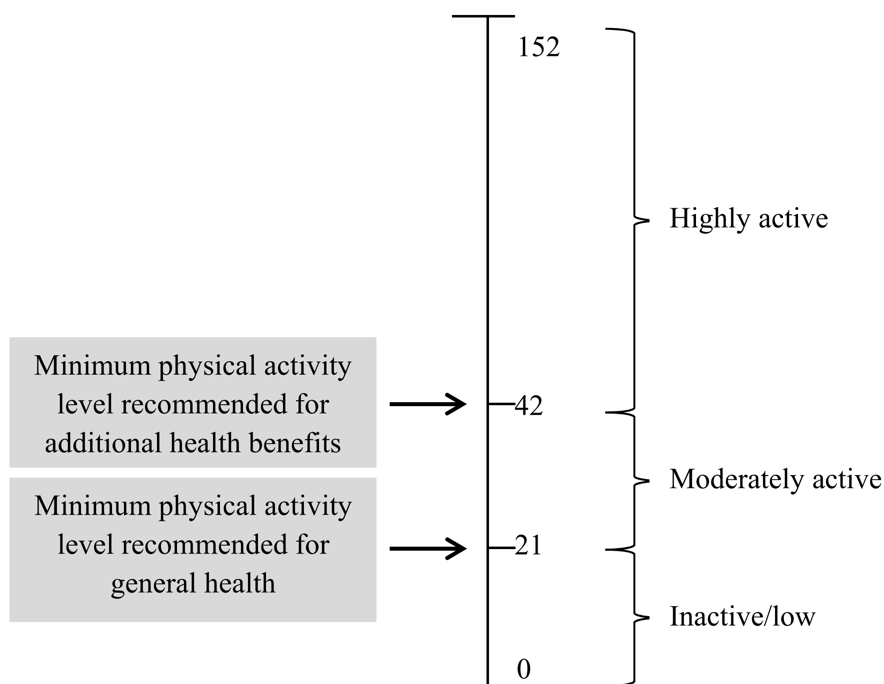

Figure 1: Categorization of scores using the physical activity scale
Notes: Consensus recommendations from the American College of Sports Medicine (ACSM) [22] and World Health Organization (WHO) [23]

Other baseline measures

Body Mass Index (BMI) was calculated based on self-reported height and height (weight(kg)/height2(m2). The EQ-5D assessed patient's overall health status [24]. We report two key dimensions: daily activities affected (somewhat - severely), and pain/discomfort

(moderate - severe). Employment status was assessed by a single question with nine response alternatives: Four items (Student, Employed, Business owner, Temporary work absence) were merged and coded ‘Employed/Student’; all other responses were coded ‘Unemployed’. Education was coded on a 5-point scale, with the last two items, post-secondary and university coded as ‘tertiary’. Hazardous alcohol consumption and binge drinking were assessed using the Alcohol Use Disorders Identification Test (AUDIT) [25] with recommended cut-offs [26]. Tobacco use was assessed with a single question: ‘Do you smoke or use ‘snus’ daily?’

Depression treatment

Participants received either ICBT or ‘usual care’ for depression administered by their physician. Patients randomized to ICBT received treatment through a secure website. Treatment involved the patient working through a self-help manual available online in the form of modules which take about one week each to complete. Initial modules addressed problems related to depressive symptoms in general, such as inactivity and avoidance behaviours. Subsequent modules were tailored to the patients’ specific needs and targeted related conditions, e.g. social anxiety, insomnia and pain. Responses were monitored on a weekly basis by a qualified clinical psychologist, and patients could contact their assigned therapist via a secure messaging system. Those who were inactive on the website for one week or more were prompted to continue treatment. Patients’ randomized to usual care received either face-to-face CBT with a clinical psychologist or supportive counseling. Twenty-seven percent of usual care patients indicated receiving no formal psychological treatment. One third of all study participants (ICBT and usual care combined) reported taking anti-depressant medication at the start of the 12-week intervention. A description of the treatment process has previously been published [16].

Statistical analysis

Data were cross-checked for accuracy and any discrepancies resolved. The distribution of socio-demographic variables was examined stratified by physical activity level. Analysis of variance (ANOVA) and Chi-square test were used to assess differences between continuous and categorical variables, respectively. Paired sample t-tests assessed the change in depression severity over time within each activity group. Multiple linear regression models examined the association between habitual physical activity levels (self-reported at baseline) and the change in depression severity at 3-month follow-up, expressed as a percentage. In a second analytic

step, a binary exposure variable was created consisting of participants with low-to-moderate physical activity levels (<42 points) versus high activity levels (≥42 points). This cut-off corresponds to the level of physical activity recommended by the ACSM and WHO for achieving 'additional health benefits' [22, 23]. Unstandardized regression coefficients (β) with 95% confidence intervals (95%-CI) are reported. Crude and adjusted models are presented. Covariates in the adjusted models include age, gender, Body Mass Index (BMI), treatment group, anti-depressant use, pain, and hazardous alcohol use. The covariates were initially chosen on the basis of previous research indicating associations between each factor and the primary outcome. In the final adjusted models, only those factors that were significantly associated with the outcome in separate bivariate analyses were included (data not shown). To explore possible gender effects, a gender x physical activity level interaction term was included in Model 2 only. Multicollinearity assessed using the variance inflation factor (VIF) was not problematic (all values <10). Outliers were identified using Cook's distance (>4/n). There were no significant differences between the sample with outliers (reported here) and with outlier removed. Statistical significance was set at the α=0.05 level, and all analyses were performed using SPSS version 22.

RESULTS

In total, 629 patients (75% women) participated in the study. The questionnaire response rate was 78%. Those who did not complete the questionnaire were excluded from the analyses. Participant characteristics are shown in Table 1. Mean age was 43 years, approximately 80% were employed or studying at the time of inclusion. Based on the MINI neuropsychiatric interview at baseline, sixty-six percent of all participants had a concurrent depressive-anxiety disorder; 8% were exclusively suffering from depression and 21% exclusively from anxiety. The remaining 5% met the inclusion criteria for the study but were sub-threshold on the MINI. The mean self-reported physical activity score (all participants) was 28.59 (± 26.49) indicating that almost half (48.4%) were physically inactive; that is, at levels below public health recommendations. Of the total sample, 27.3% were moderately active, and 24.3% were highly active. The mean physical activity scores and standard deviations for each group are shown in Table 1. Five individuals (<1%) scored 0 on the activity scale. There were no gender differences in physical activity levels at baseline, $X^2(2)=1.15$, $p=0.56$. Between treatment groups (ICBT and TAU), physical activity levels were not significantly different: $X^2(2)=2.90$, $p=0.24$.

Figure 2 shows the change in depression severity over time by physical activity level at baseline. Severity reduced significantly over time in all three groups: inactive, $t(218) = -15.09$, $p<0.01$; moderately active $t(131) = -10.41$ $p<0.01$; and highly active, $t(111) = -12.54$, $p<0.01$. At post treatment (3 months), depression severity differed significantly between the three activity groups ($F(2, 469)=3.60$, $p<0.05$).

Table 1: Participant characteristics

	All	Inactive/Low	Moderately active	Highly active
N (%)	629	295 (48.4)	166 (27.3)	148 (24.3)
Age ±SD	42.99 ± 12.17	43.81 ± 12.02	44.16 ± 12.39	41.08 ± 12.1*
Women	469 (74.6)	223 (75.6)	127 (76.5)	106 (71.6)
Body Mass Index (BMI) ±SD	25.6 ± 4.7	25.9 ± 4.7	25.6 ± 4.9	25.3 ± 4.7
Treatment group				
TAU	312 (49.6)	147 (48.5)	90 (29.7)	66 (21.8)
ICBT	317 (50.4)	148 (48.4)	76 (24.8)	82 (26.8)
Moderate-severe pain	426 (68.2)	207 (70.4)	108 (65.9)	95 (65.1)
Hazardous drinker	136 (21.9)	58 (20.1)	40 (24.5)	33 (22.4)
Anti-depressant use	163 (27.6)	84 (30.4)	49 (30.8)	24 (17.4)*
Depression severity (MADRS)				
Baseline	21.60 ± 7.05	22.19 ± 7.06	20.75 ± 6.44	21.04 ± 7.28**
Post-treatment (12 weeks)	12.12 ± 8.17	13.17 ± 8.33	11.76 ± 7.71	10.66 ± 8.29*
Change	-8.79 ± 8.63	-8.29 ± 8.75	-7.59 ± 8.38	-10.35 ± 8.74*
Physical activity score	29.02 ± 26.61	9.38 ± 5.71	28.81 ± 5.73	66.66 ± 24.69**

Note: Inactive/low = 0-20 points on the self-reported physical activity scale; Moderately active = 21-41 points on the physical activity scale; and Highly active = 42-152 points on the physical activity scale. MADRS = Montgomery-Åsberg Depression Rating Scale. Group differences significant at *p<0.05 and **p<0.01

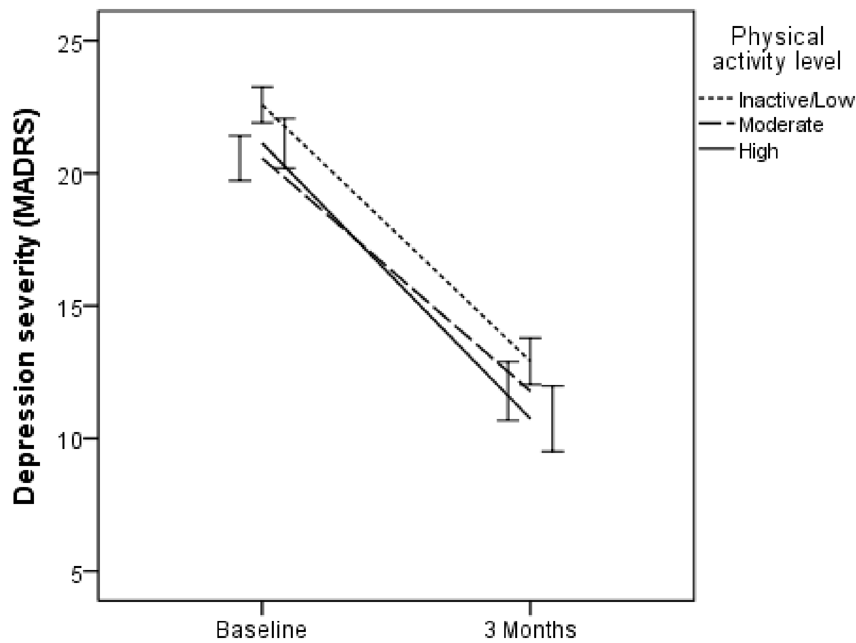

Figure 2: Change in depression severity by physical activity level

Table 2 shows estimates of the association between habitual physical activity levels and the mean percentage change in depression severity before (crude model) and after adjusting for covariates (models 1 and 2). Overall, being highly active was associated with larger reductions in depression severity compared to both inactivity (β= -8.59, 95% CI= -18.24, 1.06, p=0.081) and moderate physical activity (β= -12.03, 95% CI = -22.72, -1.34, p<0.05). There was no difference in the relative post-treatment change between inactive and moderately active participants (final adjusted model, p=0.46). Using a dichotomized exposure variable, highly active patients reported significantly lower post-treatment depression severity compared to those engaging in low-to-moderate levels of activity (β= -11.48, 95% CI= -20.30, -2.65, p<0.05: adjusted model). The gender x physical activity interaction was not statistically significant in any of the regression models. Separate stratified analyses revealed no differences between the ICBT and TAU groups in depression severity post-treatment (data not shown).

Table 2: Association between self-reported physical activity level and post-treatment depression severity (percentage change)

	Crude		Model 1		Model 2	
	Inactive/Low as reference	Moderately active as reference	Inactive/Low as reference	Moderately active as reference	Inactive/Low as reference	Moderately active as reference
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Inactive/Low	-		-		-	
Moderately active	2.75 (-6.15, 11.65)	-	-3.44 (-12.60, 5.72)	-	-0.45 (-9.47, 10.37)	-
Highly active	-10.67 (-20.06, -1.29)*	-13.42 (-23.80, -3.04)*	-8.59 (-18.24, 1.06)^	-12.03 (-22.72, -1.34)*	-13.24 (-24.09, -2.40)*	-13.69 (-26.13, -1.26)*

Notes: Model 1 adjusted for age, gender, body mass index (BMI), treatment group, anti-depressant use, pain and hazardous alcohol consumption. Model 2 adjusted for age, gender, body mass index (BMI), treatment group, anti-depressant use, pain, hazardous alcohol consumption and gender-physical activity interaction. * $p<0.05$, ^$p= 0.081$

DISCUSSION

This is one of the first studies to examine the prospective relationship of self-reported habitual physical activity levels with treatment outcomes in depression. Overall, the findings indicate that those who routinely engage in high levels of habitual physical activity respond more favourably to CBT-focused depression treatment than those who engage in low-to-moderate levels of activity. Also relevant is that the optimal level of physical activity corresponds to both ACSM and WHO recommendations for maximizing health benefits [22, 23]. These associations were found after adjusting for factors previously reported to influence the response to depression treatment. No gender differences were observed, and there were no significant differences between low and moderately active participants, or between treatment groups (ICBT versus TAU).

Previous longitudinal studies have reported associations between physical activity and depressive symptoms in the general population. For example, Gudmundsson *et al* (2015) prospectively followed 676 women over 32 years (1974-2005) using self-report measures of physical activity and depressive symptoms. At baseline, lower levels of activity were associated with higher depression scores, and those with decreasing physical activity levels reported significantly higher depression severity scores at follow-up [13]. Lindwall *et al* (2013), examined prospective associations between physical activity levels and mental health in 3717 healthcare workers (mean age=46.9 years) across four measurement points spanning 6 years. The authors found that positive changes in physical activity were associated with positive changes in depression, anxiety, and burnout across time [14]. In a prospective study involving 424 depressed adults, Harris *et al* (2006) found that higher levels of leisure-time physical activity were associated with lower depression severity at four assessment points spanning 10 years [27]. As in previous studies, the authors focussed on longitudinal associations generally, rather than the relationship between baseline physical activity and the response to depression treatment *per se*. The present study extends this research by adding the observation that those who routinely engage in higher levels of physical activity respond better to depression treatment than those who are less active.

Our findings should also be considered in the context of previous experimental research. Gerber *et al* (2014) found that objectively assessed vigorous physical activity was associated with mental health benefits beyond 'moderate' physical activity. Specifically, vigorous exercise reduced stress, pain and depressive symptoms significantly more than lower intensity

exercise [28]. In an often cited study, Dunn *et al* (2005) explored dose-response relationships to 12-weeks of exercise in 80 adults aged 20-45 years with mild-to-moderate depression.[2]. The results showed a main effect of energy expenditure in reducing depression severity. Importantly, those who exercised at the 'public health dose' (that is, 17.5-kcal/kg/week) reported significantly lower post-treatment depression severity scores than those exercising at the 'low' dose (7.0-kcal/kg/week). While the methodological approach used in the present study differs from these experimental studies, collectively, the investigations support the conclusion that engaging in higher levels of physical activity can improve the response to depression treatment. Within this context, we acknowledge a recent systematic review and meta-analysis by Stubbs *et al* (2015) demonstrating that control groups in exercise and depression studies experience marked improvements in depressive symptoms (41 studies, 1122 adults; SMD -0.920, 95 % CI -1.11 to -0.729) [29]. The authors concluded that in order to demonstrate effectiveness, exercise has to overcome a powerful control group response of approximately double that reported for antidepressant RCTs.

Animal experimental models may offer some support for a beneficial neurobiological effect of higher physical activity 'dosages' on mental health. Depression is reported to be associated with reduced levels of neural growth factor expression, serotonin signalling, and a hyperactive hypothalamic-pituitary-adrenal (HPA) axis stress-response [30]. Exercise has been shown to modulate the HPA-axis, along with serotonergic release [31], neural growth factor expression and neurogenesis in the brain [32]. Inflammatory markers are thought to play a role in the aetiology of depression by regulating HPA axis activation, neurotransmitter systems, and neuroplasticity [33]. Reductions in pro-inflammatory cytokine levels have been demonstrated following regular exercise [34], and these effects have been linked to clinical efficacy [35].. A recent systematic review found associations between depressive symptom improvement and hippocampus volume and IL-1β [36]. Exercise also potentially promotes long-term adaptations of copeptin and thiobarbituric acid reactive species (TBARS). However, due to a paucity of studies and methodological limitations, definitive conclusions regarding the underlying neurobiological explanations for the antidepressant effect of exercise in depression are not currently possible [36].

Another possible explanation concerns sedentary behaviour; that is, those behaviours that do not increase energy expenditure above resting levels, such as sitting and lying down [37]. Sedentary behaviour is an independent risk factor for a range of health conditions, including

depression [38]. Depressed adults are more sedentary and less physically active than non-depressed adults [39, 40], and a high proportion (48.4%) of participants in the present study were inactive. Although sedentary behaviour was not objectively assessed here, it is possible that highly active adults reduced their sedentary behaviour more than did the inactive or moderately active adults, resulting in better mood states and lower depression severity. This hypothesis remains to be tested.

The large participant sample and high response rate are strengths of the study. The comprehensive survey enabled relevant covariates to be identified and adjusted. The physical activity score was based on the estimated intensity, duration and frequency of total activity, not only planned exercise, and the scale has been objectively validated against recommended cut-offs (see supplementary material). A notable study limitation is that the exposure variable was measured using self-report questionnaires, not objectively measured physical activity. A previous review found that many self-report measures have poor reliability and accuracy in people with severe mental illness [41]; however, the extent to which mild-to-moderate depression affects the reliability of self-reported survey data is less clear. Furthermore, although the scale has been validated against objective assessments of physical activity (see supplement for details), it may not be directly comparable with some instruments, such as the International Physical Activity Questionnaire (IPAQ) or the Global Physical Activity Questionnaire (GPAQ) [42, 43]. Another possible limitation is that physical activity was not assessed during the intervention. This might provide further information regarding the effects of physical activity on depression treatment outcomes.

Clinical implications and future research

Our findings indicate that those who habitually engage in high levels of physical activity respond more favourably to CBT-focused depression treatment than those who are less physically active. The results have clinical implications and suggest that treatment outcomes may be optimized by encouraging patients with mild-to-moderate depression to not only exercise, but also engage in higher levels of physical activity generally. Patients who describe low levels of habitual activity could be encouraged by clinicians to increase their activity levels before and during treatment with CBT and/or anti-depressant medication. Interventions that encourage an overall lifestyle change oriented towards more activity and invariably, less sedentary behaviour, will likely benefit this patient group. Future studies should include objective measures of activity and sedentary behaviour with long-term follow-up assessments. We also acknowledge the wider need for research on the motivational processes linked to the

adoption and maintenance of physically active lifestyles in people with affective disorders [44].

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