



## Effects of structured exercise and pharmacotherapy vs. pharmacotherapy for adults with depressive symptoms: A randomized clinical trial



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### ABSTRACT

**Objective:** Physical exercise has been consistently documented as a complementary therapy in the treatment of depressive disorders. However, despite a higher prevalence among women compared to men, the trials developed in women are scarce. In addition, the optimal dosage of exercise capable of producing benefits that reduce depressive symptoms remains unclear. This clinical trial is designed to measure the effect of a structured physical exercise program as a complement to antidepressant medication in the treatment of women with depression.

**Methods:** From July 2013 to May 2014, we implemented a randomized controlled trial (HAPPY BRAIN study). A total of 26 women (aged  $50.16 \pm 12.08$ ) diagnosed with clinical depression were randomized either to a supervised aerobic exercise group (45–50 min/week three times a week for four months) plus pharmacotherapy (intervention group), or only antidepressant medication (control group).

**Results:** The exercise group presented a decrease in BDI-II and DASS-21 total score scales. Relatively to DASS-21, it showed a significant decrease in anxiety and stress. The exercise group when compared to a control group showed improvement in relation to physical functioning parameters between baseline and post-intervention. Moreover, anthropometric parameters presented only significant differences between groups in fat mass percentage. Nonetheless, no differences were found between groups in weight, body mass index, waist circumference, and self-esteem.

**Conclusion:** Our results showed that supervised structured aerobic exercise training could be an effective adjuvant therapy for treating women with depression, reducing depressive symptomatology and improving physical fitness. A key factor of this improvement included strict control of exercise workload parameters and adjustment to each subject's capacity.

In our study, due to the sample size there is an increase in the probability of type II errors.

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## 1. Introduction

Depression affects over 120 million people worldwide (Lepine and Briley, 2011) and is much more common among women than

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men, with female/male risk ratios roughly 2:1 (Kessler, 2003). Indeed, the increasing burden of depression makes it essential to search for an extended understanding of causes and for development of complementary effective treatments. The American Psychiatric Association has supported the inclusion of physical exercise (PE) treatment in patients with major depressive disorder (MDD) (American Psychiatric Association, 2010), and according to their practice guidelines, new research should include evaluation of benefits of PE in reducing side effects of other therapies and in improving health. Despite the current gold standard for the

treatment for MDD including antidepressant medication and psychotherapy, data indicate that only 55% of individuals seek treatment (Lepine and Briley, 2011). Thus, PE has been proposed as a rehabilitation strategy and a complementary treatment to reduce symptoms of depression. Indeed, evidence from other studies including systematic reviews and meta-analysis of the literature (Knapen et al., 2014; Rethorst et al., 2009; Silveira et al., 2013), supports the efficacy of exercise in the treatment of depression. Therefore, several biological and psychological hypotheses have been posited to explain the mechanisms that mediate the impact of exercise on depression. For instance, PE has shown to have anti-inflammatory effects in non depressed subjects (Gleeson et al., 2011), and thus, in the long term, regular aerobic exercise leads to lower levels of several circulating pro-inflammatory biomarkers, including Interleukin-6 (IL-6) and C-reactive protein (CRP) (Kohut et al., 2006), which are increased in depressed patients (Dowlati et al., 2010). Furthermore, PE induces the release of proteins such as brain-derived neurotrophic factor (BDNF) (Heyman et al., 2012), which is a neurotrophin responsible for the stimulation and control of neurogenesis, and altering the hypothalamic–pituitary axis function through decreasing long-term basal levels of cortisol (Sousa e Silva et al., 2010). Additionally, PE increases self-esteem (Callaghan et al., 2011), reduces tendency to ruminate (Craft, 2005), and restores psychosocial function (Mota-Pereira et al., 2011).

Thus, PE remains an area of active investigation and raises questions regarding dose–response and the best type of exercise for various depressed patients. However, researchers investigating this association in women are limited, with most focusing on postnatal depressed women (Teychenne and York, 2013) and others emphasizing observational studies that examined walking, yoga or recreational physical activity (Shahidi et al., 2011). In most of the studies women were not recruited by psychiatrists but by physicians, advertisements placed in local newspapers, posted fliers and university communities (Callaghan et al., 2011; Chu et al., 2009). Regarding the limitations and importance incidences of depression in women, the aim was to evaluate the efficacy of four months of aerobic exercise intervention in a group of women referred by psychiatrists.

## 2. Methods

Recruitment for the trial took place from July to December 2013. A total of 26 women (aged  $50.16 \pm 12.08$ ) were randomized. This research protocol was performed according to the Declaration of Helsinki, and was approved by the Ethics Committee of Centro Hospitalar de São João (March 11, 2013) with ethics reference number 112/13.

### 2.1. Inclusion criteria

The inclusion criteria consisted of (1) women aged 18–65; (2) who were able and willing to provide informed consent and accept randomized group assignment; (3) with current diagnosis of ICD-10 (International Classification of Diseases, 10th revision): F32.1 (depressive episode moderate), F33.1 (recurrent depressive disorder, moderate current episode), F34.1 (dysthymia) and confirmed by a psychiatrist; (4) physical fitness to endure exercise confirmed in writing by general practitioners; (5) normal ECG; and (6) sedentary (engaged in sports activity for less than one hour per week).

### 2.2. Exclusion criteria

The exclusion criteria consisted of (1) psychiatric co-

morbidities; (2) current participation in other clinical trials; (3) medical background indicating significant medical constraints; (4) current active alcohol/drug abuse or dependence; (5) pregnant or planning a pregnancy in the following year; (6) taking beta-blocking medications; (7) change of pharmacological therapy during PE program; (8) alteration of drug therapy in the past six weeks; (9) exhibiting significant exacerbation of symptoms; (10) minimal overall attendance of 60% of sessions; (11) undergoing complementary therapies (such as psychotherapy).

### 2.3. Trial design

This trial was randomized and two-armed. Due to the nature of the intervention none of the participants, physical training teacher, general practitioners, psychiatrists or researchers performing the outcome assessments were blinded in relation to treatment allocation.

If patients were considered eligible for inclusion and accepted participation in the study, they were referred for randomization. These were randomized following a 1:2 scheme to one of two groups: control (N = 10) and aerobic exercise (N = 9). Randomization was implemented with sequentially numbered opaque, sealed envelopes.

## 3. Intervention

### 3.1. Exercise group

Nine individuals were assigned to moderately intense exercise in addition to their usual pharmacology therapy. Exercise consisted of 45–50 min per session, three times a week, for a total of 16 weeks (36 sessions). Sessions took place at the Faculty of Sport at the University of Porto, Portugal, between January and April 2013, in the presence of a physical training teacher. The intensity for each patient was based on the baseline fitness (physical fitness tests). All patients in the aerobic group wore a heart-rate monitor (Polar FT1, Finland) during every session to ensure they exercised in prescribed pulse intervals. Moreover, downloading was done after each session, which allowed for precise data from participants, and, consequently, they were informed of their goal achievement. Each individual began PE sessions at individually prescribed exercise intensity. A rate of perceived exertion was used (Borg scale) to have a measure of the subjective intensity of exercise. Participants maintained a diary of frequency and intensity of all sessions. Regarding guidelines for prescribing PE, the National Institute for Health and Clinical Excellence (NICE) (2009) suggests three sessions/week of 45–60 min. The frequency and duration sessions of the program fulfilled the NICE requirements. Regarding intensity, the average number for four months was 65%, 73%, 74% and 76% HRmax respectively (RPE = 12–13).

The aerobic exercise program was designed to (1) improve physical fitness; (2) distract attention from worries and ruminations; (3) provide social support and reduce loneliness; (4) increase sense of control and self-esteem; (5) enhance a sense of achievement/mastery; and (6) promote behavioral change by acquiring a healthy lifestyle.

The program started with ten minutes of a general low-intensity warm-up. This was followed by 30 min of aerobics and a 5-min low-intensity cool down period. The aerobic exercise included traditional games, indoor/outdoor natural circuit workouts with resistance bands, jump ropes, fitness balls, brisk walking, and dancing. These were all done at an intensity that would maintain the participant's heart rate in the assigned training target load. The general aim of a cool down period was to decrease post-exercise stress level; therefore, we included flexibility exercises. Aiming to

maintain cohesion in the group, at least once per week the session ended with group choreography.

The objectives throughout the course of the PE intervention were for patients, during the first month, to work at intensity levels that corresponded to at least 65% of their percent of the maximum HR (%HRmax), to increase to 70% in the second month and 80% in the third month. The exercise program was designed to optimize patients' adherence, and several strategies were included, as there is not only one effective strategy for all individuals. Therefore, motivational strategies were implemented. These included (1) multidisciplinary teams; (2) creation of a Facebook page HAPPY BRAIN to maintain an online interactive system that provided support/cohesion among exercise program patients; (3) adherence feedback from HAPPY BRAIN – Facebook and physical training teacher; (4) PE done in group as an effective way to enhance psychosocial behavior and social interaction; (5) multiple activity regimes, including outings in the sunlight and in pleasant settings (contact with nature); (6) PE adapted to each patient's functional capacity; (7) choice of enjoyable activities; (8) phone calls to patients whenever they missed exercise sessions; (9) wearing group tee shirts with logos chosen by participants; (10) having an experienced exercise leader to supervise; (11) exercising with patients' musical preferences; (12) setting realistic goals (possible goals can increase sense of self-esteem/helpfulness); (13) creating cheer choreography; (14) awarding monthly prizes for assiduity; (15) self-monitoring of daily performance (heart rate, RPE); and (16) encouraging patients to start exercising on their own at least once a week (brisk walking).

### 3.2. Control group

The control group consisted of ten patients who continued their usual pharmacological therapy but were not assigned to any exercise. Control subjects were instructed to maintain their habitual activities.

All participants were assessed for depressive symptoms, functional assessment and anthropometric parameters at baseline (time 0: before starting PE program), and at 16 weeks. Participants met with a psychiatrist throughout the study to assess symptomatology and medication tolerance. The medication dosage was kept constant in both groups. All patients were medicated with selective serotonin reuptake inhibitor (SSRIs); fluoxetine, escitalopram, sertraline and paroxetine. When convenient, benzodiazepines diazepam, lorazepam and estazolam were used as anxiolytic or hypnotics.

## 4. Assessment procedures

Patients underwent medical screening by a clinical physician before participating in the study. If a patient was found to have any significant medical condition that contraindicated safe participation, they were excluded.

### 4.1. Demographic questionnaire

Patients filled in a demographic questionnaire, which evaluated variables including age, marital status, education and occupational status.

### 4.2. Psychiatric evaluation

Patients were considered eligible if they were referred by a psychiatrist and fulfilled the ICD-10 criteria. Depression was assessed by self-report depressive symptoms, using the Portuguese Version of the Beck Depression Inventory-II (BDI-II), which is a

questionnaire with 21 items (Campos and Gonçalves, 2011). Total scores ranged from 0 to 63 points, with a high score reflecting a higher level of depressive symptoms. In addition, the Portuguese version of the Depression Anxiety Stress Scale-21 (DASS-21) measured the severity of core symptoms of depression, anxiety, and stress (Vasconcelos-Raposo et al., 2013).

### 4.3. Self-esteem

The Portuguese Version of Rosenberg's Global Self-Esteem Scale was used to measure global self-esteem (Vasconcelos-Raposo et al., 2012). The scale consists of 10 statements relating to feelings of self-worth. Total scores can range from 10 to 50, with a high score indicating a higher level of self-esteem.

### 4.4. Physical examination

Through the use of eight polar electrodes, the Tanita BC-418 Segmental Body Composition Analyzer showed a complete body composition profile in seconds including weight, body fat percentage, and body mass index (BMI). Moreover, waist circumference was measured at the end of a normal expiration, with a tape placed horizontally directly on the skin and reported as the mean of three measurements.

### 4.5. Physical functioning

To evaluate physical functioning, a short physical performance battery was used. Participants were assessed based on the distance walked in six minutes, the number of times they could sit and stand from a chair in 30 s, and a seated medicine ball throw.

### 4.6. Compliance

Overall compliance was calculated as the average adherence over the 16 weeks. Adherence was defined when at least 60% of sessions were completed.

### 4.7. Statistical analysis

All dependent variables were tested for normality according to the Shapiro–Wilks method. For baseline demographic and clinical characteristics of participants and differences between treatment groups in the change from baseline to endpoint (16 weeks), independent sample *t*-tests and multivariate analysis of variance (MANOVA) were used. Tests were considered significant at a  $p < 0.05$ . Statistical analyses were performed using IBM SPSS Statistics 21. Data were also analyzed for practical significance using magnitude-based inferences (Hopkins et al., 2009). The effect size partial eta-squared ( $\eta^2_p$ ) was computed and reported for MANOVA, which is provided by statistical software packages SPSS. Cohen (1988) provided benchmarks to define small ( $\eta^2 = 0.01$ ), medium ( $\eta^2 = 0.06$ ), and large ( $\eta^2 = 0.14$ ) effects. The effect size Cohen's *d* was performed using the software ESCI (Exploratory Software for Confidence Intervals) (Cumming, 2013a) and reported for independent sample *t*-tests. Cohen's *d* magnitude thresholds for difference in a mean were described using the following scale: 0–0.2 trivial, >0.2–0.6 small, >0.6–1.2 moderate, >1.2–2.0 large, and >2.0 very large (Hopkins, 2010). This qualitative approach refers to recommended practices, including estimation based on effect sizes and confidence intervals (Cumming, 2013b). If 95% confidence intervals overlapped small positive and negative values, the magnitude was deemed to be the observed magnitude (Hopkins et al., 2009).

## 5. Results

### 5.1. Study population and baseline values

From July to December 2013, 78 potential individuals were referred to the trial by their psychiatrists during routine external consultations at Psychiatry and Mental Health Clinic, Centro Hospitalar São João, Porto, Portugal. Out of these, 52 were excluded and 26 patients were enrolled and randomized; 13 were allocated to the aerobic exercise group versus 13 to the control group. The main reasons for exclusion were declining participation ( $N = 9$ ), psychiatric comorbidity ( $N = 11$ ) and age over 65 ( $N = 12$ ). Fig. 1 presents the flow of participants in the HAPPY BRAIN study. Out of the 26 patients enrolled, 7 were excluded before completing the

full 16 weeks, 4 from the exercise group (23%). One participant emigrated; one had medical contraindication after the assignment; one was noncompliant with 60% of sessions; one had worsening of symptoms. Three participants were excluded from the control group (31%). One detected lung cancer and two reasons were unknown due to difficulties in contacting patients.

Most patients were married (47.4%), the majority had elementary schooling, were unemployed and the men age was 50.2 ( $SD = 12.1$ ). In relation to weight and fitness, the average weight was 71.6 kg ( $SD = 12.8$ ), with 36.6% ( $SD = 6.4$ ) fat mass and a mean body mass index calculated as  $\text{kg}/\text{m}^2$  of 29.3 ( $SD = 5.7$ ). Moreover, most patients (73.7%) had a diagnosis of dysthymia. Fluoxetine was the most commonly used SSRI (66.7%), followed by escitalopram (22.2%). In baseline, the patients included in the exercise group did

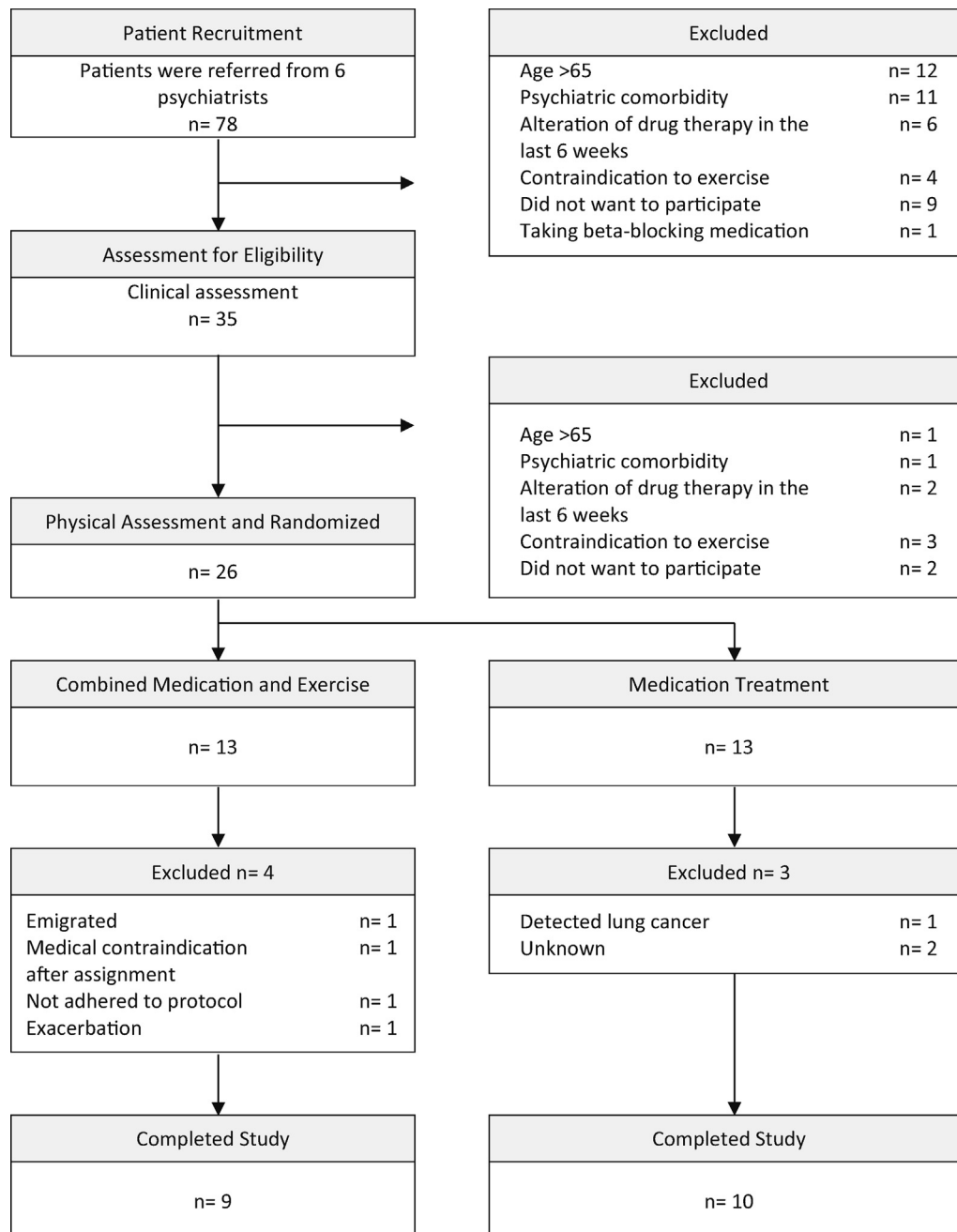


Fig. 1. Flow diagram for the HAPPY BRAIN trial.

not differ significantly from individuals in the control group in the variables analyzed (Table 1).

## 5.2. Mean changes from baseline to last observation

At the end of the exercise intervention program, the exercise group when compared to the control group showed improvement in relation to depression and functioning parameters, by having lower BDI-II and higher physical fitness (Table 2). In relation to DASS-21, the exercise group showed a decrease in anxiety and stress when compared to the control group. Furthermore, anthropometric parameters showed only significant differences between groups in fat mass percentage.

## 6. Discussion

The HAPPY BRAIN trial (implemented from July 2013 to May 2014), aimed to assess the efficacy of a four-month exercise intervention as complementary therapy in a group of patients referred by psychiatrists. Results suggest that 16 weeks of aerobic exercise improved functional functioning and reduced depressive symptomatology. These results are similar to several previous trials that described positive effects of aerobic exercise as adjuvant treatment for patients with clinical depression (Mota-Pereira et al., 2011; Schuch et al., 2011). Corroborating these findings, PE has received considerable and growing attention, and a large number of studies

have shown therapeutic benefits when used not only as adjuvant treatment but also as a first option (Dunn et al., 2005; Trivedi et al., 2011). However, according to the available literature, results have not always been so consistent. Indeed, Krogh et al. (2011) published a highly cited systematic review and meta-analysis that exclusively assessed trials recruiting patients from a clinical setting, and the results showed a small benefit in reducing depressive symptoms (standardized mean differences (SMD) of  $-0.4$ ). Although there has been an increase of scientific productivity with better designed studies in this area, the authors that conducted the most recent review for the Cochrane database made an urgent call for higher quality trials (Cooney et al., 2013) obeying stringent criteria to sustain the effect of PE on depressive pathology. This review included 39 trials (2326 participants) and indicated a moderate clinical effect. The pooled SMD for the primary outcome of depression at the end of the treatment was  $-0.62$  (95% confidence interval (CI)  $-0.81$  to  $-0.42$ ). However, when only six robust clinical trials (464 participants) with adequate allocation concealment, intention-to-treat analysis, and blinded outcome assessment were included, the pooled SMD for this outcome was not statistically significant ( $-0.18$ , 95% CI  $-0.47$  to  $0.11$ ). These results are not surprising and seem to be similar to another review published by Cochrane (Rimer et al., 2012), which included only trials with rigorous criteria. In these trials the pooled SMD was  $-0.31$  (95% CI  $-0.63$  to  $-0.01$ ), indicating a small effect in favor of exercise. Recently, some authors (Daley and Jolly, 2012; Rosenbaum et al.,

**Table 1**  
Comparison between intervention and control group at baseline.

	Exercise (N = 9)	Control (N = 10)	Difference (95% CI) Exercise vs Control	p Value	$\eta^2_p$
<b>Demographic</b>					
Age (years), mean (SD)	52.78 ± 7.66	47.80 ± 15.05	-0.42 (-6.63, 16.59)	0.373	
<b>Marital status, n (%)</b>					
Married	3 (33.3)	6 (60)			
Divorced	3 (33.3)	2 (20)			
Single	2 (22.2)	2 (20)			
Widow	1 (11.1)	0 (0)			
<b>Education, n (%)</b>					
Elementary school	7 (77.8)	5 (50)			
Junior high school	1 (11.1)	3 (30)			
Secondary School	0 (0)	1 (10)			
Higher education	1 (11.1)	1 (10)			
<b>Occupational Status, n (%)</b>					
Student	0 (0)	1 (10)			
Employed	2 (22.2)	1 (10)			
Unemployed	5 (55.6)	2 (20)			
Retired	1 (11.1)	4 (40)			
Sick leave	1 (11.1)	2 (20)			
<b>Weight and fitness, mean (SD)</b>					
Weight, kg	74.08 ± 11.58	69.31 ± 13.99	-0.37 (-7.75, 17.28)	0.433	
Body mass index, kg/m <sup>2</sup>	31.10 ± 5.84	27.72 ± 5.37	-0.60 (-2.04, 8.81)	0.205	
Fat mass, %	38.67 ± 4.00	34.60 ± 7.87	-0.65 (-2.35, 10.49)	0.192	
Waist circumference, cm	95.67 ± 11.68	92.60 ± 14.24	-0.24 (-9.63, 15.76)	0.617	
<b>Functional assessment, mean (SD)</b>					
Walk test, 6 min	467.33 ± 82.67	398.80 ± 74.33	-0.87 (-743, 144.50)	0.074	
Medicine ball throw, seated	2.74 ± 0.30	2.94 ± 0.26	0.71 (-0.47, 0.07)	0.134	
Chair stand test, 30 s	19.56 ± 3.28	18.00 ± 4.85	-0.38 (-2.50, 5.62)	0.430	
<b>Depression characteristics, n (%)</b>					
Moderate depressive episode	1 (11.1)	0 (0)			
Recurrent depressive disorder	1 (11.1)	3 (30)			
Dysthymia	7 (77.8)	7 (70)			
<b>Symptom severity, mean (SD)</b>					
BDI-II	45.56 ± 9.65	46.10 ± 11.52	0.05 (-10.90, 9.81)	0.913	
DASS-21	36.33 ± 21.26	34.10 ± 13.58	-0.13 (-14.84, 19.31)	0.786	
Depression	12.78 ± 6.82	11.30 ± 5.48	(9.06, 15.0)	0.607	0.016
Anxiety	10.22 ± 8.18	9.70 ± 6.48	(6.41, 13.51)	0.879	0.001
Stress	13.33 ± 7.09	13.10 ± 4.25	(10.42, 16.01)	0.931	0.000
Self-esteem, mean (SD)	28.89 ± 2.57	29.90 ± 2.33	0.41 (-3.38, 1.36)	0.381	

Abbreviations: BDI = Beck Depression Inventory; DASS-21 = Depression Anxiety Stress Scale-21.

**Table 2**  
Comparison between intervention and control group after 4 months of exercise intervention.

	Exercise (N = 9)	Control (N = 10)	Difference (95% CI) Exercise vs Control	p Value	$\eta^2p$
<b>Weight and fitness, mean (SD)</b>					
Weight, kg	72.68 ± 11.65	68.75 ± 14.24	−0.30 (−2.12, 3.80)	0.557	
Body mass index, kg/m <sup>2</sup>	30.54 ± 5.98	27.44 ± 5.24	−0.55 (−3.80, 2.12)	0.557	
Fat mass, %	35.32 ± 5.61	34.50 ± 7.18	−0.13 (−5.27, −1.22)	<b>0.004</b>	
Waist circumference, cm	91.89 ± 11.31	91.80 ± 13.29	−0.01 (−6.17, 0.22)	0.066	
<b>Functional assessment, mean (SD)</b>					
Walk test, 6 min	600.56 ± 61.56	395.90 ± 69.79	−3.11 (−186.58, −85.67)	<b>&lt;0.001</b>	
Medicine ball throw, seated	3.49 ± 0.37	2.90 ± 0.58	−1.21 (−1.13, −0.48)	<b>&lt;0.001</b>	
Chair stand test, 30 s	26.11 ± 3.30	17.00 ± 5.68	−1.96 (−10.83, −4.29)	<b>&lt;0.001</b>	
<b>Symptom severity, mean (SD)</b>					
BDI II	34.89 ± 10.56	49.40 ± 16.72	1.04 (−26.48, −1.45)	<b>0.031</b>	
Self-esteem, mean (SD)	29.78 ± 1.64	29.80 ± 1.62	0.01 (−3.19, 1.21)	0.357	
DASS-21	20.33 ± 19.15	35.60 ± 16.43	0.94 (−31.92, −3.08)	<b>0.020</b>	
Depression	7.33 ± 6.12	11.90 ± 6.52	(−0.92, 5.76)	0.073	0.177
Anxiety	5.89 ± 6.94	10.80 ± 6.75	(−0.72, 3.95)	<b>0.025</b>	0.262
Stress	7.11 ± 6.64	12.90 ± 4.43	(0.95, 5.48)	<b>0.012</b>	0.316

Abbreviations: BDI = Beck Depression Inventory; DASS-21 = Depression Anxiety Stress Scale-21. The bold values show *p* values less than 0.05, reported as statistically significant.

2014) have reported similar arguments for this heterogeneity of results, which can be attributed to methodological limitations, such as different degrees of disease severity, different pharmacotherapy and study designs, different outcome evaluations and a lack of objective measurement of PE interventions, lack of measuring longer term outcomes and using standardized clinical interviews to diagnose depression, and a lack of psychometric pitfalls of depression assessment scales. Parker (2005) also argued that the MDD concept classifies a heterogeneous group of patients who may have different clinical symptoms (e.g. weight loss or weight gain) in a diagnosis.

In this study, baseline characteristics were compared between groups and their values did not differ (Table 1). After the PE intervention, we found that patients allocated to the exercise group showed significant reduction in BDI-II ( $p = 0.031$ ) and DASS-21 ( $p = 0.020$ ). The effect size for the BDI-II and DASS-21 outcome was moderate. When comparing exercise group versus control group, the treatment effect was 1.04 (95% CI −26.48 to −1.45) for BDI and −0.94 (95% CI −31.92 to −3.08) for DASS-21. This result is in accordance with similar studies that used the BDI scale to measure the severity of depression (Callaghan et al., 2011; Mota-Pereira et al., 2011). When analyzing the three dimensions of DASS-21 in relation to treatment groups, we did not achieve a statistically significant result  $F(3, 15) = 2.77, p = 0.078$ ; Wilk's  $\Lambda = 0.643$ , partial  $\eta^2p = 0.357$ . However, the reduced power of a statistical test ( $\pi$ ) = 0.550 and the small sample size ( $n = 19$ ) could explain the absence of statistical significance. In fact, a large effect size was observed ( $\eta^2p = 0.357$ ). From a clinical perspective, the presence or absence of statistically significant differences is of limited value. Indeed, a non-significant outcome does not automatically imply that the treatment was not clinically effective, as small sample sizes and measurement variability can influence statistical results (Batterham and Hopkins, 2006). When analyzing how dependent variables differ from independent variables, results showed that the treatment group had a statistically significant and large effect on both anxiety ( $p = 0.025$ ;  $\eta^2p = 0.262$ ) and stress ( $p = 0.012$ ;  $\eta^2p = 0.316$ ) scores. It is important to note that despite not finding a statistically significant result for variable depression ( $p = 0.073$ ), we did observe a large effect size ( $\eta^2p = 0.177$ ). In the present study after 16 weeks no significant statistical differences in self-esteem were found 0.01 (95% CI −3.19 to 1.21;  $p = 0.357$ ) between treatment groups. Nevertheless, within groups, the analysis indicated that only the exercise group showed slight enhancement in self-

esteem. However, this improvement was very small, and all psychiatric patients had lower self-esteem. These results suggest that the decrease in depressive symptomatology observed at the end of the PE intervention was not a consequence of changes in self-esteem. Moreover, the PE training did not induce significant changes in anthropometric parameters. Results revealed only significant differences −0.13 (95% CI −5.27 to −1.22;  $p = 0.004$ ) in percentage of body fat mass. Considering that body image often influences self-esteem (Bolton et al., 2010), the absence of results in the anthropometric parameters could explain the lack of increase in self-esteem. PE may reduce depression through its impact on the perceptions on the physical self. A last justification, and probably the most plausible, pertains to the fact that the degree of low self-esteem in the psychiatric disorder varies with psychiatric diagnosis and gender (Salsali and Silverstone, 2003), and lower self-esteem is one of the diagnosis criteria for dysthymic disorder (Silverstone and Salsali, 2003).

In the study by Krogh et al. (2012) a tendency for improved metabolic parameters (lower waist circumference, lower fasting plasma glucose and insulin) as a result of aerobic exercise was observed. Thus, present findings suggest that reductions in symptoms of depression cannot be explained by changes in anthropometric parameters, but other factors may be responsible for the favorable effect on depression. For instance, inclusion of supervised exercise sessions was probably favorable in increasing physical fitness and decreasing symptoms of depression. Accordingly, several studies support a direct relationship between increased PE and decreased depression (Fabricatore et al., 2011; Greer and Trivedi, 2009). One prospective study (Brown et al., 2005) developed only with middle-aged women, showed a clear dose–response relationship between the increase of physical activity and decrease of depressive symptoms. Nonetheless, this study had a key limitation, as it relied on self-report measures of physical activity and depressive symptoms. Indeed, investigators examining antidepressant effects of PE have mainly used supervised, hospital exercise protocols, with fewer studies opting for home-based exercise (Craft et al., 2007). Furthermore, two trials found that supervised exercise leads to large improvements in functional fitness when compared to home-based exercise (Blumenthal et al., 2007; Kerse et al., 2010), and greater energy expenditure is related to larger reductions in depressive symptoms (Singh et al., 2005). Moreover, psychological factors have been amply demonstrated in literature so as to explain the effect that exercise has on depressive

mood, including increased self-efficacy, sense of mastery, positive thoughts, and distraction from negative thoughts. However, the most recent and convincing approach, although less clear, involves possible neurobiological mechanisms that mediate the effects of exercise. This approach indicates that exercise reduces activity of the hypothalamic–pituitary axis (decreasing long-term basal levels of cortisol) (Sousa e Silva et al., 2010), improving the transmission rate of neurotransmission on the brain such as monoamines and beta-endorphins (Kubryak et al., 2012). It further reduces the levels of serum inflammatory markers such as the tumor necrosis factor (TNF), C reactive protein (CRP), IL-6 and IL-18 (Gleeson et al., 2011), and increases levels of other neurotrophic/growth factors, such as the brain-derived neurotrophic factor (BDNF) (Heyman et al., 2012).

Nevertheless, results of the present study must be carefully analyzed since the sample included a small number of patients. According to Faulkner et al. (2008), a wide interval expresses lack of precision and a narrower interval indicates relatively better precision. Conversely, these trials also have benefits. These patients obtain personalized attention and are closely supervised to ensure their evolution, and small exercise classes are suitable to develop task and social cohesion. It should be noted that many of these patients show discomfort about exercising in large groups, as they feel unfit, and assume others will be more competent to exercise. Therefore, exercising in small classes may facilitate self-perception in comparison with others.

The difficult compliance to exercise intervention in this clinical population has been widely acknowledged. According to several authors, adherence and patient displacement to PE programs is a critical aspect in long-term trials of patients with psychiatric disorders (Dunn et al., 2005; Rosenbaum et al., 2014). Adherence rates, especially for middle-aged depressed women, are not well documented and previous qualitative researches show low levels of attendance (Callaghan et al., 2011). In this study the percentage of adherence was 82%, similar to other RCT's (Blumenthal et al., 2007; Brenes et al., 2007) with the same duration of PE intervention. It should be emphasized that patients enrolled in the PE intervention between January and April 2013, and throughout the four months attendance was 86%, 77%, 84% and 81% respectively. These levels of compliance are remarkable and showed treatment fidelity. Thus, it is important to bear in mind that initial acceptance is one of the major difficulties of the use of PE as a treatment (Schuch and Fleck, 2013). Moreover, the first two months of PE intervention coincided with decreased exposure to bright light that associated with key symptoms of MDD (such as tiredness, lack of motivation, loss of energy and generalized fatigue) and that can be a barrier to attendance (Leppamaki et al., 2002). According to Rimer et al. (2012), it is of utmost importance for researchers to define motivational strategies with the aim of reducing dropout rates. Hence, the exercise program was designed to optimize patients' adherence and several implemented strategies were determinants for the treatment fidelity observed (82%).

There were many strengths of this trial and they included: random allocation, inclusion of patients only recruited directly during routine external consultations by a psychiatrist, definition strategies before PE intervention promoting behavioral adherence that maximizes adhesion, and definition of specific goals for each patient that take into account their functional capacity. Additionally, for 16 weeks all patients were followed through routine psychiatric consultations with access to multidisciplinary teams of professionals from diverse areas (psychiatrists, physical training teachers, professor of exercise physiology). For post-intervention analyses, patients were assessed by their psychiatrists. In addition, we used a self-report rating scale. Their metabolic fitness and body composition parameters were evaluated before and after PE intervention. Nevertheless, some methodological weaknesses must

be considered when interpreting results. For instance, we were not able to formally follow up the participants due to lack of funding and this is a potential limitation. Moreover, although this trial included a small number of patients, it focused specifically on women, and trials in depressed women are scarce (Callaghan et al., 2011). However, we should bear in mind that low statistical power negatively affects the likelihood that a statistically significant finding actually reflects a true effect due to the simple size (Button et al., 2013). Therefore, replication studies with larger samples are recommended.

## 7. Conclusion

This study demonstrated that PE is an effective treatment, adjuvant to pharmacological therapy for depressed women. Furthermore, we concluded that 16 weeks of aerobic PE resulted in decreasing the parameters of depression (BDI-II) and physical functioning. Nonetheless, no differences in anthropometric (weight, body mass index and waist circumference) and self-esteem between groups were found. We also observed that a multi-disciplinary team and the defined strategies could effectively enhance treatment fidelity.

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## Author contributions

Author Lara S. F. Carneiro designed the study, wrote the protocol, analyzed the data, undertook the statistical analysis and produced the first draft of the manuscript under the oversight of authors Professor José Vasconcelos-Raposo and Professor Maria Paula Mota. Author Professor Maria Augusta Vieira-Coelho identified potentially eligible patients for the clinical trial, and conducted the clinical evaluation of screened patients. Author Professor António Manuel Fonseca contributed to the manuscript. All authors made important contributions to the final manuscript and provided important intellectual content.

## Conflict of interest

All authors report no conflict of interest.

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