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Improvements in psychosocial functioning and health-related quality of life following exercise augmentation in patients with treatment response but non-remitted major depressive disorder: Results from the TREAD study

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Abstract

BACKGROUND—Functional impairments often remain despite symptomatic improvement with antidepressant treatment, supporting the need for novel treatment approaches. The present study examined the extent to which exercise augmentation improved several domains of psychosocial functioning and quality of life among depressed participants. **METHODS** Data were collected from 122 partial responders to antidepressant medication. Participants were randomized to either high (16 kilocalories per kilogram of weight per week [KKW]) or low dose (4KKW) exercise. Participants completed a combination of supervised and home-based exercise for 12 weeks. The

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DISCLOSURES

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Short-Form Health Survey, Work and Social Adjustment Scale, Social Adjustment Scale, the Quality of Life Enjoyment and Satisfaction Questionnaire, and the Satisfaction with Life Scale were collected at 6 and 12 weeks. Participants with data for at least one of the two follow-up time points (n=106) were analyzed using a linear mixed model to assess change from baseline within groups and the difference between groups for each psychosocial outcome measure. All analyses controlled for covariates, including baseline depressive symptomatology.

RESULTS—Participants experienced significant improvements in functioning across tested domains, and generally fell within a healthy range of functioning on all measures at Weeks 6 and 12. While no differences were found between exercise groups, improvements were observed across a variety of psychosocial and quality-of-life domains, even in the low exercise dose group.

CONCLUSIONS—These findings support exercise augmentation of antidepressant treatment as a viable intervention for treatment-resistant depression to improve function in addition to symptoms.

Keywords

functional improvement; depression; physical activity; behavioral interventions; adjunct treatments

INTRODUCTION

Major Depressive Disorder (MDD) often adversely affects psychosocial functioning and quality of life. Patients with MDD report a wide range of functional impairments and reduced health-related quality of life (HRQoL)[1], including poor occupational functioning, role functioning, social functioning, and physical health [2–5], as well as high levels of disability [6; 7]. Specific functional consequences of depressive symptoms and diagnoses range from deficits in romantic competency [8] and interpersonal problem-solving [9] that impair social relationships, to high rates of presenteeism, or reduced productivity while at the workplace [10]. Despite the prevalence of psychosocial functioning deficits in patients with MDD, relatively few studies have examined the effects of MDD treatment on psychosocial functioning as a primary outcome measure [11–14]. The limited research available suggests that domains of psychosocial functioning do improve with treatment [11; 12; 15], although residual psychosocial and HRQoL dysfunction frequently remain despite improvements and even resolution of depressive symptoms [16–18]. Furthermore, subsequent deteriorations in psychosocial functioning have been found to predict future depression relapse and recurrence [19], suggesting adverse consequences for the course of the disorder if functional improvements are not achieved or maintained.

Given the pervasive and negative impact of functional deficits on individuals with depression, there is a need to focus on functional remission, in addition to symptomatic remission, as a target of antidepressant treatments [20; 21]. The prevalence of partial response to MDD treatment and persistent residual psychosocial dysfunction following treatment with traditional antidepressant medications highlights the need for novel augmentation strategies. One such promising augmentation treatment is exercise.

Exercise has been shown to be an effective treatment for mild to moderate depression, both as a monotherapy and as an adjunctive treatment [22–27]. Evidence also indicates

improvements in psychosocial functioning following exercise. Increased physical activity has been positively associated with improvements in health-related quality of life in healthy individuals [28; 29], and has resulted in decreased fatigue and increased energy among patients with a variety of chronic illnesses [30]. A recent meta-analysis reported a moderate effect of exercise on improvements in quality of life in individuals with mental illness, with the authors noting that few studies report such outcomes [31]. An earlier review of studies investigating the effects of exercise on quality of life outcomes specifically in depression also noted moderate to large effects of exercise, again with the limitation that few studies examined such outcomes, and those that did had significant methodological limitations (e.g., restricted samples [small sample sizes; predominantly older adults], lack of allocation concealment and blinding of outcome measures) that weaken the conclusions [27].

Additional studies that have included patients with depression have noted improved global, social and family functioning among depressed adolescents [32] and increased motivation and self-esteem among depressed patients with traumatic brain injury [33]. In addition, in a small study [34; 35] comparing psychosocial outcomes between depressed patients randomized to maintain antidepressant treatment as usual (TAU) or to TAU plus exercise, exercise augmentation was associated with improvements in global functioning [35] as well as social and physical functioning [34], although some psychosocial domains did not change in either group. Similarly, Schuch et al. found significant improvements in physical and psychological QoL domains in severely depressed, hospitalized patients who added exercise to TAU, in comparison to patients who received TAU alone [36]. Taken together, these data support using exercise to target functional outcomes in depressed individuals, particularly as an augmentation treatment strategy, in trials that are designed to overcome some of the previously noted methodological concerns in this area.

This paper examines the effect of exercise augmentation on physical and social functioning as well as HRQoL and life satisfaction among participants in the Treatment with Exercise Augmentation for Depression (TREAD) study. The purpose of TREAD was to examine two doses of exercise as augmentation strategies for non-remitted MDD following SSRI treatment. The primary depressive symptom outcomes have been reported elsewhere [37]. The objectives of the current analyses were to examine the effect of the two exercise doses on several domains of psychosocial functioning and HRQoL among participants with partial response to SSRI treatment. We also clarify the extent to which participants achieved healthy functioning by comparing follow-up values of functional outcomes after exercise augmentation with established norms for healthy ranges of functioning. The TREAD study was designed [38] to address many methodological issues known to dilute the confidence of our understanding of the efficacy of exercise in depression and its impact on symptom and functional outcomes including: allocation concealment, clinical raters that are blind to treatment assignment, thorough diagnostic evaluation and requirement of a clinical diagnosis of MDD for inclusion, and the use of well-validated diagnostic and symptom severity measures [26; 27]. Additionally, TREAD utilized a comprehensive assessment to thoroughly capture treatment history, including adequacy of both dose and duration of previous antidepressant treatment. Furthermore, individualized aerobic exercise was prescribed to participants, conducted independently (i.e., in a non-group setting) in order to minimize social effects. Importantly, this report adds to a growing literature that focuses on functional

outcomes, which are of critical importance to depressed patients, but have been understudied with respect to exercise specifically, as well as depression treatments in general.

METHODS

The study design and rationale have been published previously [38] and are described briefly below. The research was conducted in compliance with the Declaration of Helsinki and the standards of the UT Southwestern and the Cooper Institute's Institutional Review Boards. Written informed consent was obtained from all participants after the study's protocol and procedures were fully explained.

Participants

Participants, aged 18–70, with nonpsychotic, non-remitted major depressive disorder (MDD) following adequate SSRI treatment were recruited. Participants reported some response to their pre-study antidepressant treatment, but were still symptomatic (i.e., non-remitted) at study entry, defined as a score of 14 or greater on the 17-item Hamilton Rating Scale for Depression (HRSD₁₇) [39]. Participants had not engaged in regular physical activity over the past month and were medically cleared to exercise, based on physical examination, fasting blood draw, and a maximal exercise test. SSRI dose at study entry was maintained throughout the trial.

Exercise Intervention

Eligible participants (n=126) were randomized to receive augmentation with either a high dose (16 kilocalories per kilogram of body weight [KKW] (n=64) or a low dose (4 KKW) of exercise (n=62). The 16 KKW dose was selected to meet and exceed current public health physical activity recommendations (approximately 150 minutes per week of moderate intensity exercise) [40]. The exercise dose for the high dose group was increased gradually; the prescribed energy expenditure was 10 KKW during the first week, 13 KKW in the second week, and 16 KKW in weeks 3–12. Participants in both groups completed a combination of supervised and home-based exercise sessions. Supervised sessions were conducted by trained personnel at the Cooper Institute (CI), while home-based sessions were completed as needed to fulfill the weekly exercise prescription. Participants received three supervised sessions during Week 1 and two supervised sessions during Week 2. After Week 3, participants reported to CI weekly to complete one supervised exercise session and address any exercise-related concerns with staff. Participants used treadmills, cycle ergometers, or a combination of both in the exercise lab. Training intensity was self-selected, with a target of moderate intensity. Data from each home-based exercise session were recorded on a heart rate monitor (Polar SI610) and downloaded during visits to CI. Participants recorded frequency, duration, and intensity of all exercise sessions via the study website.

Assessment Visits and Outcome Measures

Trained personnel blinded to group assignment completed clinician-rated measures and administered self-report measures prior to the first exercise session of each week. All personnel received comprehensive training in human subjects research, HIPAA regulations,

and assessment administration. Interrater reliability sessions for clinician-rated measures were conducted quarterly, and established safety protocols were maintained.

Psychosocial/HRQoL Measures

The following measures, administered at baseline, Week 6, and Week 12, were selected to assess changes in specific domains of perceived HRQoL and psychosocial functioning.

Physical and Social Functioning—The following assessments generally assess characteristics such as perceived health – both physical and emotional – and functioning in various areas of life (e.g., work, school).

Short-Form Health Survey (SF-36 - Version 2) [41; 42]: The SF-36 is a self-report inventory that contains eight scales measuring different domains of HRQoL: Physical Functioning, Physical Role Functioning, Bodily Pain, General Health, Vitality, Social Functioning, Emotional Role Functioning, and Mental Health. Each scale score ranges from 0 to 100, with higher scores indicating better perceived health and functioning. Reliability statistics for the eight scales exceed 0.70 in more than 25 studies [43], and factor-analytic studies have yielded good construct validity for the measurement of physical and mental components of health [44].

Social Adjustment Scale - Self-Report (SAS-SR) [45]: The SAS-SR is a 54-item self-report measure of instrumental and expressive role performance. Items are rated on a 5-point scale (1 to 5) and averaged to create a total scale score, with higher scores indicating impairment. The SAS-SR has adequate criterion validity ($r = 0.72$ with clinical interview) and interrater reliability ($ICC = 0.62$) for overall social adjustment in acute depression.

Work and Social Adjustment Scale (WSAS) [46]: The WSAS is a 5-item self-report measure designed to identify functional impairment that is attributed to an identified problem or condition and has been used in studies of depression and anxiety. Each question is rated on a 0 to 8 scale, with 0 indicating no impairment, and 8 indicating very severe impairment. WSAS scores above 20 suggest moderately severe or worse psychopathology. Cronbach's α measure of internal consistency ranges from 0.80 to 0.94, with test-retest reliability of 0.73. The WSAS also has good convergent and discriminant validity ($r = 0.76$ with depression severity) and is sensitive to patient differences in severity, as well as treatment-related change.

Life Satisfaction—Assessments of life satisfaction assess general satisfaction, either globally or with respect to functional areas, rather than functioning itself. Such measures used in TREAD are as follows:

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) [47]: The Q-LES-Q is a self-report measure designed to assess subjective satisfaction and enjoyment, as opposed to functioning, in various domains including physical health, feelings, work, household duties, school/course work, leisure time activities, social relations, and general activities. The raw score is converted into a percent of the maximum possible score and ranges from 0 to 100. Higher scores indicate greater enjoyment and satisfaction. The Q-LES-Q summary

scales showed good test-retest reliability (ranging from 0.63 to 0.89) and high internal consistency (α ranging from 0.90 to 0.96) in a group of depressed outpatients. The Q-LES-Q also has high concurrent validity with measures of illness severity, depression, and change/improvement.

Satisfaction with Life Scale (SWLS) [48; 49]: The SWLS is a 5-item self-report inventory that measures global life satisfaction. Higher scores indicate greater satisfaction. The SWLS has high internal consistency ($\alpha = 0.87$) and good construct validity with factorial invariance across male and female groups.

Depressive Symptom Severity Measures

Clinician-rated measures of depression included the Inventory of Depressive Symptomatology (IDS-C₃₀) [50–52] and the HRSD₁₇ [39]. Participants also completed the self-report version of the IDS (IDS-SR₃₀) [51; 52] weekly.

Statistical Analyses

Only participants with a baseline visit and at least one post-baseline visit on the psychosocial measures (i.e., Week 6 or Week 12) were included in analyses. Groups were compared with regard to baseline characteristics using t-tests or chi square tests as appropriate. For each psychosocial outcome measure the change from baseline within groups and the difference between groups was assessed using a linear mixed model (also known as a random regression or mixed-effects model) as implemented in SAS V9.3 (Proc Mixed). The model contained terms for visit (weeks 6, 12), treatment group, and treatment group by visit interaction. The baseline value of the outcome measure was always used as a covariate. The following covariates were also included for each outcome measure: the 16-item Quick Inventory of Depressive Symptomatology–Clinician-Rated [51; 52] (QIDS-C₁₆; derived from IDS-C₃₀ scores), African-American race (yes/no), family history of mental illness (yes/no), recurrent MDD episode status, and gender. These covariates were determined based on an exhaustive model search conducted for the analysis of the primary outcome of IDS-C₃₀ remission using a previously described method [37].

Conducting multiple tests on the same outcome measure will inflate the probability of erroneously concluding there is a significant difference within or between groups when there is no difference. The Bonferroni correction procedure (i.e., adjusting the level of significance by dividing the desired alpha level of 0.05 by the number of tests conducted) will guarantee the alpha level for each outcome measure remains at or below 0.05 [53]. The SAS-SR, WSAS, SWLS have no subscales, therefore the Bonferroni corrected p-value to assess significance for these outcomes is $0.05/2 = 0.025$ because tests are conducted at Week 6 and Week 12. The SF-36 has 8 subscales tested at two time points, therefore the p-value to assess significance is $0.05/16 = 0.003$, and the adjusted p-value for the Q-LES-Q (with 7 subscales) is $0.05/14 = 0.004$.

Effect sizes were measured by Cohen's d. Applying benchmarks from Cohen [54], effect sizes of 0.2, 0.5, and 0.8 can be interpreted as small, medium, and large, respectively. In addition, the percentage of participants who were functioning in a healthy range at baseline,

Week 6 and Week 12 was calculated. Data for normative comparisons to calculate the healthy range of functioning were obtained from the published reports of Q-LES-Q [55] and WSAS [56] with the largest numbers of healthy controls, the initial published reports of SAS-SR [45] and SWLS [48], and the SF-36 manual [42]. Healthy range of functioning was defined as 1.28 SD from the mean of the best available normative sample using the methods outlined by Vittengl and colleagues [57; 58]. As lower values on the SAS-SR and WSAS suggest greater functioning, participants with outcome measures lower than (Mean) + (1.28SD) were identified as normal/healthy. Conversely, as higher values on SF-36, Q-LES-Q, and SWLS suggest higher functioning, participants with outcome measures greater than (Mean) - (1.28SD) were identified as normal/healthy. The two treatment groups were also compared for the number of participants in the healthy range using the chi-square test. Changes from baseline to Week 6 and baseline to Week 12 were also tested using McNemar's test.

RESULTS

Of 126 participants randomized to the intervention, 106 participants (58 in 4 KKW group and 48 in 16 KKW group) contributed data at Week 6 and 101 at Week 12. Participants who discontinued participation prior to those assessment timepoints discontinued for the following reasons: inconvenience/time (n=10), non-compliance (n=7), wanted a different treatment (n=5), AE (n=2), and lost to follow-up (n=1). Table 1 presents baseline participant characteristics for key variables. Participants were primarily Caucasian (86.7%) and female (84.9%) with moderate depressive symptom severity at study entry. No group differences were observed on any baseline variables.

Tables 2 and 3 show the covariate adjusted means from baseline to Week 6 and Week 12 for each outcome measure within each exercise treatment group. As expected, by Week 12, the high dose group demonstrated benefit across nearly all measures of psychosocial functioning, with the exception of the Physical Functioning, Bodily Pain and Physical Role subscales from the SF-36 and the Work subscale of the Q-LES-Q. These effects were largely in the medium to large range, as defined by Cohen's *d*. Unexpectedly, the low dose group also demonstrated substantial psychosocial/HRQoL benefit across nearly all measures, also with predominantly medium to large effect sizes. Only one difference was found between the high and low dose exercise groups (SAS-SR at Week 6). However, this finding ($p = .035$) was no longer significant after applying the Bonferroni correction. Numerically greater improvements were observed for high dose exercise at Week 6 among certain domains of functioning. Additionally, the 16 KKW group showed significant improvements in SF-36 Social Functioning, Q-LES-Q Subjective Feelings, Q-LES-Q Social Relationships, and SWLS at the Week 6 timepoint that were not observed in the 4 KKW group. The percent of individuals in the healthy range are presented for each group at each timepoint.

Changes in percentage points of individuals in the healthy range from baseline to Weeks 6 and baseline to Week 12 across psychosocial/HRQoL and life satisfaction measures are depicted in Figures 1 and 2, respectively. There was no significant difference between the two treatment groups in terms of the percentage of participants with functioning in the healthy range at Week 6 or Week 12. However, the high dose group showed significantly

higher increases in percent of individuals in the healthy range on the SF-36 Vitality subscale, SAS-SR, and Q-LES-Q Physical Health and Subjective Feelings subscales at the Week 6 timepoint that were not observed at that timepoint in the low dose group. In the Q-LES-Q Subjective Feelings and General Activities subscales, the SAS-SR, and the SF-36 Vitality, Role Emotional, and Social Functioning subscales, the low dose group achieved significant increases in percent in the healthy range by the Week 12 timepoint. Additionally, the Q-LES-Q Physical Functioning and Social Relationships subscales, SF-36 Mental Health subscale, and SWLS measures showed a significant increase in percent of individuals in the high dose group in the healthy range from baseline to Week 12; percent of individuals in the healthy range did not change significantly in the low dose group. Interestingly, percent of healthy individuals in the low dose group for the Q-LES-Q General Activities subscale increased from baseline to Week 6 and Week 12 in the low dose group, but not the high dose group.

DISCUSSION

Our analyses revealed significant improvements in psychosocial functioning and HRQoL following exercise augmentation in participants with nonremitted MDD. Specifically, we found that across both levels of exercise group and follow-up timepoints, the majority of our indices of psychosocial functioning and HRQoL were significantly improved after exercise augmentation, compared to baseline level of functioning. There were no significant differences between doses after applying the Bonferroni correction, suggesting that both exercise groups yielded psychosocial improvements. The breadth of improvements was substantial, spanning several domains of functioning including physical and mental health, social/interpersonal relationships, work and other role functioning, and general life satisfaction. Psychosocial improvements continued to be statistically significant even after controlling for baseline depression severity. Given that psychosocial impairments often remain after pharmacological treatment and resolution of depressive symptoms [16–18], these findings are particularly important and highlight the significance of using exercise as augmentation in MDD to improve residual deficits in psychosocial functioning.

Using normative values across all domains, we also found that after receiving either high or low dose exercise augmentation, the percentage of individuals in a healthy range of functioning was substantially increased. Several measures showed an increased percentage of individuals in the healthy range for the high dose group that occurred earlier than for those in the low dose group, suggesting that high dose exercise confers a quicker positive response in those functional domains. Additionally, some measures showed increases in percent of individuals in the healthy range only for participants in the high dose group, again showing some advantage of the higher dose of exercise.

Our findings are in agreement with other studies suggesting that as little as 60–70 minutes of moderate intensity physical activity weekly (as compared to the recommended guidelines of 150 minutes per week) has significant functional benefit. For example, both stretching (< 4 KKW) and vigorous exercise (> 12 KKW) significantly reduced depressive symptomatology and improved adolescent's functioning at school and in interpersonal relationships with friends and parents [32]. Furthermore, a study comparing the benefits of three doses of

supervised exercise to a no-exercise control in sedentary, overweight, postmenopausal women with high blood pressure also found functional improvements across exercise doses [59]. In addition to improvements in fitness, exercise training resulted in improvements on all measures of the SF-36 except Bodily Pain and Role Physical, with the low dose (4 KKW) group demonstrating significant improvements in the General Health, Vitality and Mental Health subscales. These findings suggest dose-dependent effects, with numerically greater benefits in individuals receiving higher levels of exercise [60]. Nonetheless, significant benefits were observed even when individuals receiving a low amount of exercise were compared to control groups who received no exercise.

Our previously reported results suggested reductions in depressive symptomatology with both exercise groups in the TREAD study [37]. However, dose-dependent effects were seen with respect to rates of remission at Week 12, with a trend in favor of the high-exercise dose group (28.3%, $p < 0.06$). The current report also describes significant improvements over time following both low and high dose exercise, with potential additional benefits of high dose exercise, such as improvements earlier in the course of treatment. Four functional measures significantly improved from baseline in the high dose exercise group at Week 6, but significant improvements on these same measures were not achieved until Week 12 in the lower dose exercise group.

It is conceivable that different mechanisms are at work with respect to the high and low exercise doses; the higher exercise dose could be essential for physiologically-based antidepressant effects, such as the reduction of inflammation and oxidative stress via neuroimmune mechanisms [61; 62] or the production of endorphins and increases in levels of BDNF, endocannabinoids, serotonin, dopamine, and norepinephrine [63–65], while the low exercise dose could elicit effects through behavioral activation [66] and increased self-efficacy [67]. Given that psychosocial impairment following treatment is associated with an increased risk of recurrence of depression [68], our finding that psychosocial improvements can be realized even with low dose exercise are promising. Added to our previous findings in this sample suggesting that exercise decreases depressive symptoms [37] and improves self-reported sleep quality [69] and cognitive function [70], this research would suggest that exercise augmentation is likely to improve long-term treatment outcomes by reducing several risk factors for depression recurrence.

The major limitation of the current study is the lack of a true control group – because both low and high exercise doses improved psychosocial functioning to a similar degree, it is unclear whether these effects were due to the exercise intervention or due to nonspecific factors such as increased interactions and support from research staff. However, it is important to note that the study was designed to minimize social interactions, with supervised exercise conducted individually (i.e., non-group settings), and the majority of sessions conducted at home. Future work should be designed with a non-exercise active control group in order to tease apart potential nonspecific effects. Other limitations include the relative homogeneity of the sample (i.e., predominantly middle-class Caucasian females, selection of partial responders to antidepressant treatment), which may limit external validity. Future work should aim to replicate these findings with a more diverse population. Furthermore, participants completed exercise under the supervision of CI staff, thereby

limiting the possibility of social interaction through workout "buddies" or groups and introducing an accountability procedure that may be lacking from the majority of exercise programs. While this is a design strength, it may reduce generalizability. Allowing participants to exercise at home is a noteworthy strength that improved our generalizability and likely reduced participant burden. The comprehensive evaluation of psychosocial symptoms is an additional strength of the study.

The results of the current study also suggest potential areas for future work. First, given the apparent effect of a low dose of exercise, research is needed to determine the optimal dose required for alleviation of depressive symptoms and co-occurring psychosocial dysfunction. Additional work will inform whether high dose exercise offers improvements above and beyond those obtained at lower doses. Additionally, this study manipulated volume of exercise in terms of energy expenditure, but future research may inform whether effects vary by additional factors such as intensity, exercise type (aerobic vs. weight training), exercise setting, etc. In addition, other factors that may mediate or moderate the effect of exercise on QoL in depression should be examined. The current analysis included covariates known to be relevant to the interpretation of exercise efficacy on depressive outcomes, but further exploration of covariates specifically related to functional outcomes and/or response to exercise (e.g., medical comorbidities, fat/muscle mass, duration of illness) is an important area of future investigation.

CONCLUSIONS

Our findings support the use of exercise augmentation as a potentially efficacious way to improve psychosocial functioning and quality-of-life. This work further supports the use of exercise as an augmentation strategy for non-remitted MDD, as well as the need to assess functional outcomes both as part of clinical care and as targeted research outcomes.

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Figure 1. (a&b). Percentage point changes of individuals in the healthy range on physical and social functioning measures from baseline to Week 6 (1a) and baseline to Week 12 (1b) by exercise group.

Figure 2.
(a&b). Percentage point changes of individuals in the healthy range on life satisfaction measures from baseline to Week 6 (2a) and baseline to Week 12 (2b) by exercise group.

Table 1

Baseline demographic and clinical characteristics* (N = 106)

Baseline Characteristic	4-KKW Exercise Group (n=58)	16-KKW Exercise Group (n=48)	df	p Value
Age, mean (SD), y	48.9 (9.1)	46.4 (10.2)	95	.18
Sex , female, n (%)	47 (81.0%)	43 (89.6%)	1	.22
Race, n (%)			2	.62
White	52 (89.7%)	40 (83.3%)		
Black	5 (8.6%)	7 (14.6%)		
Other	1 (1.7%)	1 (2.1%)		
Body mass index, mean (SD)	31.4 (5.6)	29.5 (6.3)	93	.12
Family history of mental illness, n (%)	42 (72.4%)	31 (64.6%)	1	.39
Depression, mean (SD)				
Age at onset, y	27.3 (12.1)	26.6 (10.6)	104	.75
Length of current episode, mo	91.2 (100)	74.4 (90.9)	103	.37
Weeks of adequate dose of SSRI	6.7 (4.1)	8.7 (8.6)	57	.17
SSRI, n (%)				
Citalopram (%)	3.4	4.2	1	.85
Escitalopram (%)	70.7	77.1	1	.46
Fluoxetine (%)	3.4	2.1	1	.67
Paroxetine CR (%)	1.7	6.3	1	.22
Paroxetine (%)	3.4	0.0	1	.19
Sertraline (%)	15.5	10.4	1	.44
Depression symptom severity, mean (SD)				
HRSD ₁₇	18.2 (3.8)	18.0 (4.0)	99	.83
IDS-C ₃₀	35.1 (7.6)	33.8 (7.5)	101	.39
Physical and social functioning, mean (SD)				
SF-36 Physical Functioning	79.4 (20.9)	79.5 (19.5)	102	.98
SF-36 Role-Physical	74.8 (29.7)	74.6 (28.0)	93	.97
SF-36 Bodily Pain	67.0 (24.2)	72.2 (18.5)	103	.22
SF-36 General Health	60.8 (20.6)	59.2 (20.1)	101	.69
SF-36 Vitality	28.2 (19.7)	27.2 (17.3)	104	.78

Baseline Characteristic	4-KKW Exercise Group (n=58)	16-KKW Exercise Group (n=48)	t or χ^2	df	p Value
SF-36 Social Functioning	49.4 (28.2)	57.6 (23.6)	-1.6	104	.11
SF-36 Role-Emotional	47.3 (26.1)	50.3 (26.5)	-0.6	100	.55
SF-36 Mental Health	49.1 (15.9)	50.7 (13.9)	-0.5	104	.58
SAS-SR	2.4 (0.4)	2.5 (0.4)	-0.3	104	.73
WSAS	20.8 (9.9)	18.7 (7.1)	1.3	102	.20
Life satisfaction, mean (SD)					
Q-LES-Q Physical Health	52.4 (13.4)	55.2 (10.3)	-1.2	99	.24
Q-LES-Q Subjective Feelings	64.0 (11.2)	62.9 (10.1)	0.5	102	.59
Q-LES-Q Work	68.2 (14.9)	66.3 (13.4)	0.6	86	.54
Q-LES-Q Household Duties	57.3 (19.7)	57.9 (14.9)	-0.2	92	.88
Q-LES-Q Leisure Time Activities	62.2 (16.4)	62.6 (15.8)	-0.1	102	.90
Q-LES-Q Social Relationships	68.2 (13.0)	67.8 (12.0)	0.2	101	.86
Q-LES-Q General Activities	60.7 (10.9)	60.2 (10.2)	0.2	101	.82
SWLS	14.3 (6.7)	13.4 (6.0)	0.8	103	.45

Abbreviations: KKW = kcal/kg/wk; SSRI = selective serotonin reuptake inhibitor; HRSD17 = 17-Item Hamilton Rating Scale for Depression; IDS-C30 = 30-Item Inventory of Depressive Symptomatology, Clinician-Rated; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey; SAS-SR = Social Adjustment Scale, Self-Report; WSAS = Work and Social Adjustment Scale; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; SWLS = Satisfaction with Life Scale

Table 2

Means (standard deviations) for changes from baseline to follow-up for measures of physical and social functioning across both exercise groups

Measure	4-KKW Group	Effect Size ^d	p	N (%) in Healthy Range	16-KKW Group	Effect Size ^d	p	N (%) in Healthy Range	p (btwn groups)
SF-36 Physical Functioning									
Baseline	79.4 (20.9)			51 (89.5)	79.5 (19.5)			41 (85.4)	
Week 6	82.5 (19.2)	0.15	0.250	51 (92.7)	87.8 (13.8)	0.54	<0.001*	45 (100.0)	0.052
Week 12	85.0 (19.2)	0.37	0.007	45 (91.8)	85.3 (18.7)	0.38	0.011	40 (88.9)	0.993
SF-36 Role-Physical									
Baseline	74.8 (29.7)			41 (78.9)	74.6 (28.0)			35 (79.6)	
Week 6	75.2 (26.4)	0.03	0.829	47 (87.0)	82.7 (17.8)	0.33	0.029	41 (95.4)	0.077
Week 12	79.7 (24.8)	0.17	0.230	41 (87.2)	81.5 (20.0)	0.23	0.120	41 (95.4)	0.759
SF-36 Bodily Pain									
Baseline	67.0 (24.2)			53 (91.4)	72.2 (18.5)			46 (95.8)	
Week 6	71.6 (23.5)	0.07	0.579	51 (91.1)	70.6 (20.5)	0.01	0.957	42 (93.3)	0.683
Week 12	72.3 (24.5)	0.16	0.259	43 (87.8)	72.6 (21.1)	0.08	0.606	42 (93.3)	0.683
SF-36 General Health									
Baseline	60.8 (20.6)			45 (77.6)	59.2 (20.1)			36 (75.0)	
Week 6	67.3 (18.5)	0.45	0.001*	49 (87.5)	66.8 (18.9)	0.51	0.001*	40 (88.9)	0.768
Week 12	69.5 (18.5)	0.57	<0.001*	43 (89.6)	66.8 (19.7)	0.54	<0.001*	36 (81.8)	0.852
SF-36 Vitality									
Baseline	28.2 (19.7)			22 (37.9)	27.2 (17.3)			15 (31.3)	
Week 6	39.8 (21.3)	0.55	<0.001*	33 (60.0)	39.2 (17.9)	0.59	<0.001*	27 (60.0)	0.830
Week 12	44.1 (24.4)	0.83	<0.001*	31 (63.3)	43.5 (21.2)	0.79	<0.001*	31 (68.9)	0.823
SF-36 Social Functioning									
Baseline	49.4 (28.2)			24 (41.4)	57.6 (23.6)			25 (52.1)	
Week 6	58.7 (28.8)	0.33	0.014	34 (60.7)	66.1 (21.9)	0.52	0.001*	30 (66.7)	0.327
Week 12	64.8 (26.0)	0.64	<0.001*	32 (65.3)	76.4 (21.8)	0.95	<0.001*	36 (81.8)	0.116
SF-36 Role-Emotional									
Baseline	47.3 (26.1)			18 (31.0)	50.3 (26.5)			16 (33.3)	
Week 6	63.4 (31.6)	0.61	<0.001*	31 (55.4)	64.4 (26.0)	0.61	<0.001*	21 (46.7)	0.993

Measure	4-KKW Group	Effect Size ^d	p	N (%) in Healthy Range	16-KKW Group	Effect Size ^d	p	N (%) in Healthy Range	p (btwn groups)
Week 12	70.1 (26.4)	0.91	<0.001 *	33 (67.4)	70.2 (25.3)	0.83	<0.001 *	30 (66.7)	0.673
SF-36 Mental Health									
Baseline	49.1 (15.9)			27 (46.6)	50.7 (13.9)			20 (41.7)	
Week 6	58.6 (18.0)	0.52	<0.001 *	35 (62.5)	61.5 (17.8)	0.62	<0.001 *	30 (66.7)	0.594
Week 12	62.4 (21.0)	0.80	<0.001 *	34 (69.4)	67.2 (18.5)	0.95	<0.001 *	33 (73.3)	0.460
SAS-SR									
Baseline	2.4 (0.4)			11 (19.0)	2.5 (0.4)			3 (6.3)	
Week 6	2.3 (0.4)	0.38	0.004 *	16 (28.6)	2.2 (0.4)	0.80	<0.001 *	18 (40.0)	0.035
Week 12	2.1 (0.5)	0.99	<0.001 *	24 (49.0)	2.1 (0.4)	0.93	<0.001 *	20 (44.4)	0.804
WSAS									
Baseline	20.8 (9.9)			3 (5.2)	18.7 (7.1)			2 (4.2)	
Week 6	16.8 (9.7)	0.43	0.001 *	5 (9.1)	15.8 (9.2)	0.42	0.006 *	5 (11.1)	0.957
Week 12	14.6 (10.8)	0.75	<0.001 *	9 (18.0)	12.0 (9.8)	0.81	<0.001 *	12 (26.7)	0.726

Note:

^dEffect sizes follow the convention for Cohen's *d* and measure the strength of the covariate-adjusted mean change between each time point and baseline;

* significant change from baseline after applying Bonferroni correction. No significant between-group differences were found.

Table 3

Means (standard deviations) for changes from baseline to follow-up for measures of life satisfaction across both exercise groups

Measure	4- KKW Group	Effect Size ^d	p	N (%) in Healthy Range	16- KKW Group	Effect Size ^d	p	N (%) in Healthy Range	p (btwn groups)
Q-LES-Q Physical Health									
Baseline	52.4 (13.4)			19 (34.6)	55.2 (10.3)			16 (34.0)	
Week 6	59.3 (14.5)	0.44	0.001 [*]	31 (57.4)	61.7 (14/3)	0.58	<0.001 [*]	25 (56.8)	0.494
Week 12	62.7 (14.8)	0.78	<0.001 [*]	30 (62.5)	66.2 (13.7)	0.86	<0.001 [*]	28 (63.6)	0.686
Q-LES-Q Subjective Feelings									
Baseline	64.0 (11.2)			21 (37.5)	62.9 (10.1)			12 (25.0)	
Week 6	66.2 (13.3)	0.19	0.150	26 (46.4)	68.6 (10.1)	0.51	0.001 [*]	28 (62.2)	0.112
Week 12	71.6 (13.5)	0.77	<0.001 [*]	32 (65.3)	72.8 (12.2)	0.84	<0.001 [*]	32 (71.1)	0.750
Q-LES-Q Work									
Baseline	68.2 (14.9)			33 (70.2)	66.3 (13.4)			25 (61.0)	
Week 6	70.4 (13.9)	0.17	0.187	39 (79.6)	70.3 (12.8)	0.18	0.219	32 (82.1)	0.977
Week 12	73.3 (17.4)	0.39	0.006	34 (77.3)	74.2 (14.6)	0.43	0.004	31 (79.5)	0.838
Q-LES-Q Household Duties									
Baseline	57.3 (19.7)			32 (61.5)	57.9 (14.9)			26 (60.5)	
Week 6	62.5 (18.8)	0.37	0.006	33 (63.5)	60.4 (13.9)	0.24	0.105	31 (72.1)	0.514
Week 12	69.8 (16.4)	0.79	<0.001 [*]	37 (80.4)	64.2 (15.9)	0.47	0.002 [*]	32 (71.1) ^b	0.087
Q-LES-Q Leisure Time Activities									
Baseline	62.2 (16.4)			29 (50.0)	62.6 (15.8)			30 (62.5)	
Week 6	67.8 (16.5)	0.38	0.005	36 (66.7)	67.4 (13.1)	0.41	0.006	33 (73.3)	0.902
Week 12	69.7 (18.9)	0.53	<0.001 [*]	35 (70.0)	71.3 (14.9)	0.66	<0.001 [*]	34 (77.3)	0.509
Q-LES-Q Social Relationships									
Baseline	68.2 (13.0)			46 (79.3)	67.8 (12.0)			36 (76.6)	
Week 6	72.3 (13.5)	0.37	0.005	47 (83.9)	73.7 (12.7)	0.55	<0.001 [*]	43 (95.6)	0.361
Week 12	76.3 (14.3)	0.77	<0.001 [*]	44 (88.0)	78.0 (10.9)	0.85	<0.001 [*]	44 (97.8)	0.646
Q-LES-Q General Activities									
Baseline	60.7 (10.9)			30 (51.7)	60.2 (10.2)			24 (51.1)	

Measure	4- KKW Group	Effect Size ^d	p	N (%) in Healthy Range	16- KKW Group	Effect Size ^d	p	N (%) in Healthy Range	p (btwn groups)
Week 6	66.3 (11.9)	0.53	<0.001 *	42 (76.4)	67.0 (11.5)	0.57	<0.001 *	31 (68.9)	0.839
Week 12	70.2 (13.5)	0.93	<0.001 *	38 (77.6)	70.3 (11.9)	0.85	<0.001 *	36 (80.0)	0.737
SWLS									
Baseline	14.3 (6.7)			22 (37.9)	13.4 (6.0)			17 (35.4)	
Week 6	15.7 (6.9)	0.28	0.035	26 (47.3)	16.6 (7.1)	0.49	0.001 *	24 (53.3)	0.294
Week 12	17.7 (8.4)	0.61	<0.001 *	28 (56.0)	19.1 (8.0)	0.93	<0.001 *	28 (62.2)	0.114

Note:

^aEffect sizes follow the convention for Cohen's *d* and measure the strength of the covariate-adjusted mean change between each time point and baseline;

^bMore people were in the healthy range in Week 12 than in Week 6, but the percentage is lower - this was due to availability of data for 43 subjects at Week 6 and 45 in Week 12.

* Significant change from baseline after applying Bonferroni correction. No significant between-group differences were found.