# Exercise Treatment for Depression
## Efficacy and Dose Response

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**Background:** This study, conducted between 1998 and 2001 and analyzed in 2002 and 2003, was designed to test (1) whether exercise is an efficacious treatment for mild to moderate major depressive disorder (MDD), and (2) the dose–response relation of exercise and reduction in depressive symptoms.

**Design:** The study was a randomized $2\times2$ factorial design, plus placebo control.

**Setting/ Participants:** All exercise was performed in a supervised laboratory setting with adults ($n=80$) aged 20 to 45 years diagnosed with mild to moderate MDD.

**Intervention:** Participants were randomized to one of four aerobic exercise treatment groups that varied total energy expenditure (7.0 kcal/kg/week or 17.5 kcal/kg/week) and frequency (3 days/week or 5 days/week) or to exercise placebo control (3 days/week flexibility exercise). The 17.5-kcal/kg/week dose is consistent with public health recommendations for physical activity and was termed "public health dose" (PHD). The 7.0-kcal/kg/week dose was termed "low dose" (LD).

**Main Outcome Measures:** The primary outcome was the score on the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$).

**Results:** The main effect of energy expenditure in reducing $HRSD_{17}$ scores at 12 weeks was significant. Adjusted mean $HRSD_{17}$ scores at 12 weeks were reduced 47% from baseline for PHD, compared with 30% for LD and 29% for control. There was no main effect of exercise frequency at 12 weeks.

**Conclusions:** Aerobic exercise at a dose consistent with public health recommendations is an effective treatment for MDD of mild to moderate severity. A lower dose is comparable to placebo effect.
(Am J Prev Med 2005;28(1):1–8) © 2005 American Journal of Preventive Medicine

## Introduction

The Global Burden of Disease study[1] found that mild to moderate major depressive disorder (MDD) ranks second behind ischemic heart disease for years of life lost due to premature death or disability. Although effective pharmacologic and psychotherapeutic treatments for MDD are available, many people do not seek treatment or do not receive adequate treatment.[2] National estimates indicate that only 23% of people with this disease seek treatment,[2] and only 10% receive adequate treatment, in part because of the social stigma associated with treatment.[3]

Exercise may be a viable treatment because it can be recommended for most individuals, and does not carry a negative social stigma. However, exercise has not yet met established efficacy standards,[4,5] although some studies have demonstrated reductions in depressive symptoms with exercise.[6–10] A recent randomized controlled trial (RCT)[11] compared exercise, antidepressant medication, and combined medication and exercise in older adults with MDD and found that all treatments were effective. This study adequately diagnosed depression and treatment outcomes, but because exercise was done in a group setting, a question remains of whether social support influenced treatment response. Isolating the effects of exercise from social support, examining effects in different age groups, and quantifying the amount of exercise needed to reduce symptoms of

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MDD is important for establishing the efficacy of exercise as a monotherapy.

Using scores from the 17-item Hamilton Rating Scale for Depression (HRSD$_{17}$)[12,13] as the primary outcome measure, our purpose was to test: (1) whether the mean change in HRSD$_{17}$ score from baseline was greater after 12 weeks for active exercise conditions compared with an exercise placebo; and (2) whether there was a dose–response relation between the exercise doses and reduction in HRSD$_{17}$ score. Secondary aims were to examine rates of treatment response (50% reduction in HRSD$_{17}$ score) and rates of remission (HRSD$_{17}\leq 7$).[5,14]

## Methods

The rationales for the study design and detailed methods have been published elsewhere[15]; the methods and design are briefly outlined here.

### Participants

This study was conducted from July 1998 to October 2001 at the Cooper Institute (CI) and the University of Texas Southwestern Medical Center Depression and Anxiety Disorders Program, in Dallas TX. The Institutional Review Boards from both research centers approved the protocol every year. All participants provided written informed consent.

### Inclusion Criteria

Study participants were men and women ($n =80$) aged 20 to 45 years with mild (HRSD$_{17}$ score of 12 to 16) to moderate (HRSD$_{17}$ score of 17 to 25) MDD, and diagnosed using the Structured Clinical Interview for Depression (SCID) according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV).[16] Trained and certified raters conducted all HRSD$_{17}$ measurements and SCID interviews. Other inclusion criteria included being sedentary, that is, exercising less than three times per week for $\geq 20$ minutes for each bout; living within a 15-mile radius of the CI and able to exercise at CI for up to 5 days each week; not receiving any other treatment for depression; and being able to read, understand, and provide written informed consent.

### Exclusion Criteria

Exclusion criteria included $\geq 160\%$ over ideal weight defined by the 1983 Metropolitan Insurance Company height and weight tables for large frame,[17] consumption of $>21$ alcoholic drinks per week, attempt of suicide in the last 2 years or at suicidal risk assessed by SCID interview, hospitalization for a psychiatric disorder in the last 5 years, current participation in other clinical trials, plans to move from the Dallas area in the next 6 months, current substance abuse or recreational drug use ascertained by SCID diagnosis and urinalysis testing, inability to exercise due to a medical condition, and for women, planned pregnancy or current pregnancy.

### Eligibility Screening

Eligibility was determined by telephone prescreen and three screening visits (SV1, SV2, SV3) to assess depressive symptoms and severity of depressive symptoms (SV1), diagnose MDD (SV2), and ensure that participants could safely exercise (SV3) (Figure 1). After SV3, 95 participants were eligible for the 2-week run-in period to assess ability to adhere to scheduled exercise. During the run-in, participants were required to complete six 15-minute sessions of light-intensity exercise, including stretching, cycling, and treadmill walking.

### Study Design

The study used a $2\times 2$ factorial design, plus an exercise placebo control group. The two exercise factors were total weekly energy expenditure (7 kcal/kg/week, low dose [LD] or 17.5 kcal/kg/week; public health dose [PHD]) and frequency (3 days/week or 5 days/week). The dose of exercise was determined using exercise prescription guidelines established by the American College of Sports Medicine,[18] and consensus public health recommendations for physical activity.[19] Each energy expenditure group was divided into 3- or 5-day/week groups. Therefore, the four aerobic exercise groups were LD/3, LD/5, PHD/3, and PHD/5. The exercise placebo control group was defined as 3 days/week of stretching flexibility exercise for 15 to 20 minutes per session.

Participants were randomized to LD/3, LD/5, PHD/3, PHD/5, or the exercise placebo control group, as they became eligible for trial entry following the run-in. Randomization was implemented with sequentially numbered, opaque, sealed envelopes.[20]

After randomization, participants exercised on a treadmill (Technogym RunRace, Gambettola, Italy) or stationary bicycle (Technogym BikeRace) under supervision in the laboratory for 12 weeks. Participants exercised individually in rooms by themselves, and were monitored by laboratory staff. Treatment adherence was defined as attending scheduled sessions.

### Outcome Measures

The primary outcome measure was the change in the HRSD$_{17}$ score from baseline to 12 weeks. The HRSD$_{17}$ was selected because it measures severity of symptoms and is widely used in efficacy studies of antidepressant treatments.[21] Response and remission were secondary outcomes. Response was defined as a 50% reduction in symptoms calculated from each individual's baseline score during the run-in period. Remission of depressive symptoms was defined as an HRSD$_{17}$ score of $\leq 7$.[14] Trained research assistants, blinded to treatment conditions, conducted all weekly HRSD$_{17}$ measures before each person's exercise session.

### Statistical Analysis

Statistical analysis took place in the summers of 2002 and 2003, and included both intent-to-treat analysis of randomized participants at last observation, and efficacy analysis of treated-only participants over 12 weeks. The intent-to-treat sample ($n =80$) included all randomized participants, while the efficacy sample ($n =72$) excluded participants who re-
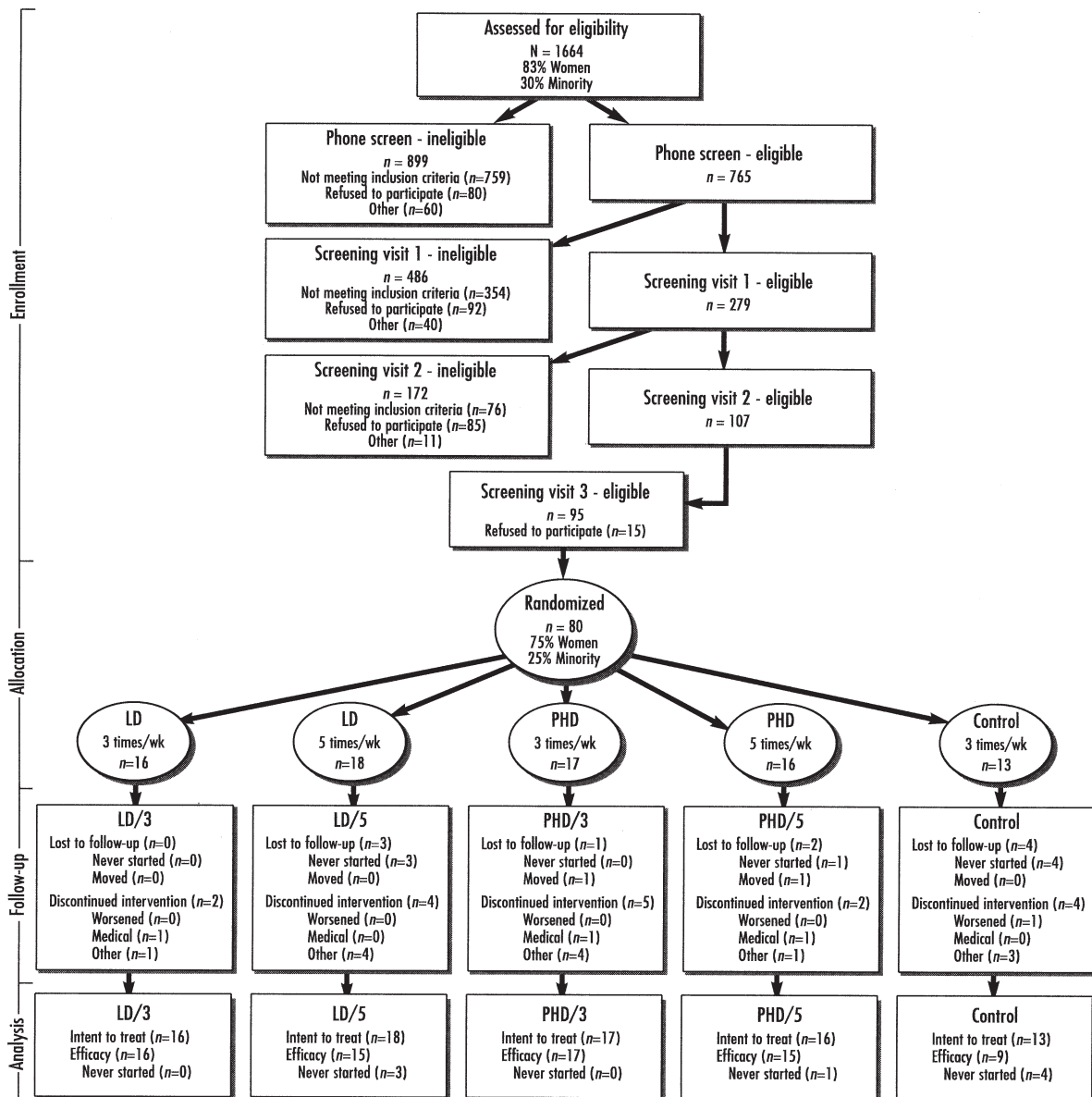
**Figure 1.** Participant flow from enrollment to analysis. LD, low dose; PHD, public health dose.

fused their treatment assignments and provided no outcome data. In the intent-to-treat analysis, mean $HRSD_{17}$ scores were compared using analysis of covariance, while response and remission rates were compared using logistic regression. In the efficacy analysis, evaluation of treatment effects on $HRSD_{17}$ scores was based on generalized estimating equations (GEEs)[22] for repeated measures in longitudinal data. The linear trend in mean $HRSD_{17}$ scores across weeks was modeled for each group, with individual scores modeled as correlated within subjects but independent between subjects. The model was adjusted for participant age, gender, and baseline $HRSD_{17}$ score, the average of two weekly measures taken in the run-in period prior to treatment. All observed weekly $HRSD_{17}$ scores of all randomized participants who entered treatment were included in the GEE analyses. No missing scores were imputed or carried forward. Since response or remission may be transient states from week to week, trends were modeled in the weekly prevalence of

response and remission, rather than model time to first transition, using the logistic link. Results of the GEE analyses are expressed as model-based adjusted means at 12 weeks, adjusted to overall average values of baseline scores, age, and gender. Preliminary analyses showed that body mass index $(kg/m^2)$ differed little by treatment condition and did not predict $HRSD_{17}$ scores over 12 weeks; consequently, this variable was omitted from the models. Attrition rates after trial entry were modeled using Cox regression. The log-rank test was used to compare attrition rates between treatment groups. Treatment adherence, a skewed variable, was compared between groups using the Mann–Whitney rank-sum test.

## Results

Approximately 5% of the 1664 prescreened participants were ultimately randomized to treatment. Figure

**Table 1.** Baseline characteristics

| Characteristic | LD/3 (n=16) | LD/5 (n=18) | PHD/3 (n=17) | PHD/5 (n=16) | Control (n=13) | All participants (n=80) | Difference between groups (p) |
|---|---|---|---|---|---|---|---|
| **Age (SD), years** | 35.8 (6.1) | 37.7 (5.1) | 33.2 (6.7) | 37.9 (6.3) | 34.5 (7.3) | 35.9 (6.4) | $p = 0.15$ |
| **Female, %** | 81 | 72 | 76 | 81 | 62 | 75 | $p = 0.73$ |
| **BMI (SD), kg/m$^2$** | 27.1 (6.8) | 31.6 (8.6) | 27.8 (7.5) | 28.7 (8.1) | 30.3 (6.1) | 29.0 (7.5) | $p = 0.27$ |
| **Ethnicity, %** | | | | | | | $p = 0.39$ |
|   White | 100 | 61 | 76 | 81 | 54 | 75 | |
|   African American | 0 | 17 | 12 | 13 | 15 | 11 | |
|   Hispanic | 0 | 17 | 12 | 6 | 23 | 11 | |
|   Other | 0 | 6 | 0 | 0 | 8 | 3 | |
| **Marital status, %** | | | | | | | $p = 0.20$ |
|   Married | 50 | 80 | 44 | 56 | 33 | 55 | |
|   Single | 38 | 10 | 44 | 44 | 33 | 33 | |
|   Divorced | 13 | 10 | 11 | 0 | 33 | 12 | |
| **Mean HRSD$_{17}$ (SD) at SV1** | 19.3 (2.6) | 19.2 (2.3) | 19.1 (1.8) | 19.1 (2.2) | 20.5 (2.4) | 19.4 (2.3) | $p = 0.41$ |
| **MDD episodes, %** | | | | | | | $p = 0.08$ |
|   First | 27 | 12 | 29 | 14 | 0 | 17 | |
|   Previous single | 0 | 12 | 6 | 21 | 38 | 14 | |
|   Recurrent | 73 | 76 | 65 | 64 | 62 | 68 | |
| **Age at first onset (SD), years** | 24.5 (9.8) | 22.8 (12.8) | 23.5 (8.5) | 25.8 (12.6) | 26.2 (10.0) | 24.4 (10.6) | $p = 0.91$ |

HRSD$_{17}$, Hamilton Rating Scale for Depression-17 item; LD/3, low dose, 3 days per week; LD/5, low dose, 5 days per week; MDD, mild to moderate depressive disorder; PHD/3, public health dose, 3 days per week; PHD/5, public health dose, 5 days per week; SD, standard deviation; SV1, screening visit 1.

1 shows the reasons for exclusion. A total of 80 participants were randomized to the four conditions—LD/3, LD/5, PHD/3, or PHD/5—or the exercise placebo control. For the two independent variables of energy expenditure and exercise frequency, this included 34 participants in the two LD conditions and 33 in the two PHD conditions, and 33 participants in the two 3-day/week conditions and 34 participants in the two 5-day/week conditions. There were 13 participants in the exercise placebo control condition (Figure 1).

Baseline characteristics of the participants are shown in Table 1. Among randomized participants, women outnumbered men by 3 to 1, with median age 35.9 years and interquartile range 31 to 41 years. In all, 25% were minorities.

## Primary Outcome: HRSD$_{17}$ Scores

Of the 80 randomized participants (intent-to-treat sample), 72 began exercise treatment and provided one or more weekly HRSD$_{17}$ measures (the efficacy sample). Of the 72, 19 did not finish the 12th week of treatment. The mean number of weekly HRSD$_{17}$ measures was 9.2 of a possible 12 weeks (6.8 for the control group, and ranging from 9.1 for PHD/3 to 10.2 for LD/3). The mean HRSD$_{17}$ score by week is shown in Figures 2 and 3 for each factor, energy expenditure, and frequency.

**Intent-to-treat analysis: HRSD$_{17}$ scores at last observation.** Table 2 shows the last weekly HRSD$_{17}$ scores at last observation for each of the four aerobic treatment conditions and the exercise placebo control for the

intent-to-treat sample ($n = 80$). The mean HRSD$_{17}$ score for all groups was reduced by 30% overall, from the mean HRSD$_{17}$ baseline score of 16.2. Among the five groups, the lowest mean HRSD$_{17}$ score was for PHD/3, while the highest was for the exercise placebo control group. For the combined PHD condition, the mean (standard deviation) HRSD$_{17}$ score was 9.5 (4.6) at the last observation, compared with 12.3 (5.3) for the combined LD condition. For the combined 3-day/week conditions, the mean HRSD$_{17}$ score was 10.3 (4.9) at
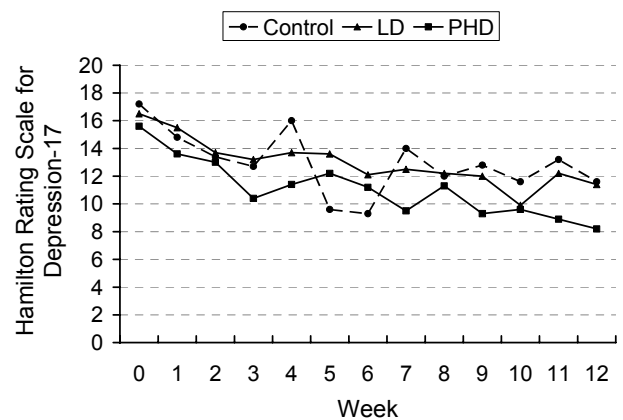


**Figure 2.** Weekly 17-item Hamilton Rating Scale for Depression by energy expenditure. All groups—control, low dose (LD), and public health dose (PHD)—had reductions in symptoms during the 12 weeks of treatment. Energy expenditure had an independent effect on reduction of symptoms. The greatest reduction in symptoms was for the PHD group.
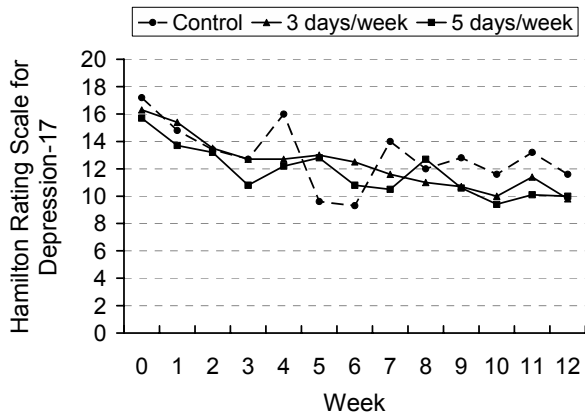
**Figure 3.** Weekly 17-item Hamilton Rating Scale for Depression by exercise frequency. All groups—control, 3 days/week, and 5 days/week—had reductions in symptoms during the 12 weeks of treatment. There was no independent effect of frequency on reduction of symptoms.

the last observation, compared with 11.5 (5.4) for 5 days/week.

**Efficacy analysis: last observation and change in $HRSD_{17}$ by total energy expenditure and exercise frequency.** Table 3 shows the last weekly adjusted mean $HRSD_{17}$ observation scores at 12 weeks for each of the four aerobic treatment conditions and the exercise placebo control for the efficacy sample ($n = 72$). Repeated-measures GEE analysis of weekly $HRSD_{17}$ scores showed a decreasing linear trend in weekly $HRSD_{17}$ scores. At 12 weeks, the reductions in adjusted mean $HRSD_{17}$ scores were significant for the PHD condition ($-47\%$ from baseline, $p < 0.001$); LD condition ($-30\%$, $p = 0.006$); 3-day/week condition ($-39\%$, $p < 0.001$); 5-day/week condition ($-38\%$, $p < 0.001$); and exercise placebo control group ($-29\%$, $p = 0.02$). Comparing main treatment effects of energy expenditure and exercise frequency at 12 weeks (Figures 4 and 5), the PHD condition was significantly more effective than the LD and control conditions in reducing weekly

$HRSD_{17}$ scores ($p = 0.04$ and $p = 0.03$, respectively). The LD condition was not significantly different from the control condition ($p = 0.88$). The 3-day/week condition was not significantly different from the 5-day/week condition ($p = 0.93$). There was no significant interaction between the effects of exercise frequency and energy expenditure ($p = 0.35$) on weekly mean $HRSD_{17}$ scores. Age ($p = 0.77$) and gender ($p = 0.12$) were not significant effects.

## Secondary Outcomes: Response and Remission

At the last observation, 24 of the 80 randomized participants had responded to treatment (mean $HRSD_{17}$ score 5.9 [2.3]), and 20 of the 80 had achieved remission (mean $HRSD_{17}$ score 5.0 [1.5]). The greatest response rate was for PHD/5, and the greatest remission rate was for PHD/3. The smallest response and remission rates were for LD/5 (Table 2).

**Response rates.** Additional GEE analysis of weekly $HRSD_{17}$ scores showed an increasing trend in probabil-

**Table 3.** Efficacy analysis—scores at 12 weeks[a]

| Group | n | $HRSD_{17}$[b] | Response[c] (%) | Remission[d] (%) |
|---|---|---|---|---|
| LD/3 | 16 | 10.5 ± 1.2 | 31 ± 13 | 31 ± 14 |
| LD/5 | 15 | 11.9 ± 1.6 | 19 ± 16 | 19 ± 15 |
| PHD/3 | 17 | 9.0 ± 1.0 | 31 ± 12 | 31 ± 15 |
| PHD/5 | 15 | 7.9 ± 1.3 | 64 ± 11 | 55 ± 15 |
| | | **p = 0.03*** | **p = 0.001*** | **p = 0.005*** |
| Control | 9 | 11.3 ± 1.0 | 15 ± 6 | 11 ± 6 |
| Total | 72 | 10.0 ± 0.6 | 32 ± 6 | 30 ± 7 |

$HRSD_{17}$, Hamilton Rating Scale for Depression-17 item; LD/3, low dose, 3 days per week; LD/5, low dose, 5 days per week; PHD/3, public health dose, 3 days per week; PHD/5, public health dose, 5 days per week.
[a]Values are least-squares means for generalized estimating equations ± standard errors at 12 weeks, adjusted for age, gender, and baseline score.
[b]Mean standard deviation $HRSD_{17}$ at baseline, 16.2 (4.1).
[c]Percent with $HRSD_{17} \leq 50\%$ of participant's score at baseline.
[d]Percent with $HRSD_{17} \leq 7$.
*$p$ value vs control (bolded).

**Table 2.** Intent to treat analysis—scores at last observation

| Group | n | $HRSD_{17}$[a] Mean (SD) | Response[b] | Remission[c] |
|---|---|---|---|---|
| LD/3 | 16 | **11.7 (5.8)*** | 38% | 25% |
| LD/5 | 18 | 12.8 (5.0) | 6% | 11% |
| PHD/3 | 17 | **9.0 (3.6)*** | 41% | 41% |
| PHD/5 | 16 | **10.0 (5.5)*** | 44% | 31% |
| Control | 13 | 14.0 (4.9) | 23% | 15% |
| Total | 80 | 11.4 (5.2) | 30% | 25% |

$HRSD_{17}$, Hamilton Rating Scale for Depression-17 item; LD/3, low dose, 3 days per week; LD/5, low dose, 5 days per week; PHD/3, public health dose, 3 days per week; PHD/5, public health dose, 5 days per week; SD, standard deviation.
[a]Mean (SD) $HRSD_{17}$ at baseline, 16.2 (4.1)
[b]Percent with $HRSD_{17} \leq 50\%$ of participant's score at baseline.
[c]Percent with $HRSD_{17} \leq 7$.
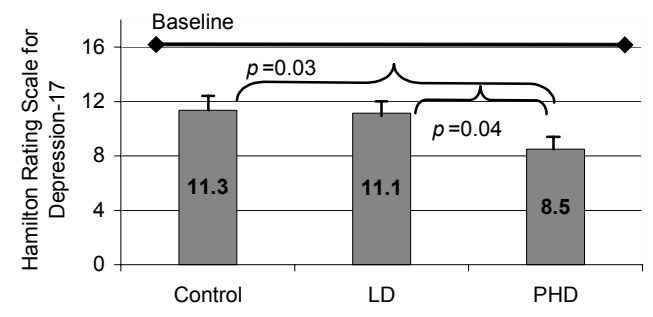*$p \leq 0.05$ vs control (bolded).



**Figure 4.** Twelve-week responses by total energy expenditure. Results for combined low dose (LD) and public health dose (PHD) indicated a significant difference between the control group and PHD ($p = 0.03$), and between low-dose (LD) and PHD groups ($p = 0.04$). There was no significant difference between the control and LD groups.
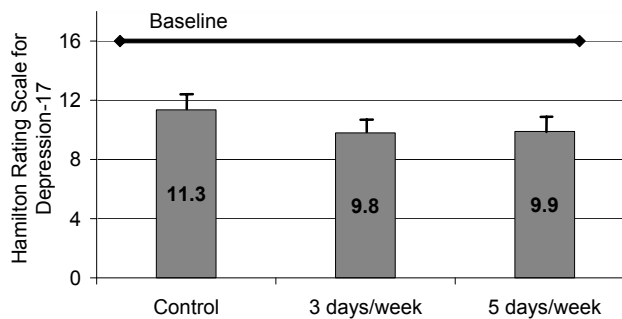
**Figure 5.** Twelve-week response by exercise frequency. Results for combined 3 days per week and 5 days per week indicated no differences between the control group and 3 days per week and 5 days per week.

ity of response to treatment ($HRSD_{17}$ (50% of baseline) over 12 weeks in the efficacy sample. The increasing trend was significant for the PHD and LD conditions ($p < 0.001$ and $p = 0.01$, respectively), and also for the 3-day/week and 5-day/week conditions ($p < 0.001$ for each), but not for exercise placebo controls ($p = 0.20$). At 12 weeks, the adjusted probabilities of response (mean±standard error of the mean) were 0.26±0.10 for LD, 0.46±0.09 for PHD, 0.31±0.08 for 3 days/week, 0.40±0.12 for 5 days/week, and 0.15±0.06 for control group. There was no significant interaction ($p = 0.20$) between exercise frequency and energy expenditure on weekly response probabilities. Comparing main treatment effects at 12 weeks, the PHD condition was not significantly more effective than the LD condition in eliciting response to treatment ($p = 0.17$), but was significantly more effective than the control condition ($p = 0.008$). The LD condition was not significantly different from the control condition ($p = 0.38$). The 3-day/week condition was not significantly different from the 5-day/week condition ($p = 0.58$).

**Remission rates.** Further GEE analysis of weekly $HRSD_{17}$ scores showed an increasing trend in probability of remission ($HRSD_{17} \leq 7$) over 12 weeks in the efficacy sample. The increasing trend was significant for the PHD and LD conditions ($p < 0.001$ and $p = 0.004$, respectively) and also for the 3-day/week and 5-day/week conditions ($p < 0.001$ each), but not for the control group ($p = 0.32$). At 12 weeks, the adjusted probabilities of remission—mean (± standard error of mean)—were 0.42±0.09 for PHD, 0.26±0.10 for LD, 0.31±0.10 for 3 days/week, 0.35±0.12 for 5 days/week, and 0.11±0.06 for controls. There was no significant interaction ($p = 0.32$) between exercise frequency and energy expenditure on weekly remission probabilities. Comparing main treatment effects at 12 weeks, the PHD condition was not significantly more effective than the LD condition in eliciting remission ($p = 0.25$), but was significantly more effective than the control condition ($p = 0.01$). The LD condition was not significantly different from the control condition ($p = 0.15$).

The 3-day/week condition was not significantly different from the 5-day/week condition ($p = 0.81$).

**Rates of treatment adherence, discontinuation, and adverse events.** Exercise adherence, the percentage of prescribed exercise sessions completed to protocol after randomization, differed significantly between the control and exercise conditions, but not among exercise conditions, in the intent-to-treat sample. Adherence for the control group averaged 42% compared with 72% for the combined four aerobic exercise groups ($p = 0.03$). Adherence for participants in the PHD conditions averaged 71% compared with 72% for the LD conditions ($p = 0.89$). Adherence for participants in the aerobic exercise groups exercising 3 days/week averaged 78%, compared with 65% for those exercising 5 days/week ($p = 0.46$). When considered as a predictor of $HRSD_{17}$ scores, greater adherence was not significantly associated with lower scores ($p = 0.23$).

Dropout rates after randomization varied significantly between control and exercise conditions, but not among exercise conditions, in the intent-to-treat sample. Eight of 13 (62%) control group participants and 19 of 67 (28%) aerobic exercise group participants did not finish the 12th week of treatment (log-rank $p = 0.002$ for difference). However, in the aerobic exercise groups, 10 (30%) participants in the PHD conditions dropped out compared with 9 (26%) in the LD conditions (log-rank $p = 0.78$). Eight (24%) participants exercising 3 days/week discontinued, compared with 11 (32%) of those exercising 5 days/week (log-rank $p = 0.40$). Baseline $HRSD_{17}$ scores were not predictive of dropout rates ($p = 0.74$). Running total weekly $HRSD_{17}$ scores were not associated with dropout ($p = 0.83$). Running total missed days of exercise were nonsignificantly associated with greater dropout rates ($p = 0.33$). Running total missed days of exercise ($p = 0.33$), age ($p = 0.27$), female gender ($p = 0.50$), and body mass index ($p = 0.75$) were not associated with dropout rates.

Adverse events included increased severity of depressive symptoms ($n = 1$), chest pain ($n = 1$), and joint pain/swelling ($n = 1$). All of these participants discontinued exercise and were referred to their primary care physicians for further follow-up.

## Discussion

The major finding was that the public health dose (PHD) of exercise is an effective monotherapy for mild to moderate MDD. In the efficacy analysis, mean $HRSD_{17}$ scores at 12 weeks were reduced 47% from baseline for the PHD condition, significantly better than the LD and control conditions. Forty-six percent of participants in the PHD group had a therapeutic response to treatment, defined as a 50% reduction in baseline $HRSD_{17}$ score, and 42% of the PHD group had

remission of symptoms, defined as an $HRSD_{17} \leq 7$. In contrast, the LD group did not respond any better than the exercise placebo control group, although both groups had reductions in depressive symptoms. While the reduction in depressive symptoms was greatest in participants who accepted and adhered to treatment, qualitatively similar and significant reductions were observed on an intent-to-treat basis. Research suggests that this is the first study showing efficacy for a specific dose of aerobic exercise in a well-characterized sample of participants with diagnosed MDD.

The response and remission rates in the PHD group are comparable to other depression treatments, such as medication or cognitive behavioral therapy. For example, in the Collaborative Depression Study conducted by the National Institute of Mental Health,[23] rates of remission were 36% for cognitive behavioral therapy and 42% for antidepressant medication (imipramine hydrochloride), similar to the 42% remission rate in this study. The results also are consistent with remission responses to exercise reported by others, such as the 47% remission rate in an RCT comparing exercise and medication in older adults.[11] The reductions in symptoms in the LD and control groups are similar to those seen in other placebo groups in antidepressant treatment studies.[23]

The finding of no difference in results for the 3-day/week and the 5-day/week conditions suggests that the determining factor for reduction and remission of symptoms is total energy expenditure. The total energy expenditure is consistent with consensus public health recommendations for physical activity that advise all adults to engage in $\geq 30$ minutes of moderate-intensity physical activity on most and preferably all days of the week to reduce their risk of early death and morbidity from a variety of diseases such as cardiovascular disease. This amount of exercise can be obtained in 3 days or 5 days, as the data show that these frequencies produce similar results.

A frequent criticism to exercise treatment for depression is that acceptable adherence with treatment regimens is not possible. The adherence rate of study participants was comparable to many medication trials where rates vary from 60% to 80%.[4,5] Furthermore, the adherence rates that have been documented from other trials of exercise in depressed patients are similar to the rates observed in this study.[9,11,24] Also, data on adverse events and adherence indicate that exercise was an acceptable treatment to participants with few side effects.

There were limitations in the study. First, participants were unable to be blinded to treatment assignment; therefore, some participants regarded being assigned to the exercise placebo to be unacceptable and immediately dropped out. Despite efforts to encourage acceptability of all group assignments, it was difficult to maintain adherence in the exercise placebo control

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**What This Study Adds . . .**

There is scientific evidence to suggest that exercise alleviates symptoms of depression and may be useful in the treatment of mild to moderate major depressive disorder (MDD).

This tightly controlled study shows that exercise by itself is effective in the treatment of mild to moderate MDD, and that the amount of exercise needed is equivalent to consensus public health recommendations.

A lower amount of exercise is not effective and is similar to placebo control.

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group. Second, participants were required to exercise under supervision at CI to overcome many of the criticisms of previous studies, such as controlling for social support and strictly monitoring exercise dose. Because monitoring exercise dose was a major question in this study, it was critical to maintain high internal validity. The high internal validity of this study compromises external validity; therefore, it is unknown how the PHD exercise treatment might work in clinical practice. Finally, the sample is relatively small compared to many pharmacologic treatment studies. However, consistent and clinically meaningful differences were found between the PHD and LD groups, indicating that power was adequate.

In summary, aerobic exercise in the amount recommended by consensus public health recommendations was effective in treating mild to moderate MDD. The amount of exercise that is less than half of these recommendations was not effective. Rates of response and remission with a PHD dose are comparable to the rates reported in trials of cognitive behavioral therapy, antidepressant medication, and other exercise studies.

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