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The Antidepressive Effects of Exercise
A Meta-Analysis of Randomized Trials

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Abstract

Several meta-analyses examining the effects of exercise on depression have been criticized for including studies of poor methodological integrity. More recent meta-analyses addressed the most common criticism by including only randomized control trials; however, these analyses suffer from incomplete literature searches and lack of moderating variable analyses. Using a more extensive search procedure, the current meta-analysis examines the effects of exercise on depressive symptoms in 58 randomized trials (n = 2982). An overall effect size of –0.80 indicates participants in the exercise treatment had significantly lower depression scores than those receiving the control treatment.

This 3/4 SD advantage represents level 1, Grade A evidence for the effects of exercise upon depression. Analysis of moderating variables examined the influence of population characteristics, exercise characteristics and methodological characteristics. Examination of clinical significance in 16 trials with clinically depressed patients found 9 of 16 exercise treatment groups were classified as 'recovered' at post-treatment, with another three groups classified as 'improved'. Analysis showed dropout rates for the exercise treatment were similar to those found in psychotherapeutic and drug interventions.

Depression disorders have become a widespread health concern throughout the world. In 1990, The Global Burden of Disease project ranked depressive disorders fourth in terms of global burden.[1] The worldwide prevalence of depression has been estimated at 10.4%.[2] Along with the prevalence of depressive disorders, the cost to treat these disorders has grown. In 2000, the National Institute of Mental Health (NIMH) estimated the cost to treat depressive disorders in the US at $US26 billion annually. In addition to the escalating costs associated with treatment, the accessibility and effectiveness of these treatments limit their impact. Only 55% of people afflicted with a depressive disorder are receiving treatment,[3] while alleviation of depressive symptoms was seen in only 32% of those receiving treatment. More recent research evidence has found that only 27.5% of depressed participants go into remission with initial medication treatment.[4] Of those who did not respond to initial treatment, between 17.6% and 24.8% responded to a switch in medication[5] and 30% responded to augmented medication.[6] These statistics indicate the need for more cost-effective, accessible and alternative treatments for depressive disorders.

One such adjunct or alternative treatment that has been proposed is exercise. In Australia, the government has recently included the services of an exercise physiologist under the nation's Medicare programme, allowing general practitioners to refer patients for a number of medical conditions including depression.[7] A similar movement has begun in the UK where in 2005 the Mental Health Foundation released a report encouraging general practitioners to use exercise as a frontline treatment for mild to moderate depression.[8]

The effects of exercise on depression have been examined in hundreds of studies since the early 1900s. In an effort to reach a consensus finding for these studies, several meta-analyses have been conducted in the area.[9-11] The effect sizes of these meta-analyses ranged from 0.53 to 0.88, indicating a moderate to large effect. These results were consistent across all ages, sexes and various modes of exercise. Examination by North et al.[11] of moderating variables indicated larger effects associated with longer intervention durations and more exercise sessions,[11] while Craft and Landers[9] found similar results associated with longer intervention durations, and also found larger effects for groups with higher initial depression scores.[9]

While these results provide evidence demonstrating the alleviation of depressive symptoms through exercise, these studies can be criticized for including studies of poor methodological integrity, such as quasi-experimental trials and cross-sectional studies. Guyatt et al.[12] developed guidelines for assessing the quality of research evidence based on the strength and consistency of results, methodology, sample size and cost/benefit ratio.[12] According to these guidelines, Level 1, Grade A evidence, the highest level of recommendation, is the result of strong, clear-cut results from randomized controlled trials with very large sample sizes. These studies greatly reduced the likelihood of type I and type II errors through rigorous methodological procedures and a large sample size, respectively. Level 1, Grade A evidence can be provided either through one large randomized controlled trial or through a meta-analysis of smaller (Level II, Grade B) randomized controlled trials. Level II, Grade B studies

are similar to Level 1, Grade A studies in that they are randomized controlled trials. However, these studies have smaller sample sizes and thus are susceptible to type II errors.

A recent meta-analysis addressed this criticism by including only randomized controlled trials. Examining ten randomized trials (n = 479), Lawlor and Hopker[13] found an effect size of −1.1 (95% CI −0.6, −1.5), indicating that participants in exercise experimental groups had post-intervention depression scores 1.1 standard deviation units lower than those receiving no treatment or a wait-list control treatment. However, Lawlor and Hopker argue that this evidence does not support the use of exercise in the treatment of depression, due to methodological weaknesses, including the lack of treatment concealment, the lack of intent to treat, and the lack of a clinical interview to confirm the diagnosis of the included studies.

Lawlor and Hopker[13] characterized a study as using intent-to-treat analysis "if all the patients were analysed in the groups to which they were randomly allocated. If only those who started treatment or only those who completed treatment were included in the analysis we defined the study as not using [intent-to-treat] analysis" (p. 2). Likewise, a study was identified as using adequate concealment of allocation if treatment group assignment included "central randomisation at a site remote from the study, computerised allocation in which records are in a locked, unreadable file that can be accessed only after entering patient details, or the drawing of sealed and opaque sequentially numbered envelopes, and inadequately concealed if assignment procedures included open list or tables of random numbers, open computer systems or drawing of non-opaque envelopes, and unclear if no information in report, and the authors either did not respond to requests for information or were unable to provide information" (p. 2). Finally, Lawlor and Hopker believe that these results cannot be deemed clinically significant without a change in depression diagnosis as measured by a clinical interview by a psychologist.

Lawlor and Hopker do not empirically derive these potential methodological problems through examination of moderating variables within their own analysis. Instead, they cite a study of pregnancy and childbirth data[14] that identifies potential methodological weaknesses to argue that a lack of treatment concealment and intent to treat might exaggerate the effectiveness of interventions by 20–40%. In other words, Lawlor and Hopker's conclusion is speculative and the generalization of the findings may not be appropriate to a study of depression. Instead, these methodological weaknesses should be examined as moderating variables within a meta-analysis on exercise and depression.

A narrative review by Brosse et al.[15] concurs with the conclusions drawn by Lawlor and Hopker. Brosse et al. conclude that while research 'suggests' that exercise is an effect treatment for depression, "the majority of studies suffer from significant methodological shortcomings". However, not all scholars are as quick to dismiss the meta-analytical results. Biddle[16] states that "even though the research designs included in the analysis were weak, the effect size was large" and in the same direction as found in narrative reviews[17] of experimental and epidemiological studies on this topic. Mutrie[18] argues that Lawlor and Hopker's large effect size provides evidence of the effectiveness of exercise in decreasing depressive symptoms. Even if the methodological weaknesses are present in many of the studies, Callaghan[19] maintains that the Lawlor and Hopker results would not disappear, but only be weakened. According to Callaghan, a 40% reduction in effect size of 1.10 would still result in an overall effect size of 0.66 or a decrease of 7.3 on the Beck Depression Inventory (BDI).

Stathopoulou et al.[20] conducted a similar meta-analysis, which included 11 randomized, controlled trials examining the effects of exercise on participants with affective disorders, and found an overall effect size of 1.39 (95% CI 0.89, 1.88). The larger effect size of this analysis compared with that of Lawlor and Hopker is most likely due to the exclusion of studies not published in peer-reviewed journals. Also, Stathopoulou et al. failed to address the methodological criticisms presented by Lawlor and Hopker, analyse moderating variables or conduct an

analysis of participant dropout rates. A final short-coming of this analysis is that Stathopoulou et al. base their recommendations for exercise dose on the few studies that directly compare varying doses of exercise rather than an examination of exercise dose as a moderating variable.

The purpose of the current meta-analysis was to provide Level 1, Grade A evidence for the relationship between exercise and depression, marking the first time Level 1, Grade A evidence has been produced relative to the exercise-depression relationship. Analysis of moderating variables includes examination of exercise dose (e.g. intensity, duration and weeks of training) and is examined in the overall study sample and separately within those studies consisting of clinically depressed patients. In addition, this analysis examines the methodological characteristics of the included studies (e.g. lacking clinical interviews, treatment concealment and intent to treat) to determine the validity of the criticisms raised in the Lawlor and Hopker meta-analysis. Finally, the viability of the use of exercise in the treatment of clinically depressed populations and the potential mechanisms responsible for exercise reducing depression are discussed.

Based on the results of previous meta-analyses, it is hypothesized that aerobic and resistance exercise programmes significantly alleviate depressive symptoms. In addition, participants with clinical levels of depression show improvements greater than those of the general population. Finally, intervention duration is hypothesized to be positively correlated with improvements in depression.

1. Methods

1.1 Literature Search

An electronic literature search was conducted for all articles published in 2005 or prior using PubMed, PsycINFO, SportDiscus® and Dissertations Abstracts International using the terms 'exercise', 'physical activity', 'running', 'jogging', 'walking', 'weight lifting', 'weight training', 'depression' and 'mental health' to identify potential studies for inclusion. In addition, bibliographies of all articles found through electronic search on the topic were also examined to identify additional studies.

1.2 Inclusion Criteria

To be included in the analysis, a trial must have used a form of moderate to vigorous exercise (aerobic or resistance) as a treatment condition and must have measured depression as a dependent variable. Only randomized controlled trials were included in the analysis. Studies were included if the control conditions were a no-treatment or wait-list control. Studies that used control groups who participated in light exercise, such as stretching or walking, were excluded from the analysis.

1.3 Data Extraction and Collection

Data were extracted from the included studies entered into an electronic database by the two lead authors. In cases where all relevant data were not included in the published manuscript, the authors were contacted via postal mail. If no correspondence was received from the authors, contact was attempted through phone or electronic mail. At this time, authors were also asked to report if they were aware of any other studies that examined exercise and depression. Studies were first coded based on the population of the study (general population vs clinically depressed population). Studies were coded as using a clinically depressed population if they were identified by the original studies as being clinically depressed, either through a clinical interview or a screening and the depression was not associated with other physical or psychological ailments such as fibromyalgia, cardiac infarction or chemical dependence. Studies were then coded for moderating variables including sex, dependent variable measurement, fitness improvement, intervention duration, exercise bout intensity, frequency and duration, and were examined in the overall population and within the clinically depressed population. The first author coded the studies and the second author coded a random sample of ten studies to examine coding reliability.

1.4 Statistical Analysis

The effect sizes (ESs) for each study were calculated using Hedges' g, $g = (M_T - M_C)/SD_{pooled}$, where M_T is the post-treatment mean of the treatment group and M_C is the post-treatment mean of the control group.[21] In the 31 studies that contained multiple treatment groups or used multiple measures of depression, a single average effect was calculated. ESs were corrected for sample size according to procedures outlined by Hedges and Olkin.[21] Finally, based on the recommendations of Hedges and Olkin and Hunter and Schmidt,[22] a random effects model was used, and ESs were weighted by the inverse of the variance to calculate the overall ES.[23] Additionally, gains ESs were calculated for exercise and control groups, in which case the calculation for ES becomes $M_{Post} - M_{Pre}/SD_{Pooled}$, where M_{Post} is the post-treatment mean of the intervention group and M_{Pre} is the pre-treatment mean of the intervention group. A one-sample t-test was used to compare the overall effect size with zero.

An overall Q value and I^2 value were calculated to test for homogeneity of variance among the ESs. This Q value represents the total amount of variance among the set of ESs and was tested against a χ^2 distribution, in which $df = k - 1$, where k = number of ESs. I^2 is calculated using the formula $I^2 = 100\% \times (Q - df)/Q$. According to Higgins et al.,[24] this provides a precise, easily interpreted measure of heterogeneity. I^2 values of 25%, 50% and 75% represent low, medium and high heterogeneity, respectively. A significant Q value indicates that the data are heterogeneous, and would warrant the examination of moderator variables by dividing the variance into Qw and Qb. Qb values are also tested against a χ^2 distribution, in which df = number of categories of the moderator variable – 1. A significant Qb value indicates that the moderator variable contributes to the variance among ESs. Weighted ESs and standard errors were then calculated for each category within the moderator variables, and 95% confidence intervals were calculated to determine whether or not each ES was significantly different from zero.[25] To determine significant differences between levels of each moderating variable, planned comparisons were calculated for all moderating variables that yielded a significant Qb.[21] The significance test for each planned comparison compared χ^2 to a Bonferroni-adjusted critical value (0.05/number of comparisons within moderating variable). Moderating variable analysis was conducted for the entire sample of ESs and also across the clinical population.

The volume of exercise used in each study was estimated in units of energy (kcal/kg) expended during exercise, assuming 5 kcal/mL O_2 consumed. Total O_2 consumed/kg/wk was calculated as:

$$\text{Total } O_2 \text{ consumed} = (\dot{V}O_{2\,max}) \times (\text{intensity}) \times (\text{bout duration}) \times (\text{frequency})$$

where total O_2 units are mL/kg/wk, $\dot{V}O_{2max}$ (maximum oxygen uptake) units are mL/kg/min, average exercise bout intensity is in $\%\dot{V}O_{2max}$, average bout duration is in minutes, and exercise frequency is number of exercise bouts per week. For determining volume of exercise, only those studies reporting $\dot{V}O_{2max}$ were used, and pre- and post-intervention $\dot{V}O_{2max}$ measurements were averaged in the calculation.[26]

After calculating exercise dose, the data were examined for outliers. Any exercise dose >3 standard deviations away from the mean were considered outliers, and were removed from the analysis.[27] Pearson's product-moment correlations were then calculated between exercise dose and the corresponding ESs for the exercise groups. Additionally, a multiple regression analysis was used to examine a potential nonlinear relationship between exercise dose and effect size.

2. Results

2.1 Overall Results

The literature search resulted in 149 articles that were examined for inclusion criteria, with 75 of the studies meeting all inclusion criteria. Reasons for exclusion included the lack of a no-treatment control group, experimental groups receiving exercise in combination with another treatment, or the lack of true randomization.

Of these studies, sufficient information to calculate effect sizes was obtained from 58 of the studies,[28-91] with a total population of 2982. Participants in the exercise treatment had significantly lower depression scores than those receiving the control treatment (ES = –0.80, 95% CI –0.92, 0.67). Fifty-six studies contained sufficient information to calculate gains effect sizes. Analysis of gains effect sizes revealed the average effect size for exercise treatment groups was 1.07, which is significantly different from zero ($t(55) = -5.505$; $p < 0.05$; 95% CI –1.458, –0.680). The average effect size for the control groups was –0.20, which was found to be not statistically different from zero ($t(55) = -1.413$; $p > 0.05$; 95% CI –0.481, 0.083). The average difference in BDI between treatment and control groups in the overall samples was 3.83 and the average difference on the Hamilton Rating Scale for Depression (HRSD) was 3.43. The test for homogeneity of variance was found to be significant ($Q = 364.25$; $p < 0.001$), warranting the examination of moderating variables. I^2 was calculated to be 84.35%. Inter-rater reliability for the coding of moderating variables was found to be 0.93. Results from analysis of moderating variables can be found in table I and table II. Significant Qb values were found for intervention duration, exercise type, bout duration, exercise frequency, clinical diagnosis and exercise intensity (tables III–VI).

2.2 Moderating Variables: Population Characteristics

2.2.1 Clinical Depression versus Non-Clinical Depression

Seventeen studies examined the effect of exercise on clinically depressed participants (n = 574). Clinically depressed participants in the exercise treatment had significantly lower depression scores than those receiving the control treatment (ES = –1.03). Within the clinically depressed population, the average change in BDI was 10.60, while the average change in HRSD was 8.11. In the 40 studies that examined non-clinical samples (n = 2408), participants had significantly lower depression scores than those receiving the control treatment (ES = –0.59). Within the non-clinical population, the average BDI change was 2.64 and no studies used the HRSD. A planned comparison revealed the effect size of the clinical population was significantly larger than that of the general population ($\chi^2[1, n = 58] = 19.20$; $p < 0.05$; 95% CI 0.246, 0.645).

2.3 Moderating Variables: Exercise Characteristics

2.3.1 Intervention Duration

Within the overall population, planned comparisons revealed that the effects of interventions lasting 4–9 weeks were significantly greater than the effects of interventions lasting 17–26 weeks ($\chi^2[1, n = 24] = 7.72$; $p = 0.0055$; 95% CI –0.677, –0.117). Interventions lasting 10–16 weeks resulted in significantly larger effects compared with interventions lasting 17–26 weeks ($\chi^2[1, n = 64] = 13.22$; $p = 0.0003$; 95% CI –0.765, –0.229) and >26 weeks ($\chi^2[1, n = 31] = 7.53$; $p = 0.0061$; 95% CI –0.543, –0.090). Within the clinical population, a planned comparison revealed that interventions of 10–16 weeks in duration resulted in significantly larger effects compared with interventions of 4–9 weeks in length ($\chi^2[1, n = 15] = 4.87$; $p = 0.0273$; 95% CI 0.102, –0.870).

2.3.2 Exercise Type

Within the overall population, planned comparisons revealed that a regimen of combined aerobic and resistance exercise resulted in significantly larger effects than aerobic exercise ($\chi^2[1, n = 52] = 22.93$; $p < 0.0001$; 95% CI 0.643, 1.533) and resistance exercise ($\chi^2[1, n = 54] = 20.71$; $p < 0.0001$; 95% CI 0.674, 1.694). However, within the clinically depressed population, no significant differences were found between exercise types.

2.3.3 Exercise Bout Duration

Within the overall population, planned comparisons revealed that bout durations of 20–29 minutes resulted in significantly larger effects than exercise bouts of 45–59 minutes ($\chi^2[1, n = 20] = 6.70$; $p = 0.0096$; 95% CI –0.601, –0.083) and ≥60 minutes ($\chi^2[1, n = 24] = 7.64$; $p = 0.0057$; 95% CI –0.558, –0.095). Within the clinical

Table I. Methodological details of studies comparing exercise vs a no-treatment control group

Study	Depression measure	ES	N	Population	Sex	Age (y) [mean or range]	Exercise type	Intervention length (wk)	Exercise frequency	Bout duration (min)	Intensity
Antunes et al.[28] (2005)	GDS	−1.48	46	NC	M	66.97	Aerobic	24	3/wk	20–60	50–60% $\dot{V}O_{2max}$
Bartholomew et al.[29] (2005)	POMS-D	−0.26	40	C	X	38.10	Aerobic	Acute	NA	30	60–70% HR_{max}
Berger et al.[30] (1988)	POMS-D	−0.12	305	NC	X	20.00	Aerobic	12	3/wk	20+	65–80% HR_{max}
Blumenthal et al.[31] (1991)	BDI	−0.18	101	NC	X	67.00	Aerobic	16	3/wk	30	70% HR_{max}
Blumenthal et al.[32] (2005)	BDI	−3.14	134	NC	X	63.00	Aerobic	16	3/wk	35	70–85% HR_{max}
Broocks et al.[33] (1998)	Multiple[a]	−1.24	37	C	X	46.00	Aerobic	10	3–4/wk	NA	NA
Brown et al.[34] (2001)	Multiple[a]	−0.63	104	NC	F	42.00	Aerobic	8	5/wk	20	60% HR_{max}
Burrus[35] (1984)	DACL	−0.32	45	C	X	16.20	Aerobic	9	4/wk	35	NA
Castro et al.[36] (2002)	BDI	−0.30	85	NC	F	62.00	Aerobic	52	3–4/wk	30–40	60–75% HR_{max}
Chin A Paw et al.[37] (2004)	GDS	0.18	173	NC	X	64–94	Resistance	6 mo	2/wk	45–60	NA
Cramer et al.[38] (1991)	POMS-D	−0.44	35	NC	X	34.00	Aerobic	15	5/wk	45	60% HR_{max}
Crews et al.[39] (2004)	BDI	−0.89	66	NC	X	9.00	Aerobic	6	3/wk	20	134 bpm
Deivert[40] (1990)	Multiple[a]	−1.90	40	NC	X	31.00	Aerobic	8	3/wk	20	NA
DePalma[41] (1989)	BDI	−0.55	77	NC	X	20.27	Aerobic	12	3/wk	20–40	NA
DiLorenzo et al.[42] (1998)	Multiple[a]	−0.70	111	NC	X	32.00	Aerobic	12	4/wk	24 or 48	70–85% HR_{max}
Dugmore et al.[43] (1999)	TAS-D	−4.07	124	NC	X	55.00	Combined	52	3/wk	NA	65–80% $\dot{V}O_{2max}$
Dunn et al.[44] (2005)	HRSD	−0.64	80	C	X	35.00	Aerobic	12	3/wk	NA	NA
Eby[45] (1984)	Zung	−0.07	39	NC	X	19–31	Combined	NA	3/wk	60–90	NA
Emery et al.[46] (1998)	Multiple[a]	−0.42	74	NC	X	66.60	Aerobic	10	NA	NA	NA
Epstein[47] (1986)	Multiple[a]	−0.84	26	C	X	39.42	Aerobic	8	3/wk	30	NA
Favilla[48] (1992)	GDS	−0.57	64	NC	X	73.00	Resistance	6	3/wk	NA	80% 1 RM
Gowans et al.[49] (2001)	Multiple[a]	−0.83	31	NC	X	47.00	Aerobic	23	3/wk	30	60–75% HR_{max}
Gowans et al.[50] (2002)	Multiple[a]	−0.75	31	NC	X	47.00	Aerobic	23	3/wk	30	60–75% HR_{max}
Hembree et al.[51] (2000)	BDI	−0.69	53	NC	F	79.83	Combined	4	5/wk	NA	NA
Hilyer et al.[52] (1982)	Multiple[a]	−1.14	43	NC	M	15–18	Combined	20	3/wk	90	NA
Jorgensen[53] (1986)	SCL-90-D	0.00	11	C	X	36.40	Aerobic	6	3/wk	1 h	TZHR
Kanner[54] (1990)	Multiple[a]	−0.73	68	C	X	13.32	Aerobic	8	3/wk	60	70–85% HR_{max}
King et al.[55] (1989)	Own	−0.16	113	NC	X	48.00	Aerobic	24	5/wk	50	65–77% HR_{max}
King et al.[56] (1993)	BDI	−0.12	300	NC	X	50–65	Aerobic	52	3/wk	40	73–88% HR_{max}
Koukouvou et al.[58] (2004)	Multiple[a]	−1.66	26	NC	M	52.50	Aerobic	24	3–4/wk	60	50–75% $\dot{V}O_{2max}$
Lennox et al.[59] (1990)	DACL	−0.29	47	NC	X	45.00	Combined	13	3/wk	50–60	NA
Levin[60] (1983)	Multiple[a]	−0.67	38	C	X	26–35	Aerobic	10	3/wk	60	NA
Martinsen et al.[61] (1985)	BDI	−1.14	43	C	X	40.00	Aerobic	9	3/wk	60	50–70% HR_{max}

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Table I. Contd

Study	Depression measure	ES	N	Population	Sex	Age (y) [mean or range]	Exercise type	Intervention length (wk)	Exercise frequency	Bout duration (min)	Intensity
McCann and Holmes[62] (1984)	BDI	−1.01	43	C	F	NA	Aerobic	10	2/wk	60	NA
McNeil et al.[63] (1991)	BDI	−1.02	30	C	X	72.50	Aerobic	6	3/wk	40	NA
Mutrie[64] (1998)	Multiple[a]	−1.51	24	C	X	42.10	Combined	4	3/wk	20	NA
Neidig et al.[65] (2003)	Multiple[a]	−0.53	48	NC	X	36.00	Aerobic	12	3/wk	60	60–80% $\dot{V}O_{2max}$
Newton et al.[66] (1991)	Multiple[a]	−0.48	22	NC	X	<70	Aerobic	10	3/wk	60	60–80% HR_{max}
Norris et al.[67] (1992)	MAACL	0.10	80	NC	X	16.50	Aerobic	10	2/wk	25–30	70–75% HR_{max}
Norvell and Belles[68] (1993)	SCL-90-D	−1.17	29	NC	M	32.84	Resistance	16	3/wk	20	NA
Petajan et al.[69] (1996)	POMS-D	−1.41	54	NC	X	40.00	Aerobic	15	3/wk	50	NA
Pierce et al.[70] (1993)	STAI-D	−0.10	99	NC	X	45.00	Aerobic	16	3/wk	50	70% $\dot{V}O_{2max}$
Pinchasov et al.[71] (2000)	HRSD	−3.52	18	C	X	35.20	Aerobic	1	7/wk	60	75% HR_{max}
Roth et al.[72] (1987)	BDI	−0.20	36	NC	X	18.90	Aerobic	11	3/wk	30	75% HR_{max}
Roth and Homes[73] (1989)	POMS-D	−2.66	80	NC	X	20.80	Aerobic	NA-Acute	NA-acute	20	115–160 bpm
Setaro[74] (1985)	MMPI-D	−1.08	75	C	X	18–35	Aerobic	10	2/wk	NA	NA
Simons and Birkimer[75] (1988)	POMS-D	−0.10	128	NC	X	43.20	Aerobic	8	2/wk	90	NA
Singh et al.[76] (1997)	Multiple[a]	−2.20	32	C	X	71.00	Resistance	10	3/wk	45	80% 1 RM
Singh et al.[77] (2001)	BDI	−0.67	32	C	X	71.30	Resistance	20	3/wk	45	80% 1 RM
Singh et al.[78] (2005)	Multiple[a]	−0.58	60	C	X	60+	Resistance	8	3/wk	60	80% 1 RM
Sorensen et al.[79] (1999)	GHQ	−0.28	219	NC	X	44.90	Aerobic	52	3/wk	60	60–80% HR_{max}
Taylor[80] (1991)	BDI	−0.49	102	NC	F	39.10	Aerobic	6	3/wk	20	NA
van den Berg et al.[81] (2004)	HADS-D	−0.38	34	NC	X	58.60	Aerobic	3 mo	2/wk	1 h	60% HR reserve
Veale et al.[82] (1992)	Multiple[a]	−3.03	83	C	X	35.50	Aerobic	12	3/wk	NA	NA
Wigers et al.[83] (1996)	VAS-D	−0.31	48	NC	X	44.00	Aerobic	14	3/wk	45	60–70% HR_{max}
Williams and Lord[84] (1997)	DASS	−0.22	187	NC	F	71.70	Aerobic	42	2/wk	60	NA
Wilson[85] (1985)	Zung	−1.30	34	NC	F	31.00	Aerobic	16	3/wk	40	70–85% HR_{max}
Zentner[86] (1981)	POMS-D	−0.75	80	NC	X	41.00	Aerobic	10	3/wk	60	NA

a Broocks – MADRS, BDI; Brown – CES-D, GWB-D, POMS-D; Deivert – POMS-D, BDI; DiLorenzo – BDI, POMS-D; Emery – CES-D, SCL-90-D; Epstein – BDI, Zung; Gowans – BDI, MHI-D; Gowans – BDI, CES-D, FIQ-D, MHI-D; Hilyer – BDI, POMS-D; Kanner – CDI, ISC; Koukouvou – BDI, HADS-D; Levin – POMS-D, SCL-90-D; Mutrie – BDI, POMS-D; Neidig – CES-D, BDI, POMS-D; Newton – POMS-D, BDI; Singh – BDI, HRSD, GDS, DSM-IV; Singh – GDS, HRSD; Veale – CIS, BDI.

BDI = Beck Depression Inventory; **bpm** = beats/min; **C** = clinical; **CDI** = Children's Depression Inventory; **CES-D** = Center for Epidemiologic Studies Depression Scale; **CIS** = Clinical Interview Schedule; **DACL** = Depression Adjective Checklist; **DASS** = Depression Anxiety Stress Scales, Depression subscale; **DSM-IV** = Diagnostic and Statistical Manual, Depression symptoms; **ES** = effect size; **F** = female; **FIQ-D** = Fibromyalgia Impact Questionnaire, Depression subscale; **GDS** = Geriatric Depression Scale; **GHQ** = General Health Questionnaire, Depression subscale; **GWB-D** = General Well-Being Schedule, Depression subscale; **HADS-D** = Hospital Anxiety and Depression Scale, Depression subscale; **HR_{max}** = maximum heart rate; **HRSD** = Hamilton Rating Scale for Depression; **ISC** = Interview Schedule for Children; **M** = male; **MAACL** = Multiple Affect Adjective Checklist, Depression subscale; **MADRS** = Montgomery-Asberg Depression Rating Scale; **MHI-D** = Mental Health Inventory, Depression subscale; **MMPI-D** = Minnesota Multiphasic Personality Inventory, Depression subscale; **NA** = not available; **NC** = non-clinical; **POMS-D** = Profile of Mood States, Depression subscale; **RM** = repetition maximum; **SCL-90-D** = Symptom Checklist-90, Depression subscale; **STAI-D** = State Trait Anxiety Inventory, Depression subscale; **TAS-D** = Toronto Attitude Scale, Depression subscale; **TZHR** = theoretical zone heart rate; **VAS-D** = Visual Analogue Scales of Depression; **$\dot{V}O_{2max}$** = maximum oxygen uptake; **X** = mixed sex; **Zung** = Zung Self-Rating Depression Scale.

Table II. Methodological characteristics of clinically depressed population studies

Study	Concealment	Intent to treat	Clinical interview
Bartholomew et al.[29] (2005)	No	No	Yes
Broocks et al.[33] (1998)	Yes	Yes	Yes
Burrus[35] (1984)	No	No	No
Dunn et al.[44] (2005)	Yes	Yes	Yes
Epstein[47] (1986)	No	No	Yes
Kanner[54] (1990)	No	No	Yes
Levin[60] (1983)	No	No	No
Martinsen et al.[61] (1985)	Yes	No	No
McCann and Holmes[62] (1984)	No	No	Yes
McNeil et al.[63] (1991)	No	No	Yes
Mutrie[64] (1998)	No	No	Yes
Pinchasov[71] et al. (2000)	No	No	Yes
Setaro[74] (1985)	No	No	No
Singh et al.[76] (1997)	No	No	No
Singh et al.[77] (2001)	Yes	No	Yes
Singh et al.[78] (2005)	No	No	No
Veale et al.[82] (1992)	Yes	Yes	Yes

population, planned comparisons revealed a significantly larger effect for exercise bouts of 45–59 minutes compared with exercise bouts of 30–44 minutes (χ^2[1, n = 7] = 10.75; p = 0.0010; 95% CI 0.443, 1.762) and ≥60 minutes (χ^2[1, n = 9] = 6.29; p = 0.0122; 95% CI −1.42, −0.219).

2.4 Moderating Variables: Methodological Characteristics

The methodological characteristics of the studies with a clinically depressed population are described in table II.

2.4.1 Concealment of Treatment

In the clinically depressed population, the effect sizes of studies that used adequate concealment were significantly larger than the effect sizes of studies that did not use adequate concealment (χ^2[1, n = 17] = 5.45; p = 0.0196; 95% CI 0.106, 0.893).

2.4.2 Intent to Treat

In the clinically depressed population, a planned comparison revealed that studies that used adequate intent to treat resulted in significantly higher effect sizes than those that did not (χ^2[1, n = 17] = 10.76; p = 0.0010; 95% CI 0.357, 1.340).

2.4.3 Clinical Interview

A planned comparison indicated the effect sizes of studies that used a clinical interview to confirm a depression diagnosis did not significantly differ from those studies that did not conduct a clinical interview (χ^2[1, n = 17] = 0.43; p = 0.3818; 95% CI −0.484, 0.242).

2.5 Treatment Adherence

Of the 18 studies that included clinically depressed patients, 16 studies reported participant dropout rates. In those studies, the average percentage of dropout in the exercise group was 14.6%, while the percentage of dropout in control groups was 11.4%. The dropout rates of each group were not significantly different from each other (F[1, 13] = 0.272; p > 0.05).

2.6 Exercise Compared with Other Treatments

2.6.1 Exercise versus Psychotherapy

Four studies[47,57,74,87] compared exercise with psychotherapy, resulting in an overall effect size of −0.26, indicating that exercise resulted in larger antidepressive effects than psychotherapy. However, this difference was not significant (t = 1.686; p > 0.05; 95% CI −0.628, 0.116).

2.6.2 Exercise versus Antidepressant Medication

Three studies[32,86,87] compared exercise versus antidepressants and found an overall effect size of 0.02. This difference was not significant (t = 0.223; p > 0.05; 95% CI −0.152, 0.184).

2.7 Dose Response

Twelve studies provided adequate data to calculate exercise volume. One study yielded an exercise dose that was >3 standard deviations above the mean of all exercise doses and was removed from the analysis. Some of the remaining 11 studies included multiple exercise groups, resulting in 25 exercise groups. The Pearson product-moment correlation for exercise dose and effect sizes was found to be nonsignificant (r = −0.040; p > 0.05). Multiple regression analysis also

Table III. Moderating variables for the overall population

Category	df	Qb	Level	k	ES	SE	Upper CI	Lower CI
Population	1	19.19883*	Non-clinical	41	−0.58685	0.043453	−0.50049	−0.67082
			Clinical	17	−1.03137	0.091975	−0.85110	−1.21164
Age (y)	3	5.108655	<21	9	−0.67545	0.095481	−0.48831	−0.86259
			21–34	8	−0.88846	0.116993	−0.65915	−1.11776
			35–55	22	−0.58707	0.064817	−0.46003	−0.71411
			>55	17	−0.65607	0.069295	−0.52026	−0.79189
Sex	2	4.339101	Male	7	−0.72193	0.128623	−0.46982	−0.97403
			Female	7	−0.49163	0.093083	−0.30918	−0.67407
			Mixed	44	−0.7031	0.046652	−0.61166	−0.79453
Intervention duration (wk)	4	45.9213*	Acute	2	−1.50348	0.220743	−1.07082	−1.93613
			4–9	16	−0.64662	0.075876	−0.49791	−0.79534
			10–16	26	−0.74666	0.063409	−0.62238	−0.87094
			17–26	8	−0.24955	0.121108	−0.01218	−0.48692
			>26	5	−0.43008	0.096417	−0.24111	−0.61906
Exercise type	2	23.85307*	Aerobic	48	−0.64056	0.042285	−0.55768	−0.72344
			Resistance	6	−0.54462	0.133631	−0.2827	−0.80653
			Combined	4	−1.72853	0.22322	−1.29102	−2.16604
Bout duration (min)	2	10.3643*	20–29	9	−0.79508	0.092961	−0.61287	−0.97728
			30–44	14	−0.65653	0.083749	−0.49238	−0.82068
			45–59	11	−0.45277	0.093997	−0.26854	−0.637
			≥60	15	−0.46854	0.072793	−0.32586	−0.61121
Exercise frequency (/wk)	2	28.75021*	2	7	−0.24831	0.089114	−0.07365	−0.42298
			3–4	44	−0.78172	0.04868	−0.6863	−0.87713
			5	4	−0.52009	0.12201	−0.28095	−0.75923
Exercise intensity (%)	2	17.28126*	50–60	3	−0.76479	0.154123	−0.16667	−1.06687
			61–74	11	−0.33339	0.08506	−0.16667	−0.50011
			≥75	10	−0.8478	0.09814	−0.65544	−1.04015

df = degrees of freedom; **ES** = effect size; **k** = number of effect sizes; **Qb** = measure of homogeneity, see text; **SE** = standard error; * $p < 0.05$.

revealed a nonsignificant relationship ($F[1,23] = 0.037$; $p > 0.05$).

3. Discussion

Aerobic and resistance exercise programmes were hypothesized to significantly alleviate depressive symptoms. The overall effect size indicates an improvement in depression scores of 0.80 standard deviation units following an exercise programme. Analysis of moderating variables indicates aerobic and resistance exercises are equally effective. This finding supports the initial hypothesis and is consistent with the findings of Craft and Landers.[9] In the overall sample, analysis of moderating variables indicated that exercise interventions that combined aerobic and resistance exercise resulted in larger effects than aerobic or resistance exercise alone. It should be noted, however, that this effect size is based on only four trials, and further research must be conducted to confirm this finding. Additionally, within the clinically depressed population, aerobic and resistance exercises were found to be equally effective in alleviating depressive symptoms.

The second hypothesis of this study stated that participants with clinical levels of depression would show improvements greater than those of the general population. Improvements within

the clinically depressed population were 1.01 standard deviation units compared with 0.59 in the general population. This difference was found to be statistically significant and in line with the initial hypothesis and the previous findings of Craft and Landers.[9]

The final hypothesis of this study was that longer intervention durations would result in greater improvements in depressive symptoms. This hypothesis was based on the findings of North et al.[11] and Craft and Landers[9] in which longer intervention durations resulted in larger decreases in depression scores. Analysis of moderating variables supports this hypothesis within the clinically depressed population, where interventions of 10–16 weeks resulted in larger effects than interventions lasting 4–9 weeks. However, within the overall population, interventions of 4–9 weeks resulted in significantly larger effects than interventions of 17–26 weeks, while interventions of 10–16 weeks resulted in significantly larger effects than interventions of 16–26 weeks and >26 weeks. One possible explanation for these differences is a floor effect in the general population, where maximum improvements were achieved in the first 16 weeks of exercise training.

Analysis also indicated significant differences in moderating variable categories that were not hypothesized. Within the overall population, exercise bouts of 20–29 minutes resulted in larger effects than bouts of ≥45 minutes, while within the clinically depressed population, exercise bouts of 45–49 minutes resulted in larger effects than bouts of 30–44 minutes and of ≥60 minutes. Once again, however, the analysis of moderating variables within the clinically depressed population includes a small number of trials, and more research must be done before conclusions can be drawn on the optimal exercise bout duration.

Significant differences were also present across categories of exercise intensity across the overall population, with exercise of 61–74% maximum

Table IV. Planned comparisons for moderating variables (overall population)

Category	Comparison	χ^2	p-Value
Population	Clinical vs non-clinical	19.199**	<0.0001**
Intervention duration (wk)	4–9 vs 10–16	1.0234	0.3118
	4–9 vs 17–26	7.7196	0.0055**
	4–9 vs >26	0.7339	0.3916
	10–16 vs 17–26	13.223	0.0003**
	10–16 vs >26	7.5258	0.0061**
	17–16 vs >26	1.3601	0.2435
Exercise type	Aerobic vs resistance	0.4686	0.4934
	Aerobic vs combined	22.933**	<0.0001**
	Resistance vs combined	20.709**	<0.0001**
Bout duration (min)	20–29 vs 30–44	1.2261	0.2682
	20–29 vs 45–59	6.7042**	0.0096*
	20–29 vs ≥ 60	7.6487**	0.0057**
	30–44 vs 45–59	2.6195	0.1055
	30–44 vs ≥60	2.8703	0.0902
	45–49 vs ≥60	0.0176	0.8945
Exercise frequency (/wk)	2 vs 3–4	27.593**	<0.0001**
	2 vs 5	3.2356	0.0721
	3–4 vs 5	3.9667	0.0464*
Exercise intensity (%)	50–60 vs 61–74	6.0056*	0.0143**
	50–60 vs ≥75	0.2064	0.6496
	61–74 vs ≥75	15.689**	<0.0001**

*p < 0.05, ** p < Bonferroni-adjusted p-value.

Table V. Moderating variables for clinical population

Category	df	Qb	Level	k	ES	SE	Upper CI	Lower CI
Age (y)	3	5.251954	<21	2	−0.56676	0.236152	−0.1039	−1.02962
			21–34	2	−0.89392	0.228353	−0.44635	−1.34150
			35–55	8	−1.27989	0.146603	−0.99254	−1.56722
			>55	4	−1.0051	0.199561	−0.61396	−1.39624
Sex	1	0.000269	Female	1	−1.01316	0.325082	−0.3760	−1.65032
			Mixed	16	−1.03296	0.095894	−0.8450	−1.22091
Intervention duration (wk)	2	13.29871**	Acute	1	−0.26461	0.317609	0.357902	−0.88712
			4–9	8	−0.90384	0.142851	−0.62385	−1.18383
			10–16	7	−1.34226	0.138093	−1.0716	−1.61292
Exercise type	1	0.001189	Aerobic	14	−1.03779	0.101263	−0.83931	−1.23626
			Resistance	3	−1.00114	0.219851	−0.57023	−1.43205
Bout duration (min)	3	46.11954**	20–29	1	−1.50875	0.570179	−0.3912	−2.6263
			30–44	4	−0.49985	0.198906	−0.11	−0.88971
			45–59	3	−1.60254	0.271284	−1.07082	−2.13426
			≥60	5	−0.82846	0.216866	−0.40340	−1.25352
Exercise frequency (/wk)	2	16.68409**	2	2	−1.04986	0.221579	−0.61557	−1.48416
			3–4	13	−1.06424	0.107732	−0.85308	−1.27539
			5	1	−3.51607	0.752085	−2.04198	−4.99015
Exercise intensity (%)	1	51.69517**	61–74	1	−0.26461	0.317609	0.357902	−0.88712
			≥75	4	−0.78516	0.189078	−0.41456	−1.15575
Clinical interview	1	0.428708	Yes	11	−1.09942	0.120473	−0.86330	−1.33555
			No	6	−0.93628	0.142408	−0.65716	−1.21540
Intent to treat	1	11.45184**	No	14	−0.90001	0.100313	−0.70340	−1.09662
			Yes	3	−1.72456	0.230435	−1.27291	−2.17622
Concealment	1	6.180855*	No	12	−0.89263	0.109516	−0.67798	−1.10728
			Yes	5	−1.36348	0.169438	−1.03139	−1.69558

df = degrees of freedom; **ES** = effect size; **k** = number of effect sizes; **Qb** = measure of homogeneity, see text; **SE** = standard error; * $p < 0.05$, ** $p < 0.01$.

heart rate resulting in lower effects than exercise of lower intensity (50–60%) and higher intensity (≥75%). Within the clinically depressed population, no significant differences were found. This finding was also supported by the separate dose-response analysis that indicated there was not a significant relationship between energy expenditure and changes in depression score. This is another area that will require further research because only 24 studies reported adequate information pertaining to exercise intensity, while only five studies within the clinically depressed population reported sufficient exercise intensity. In addition, all studies that reported exercise intensity used intensities ranging from 50% to 85%. Future research must also examine exercise intensities outside of this range.

Finally, significant differences in effects were found for exercise frequency within the clinically depressed population, as exercising five times per week resulted in a significantly larger effect than exercise two to four times per week. However, only one study utilized a protocol of five exercise sessions per week.

3.1 Mechanisms of Antidepressive Effects

It has been hypothesized that decreased rates of adult neurogenesis are, at least in part, responsible for depressed mood.[92] Recent research has found that current antidepressant medications result in hippocampal neurogenesis in laboratory animals.[93] From these results, Ernst et al.[94] hypothesize that antidepressive effects of

exercise are due to physiological changes that result in hippocampal neurogenesis.

Ernst et al. identify four mechanisms by which exercise could potentially facilitate this neurogenesis. Firstly, an increase in β-endorphins, which have been linked to neurogenesis,[95] have also been found to be increased following exercise.[96] Similarly, vascular endothelial growth factor (VEGF) increases during exercise[97] and has been linked to hippocampal neurogenesis in adult rats,[98,99] while blockage of VEGF eliminated exercise-induced neurogenesis.[100]

A third potential mechanism identified by Ernst et al. is brain-derived neurotrophic factor (BDNF), which has been shown to be increased by exercise in a number of studies,[101] while Wozniak[102] identified BDNF as having a crucial role in neuronal development and survival. Furthermore, when exercise is combined with antidepressants, BDNF levels were found to increase in as little as 2 days, compared with 2 weeks with antidepressants alone.[103]

Finally, Ernst et al. examined the role of serotonin in the antidepressive effects of exercise. Jacobs[104] reported depressed patients typically have lower levels of serotonin. In fact, most current antidepressant medications target the release and reuptake of serotonin. Exercise increases tryptophan hydroxylase,[105] which is necessary for serotonin synthesis, while Brezun and Daszuta[106] linked increases in serotonin to neurogenesis, and decreases in serotonin with decreased neurogenesis in adult rats. Results of animal studies indicate that physical activity can increase the neural discharge of serotonin.[104,105] Serotonin levels may also be influenced by exercise-induced changes in sleep. Meta-analytical reviews have shown that exercise results in increased total sleep, increased slow-wave sleep and decreased REM sleep.[107,108] Serotonin discharge decreases significantly during REM sleep,[109] meaning that decreasing REM sleep will limit the times in which serotonin discharge is at its lowest.

In addition to the hippocampal neurogenesis hypothesis put forth by Ernst et al., other physiological and psychological changes may be responsible for the antidepressive effects of exercise. Dietrich and McDaniel[110] explored the role of endocannabinoids in exercise-induced analgesia, sedation and anxiolysis. The endocannabinoid system consists of two receptors, CB_1 and CB_2, which are activated by two naturally occurring ligands, anandamide and 2-arcachidonylglycerol. Activation of the endocannabinoid system has been found to have an analgesic effect.[111] Sparling et al.[112] discovered increased anandamide levels following a bout of exercise, suggesting that exercise activates the endocannabinoid system.

Other potential physiological mechanisms include altered hypothalamic-pituitary-adrenal (HPA) axis functioning and increased levels of noradrenaline (norepinephrine). Altered regulation of the HPA axis, resulting in increased secretion of corticotrophin-releasing hormone, has been associated with depression,[113] while exercise has been found to produce changes in basal HPA function.[114] A review of animal studies[115] concluded that exercise training results in a delayed HPA axis response to stress. In humans, it has been found that exercise-trained individuals exhibit an attenuated HPA axis response to physical and mental stress.[116-118] Depression has also been linked with lowered levels of noradrenaline. Current antidepressant medications have been shown to increase noradrenaline levels,[119] while Dishman[120] reports lower levels of noradrenaline metabolites in the urine of depressed patients and increased noradrenaline levels following exercise.

Table VI. Planned comparisons for moderating variables (clinical population)

Category	Comparison	χ^2	p-Value
Intervention duration (wk)	4–9 vs 10–16	4.8690	0.0273**
Bout duration (min)	30–44 vs 45–59	10.745	0.0010**
	30–44 vs ≥60	1.7788	0.1823
	45–59 vs ≥60	6.2864	0.0122**
Exercise frequency (/wk)	2 vs 3–4	0.0034	0.9535
Clinical interview	Yes vs no	0.7649	0.3818
Intent to treat	Yes vs no	10.7641**	0.0010**
Concealment	Yes vs no	5.4470*	0.0196**

* $p < 0.05$, ** $p <$ Bonferroni-adjusted p-value.

In addition to these physiological mechanisms, psychological factors have the potential to influence the relationship between physical activity and depression. In a study of clinically depressed women, Ossip-Klein et al.[121] found that both aerobic and resistance training resulted in enhanced self-esteem, which was attributed to improved body image and an increased sense of mastery. This enhanced self-esteem was accompanied by a decrease in depressive symptoms, suggesting that an enhancement of self-esteem may be responsible for the alleviation of depressive symptoms.

3.2 Using Exercise as a Treatment for Depression in Clinically Depressed Populations

The overall findings of the current meta-analysis are similar to those of past meta-analyses that used primarily cross-sectional or correlational data and those meta-analyses consisting of only randomized trials, including Lawlor and Hopker.[13] However, Lawlor and Hopker dismissed their findings based on perceived methodological weaknesses including concealment of treatment, lack of a clinical interview, and intent to treat. The judgment of methodological weakness relied on a study of pregnancy and childbirth data,[14] which may not be applicable to the study of depression. Our analysis of moderating variables included examination of these methodological characteristics and found no significant difference in effect size due to the presence or absence of a clinical interview. The significant effects of concealment of treatment and intent-to-treat analysis are actually the opposite of that predicted by Lawlor and Hopker, with those studies using concealment of treatment and intent-to-treat analysis achieving larger effects than those that did not. These results suggest that the findings of Schulz et al.[14] cannot be generalized to research studying treatments for major depression.

Lawlor and Hopker's second criticism of their results was based on the use of self-report measures of depression, stating that such instruments are ''difficult to interpret clinically''. They believe that a dichotomous result (depressed vs not depressed) would be more easily understood and more meaningful than reporting changes in depression scale scores. However, a growing base of literature has been devoted to the development of procedures that can assess the clinical significance of changes in self-report measures. Jacobsen et al.[122] proposed a two-step method for analysing clinical significance by examining a change in score from pre-test to post-test. The first step is to establish a cutoff point that must be crossed in moving from the depressed population to the general population. The second criterion used to establish clinical significance is a change in score greater than a pre-established reliable change index (RCI). According to Jacobsen et al., individuals can be classified as 'recovered' if they pass both criteria, 'improved' if they meet one of the criteria, 'unchanged' if they do not improve on either, or 'deteriorated' if their scores are higher post-treatment.

Seggar et al.[123] examined existing literature to establish a cutoff point (14.29) and RCI (8.46) for the BDI. Examination of the mean pre- and post-BDI scores of studies included in this meta-analysis that used clinically depressed samples (table VII) showed that six of the nine treatment groups crossed over the cutoff and exceeded the required RCI, indicating that the average score of the sample could be classified as 'recovered' following treatment. Of the three treatment groups that did not reach 'recovered' criteria, two met the criteria for 'improvement' by crossing the cutoff point, but not exceeding the required RCI. This could be attributed to lower pretreatment scores in these two samples.[33,63] Only one treatment group[64] could be classified as 'unchanged' at post-treatment. The average score for this study fell just short of meeting both criteria, with a post-treatment BDI score of 14.63 and an RCI of 7.23.

Similarly, Grundy et al.[124] established a cutoff point (11.78) and RCI (7.74) for the HRSD. In examining the mean pre- and post-HRSD scores of studies that used clinical samples in this meta-analysis (table VIII), three of the seven treatment groups crossed over the cutoff and exceeded the required RCI, indicating that the

Table VII. Assessing clinical significance in studies using the Beck Depression Inventory

Study	Treatment group	Pre	Post	Change
Martinsen et al.[61] (1985)[a]	Exercise	25.2	12.1[b]	13.1[c]
	Control	31.5	22.8	8.7
Singh et al.[77] (2001)[a]	Exercise	21	9.2[b]	11.8[c]
	Control	18.4	11	7.4
Singh et al.[76] (1997)[a]	Exercise	21.3	9.8[b]	11.5[c]
	Control	18.4	13.8	4.6
Veale et al.[82] (1992)[a]	Exercise	22.91	13.94[b]	8.97[c]
	Control	26.66	17.79	8.87
McNeil et al.[63] (1991)	Exercise	16.6	11.1[b]	5.5
	Control	15.2	14.7	0.5
Epstein[47] (1986)[a]	Exercise	25.29	9[b]	16.29[c]
	Control	22	16.3	5.7
Broocks et al.[33] (1998)	Exercise	15.2	7.2[b]	8
	Control	18.3	15.8	2.5
Mutrie[64] (1998)[a]	Exercise	22.44	9.46[b]	12.98[c]
	Exercise	21.86	14.63	7.23
	Control	23	21.42	1.58

a Clinically significant change in depression scores.

b Post-treatment scored crossing the cutoff point of 14.29.

c Pretreatment to post-treatment change >8.46.

average score of the sample could be classified as 'recovered' following treatment. Of the four treatment groups that did not reach 'recovered' criteria, one met the criteria for 'improvement' by crossing the cutoff point, but not exceeding the required RCI.[76] This could be attributed to lower pretreatment scores in this sample. The three treatment groups that could be classified as 'unchanged' at post-treatment were all comparison groups that used lower intensity exercise than treatment groups that showed 'recovery'. The two treatment groups that were 'unchanged' in the Dunn et al.[44] study exercised at an intensity of 7 kcal/wk compared with 17.5 kcal/wk for those groups that were 'recovered' at post-treatment measurement. In the study by Singh et al.,[78] the 'unchanged' group participated in resistance exercise using 20% of one-repetition maximum compared with the 'recovered' group exercising using 80% of one-repetition maximum.

Ideally, the clinical significance protocol would be applied to individuals rather than group means. Therefore, some caution must be taken in interpreting the clinical significance results. A group treatment score reaching the 'recovered' criteria does not indicate that all participants in that group had reached the 'recovered' criteria. However, assuming a normal distribution of depression scores, the majority of participants in these groups would have reached 'recovered' criteria. A second cause for caution is the terms used in labelling the observed changes. Even though a change in depression score is labelled as 'recovered,' this does not necessarily mean that these individuals are free of depressive symptoms. Despite this shortcoming, previous research has found significant differences in those individuals reaching 'recovered' status. Using the same statistical method and a similar BDI cutoff point of 14.47, McGlinchey et al.[125] found that those patients classified as 'recovered' following treatment were less likely to relapse than those who did not reach 'recovered' status.

In the analysis of clinical significance, three of the four 'unchanged' treatment groups exercised at a lower intensity, suggesting a potential dose-response relationship. In addition, within the clinically depressed population there was a trend towards greater effect sizes with longer durations. However, our analysis of the dose-response relationship resulted in a nonsignificant finding, and examination of moderating variables revealed a nonsignificant effect for exercise intensity. One

Table VIII. Assessing clinical significance in treatment groups using the Hamilton Rating Scale for Depression

Study	Treatment group	Pre	Post	Change
Singh et al.[78] (2005)	Exercise	18	8.5[a]	9.5[b]
	Exercise	19.5	12.4	7.1
	Control	18.7	14.4	4.3
Singh et al.[76] (1997)	Exercise	12.3	5.3[a]	7
	Control	11.4	8.5	2.9
Dunn[44] (2005)	Exercise	19.3	11.7	7.6
	Exercise	19.2	12.8	6.4
	Exercise	19.1	9[a]	10.1[b]
	Exercise	19.1	10[a]	9.1[b]
	Control	20.5	14	6.5

a Post-treatment scored crossing the cutoff point of 11.28.

b Pretreatment to post-treatment change >7.74.

potential explanation for the nonsignificant finding is the small sample size. Of the 58 studies included in the meta-analysis, only 12 studies provided adequate information to calculate an exercise dose. In addition, only three studies in the meta-analysis compared different intensities of exercise.[44,55,78] Future research should focus on examining the effects of various exercise intensities, durations and frequencies.

Lawlor and Hopker assumed that the dropout rate for exercise would be 'similar or worse' than that of medication or psychotherapy. This is a long-standing assumption based on Zipf's 'principle of least effort',[126] that postulates that people's choices are made with an emphasis on minimizing effort over time. Following this logic, people would likely choose medication or psychotherapy as a treatment because they require less physical effort than exercise. The current analysis found that the dropout rates of exercise treatment groups were no different than the dropout rates for control groups. The exercise dropout rate of 14.6% is at least equivalent to, if not lower than, the dropout rates that have been calculated for antidepressant treatment, which has been found to be 21–33%,[127-130] and psychotherapy, which has been reported to range from 17.2% to 26%.[131]

Finally, to completely assess the quality of a potential treatment, one must examine the cost-benefit ratio of the intervention. The costs and health risks associated with exercise include time, cost of gym memberships, muscle soreness, perspiration, fatigue and effort expenditure. Conversely, the costs and health risks of the most recommended treatments for depression – psychotherapy and drug treatments – include high monetary costs, and in the case of drug treatments include mania, lethargy, sleep disturbances, weight loss, bleeding, sexual dysfunction, seizures and suicidal ideations,[132] while the benefits of these treatments typically do not expand beyond alleviation of depression. Additional benefits of exercise include: (i) reduced risk of cardiovascular disease, high blood pressure, colon, breast and prostate cancers, and non-insulin-dependent diabetes; (ii) improved mortality rates and cognitive functioning; and (iii) maintenance of normal strength, joint structure and function, and peak bone mass.[133-136]

In Australia, referral to an exercise physiologist is now reimbursable under the nation's Medicare system.[137] The Mental Health Foundation of the UK recommends that general practitioners should be offering an exercise programme to all patients with depression. Despite this recommendation, only 5% of general practitioners use exercise referral as one of the three most recommended treatment options, while 92% use antidepressants as one of the three most recommended treatments. This disparity is explained by the fact that only 41% of general practitioners believe exercise to be 'very effective' or 'quite effective' in treating depression.[8] In the US, neither the American Psychological Association nor the NIMH recognize exercise as a treatment for depression.

4. Conclusion

In order for exercise to become a recommended form of treatment for depressive disorders in the US, researchers must provide conclusive results that demonstrate the effectiveness of exercise in treating depression. The current meta-analysis is the first step in providing those conclusive results. By including only randomized trials with a cumulative sample of nearly 3000 participants, the results of this meta-analysis provide Level 1, Grade A evidence supporting the use of exercise for the alleviation of depressive symptoms. Furthermore, a very large effect size was found within the clinically depressed population of over 500 participants, with the majority of those studies showing improvement that was clinically significant. These findings support the use of exercise in the treatment of major depression. However, further research is needed in a number of areas. First, while our analysis suggests the possibility of a dose-response relationship in terms of intervention duration, exercise intensity, bout duration and exercise frequency, further research is needed to confirm these findings. Other individual studies[44,78] have found significant differences between exercises of different intensities, yet these findings are not

enough to draw concrete conclusions regarding a dose-response relationship. Secondly, the current analysis found no significant differences between exercise and psychotherapy or antidepressant medications. However, this is based on only a few studies that have directly compared the effects of exercise to these recognized treatments for depression. In addition to comparing exercise with antidepressant medications and psychotherapy, future research should also examine the use of exercise as an adjunct to these recognized treatments. Finally, the studies included in this analysis focus on the immediate effects of exercise on depression. Follow-up research is needed that examines the sustainability of these effects after exercise has ceased.

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