REVIEW ARTICLE

Effect of Exercise Training on Depressive Symptoms Among Patients With a Chronic Illness

A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Background: Physical inactivity and comorbid depressive symptoms are prevalent among patients with a chronic illness. To our knowledge, randomized controlled trials of the effects of exercise training on depressive symptoms among patients with a chronic illness have not been systematically reviewed. We estimated the population effect of exercise training on depressive symptoms and determined whether the effect varied according to patient characteristics and modifiable features of exercise exposure and clinical settings.

Methods: Articles published before June 1, 2011, were located using the Physical Activity Guidelines for Americans Scientific Database, Google Scholar, MEDLINE, PsycINFO, PubMed, and Web of Science. Ninety articles involving 10 534 sedentary patients with a chronic illness were selected. Included articles required (1) randomized allocation to an exercise intervention or nonexercise comparison condition and (2) a depression outcome assessed at baseline and at mid- and/or postintervention. Hedges *d* effect sizes were computed, study quality was evaluated, and random effects models were used to estimate sampling error and population variance of the observed effects.

Results: Exercise training significantly reduced depressive symptoms by a heterogeneous mean effect size delta (Δ) of 0.30 (95% CI, 0.25-0.36). Larger antidepressant effects were obtained when (1) baseline depressive symptoms were higher, (2) patients met recommended physical activity levels, and (3) the trial primary outcome, predominantly function related, was significantly improved among patients having baseline depressive symptoms indicative of mild-to-moderate depression.

Conclusions: Exercise reduces depressive symptoms among patients with a chronic illness. Patients with depressive symptoms indicative of mild-to-moderate depression and for whom exercise training improves function-related outcomes achieve the largest antidepressant effects.

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Physical inactivity and comorbid depressive disorders are common among patients with a chronic illness and are prevalent public health problems.[1] The relationship between depression and chronic illness is bidirectional.[2] Depression is associated with increased risk of a chronic illness[3] and mortality[4]; conversely, several chronic illnesses increase the risk of depression.[5]

The adverse health outcomes associated with comorbid depressive symptoms among chronically ill patients are well established.[1] Depressive symptoms are associated with reduced adherence to prescribed medical treatments[6] and health-related quality of life,[7] as well as increased symptom burden,[8] disability,[9] functional and role impairment,[10] and use of health care services.[10,11]

Recent evidence has questioned the efficacy of pharmacotherapy for individuals with mildly to moderately elevated depressive symptoms[12] and among patients with comorbid chronic illnesses.[13] Thus, there continues to be interest in alternative therapies, including somatic treatments, herbal remedies, relaxation, and exercise.[14]

Although exercise training is associated with improved physical and mental health outcomes, including reduced mortality[15] and anxiety symptoms,[16] among patients with chronic illness, early trials in those with heart disease reported mixed effects of exercise on depressive symptoms.[17-19] Methodologic shortcomings of those trials (eg, now outdated outcome measures or insufficient reporting of score distributions) preclude meaningful comparison with effects from contemporary trials. Meta-analytic reviews of exercise effects on depressive symptoms have since focused on patients having a diagnosis of a depressive disorder,[20-22] adults with or without depression,[23] and women with

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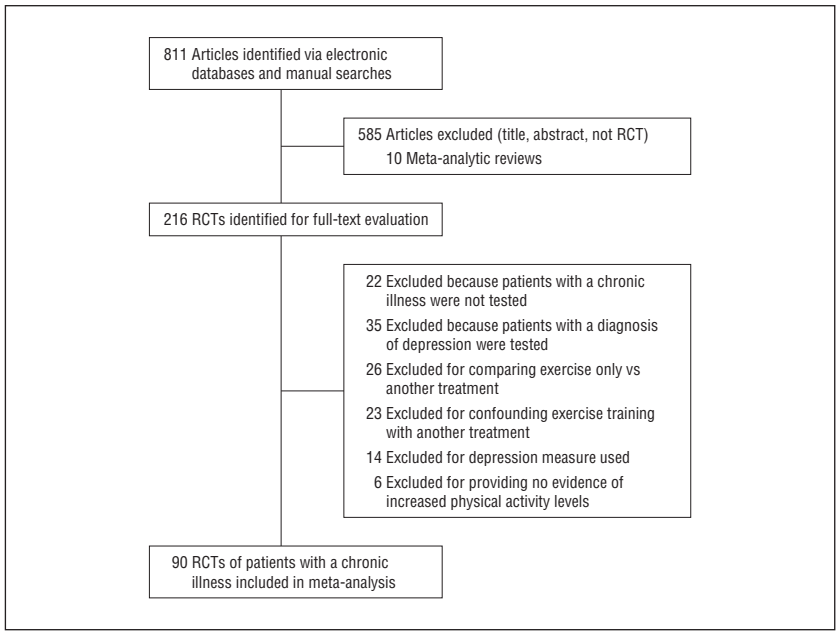

Figure 1. Flowchart of study selection. RCTs indicates randomized controlled trials.

postnatal depression.[24] Meta-analytic reviews of patients with cardiovascular disease,[25] chronic obstructive pulmonary disease,[26] fibromyalgia,[27] and Parkinson disease[28] also have supported the antidepressant effects of exercise, but they included nonrandomized trials likely influenced by self-selection bias.

We used the results of randomized controlled trials to evaluate the effects of exercise training on depressive symptoms among chronically ill patients who did not have a diagnosis of a depressive disorder. Prior reviews[20,22] have faulted exercise trials for small sample sizes, insufficient blinding of participant allocation, inadequate control comparisons, and lack of intent-to-treat analyses. We weighted effects by trial size and included in moderator analysis whether trials used blinded allocation, attention-control comparisons, and intent-to-treat analyses. Our further evaluation of practical variables, including illness type, physical activity exposure, and baseline symptom severity, has the potential to assist clinicians by providing evidence on which to base exercise prescriptions. The objectives of the review reported here were to estimate the population effect of exercise on depressive symptoms and to determine whether the effect varied according to patient characteristics and modifiable features of exercise exposure and clinical settings.

METHODS

This systematic review and meta-regression analysis was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement guidelines.[29]

DATA SOURCES AND SEARCHES

Articles published before June 1, 2011, were located using searches of the Physical Activity Guidelines for Americans Scientific Database, Google Scholar, MEDLINE, PsycINFO, PubMed, and Web of Science using combinations of *exercise training*, *physical activity*, *depression*, *chronic illness*, *patients*, *randomized trial*, and *randomized controlled trial*. Reference lists from retrieved articles were manually reviewed.

STUDY SELECTION

Inclusion criteria were (1) publications available in English, (2) sedentary adults with a chronic illness, (3) randomized allocation to either exercise training or a nonexercise comparison, and (4) a depression outcome measured at baseline and during and/or after exercise training.

Excluded investigations (1) sampled patients with a clinical diagnosis of depression, (2) included exercise as one part of a multicomponent intervention but did not include the additional component in a comparison condition, (3) compared exercise only with an active treatment (eg, pharmacotherapy or another mode of exercise), (4) used education or promotion interventions aimed at increasing physical activity but failed to show increased physical activity, and/or (5) did not use a screening or clinical measure of depressive symptoms. **Figure 1** presents a flowchart of study selection.

STUDY CHARACTERISTICS

One hundred sixty-eight effects were derived from 90 studies: 39 from patients with a cardiovascular or cardiometabolic disease, 37 from patients with chronic pain other than fibromyalgia (eg, knee osteoarthritis or back pain), 32 from patients with fibromyalgia, 16 from obese patients, 15 from patients with cancer, 8 from patients with neurologic disorders other than multiple sclerosis (eg, spinal cord injury or Alzheimer disease), 6 from patients with chronic obstructive pulmonary disease, 6 from patients with multiple sclerosis, 5 from patients categorized as having "other medical illnesses" (eg, human immunodeficiency virus disease), and 4 from patients with psychological disorders other than depression (see eReferences; http://www.archinternmed.com).

Depressive symptoms were the primary outcome for only 3 studies.[30-32] Primary outcomes were a variety of objective (eg, body weight, body mass index, fat mass, 6-minute walk, treadmill time, peak power output during cycling, peak oxygen uptake, peak leg torque, and left ventricular ejection fraction) and self-reported (eg, dyspnea, pain, fatigue, physical function, and multidimensional quality of life) function-related measures.

The mean (SD) age was 51 (15) years. The mean percentage of women was 61% (34%). Exercise training consisted of 3 (1) sessions per week, 42 (18) minutes per session, and 17 (13) weeks' duration. The mean exercise training adherence rate was 77% (13%) of prescribed sessions. Adherence was reported for 104 of 168 of the effects (61.9%). The most frequently used depression measures were the Beck Depression Inventory[33] ($k=40$), the Center for Epidemiological Studies Depression Scale[34] ($k=40$), and the depression scale of the Hospital Anxiety and Depression Scale[35] ($k=27$).

DATA EXTRACTION AND QUALITY ASSESSMENT

We independently assessed study quality. A widely used method[36] was ex-

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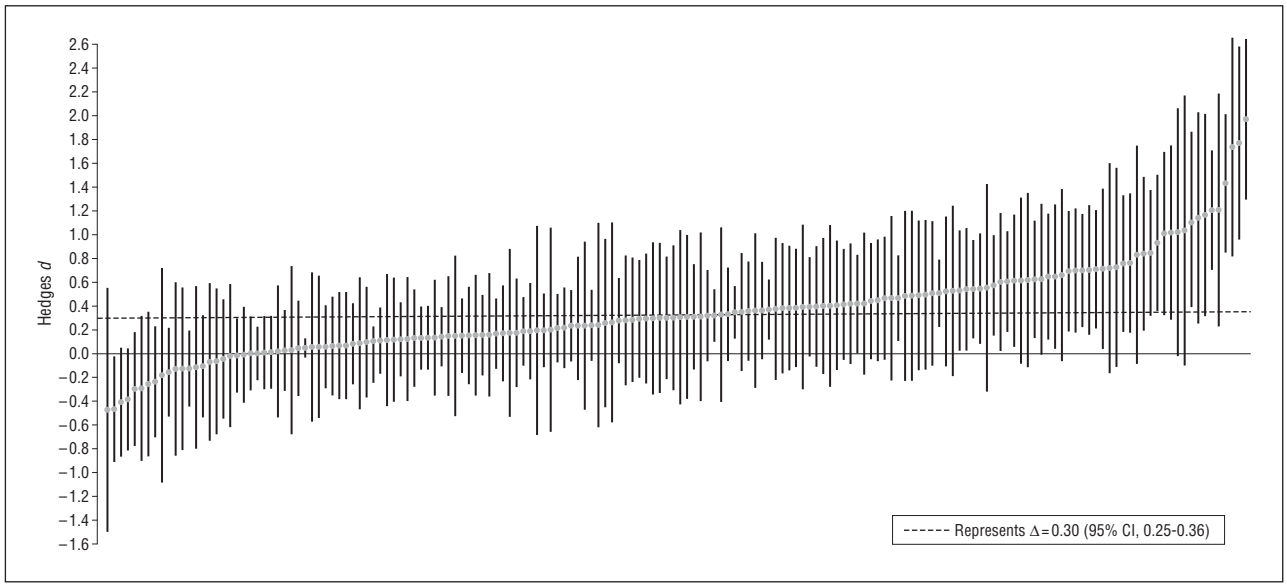

Figure 2. Forest plot of unweighted distribution of Hedges *d* effect sizes.

tended to include assessments of randomization methods, blinding of allocation to treatment, attention-control use, depression measure quality, adherence, intent-to-treat analyses, and exercise program descriptions.

EFFECT SIZE CALCULATION

Effect sizes were calculated by subtracting the mean change in the comparison condition from the mean change in the exercise condition and dividing the difference by the pooled standard deviation of baseline scores.[37] Effect sizes were adjusted for small sample size bias and calculated; a larger decrease in depressive symptoms among exercising patients resulted in a positive effect size.[37] When exact means and standard deviations were not provided ($k=8$), effect sizes were estimated[38] from exact F test values with 1 df,[39] from exact P values,[40-44] and from a figure shown in the article reviewed.[45,46] When an SD was not reported ($k=1$),[47] it was estimated from the largest other study[48] of the same illness type, using the same depression measure.

DATA SYNTHESIS AND ANALYSIS

Meta-regression was used as the overall analysis of moderator effects to reduce the probability of type I error by computing simultaneous estimates of independent effects by multiple moderator variables on the variation in effect size across trials. With macros (SPSS MeanES, MetaReg; SPSS, Inc), we used random effects models to aggregate mean effect size delta (Δ) and to test variation in effects according to moderator variables.[37,49] Heterogeneity was indicated if Q_{Total} reached a significance level of $P<.05$ and the sampling error accounted for less than 75% of the observed variance.[37] Heterogeneity also was assessed by examination of the I^2 statistic.[50] The number of unpublished or unretrieved studies of null effect that would diminish the significance of observed effects to $P>.05$ was estimated as fail-safe N.[51] Potential publication bias (ie, smaller studies showing larger effects) also was addressed by evaluation of a funnel plot. Two-way (effects × raters) intraclass correlation coefficients for absolute agreement were calculated to examine interrater reliability for depressive symptom effect sizes and moderators. The initial intraclass correlation coefficients, based on 36 effects, were 0.93 or larger. Discrepancies were resolved by adjudication after recalculation and/or recoding.

PRIMARY MODERATORS

To provide focused research hypotheses about variation in effect size,[52] baseline depressive symptom scores, as well as 7 primary moderators, were selected a priori on the basis of logical, theoretical, or empirical relations to depression (see eTable 1): physical activity exposure, change in fitness (ie, increased aerobic capacity or muscular strength),[53] illness type (categorized as physical or psychosomatic /neurologic),[54] trial primary outcome change,[55] blinded allocation, attention-control use, and intent-to-treat analysis.

PRIMARY MODERATOR ANALYSIS

Each of the 7 primary moderators was coded according to planned contrasts[56] ($P\leq.05$) among its levels. Primary moderators and baseline depressive symptom scores were included in mixed-effects multiple linear regression analysis with maximum likelihood estimation,[37,49] adjusting both for depression measure and nonindependence of multiple effects contributed by single studies.[57] Tests of the regression model (Q_R) and its residual error (Q_E) are reported. A follow-up meta-regression model was used to test 2-way interactions among significant primary moderators. A significant interaction between baseline depressive symptoms and the primary trial outcome was decomposed by post hoc contrasts of interaction combinations based on whether baseline depressive symptoms were indicative of mild-to-moderate depression[58-62] and whether the primary trial outcome was favorable.

SECONDARY MODERATORS AND ANALYSIS

Secondary moderators were selected for descriptive, univariate analyses (see eTable 1). Random effects models were used to calculate mean effect sizes (Δ) and 95% CIs for continuous and categorical variables.[49]

RESULTS

One hundred forty-five of 168 effects (86.3%) were larger than zero. A forest plot and annotated table of the unweighted distribution of effects are presented in **Figure 2** and **Table 1**. The mean effect size Δ was 0.30 (95% CI, 0.25-0.36; $z=10.51$;

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Table 1. Annotated Descriptors of Unweighted Hedges *d* Effect Sizes

Source[a]	Total No.	Illness Type[b]	Exposure[c]	Fitness Change[d]	Primary Outcome[e]	Hedges *d* Effect Size (95% CI)
Moug et al,[e12] 2003	17	CV	No	No	No	–0.47 (–1.50 to 0.55)
Jones et al,[e48] 2008	80	FM	No	No	No	–0.47 (–0.91 to –0.02)
Witham et al,[e20] 2005	82	CV	No	No	No	–0.41 (–0.87 to 0.05)
Jones et al,[e48] 2008	85	FM	No	No	Yes	–0.39 (–0.82 to 0.04)
Witham et al,[e20] 2005	82	CV	No	No	No	–0.30 (–0.78 to 0.18)
Clark et al,[e23] 2000	27	Pain	No	No	Yes	–0.29 (–0.90 to 0.32)
Clark et al,[e23] 2000	37	Pain	No	No	Yes	–0.26 (–0.86 to 0.35)
Kiernan et al,[e59] 2001	73	Obesity	No	Yes	No	–0.24 (–0.70 to 0.23)
Cakit et al,[e82] 2010	19	MS	No	No	No	–0.18 (–1.09 to 0.72)
Thorsen et al,[e73] 2005	111	Cancer	No	Yes	Yes	–0.16 (–0.53 to 0.22)
Donesky-Cuenco et al,[e77] 2009	29	COPD	No	No	No	–0.13 (–0.86 to 0.60)
Thomson et al,[32,e62] 2010	34	Obesity	No	NR	No	–0.13 (–0.81 to 0.56)
Neuberger et al,[e31] 2007	152	Pain	No	No	No	–0.13 (–0.45 to 0.19)
Thomson et al,[32,e62] 2010	34	Obesity	No	NR	No	–0.12 (–0.80 to 0.57)
Fontaine et al,[e44] 2010	92	FM	No	Yes	Yes	–0.11 (–0.54 to 0.32)
Hospes et al,[e80] 2009	35	COPD	No	No	No	–0.07 (–0.73 to 0.59)
Haworth et al,[e74] 2009	41	Neurologic	No	No	No	–0.07 (–0.68 to 0.55)
Rooks et al,[63,e51] 2007	62	FM	No	Yes	Yes	–0.05 (–0.55 to 0.46)
Haworth et al,[e74] 2009	42	Neurologic	No	No	No	–0.02 (–0.62 to 0.58)
Neuberger et al,[e31] 2007	141	Pain	No	No	Yes	–0.02 (–0.33 to 0.29)
Fransen et al,[e25] 2007	97	Pain	No	No	No	–0.01 (–0.41 to 0.39)
Courneya et al,[48,e65] 2007	160	Cancer	Vigorous	No	No	0 (–0.31 to 0.31)
Hurley et al,[e27] 2007	342	Pain	No	No	No	0 (–0.23 to 0.28)
Neuberger et al,[e31] 2007	153	Pain	No	NR	No	0.01 (–0.30 to 0.31)
Courneya et al,[48,e65] 2007	164	Cancer	Vigorous	Yes	No	0.01 (–0.30 to 0.32)
Carei et al,[e88] 2010	50	Psychological	No	NR	No	0.02 (–0.54 to 0.57)
Mannerkorpi et al,[e50] 2009	133	FM	No	No	No	0.03 (–0.31 to 0.37)
Gary et al,[30,e6] 2010	31	CV	No	No	No	0.03 (–0.68 to 0.74)
Sorensen et al,[e17] 1999	97	CV	Moderate	NR	No	0.04 (–0.36 to 0.44)
Flynn et al,[40,e4] 2009	2330	CV	Vigorous	Yes	Yes	0.05 (–0.04 to 0.13)
Clark et al,[e23] 2000	34	Pain	No	No	Yes	0.05 (–0.57 to 0.68)
Oken et al,[e84] 2004	35	MS	No	NR	No	0.06 (–0.54 to 0.65)
Pengel et al,[e34] 2007	113	Pain	Moderate	NR	Yes	0.06 (–0.29 to 0.40)
Courneya et al,[e64] 2003	93	Cancer	No	No	No	0.06 (–0.35 to 0.48)
Giubilei et al,[e26] 2007	76	Pain	No	No	No	0.23 (–0.38 to 0.52)
Giubilei et al,[e26] 2007	76	Pain	No	No	No	0.23 (–0.38 to 0.52)
Pengel et al,[e34] 2007	118	Pain	Moderate	NR	Yes	0.08 (–0.26 to 0.42)
Cadmus et al,[e63] 2009	50	Cancer	Moderate	NR	No	0.09 (–0.47 to 0.64)
Daltroy et al,[e24] 1995	71	Pain	No	No	Yes	0.10 (–0.37 to 0.56)
Mannerkorpi et al,[e50] 2009	125	FM	No	No	No	0.10 (–0.25 to 0.23)
Anderson et al,[e85] 2005	193	Other	No	Yes	No	0.11 (–0.17 to 0.39)
Carei et al,[e88] 2010	50	Psychological	No	NR	No	0.11 (–0.44 to 0.67)
Smith et al,[31,e16] 2007	66	CV	Vigorous	NR	No	0.12 (–0.41 to 0.64)
Neuberger et al,[e31] 2007	142	Pain	No	NR	No	0.12 (–0.19 to 0.43)
Schachter et al,[e52] 2003	92	FM	No	No	No	0.12 (–0.40 to 0.64)
Weiner et al,[e41] 2008	93	Pain	No	NR	No	0.13 (–0.28 to 0.54)
Belza et al,[e22] 2002	220	Pain	No	NR	Yes	0.13 (–0.14 to 0.40)
Patrick et al,[e33] 2001	225	Pain	No	NR	No	0.13 (–0.14 to 0.40)
Tench et al,[e38] 2003	62	Pain	No	No	No	0.13 (–0.35 to 0.62)
Penninx et al,[41,e35] 2002	248	Pain	No	No	Yes	0.14 (–0.11 to 0.39)
Rooks et al,[63,e51] 2007	62	FM	No	Yes	Yes	0.15 (–0.36 to 0.65)
Gary et al,[30,e6] 2010	37	CV	No	NR	No	0.15 (–0.53 to 0.82)
Jolly et al,[e7] 2009	157	CV	Vigorous	NR	No	0.15 (–0.16 to 0.46)
Weiner et al,[e41] 2008	93	Pain	No	NR	No	0.15 (–0.26 to 0.56)
Schachter et al,[e52] 2003	87	FM	No	Yes	No	0.15 (–0.35 to 0.66)
Rolland et al,[e76] 2007	110	Neurologic	No	No	No	0.15 (–0.19 to 0.49)
Mannerkorpi et al,[e49] 2000	57	FM	No	Yes	Yes	0.16 (–0.36 to 0.68)
Mutrie et al,[e70] 2007	177	Cancer	No	Yes	No	0.17 (–0.13 to 0.46)
van Vilsteren et al,[e19] 2005	96	CV	No	No	No	0.17 (–0.23 to 0.57)
Gowans et al,[e46] 2001	31	FM	No	No	No	0.17 (–0.53 to 0.88)
Cadmus et al,[e63] 2009	50	Cancer	Moderate	NR	No	0.17 (–0.28 to 0.63)
Yu et al,[e21] 2004	204	CV	Vigorous	NR	No	0.19 (–0.10 to 0.47)
Fransen et al,[e25] 2007	96	Pain	No	No	No	0.19 (–0.22 to 0.59)
Payne et al,[47,e71] 2008	20	Cancer	No	NR	Yes	0.19 (–0.68 to 1.07)
Jolly et al,[e7] 2009	161	CV	Vigorous	No	No	0.19 (–0.12 to 0.50)

(Continued)

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Table 1. Annotated Descriptors of Unweighted Hedges *d* Effect Sizes (continued)

Source[a]	Total No.	Illness Type[b]	Exposure[c]	Fitness Change[d]	Primary Outcome[e]	Hedges *d* Effect Size (95% CI)
Hicks et al,[e75] 2003	21	Neurologic	No	No	No	0.20 (–0.66 to 1.06)
Yu et al,[e21] 2004	269	CV	Vigorous	NR	Yes	0.21 (–0.08 to 0.50)
Rolland et al,[e76] 2007	117	Neurologic	No	No	No	0.22 (–0.12 to 0.56)
O'Reilly et al,[e32] 1999	180	Pain	No	Yes	Yes	0.23 (–0.07 to 0.53)
Kitzman et al,[e8] 2010	46	CV	No	Yes	Yes	0.23 (–0.22 to 0.81)
Gowans et al,[e46] 2001	31	FM	No	No	No	0.23 (–0.47 to 0.94)
Mutrie et al,[e70] 2007	174	Cancer	No	Yes	No	0.24 (–0.06 to 0.53)
Monga et al,[e69] 2007	21	Cancer	Vigorous	Yes	Yes	0.24 (–0.62 to 1.10)
Dalgas et al,[e83] 2010	31	MS	Vigorous	No	No	0.26 (–0.45 to 0.96)
Cakit et al,[e82] 2010	23	MS	No	Yes	No	0.26 (–0.58 to 1.10)
Sorensen et al,[e17] 1999	122	CV	Moderate	NR	Yes	0.28 (–0.08 to 0.63)
Fontaine et al,[e45] 2011	53	FM	No	No	No	0.28 (–0.27 to 0.82)
Schachter et al,[e52] 2003	92	FM	No	No	No	0.28 (–0.24 to 0.81)
Jessep et al,[e28] 2009	48	Pain	No	NR	Yes	0.29 (–0.20 to 0.79)
Dugmore et al,[e3] 1999	52	CV	No	NR	Yes	0.29 (–0.25 to 0.84)
Seki et al,[e15] 2003	38	CV	No	Yes	No	0.29 (–0.35 to 0.94)
Clark et al,[e23] 2000	22	Pain	No	No	Yes	0.30 (–0.33 to 0.93)
Dimeo et al,[e68] 1999	59	Cancer	Moderate	NR	No	0.30 (–0.22 to 0.81)
Oken et al,[e84] 2004	42	MS	No	NR	No	0.30 (–0.31 to 0.91)
Thomson et al,[32,e62] 2010	29	Obesity	No	NR	No	0.30 (–0.43 to 1.04)
Gary et al,[30,e6] 2010	35	CV	No	No	No	0.31 (–0.38 to 1.00)
Kiernan et al,[e59] 2001	79	Obesity	No	Yes	Yes	0.31 (–0.14 to 0.75)
Gowans et al,[e46] 2001	31	FM	No	No	No	0.31 (–0.40 to 1.02)
Gusi et al,[e58] 2008	106	Obesity	No	No	Yes	0.32 (–0.07 to 0.70)
White et al,[e87] 2011	319	Other	No	Yes	Yes	0.32 (0.10 to 0.54)
Thomson et al,[32,e62] 2010	29	Obesity	No	NR	No	0.33 (–0.41 to 1.06)
Smeets et al,[e36] 2008	103	Pain	Moderate	NR	No	0.33 (–0.06 to 0.72)
White et al,[e87] 2011	320	Other	No	Yes	Yes	0.35 (0.12 to 0.57)
Jessep et al,[e28] 2009	57	Pain	No	NR	No	0.35 (–0.15 to 0.84)
Blumenthal et al,[e2] 2005	90	CV	Vigorous	No	No	0.36 (–0.06 to 0.77)
Gary et al,[30,e6] 2010	37	CV	No	NR	No	0.36 (–0.29 to 1.01)
Lai et al,[e11] 2006	80	CV	No	NR	No	0.36 (–0.05 to 0.77)
Penninx et al,[41,e35] 2002	244	Pain	Vigorous	Yes	Yes	0.37 (0.12 to 0.62)
Haworth et al,[e74] 2009	44	Neurologic	No	NR	Yes	0.38 (–0.22 to 0.97)
Fontaine et al,[e45] 2011	53	FM	No	No	No	0.38 (–0.17 to 0.93)
Mannerkorpi et al,[e49] 2000	57	FM	No	Yes	Yes	0.38 (–0.14 to 0.91)
Rooks et al,[63,e51] 2007	65	FM	No	Yes	Yes	0.38 (–0.11 to 0.88)
Gary et al,[30,e6] 2010	37	CV	No	NR	No	0.39 (–0.30 to 1.08)
Williams et al,[e42] 2009	90	Pain	No	No	No	0.39 (–0.03 to 0.81)
Rooks et al,[63,e51] 2007	62	FM	No	Yes	Yes	0.40 (–0.11 to 0.90)
Emery et al,[43,e78] 1998	54	COPD	Moderate	Yes	No	0.40 (–0.17 to 0.97)
vandenBerg-Emons et al,[e18] 2004	34	CV	No	No	No	0.40 (–0.28 to 1.08)
Daley et al,[e56] 2006	53	Obesity	No	No	Yes	0.41 (–0.14 to 0.95)
Dugmore et al,[e3] 1999	72	CV	Vigorous	NR	Yes	0.41 (–0.05 to 0.88)
Rooks et al,[63,e51] 2007	62	FM	No	Yes	Yes	0.42 (–0.09 to 0.93)
Wand et al,[e39] 2004	94	Pain	No	NR	Yes	0.42 (0.001 to 0.83)
Leibetseder et al,[45,e29] 2007	44	Pain	No	NR	No	0.42 (–0.18 to 1.02)
Wang et al,[e55] 2010	66	FM	No	No	Yes	0.44 (–0.05 to 0.93)
Neidig et al,[e86] 2003	60	Other	Vigorous	No	No	0.45 (–0.06 to 0.96)
Neidig et al,[e86] 2003	60	Other	Vigorous	No	No	0.46 (–0.05 to 0.98)
Gary et al,[30,e6] 2010	31	CV	No	No	No	0.46 (–0.23 to 1.16)
Courneya et al,[e66] 2009	122	Cancer	Vigorous	Yes	Yes	0.47 (0.11 to 0.83)
Gowans et al,[e46] 2001	31	FM	No	Yes	No	0.48 (–0.23 to 1.20)
Sarsan et al,[e61] 2006	40	Obesity	No	Yes	No	0.49 (–0.14 to 1.12)
Wang et al,[e40] 2009	40	Pain	No	No	Yes	0.49 (–0.14 to 1.12)
Nieman et al,[e60] 2000	43	Obesity	Moderate	Yes	No	0.51 (–0.10 to 1.11)
Scholz et al,[e14] 2006	198	CV	No	NR	No	0.51 (0.22 to 0.79)
Wang et al,[e40] 2009	40	Pain	No	No	No	0.52 (–0.11 to 1.15)
Dalgas et al,[e83] 2010	31	MS	Vigorous	Yes	Yes	0.53 (–0.19 to 1.24)
Daley et al,[e67] 2007	62	Cancer	Vigorous	No	Yes	0.53 (0.02 to 1.03)
Schachter et al,[e52] 2003	87	FM	No	No	Yes	0.54 (0.02 to 1.05)
Lai et al,[e11] 2006	93	CV	No	Yes	No	0.54 (0.13 to 0.95)
Merom et al,[e89] 2008	74	Psychological	Moderate	NR	No	0.54 (0.08 to 1.01)
Hicks et al,[e75] 2003	21	Neurologic	No	No	No	0.55 (–0.32 to 1.42)
Williams et al,[e42] 2009	90	Pain	No	NR	Yes	0.57 (0.15 to 0.99)
Nieman et al,[e60] 2000	48	Obesity	Moderate	No	No	0.60 (0.02 to 1.18)

(Continued)

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Table 1. Annotated Descriptors of Unweighted Hedges *d* Effect Sizes (continued)

Source[a]	Total No.	Illness Type[b]	Exposure[c]	Fitness Change[d]	Primary Outcome[e]	Hedges *d* Effect Size (95% CI)
Williams et al,[e42] 2009	90	Pain	No	NR	Yes	0.60 (0.18 to 1.03)
Dugmore et al,[e3] 1999	52	CV	No	No	Yes	0.61 (0.06 to 1.17)
Gary et al,[30,e6] 2010	33	CV	No	Yes	No	0.61 (–0.09 to 1.31)
Tomas-Carus et al,[e53] 2008	30	FM	Moderate	No	Yes	0.62 (–0.12 to 1.35)
Wang et al,[e55] 2010	66	FM	No	No	Yes	0.62 (0.13 to 1.12)
Wang et al,[e40] 2009	40	Pain	No	No	Yes	0.62 (–0.01 to 1.26)
Daley et al,[e56] 2006	49	Obesity	No	No	Yes	0.65 (0.12 to 1.18)
Kulcu et al,[e10] 2007	44	CV	Moderate	No	Yes	0.65 (0.04 to 1.25)
Gowans et al,[e46] 2001	31	FM	No	Yes	No	0.66 (–0.06 to 1.38)
Rooks et al,[63,e51] 2007	65	FM	No	Yes	Yes	0.69 (0.18 to 1.20)
Valim et al,[e54] 2003	76	FM	No	No	No	0.70 (0.17 to 1.22)
Dugmore et al,[e3] 1999	72	CV	Vigorous	No	Yes	0.70 (0.22 to 1.17)
Ghroubi et al,[e57] 2009	55	Obesity	No	Yes	Yes	0.70 (0.16 to 1.25)
Daley et al,[e67] 2007	66	Cancer	Vigorous	Yes	Yes	0.71 (0.21 to 1.21)
Aylin et al,[e1] 2009	36	CV	Moderate	Yes	Yes	0.71 (0.04 to 1.39)
Hakkinen et al,[e47] 2001	21	FM	No	Yes	No	0.72 (–0.17 to 1.60)
Paz-Diaz et al,[e81] 2007	24	COPD	Vigorous	NR	Yes	0.72 (–0.11 to 1.56)
Daley et al,[e56] 2006	50	Obesity	No	No	Yes	0.76 (0.18 to 1.33)
Emery et al,[43,e78] 1998	54	COPD	Moderate	Yes	No	0.76 (0.17 to 1.35)
Skrinar et al,[44,e90] 2005	20	Psychological	Vigorous	No	No	0.83 (–0.09 to 1.75)
Sarsan et al,[e61] 2006	40	Obesity	Moderate	Yes	No	0.84 (0.19 to 1.48)
Valim et al,[e54] 2003	76	FM	No	Yes	Yes	0.85 (0.32 to 1.37)
Dugmore et al,[e3] 1999	52	CV	No	Yes	Yes	0.93 (0.36 to 1.50)
Gary et al,[30,e6] 2010	37	CV	No	NR	Yes	1.01 (0.32 to 1.69)
Hicks et al,[e75] 2003	21	Neurologic	No	No	No	1.02 (0.28 to 1.75)
Etnier et al,[39,e43] 2009	16	FM	Moderate	Yes	Yes	1.02 (–0.02 to 2.06)
Segar et al,[e72] 1998	20	Cancer	No	NR	No	1.03 (–0.10 to 2.17)
Guell et al,[e79] 2006	35	COPD	Moderate	Yes	Yes	1.10 (0.39 to 1.86)
Gary and Lee,[e5] 2007	23	CV	No	No	No	1.14 (0.25 to 2.03)
Koukouvou et al,[e9] 2004	26	CV	Moderate	Yes	Yes	1.16 (0.31 to 2.01)
Dugmore et al,[e3] 1999	72	CV	Vigorous	Yes	Yes	1.21 (0.70 to 1.71)
Strombeck et al,[e37] 2007	19	Pain	No	NR	Yes	1.21 (0.23 to 2.19)
Ghroubi et al,[e57] 2009	57	Obesity	Moderate	NR	Yes	1.43 (0.85 to 2.01)
Koukouvou et al,[e9] 2004	26	CV	Moderate	Yes	Yes	1.74 (0.82 to 2.65)
Ouzouni et al,[e13] 2009	33	CV	Moderate	Yes	Yes	1.77 (0.96 to 2.58)
Lim et al,[46,e30] 2005	50	Pain	Moderate	Yes	Yes	1.97 (1.29 to 2.64)
Overall mean effect	10 534					Δ = 0.30 (0.25 to 0.36)

Abbreviations: COPD, chronic obstructive pulmonary disease; CV, cardiovascular; FM, fibromyalgia; MS, multiple sclerosis; NR, not reported.
[a] Studies with an *e* before the number appear in the online-only material (eReferences).
[b] Neurologic indicates disorders other than MS; Pain, chronic pain disorders other than FM; Psychological, disorders other than depression.
[c] Moderate indicates meeting moderate physical activity recommendations; No, not meeting any physical activity recommendation; Vigorous, meeting vigorous physical activity recommendations.
[d] No indicates 95% CI for fitness effect included zero; NR, not enough fitness information was reported; Yes, 95% CI for fitness effect did not include zero.
[e] No indicates 95% CI for primary outcome effect included zero; Yes, 95% CI for primary outcome effect did not include zero.

$P<.001$). The significant improvement in depressive symptoms after exercise training was moderately heterogeneous ($Q_{167}=314.81$; $P<.001$; $I^2=47\%$), with sampling error accounting for 49.5% of the observed variance. A sensitivity analysis revealed similar depressive symptom reductions among trials in which depressive symptoms were ($\Delta=0.29$; 95% CI, 0.05-0.52; $P=.02$; $k=13$) or were not ($\Delta=0.31$; 95% CI, 0.25-0.36; $P<.001$; $k=155$) the primary outcome. The fail-safe number of effects was 8173, and examination of a funnel plot also revealed a lack of publication bias (see eFigure 1).

PRIMARY MODERATOR ANALYSES

The overall meta-regression model was significant ($Q_{R10}=43.36$; $P<.001$; $R^2=0.30$; $Q_{E150}=99.51$; $P>.99$). Baseline depressive symptom scores ($\beta=0.26$; $z=2.86$; $P=.004$), physical activity exposure ($\beta=0.25$; $z=2.61$; $P=.01$), and primary trial outcome change ($\beta=0.31$; $z=3.32$; $P<.001$) accounted for significant variation in the overall effect of exercise on depressive symptoms. Effects were larger when (1) patients were meeting moderate or vigorous physical activity recommendations ($\Delta=0.46$; 95% CI, 0.35-0.56) compared with not meeting either recommendation ($\Delta=0.24$; 95% CI, 0.18-0.31; $z=3.29$; $P=.001$) and (2) the primary trial outcome was significantly improved ($\Delta=0.43$; 95% CI, 0.34-0.52) compared with no significant change ($\Delta=0.22$; 95% CI, 0.14-0.29; $z=3.67$; $P<.001$). Fitness change ($\beta=0.14$; $z=1.53$; $P=.13$), illness type ($\beta=0.09$; $z=0.88$; $P=.09$), blinded allocation ($\beta=0.17$; $z=1.66$; $P=.10$), attention-control use ($\beta=-0.09$; $z=-1.02$; $P=.31$), and whether intent-to-treat analysis was used ($\beta=-0.12$; $z=1.36$; $P=.17$) were not related to effect size.

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A 2-way interaction was found between baseline depressive symptoms and primary trial outcome change ($\beta = 0.43$; $z = 2.41$; $P = .02$). All other 2-way interactions were statistically nonsignificant (primary trial outcome by exposure: $\beta = 0.14$; $P = .22$, and baseline depressive symptoms by exposure: $\beta = 0.14$; $P = .34$). At least 1 level of all moderators had sufficient heterogeneity (I^2 range, 50%-70%) and number of effects ($k = 23$-98) to permit a good test of interactions.

Decomposition of the interaction showed significantly larger improvements for investigations in which the primary outcome was significantly improved among patients with baseline depressive symptoms indicative of mild-to-moderate depression ($\Delta = 0.79$; 95% CI, 0.58-1.01) when contrasted with the average effect of other interaction combinations ($\Delta = 0.27$; 95% CI, 0.21-0.33; $z = 4.57$; $P < .001$).

SECONDARY MODERATOR ANALYSES

The results of univariate moderator analyses for primary and secondary moderators are presented in **Table 2**. The number of effects (k), mean effect size Δ, 95% CI, and P value are provided for each level of each moderator variable.

Table 2. Summary of Univariate Moderator Analysis

Effect Moderator	Contrast Weights	Effects (k)	Δ (95% CI)	Contrast P Value
Fitness change				
No change	−1/2	68	0.22 (0.13 to 0.31)	
Increased fitness	1	50	0.43 (0.333 to 0.54)	.005[a]
Not reported	−1/2	50	0.28 (0.18 to 0.38)	
Physical activity exposure				
Moderate	1/2	24	0.59 (0.43 to 0.75)	
Vigorous	1/2	23	0.35 (0.20 to 0.49)	.001[a]
Not meeting either level	−1	121	0.24 (0.18 to 0.31)	
Primary trial outcome change				
Not significant	−1	99	0.22 (0.14 to 0.29)	<.001[a]
Yes, significant	1	69	0.43 (0.34 to 0.52)	
Blinded allocation				
Yes	1	79	0.28 (0.20 to 0.36)	.39
No	−1	89	0.33 (0.25 to 0.41)	
Attention-control use				
Yes	1	70	0.26 (0.18 to 0.35)	.20
No	−1	98	0.34 (0.26 to 0.41)	
Intent-to-treat analysis				
Yes	1	53	0.24 (0.15 to 0.33)	.08
No	−1	115	0.34 (0.27 to 0.42)	
Medical illness				
Cancer	1/5	15	0.22 (0.04 to 0.41)	
Cardiovascular	1/5	39	0.38 (0.26 to 0.50)	
COPD	1/5	6	0.46 (0.12 to 0.81)	
Fibromyalgia	−1/5	32	0.29 (0.16 to 0.43)	
Pain	−1/5	37	0.23 (0.11 to 0.34)	.08
Psychological	−1/5	4	0.33 (−0.07 to 0.72)	
MS	−1/5	6	0.22 (−0.15 to 0.59)	
Neurologic	−1/5	8	0.24 (−0.04 to 0.53)	
Obesity	1/5	16	0.44 (0.25 to 0.64)	
Other	. . .	5	0.32 (0.03 to 0.60)	
Function-related primary trial outcome				
Not function related	0	27	0.37 (0.22 to 0.53)	
Self-report	−1	111	0.30 (0.23 to 0.37)	.97
Objective	1	30	0.27 (0.13 to 0.41)	
Depression measure				
BDI	. . .	40	0.41 (0.29 to 0.53)	
CES-D	. . .	40	0.23 (0.11 to 0.34)	
HAD	. . .	27	0.19 (0.05 to 0.33)	
DASS	. . .	5	0.16 (−0.13 to 0.45)	
FIQ	. . .	11	0.12 (−0.10 to 0.33)	
GDS	. . .	6	0.36 (0.08 to 0.65)	. . .
HAM-D	. . .	8	0.41 (0.11 to 0.71)	
SCL-90	. . .	4	0.70 (0.28 to 1.11)	
TAS	. . .	6	0.69 (0.39 to 0.99)	
Other	. . .	21	0.34 (0.18 to 0.50)	
Exercise intensity				
Low	−1	14	0.05 (−0.14 to 0.24)	
Moderate	1/2	77	0.34 (0.25 to 0.42)	.66
Vigorous	1/2	21	0.32 (0.17 to 0.47)	
Not reported	0	56	0.32 (0.22 to 0.42)	
Exercise mode				
Aerobic	1/2	65	0.34 (0.25 to 0.44)	
Resistance	1/2	10	0.31 (0.07 to 0.56)	
Aerobic + resistance	−1/6	27	0.26 (0.12 to 0.39)	
Aerobic+[b]	−1/6	23	0.28 (0.13 to 0.42)	.03
Resistance+[b]	−1/6	5	−0.08 (−0.50 to 0.33)	
Mixed	−1/6	24	0.30 (0.16 to 0.45)	
Yoga	−1/6	7	0.31 (0.03 to 0.59)	
Tai chi	−1/6	6	0.42 (0.11 to 0.73)	
Other	0	1		
Exercise timing				
Continuous	1	87	0.30 (0.22 to 0.38)	
Intermittent	−1	77	0.31 (0.23 to 0.40)	.88
Not reported	0	4	0.24 (−0.09 to 0.57)	

(Continued)

COMMENT

The cumulative evidence summarized here indicates that exercise training reduces depressive symptoms among chronically ill patients. The magnitude of the overall mean effect is small but comparable to (1) exercise effects on related mental health outcomes among patients, including anxiety,[16] fatigue,[64] pain,[65] and quality of life,[66] and (2) the effect of pharmacotherapy on depressive symptoms among patients with stroke[67] and fibromyalgia.[68] Expressed as a binomial effect,[69] the effect of exercise is equivalent to a clinical effect of 7.5% beyond chance for patients exposed to exercise, hypothetically benefiting approximately 790 of the 10 534 patients included in the reviewed trials. Expressed as a function of absolute risk reduction,

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Table 2. Summary of Univariate Moderator Analysis (continued)

Effect Moderator	Contrast Weights	Effects (*k*)	Δ (95% CI)	Contrast *P* Value
Setting				
Home	1	38	0.29 (0.17 to 0.40)	.64
Clinic	–1/3	90	0.35 (0.27 to 0.43)	
Community facility	–1/3	7	0.26 (0.02 to 0.51)	
Mixed	–1/3	33	0.23 (0.11 to 0.35)	
Social interaction				
Alone	1	24	0.20 (0.06 to 0.34)	.09
One-to-one with a leader	–1/3	14	0.48 (0.28 to 0.69)	
Group	–1/3	56	0.33 (0.23 to 0.43)	
Mixed	–1/3	74	0.30 (0.21 to 0.38)	
Frequency, sessions/wk				
1	. . .	0	0.09 (–0.15 to 0.34)	. . .
2	. . .	36	0.25 (0.12 to 0.37)	
3	. . .	90	0.33 (0.26 to 0.41)	
4	. . .	8	0.28 (0.01 to 0.55)	
5	. . .	20	0.29 (0.12 to 0.45)	
7	. . .	2	0.80 (0.31 to 1.30)	
Not reported	. . .	2	0.47 (0.02 to 0.91)	
Program length, wk				
3-12	1	91	0.35 (0.27 to 0.43)	.08
13-26	–1/2	57	0.22 (0.13 to 0.32)	
>26	–1/2	19	0.34 (0.18 to 0.50)	
Not reported	. . .	1		
Exercise session duration, min				
10-20	–1/2	13	0.08 (–0.14 to 0.29)	.88
21-30	–1/2	44	0.38 (0.27 to 0.49)	
31-45	1/2	49	0.27 (0.17 to 0.38)	
>45	1/2	45	0.34 (0.23 to 0.45)	
Not reported	0	17	0.26 (0.08 to 0.44)	
Intervention type				
Exercise alone	1	143	0.33 (0.26 to 0.39)	.07
Multicomponent	–1	25	0.18 (0.03 to 0.33)	
Comparison type				
No treatment	. . .	16	0.73 (0.50 to 0.95)	. . .
Usual care	. . .	52	0.26 (0.16 to 0.36)	
Wait list	. . .	24	0.26 (0.11 to 0.41)	
Usual care during wait list period	. . .	28	0.39 (0.25 to 0.53)	
Placebo or second treatment	. . .	48	0.23 (0.12 to 0.33)	
Age, y				
<30	–1/2	14	0.30 (0.08 to 0.52)	.35
30-60	1	108	0.32 (0.25 to 0.39)	
>60	–1/2	46	0.26 (0.15 to 0.37)	
Sex makeup of patient group				
Female	. . .	41	0.33 (0.21 to 0.45)	. . .
Mixed	. . .	113	0.29 (0.22 to 0.36)	
Male	. . .	12	0.39 (0.17 to 0.61)	
Timing of effect				
During treatment	1/2	24	0.36 (0.20 to 0.51)	.36
After treatment	1/2	118	0.31 (0.24 to 0.38)	
Follow-up	–1	26	0.24 (0.10 to 0.39)	
Indoor-outdoor				
Indoor	1	128	0.33 (0.26 to 0.39)	.20
Outdoor	–1/2	2	0.55 (–0.003 to 1.10)	
Mixed	–1/2	15	0.26 (0.07 to 0.46)	
Not reported	0	23	0.18 (0.03 to 0.33)	
Author-reported fitness significance				
Not significant	–1/2	46	0.16 (0.05 to 0.27)	.002[a]
Yes, significant	1	72	0.41 (0.32 to 0.50)	
Not reported	–1/2	50	0.28 (0.18 to 0.38)	

Abbreviations: BDI, Beck Depression Inventory; CES-D, Center for Epidemiological Studies Depression Scale; COPD, chronic obstructive pulmonary disease; DASS, Depression Anxiety Stress Scales; ellipses, not applicable; FIQ, Fibromyalgia Impact Questionnaire; GDS, Geriatric Depression Scale; HAD, Hospital Anxiety and Depression Scale; HAM-D, Hamilton Rating Scale for Depression; MS, multiple sclerosis; SCL-90, Symptom Checklist-90; TAS, Toronto Attitude Scale.

[a] $P < .005$.

[b] The plus sign indicates that this moderator level comprised effects derived from trials in which resistance exercise plus an additional form of exercise that was not aerobic exercise, or in which aerobic exercise plus an additional form of exercise that was not resistance exercise, was used. These levels of moderators are defined in eTable 1.

the lowered depressive symptoms found among exercising patients are equivalent to a number needed to treat[70] of approximately 6; depressive symptom reductions could be expected to occur for at least 1 patient for every 6 chronically ill patients experiencing depressive symptoms who would engage in exercise training. Even mild-to-moderate depressive symptoms among chronically ill patients are associated with restrictions in social and recreational activities[71] and with lower adherence to lifestyle changes recommended by physicians to reduce future health risks.[72] Hence, the evidence reported here should encourage physicians to recommend exercise as a clinically meaningful way to reduce depressive symptoms in several patient populations.

The purpose of our meta-regression was to examine patient characteristics and features of exercise and clinical settings that could be modified to optimize the effect of exercise on depressive symptoms. The purpose was not to test whether those factors might help to explain the effect of exercise. That purpose would require that trials assess plausible mediators of exercise effects, which was rarely the case in the included trials. Depressive symptom reductions were larger in patients with higher symptom scores at baseline regardless of the depression measure used. The review reported herein did not focus on exercise training effects among patients with a diagnosis of a depressive disorder. Nonetheless, 34 of 168 effects (20.2%) came from symptom scores high enough to suggest a clinical elevation. Based on cutoff scores commonly used for clinical screening,[58-62] larger effects were found among patients with baseline scores indicative of mild-to-moderate depression. Although depression was not diagnosed in the trials reviewed herein, it is likely that patients with clinical depression were included.

The largest depressive symptom reductions were found when the primary trial outcome, predominantly categorized as function related, was improved among patients with elevated baseline depressive symptoms. Most effects (141 of 168) stemmed from studies of function-related primary outcomes, includ-

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ing pain, physical function, and function-related quality of life. This finding is noteworthy given the importance of functional improvements among patients.[55,73] Elevated depressive symptoms predict functional decline in older adults,[74] and exercise training may improve function by first reducing depressive symptoms. It is also plausible that depressive symptom reductions are explained in part by significant improvements in function-related outcomes among patients. The largest symptom reductions were observed for the 12 of 14 effects for which function-related outcomes were significantly improved among patients with baseline depressive symptoms indicative of mild-to-moderate depression. It also is noteworthy that these 14 effects resulted from investigations of patients with fibromyalgia or cardiovascular disorders, who often are characterized as having increased pain and impaired physical function. For example, a 16-week single-blind, randomized attention-controlled trial of 65 patients with fibromyalgia with baseline Beck Depression Inventory scores indicative of mild-to-moderate depression revealed a large reduction in depressive symptoms (Hedges $d=0.69$) and a correspondingly large, statistically significant reduction in symptoms of pain, physical function, and fibromyalgia-related quality of life (Hedges $d=1.04$).[63]

Those findings should be interpreted with caution because only 30 of the 141 function-related effects (21.3%) were derived from investigations of objective, function-related outcomes. Although the method of measuring function-related outcomes (self-report vs objective) was not a significant moderator of effects overall, reductions in depressive symptoms in trials that used a self-report assessment of a function-related outcome were larger when the outcome was significantly improved. This finding suggests that the relation between exercise-induced improvements in function-related outcomes and depressive symptom reductions may have been confounded in some studies by a common method bias of using self-report measures.

Our analysis did not permit a rigorous test of the minimal or optimal effective dose of physical activity, mostly because many trials used a similar prescription consistent with long-standing recommendations for increasing or maintaining fitness.[75,76] Nevertheless, using the reported types, intensities, and timing of physical activity, we were able to estimate whether each trial met contemporary physical activity recommendations.[77,78] Depressive symptom reductions were significantly larger among patients who met moderate or vigorous physical activity recommendations. This finding provides support for the use of current physical activity recommendations to reduce depressive symptoms among patients. Because it is possible that healthier participants were recruited into the trials that used exercise interventions that were consistent with currently recommended guidelines, optimal dosing of exercise exposure needs experimental confirmation.

Although double-blind allocation is not feasible in exercise interventions, 79 effects were derived from trials that concealed treatment allocation from the staff who conducted depressive symptom assessments. Symptom reductions were similar for trials that reported blinded allocation and trials that did not. Depressive symptom reductions in trials that used a no-treatment comparison did not differ significantly from reductions in trials that used an attention-control comparison. Thus, exercise effects were not solely attributable to attention from researchers. The use of intent-to-treat analysis did not alter effect size alone or independently of other moderators. Exercise adherence was not a significant moderator and was not lower in intent-to-treat trials, but adherence data were reported for more effects in intent-to-treat trials ($k=41$ of 53 [77.4%]) than efficacy trials ($k=63$ of 115 [54.8%]).

Well-designed randomized controlled trials of exercise effects on depressive symptoms are needed that focus on patients with a chronic illness who have had a depressive disorder diagnosed. Future trials should use objective measures of function to examine the potential mediating effect of function-related improvements in patients with elevated depressive symptoms. Also needed are well-designed investigations that examine the effects of overall exercise training dose in the context of whether patients are meeting recommended levels of physical activity.

CONCLUSIONS

Depressive symptom reduction is a favorable adventitious outcome of exercise training interventions designed as treatments for chronic illnesses other than depression. The present findings provide evidence to recommend exercise training to patients as a potential low-risk, adjuvant treatment for depressive symptoms that may develop during chronic illness. The findings also suggest that larger depressive-symptom reductions will be achieved by focusing on the improvement of function-related outcomes among chronically ill patients with mild-to-moderate elevations in depressive symptoms.

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