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Dose-response effects of aerobic exercise on reducing depression in patients with chronic illness and comorbid depression: a systematic review and meta-analysis

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ABSTRACT

Importance Aerobic exercise is an evidence-based treatment for depression. However, current exercise recommendations do not account for the limited functional capacity of patients with chronic illness and comorbid depression. Consequently, these recommendations risk being inappropriate and having low therapeutic application in this population.

Objective To examine the dose-response relationship between aerobic exercise volume and the severity of depressive symptoms, and to determine the exercise volume needed to alleviate depressive symptoms to the minimally important difference (MID) threshold in patients with chronic illness and comorbid depression.

Data sources We searched four databases (PubMed, Embase, Web of Science and PsycINFO) for randomised controlled trials published between database inception and May 2025, without language restrictions.

Study selection We included studies that compared the effects of aerobic exercise interventions with passive controls on depressive symptoms in adults with chronic illness and comorbid depression.

Data extraction and synthesis Data extraction was performed independently by two reviewers using a standardised form. A random-effects meta-analysis was employed to calculate the pooled estimate (Hedges' g) and the 95% CI. Meta-regression was conducted to determine the dose-response relationship between aerobic exercise volume and the severity of depressive symptoms.

Main outcome and measure The prespecified primary outcome was depressive symptoms and was assessed using validated depression rating scales.

Results 36 randomised controlled trials involving 2500 patients were included. Aerobic exercise compared with passive controls reduced the severity of depressive symptoms in patients with chronic illness and comorbid depression (Hedges' g: −0.73, 95% CI −0.99 to −0.46, p<0.001, I^2=81%). Additionally, aerobic exercise had a dose-response effect of −0.01 (95% CI −0.016 to −0.002, p=0.014) per 10 metabolic equivalent of task minutes per week (MET-min/week) on the severity of depressive symptoms. A weekly volume of 405 MET-min/week was found to alleviate depressive symptoms to an extent perceived as important (MID) by patients with chronic illness and comorbid depression.

Conclusions and relevance This study presents a dose-response relationship between aerobic exercise volume and the severity of depressive symptoms, suggesting that minimal volumes of aerobic exercise can confer improvements. Importantly, it informs stakeholders that achieving the WHO recommendation of 450 MET-min/week is not mandatory to elicit improvements in depressive symptoms. These findings underscore that irrespective of the functional capacity of patients with chronic illness and comorbid depression, aerobic exercise remains a viable strategy to manage their depressive symptoms.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Aerobic exercise alleviates depressive symptoms in patients with chronic illness and comorbid depression.
⇒ Current exercise recommendations lack consideration for the limited functional capacity of this population and may risk setting unrealistic thresholds to achieve.

WHAT THIS STUDY ADDS

⇒ We found a dose-response relationship between weekly aerobic exercise volume (metabolic equivalent of task minutes per week (MET-min/week)) and the severity of depressive symptoms.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This informs stakeholders that minimal volumes of aerobic exercise can confer improvements and that achieving the WHO's recommendation of 450 MET-min/week is not mandatory to alleviate depressive symptoms in patients with chronic illness and comorbid depression.
⇒ These findings underscore that the prescription of aerobic exercise for depressive symptoms in this population can be person-centred and adjusted according to the functional capacity of the patient.

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INTRODUCTION

Comorbid depression in patients with chronic illness is an undertreated public health crisis.[1 2] Patients with chronic illness have a 1.5-fold to 3.5-fold greater risk of developing depression when compared with healthy individuals.[3 4] In patients with cardiac diseases, stroke, diabetes and cancer, comorbid depression exacerbates disease prognosis by increasing the number and severity of complications and by worsening functional capacity. Moreover, comorbid depression significantly compounds their risk of mortality by 1.3-fold to 3-fold relative to their non-depressed counterparts.[5–12] Current management guidelines for most chronic illnesses lack specific recommendations for treating comorbid depression.[2 13–15] Consequently, routine treatments for depression, such as pharmacotherapy and psychotherapy, are adopted.[13–15] These treatments, however, are limited in patients with chronic illness due to concerns regarding accessibility, costs, drug interactions and adverse events.[10 16]

A promising treatment for comorbid depression in patients with chronic illness is aerobic exercise.[17] However, its current application in patient populations is limited, as exercise recommendations provided by guidelines on depression do not account for their reduced functional capacity.[18–21] Indeed, treatment guidelines for depression often align their exercise recommendations with international physical activity guidelines, such as the 450 metabolic equivalent of task minutes per week (MET-min/week) exercise volume (150 min of moderate-intensity (3 METs) aerobic physical activity per week) endorsed by the WHO.[22 23] This recommendation, however, may be impractical for patients with chronic illness. For instance, a meta-analysis by Taylor and colleagues on 3990 patients with heart failure found that the functional capacity of these patients was only 65% that of healthy individuals in the same age group.[24] Moreover, data from over 400 000 adults in the 2019 Behavioural Risk Factor Surveillance System illustrated that 76% of adults with chronic illness did not meet the WHO recommendation of 450 MET-min/week.[25] This underscores the difficulty of implementing and advocating exercise recommendations meant for the general population in patients with chronic illness. Accordingly, given the reduced functional capacity of patients with chronic illness, the need to identify whether minimal volumes of aerobic exercise can alleviate depression in this population is greatly warranted. In addition, identifying an exercise volume that can alleviate depression to a threshold perceived as important by the patients (termed the minimally important difference (MID)) may be of particular value to stakeholders.

To date, no studies have comprehensively investigated the dose-response relationship between aerobic exercise volume and depressive symptoms, and the volume of aerobic exercise necessary to alleviate depression to the MID threshold in patients with chronic illness and comorbid depression. Here, we conducted a systematic review and meta-analysis to determine the effectiveness of aerobic exercise in alleviating depressive symptoms in patients with chronic illness and comorbid depression. Furthermore, we examined the dose-response relationship between aerobic exercise volume and depressive symptoms and established an exercise volume that alleviates depression to the MID threshold in this population.

METHODS

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guideline (see online supplemental appendix 1),[26] and is registered in PROSPERO (CRD42021282103).

Selection criteria

Studies were eligible if they were randomised controlled trials (RCTs) that employed aerobic exercise as the intervention and included participants aged 18 years or older with chronic illness and depression. The study population met eligibility if their chronic illness is listed in the WHO's 11th revision of the International Classification of Diseases (ICD-11),[27] and if their depression is diagnosed by a physician or identified by self-report through meeting clinical cut-offs of validated depression rating scales.

Aerobic exercise was defined according to the American College of Sports Medicine (ACSM) as 'any activity that uses large muscle groups, can be maintained continuously, and is rhythmic in nature'.[28] There were no restrictions concerning the frequency, intensity, session duration and type of aerobic exercise. Studies were excluded if the intervention used other exercise modalities (eg, resistance training), combined aerobic exercise with depression treatments and/or other exercise modalities, or lasted for less than 4 weeks. The comparison group included passive control conditions including usual care, waitlist and patient education.

Outcomes

The primary outcome was the severity of depressive symptoms and was defined as the depression score assessed by validated depression rating scales at follow-up. Studies that measured the severity of depressive symptoms using multiple scales were handled using a hierarchical protocol, whereby the most frequently employed scale was used in the meta-analysis.[29] The secondary outcome was drop-out, defined as the number of participants who dropped out of the study before intervention completion.

Information sources and study selection

Four databases (PubMed, Embase, Web of Science and PsycINFO) were searched, without language restriction, for articles published between database inception and 9 May 2025. The search strategy was formulated based on the PICO (Population, Intervention, Comparison, and Outcome) framework (see online supplemental appendix 2). The full texts of all the included studies in three relevant systematic reviews were also assessed.[17 30 31] Study selection was performed by two independent reviewers, who screened the title and abstract of all records and full-text reports using Covidence. Conflicts were resolved through discussion or by consensus with a third reviewer when needed. Study investigators were contacted when information pertaining to the eligibility of their study required clarification.

Data extraction

Data extraction was performed independently by two reviewers using a standardised form embedded in an electronic spreadsheet. Summary statistics used to calculate the effect sizes for the primary and secondary outcomes were extracted, including sample sizes, depressive symptoms scores, SD and the number of drop-outs in each study. Intention-to-treat estimates were pooled. Study investigators were contacted when summary statistics were unreported or reported with insufficient detail. If the study investigators did not respond, then the summary statistics, where appropriate, were calculated using methods recommended by Cochrane (see online supplemental appendix 3).[32] Trial characteristics (author, year, country and funding status), participant characteristics (age, sex, chronic illness type, baseline severity of depressive symptoms and functional capacity) and comparator and intervention characteristics (control condition type, aerobic exercise type, exercise frequency, intensity, session duration, intervention duration and weekly volume) were also extracted. Chronic illness type was coded according to the ICD-11.[27] Functional capacity was coded by benchmarking reference values of age-matched healthy adults.[33 34] Intensity of aerobic exercise was coded according to ACSM's classification of exercise intensity and was coded as categories of intensity (very light, light, moderate and vigorous) and as metabolic equivalents (METs).[28] The weekly volume of aerobic exercise was coded as MET-min/week and was determined by multiplying aerobic exercise frequency (times per week) by intensity (METs) and session duration (min). Coding details are provided in online supplemental appendix 4 and 5.

Risk of bias and certainty of evidence assessment

Risk of bias was assessed using Cochrane's risk-of-bias tool for randomised trials by two independent reviewers.[35] Certainty of evidence for the effects of aerobic exercise on alleviating depressive symptoms in patients with chronic illness and comorbid depression was assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluation).[36]

Statistical analyses

Statistical analyses were conducted using dmetar and metafor packages in the statistical software R (V.4.4.0) with statistical significance set at $p<0.05$.[37]

Hedges' g was calculated to estimate the effect size between the aerobic exercise intervention and the control condition for depressive symptoms. In line with previous meta-analyses, negative effect sizes denote the superior effects of aerobic exercise interventions on depression when compared with control conditions. To account for the variability in participant, comparator and intervention characteristics and its resulting between-study heterogeneity, a random-effects model using the inverse-variance method and Hartung-Knapp adjustment was employed to estimate the summary Hedges' g and its 95% CI.[37 38] The effect measure for drop-out was adjusted risk ratio (RR) and was estimated using modified Poisson regression with robust sandwich SEs applied to account for within-study clustering.[39] The estimation of RR was adjusted for type of illness and age. A forest plot was presented for the meta-analysis and was accompanied by the I^2 statistic, which was used to quantify between-study heterogeneity. I^2 was interpreted according to Cochrane's handbook.[32]

In addition, a meta-regression was performed to explore the dose-response relationship between weekly aerobic exercise volume and the severity of depressive symptoms. To determine the dose-response, the weekly aerobic exercise volume (MET-min/week) was used as the predictor variable. If the weekly volume of the aerobic exercise intervention could not be computed, the study was included in the meta-analysis but excluded from the meta-regression (see online supplemental appendix 5). Furthermore, we determined the weekly volume of aerobic exercise necessary to reduce the severity of depressive symptoms by the MID threshold by adopting the effect size of 0.5 standardised mean difference (SMD) as the threshold. This effect size provides MID estimates that correspond closely to clinical anchor-based MID estimates of validated depression rating scales.[40 41]

Additional analyses

Sources of heterogeneity were explored by performing moderator analyses for trial, participant, comparator and intervention characteristics. Sensitivity analyses were conducted by excluding studies judged to be outliers, at high risk of bias and by accounting for baseline severity of depressive symptoms. Publication bias was examined by funnel plot and Pustejovsky's regression,[42–44] with $p<0.05$ indicating funnel plot asymmetry. Subgroups with less than five studies were either combined or excluded from the moderator analyses to reduce false positives and false negatives resulting from multiple comparisons and inadequate power.[45]

Equity, diversity and inclusion statement

The author group consists of junior, mid-career and senior researchers from both genders, different countries and disciplines. Our study population included both male and female adults with chronic illness and comorbid depression from different demographics, socioeconomics and comorbidities. Our findings may be generalisable to a wide range of individuals.

RESULTS

Search results

We identified 23 481 records from the literature search and screened 15 119 titles and abstracts. This, in combination with the full texts identified from the three systematic reviews,[17 30 31] resulted in 269 reports for full-text assessment (figure 1). Overall, 36 unique studies including 2500 patients with chronic illness and comorbid depression met the eligibility criteria. The meta-analysis of the primary outcome included 36 studies (k=37) while the secondary outcome included 30 studies (k=31). A list of the excluded studies and the consensus reason for exclusion is provided in online supplemental appendix 6.

Study characteristics

A summary of the characteristics of the included studies is presented in table 1. All 36 studies were RCTs with most studies being funded (n=17) and conducted in Asia (n=11). Study populations mainly had mild-to-moderate severity of depression (n=33) and were comorbid with the following categories of chronic illness: chronic pain (n=8), cardiovascular diseases (n=6), metabolic disorders (n=6), neurological disorders (n=5), cancers (n=3), autoimmune diseases (n=2), respiratory diseases (n=2) and others (n=4) including renal disease, insomnia, anxiety disorder and traumatic brain injury. Although the type of chronic illness varied, a key commonality shared among the studies is the reduced functional capacity of their patients. The median functional capacity relative to age-matched healthy adults is 65% (IQR 51–72) with 74% of the studies reporting a functional capacity of 70% or less in their population when compared with age-matched healthy counterparts. Aerobic exercise interventions were primarily administered as walking or jogging (n=12) or mixed modalities (n=14). Interventions were generally implemented at a moderate intensity (n=20) with the median exercise frequency, session duration and intervention duration being three times per week (IQR 2.5–3), 30 min per session (IQR 30–39) and 12 weeks in length (IQR 8–16).

Risk of bias and GRADE

Overall risk of bias was rated as some concerns in 28 studies and high risk in 8 studies, with no studies rated as low risk of bias. The risk of bias rating for individual studies is provided in online supplemental appendix 7. Risk was mostly attributed to the second and fourth domain, which relate to issues of blinding and self-report. Specifically, a primary concern of exercise interventions involving self-report measures is that participants' awareness of their assigned intervention can influence their assessment of the outcome.[46] Therefore, this potential source of bias should be considered when interpreting the results. Based

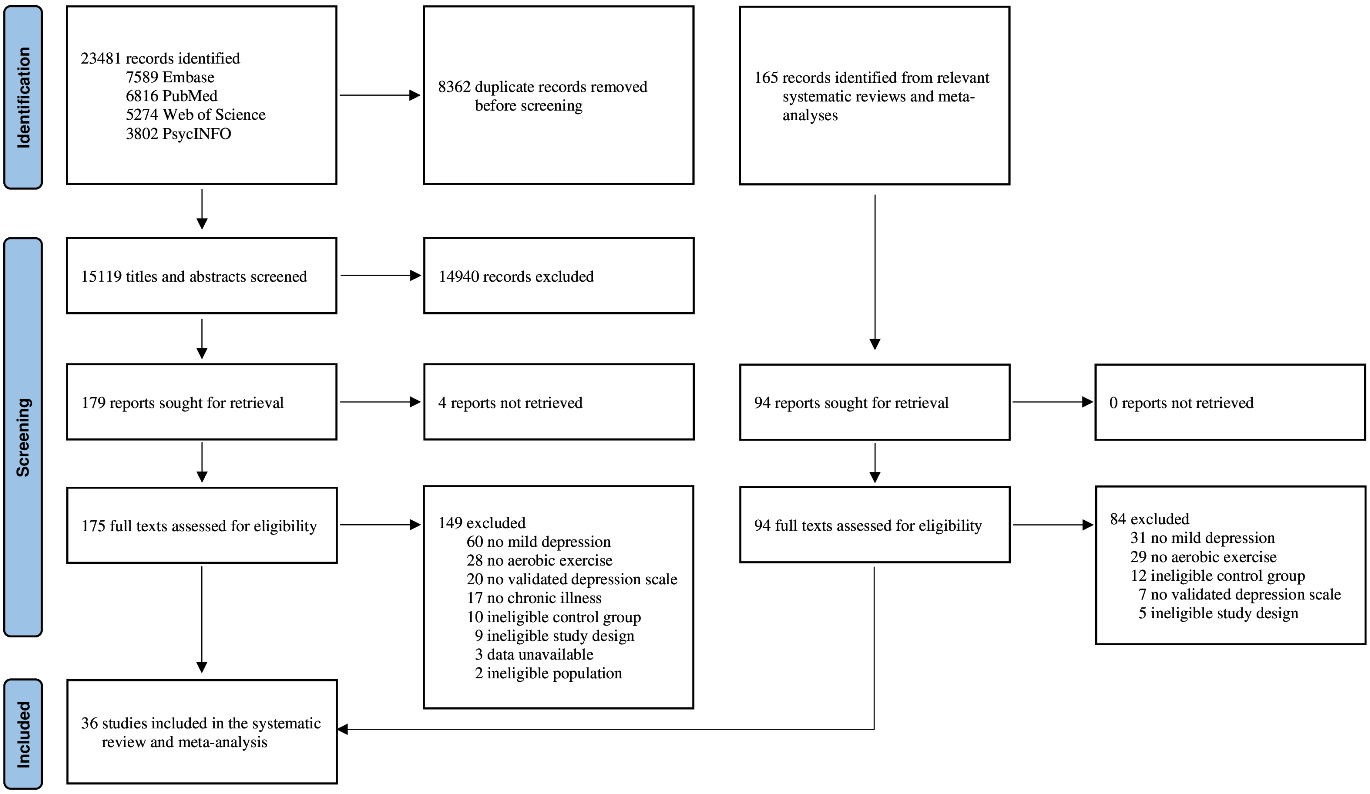

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

on the GRADE approach, there is low certainty of evidence that the true effect is close to the estimated effect of aerobic exercise on depressive symptoms in patients with chronic illness and comorbid depression (see online supplemental appendix 8). The certainty of evidence was downgraded by two levels due to eight studies being rated as high risk of bias in addition to the high level of heterogeneity in study characteristics.

Effects of aerobic exercise on depressive symptoms and drop-out

Aerobic exercise reduced the severity of depressive symptoms by a large effect size of −0.73 (Hedges' g) compared with passive controls in adults with chronic illness and comorbid depression (95% CI −0.99 to –0.46, p<0.001, I^2=81%, figure 2). Consistent with the main effect, sensitivity analyses excluding studies rated as high risk of bias (Hedges' g: −0.63, 95% CI −0.89 to –0.38, p<0.001, I^2=78), outliers (Hedges' g: −0.51, 95% CI −0.64 to –0.38, p<0.001, I^2=33%) and accounting for baseline severity of depressive symptoms (Hedges' g: −0.95, 95% CI −1.46 to –0.44, p=0.001, I^2=90%) remained statistically significant with moderate to large effect sizes (see online supplemental appendix 9). Publication bias was examined using funnel plot and Pustejovsky's regression and was not statistically significant (p=0.065, see online supplemental appendix 9 and 10).[47] For drop-out, aerobic exercise reported an 18% lower risk when compared with passive controls after accounting for type of illness and age (RR: 0.82, 95% CI 0.69 to 0.98, p=0.028).

Dose-response of aerobic exercise and depressive symptoms

Meta-regression of weekly aerobic exercise volume on the severity of depressive symptoms displayed a dose-response effect of −0.01 (95% CI −0.016 to –0.002, p=0.014, figure 3) per 10 MET-min/week. Sensitivity analyses excluding studies rated as high risk of bias (−0.010, 95% CI −0.018 to –0.002, p=0.015), outliers (−0.005, 95% CI −0.011 to –0.001, p=0.047) and accounting for baseline severity of depressive symptoms (−0.014, 95% CI −0.026 to –0.001, p=0.028) demonstrated consistent findings, illustrating a significant dose-response relationship between weekly aerobic exercise volume and the severity of depressive symptoms (see online supplemental appendix 11-13). Furthermore, a weekly aerobic exercise volume of 405 MET-min/week was found to achieve the MID threshold of 0.5 SMD.

Moderator analyses

The results of the moderator analyses are presented in online supplemental appendix 14. Briefly, none of the chosen moderators for meta-regression (other than weekly aerobic exercise volume) exhibited a dose-response effect. Subgroup analyses for funding status, severity of baseline depression, type of control, type of aerobic exercise, exercise frequency, intensity and session duration did not present significant between-group differences and were comparable in effect sizes. However, the subgroup analysis of chronic illness type did reveal that populations with neurological disorders had lower effect sizes.

DISCUSSION

This meta-analysis supports the effectiveness of aerobic exercise for alleviating depressive symptoms and extends previous reviews by presenting a novel dose-response relationship between weekly aerobic exercise volume and the severity of depressive symptoms in adults with chronic illness and comorbid depression. The identification of this dose-response relationship informs guidelines, healthcare professionals and stakeholders that even minimal volumes of aerobic exercise can alleviate depressive symptoms in this population. This finding holds particular significance to patients with chronic illness and comorbid depression, who are

Table 1 Study characteristics*

Study	Funding	Age, mean (SD)		Illness	Severity of depression	Aerobic exercise type	Duration	Sample, n (female)		Measure of depression	Measure of functional capacity	Functional capacity†
		Exercise	Control					Exercise	Control			
Abdelbasset 2019	NR	52.6 (7.1) 53.4 (6.3)	52.9 (7.8)	Heart failure	Moderate	Walk, jog	12 weeks	23 (7) 23 (5)	23 (6)	PHQ-9≥5	VO_{2max}	45%
Abrahão 2016	NR	43.8 (14.6)	46.1 (14.1)	Systemic lupus erythematosus	Moderate	Walk, jog, cycle	12 weeks	21 (NR)	21 (NR)	BDI≥10	12MWT	NA
Baptista 2012	NR	49.5 (NR)	49.1 (NR)	Fibromyalgia	Moderate	Dance	16 weeks	40 (40)	40 (40)	BDI≥10	6MWT	58%
Baquet 2018	Y	38.2 (9.6)	39.6 (9.7)	Multiple sclerosis	Mild	Cycle	12 weeks	34 (21)	34 (25)	QIDS-SR16≥6	6MWT	72%
Blumenthal 2012a	Y	56.7 (10.4)	55.3 (11.9)	Chronic heart failure	Moderate	Walk, jog, cycle	12 weeks	337 (28)	316 (28)	BDI-II≥14	6MWT	60%
Blumenthal 2012b	Y	64.7 (11.0)	63.5 (11.4)	Coronary heart disease	Mild	Walk, jog	16 weeks	37 (13)	24 (4)	HAM-D≥8	VO_{2max}	65%
Boing 2023	NR	55.0 (9.9)	56.8 (11.2)	Breast cancer	Mild	Dance	16 weeks	25 (25)	24 (24)	BDI≥10	NA	NA
Briken 2014	Y	49.1 (8.5) 48.8 (6.8)	50.4 (7.6)	Multiple sclerosis	Mild	Cycle, arm ergometry	8–10 weeks	12 (5) 12 (6)	11 (6)	IDS-SR30≥14	6MWT	50%
Davis 2024	N	38.6 (8.6)	34.1 (9.0)	Obesity	Mild	Walk, cycle	12 weeks	16 (16)	17 (17)	PHQ-9≥5	VO_{2max}	51%
de Groot 2019	Y	54.6 (10.7)	54.2 (10.4)	Type 2 diabetes	Moderate	Walk, jog, cycle	12 weeks	34 (26)	36 (27)	BDI-II≥14	6MWT	67%
Eisenhut 2022	N	49.1 (13.1)	53.0 (10.8)	High-grade glioma	Mild	Walk, jog, cycle	6 weeks	10 (NR)	8 (NR)	BDI≥10	6MWT	84%
Gary 2010	Y	NR	NR	Heart failure	Mild	Walk	12 weeks	20 (NR)	17 (NR)	HAM-D≥8	6MWT	59%
Gonçalves 2008	Y	NR	NR	Asthma	Mild	Walk, jog	12 weeks	10 (7)	10 (6)	BDI≥10	VO_{2max}	51%
Gowans 2001	Y	44.6 (8.7)	49.8 (7.3)	Fibromyalgia	Moderate	Walk, jog	23 weeks	27 (24)	23 (20)	BDI≥10	6MWT	68%
Guo 2023	Y	20.0 (1.5)	20.8 (1.8)	Obesity	Mild	HIIT	4 weeks	23 (23)	25 (25)	SDS≥50	VO_{2max}	101%
Hartescu 2015	NR	59.5 (10.6)	60.1 (8.5)	Insomnia	Mild	Walk	26 weeks	20 (15)	21 (15)	BDI≥10	NA	NA
He 2022	N	48.0 (8.6)	48.3 (10.0)	Breast cancer	Mild	Dance	16 weeks	88 (88)	88 (88)	PHQ-9≥5	NA	NA
Hernando-Garijo 2021	Y	51.8 (9.1)	55.1 (8.5)	Fibromyalgia	Mild	Callisthenics	15 weeks	17 (17)	17 (17)	HADS-D≥8	6MWT	69%
Herring 2011	Y	20.7 (3.0)	24.2 (6.3)	Generalised anxiety disorder	Mild	Cycle	6 weeks	10 (10)	10 (10)	BDI-II≥14	NA	NA
Hoffman 2010	NR	39.7 (NR)	37.1 (NR)	Traumatic brain injury	Moderate	Walk, jog, cycle, row	10 weeks	42 (NR)	42 (NR)	BDI≥10	6MWT	65%
Kanli 2024	N	34.5 (7.0)	24.8 (6.5)	Chronic low back pain	Moderate	Walk, cycle	6 weeks	17 (10)	17 (6)	BDI≥10	NA	NA
Koukouvou 2004	NR	52.3 (9.2)	52.8 (10.6)	Chronic heart failure	Moderate	Walk, jog, cycle, callisthenics	26 weeks	16 (0)	10 (0)	BDI≥10	VO_{2max}	62%
Kulcu 2007	NR	58.3 (10.5)	60.4 (11.0)	Congestive heart failure	Moderate	Walk	8 weeks	23 (6)	21 (6)	BDI≥10	VO_{2max}	64%
Lin 2021	Y	62.0 (9.5)	62.1 (12.3)	End-stage renal disease	Mild	Cycle	12 weeks	32 (10)	32 (13)	BDI≥10	NA	NA
Maharaj 2023	N	40.4 (7.2)	39.9 (5.8)	Type 2 diabetes	Moderate	Walk	12 weeks	25 (25)	24 (24)	BDI-II≥14	NA	NA
Mendes 2010	Y	NR	NR	Asthma	Mild	NR	12 weeks	44 (39)	45 (35)	BDI≥10	NA	NA
Miyamoto 2019	NR	53.4 (8.6)	51.3 (8.7)	Primary Sjögren's syndrome	Moderate	Walk	16 weeks	23 (23)	22 (22)	BDI≥10	VO_{2max}	66%
Negaresh 2019a	NR	31.2 (3.1)	29.1 (3.0)	Multiple sclerosis	Moderate	Cycle, arm ergometry	8 weeks	17 (11)	14 (9)	BDI-II≥14	VO_{2max}	43%
Negaresh 2019b	NR	32.1 (2.1)	32.2 (3.3)	Multiple sclerosis and overweight	Moderate	Cycle, arm ergometry	8 weeks	17 (11)	13 (9)	BDI-II≥14	VO_{2max}	41%
Norouzi 2020	Y	35.5 (2.4) 35.5 (2.4)	35.4 (2.8)	Fibromyalgia	Severe	Walk, jog, dance	12 weeks	20 (20) 20 (20)	20 (20)	BDI-II≥14	NA	NA

Continued

Table 1 Continued

Study	Funding	Age, mean (SD)		Illness	Severity of depression	Aerobic exercise type	Duration	Sample, n (female)		Measure of depression	Measure of functional capacity	Functional capacity†
		Exercise	Control					Exercise	Control			
Rahimian-Bougar 2022	N	NR	NR	Chronic joint pain	Moderate	HIIT	8 weeks	40 (0)	40 (0)	DASS-21≥5	NA	NA
Rooks 2007	Y	48.0 (11.0)	51.0 (12.0)	Fibromyalgia	Mild	Walk, jog	16 weeks	51 (51)	50 (50)	BDI≥10	6MWT	78%
Sadeghi-Bahmani 2019	N	38.0 (8.7)	37.9 (9.9)	Multiple sclerosis	Moderate	Walk, jog, cycle	8 weeks	26 (26)	21 (21)	BDI-FS≥4	NA	NA
Sañudo 2010	Y	55.9 (7.5)	56.6 (8.7)	Fibromyalgia	Severe	Walk, jog, dance	24 weeks	22 (22)	21 (21)	BDI≥10	6MWT	85%
Sarsan 2006	NR	41.7 (7.6)	43.6 (6.5)	Obesity	Mild	Walk, cycle	12 weeks	20 (20)	20 (20)	BDI≥10	6MWT	78%
Taheri 2018	NR	NR	NR	Obesity	Mild	Walk, jog	8 weeks	8 (8)	8 (8)	BDI≥10	NA	NA
Williams 2008	Y	NR	NR	Alzheimer's disease	NA	Walk	16 weeks	17 (NR)	12 (NR)	CSDD-19≥7	NA	NA

*Studies with two or more aerobic exercise interventions were combined to prevent double-counting of participants in the control group.
†Functional capacity measured using 6MWT and VO_{2max} was benchmarked to the normative values of age-matched healthy adults reported in Casanova *et al* and Edvardsen *et al*.[34 35]
BDI, Beck Depression Inventory; CSDD, Cornell Scale for Depression in Dementia; DASS, Depression Anxiety and Stress Scale; HADS, Hospital Anxiety and Depression Scale; HAM-D, Hamilton Depression Rating Scale; HIIT, high-intensity interval training; IDS, Inventory of Depressive Symptomatology; 6MWT, 6-minute walk test; 12MWT, 12-minute walk test; N, no; NA, not applicable; NR, not reported; PHQ-9, Patient Health Questionnaire-9; QIDS, Quick Inventory of Depressive Symptomatology; SDS, Zung Self-rating Depression Scale; VO_{2max}, maximal oxygen consumption; Y, yes.

often burdened by a reduced functional capacity, as it underscores aerobic exercise as a viable therapeutic strategy to manage their depressive symptoms. This study further identified that achieving a weekly aerobic exercise volume of 405 MET-min/week can reduce depressive symptoms to an extent that is of perceivable importance (MID) to the population.

Existing treatment guidelines for depression lack evidence-based exercise recommendations tailored to adults with chronic illness and comorbid depression.[13 14 48] Consequently, guidelines commonly adopt physical activity recommendations meant for the general population, such as the WHO recommendation of at least 450 MET-min/week of aerobic physical activity.[22 23] While this recommendation may be achievable for adults who are depressed but otherwise healthy, for those who have chronic illness and comorbid depression this recommendation may pose a significant barrier given that their chronic conditions result in substantial physical and functional impairments, which limit their functional capacity.[11] Moreover, as comorbid depression worsens fatigue and motivation, this can magnify the difficulty of achieving this recommendation in patients with chronic illness. Accordingly, advocating and implementing exercise recommendations meant for the general population in this population may be inappropriate and risk setting an unrealistic threshold. Thus, potentially discouraging these patients from engaging in any aerobic exercise activity. In this study, 74% of the studies reported a functional capacity of 70% or less compared with age-matched healthy counterparts. This observation is consistent with the literature. For example, patients with heart failure were shown to walk 363 m in the 6-minute walk test whereas healthy adults in the same age group walked 559 m.[24] Similarly, adults with multiple sclerosis performed significantly fewer daily steps (5840 steps per day) compared with age-matched healthy counterparts (9685 steps per day).[49] Compounding this reduced functional capacity in patients with chronic illness, comorbid depression is further associated with greater disability. Indeed, 46% of adults with chronic illness and comorbid depression experience moderate-to-severe disability compared with 17% in those with chronic illness only.[50] Collectively, these considerations underscore the need to determine whether minimal volumes of aerobic exercise can alleviate depressive symptoms in this population.

This study presents a dose-response relationship between weekly aerobic exercise volume and the severity of depressive symptoms, suggesting that even minimal volumes of aerobic exercise can confer improvements. This frames aerobic exercise as a viable strategy for depressive symptoms in patients with chronic illness regardless of their functional capacity. Additionally, it informs stakeholders that adhering to the WHO's weekly aerobic exercise target of 450 MET-min/week is not required to see improvements in depressive symptoms. This may lower perceived barriers to exercise adoption in patients with chronic illness. Furthermore, this study found that a weekly volume of 405 MET-min/week can reduce depressive symptoms to an extent that is of perceivable importance (MID) to the patients. Therefore, patients with chronic illness and comorbid depression, if given the functional capacity, time and willingness, may consider exercising at this weekly volume to potentially observe a reduction in depressive symptoms that is meaningful. Of note, the reference exercise volume of 405 MET-min/week aligns closely with the WHO recommendation of 450 MET-min/week. As the median functional capacity was 65% in this study, we acknowledge that it is unlikely that patients with chronic illness will readily achieve the reference

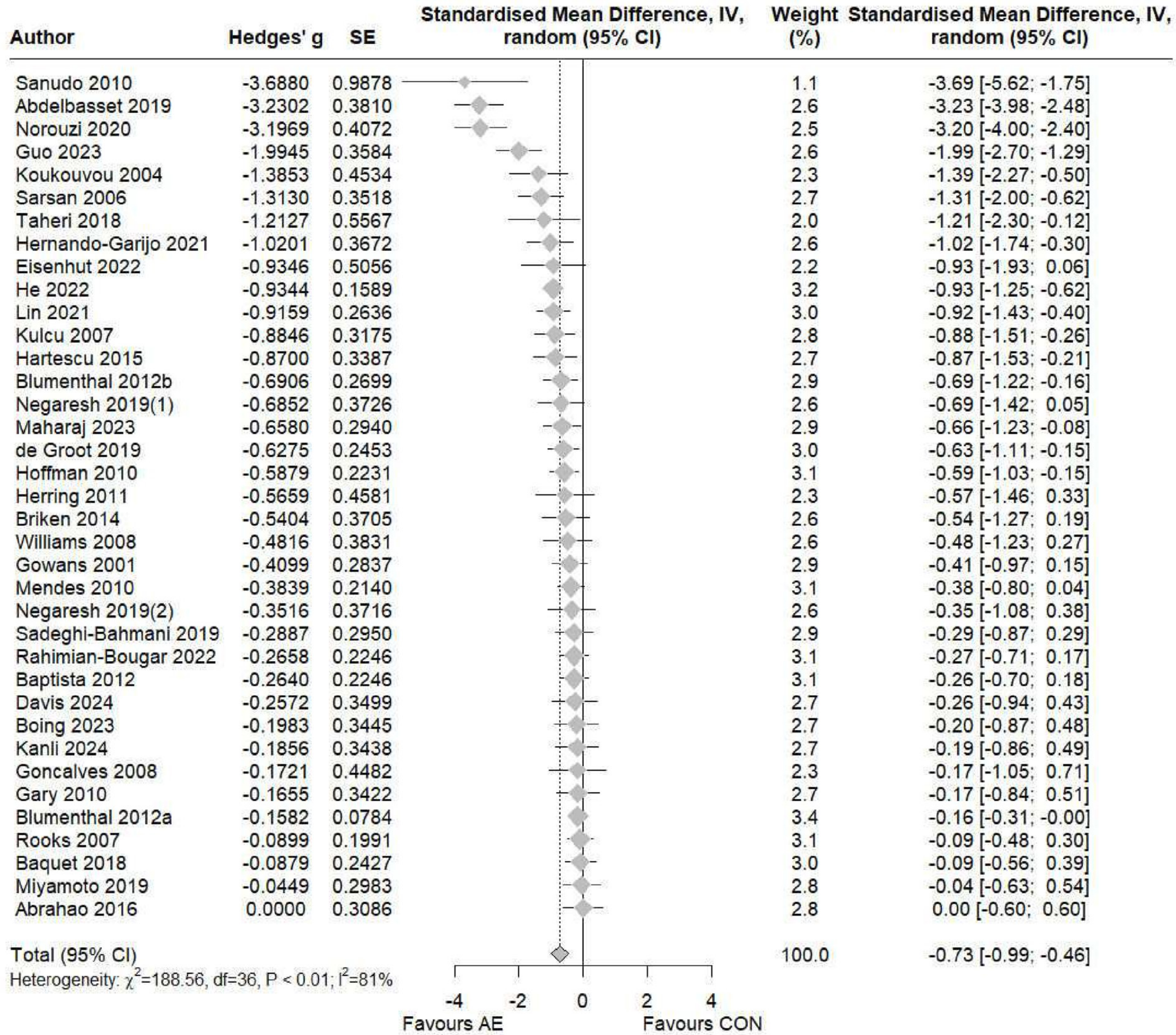

Figure 2 Forest plot of the effect of aerobic exercise on the severity of depressive symptoms in adults with chronic illness and comorbid depression. AE, aerobic exercise; CON, control;

exercise volume. Thus, most patients with chronic illness will need to start small and gradually progress to this reference exercise volume. Encouragingly, the dose-response relationship supports that any volume of exercise is beneficial, as such a stepwise approach to achieving the reference exercise volume via incremental increases is appropriate.

This meta-analysis corroborates previous reviews but advances the field in two key aspects.[30 31] First, this study is the first to demonstrate a dose-response relationship between weekly aerobic exercise volume and the severity of depressive symptoms in patients with chronic illness, supplemented by a weekly volume to achieve an MID reduction in depressive symptoms. Second, this study reports a larger effect size for aerobic exercise than previous reviews. This is likely due to the exclusion of studies that did not meet the threshold for mild depression, whereas previous reviews included studies with baseline depression scores in the normal range. Several limitations warrant consideration. First, there was considerable heterogeneity across study populations, as the type of chronic illness varied. This reduced the specificity of the results. However, this heterogeneity is also a strength as it increases the generalisability of the findings. Moreover, given the importance of identifying a dose-response in this population, we chose to employ an inclusive approach. Future research should validate whether the observed linear pattern persists or shifts towards a curvilinear trajectory as additional studies accumulate, especially within specific chronic illness types. Second, methodological limitations necessitate cautious interpretation of the findings. The between-study effect size distribution for the primary outcome exhibited skewness and may have affected the pooled estimates.[51] Although the sensitivity analysis excluding outliers presented a normal distribution and corroborated the main findings. There is also a possibility of small-sample bias as four included studies had a sample size of ≤10 per group.[52] Additionally, the estimation of RR may be influenced by sparse-data bias due to the low cases of drop-out across all included studies.[53] Third, moderator analyses were exploratory and likely to be underpowered. Thus, its findings and application should also be interpreted with caution. Fourth, most studies did not report adverse events; this prevented definitive conclusions about the safety of aerobic exercise as a treatment strategy for depression. Indeed, while the adjusted RR for dropout in the aerobic exercise is 0.82 (95% CI 0.69 to 0.98), this estimate should be interpreted cautiously as the CI is wide.

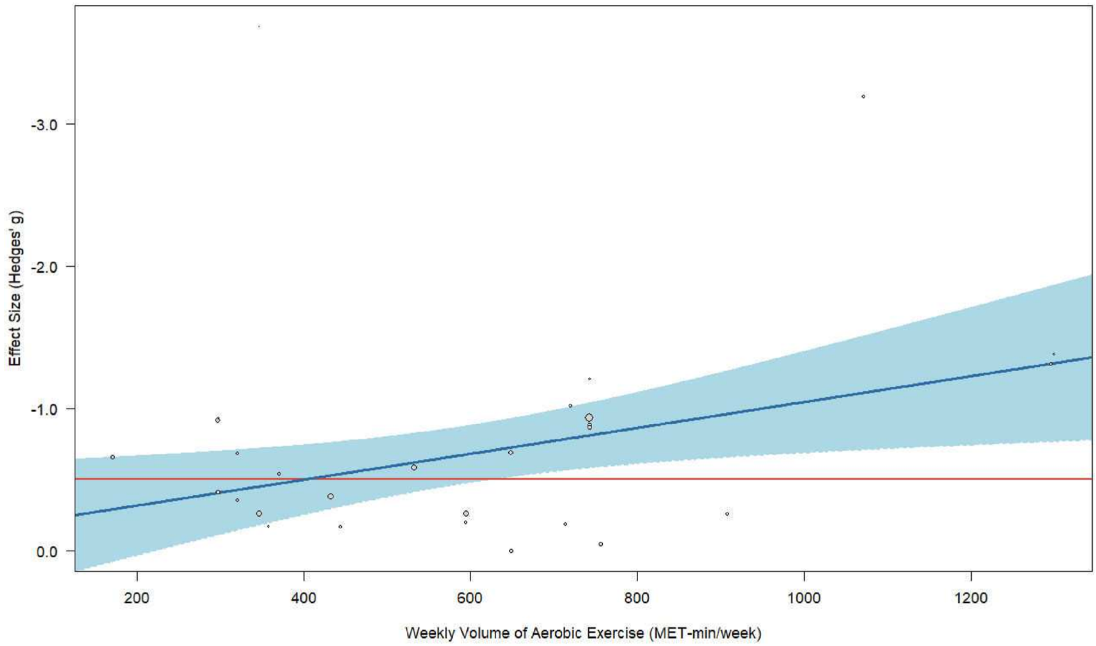

Figure 3 Dose-response effect of weekly aerobic exercise volume on the severity of depressive symptoms in adults with chronic illness and comorbid depression. Meta-regression of weekly aerobic exercise volume on the severity of depressive symptoms displayed a dose-response effect of −0.01 (95% CI −0.016 to −0.002, p=0.014, k=28) per 10 MET-min/week. The shaded area represents the 95% confidence band. The plotted points correspond to the individual studies with the point size representing the study's weight in the meta-regression. The red line corresponds to 0.5 SMD and represents the MID threshold. MET-min/week, metabolic equivalent of task minutes per week; MID, minimally important difference; SMD, standardised mean difference.

Overall, our findings suggest that performing any volume of aerobic exercise is beneficial for reducing depressive symptoms in patients with chronic illness and comorbid depression. Specifically, performing aerobic exercise at 405 MET-min/week can lead to reductions in depressive symptoms that are of perceivable importance to the patients themselves. These findings offer exercise recommendations that are applicable to patients with chronic illness and comorbid depression, and indicate that the prescription of aerobic exercise for depressive symptoms in this population can be person-centred and adjusted according to the functional capacity of the patient.

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