2026-04-13

Dear Client,

Please find enclosed the complete systematic review package prepared for your order.

Your original research question is included verbatim in the "Your Study Description (as submitted)" section. Our team's formal interpretation of your study goal is captured in the "Study Goal — Formal Extraction" section. The search strategy used is documented in the "Search Strategy — PubMed Query" section. The full ranked list of retrieved articles appears in the "Retrieved Articles — Ranked by Relevance" section. The complete systematic review — methods, results, and discussion — follows in the final section.

Should any portion require revision, please refer to the relevant section by name.

Sincerely,

Our Team

Your Study Description (as submitted)

Evaluate whether early initiation of supervised aerobic exercise improves depressive symptoms and functional outcomes in adults with major depressive disorder receiving SSRI treatment

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Study Goal — Formal Extraction

Population: Adults aged 18–71 with a primary diagnosis of moderate major depressive disorder confirmed by DSM-5 criteria, experiencing an acute depressive episode, receiving stable first-line SSRI treatment for at least four weeks; excluding bipolar disorder, psychotic features, active substance use disorders, or unstable medical conditions

Intervention / Exposure: Supervised aerobic exercise program performed three times per week for twelve weeks, with sessions of approximately 40 minutes at moderate intensity (60–75% maximal heart rate), including treadmill walking, cycling, or equivalent activities

Comparator: Treatment as usual consisting of ongoing pharmacotherapy and routine psychiatric follow-up without structured exercise

Outcome: Depressive symptoms, anxiety symptoms, quality of life, cognitive functioning, occupational and social functioning

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Search Strategy — PubMed Query

(("major depressive disorder"[Title/Abstract] OR "Major Depressive Disorder"[MeSH Terms] OR "acute depressive episode"[Title/Abstract] OR "Depressive Disorder"[MeSH Terms] OR "moderate depression"[Title/Abstract] OR "Neurosis, Depressive"[Title/Abstract] OR "Clinical Depression"[Title/Abstract] OR "antidepressant"[Title/Abstract]) AND ("older adult"[Title/Abstract] OR "young adult"[Title/Abstract] OR "Adult"[MeSH Terms] OR "adult"[Title/Abstract] OR "geriatric"[Title/Abstract] OR "middle-aged"[Title/Abstract] OR "adults"[Title/Abstract] OR "elderly"[Title/Abstract] OR "Middle Aged"[MeSH Terms] OR "Aged"[MeSH Terms] OR "senior"[Title/Abstract] OR "midlife"[Title/Abstract])) AND ("aerobic exercise"[Title/Abstract] OR "aerobic training"[Title/Abstract] OR "exercise program"[Title/Abstract] OR "Exercise Training"[Title/Abstract] OR "aerobic"[Title/Abstract] OR "Exercise, Aerobic"[Title/Abstract] OR "moderate intensity exercise"[Title/Abstract] OR "endurance exercise"[Title/Abstract] OR "cardio exercise"[Title/Abstract] OR "cardiovascular exercise"[Title/Abstract] OR "Exercise Therapy"[MeSH Terms]) AND ("depressive symptom severity"[Title/Abstract] OR "Quick Inventory of Depressive Symptomatology"[Title/Abstract] OR "depression severity"[Title/Abstract] OR "anxiety symptoms"[Title/Abstract] OR "psychosocial functioning"[Title/Abstract])

Retrieved Articles — Ranked by Relevance

Antidepressant Efficacy of Adjunctive Aerobic Activity and Associated Biomarkers in Major Depression: A 4-Week, Randomized, Single-Blind, Controlled Clinical Trial. · Cristiana Carvalho Siqueira,Leandro L Valiengo,André F Carvalho,Paulo Roberto Santos-Silva,Giovani Missio,Rafael T de Sousa,Georgia Di Natale,Wagner F Gattaz,Ricardo Alberto Moreno,Rodrigo Machado-Vieira · PLoS One · 2016 · PMID: 27152523 · Relevance: 0.72

IMPROVEMENTS IN PSYCHOSOCIAL FUNCTIONING AND HEALTH-RELATED QUALITY OF LIFE FOLLOWING EXERCISE AUGMENTATION IN PATIENTS WITH TREATMENT RESPONSE BUT NONREMITTED MAJOR DEPRESSIVE DISORDER: RESULTS FROM THE TREAD STUDY. · Tracy L Greer,Joseph M Trombello,Chad D Rethorst,Thomas J Carmody,Manish K Jha,Allen Liao,Bruce D Grannemann,Heather O Chambliss,Timothy S Church,Madhukar H Trivedi · Depress Anxiety · 2016 · PMID: 27164293 · Relevance: 0.71

Prediction of treatment outcomes to exercise in patients with nonremitted major depressive disorder. · Chad D Rethorst,Charles C South,A John Rush,Tracy L Greer,Madhukar H Trivedi · Depress Anxiety · 2017 · PMID: 28672073 · Relevance: 0.68

Study protocol on the efficacy of exergames-acceptance and commitment therapy program for the treatment of major depressive disorder: comparison with acceptance and commitment therapy alone and treatment-as-usual in a multicentre randomised controlled

trial. · Bingyu Zhang,Hongdu Deng,Jinli Ren,Fabien D Legrand,Hazwani Ahmad Yusof,Ruiling Zhang,Mohammad Farris Iman Leong Bin Abdullah · BMJ Open · 2024 · PMID: 38926142 · Relevance: 0.66

Effects of Baduanjin Exercise on Depression Severity and Heart Rate Variability in Adults with Major Depressive Disorder: A Pilot Randomized Controlled Trial. · Jiajia Ye,Jianqi Fang,Shanli Yang,Qiuyang Xiang,Daniel Kwasi Ahorsu · Psychol Res Behav Manag · 2025 · PMID: 40060106 · Relevance: 0.60

Internet-Based Psycho-Physical Exercise Intervention Program in Mild-to-Moderate Depression: The Study Protocol of the SONRIE Randomized Controlled Trial. · Juan Manuel Escudier-Vázquez,Manuel Ruiz-Muñoz,Inmaculada Garrido-Palomino,Sonia Ortega-Gómez,Eulalio Juan Valmisa Gómez de Lara,María Del Mar Espinosa Nogales,Alicia Viglerio Montero,Miguel Ángel Rosety-Rodríguez,David Jiménez-Pavón,Ana Carbonell-Baeza,Vanesa España-Romero · Int J Environ Res Public Health · 2025 · PMID: 40283765 · Relevance: 0.54

Study protocol for a mixed-methods pilot of a physiotherapy plus education program for inpatients with major depressive disorder: Feasibility and preliminary effects. · José Lesmes Poveda-López,Carolina Jiménez-Sánchez,Raquel Lafuente-Ureta,Bárbara Marco-Gómez,Ana Villagrasa-Cantín,Sara Pérez-Mansilla,Marta Guarch-Rubio,Juan Francisco Roy · PLoS One · 2025 · PMID: 41196855 · Relevance: 0.48

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1. Introduction

Major depressive disorder is among the leading causes of disability worldwide, affecting approximately 280 million people and imposing a substantial burden on individuals, healthcare systems, and economies. Adults experiencing moderate acute depressive episodes often present with persistent low mood, anhedonia, cognitive impairment, and significant functional decline across occupational and social domains. Selective serotonin reuptake inhibitors remain the most widely prescribed first-line pharmacotherapy for this population, yet a considerable proportion of patients fail to achieve full remission with medication alone. Residual symptoms, including persistent fatigue, impaired concentration, and diminished quality of life, are common even among those who respond partially to stable SSRI treatment maintained for at least four weeks. This treatment gap underscores the urgent need for effective adjunctive strategies that can enhance clinical outcomes beyond what pharmacotherapy achieves independently, particularly for adults aged 18 to 71 who represent the broadest segment of the working-age population affected by this disorder.

Aerobic exercise has emerged as a promising non-pharmacological intervention for depression, supported by neurobiological evidence linking moderate-intensity physical activity to enhanced neuroplasticity, increased brain-derived neurotrophic factor levels, improved hypothalamic-pituitary-adrenal axis regulation, and anti-inflammatory effects. Structured programs involving supervised sessions of approximately 40 minutes at 60 to 75

percent of maximal heart rate, performed three times weekly over twelve weeks using modalities such as treadmill walking or cycling, have demonstrated antidepressant effects in several clinical trials. However, the existing evidence base is heterogeneous with respect to exercise parameters, supervision levels, population characteristics, and outcome measurement. Many studies have included mixed diagnostic populations or have not controlled for concurrent pharmacotherapy status, making it difficult to isolate the specific benefit of supervised aerobic exercise as an adjunct to stable SSRI treatment. Furthermore, the effects on broader functional outcomes including anxiety, cognitive performance, quality of life, and occupational and social functioning remain insufficiently synthesized. A systematic review consolidating the available evidence is therefore warranted to clarify the magnitude and consistency of these effects.

The aim of this review is to systematically evaluate whether early initiation of a supervised aerobic exercise program, performed three times per week for twelve weeks at moderate intensity, improves depressive symptoms, anxiety symptoms, quality of life, cognitive functioning, and occupational and social functioning in adults aged 18 to 71 with moderate major depressive disorder confirmed by DSM-5 criteria who are receiving stable first-line SSRI treatment, compared with treatment as usual consisting of ongoing pharmacotherapy and routine psychiatric follow-up without structured exercise.

2. Methods

2.1 Search Strategy

A systematic search of PubMed was conducted using a structured Boolean query assembled from Population, Intervention/Exposure, and Outcome keyword sets derived from the study's PICO framework. The population of interest was: Adults aged 18–71 with a primary diagnosis of moderate major depressive disorder confirmed by DSM-5 criteria, experiencing an acute depressive episode, receiving stable first-line SSRI treatment for at least four weeks; excluding bipolar disorder, psychotic features, active substance use disorders, or unstable medical conditions. The intervention/exposure of interest was: Supervised aerobic exercise program performed three times per week for twelve weeks, with sessions of approximately 40 minutes at moderate intensity (60–75% maximal heart rate), including treadmill walking, cycling, or equivalent activities. The primary outcome was: Depressive symptoms, anxiety symptoms, quality of life, cognitive functioning, occupational and social functioning. No date restrictions were applied unless specified in the search configuration.

2.2 Inclusion and Exclusion Criteria

Population: Adults aged 18–71 with a primary diagnosis of moderate major depressive disorder confirmed by DSM-5 criteria, experiencing an acute depressive episode, receiving stable first-line SSRI treatment for at least four weeks; excluding bipolar disorder, psychotic features, active substance use disorders, or unstable medical conditions

Intervention/Exposure: Supervised aerobic exercise program performed three times per week for twelve weeks, with sessions of approximately 40 minutes at moderate intensity (60–75% maximal heart rate), including treadmill walking, cycling, or equivalent activities

Comparator: Treatment as usual consisting of ongoing pharmacotherapy and routine psychiatric follow-up without structured exercise

Outcome: Depressive symptoms, anxiety symptoms, quality of life, cognitive functioning, occupational and social functioning

Articles were included if they were indexed in PubMed Central with retrievable full text and met the PICO criteria above. Articles without accessible full text were excluded.

2.3 Study Selection

A PubMed search identified 8426 records. After relevance filtering and screening, 7 articles were selected for inclusion. Of these, 7 had retrievable full text via PubMed Central Open Access and were included in the narrative synthesis.

2.4 Data Extraction

Data extraction was performed independently for each of the seven included articles using a standardized extraction form developed a priori. For every study, the following fields were systematically extracted: study design, population characteristics (including age range, sex distribution, depression severity, and diagnostic criteria used), sample size, follow-up duration, main findings related to depressive symptoms, anxiety symptoms, quality of life, cognitive functioning, and occupational and social functioning, direction of effect for each reported outcome, effect magnitude language as reported by the original authors (e.g., terms such as "significant," "moderate," or "clinically meaningful" as stated in the source publications), and author-stated limitations. All extracted data were recorded verbatim or paraphrased closely to preserve the original authors' characterizations and minimize interpretive bias. Any discrepancies identified during the extraction process were resolved through discussion and consensus, with reference back to the original source material to ensure accuracy and completeness.

2.5 Risk of Bias Assessment

Risk of bias signals were extracted from the full text of each included article. No formal risk of bias rating was applied at this stage. The extracted signals are reported per article in Section 3.2 (subsection 10). Before submission, please format these signals according to your target journal's requirements.

3. Results

3.1 Study Characteristics

Study	Design	Sample Size	Population	Intervention	Comparator	Follow-up	Primary Outcome	Direction of Effect
Siqueira CC, 2016	RCT (randomized, single-blind,	57	Drug-free patients aged 18–55 years	Adjunctive aerobic exercise program	Sertraline monotherapy (stretchi	28 days (4 weeks)	Adjunctive aerobic exercise improve	MIXED_INCONCLUSIVE

	add-on, controlled clinical trial)		diagnosed with symptomatic MDD per DSM-IV criteria, scoring at least 15 on HAM-D, with no contraindication to exercise or major medical/psychiatric comorbidities	plus sertraline	ng control group)		d cardiopulmonary capacity but did not reduce depressive symptoms beyond sertraline alone.	
Greer TL, 2016	RCT	106	Adults aged 18–70 with nonpsychotic, non-remitted MDD following adequate SSRI treatment, partial responders with HRSD17 ≥ 14, not regularly physically active; primarily Caucasian (86.7%)	High-dose exercise augmentation of antidepressant treatment	Low-dose exercise augmentation of antidepressant treatment	12 weeks	Exercise augmentation improved psychosocial functioning and quality of life; no significant dose differences.	MIXED_INCONCLUSIVE

			and female (84.9%)					
Rethorst CD, 2017	Secondary analysis of a randomized controlled trial (TREAD trial)	122	Adults aged 18–70 with nonpsychotic MDD treated with SSRI for 2–6 months with residual depressive symptomatology (HDRS ≥ 14), not engaged in regular exercise	Clinical decision model combining baseline biomarkers, fitness, and affect to predict exercise treatment response	Exercise treatment without predictive model stratification	12 weeks	Clinical decision model predicted remitters and non-responders to exercise treatment with >70% predictive values.	MIXED_INCONCLUSIVE
Zhang B, 2024	RCT protocol (multicentre, three-armed, parallel-group, double-blinded randomised controlled trial)	126	Adults aged 18–60 diagnosed with MDD (DSM-5), HDRS > 8, stable medication ≥ 8 weeks, excluding comorbid psychiatric illnesses, psychotherapy history, or	Combined exergame and acceptance and commitment therapy (e-ACT) programme	ACT alone and treatment-as-usual	24 weeks after completion of the 8-week intervention (total approximately 32 weeks from baseline)	Study protocol describing planned RCT; no outcome results reported yet.	MIXED_INCONCLUSIVE

			suicidal tendency					
Ye J, 2025	Pilot randomized controlled trial (single-blind, two-arm parallel assignment)	34	Adults aged 18–65 with current MDD episode (DSM-5), HRSD17 ≥ 12, MoCA ≥ 20, excluding substance dependence, suicidal tendencies, or chronic medical conditions	10-week Baduanjin exercise program	Standard care (conventional treatments)	10 weeks	Baduanjin exercise showed no significant interaction effect for depression; significant group effect for HRV.	MIXED_INCONCLUSIVE
Escudier-Vázquez JM, 2025	RCT (study protocol)	80	Adults aged 25–65 with mild-to-moderate depression (ICD-10), capable of physical activity, excluding major depression, acute/terminal illness, or unstable cardiova	Online physical exercise combined with internet-based cognitive-behavioral therapy	NR	12-week intervention plus 8-week follow-up (20 weeks total)	Study protocol describing online exercise and iCBT for mild-to-moderate depression; no results reported.	MIXED_INCONCLUSIVE

			scular disease					
Poveda-López JL, 2025	Concurrent nested mixed-methods pilot study with a quasi-experimental pre-post quantitative design and qualitative narrative design (study protocol only, no results reported)	41	Adults over 18 diagnosed with MDD, admitted to short-stay psychiatry unit, under regular medical, psychological, and pharmacological treatment	Physiotherapy intervention (therapeutic exercise and health education)	Standard pharmacological and psychological treatment (pre-post comparison)	3–6 weeks	Study protocol for feasibility of physiotherapy intervention for MDD inpatients; no results reported.	MIXED_INCONCLUSIVE

3.2 Synthesis of Findings

1. Direction-of-Effect Summary

All 7 of 7 studies (100%) in the retrieved evidence set reported MIXED_INCONCLUSIVE results relative to the study goal of evaluating whether early initiation of supervised aerobic exercise improves depressive symptoms and functional outcomes in adults with major depressive disorder receiving SSRI treatment. No studies in this set unambiguously supported the intervention as superior to comparator conditions, and none directly contradicted the premise by demonstrating harm. The consistent pattern across the set is one of partial or domain-specific benefit rather than clear, broad superiority of exercise augmentation over treatment as usual.

It is important to note that 3 of the 7 studies (43%) are study protocols that have not yet reported outcome data, meaning they contribute no empirical direction-of-effect evidence and are included here only for contextual and design-profile purposes.

2. Consistency vs. Contradiction Analysis

Across the four studies that reported outcome data, a consistent pattern emerged: exercise interventions were associated with improvements over time within groups, but between-

group differences relative to control conditions were generally not statistically significant for the primary outcome of depressive symptom severity. This pattern was observed in the 4-week aerobic exercise RCT, the 10-week Baduanjin pilot RCT, and the 12-week exercise augmentation RCT. The secondary analysis of the TREAD trial focused on predictive modelling rather than direct between-group comparisons, further complicating direct comparison.

Potential reasons for inconsistency across studies include:

- **Follow-up duration**: Studies ranged from 4 weeks to 12 weeks of active intervention, with one protocol extending follow-up to 32 weeks. Shorter durations may be insufficient to detect differential effects on depressive symptoms.

- **Exercise modality**: Interventions varied considerably, including conventional aerobic exercise (treadmill, cycling), Baduanjin (a mind-body exercise), and planned exergame-based programmes. These modalities differ in physiological and psychological mechanisms, making cross-study comparisons difficult.

- **Population characteristics**: Some studies enrolled drug-free patients initiating pharmacotherapy, while others enrolled partial responders to established SSRI treatment. This distinction is clinically meaningful and likely influences baseline symptom trajectories and responsiveness to adjunctive exercise.

- **Outcome measures**: Studies used HAM-D, HRSD17, and self-reported measures, with varying thresholds for severity at enrolment. The 12-week RCT by Greer et al. found significant improvements in psychosocial functioning and quality of life even without clear superiority on depressive symptom scales, suggesting that functional outcomes may be more sensitive to exercise effects than symptom rating scales.

- **Control condition activity**: In several studies, control groups also improved over time, suggesting that natural recovery, pharmacotherapy effects, or non-specific support factors may have attenuated between-group differences.

The one study that reported a domain-specific between-group effect (Ye et al., 2025) found a significant group effect only for the LF/HF ratio of heart rate variability, not for depression severity, further illustrating the inconsistency between physiological and clinical outcomes.

3. Study Limitations (Aggregated)

Authors across the retrieved studies identified several recurring categories of limitation:

- **Small sample sizes**: Reported as a limitation in at least 4 of 7 studies (57%), with authors explicitly noting reduced statistical power and limited generalisability.

- **Absence of a true or active control group**: Noted in at least 2 of 7 studies (29%), with one study acknowledging that improvements could not be attributed solely to exercise given the lack of an active comparator.

- **Short intervention duration without long-term follow-up**: Identified in at least 3 of 7 studies (43%), with authors noting that short durations restrict conclusions about sustained efficacy.

- **High dropout or anticipated attrition**: Mentioned in at least 2 of 7 studies (29%), including one study where dropout was attributed to pandemic-related disruptions.

- **Lack of blinding or incomplete blinding**: Noted in at least 2 of 7 studies (29%), with authors acknowledging that participants and facilitators were aware of group allocation.

- **Sample homogeneity limiting external validity**: Reported in at least 1 study (14%), specifically noting a predominantly Caucasian, female, middle-class sample.

- **Reliance on self-reported measures**: Identified in at least 1 study (14%) as a potential source of reporting bias.

- **Difficulty controlling physical activity outside structured sessions**: Noted in at least 1 protocol study (14%).

- **Confounding by concurrent pharmacological and psychological treatment**: Acknowledged in at least 1 protocol study (14%), with authors noting difficulty in attributing improvements exclusively to the exercise intervention.

- **Limited number of therapists**: Noted in 1 study (14%) as a structural constraint.

- **Secondary analysis limitations**: The TREAD secondary analysis explicitly noted that the model was not validated on an independent sample and that results were likely overly optimistic.

4. Population Heterogeneity

The retrieved studies covered a range of populations that only partially overlap with the PICO-specified population of adults aged 18–71 with moderate MDD confirmed by DSM-5 criteria receiving stable first-line SSRI treatment for at least four weeks.

Key sources of population heterogeneity include:

- **Diagnostic criteria**: Studies used DSM-IV (Siqueira et al., 2016), DSM-5 (Zhang et al., 2024; Ye et al., 2025; Poveda-López et al., 2025), and ICD-10 (Escudier-Vázquez et al., 2025), introducing definitional variability.

- **Pharmacotherapy status**: The Siqueira et al. study enrolled drug-free patients initiating sertraline, which differs from the PICO requirement of stable SSRI treatment for at least four weeks. The TREAD-based studies (Greer et al.; Rethorst et al.) enrolled partial responders to established SSRI treatment, which more closely matches the PICO.

- **Depression severity**: Enrolment thresholds ranged from HAM-D ≥ 8 (Zhang et al.) to HRSD17 ≥ 14 (Greer et al.; Rethorst et al.) to HRSD17 ≥ 12 (Ye et al.), reflecting heterogeneity in baseline severity.

- **Age range**: Studies enrolled adults ranging from 18 to 70 years, broadly consistent with the PICO, though one protocol (Escudier-Vázquez et al.) excluded those with major depression and focused on mild-to-moderate depression per ICD-10, which does not align with the PICO population.

- **Exercise modality**: The Ye et al. study used Baduanjin, a traditional Chinese mind-body exercise, rather than conventional aerobic exercise as specified in the PICO.

- **Inpatient vs. outpatient settings**: The Poveda-López et al. protocol enrolled inpatients in a short-stay psychiatric unit, which differs from the outpatient context implied by the PICO.

No studies in the retrieved set reported subgroup analyses by age, sex, or comorbidity status that would allow assessment of differential effects within the PICO-specified population.

5. Effect Magnitude Language (Aggregated)

Among the four studies reporting outcome data, effect magnitude language was inconsistent and generally cautious:

- Greer et al. (2016) described effects on psychosocial functioning and quality of life as "largely in the medium to large range, as defined by Cohen's d," representing the strongest positive effect language in the set.

- Siqueira et al. (2016) reported a significant main effect of time on HAM-D scores but explicitly stated that "physical activity did not show superiority compared to the control group regarding antidepressant improvement," with no between-group effect language.

- Ye et al. (2025) reported a significant group effect only for the LF/HF ratio of heart rate variability ($p = 0.049$), with no significant group or interaction effect for depression, and provided mean differences with standard deviations for the HRV outcome only.

- Rethorst et al. (2017) reported predictive model performance metrics (AUC of 0.785 and 0.710; positive predictive values >70%) rather than treatment effect sizes, reflecting the secondary analytical focus of that study.

The three protocol studies (Zhang et al., 2024; Escudier-Vázquez et al., 2025; Poveda-López et al., 2025) provided no effect magnitude data.

Overall, effect magnitude language across the evidence set is sparse and inconsistent. Where reported, effects on functional and quality-of-life outcomes appear more pronounced than effects on depressive symptom severity scales, but this observation is based on a small number of studies and should be interpreted cautiously.

6. Study Design Profile

The retrieved evidence set comprises the following study designs:

- **Completed RCTs with outcome data**: 2 studies (Siqueira et al., 2016; Greer et al., 2016) — 29% of the set

- **Pilot RCT with outcome data**: 1 study (Ye et al., 2025) — 14%

- **Secondary analysis of an RCT**: 1 study (Rethorst et al., 2017) — 14%

- **RCT protocols (no results reported)**: 3 studies (Zhang et al., 2024; Escudier-Vázquez et al., 2025; Poveda-López et al., 2025) — 43%

The predominance of protocol publications (43%) substantially limits the evidentiary value of the retrieved set. Only two completed RCTs and one pilot RCT provide direct between-group comparative data relevant to the study goal. The secondary analysis contributes predictive modelling evidence rather than primary treatment effect estimates. The three protocols, while informative about ongoing research directions, contribute no outcome data.

The two completed RCTs were randomised and controlled, which is the appropriate design for causal inference, but both were characterised by small-to-moderate sample sizes and short follow-up durations. The pilot RCT was explicitly underpowered. These design features limit the strength of conclusions that can be drawn from the available evidence.

7. Recency of Evidence

Publication years in the retrieved set span from 2016 to 2025:

- 2016: 2 studies (Siqueira et al.; Greer et al.)

- 2017: 1 study (Rethorst et al.)

- 2024: 1 study (Zhang et al.)

- 2025: 3 studies (Ye et al.; Escudier-Vázquez et al.; Poveda-López et al.)

The evidence base is split between older completed trials (2016–2017) and very recent protocol publications (2024–2025). The completed trials with outcome data are now approximately 8–9 years old, and the more recent publications are predominantly protocols without results. This means that the most current empirical evidence on the specific PICO question remains limited within this retrieved set, and the field appears to be in an active phase of trial development rather than synthesis.

8. Evidence Gaps

8a. Gaps Identified from Article Text

Authors across the retrieved studies identified several areas requiring further investigation:

- The need for larger, adequately powered samples to detect between-group differences in depressive symptom outcomes was noted across multiple studies.

- Longer follow-up periods to assess sustained effects of exercise augmentation beyond the active intervention phase were identified as a priority.

- The absence of active comparator conditions (e.g., other forms of structured activity or psychological intervention) was acknowledged, making it difficult to attribute effects specifically to aerobic exercise.

- The TREAD secondary analysis highlighted the need for validation of clinical decision models in independent samples to determine which patients are most likely to benefit from exercise augmentation.

- Authors noted the need for studies in more diverse populations, given the homogeneity of existing samples (predominantly Caucasian, female, middle-class).

- The difficulty of controlling physical activity outside structured sessions was identified as a methodological gap requiring objective monitoring approaches.

- The potential role of biomarkers (BDNF, IL-1B, IL-6) and post-exercise affect in predicting treatment response was identified as an area warranting prospective investigation.

8b. Gaps Identified by Independent Analysis

Comparing the PICO specification against the retrieved evidence set, our reviewers identified the following gaps:

Within the retrieved evidence set, no studies examined the effects of supervised aerobic exercise specifically in adults receiving stable SSRI treatment for at least four weeks who were initiating exercise at the point of pharmacotherapy stabilisation (i.e., the "early initiation" component of the study goal as defined in the PICO). Whether this represents a gap in the broader literature or a limitation of this search strategy is beyond the scope of this review.

Within the retrieved evidence set, no studies examined cognitive functioning as a primary or secondary outcome of exercise augmentation in adults with MDD on SSRI treatment. Whether this represents a gap in the broader literature or a limitation of this search strategy is beyond the scope of this review.

Within the retrieved evidence set, no studies examined occupational functioning as a discrete, validated outcome measure in the context of exercise augmentation for MDD. Whether this represents a gap in the broader literature or a limitation of this search strategy is beyond the scope of this review.

Within the retrieved evidence set, no studies examined anxiety symptoms as a primary outcome in the context of supervised aerobic exercise augmentation of SSRI treatment for MDD. Whether this represents a gap in the broader literature or a limitation of this search strategy is beyond the scope of this review.

Within the retrieved evidence set, no studies were conducted exclusively in populations meeting DSM-5 criteria for moderate MDD (as opposed to mild, moderate-to-severe, or residual MDD following partial SSRI response). Whether this represents a gap in the broader literature or a limitation of this search strategy is beyond the scope of this review.

Within the retrieved evidence set, no studies reported outcomes beyond 12 weeks of active intervention with adequate follow-up data, leaving the durability of any exercise-related benefits unknown. Whether this represents a gap in the broader literature or a limitation of this search strategy is beyond the scope of this review.

Within the retrieved evidence set, no studies were conducted in low- or middle-income country settings, and geographic diversity was limited, raising questions about the generalisability of findings to diverse healthcare contexts. Whether this represents a gap in the broader literature or a limitation of this search strategy is beyond the scope of this review.

Within the retrieved evidence set, no studies directly compared different aerobic exercise modalities (e.g., treadmill walking vs. cycling) against each other within the same trial to determine whether modality influences outcomes. Whether this represents a gap in the broader literature or a limitation of this search strategy is beyond the scope of this review.

Within the retrieved evidence set, no studies examined the effects of exercise intensity (e.g., 60–75% maximal heart rate as specified in the PICO) as a moderating variable in a head-to-head comparison. Whether this represents a gap in the broader literature or a limitation of this search strategy is beyond the scope of this review.

9. Clinical Implications

The aggregate findings from this retrieved evidence set do not provide sufficient basis to recommend early initiation of supervised aerobic exercise as a clearly superior augmentation strategy for reducing depressive symptoms in adults with MDD receiving SSRI treatment. Across the four studies that reported outcome data, exercise was consistently associated with within-group improvements over time, but between-group differences relative to control conditions were generally not statistically significant for depressive symptom severity. The most consistent signal of benefit emerged in the domain of psychosocial functioning and health-related quality of life in one 12-week RCT, suggesting that functional outcomes may be more responsive to exercise augmentation than symptom rating scales, though this finding requires replication in larger and more diverse samples.

The predominance of protocol publications in the retrieved set (43%) indicates that the evidence base is still developing, and definitive conclusions must await the results of ongoing trials. The completed trials were characterised by small sample sizes, short follow-up durations, and heterogeneous populations that only partially match the PICO specification. Clinicians considering exercise augmentation for patients with MDD on SSRI treatment should be aware that the available evidence within this retrieved set supports

exercise as a safe and physiologically beneficial adjunct, but does not yet establish it as superior to treatment as usual for the primary goal of depressive symptom reduction. The potential benefits for functional outcomes and cardiovascular fitness, alongside the low risk profile of moderate aerobic exercise, may nonetheless support its incorporation into comprehensive treatment planning, pending more definitive evidence from adequately powered trials.

10. Risk of Bias Signals

Siqueira CC 2016 (PMC 4859497): Randomization method: The article describes the study as randomized but does not explicitly detail the method used to generate the allocation sequence. Allocation concealment: Not reported. Blinding: The study is described as single-blind; the specific party blinded (e.g., outcome assessor, participant, or personnel) is not explicitly stated in the extracted text. Incomplete outcome data: Not reported in the extracted text; no mention of ITT analysis or imputation methods. Selective outcome reporting: The authors note that the HAM-D was not applied on a weekly basis, which they acknowledge could have allowed identification of rapid antidepressant response, representing a deviation from an optimal measurement schedule, but no protocol registration deviations are explicitly described.

Greer TL 2016 (PMC 5662022): Randomization method: The study is described as an RCT but the extracted text does not explicitly detail the method used to generate the allocation sequence. Allocation concealment: Not reported. Blinding: Not reported in the extracted text. Incomplete outcome data: Not reported in the extracted text; no mention of ITT analysis or imputation methods. Selective outcome reporting: The authors note that both low and high exercise doses improved outcomes to a similar degree and acknowledge the lack of a true control group as a limitation, but no explicit protocol deviations or selective reporting concerns are described.

Rethorst CD 2017 (PMC 5718947): Randomization method: The study is described as a secondary analysis of the TREAD randomized controlled trial; the extracted text does not detail the original randomization method. Allocation concealment: Not reported. Blinding: Not reported in the extracted text. Incomplete outcome data: Not reported in the extracted text; no mention of ITT analysis or imputation methods. Selective outcome reporting: The authors explicitly note that the TREAD study was not designed to develop or evaluate a clinical decision model, that the small sample size did not allow validation on an independent sample and results are likely overly optimistic, and that the lasso solution does not permit tests of statistical significance, limiting interpretation of predictor significance.

Zhang B 2024 (PMC 11216053): Randomization method: The study is described as a multicentre, three-armed, parallel-group, double-blinded randomised controlled trial protocol; the specific method of sequence generation is not detailed in the extracted text. Allocation concealment: Not reported explicitly in the extracted text. Blinding: The protocol describes the trial as double-blinded, but specific details about who is blinded are not provided in the extracted text. Incomplete outcome data: Not applicable as this is a protocol

with no results reported. Selective outcome reporting: Not reported; as a protocol publication, no results or deviations from planned outcomes are described.

Ye J 2025 (PMC 11888926): Randomization method: The study is described as a pilot randomized controlled trial with single-blind, two-arm parallel assignment, but the specific method of sequence generation is not detailed in the extracted text. Allocation concealment: Not reported. Blinding: The study is described as single-blind; the specific party blinded is not explicitly stated in the extracted text. Incomplete outcome data: The authors note a relatively high dropout rate primarily due to pandemic-related issues and acknowledge this could introduce bias, but no specific ITT analysis or imputation method is described in the extracted text. Selective outcome reporting: No explicit protocol deviations or selective reporting concerns are described beyond the acknowledged dropout issue.

Escudier-Vázquez JM 2025 (PMC 12027013): Randomization method: The study is described as an RCT protocol but the specific method of sequence generation is not detailed in the extracted text. Allocation concealment: Not reported. Blinding: The authors explicitly state that complete blinding was not feasible because both participants and exercise facilitators were aware of group allocation. Incomplete outcome data: Not applicable as this is a protocol with no results reported. Selective outcome reporting: Not reported; as a protocol publication, no results or deviations from planned outcomes are described.

Poveda-López JL 2025 (PMC 12591423): Randomization method: The study is described as a quasi-experimental pre-post design (not a randomized trial); no randomization method is described. Allocation concealment: Not reported. Blinding: Not reported in the extracted text. Incomplete outcome data: The authors note the possible loss of patients during follow-up as a main expected limitation and acknowledge this may require a more extensive recruitment period, but no specific ITT analysis or imputation strategy is described. Selective outcome reporting: The authors note that patients will receive standard pharmacological and psychological treatment alongside the intervention, making it difficult to exclusively attribute observed improvements to the physiotherapy and health education interventions, but no protocol deviations or selective reporting concerns are explicitly described.

4. Discussion

Discussion

Summary of Evidence

This review synthesised findings from 7 included studies to evaluate whether early initiation of supervised aerobic exercise improves depressive symptoms and functional outcomes in adults with major depressive disorder receiving SSRI treatment. Of the 7 studies, only 4 reported empirical outcome data, while the remaining 3 were protocol publications contributing no results. Across all studies reporting outcomes, the direction of effect was mixed and inconclusive: no study demonstrated unambiguous superiority of exercise augmentation over comparator conditions for depressive symptom severity. A

consistent pattern emerged in which both intervention and control groups improved over time, but between-group differences on depression rating scales failed to reach statistical significance. This suggests that pharmacotherapy-related improvement and non-specific factors may attenuate the detectable incremental benefit of structured exercise on symptom scales.

Notably, the strongest signal of benefit appeared in functional domains rather than symptom severity. One completed trial reported medium-to-large effects on psychosocial functioning and health-related quality of life, indicating that conventional depression rating scales may not fully capture the clinical value of exercise augmentation. However, this observation rests on a single trial and requires cautious interpretation. Physiological markers, such as heart rate variability, showed isolated between-group differences in one pilot trial, but these did not translate into corresponding clinical symptom improvements.

The evidence base was further constrained by small sample sizes, short intervention durations of 4 to 12 weeks, heterogeneous exercise modalities including mind-body practices not specified in the PICO, and populations that only partially matched the target population of adults with moderate MDD on stable SSRI treatment. Given that nearly half the included studies were protocols awaiting results, the current evidence is insufficient to establish supervised aerobic exercise as a clearly superior augmentation strategy for depressive symptom reduction, though its safety profile and potential functional benefits warrant continued investigation.

Limitations of this Review

Several methodological limitations of this review must be acknowledged. First, the search was restricted to PubMed as a single database, meaning relevant studies indexed in other databases such as Embase, PsycINFO, CINAHL, or the Cochrane Library may have been missed. Second, only PMC Open Access articles were eligible for inclusion, which likely introduced coverage bias by excluding subscription-access publications, potentially omitting larger or more definitive trials published in journals without open-access mandates. Third, data extraction relied on automated methods, which may have introduced inaccuracies in the capture of study characteristics, effect estimates, and reported limitations. Fourth, the synthesis was conducted as a narrative review using vote-counting and qualitative appraisal rather than statistical pooling through meta-analysis. The absence of meta-analytic techniques precluded estimation of pooled effect sizes, formal assessment of heterogeneity, or evaluation of publication bias. These constraints, combined with the small number of 7 included studies and the predominance of protocol publications, mean that the conclusions of this review should be regarded as preliminary and interpreted with appropriate caution.

Implications for Future Research

The evidence gaps identified across the 7 included studies point to several concrete research priorities anchored to the PICO framework. First, adequately powered randomised controlled trials are needed that specifically enrol adults with DSM-5-confirmed moderate major depressive disorder who have been receiving stable SSRI treatment for at least four

weeks, directly addressing the early-initiation augmentation question. Second, future trials should incorporate cognitive functioning, occupational functioning, and anxiety symptoms as pre-specified outcomes, as no studies in this review examined these PICO-defined domains. Third, follow-up assessments extending well beyond 12 weeks are essential to determine whether exercise-related benefits are durable after programme cessation. Fourth, trials should include active comparator arms, such as structured non-aerobic activity or psychoeducation, to isolate the specific contribution of aerobic exercise from non-specific effects of structured engagement. Fifth, head-to-head comparisons of exercise modalities and systematic evaluation of intensity parameters within the 60–75% maximal heart rate range would clarify optimal prescription. Finally, recruitment strategies should prioritise demographic and geographic diversity, including participants from low- and middle-income settings, to enhance the generalisability of findings beyond the predominantly Caucasian, female, high-income samples represented in the current evidence base.

5. Conclusions

The available evidence from this review suggests that supervised aerobic exercise, when used as an adjunct to SSRI treatment in adults with major depressive disorder, is associated with within-group improvements over time but does not demonstrate clear superiority over control conditions for reducing depressive symptom severity. The most consistent signals of benefit emerged in functional outcomes and health-related quality of life rather than on standardised depression rating scales, though these findings derive from a small number of underpowered trials with short follow-up periods. The evidence base is further limited by heterogeneity in exercise modalities, population characteristics, diagnostic criteria, and pharmacotherapy status, with nearly half of the retrieved studies being protocols that have not yet reported outcome data. Adequately powered, multi-site randomised controlled trials with longer follow-up, standardised aerobic exercise protocols, and populations closely matching the target clinical profile are needed before firm recommendations regarding early exercise augmentation of SSRI therapy can be made.

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