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Review article

The effect of exercise on suicidal ideation and behaviors: A systematic review and meta-analysis of randomized controlled trials

Nicholas Fabiano [a,1], Arnav Gupta [b,c,1], Jess G. Fiedorowicz [a,d,e,f], Joseph Firth [g,h], Brendon Stubbs [i,j], Davy Vancampfort [k], Felipe B. Schuch [l,o,p], Lucas J. Carr [m], Marco Solmi [a,d,e,f,n,*]

[a] *Department of Psychiatry, University of Ottawa, Ottawa, ON, Canada*
[b] *Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada*
[c] *College of Public Health, Kent State University, Kent, OH, United States*
[d] *Department of Mental Health, Ottawa Hospital, Ottawa, ON, Canada*
[e] *Ottawa Hospital Research Institute (OHRI) Clinical Epidemiology Program, University of Ottawa, Ottawa, ON, Canada*
[f] *School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada*
[g] *Division of Psychology and Mental Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK*
[h] *Greater Manchester Mental Health NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK*
[i] *Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London, UK*
[j] *Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, London, UK.*
[k] *KU Leuven Department of Rehabilitation Sciences, Leuven, Belgium*
[l] *Department of Sports Methods and Techniques, Federal University of Santa Maria, Santa Maria, Brazil*
[m] *Department of Health and Human Physiology, University of Iowa, Iowa City, IA, United States*
[n] *Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany*
[o] *Institute of Psychiatry, Federal University of Rio de Janeiro, Rio de Janeiro*
[p] *Faculty of Health Sciences, Universidad Autónoma de Chile, Providencia, Chile*

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ABSTRACT

Background: Although exercise may positively impact those with mental or other medical illnesses, there is a lack of understanding on how it influences suicidal ideation or risk.

Methods: We conducted a PRISMA 2020-compliant systematic review searching MEDLINE, EMBASE, Cochrane, and PsycINFO from inception to June 21, 2022. Randomized controlled trials (RCTs) investigating exercise and suicidal ideation in subjects with mental or physical conditions were included. Random-effects meta-analysis was conducted. The primary outcome was suicidal ideation. We assessed bias of studies with risk of bias 2 tool.

Results: We identified 17 RCTs encompassing 1021 participants. Depression was the most included condition (71 %, k = 12). Mean follow up was 10.0 weeks (SD = 5.2). Post-intervention suicidal ideation (SMD = -1.09, CI -3.08–0.90, $p = 0.20$, k = 5) was not significantly different between exercise and control groups. Suicide attempts were significantly reduced in participants randomized to exercise interventions as compared to inactive controls (OR = 0.23, CI 0.09–0.67, $p = 0.04$, k = 2). Fourteen studies (82 %) were at high risk of bias.

Limitations: This meta-analysis is limited by few, underpowered and heterogenous studies.

Conclusion: Overall, our meta-analysis did not find a significant decrease in suicidal ideation or mortality between exercise and control groups. However, exercise did significantly decrease suicide attempts. Results should be considered preliminary, and more and larger studies assessing suicidality in RCTs testing exercise are needed.

1. Introduction

Mental and physical health are inexorably intertwined. Those with chronic physical conditions are more prone to develop mental illness, while those with mental illness are more likely to suffer from a variety of other medical conditions (Evans et al., 2005; Goodwin, 2006; Patten,

* Corresponding author at: Department of Psychiatry, University of Ottawa, Ottawa, ON, Canada.
E-mail address: msolmi@toh.ca (M. Solmi).

[1] Nicholas Fabiano and Arnav Gupta contributed equally to this paper.

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2001). Mental illnesses such as depression, anxiety, and post-traumatic stress disorder (PTSD), among others, have been associated with higher incidence of cardiovascular disease, which is likely attributable to adverse impacts on sleep, autonomic and endocrine dysregulation, and lifestyle factors such as smoking, diet and physical inactivity (Cohen et al., 2015; Edmondson and von Känel, 2017; Evans et al., 2005; Lavie et al., 2015). This higher incidence of cardiovascular disease has been shown to worsen existing symptoms, creating a maladaptive cycle of worsening mental and physical health (Stubbs et al., 2018). Despite evidence-based guidelines recommending exercise (i.e., structured physical activity) as an effective treatment option for various mental health conditions with good adherence, multisystem benefits and low adverse events compared to other treatments (Stubbs et al., 2018), current practice guidelines primarily focus on pharmacotherapy and psychotherapy, which typically address mental health symptoms and without comparable multisystem benefits (Ashdown-Franks et al., 2020; Firth et al., 2020; Kandola and Stubbs, 2020; Stubbs et al., 2018). Exercise has the unique ability to simultaneously bolster the physical and mental health of an individual, even at levels below the public health recommendations, which highlights its' potential role as an accessible therapy, especially during the COVID-19 pandemic where being physically active significantly decreased mental health problems (Dragioti et al., 2022; Ettman et al., 2020; Pearce et al., 2022; Penedo and Dahn, 2005; Wilke et al., 2021). The acknowledged benefits have been recently added to the U.S. Physical Activity Guidelines, highlighting how regular physical activity improves cognitive function and decreases anxiety or depression risk ("Physical Activity Guidelines for Americans, 2nd edition," n.d.).

Various studies have shown a positive impact of exercise on depressive symptoms to the point of remission (Gujral et al., 2017; Krogh et al., 2017; Mota-Pereira et al., 2011; Nyström et al., 2015). Particularly, large scale three-armed RCTs have shown over 12 months exercise is equally beneficial as cognitive behavioral therapy (CBT) and better than care as usual (Hallgren et al., 2015). Moreover, a trial comparing the effects of antidepressants (escitalopram or sertraline) with running therapy (twice a week) in 141 outpatients with major depression over 16 weeks found comparable remission rates in both groups (antidepressants: 44.8 %; running 43.3 %), yet the running group outperformed antidepressants across multiple physical health metrics (weight, waist circumference, systolic and diastolic blood pressure, heart rate and heart rate variability) (Verhoeven et al., 2022).

In investigating potential underlying mechanisms for the effects of exercise on mental health outcomes a magnetic resonance imaging study in patients with depressive symptoms did find that those who exercised, increased their brain volumes including the hippocampus, anterior cingulate cortex, and the prefrontal cortex. Another study found increases in brain-derived neurotrophic factor (BDNF) (Gujral et al., 2017; Kerling et al., 2017). This suggests a neuroplastic effect of exercise on the brain that may alleviate symptoms. Likewise, there are multiple hypotheses regarding the molecular mechanism of exercise, including overlap with existing pharmacological interventions, and improvements in autonomic system dysfunction (Ernst et al., 2006; Herbsleb et al., 2020). In response to exercise, studies have noted upregulation of neurotransmitters including serotonin or norepinephrine, upregulation of BDNF, increased levels of endocannabinoids and alleviation of the systemic inflammatory response in patients with depression and anxiety (Crombie et al., 2021; Desai et al., 2022; Ernst et al., 2006; Lin and Kuo, 2013; Meyer et al., 2019; Russo-Neustadt et al., 2000; Wegner et al., 2014).

A global burden of disease study from 2016 estimated a 6.7 % increase in total number of deaths due to suicide, indicating a growing need to find effective methods for prevention (Naghavi, 2019). Psychotherapy and CBT are among different strategies shown to have good effect in prevent deaths due to suicide (Riblet et al., 2017). Although exercise has been shown to have a positive impact on those with mental illness in various patient populations, there is a lack of understanding on how it influences suicidal ideation or risk of suicidal behaviour (Chalder et al., 2012; Trivedi et al., 2011). Specifically, existing literature has demonstrated a protective effect of physical activity on suicidal ideation in the general population (Vancampfort et al., 2018). However, to date, there are no systemic reviews or meta-analyses formally investigating the impact of exercise on suicide-related outcomes in patients with mental or physical illness. In this work, we aim to conduct a systematic review and meta-analysis pooling data from randomized controlled trials (RCTs) administering exercise to subjects with any mental or physical, clinical or subclinical condition, and reporting on suicide-related outcomes.

2. Methods

The systematic review adhered to Preferred Reporting Items for Systematic Reviews And Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021).

2.1. Ethics

Research ethics board approval for this type of research is waived at the University of Ottawa. The protocol was uploaded to Open Science Framework a priori and can be found at: https://osf.io/gsekn/.

2.2. Search strategy and inclusion criteria

MEDLINE, EMBASE, Cochrane, and PsycINFO were searched on June 21, 2022 for RCTs investigating the effect that exercise had on suicidal outcomes in those with mental or physical illness with no limits set based on date of publication. A manual search of the Cochrane trial register and ClinicalTrials.gov was also performed. A librarian was involved to optimize the search strategy. The search terms included "suicide", "self-harm", "randomized control trial", "exercise", "aerobic", "resistance training", "yoga" or "mind-body." The search terms were entered into Google Scholar and a hand search was performed to ensure that relevant articles were not missed. The research question and inclusion and exclusion criteria was established a priori. Studies were included if they met the following criteria: (1) RCT study design with active or inactive control group, (2) participants had any mental/physical disorder (or subclinical condition/symptoms), and (3) report the role that exercise (any type, intensity level, duration, or setting) had on suicidal ideation, suicide attempts or suicide deaths, regardless of other adjuvant treatment they are receiving. Suicide-related outcomes could be primary, secondary, or exploratory in the original studies or even reported as adverse events. The complete search strategy is presented in Table A1. The studies were imported into COVIDENCE through which study screening was conducted.

2.3. Study screening

Title and full text screening was conducted in duplicate by two independent reviewers (NF, AG). Discrepancies were discussed and resolved with consensus between both reviewers. The references of included studies were also screened using the same systematic approach to capture any additional relevant articles.

2.4. Data extraction

Two reviewers (NF, AG) independently extracted relevant data from included articles and recorded the data onto a Microsoft Excel spreadsheet designed a priori. For this systematic review and meta-analysis, the primary outcomes were suicidal ideation and all-cause discontinuation (dropouts due to any cause). Secondary outcomes were suicide attempts, and suicide deaths. Data on disease-specific symptom severity, as well as clinical or subclinical diagnostic status were collected as well. Demographic data were collected including age and sex. Information regarding details of the exercise and control therapy were collected. Discrepancies were discussed and resolved on consensus.

2.5. Quality assessment/risk of bias

The Cochrane's Risk of Bias 2 tool was used to assess quality of all studies by at least two independent authors after which consensus for each criterion on the checklist was reached by discussion (Sterne et al., 2019).

2.6. Statistical analysis

Descriptive statistics such as mean, range and measures of variance (e.g., standard deviations, 95 % CI) were presented where applicable.

All statistical analyses and meta-analyses were performed using R (R Foundation for Statistical Computing, version 4.2.1). A meta-analysis was performed to calculate an odds ratio (OR) for dichotomous variables or a pooled standardized mean difference for continuous variables. Heterogeneity was considered substantial if $p > 0.10$ based on the chi-squared (χ^2) test, and was considered high if $I^2 > 50$ %. A random-effects model was used under the assumption that there was not true homogeneity among the included studies and for a more conservative estimate of the effect size. A continuity correction of 0.5 was used for studies with one arm with a zero-cell frequency. Forest plots were used to graphically present significant findings. Funnel plots were used to graphically represent potential for publication bias, and statistics (intercept, standard error, *t*-value, *p*-value) were reported where possible.

Various subgroup analyses were performed based on diagnosis, type of exercise and control group. As there was insufficient data, we could not perform a sensitivity analysis comparing studies directly measuring suicide-related outcomes to studies reporting incidental findings.

3. Results

3.1. Study characteristics

The search identified 673 studies, and after removing one duplicate, 672 studies were screened. One hundred two full-texts were reviewed of which 85 were excluded. The references and reasons for exclusion after full-text assessment are provided. The flow of study inclusion process is reported in Fig. 1. Seventeen studies met eligibility for inclusion. The studies were published between 1997 and 2021, and most commonly originated from the United States (29 %, k = 5), Denmark (18 %, k = 3), Germany (12 %, k = 2), and Austria (12 %, k = 2). Fourteen studies (82 %) focused on clinical diagnoses while three studies (18 %) focused on subclinical diagnoses. Eleven studies (65 %) studies analyzed mental diagnoses, while six studies (35 %) analyzed physical diagnoses. Depression, variably defined, was the most commonly included condition in this review (59 %, k = 10). Aerobic exercise was the most common form of exercise to which participants were randomized (53 %, k = 9), followed by mind-body (17.6 %, k = 3) and strength training (17.6 %, k = 3). Altogether, 82 % (k = 14) of the included studies compared exercise to an inactive control while 18 % (k = 3) of the included studies compared exercise to an active control. Ten studies (58.8 %) assessed suicidal ideation directly. Further study

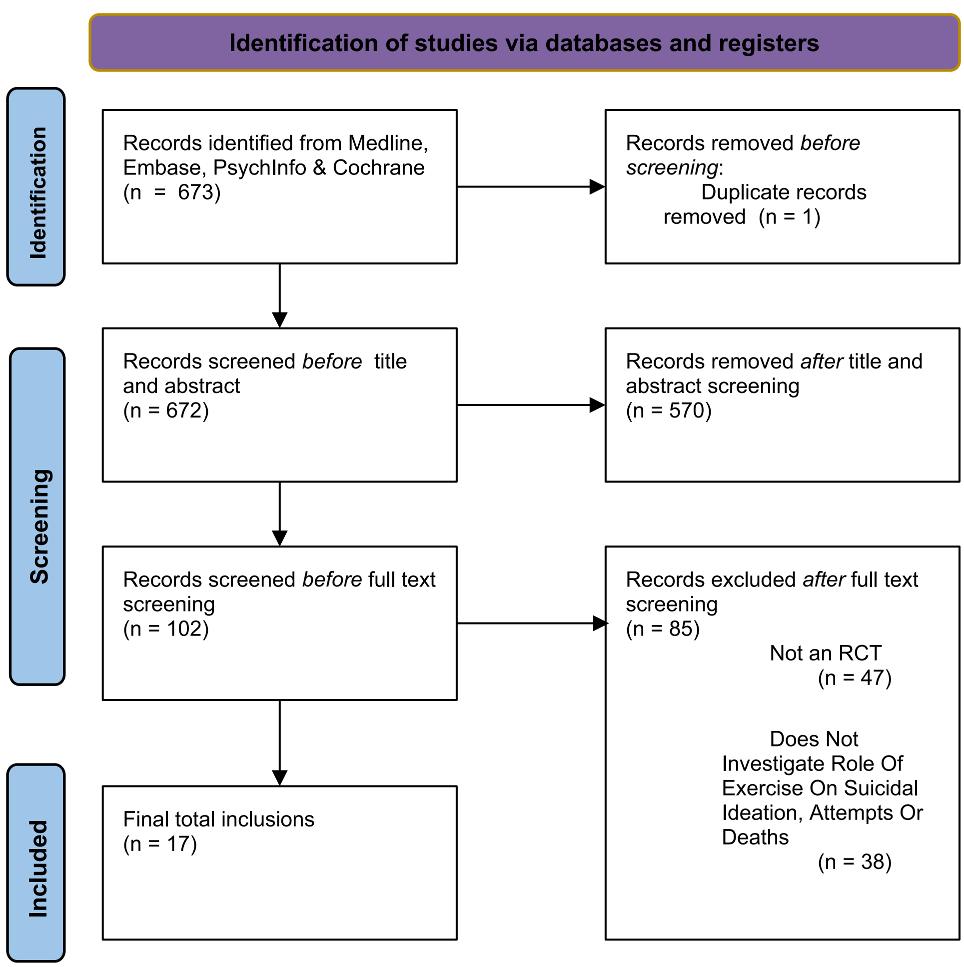

Fig. 1. PRISMA diagram.

characteristics can be found in Table 1.

3.2. Participant characteristics

A total of 1021 participants were included of whom 54 % ($n = 549$) were randomized to an exercise intervention. The mean age of the included sample was 42.7 years (SD = 13.8) and the mean follow up period was 10.0 weeks (SD = 5.2). Altogether, females represented 82 % ($n = 837$) of all participants.

3.3. Co-primary outcomes

All forest plots and corresponding funnel plots are available in Figs. 2-9 and the Supplementary Material.

3.3.1. Suicidal ideation

There was a non-significant difference in post-intervention suicidal ideation comparing exercise to all controls (SMD = -1.09, CI -3.08–0.90, $p = 0.20$, k = 5), and inactive controls (SMD = -1.28, CI -4.12–1.55, $p = 0.25$, k = 4). These results were consistent with no significant differences on incidence of suicidal ideation when comparing exercise to all controls (OR = 1.20, CI 0.36–3.95, $p = 0.69$, k = 5) and to all inactive controls (OR = 0.96, CI 0.23–4.00, $p = 0.93$, k = 4). There was no significant difference ($p = 0.60$) in suicidal ideation incidence for subgroup analyses stratifying data among participants with depression (OR = 0.92, CI 0.44–1.9, k = 2), sickle cell disease (OR = 0.32, CI 0.01–7.99, k = 1), and suicidality (OR = 3.32, CI 0.13–86.74, k = 1).

3.3.2. All-cause discontinuation

There were no significant differences in all-cause discontinuation between participants who were randomized to exercise interventions and all controls (OR = 0.85, CI 0.38–1.94, $p = 0.86$, k = 12).

All-cause discontinuation was not significantly different between participants who were randomized to exercise and inactive controls (OR = 0.81, CI 0.25–2.68, $p = 0.70$). There were non-significant differences ($p = 0.87$) when comparing participants with depression (OR = 1.26, CI 0.26–6.17, k = 6), suicidality (OR = 0.10, CI 0.10–0.10, k = 2), and Huntington Disease (OR = 0.71, CI 0.13–3.87, k = 1). Likewise, there were non-significant differences ($p = 0.20$) between participants who underwent aerobic exercise (OR = 0.95, CI 0.11–8.21, k = 6) and strength training (OR = 0.30, CI 0.00–40.43, k = 2).

All-cause discontinuation was not different between participants who were randomized to exercise and active controls (OR = 0.94, CI 0.38–2.32, $p = 0.79$, k = 3). There were non-significant differences ($p = 0.46$) when comparing participants with depression (OR = 0.85, CI 0.45–1.62, k = 2) and stress (2.29, CI 0.17–31.00, k = 1).

3.4. Secondary outcomes

3.4.1. Other suicide outcomes

Suicide attempts were found to be significantly reduced in participants who were randomized to exercise interventions as compared to inactive controls (OR = 0.23, CI 0.09–0.67, $p = 0.04$, k = 2). Suicide mortality was found to be not significantly different between participants who were randomized to exercise interventions and inactive controls (OR = 0.64, CI 0.00–54 17.93, $p = 0.70$, k = 2).

3.5. Quality assessment

Fourteen studies (82 %) were at high risk of bias while three studies (18 %) were considered to have some concerns with respect to bias. The most common reasons for higher risk of bias were deviations from intended interventions (58.8 % of included studies assessed suicidal ideation directly, k = 10) and bias in measurement of the outcomes. The risk of bias is summarized in Fig. 10. Statistics for publication bias were tabulated in Table 2**.**

4. Discussion

This systematic review synthesized 17 RCTs to investigate the role that exercise had on suicide-related outcomes in those with mental or physical illness. There was reasonable methodological homogeneity among the studies which allowed for meta-analyses of outcomes such as suicidal ideation, suicide attempts, suicide deaths, and all-cause discontinuation. While we did not find any significant findings related to our primary outcome of suicidal ideation, a secondary analysis found reduced suicide attempts with exercise among the small number of studies which measured this. Suicidal ideation is ultimately a surrogate outcome and the finding in the clinically relevant outcome of suicide attempts is therefore of interest. It should be noted that not all of the RCTs were included in the individual analyses, with only 7 studies directly measuring suicide-based outcomes, to make definitive conclusions and much more research is needed with larger trials and longer term follow up.

Despite all included studies demonstrating a decrease in measured suicidal ideation following exercise intervention, the overall sample size was modest ($n = 248$), which limited power, and there was no significant difference in suicidal ideation measured by standardized scales, which was maintained in subgroup analysis by control type or mental/physical health condition. The lack of significant effects may also be due to the follow-up period for these studies being short (8–12 weeks) and perhaps too short to observe any effects of the intervention if present. Previous research has demonstrated that regular exercise up to 12 months continued to have an increased antidepressant effect (Helgadóttir et al., 2017), which might translate into decreased suicidal ideation. Therefore, one may expect larger effect sizes based on longer duration of follow-up for exercise interventions. Moreover, most participants were randomized to exercise interventions of low intensity (Paolucci et al., 2018). A dose-response relationship exists between the intensity of exercise and overall antidepressant effect. If mediated by improvements in mood, a greater impact suicidal ideation would be expected if participants had been involved in higher intensity interventions (Paolucci et al., 2018). These findings potentially highlight the importance of both duration and intensity of exercise for reducing suicidal ideation, which should be accounted for in future RCTs.

A recent meta-analysis of cross-sectional studies by Vancamport and colleagues (2018) found that higher physical activity levels were associated with lower suicidal ideation in the general population (Vancampfort et al., 2018). It is necessary to acknowledge however that cross-sectional studies cannot discern temporal relations and are vulnerable to confounding. For instance, those who exercise regularly are more likely to adopt other health lifestyle habits, such as healthy eating and regular sleep schedules (Cobb-Clark et al., 2014). These factors have both demonstrated cross-sectional associations with reduced suicidality and could theoretically be a driver in the reduction of suicidal ideation compared to exercise itself (Goodwin and Marusic, 2008; Hwang and Choi, 2022). Interestingly, when Vancampfort and colleagues (2018) analyzed findings from exclusively interventional studies, no clear association was identified (Vancampfort et al., 2018).

There was a non-significant difference in suicidal ideation measured as a binary outcome in all controls, which was maintained in subanalysis of inactive controls. Further stratification by depression, sickle cell disease, or all-cause suicidality did not yield a significant difference. This lack of association was expected due to the high risk of bias in the measurement of this outcome. The majority of studies which reported suicidal ideation as a binary outcome only recorded this as an adverse event, and did not actively screen for suicidal ideation among participants, which likely resulted in measurement error with a presumably nondifferential misclassification. As a result, it is likely that these studies significantly underreported the incidence of suicidal ideation in both subjects randomized to exercise and control arms, biasing results in the direction of the null hypothesis. Another important consideration is that, across the literature to date, suicidal ideation is

Table 1
Study characteristics.

Title	Country	Sample size	Mean age	Condition	Exercise intervention details	Number of patients (exercise)	Control group details	Number of patients (control)
Abdollahi 2017 (Abdollahi et al., 2017)	Iran	70	49.7	Depression	5 min of flexibility exercise, 5 min of clapping hands and light movements, 20 min of walking, and 5 min of stretching and deep breathing. Completed 3 times weekly over 12 weeks.	35	CBT. Completed once a week for 12 weeks	35
Gerber 2020 (Gerber et al., 2020)	Switzerland	35	38.1	Depression	Aerobic exercise on indoor bicycles. Target heart rate was 60 to 75 % of maximal heart rate. Completed 3 times per week for 6 weeks	14	Coordination and stretching activities using a medium strength Theraband, gymnastics ball, and juggling balls. Completed 3 times per week for 6 weeks	11
Haussleiter 2020 (Haussleiter et al., 2020)	Germany	111	45.1	Depression	Endurance training with workout music for 50 min. Completed 3 times per week for 6 weeks	40	Patients encouraged by exercise therapists to perform physical activity. Completed 3 times per week for 6 weeks	36
Krogh 2009 (Krogh et al., 2009)	Denmark	165	38.9	Depression	Aerobic 10 different aerobic exercises using large muscle groups. Machines were used for cycling, running, stepping, abdominal exercises, and rowing. Additional exercises were sliding movements on small carpets, trampoline, step bench, jump rope, and Ski Fitter. During the first 8 sessions, each exercise was done twice for 2 min with a 2-min rest at an intensity level of 70 % maximal heart rate. Strength 12 repetitions of 50 % of repetition maximum (RM) 2 or 3 times per exercise; as patients progressed the number of repetitions were reduced to 10 and 8 with an increase of RM to 75 %. Exercise machines were used which included: leg extension, leg press, total abdominal, lower back, chest press, and vertical traction. Free weights and sandbags were used for exercising the calf muscles, the arm abductors, the triceps, and hip abductors. Completed 2 times per week for 16 weeks.	110	Relaxation on mattresses or bobath balls or back massage using a ball stick ball, followed by light balance activities for 10 to 20 min and relaxation exercises with alternating muscle contraction while lying down for 20 to 30 min. Completed 2 times per week for 16 weeks.	55
Krogh 2012 (Krogh et al., 2012)	Denmark	115	41.6	Depression	Aerobic training with 10 min of general low-intensity warm-up, 30 min on stationary ergometer, then 5 min low-intensity cool down period. Minutes of throwing balls. Completed 3 times per week for 12 weeks.	56	Stretching exercise group with 10 min on stationary bike, then 20 min of stretching, and 15 min of throwing balls. Completed 3 times per week for 12 weeks.	59
Martiny 2013 (Martiny et al., 2013)	Denmark	75	47.7	Depression	30 min of daily exercise with a physiotherapist. Completed 7 times per week for 1 week.	38	Wake therapy where patients were instructed to stay up the entire wake nights (Monday, Wednesday, Friday) and sleep the following day until 8 pm. Completed 3 times per week for 1 week.	37
Moody 2017 (Moody et al., 2017)	USA	70	14.5	Sickle Cell Disease	Daily 30 min yoga session with nature sounds played by yoga instructor for 1 week Completed 7 times per week for 1 week.	35	Daily 30 min session where yoga instructor played nature sounds for 1 week Completed 7 times per week for 1 week.	35
Neunhauserer 2013 (	Austria	20	43.9	Suicidal	Hikes of 2 to 2.5 h in duration. Completed 2 to 3 times per week for 9 weeks.	20	No hiking	20

(continued on next page)

Table 1 (*continued*)

Title	Country	Sample size	Mean age	Condition	Exercise intervention details	Number of patients (exercise)	Control group details	Number of patients (control)
Neunhäuserer et al., 2013)								
Noh 2020 (Noh et al., 2020)	South Korea	40	58.8	Menopause	30 min of muscle strength, stretching, and aerobic exercise; in context of Korean traditional mind-body principles	21	No exercise	19
Nyer 2018 (Nyer et al., 2018)	USA	32	36.6	Depression	90 min of Iyengar Yoga, plus four 30 min homework sessions Completed three times per week.	15	90 min of Iyengar Yoga, plus three 30 min homework sessions Completed two times per week.	15
Quin 2016 (Quinn et al., 2016)	USA	32	55.3	Huntington's Disease	50 min session of strength, aerobic and stretching. Completed 1 time per week for 12 weeks	17	No exercise	15
Singh 1997 (Singh et al., 1997)	USA	32	71.3	Depression	45 min session of high intensity progressive resistance training for 3 weeks. Resistance was set at 80 % of the one repetition maximum. Load was increased every week. Subjects performed 3 sets of 8 repetitions on each machine. Completed 3 times per week for 10 weeks.	17	Interactive health education program with lectures and discussions	15
Singh 2001 (Singh et al., 2001)	USA	32	71.0	Depression	45 min session of high intensity progressive resistance training for 3 weeks. Resistance was set at 80 % of the one repetition maximum. Load was increased every week. Subjects performed 3 sets of 8 repetitions on each machine. Completed 3 times per week for 10 weeks.	15	Health education lectures for 10 weeks	14
Sturm 2012 (Sturm et al., 2012)	Austria	20	43.1	Suicidal	2–3 h of hiking per week for 9 weeks and then no hiking at all for 9 weeks (can start either or, no washout period)	20	Started with no hiking	20
Sun 2017 (Sun et al., 2017)	Taiwan	87	54.1	Breast cancer	90–120 min of walking per week for 12 weeks	44	No exercise	43
Taylor 2020 (Taylor et al., 2020)	Australia	21	30.0	Stress	0.75–1 h of interval and/or boxfit training per week	11	1 h of trauma-informed hatha yoga per week	10
Wunram 2021 (Wunram et al., 2021)	Germany	64	15.9	Depression	30 min of ergometer cycling. Followed seven step interval scheme with steady cadence of 60–70 rpm. Completed 3–5 times per week for 6 weeks.	41	No exercise	23

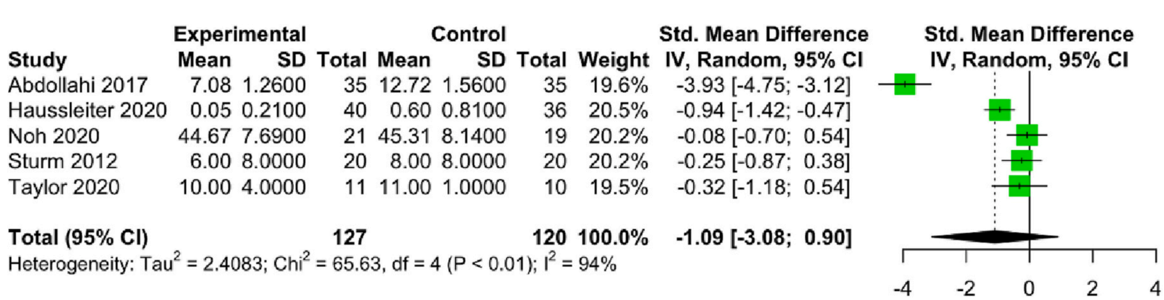

Fig. 2. Forest plot – suicidal ideation: post-intervention.

often measured only as a secondary outcome, rather than acting as the primary target of exercise interventions. Alongside this, low levels of suicidal ideation among the sample at baseline, and insensitive measurements of these constructs as secondary outcomes, could also contribute to a lack of significant effects. Therefore, the positive signals indicated from exercise interventions for suicidal behaviors/ideation in this study suggest there is a need for larger-scale, exercise intervention studies specifically designed to target this outcome in future studies among populations at elevated risk of suicidality.

We found that participants randomized to exercise had significantly less suicide attempts compared to inactive controls. This finding should be interpreted with caution, as it was based on the synthesis of 2 studies with a minimal amount of data points. However, it is in line with previous research by Grasdalsmon and colleagues (2020) who identified a dose-response relationship between exercise and suicide attempts (Grasdalsmoen et al., 2020). Indeed, behavioral lifestyle interventions

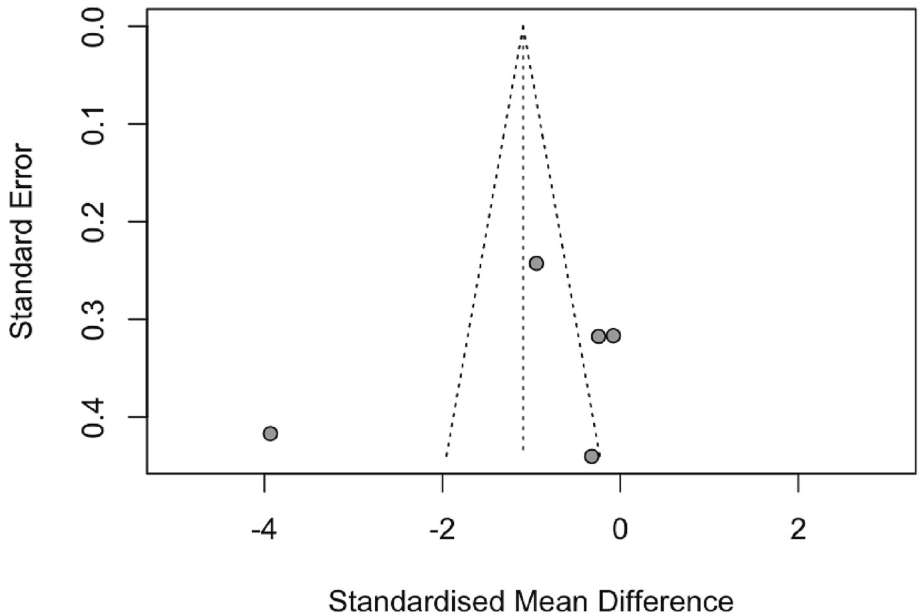

Fig. 3. Funnel plot – suicidal ideation: post-intervention.

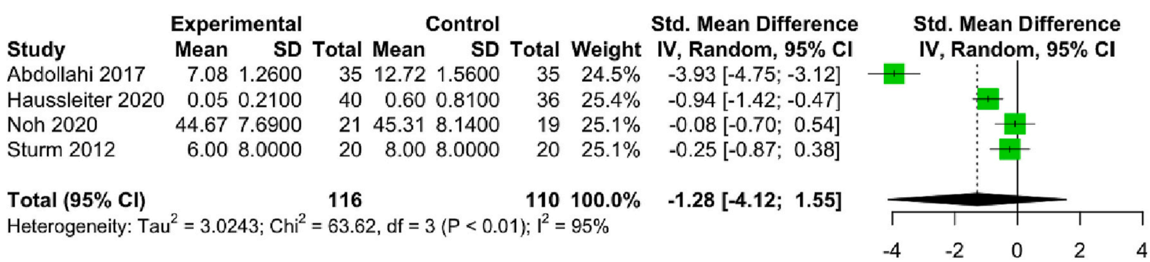

Fig. 4. Forest plot – suicidal ideation: post-intervention comparing exercise to inactive controls.

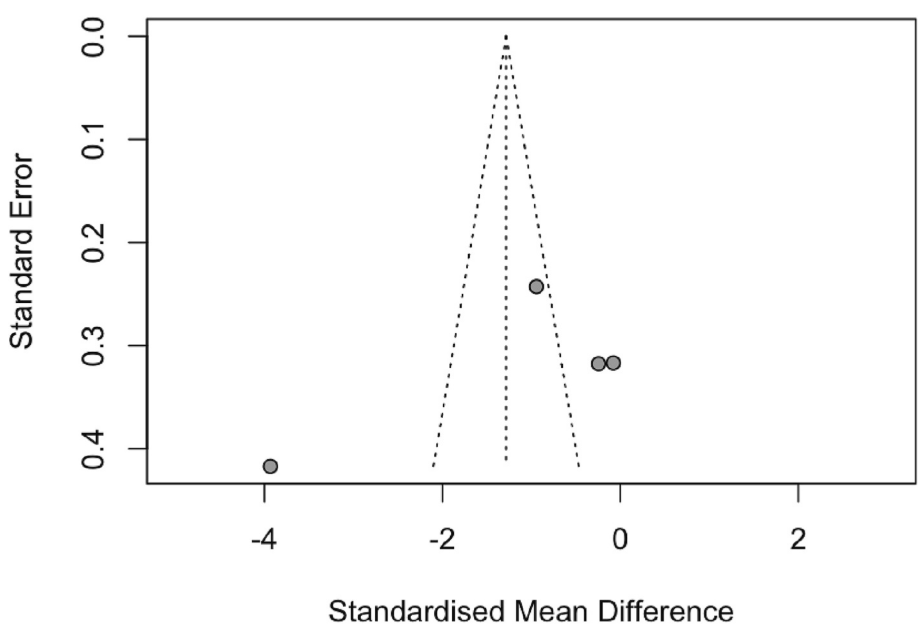

Fig. 5. Funnel plot – suicidal ideation: post-intervention comparing exercise to inactive controls.

(e.g., weight loss) have been hypothesized to reduce suicide risk by better controlling metabolic factors (e.g., glucose, cholesterol) implicated in the molecular pathogenesis of suicide, especially among patients taking antipsychotics who inherently are at higher risk (Berardelli et al., 2018; Pompili, 2012). Likewise, our observation may be explained by the ideation-to-action framework suggested by Klonsky

Study	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio MH, Random, 95% CI
Martiny 2013	1	37	1	36	23.9%	0.97 [0.06; 16.16]
Moody 2017	0	35	1	34	18.0%	0.31 [0.01; 7.99]
Neunhauserer 2013	1	19	0	20	17.7%	3.32 [0.13; 86.75]
Nyer 2018	1	14	0	15	17.5%	3.44 [0.13; 91.79]
Singh 1997	1	16	1	14	22.9%	0.87 [0.05; 15.28]
Total (95% CI)		**121**		**119**	**100.0%**	**1.20 [0.36; 3.95]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.50$, df = 4 (P = 0.83); $I^2 = 0\%$

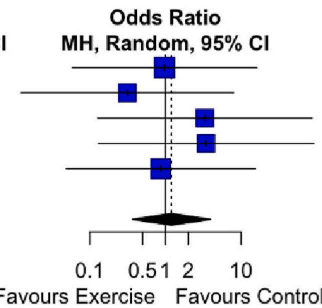

Fig. 6. Forest plot – suicidal ideation: comparing exercise to all controls.

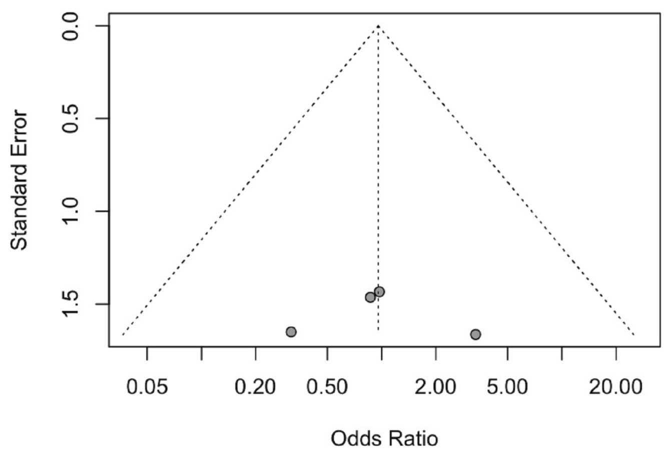

Fig. 7. Funnel plot – suicidal ideation: comparing exercise to inactive controls.

and May (2015) who argue that the development of suicidal ideation and the progression to suicide attempts are distinct processes with different influential factors (Klonsky and May, 2015). With this in mind, Javelle et al. (2022) determined that increased levels of self-reported exercise significantly reduced emotional-impulsivity (Javelle et al., 2022). As it has been demonstrated that most suicide attempts are characterized by impulsivity and low-lethality, we hypothesize that regular exercise serves as a protective factor against suicide attempts (Lopez-Castroman et al., 2016). This may also explain the non-significant difference in suicide mortality for participants randomized to exercise versus inactive controls, as exercise may more heavily influence impulsive low-lethality attempts rather than well-planned high lethality attempts. However, this finding is largely in part due to the lack of suicide events which occurred during the RCTs. Interestingly, a nationwide population based cohort study in South Korea by Lee and colleagues found that those who completed suicide were less likely to have reported a history of regular exercise (Lee et al., 2018). From this, it is evident that large and long-term RCTs are required to have sufficient power to detect such a rare event.

There was a non-significant difference in all-cause discontinuation between participants exercising and controls. This was maintained in sub-analyses by control type or mental/physical health condition, and is in line with previous research finding that exercise is well tolerated in

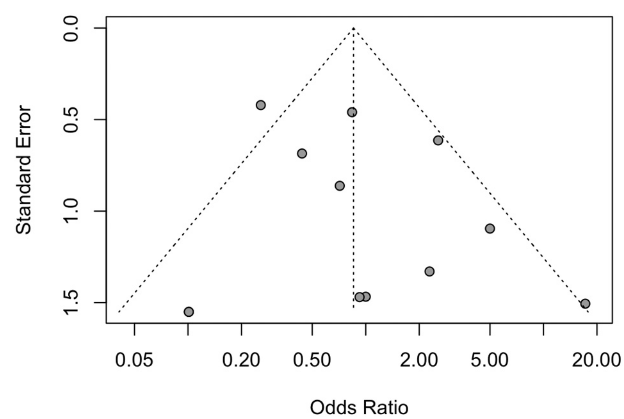

Fig. 9. Funnel plot – all cause discontinuation: comparing exercise to all controls.

Study	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio MH, Random, 95% CI
Abdollahi 2017	10	25	6	29	12.6%	2.56 [0.77; 8.51]
Gerber 2020	6	8	3	8	7.2%	5.00 [0.58; 42.80]
Haussleiter 2020	20	20	15	21	4.7%	17.19 [0.90; 328.87]
Krogh 2009	18	92	18	37	15.4%	0.26 [0.11; 0.59]
Krogh 2012	13	43	15	44	14.8%	0.84 [0.34; 2.06]
Martiny 2013	4	34	7	30	11.6%	0.44 [0.11; 1.68]
Neunhauserer 2013	0	20	3	17	4.5%	0.10 [0.00; 2.11]
Nyer 2018	1	14	1	14	4.8%	1.00 [0.06; 17.75]
Quin 2017	5	12	5	10	9.5%	0.71 [0.13; 3.87]
Singh 2001	1	14	1	13	4.8%	0.92 [0.05; 16.46]
Sturm 2012	0	20	3	17	4.5%	0.10 [0.00; 2.11]
Taylor 2020	2	9	1	9	5.6%	2.29 [0.17; 30.96]
Total (95% CI)		**311**		**249**	**100.0%**	**0.85 [0.38; 1.94]**

Heterogeneity: $Tau^2 = 0.7305$; $Chi^2 = 22.49$, df = 11 (P = 0.02); $I^2 = 51\%$

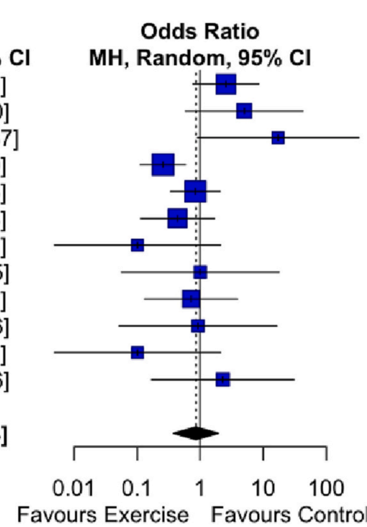

Fig. 8. Forest plot – all cause discontinuation: comparing exercise to all controls.

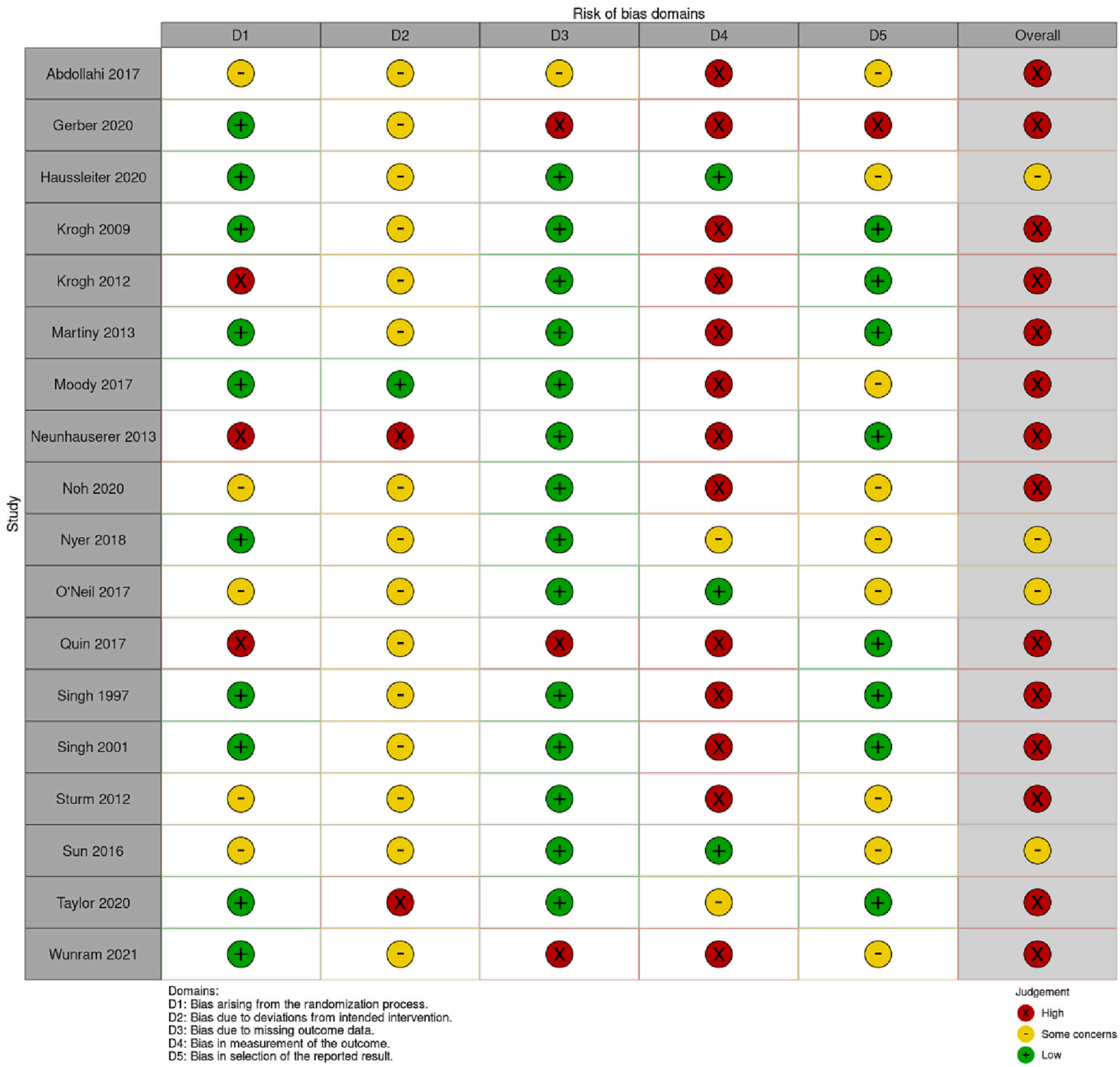

Fig. 10. Risk assessment – risk of bias domains.

those with mental or physical health conditions, with similar dropout rates between the exercise and control arms (Pilutti et al., 2014; Vancampfort et al., 2018). It is crucial to keep this in mind since people with comorbidities are often perceived not to be adherent to exercise regimes due to the nature of their illness (Searle et al., 2011). In turn, this has led to primary care providers under-prescribing exercise, resulting in further deterioration of patients' mental and physical health (Robertson et al., 2011). Therefore, we believe that the mental and physical benefits of exercise significantly outweigh the slight increased chance of non-serious adverse events (Heyman et al., 2012). As a result, we recommend that providers do not have apprehension about prescribing exercise to patients with mental or physical illness for concerns of adherence or safety.

4.1. Strengths

Our study has numerous strengths. Firstly, an a priori protocol was published, which minimizes the risk for reporting bias. Our systematic review was also conducted across various databases with a broad search strategy, with all screening done in duplicate. Our search strategy minimized publication bias by not excluding gray literature, which was graphically demonstrated by our funnel plots. We also only focused on RCTs, which is the highest hierarchy of evidence available and allows us to establish temporality between the exposure and outcome as well as address confounding through randomization. Furthermore, with respect to our included studies' controls, as adjuvant procedures were similar between both groups, thus designed to assess the impact of exercise. Finally, given that a large portion of the exercise literature has been published within the last 5 years, this systematic review benefits from having the most up-to-date information allowing for a more robust

Table 2
Summary of meta-analyses.

Analysis	SMD (CI)	OR (CI)	Heterogeneity	Publication Bias
Suicidal ideation				
Post-Intervention, Suicidal Ideation Scales	-1.09 (−3.08–0.90)	N/A	$\tau^2 = 2.08$ $\tau = 1.55$ $I^2 = 93.9$ %	N/A
Post-Intervention, Suicidal Ideation Scales: Exercise v. Inactive Controls	-1.28 (−4.12–1.55)	N/A	$\tau^2 = 3.02$ $\tau = 1.74$ $I^2 = 95.3$ %	N/A
Exercise v. All Controls	N/A	1.20 (0.36–3.95)	$\tau^2 = 0$ $\tau = 0$ $I^2 = 0$ %	−4.08 (6.77) $t = 0.63$ $p = 0.57$
Exercise v. Inactive Controls	N/A	0.96 (0.23–4.00)	$\tau^2 = 0$ $\tau = 0$ $I^2 = 0$ %	−1.17 (8.12) $t = 0.14$ $p = 0.90$
Exercise v. Inactive Controls: Depression	N/A	0.92 (0.44–1.91)	$\tau^2 = 0$ $\tau = 0$ $I^2 = 0$ %	N/A
Exercise v. Inactive Controls: Sickle Cell Disease	N/A	0.31 (0.01–7.99)	N/A	N/A
Exercise v. Inactive Controls: Suicidal	N/A	3.32 (0.13–86.75)	N/A	N/A
Suicide attempts				
Exercise v. All Controls	N/A	0.23 (0.09–0.67)*	$\tau^2 = 0$ $\tau = 0$ $I^2 = 0$ %	N/A
Suicide mortality				
Exercise v. All Controls	N/A	0.64 (0.00–54,117.93)	$\tau^2 = 0$ $\tau = 0$ $I^2 = 0$ %	N/A
All cause discontinuation				
Exercise v. All Controls	N/A	0.85 (0.38–1.94)	$\tau^2 = 0.73$ $\tau = 0.86$ $I^2 = 51.1$ %	−0.93 (0.70) $t = 0.94$ $p = 0.37$
Exercise v. Inactive Controls	N/A	0.81 (0.25–2.68)	$\tau^2 = 1.36$ $\tau = 1.16$ $I^2 = 62.4$ %	−1.19 (0.99) $t = 0.82$ $p = 0.44$
Exercise v. Inactive Controls: Depression	N/A	6.13 (0.25–6.17)	$\tau^2 = 1.45$ $\tau = 1.20$ $I^2 = 72.8$ %	N/A
Exercise v. Inactive Controls: Suicidal	N/A	0.10 (0.10–0.10)	$\tau^2 = 0$ $\tau = 0$ $I^2 = 0$ %	N/A
Exercise v. Inactive Controls: Huntington's Disease	N/A	0.71 (0.13–3.87)	N/A	N/A
Exercise v. Inactive Controls: Aerobic	N/A	0.95 (0.11–8.20)	$\tau^2 = 2.93$ $\tau = 1.71$ $I^2 = 74.1$ %	N/A
Exercise v. Inactive Controls: Strength	N/A	20.29 (0.00–40.43)	$\tau^2 = 0$ $\tau = 0$ $I^2 = 0$ %	N/A
Exercise v. Active Controls	N/A	0.94 (0.38–2.32)	$\tau^2 = 0$ $\tau = 0$ $I^2 = 0$ %	−0.46 (0.39) $t = 1.18$ $p = 0.45$
Exercise v. Active Controls: Depression	N/A	0.85 (0.45–1.62)	$\tau^2 = 0$ $\tau = 0$ $I^2 = 0$ %	N/A
Exercise v. Active Controls: Stress	N/A	2.29 (0.17–31.00)	N/A	N/A

Abbreviations: SMD – Standardized Mean Difference; OR – Odds Ratio; CI – Confidence Intervals; N/A – Not Applicable.
* $p < 0.05$.

synthesis.

4.2. Limitations

Despite this, there are some limitations which must be considered. Primarily, the meta-analyses interpretability is limited by statistical heterogeneity and modest number of participants and trials. Further, subgroup analysis by exercise type, duration, frequency, or intensity was not possible due to the small number of studies within each group, which limits our ability to make recommendations based on effectiveness of exercise modality. Moreover, there was a predominance of female participants (82 %), which may limit the generalizability of our findings. We also found that the majority of included studies were of high risk of bias mostly due to bias in the measurement of suicide outcomes. This primarily arose due to suicide-related outcomes not being recorded on a standardized scale and as an efficacy outcome, but instead as adverse events. As a result of this indirect mode of measurement, there were very few recorded suicide-related outcomes (ideation, attempts, deaths), which would require a much larger sample size to observe enough events for adequate power. Likewise, with respect to suicide attempts, there may be between-study heterogeneity in its definition which certainly adds a source of bias that is difficult to account for without standardized criteria. Finally, we mixed different populations in our analyses, limiting the inference in specific populations. However, we believe this approach reflects the inclusive concept of a pragmatic RCT which represents the heterogeneous clinical and subclinical population that is routinely seen in primary and secondary care clinical settings. We also conducted subgroup analyses in specific diagnostic groups.

4.3. Future directions

This systematic review was a crucial first step to understand the influence that exercise may have on suicide in people with mental or physical illness. In order to achieve more robust and complete evidence, higher quality RCTs investigating this topic are needed. Particularly, these RCTs must focus on larger sample sizes, better blinding practices, longer follow-up times and direct, systematic measurements of suicide-related outcomes. Lastly, the majority of studies in this review focused solely on depression, therefore future studies must aim to explore the effect of exercise in a variety of mental and physical health conditions in order to get a more complete view.

5. Conclusion

Overall, our meta-analysis did not find a significant decrease in suicidal ideation or mortality between exercise and control conditions – perhaps due to limited number and sample size of existing studies, or the secondary nature of suicide outcomes in the studies analyzed. However, exercise did significantly decrease suicide attempts (in the small number of studies measuring this) among those suffering from mental or physical illness. There was no significant difference in discontinuation between participants exercising and controls. This demonstrates that adherence for those with mental or physical illness are not as infeasible as often assumed, which should eliminate physicians' hesitation to prescribe exercise to these groups. Future RCTs examining a breadth of physical and mental health conditions with larger sample sizes, better blinding practices, longer follow-up, and direct measurements of suicide-related outcomes are necessary to validate or confute these preliminary findings.

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Conflict of interest

MS received honoraria/has been a consultant for Angelini, Lundbeck, Otsuka. NF, AG, and JGF have no conflicts of interest to declare. JF is supported by a University of Manchester Presidential Fellowship (P123958) and a UK Research and Innovation Future Leaders Fellowship (MR/T021780/1) and has received honoraria / consultancy fees from Atheneum, Informa, Gillian Kenny Associates, Big Health, Nutritional Medicine Institute, ParachuteBH, Richmond Foundation and Nirakara, independent of this work. Brendon Stubbs holds an NIHR Advanced fellowship (NIHR301206, 2021-2026). Brendon is local PI lead on exercise intervention trials unrelated to the paper 1) NIHR: Supporting Physical and Activity through Co-production in people with Severe Mental Illness (SPACES,2021-2027); 2) Mechanisms underlying the role of gut-microbiota in exercise-induced changes in cognitive function in middle-age, Reta Lila Weston Trust For Medical Research (2021-2024). Brendon's on the Editorial Mental Health and Physical Activity. Brendon has received honorarium from a co-edited a book on exercise and mental illness, and independent and unrelated advisory work from ASICS, & ParachuteBH and FitXR. The views expressed are those of the author(s) and not necessarily those of mentioned above, the NHS, the NIHR, the Department of Health and Social Care.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.02.071.

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