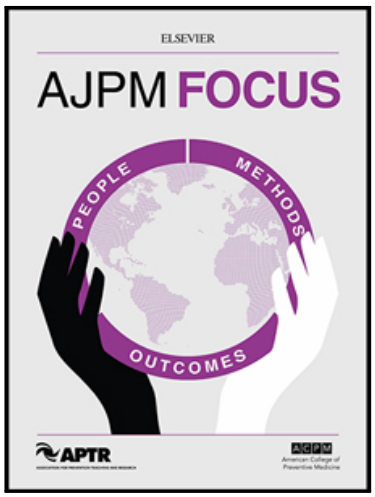

Physical activity and depression and anxiety disorders: a systematic review of reviews and assessment of causality

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Physical activity and depression and anxiety disorders: a systematic review of reviews and assessment of causality

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CONFLICT OF INTEREST STATEMENT

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Highlights

- We did a systematic review of reviews and assessment of causality.
- Most evidence was from observational studies.
- Physical activity is inversely related to incident depression and anxiety.
- Depression and anxiety are probably causally related to physical inactivity.

Graphical Abstract

ABSTRACT

Introduction

Globally, depressive and anxiety disorders are the leading contributors to mental ill health. Physical activity reduces symptoms of depression and anxiety and has been proposed as an adjunct treatment therapy for depression and anxiety. Prospective studies suggest that physical activity may reduce the incidence of depression and anxiety. We conducted a systematic review of reviews with the aim to provide a comprehensive overview of available epidemiological evidence on the strength of the association between physical activity and incident cases of depression, anxiety, and to assess the likelihood of these associations being causal.

Methods

We searched Embase and PubMed databases for systematic reviews published between 1 January 2000 to 19 March 2020 that reported findings on the strength of association between

physical activity and incidence of depression and anxiety. We updated this search to 15 October 2022. Two reviewers independently assessed the methodological quality of the included reviews using the Assessment of Multiple Systematic Reviews (AMSTAR) rating scale. We applied a modified version of GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) guidelines for our synthesis of results. We used the Bradford Hill criteria to assess the likelihood of associations being causal.

Results

The initial search yielded 770 articles, of which four remained for data extraction. Two of the included reviews were scored as high quality and two as low quality. From the two included reviews that reported pooled estimates, people with high physical activity levels were found to have a decreased risk of incident depression (adjusted relative risk 0.83, 95% confidence interval [CI]= 0.76, 0.90) and reduced odds of developing anxiety (adjusted odds ratio 0.74,95% CI = 0.62, 0.88]) when compared with those with low physical activity levels. We assessed physical activity to be probably causally related to both depression and anxiety.

Discussion

Our evidence is drawn from systematic reviews of observational data. Further high-quality studies, such as randomised control trials, would help strengthen the evidence base of the associations between physical activity and depression and anxiety. Nonetheless, our findings provide empirical support for the consideration of physical activity in strategies for the prevention of mental ill health.

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Keywords: Physical activity, anxiety, depression, mental health, risk factor.

INTRODUCTION

Globally, in 2019, mental disorders were the seventh leading cause of disability attributing to 970 million prevalent cases; depressive and anxiety disorders being the leading contributors to this burden.[1] It is estimated that lost productivity as a result of anxiety and depression, costs the global economy US$ 1 trillion each year.[2] People experiencing severe mental health conditions also die up to two decades prematurely due to preventable physical conditions.[3,4] The COVID-19 pandemic has probably made matters worse.[5,6]

Staying active regularly has been identified as essential for good mental health.[7,8] Specifically, physical activity reduces symptoms of depression and anxiety,[9,10] and has been proposed as an adjunct treatment therapy for depression and anxiety.[11-14] From a preventive approach, prospective studies suggest that physical activity may reduce the incidence of depression and anxiety.[15,16] A comprehensive review of this body of literature could help determine the best estimates of the measure of strength of the associations between physical activity and incidence of depression and anxiety. Previous systematic review of reviews and meta-analyse have focused on the topic of physical activity and mental health.[9,17,18] One review investigated the relationship between physical activity and multiple physical or mental health outcome in adults aged ≥60 years,[17] but the authours only included one study that focused on our outcomes (incident depression only).[19] A second study identified and summarized findings from systematic reviews examining physical activity and depression, anxiety, and self-esteem outcomes in children and youth.[9] However, they did not present measures of the strength of the associations. Moreover, all primary studies that they included examined physical activity and reduction of symptoms of existing depression and anxiety. The third is an update of a previous review where Biddle and colleagues present evidence on physical activity and mental health and assess the extent to which associations can be considered causal.[18] Their review is restricted to children and adolescents

and the investigation is not specific to incident cases of depression and anxiety as it includes reduction of symptoms of existing symptoms. Our study focuses on a comprehensive overview of the measures of strength of the associations between physical activity and incident cases of depression and anxiety across all ages and assesses the likelihood of these associations being causal. If the association between physical activity and depression and anxiety is confirmed and judged to be causal, this would support the adoption of physical activity in strategies for the prevention of mental ill health globally. Additionally, estimates of the strength of these associations can be used in cost effectiveness studies that model the impact of measures that increase physical activity on mental health outcomes.

Globally, it is estimated that 27.5 % of adults do not meet the World Health Organization (WHO) physical activity guidelines,[20,21] and people living in socioeconomically disadvantaged communities tend to be less active.[22,23] Combined with the large burden of mental ill health, this implies that even a modest effect of physical activity on depression and anxiety could result in a significant benefit to health and health equity from interventions that improve levels of physical activity.

This study was part of a broader project commissioned by the New South Wales (NSW) Ministry of Health, Australia, to value the health benefits of active transport. We developed the NSW Active Transport Health model and sought to include all relevant health outcomes that have sufficiently strong epidemiological evidence of an association with active transport. Against this background, we conducted this systematic review of reviews with the aim to provide a comprehensive overview of the available epidemiological evidence on the strength of the association between incident cases of depression, anxiety, and physical activity, to assess the likelihood of these associations being causal, and if justified, to derive estimates that can be used in studies estimating the health benefits of physical activity and active transport.

METHODS

Systematic review

Our study protocol took a two-step approach: first, a systematic review of reviews to establish the available epidemiological evidence on the strength of the association between physical activity and incident cases of depression, anxiety, and second, if an association was found, an assessment of the likelihood of these associations being causal. (Appendix Figure 1). The protocol was not submitted for peer review registration. However, it was prepared prior to carrying out the systematic review of reviews.

Search Strategy and inclusion criteria

We carried out our search in Embase and PubMed, two leading health and social science databases. The search terms covered the two concept areas physical activity/ active transport and mental health problems (Table 1). The search strategy was informed by guidelines for systematic reviews.[24] We prepared the review protocol according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols (PRISMA-P) 2015 statement.[25] The search strategy followed an iterative process. It was developed in consultation with a research librarian and tested and modified in PubMed and Embase. The medical subject heading search (MeSH) terminology in PubMed was used to inform the selection of search terms. We also reviewed reference lists from included reviews for suitable reviews that met the inclusion criteria.

We selected the reviews based on predefined inclusion and exclusion criteria agreed upon by four reviewers (MNW, HM, FH, JLV) (Table 2).

Data management

The identified studies were imported to EndNote X9 software. We removed the duplicate records. After the study selection process, the full text documents of reviews meeting the inclusion criteria were retrieved and saved into EndNote.

Screening

MNW ran the search and identified records from PubMed and Embase databases. HM ran the same search for confirmation. MNW screened the titles and abstracts of identified reviews based on the inclusion and exclusion criteria (Table 1). This screening was checked by two reviewers (HM, JLV). Two authors (MNW, HM) then screened the full texts of reviews that met the inclusion criteria after screening of title and abstract. The final list of reviews was discussed and agreed upon by all authors. The reasons for exclusion of reviews after full text review were documented.

Data extraction

Four reviewers (MNW, HM, FH, JLV) achieved consensus on which data to extract from the included reviews. One reviewer (MNW) extracted data from the full texts. Two other reviewers (HM and JLV) cross-checked the data extraction variables. The main areas of data extraction from each included review are shown in Appendix Table 1.

Data Synthesis

We carried out a narrative synthesis of the evidence and report our systematic review of reviews in adherence with the Preferred Reporting Items for Overviews of Reviews (PRIOR) guideline.[26] In our initial protocol, a modified version of GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) guidelines[27] was used for reporting but this was updated to PRIOR. We graded the evidence to support a judgement of a causal relationship using the World Cancer Research Fund grading system[28] that is informed by the Bradford Hill criteria.[27,29] This criteria has been used elsewhere to assess for causal associations between

physical activity and mental health in children and adults[18] and in the Global Burden of Disease studies.[30] We adopted grades of 'convincing (strong)', 'probable', 'possible (suggestive)' and 'insufficient evidence' (Appendix Table 2). Two reviewers (MNW, FH) independently assessed the methodological quality of the included systematic reviews using the Assessment of Multiple Systematic Reviews (AMSTAR) rating scale.[31] Differences were resolved through discussion. Ethics approval was not required for the systematic review of reviews.

Updated search

The updated search was run on 15 October 2022 and the identified records were saved onto EndNote X9 software. These records were then imported to Covidence software[32] where duplicates were removed, and the screening process was carried out by MNW. This was checked and discussed with JLV.

RESULTS

Study selection

We identified 770 articles in the initial database search (Embase, 418 and PubMed, 352 records). (See Figure 1 for the PRISMA[33] flow diagram and Appendix Table 3 for the search algorithm). A total of 589 records remained after removing duplicates. After screening of title and abstract, 578 records were excluded and 11 remained for full text analysis. A further seven studies were excluded with reason after full text screening (Appendix Table 4), leaving a total of four studies for data extraction.[19,34-36]

The results from the updated 15 October 2022 search are not included in our initial overview. We report the results separately and explain this at the end of the results section and in discussion.

Study characteristics

We provide details of the characteristics of included studies in Table 3. In summary, three included studies conducted systematic reviews with meta-analyses[19,35,36] and one conducted a systematic review.[34] All included studies reported both male and female participants. All four included evidence from prospective cohort studies only and almost all the primary cohort studies were from high income countries. All included reviews reported primary evidence for adults and children but two studies did not provide specific details on age.[19,36] Apart from one review that did not report participant numbers,[34] the included reviews covered large samples (ranging from 80,000 to 266,939).[19,35,36] Follow up time for primary studies in one review ranged from 1 to 27 years[34] and the other three reported average follow up time ranging from 3.5 to 7.4 years.[19,35,36] Nearly all primary studies included in the four reviews used self-reported physical activity measures. As indicated in Table 3, the four included reviews reported a variety of measures used to assess the outcomes, depression and anxiety. We assessed the included primary studies in each of the four reviews for the degree of overlap and report our findings in Table 4.

Methodological quality of the included systematic reviews

Using AMSTAR criteria,[31] we scored the methodological quality for two of the included reviews as high [19,36] and two as low [34,35] (Table 3). The independent assessment results from the two reviewers are presented in Appendix Table 5.

The association between physical activity and depression

Mammen and Faulkner [34] included prospective, longitudinal design articles examining relationships between physical activity and depression with a minimum of one year follow up. They included only primary studies that excluded individuals with depression at baseline. They found a significant inverse relationship between baseline physical activity and depression at follow up in 25 of the 30 primary studies included in their review.[34] For instance, compared to

no physical activity, engaging in physical activity for up to 150 minutes/week was associated with 8%–63% decreased risk of future depression (n=3 studies) while engaging in >150 minutes/week was associated with 19%–27% decreased risk of future depression (n=3 studies). Most primary studies that found a protective role were rated of high or modest methodologic quality. The use of inconsistent self-reported measures of physical activity between primary studies prevented Mammen and Faulkner [34] from examining the dose-response relationships between physical activity and depression. However, they presented a narrative overview of findings from seven primary studies that reported a dose-response relationships of which five were of high quality. For instance, their findings show that one high-quality primary study found that as little as 10–29 minutes of daily physical activity was preventive in the onset of depression (RR=0.90).[34] Further, higher levels of daily physical activity were associated with further decreases in the risk of developing depression (60–90 minutes/day, RR=0.84; >90 minutes/day, RR=0.80).[34] The review authors considered this as promising evidence that shows any level of physical activity, including low levels can prevent future depression. In addition, the authors report that four primary studies concluded that the protective effect of physical activity on depression is specific to women and girls. Out of their 30 included primary studies, five revealed null findings for the association between physical activity and depression. Out of these five, only one was considered high quality.[34] They attributed the low and modest scores to the failure to control for significant covariates that have been linked with depression, such as body mass and socio-economic status. They discussed that in four of these studies, the lack of precision of estimating physical activity dosage might have explained the null findings. The authors discuss that grey research literature and studies not English were excluded thus finding may be as a result of publication bias.[34]

Our second included review was a meta-analysis of prospective cohort studies.[19] Authors found a significant inverse relationship between baseline physical activity and depression at follow up. They included a total of 49 primary studies with an average follow up time of 7.4 years. Only primary studies that had at least one year of follow-up were included. Their pooled estimates showed that people with high levels of physical activity had decreased risks of developing depression compared with people with low levels of physical activity (adjusted relative risk=0.83, 95% CI=0.76, 0.90, I^2=0.00 and adjusted odds ratio=0.83, 95% CI=0.79, 0.88, I^2=0.00). The protective physical activity effect was seen for people of all ages (youths, working-age adults, elderly persons). Their findings suggested that the potential protective association of physical activity is similar for men and women.[19] In their subgroup analyses, they demonstrated that the protective effects of physical activity were found in primary studies in which the different aspects of physical activity (intensity, frequency, volume) were measured individually or when two or more aspects (metabolic equivalents/composite) were considered. Correction for publication bias slightly reduced the associations they reported, but the association remained significant (adjusted odds ratio=0.85; 95% CI=0.81, 0.89; adjusted relative risk=0.86; 95% CI=0.78, 0.96).

In all subgroup analyses, Schuch, Vancampfort [19] found protective effects for adults and older persons. But they reported mixed findings in their subgroup analyses of primary studies specific for children/adolescents (adjusted OR=0.91, 95% CI=0.84, 0.99, I^2=0.00 [3 cohorts], crude OR=0.50, 95% CI=0.21, 1.20, I^2=0.00 [2 cohorts] and crude RR/HR=0.54, 95% CI=0.25, 1.15, I^2=0.00 [2 cohorts]). The authors explored heterogeneity using subgroup and meta-regression analysis. They found that none of the investigated moderators significantly explained the variance of the effects of physical activity on depression onset in any of their analyses.

In their review, the definitions of low or high physical activity, as well as the aspects of physical activity that were captured by each instrument (intensity, frequency, volume, or two or more), varied widely between the included primary studies.[19] These limitations prevented the review from establishing a "minimum" or an "optimal" dosage of physical activity necessary to decrease the odds of incident depression. Nonetheless, the authors considered the available evidence to support the conclusion that physical activity can offer protection against the emergence of depression. Although significant publication bias was found in their analyses, the authors indicate that adjusting for this did not change the magnitude of the associations that they found.[19] Our assessment of the evidence from the two included reviews against Bradford Hill's criteria for causality[27,29] suggested that depression is *probably* causally related to physical inactivity (Table 5).

Association between physical activity and anxiety

A systematic review and meta-analysis of prospective cohort studies found that physical activity was associated with lower odds of self-reported anxiety symptoms (AORs, 0.87 [95% CI, 0.77,0.99], n=9, I^2=48.67%), diagnosis of any anxiety disorder (mean OR, 0.66 [95% CI=0.53, 0.82], n=3, I^2=62.26%), and diagnosis of generalized anxiety disorder (mean OR, 0.54 [95% CI=0.32, 0.92], n=3, I^2=0.00%).[35] The authors included a total of 24 prospective cohort studies of which thirteen were included in the meta-analyses.[35] McDowell and colleagues found a moderate degree of heterogeneity for outcomes of self-reported anxiety symptoms and a diagnosis of any anxiety disorder.[35] The small number of primary studies included in their analyses did not allow for a quantitative examination (i.e., meta-regression analysis) of potential sources of variability. They did not assess publication bias.[35]

A similar finding was seen in the meta-analysis by Schuch and colleagues.[36] They included a total of 14 cohorts of 13 unique prospective studies in their review. High self-reported physical activity levels were associated with lower rates of incident anxiety when compared with low physical activity levels (AOR = 0.74, 95% CI = 0.62, 0.88, n=11, I^2=23.96). After adjusting for publication bias, this association decreased but remained significant (AOR = 0.86, 95% CI = 0.69, 0.99). The authors explored heterogeneity using subgroup and meta-regression analysis. They identified no significant moderators via meta-regression. In subgroup analysis, the authors presented findings from one cohort specific for children/adolescents (AOR= 0.52, 95% CI= 0.29, 0.90, I^2=0.00). They found evidence of publication bias both for adjusted and crude analysis, but the results remained significant after adjusting for publication bias and the overall effect size did not change significantly.[36]

Table 5 presents a summary of the assessment against Bradford Hill's criteria for causality.[27,29] We graded the evidence from the two included review as *probable* evidence to support that anxiety is causally related to physical inactivity.

Updated search

We ran an updated search from the year 2020 (database settings did not allow us to start from 19 March, day the previous search was run) to 15 October 2022. We report the search algorithm in Appendix Table 6. We identified 669 articles (Embase, 371 and PubMed, 298 records). A total of 479 records remained after removing duplicates. We excluded 454 records at the title and abstract screening stage. We screened the full text of the remaining 25 records. In total 20 records were excluded with reason, leaving a total of five reviews for data extraction.[37-41] (See Appendix Figure 2 for the PRISMA[33] flow diagram and Appendix Table 7 for a list of excluded records and reasons for exclusion.) Of the five included studies, four investigated the outcome

incident depression[37-39,41] and one, incident anxiety.[40] We document the findings from the updated search in Table 6.

DISCUSSION

This umbrella review provides a comprehensive and systematic overview of epidemiological evidence on the strength of the association between physical activity and incident cases of depression, anxiety, and assesses the likelihood of these associations being causal. Four reviews were included: two for the outcome depression (which included 79 primary prospective cohort studies in total) and two for anxiety (which included 37 primary prospective cohort studies in total).

The consistent findings from the four reviews provide sufficient evidence to support an association between physical activity and incident cases of depression and anxiety. When assessed against Bradford Hill's criteria for causality,[27,29] we found a probable causal relationship, with higher levels of PA leading to a lower risk of depression and anxiety. Our umbrella review expands the evidence in the area of physical activity and mental health. Previous systematic review of reviews and meta-analyse have reported associations between physical activity and depression with various estimates of the strength of these associations.[9,17,18] Regarding causality, Biddle and colleagues found partial support for a causal association between depression and physical activity.[18] For the association between physical activity and anxiety, Biddle and colleagues found that there was an association but cautioned that only a small number of primary studies had been included in their review.[18] They concluded that a full analysis of causality was not possible due to the small number of primary studies found. Dale and colleagues classified the associations between physical activity and anxiety as unclear due to a small number of primary studies included in their review.[9] The measures of strength of the associations reported in these previous systematic review of reviews are not comparable to the

measures that we have reported in our study because of the difference in definition of outcomes investigated. While we restricted our outcomes to incident cases of depression and anxiety, previous systematic review of reviews included existing diagnosis or symptoms of depression and anxiety.[9,18] There have been two recent published overviews that are similar to our review of reviews. One is a systematic meta-review of top-tier evidence examining how physical activity, sleep, dietary patterns and tobacco smoking impact on the risk and treatment outcomes across a range of mental disorders.[42] They found that the evidence supports the use of physical activity in primary prevention and clinical treatment of mental disorders. For the outcome incident depression and anxiety, they included three reviews[19,35,36] that are included in this umbrella review.

The second one is an umbrella review of universally delivered preventive interventions for depression with an aim to provide an overview of the meta-analytic literature. Several preventive interventions were included in the study: psychological interventions, school-based interventions, e-health interventions and physical activity interventions. The authors give a detailed report of findings on physical activity interventions and conclude that there is meta-analytic evidence that physical activity can prevent depression.[43]

Limitations

Our review protocol was not submitted for peer review registration; however, the protocol was prepared according to set guidelines and protocol for systematic reviews including the selection of studies based on a predefined set of inclusion and exclusion criteria.[24,25] We restricted inclusion to peer reviewed studies. While this enhances the rigour of evidence, findings may be susceptible to publication bias. Further, we only included reviews published in the English language. Three included reviews also reported evidence of publication bias in their primary

studies.[19,34,36] In two reviews that adjusted for publication bias, authors found that it did not change the magnitude of the associations.[19,36]

A few other limitations of our study and the underlying evidence are worth discussing. For the strength of the associations between physical activity and depression and anxiety we rely on the evidence from previous studies – primary cohort studies summarised in systematic reviews with pooled estimates. To reduce the possibility of reverse causality (undetected illness at baseline causing lower physical activity), each of the four reviews included in our study only covered primary studies with a follow up period of more than one year. For depression, the primary studies excluded participants with depression at baseline. This reduced the risk of selection bias. However, the review authors noted that depression is a recurrent disorder and previous depressive episodes were not well documented in the primary studies. In one review,[19] a subgroup analysis of primary studies that controlled for baseline depressive symptom severity also showed significant associations between high physical activity levels and lower incidence of depression. This makes it less likely that reverse causation explains the association found.

It should be noted that our study includes a limited number of reviews. Being an umbrella review, a potential limitation of our study is the overlap in studies (Table 3). Additionally, most of the primary studies reported in the four included reviews were from high income countries and regions. Studies in low- and middle-income countries are warranted to establish any variations in the context specific measures of association between physical activity and depression and anxiety.

Another limitation is that imprecise measurement of physical activity might have weakened the associations with health outcomes. The authors of the four reviews report that most of the primary studies used self-reported physical activity, which is imprecise. Imprecise measurement of exposure leads to regression dilution bias.[44] The use of self-report questionnaires may also

have introduced recall bias; physical activity tends to be over-estimated.[45,46] Further, the review authors reported that most of the primary studies assessed physical activity at baseline only and a few assessed physical activity levels at several points in time. Tracking physical activity levels in a cohort across time permits estimation of change in exposure across follow-up, reducing the risk of misclassification bias (but increases the risk of reverse causation). Physical activity classification criteria differed across primary studies, and aspects of physical activity captured by each instrument varied widely between primary studies (intensity, frequency, volume). This prevented the authors of the four included reviews from assessing dose response relationships. Although different measures for depression and anxiety were used in the included primary studies, the review authors report that the majority of the primary studies assessed the health outcomes through well-validated high-quality measures. In the review by Schuch and colleagues, subgroup analyses showed that physical activity decreased the risk of developing depression, regardless of whether this was based on self-report measures or major depression diagnosis from structured clinical diagnostic interviews.[19]

Some caution is required as some covariates may not have been assessed in the four reviews. Examples of such covariates are genetic factors, familial history of depression and anxiety, other risk factors for depression and anxiety, such as obesity, poor diet, and use of tobacco, and other clinical comorbidities. However, despite the limitations encountered in synthesis of primary studies, authors of the four reviews consistently provided evidence to support that engaging in physical activity protects against incident cases of depression and anxiety. They also presented respective measures of the strength of these associations.

Our initial search on 19 March 2020. We have systematically updated our search to 15 October 2022 and identified a few new studies as reported in our results section. The measures of the strength of associations reported in these additional reviews are in line with our findings and

strengthen our conclusion on the association between physical activity and depression. Similar to our initial search, there were few primary studies and reviews found on the outcome anxiety. This has also been the case in previous studies.[9,18] Our study is unique in the explicit consideration of causality and the link with our companion paper that quantifies the impact of changes in the Australian population's physical activity levels on the burden of anxiety and depression and health care costs in Australia.[47]

Implications of the results for practice, policy

Our findings provide qualified support for the inclusion of physical activity in potential strategies for the prevention of mental ill health. Given the large burden of mental health problems, even small improvements can have a significant effect at population level. True benefits of measures that increase physical activity levels are likely to be even greater, because the mental health benefits would be additional to those accrued from reduction of other disease associated with physical activity such as cardiovascular disease, diabetes, several types of cancer, and other chronic health conditions.[48,49]

Strenuous physical activity may lead to repeated intense stress on the joints, or acute high stress. This could damage cartilage, ligaments, and other joint structures. Such strenuous physical activity can be seen in extreme sports but may be unlikely in the kind of physical activity levels recommended in various guidelines for health. In the long term, recommended levels of physical activity may prevent injury through increased muscle strength and flexibility hence protecting the spine and joints from injuries. Increased physical activity through active transport such as walking or bicycling on, or along busy roads could increase injury risk and may result in harm through exposure to air pollution. Physical inactivity could be a factor in the causal path to anxiety and depression. For instance, people experiencing incapacitation may develop anxiety and depression due to the inability to participate in physical activity. Tailored physical activity

interventions may be needed for various groups with specific needs. The measures of association reported in most studies are drawn from samples representative on the general population controlled for various variables. Hence, the effect from a physical activity intervention may differ between smaller proportion of populations experiencing incapacitation and larger proportions not experiencing that.

Unanswered questions and future research

Further research could strengthen the evidence base for sex and age specific measures of association between physical activity and depression, anxiety. Future research is needed to improve estimates of the dose-response relationship between physical activity and depression and anxiety. Preferably, exposure should be objectively measured and capture frequency, intensity, type (e.g., aerobic, strength), and duration of physical activity. As outcomes, continuous measures of depressive mood and anxiety are preferable to dichotomous measures.[34,35] Where possible, physical activity should be measured several times across the study, not only at baseline, to capture impact of habitual or sustained physical activity.[50] Such studies should aim for representative samples and fully account for participants lost to follow-up.[35] Future studies should also assess the size and distribution of the benefits for different socio-economic and ethnic groups.

CONCLUSION

Our evidence is drawn from systematic reviews of observational data. Further high-quality studies, such as randomised control trials, would help strengthen the evidence base of the associations between physical activity and depression and anxiety. Nonetheless, our findings provide empirical support for the consideration of physical activity in strategies for the prevention of mental ill health.

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All authors conceived the study. MNW, HM, FH and JLV conducted the systematic review of reviews. MNW led the evidence analysis with the help of HM, FH and JLV.

All authors contributed to the interpretation of findings. MNW wrote the first version of the manuscript. All authors reviewed several versions of the manuscript and provided critical feedback. All authors approved the final version for publication. No financial disclosures were reported by the authors of this paper. We acknowledge Jasmin Spinoso, Research Support Officer in the School of Medicine and Dentistry, Griffith University for her support in developing the graphical abstract.

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This systematic review of reviews was part of a larger project that aimed to identify a best practice method to cost the health benefits of active transport. The funder had no say in design/ interpretation of the study.

CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

FINANCIAL DISCLOSURE

No financial disclosures were reported by the authors of this paper.

Declaration of interests
The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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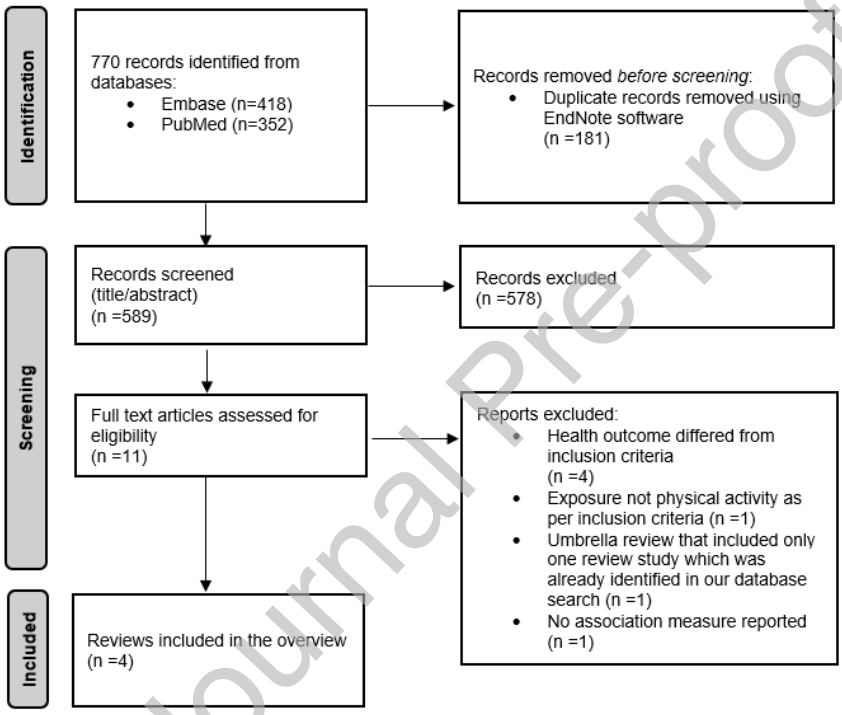
FIGURE TITLES AND FOOTNOTES

Manuscript

Figure 1: PRISMA flow diagram



Supplementary File

Figure 1: The two-step approach of our study protocol

Figure 2: PRISMA Flow diagram for updated search

TABLE TITLES AND FOOTNOTES

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Table 1: Search terms used in the systematic review

Table 2: Inclusion and exclusion criteria

Table 3: A summary of the characteristics of included reviews

Table 4: Overlap of primary studies across reviews

The search was conducted on 19 March 2020. The search terms, algorithm and identified records are reported in Appendix Table 3

Table 5: Assessing the evidence against causal criteria

RR, Relative risk

Table 6: Findings from the updated search

For the updated search conducted on 15 October 2022, data extraction and assessment of the methodological quality of the included systematic reviews was done by MNW. This was checked and discussed with JLV.

Supplementary File

Appendix Table 1: Data extraction fields

Appendix Table 2: Criteria for assessment for causal relationship and grading of evidence

Appendix Table 3: Results from the search conducted on 19 March 2020

Appendix Table 4: Reviews excluded after full-text screening

Appendix Table 5: AMSTAR scores from independent reviewers

Two reviewers (MNW, FH) independently assessed the methodological quality of the included systematic reviews using the Assessment of Multiple Systematic Reviews (AMSTAR) rating scale.[31] Differences were resolved through discussion.

Appendix Table 6: Results from the search conducted on 15 October 2022

Appendix Table 7: Updated search: reviews excluded after full-text screening

Appendix Table 8: Updated search: summary of the characteristics of included reviews

Table 1: Search terms used in the systematic review of reviews

Exposure and health outcome search terms
("physical activity" OR "physical exercise" OR walking OR bicycling OR "active transport") AND ("mental health" OR "mental disorders" OR anxiety OR "anxiety disorder*" OR depression OR "depressive disorder*")

Table 2: Inclusion and exclusion criteria

- Participants/ Population: The review included studies reporting results representative of whole populations who did not have any of the study outcomes (depression, anxiety) at baseline, covered either all ages, multiple age categories across all ages (children, youth as well as adults), or specific age groups so long as they are representative of the whole population at those ages.
- Study designs: Systematic reviews with or without meta-analyses
- Exposure: Reviews reporting findings on physical activity (physical activity) as exposure
- Outcomes: Reviews reporting findings on incident cases of depression and anxiety as outcomes.
- Publication status: Peer reviewed studies, published or in print with full text publicly available.
- Timeline: Reviews published in the year 2000 to 19 March 2020. We later updated our search to 15 October 2022.
- Language: English
- Reviews that provided risk estimates (relative risk [RR], hazard ratio [HR], or odds ratio [OR]) with confidence intervals or standard errors, or the data to calculate these.

Table 3: A summary of the characteristics of included reviews

Review	Search Dates	Study design of primary studies	Total person years of follow up / participants	Follow up time	Location of primary cohort studies as reported	Average age of participants (years)	Sex	Physical activity measurement	Measure of health outcome investigated	Covariates included in multivariable adjusted estimates	Risk of bias tool used in each review	Assessment of publication bias in each review	statistical heterogeneity	AMSTAR assessment score for each review
Mammen & Faulkner, 2013[34]	January 1976 to December 2012	Prospective cohort studies	Not stated. Harvest plot presents lowest category of study sample size as <1,000 subjects and highest as >10,000 subjects.	Reported: ranged from 1-27 years	Majority of studies in North America (n=14) and Europe (n=13). The study SF tables included the following countries: Sweden, Norway, Finland, Australia, Netherlands, USA	No age restriction reported. The study SF tables indicated population ages from 11 years to 100 years	Mixed (20 studies), female only (5 studies), male only (4 studies)	Subjective physical activity measures of aerobic activity. Only one study objectively measured physical activity via ergometer cycling	Majority of studies: validated measures such as Center for Epidemiologic Studies Depression Scale (CESD); other studies DSM-IV. More direct measures: via physician diagnosis (n=3); hospital discharge register (n=2); or use of antidepressants (n=1)	Under the study quality assessment, authors indicate the studies that assessed for confounding variables (n=11). In discussion, three low quality primary studies are reported as not accounting for BMI and social economic status	Critical Appraisal Skills Programme	Narrative	A harvest plot	Low
Schuch et al., 2018[19]	Database inception to October 18, 2017	Prospective cohort studies	N=266,939 | person-years 1,837,794	Average of 7.4 years	Australia, Norway, Germany, United States, Iceland, Canada, Ghana, India, Mexico, Russia, South Korea, England, Italy, UK, Netherlands, Sweden, Taiwan, Japan, Denmark,	Average age not stated. No age restriction reported. Results table shows age group at baseline as 'adults, children, adolescents,	Mixed: median proportion of males across studies, 47%)	Self-report questionnaire, such as the International Physical Activity Questionnaire, single or multiple questions on participation in exercise, sports, or physical activity. Only one study objectively	Semi structured diagnostic instruments or self-reported physician diagnosis of depression.	Analysis for adjusted and unadjusted measures conducted separately. In subgroup analyses, adjusted for age and sex, body mass index, smoking, and baseline	Newcastle - Ottawa Scale.	Begg and Mazumdar and Egger tests and corrected for this using the Duval and Tweedie trim and fill method	Q and I^2 Scores of 25% (low heterogeneity), 25% -50% (moderate), and >50% (high)	High

					Korea, Spain,	older adults'.		measured physical activity via pedometers		depressive symptoms				
McDowell, et al., 2019[35]	Database inception to June 2018	Prospective cohort studies	>80,000 unique individuals	Median follow-up, 4.75 years From their results table, least follow up time= 1 year, longest follow up time, 16 years	Europe (n=18), Australia (n=2), North America (n=2), Asia (n=2),	43.7 (25.6 −48.4) years. Two studies covered only children or adolescents	Mixed: median proportion of female participants =54.5% (49%–61%).	Self-report measure assessed at baseline alone (n=18) or as change over time (n=6).	Anxiety symptoms (n=8), a screening level for anxiety symptoms indicative of a disorder (n=10), self-reported diagnosis of anxiety disorder (n=1), and diagnosis of an anxiety disorder (n=5).	Analyses of AORs and unadjusted ORs from cohort studies were run separately. Covariates included in multivariable adjusted estimated not stated by the review authors.	Q-Coh	Not reported	Q statistic and I^2	Low
Schuch et al., 2019[36]	Database Inception to October 10, 2018	Prospective cohort studies	N = 75,831 | 357,424 person-years	Median of 3.5 years (Inter quantile range = 2.0–6.5).	Germany, Australia, UK, Sweden, Korea, USA, Ireland, Spain, The Netherlands,	Average age not stated. No age restriction reported. Results table shows age group at baseline as 'adults, children, adolescents, older adults'.	Mixed: median males = 50.1%)	No study used an objective measure to evaluate physical activity	Structured or semi-structured diagnostic instruments or self-reported physician diagnosis of anxiety disorders (n=10 studies), and cut-offs of anxiety screening instruments (n=4)	Analysis for adjusted OR and OR were conducted separately. In subgroup analyses, adjusted for age and sex, body mass index [BMI] and smoking,	Newcastle -Ottawa Scale	Begg and Mazumdar and Egger tests and corrected through the Duval and Tweedie trim and fill method	Q and I^2 statistic Scores of 25% (low heterogeneity), 25% -50% (moderate), and >50% (high)	High

The search was conducted on 19 March 2020. The search terms, algorithm and identified records are reported in Appendix Table 3.
AOR: Adjusted odds ratio, OR: Odds ratio, UK: United Kingdom, United States of America

Table 4: Overlap of primary studies across reviews

Outcome	Review	Search dates	Number of included primary studies	No. of overlapping primary studies between reviews
Depression	Mammen & Faulkner, 2013[34]	January 1976 to December 2012	30	14
	Schuch et al., 2018[19]	Database inception to October 18, 2017	49	
Anxiety	McDowell, Dishman, Gordon, & Herring, 2019[35]	Database inception to June 2018	24	10
	Schuch et al., 2019[36]	Database Inception to October 10, 2018	14	

Table 5: Assessing the evidence against causal criteria

Criterion	Findings for physical activity and depression	Findings for physical activity and anxiety
1.Temporality criterion: exposure preceded outcome in the included cohort studies. Inclusion of prospective based studies allowed for the examination of the temporal sequence between baseline levels of physical activity and primary prevention of depression, anxiety at follow up.	Mammen and Faulkner [34] and Schuch, Vancampfort [19] included primary results from prospective cohort studies. We considered that the evidence from these two reviews meets the temporality criteria where the exposure (physical activity) is seen to precede the effect (depression).	Both reviews by Schuch, Stubbs [36] and McDowell, Dishman [35] included only prospective cohort studies with a follow up period of more than 1 year. These two reviews assess prospective evidence where exposure (physical activity) preceded the effect (anxiety) in time. This evidence meets the temporality criterion.
2. Strength of association We used an adaptation of measures by Webb, Bain [27] to guide our classification where relative risk (RR) >3.0 (<0.33) are classified as moderately strong, >5.0 (<0.2), strong. Additional measures: RR 1.5-2.9 (0.34-0.67) classified as modest and RR <1.5 (>0.67), weak association (Appendix 1, Appendix Table 2). Though the strength of association facilitates assessment for possible causal relationship, a strong association is neither necessary nor sufficient for causality, and weakness is neither necessary nor sufficient for concluding absence of causality.	The relative effects reported in the included reviews were considered weak. Weakness of an association makes the risk of alternative explanations greater but does not preclude causality. Measures of association: Mammen and Faulkner [34] Out of 30 included primary studies, 25 reported a significant inverse relationship between PA and incident depression while 5 found no relationship. The point estimates for all studies are not reported. Below is a summary of estimates reported. -Engaging in <150 minutes/week and >150 minutes/week were associated with an 8%–63% (n=3) and 19%–27% (n=3) decreased risk of future depression, respectively. -Being physically active for >240 minutes/week (n=2) and 420 minutes/week (n=1) were protective against subsequent depression. -As little as 10–29 minutes (RR=0.90) of daily PA was preventive in the onset of depression and, higher levels of daily PA (60–90 minutes/day, RR=0.84; >90 minutes/day, RR=0.80) were significantly associated with decreased risk of developing depression (n=1). -Engaging in PA for >30 minutes/day reduced the odds of subsequent depression by 48% (n=1).	The strength of association between physical activity and anxiety was considered weak. The mean odds ratio was considered modest in strength though with a very wide confidence interval. OR values >0.67 were classified as weak associations. Measures of association: McDowell, Dishman [35] -Self-Reported Anxiety Symptoms: mean crude OR= 0.84 (95% CI=0.76, 0.93, I^2=47.31%), mean AOR= 0.87 (95% CI=0.77, 0.99, I^2=48.67%). All AORs (n=9) were <1.00. -Diagnosis of Any Anxiety Disorder: mean OR was 0.66 (95% CI=0.53, 0.82, I^2=62.26%). All AORs (n=3) were <1.00. -Diagnosis of Generalized Anxiety Disorder: mean OR was 0.54 (95% CI=0.32, 0.92, I^2=0.00%). All AORs (n=3) were <1.00. Schuch, Stubbs [36] Authours reported adjusted odds ratios from 11 primary stuies that provided this data. All 11 reported point estimates less than 1. Below are the estimates from the meta analysis across 14 cohorts of 13 unique prospective studies

	-Even "low" walking levels were associated with a decreased risk of depression of up to nearly 60% (n=2). -Even walking at an average pace of <20 minutes/day and >40 minutes/day was protective against depression of up to 6% and 17%, respectively (n=1). -Being physically active less than twice per week was associated with an increased risk (OR=1.34) of developing depression (n=1). -Being active one to two times/week or more than once per week was associated with a decreased risk of depression of up to 40% (n=2). Schuch, Vancampfort [19] Authours reported adjusted odds ratios for 36 cohorts from the 34 unique primary studies that provided this data. Of these, a total of 32 cohorts reported point estimates less than 1 and 4 reported point estimates greater than 1. Below are the estimates from the meta analysis -Compared with people with low levels of physical activity, those with high levels had lower odds of developing depression (AOR=0.83,95%CI=0.79,0.88, I^2=0.00, [n=36]; OR=0.59, 95% CI=0.51, 0.68, I^2=52.38, [n=19] and had decreased risks on adjusted and crude relative risk analyses (adjusted RR=0.83, 95% CI=0.76, 0.90, I^2=0.00, [n=18]; RR=0.68, 95% CI=0.60, 0.78, I^2=33.40 [n=17]). -Physical activity had a protective effect against the emergence of depression in youths (AOR=0.90, 95% CI=0.83, 0.98, I^2=0.00), in adults (AOR=0.78, 95% CI=0.70, 0.87, I^2=0.00), and in elderly persons (AOR=0.79, 95%CI=0.72, 0.86, I^2=0.00). -Protective effects against depression were found across geographical regions, with adjusted odds ratios ranging from 0.65 to 0.84 in Asia, Europe, North America, and Oceania, and against increased incidence of positive screen for depressive symptoms (AOR=0.84, 95% CI=0.79, 0.89, I^2=0.00) or major depression diagnosis (AOR=0.86, 95% CI=0.75, 0.98, I^2=0.00).	-People with high self- reported physical activity (versus low physical activity) were at reduced odds of developing anxiety (AOR=0.74, 95% CI=0.62, 0.88, I^2=23.96; crude OR=0.80, 95% CI=0.69, 0.92, I^2=0.00). -Protective effects for anxiety were evident in Asia (AOR =0.31, 95% CI= 0.10, 0.96, I^2=0.00) and Europe (AOR =0.82, 95% CI=0.69, 0.97, I^2=11.36); for children/adolescents (AOR=0.52, 95% CI=0.29, 0.90, I^2=0.00) and adults (AOR=0.81, 95% C =0.69, 0.95, I^2=12.18).
3. Consistency	Consistent findings were observed across the two included reviews. In their discussions, the authors of the two reviews indicated that consistency had been witnessed in the various	In the review by McDowell, Dishman [35] all crude and adjusted associations included in their meta-analyses indicated inverse associations between physical activity and subsequent anxiety. Similarly, Schuch, Stubbs [36]

	primary studies that had been carried out in different populations.	provide evidence of the protective effects of self-reported physical activity on anxiety development referencing previous cross-sectional studies. We found that there is evidence for repeated observation of an association between physical activity and anxiety from other studies in different populations under different circumstances. These findings support the criterion of consistency.
4. Dose-response relationship A dose-response relationship supports a causal interpretation.[27,29]	A dose-response relationship was reported in several primary studies included in the review by Mammen and Faulkner [34] Schuch, Vancampfort [19] did not investigate a dose-response relationship due to the varied definitions of low or high physical activity in their included primary studies.	Schuch, Stubbs [36] did not investigate a dose response relationship between physical activity exposure and anxiety. In the review by McDowell, Dishman [35] a total of 11 primary studies assessed for a dose response relationship between physical activity and various anxiety outcomes. All of which reported lower odds of anxiety outcomes for increased amounts of physical activity. In all, there is modest evidence of a dose-response relationship.
5. Biological plausibility	Mammen and Faulkner [34] and Schuch, Vancampfort [19] highlight that it is likely that no single mechanism can explain the protective effect of physical activity in the development of depression. They discuss that a range of biochemical and psychosocial factors are likely responsible, including biological mechanisms through which exercise increases neurogenesis and reduces inflammatory and oxidant markers and activates the endocannabinoid system; a neuromodulatory system involved in several mental disorders. Moreover, they report that people with depression have decreased hippocampal volumes and levels of markers of neurogenesis, and increased levels of inflammatory and oxidant markers. There is evidence that physical activity may regulate these abnormalities, increasing hippocampal volume and neurogenesis levels, as well as adjusting the imbalance between anti- and proinflammatory and oxidant markers. Also, physical activity may directly increase psychological factors such as self-esteem or perceptions of physical competence. Improved levels of fitness lead to both subjective and objective improvements in physical health status. In both reviews, the authors recommend that future research should investigate these underlying biological and psychological mechanisms.[19,34]	Though the mechanisms are largely unclear, Schuch, Stubbs [36] and McDowell, Dishman [35] presented evidence of potential biological processes that may underlie the protective effect of physical activity on incident anxiety. physical activity is known to influence similar pathways as those seen to play a role in the pathogenesis of anxiety disorders. Some of these biological processes include inflammation, oxidative and nitrogen stress, and subsequent alteration of neurotrophins, neurogenesis, and neuroplasticity. For instance, physical activity may promote neuroregeneration, or the balance between inflammatory/anti-inflammatory and oxidative/antioxidative markers. This may protect against anxiety. From a psychological perspective, physical activity may reduce the risk of developing anxiety through reduced anxiety sensitivity or improved psychological factors such as increased self-efficacy regarding the ability to exert control over potential threats.

	We concluded that the available evidence meets the biological plausibility criterion.	
6. Specificity	This criterion is not met – physical inactivity does not invariably lead to depression, and depression is not the only health condition associated with inactivity. However, this criterion was thought of in relationship to infectious agents, and seldom applies.	As with depression, this criterion is not met but of questionable relevance.
7.Coherence	We considered that the interpretation of the association between physical activity and depression does not conflict with what is known of the natural history and biology of depression.	The interpretation for the association of physical activity and anxiety does not conflict with what is known of the natural history and biology of anxiety.
Assessed against Bradford Hill's criteria for causality.[27,29] Assessment of grade of evidence: Convincing (strong) / Probable / Possible (suggestive) / Insufficient	We graded the evidence as strong enough to support a judgement of a probable causal relationship, with higher levels of physical activity probably leading to a lower risk of depression.	We considered that the evidence supports a judgement of a probable causal relationship.

AOR: Adjusted odds ratio, CI: Confidence interval, I2: I-squared statistic, OR: Odds ratio, PA: Physical activity, RR: Relative risk

Table 6: Findings from the updated search

Review	Study aim	Included primary studies and study overlap	Study findings	Data extraction and AMSTAR scores
Zimmermann, Chong, Vechiu, & Papa, 2020[40]	To identify studies that examined modifiable risk and protective factors for anxiety disorders among adults in the general population.	A total of 19 primary studies included in their review. Out of these, two prospective studies were for the outcome, incident anxiety. These 2 primary studies were included in previous reviews from our initial search.	Authors conducted a qualitative synthesis. One primary study found that when compared to no exercise, regular exercise was found to be a protective factor for Agoraphobia and Specific Phobia. Non-regular physical activity was a protective factor only for AP. The second primary study found that general physical activity did not predict the onset of any anxiety disorder, but Sports participation appeared to be a protective factor in the onset of any anxiety disorder.	We extracted data for the 2 primary studies as reported in the Zimmermann et. al. review. This is reported in Appendix Table 8 where we give a summary of the characteristics of included reviews from the updated search. Low quality review.
Brady, Brown, Hillsdon, & Mielke, 2022[41]	To systematically review the literature on accelerometer-measured physical activity and health outcomes in adults.	Out of 52 primary studies included in their review, only one was related to our review outcome (incident depression), a new primary cohort study published in 2020.	From the one primary study included for the outcome, depression, women in the lowest tertile of light physical activity (68.1 min/day) had a statistically significant increased risk of developing depressive symptoms, compared to those in the highest tertile (130.0 min/day) (HR=1.98, 95% CI=1.19-3.29), but not in men (p-interaction <0.01). (Light physical activity tertiles, mean [SD]: lowest: 68.1 [11.3] min/day, middle 95.3 [6.5] min/day, highest 130.0 [20.9] min/day.)	Since only one primary study in their review reported on our study outcome, we did not extract data for this review or assess for review quality.
Dishman, McDowell, & Herring, 2021[38]	They quantified the cumulative association of customary physical activity with incident depression and with an increase in subclinical depressive symptoms over time as reported from prospective observational studies They define incident depression by clinical diagnosis or cut points on depression screening tests.	A total of 111 reports included in their review. From their report, we could not distinguish between primary studies reporting incident depression and those reporting subclinical depressive symptoms over time. We did not carry out an analysis of the included primary studies.	Authors defined incident depression by clinical diagnosis or cut points on depression screening tests. The authors found that both odds of incident cases of depression or an increase in subclinical depressive symptoms were reduced after exposure to physical activity. They report that results were materially the same for incident depression and subclinical symptoms (OR=0.69, 95% CI= 0.63 to 0.75, I^2=93.7, and adjusted OR =0.79, 95% =0.75 to 0.82, I^2=87.6).	We did not carry out data extraction for our selected data items or assess review for quality. This was because we could not distinguish between primary studies reporting incident depression and those reporting subclinical depressive symptoms over time. From additional information in their SF, our inclusion criterion for population was not fully met for some of the primary studies.

Guo, Li, & Lu, 2022[39]	To quantify the relationship between different physical exercise doses and the risk of depression	A total of 12 primary studies all reporting on incident depression. Of these, eight prospective studies are included in previous reviews from our initial search.	Authors found a nonlinear relationship between leisure time physical activity and the risk of incident depression. The categorical dose-response association: Compared with the lowest leisure time physical activity (LTPA) category, the risk of incident depression was 23% lower for all LTPA categories (RR=0.77, 95% CI=0.68-0.86, I^2=69%) and 27%, 17%, and 8% lower for light, moderate and highest dose LTPA participants (RR= 0.73, 95% CI=0.64–0.82, I^2=43%; RR=0.83, 95% CI=0.78–0.87, I^2=46%; RR=0.93, 95% CI=0.86–0.99, I^2=79%), respectively. Continuous dose-response association: When physical activity was <25 MET-h/week, they found that the RR of depression risk was reduced by 3% for every 5 MET-h/week increase (RR=0.97, 95% CI=0.95–0.98). When physical activity was >25 MET-h/week, the increased physical activity did not further reduce the risk of depression, i.e., the risk of depression increased by 4% for every 5 MET-h/week increase (RR=1.04, 95% CI=1.02–1.05).	We extracted data and give a summary of the characteristics of study in Appendix Table 8 Low-quality review
Pearce et al., 2022[37]	To systematically review and meta-analyze the dose-response association between physical activity and incident depression from published prospective studies of adults.	A total of 15 primary studies all reporting on incident depression. Ten of these primary studies are included in previous reviews from our initial search.	The authors found an inverse curvilinear dose-response association between physical activity and incident depression, with steeper association gradients at lower activity volumes. (Those accumulating half the recommended volume of physical activity 18% [95% CI=13%-23%] lower risk of depression. Those accumulating the recommended volume had 25% [95% CI= 18%-32%] lower risk, diminishing additional potential benefits and greater uncertainty at higher volumes of physical activity.)	We extracted data and give a summary of the characteristics of study in Appendix Table 8 Low-quality review.

For the updated search conducted on 15 October 2022, data extraction and assessment of the methodological quality of the included systematic reviews was done by MNW. This was checked and discussed with JLV.
CI: Confidence interval, HR: Hazard ratio, I^2: I-squared statistic, MET: metabolic equivalent of task, MET-h/week: metabolic equivalent (MET) hours per week, Min: minute, OR: Odds ratio, RR: Relative risk, SD: Standard deviation