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Mechanisms linking physical activity with psychiatric symptoms: a protocol for a systematic review

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Manuscripts

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3 **Mechanisms linking physical activity with psychiatric symptoms: a protocol for a**
4 **systematic review.**
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ABSTRACT

Introduction: Persistent psychiatric symptomatology during childhood and adolescence predicts vulnerability to experience mental illness in adulthood. Physical activity is well-known to provide mental health benefits across the lifespan. However, the underlying mechanisms linking physical activity and psychiatric symptoms remain underexplored. In this context, we aim to systematically synthesize evidence focused on the mechanisms through which physical activity might reduce psychiatric symptoms across all ages.

Methods and analysis: With the aid of a biomedical information specialist, we will develop a systematic search strategy based on the predetermined research question in the following electronic databases: MEDLINE, Embase, Web of Science, Cochrane, and PsycINFO. Two independent reviewers will screen and select studies, extract data, and assess the risk of bias. In case of inability to reach a consensus, a third person will be consulted. We will not apply any language restriction, and we will perform a qualitative synthesis of our findings as we anticipate that studies are scarce and heterogeneous.

Ethics and dissemination: Only data that has already been published will be included. Then, ethical approval is not required. Findings will be published in a peer-reviewed journal and presented at conferences. Additionally, we will communicate our findings to healthcare providers and other sections of society (e.g., through regular channels, including social media).

PROSPERO registration number: CRD42021239440

Strengths and limitations of this study

- This protocol has been designed according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses for Protocols (PRISMA-P) guidelines and guidelines of the Cochrane Effective Practice and Organisation of Care.
- This protocol presents a cautiously designed search strategy, inclusion and exclusion criteria, and timespan and age-range coverage.
- A possible limitation is that included studies might be heterogeneous in the study design, data collection methods, and data analysis which might limit the ability to synthesize the results using a meta-analysis.
- The value of this systematic review depends on the quality and availability of the evidence on the topic.

INTRODUCTION

Persistent psychiatric symptomatology in childhood and adolescence predicts vulnerability to experience mental illness later in life¹. Specifically, individuals with mental illness have a decreased life expectancy of 10–15 years² and a lower quality of life³ than individuals from the general population. Psychiatric symptoms are typically grouped into two broad categories (i.e., internalizing/emotional, and externalizing/behavioral)⁴. Specifically, the externalizing problems include a variety of disinhibited/externally-focused behavioral symptoms such as conduct problems, rule-breaking behavior, attention-deficit/hyperactivity problems. On the contrary, the internalizing disorder include a variety of over-inhibited/internally-focused symptoms, such as depression, anxiety, or somatic symptoms. Several risk factors for psychiatric symptoms have been well established in childhood (e.g., poverty and social disadvantage)⁵ and adulthood (e.g., level of education and physical illness)⁶. However, less is known about the protective factors (e.g., physical activity) that might contribute to decreasing both child and adult psychopathology.

Physical activity is well-known to provide multiple health-related benefits across the lifespan⁷. In particular, there is a growing body of literature suggesting that physical activity has a small-to-moderate effect on psychiatric symptoms in childhood and adolescence^{5,6,7} but also in adulthood^{11,12}. However, most of the studies have focused on exploring the effect size of the association or effect in terms of dose-response, while the mechanisms underlying this relationship or effect remain underexplored. In 2016, Lubans et al.¹³ published a systematic review of the mechanisms linking physical activity and psychiatric symptoms in children and adolescents. They proposed a conceptual model, which postulated three distinct yet intertwined potential groups of mechanisms (i.e., neurobiological, psychosocial, and behavioral mechanisms). In brief, they identified a lack of available evidence for the specific mechanisms responsible for the effect of physical activity on mental and cognitive health in young people. Additionally, none of the studies included in their review examined potential mechanisms

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3 responsible for the effects of physical activity on mental health in young people using an
4 accepted statistical analysis (e.g., statistical mediation analysis)¹¹. Lastly, they only included
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7 intervention studies, and although this type of design can provide evidence for cause and effect,
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10 observational studies can also provide complementary information, particularly when there is a
11
12 lack of evidence on the topic.

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14 In adults, only narrative reviews^{12,13,14}, mainly focused on cognition¹² and
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16 depression^{13,14}, have explored the potential mechanisms that might link physical activity with
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18 psychiatric symptoms in adulthood. For instance, Stillman et al.¹² suggested that physical
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20 activity might reduce depression and anxiety via psychosocial pathways (e.g., mood).
21
22 Additionally, Kandola et al.¹⁶ presented a conceptual framework of the key biological and
23
24 psychosocial mechanisms underlying the relationship between physical activity and depressive
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26 symptoms in adults. However, no previous systematic reviews have been performed to
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28 synthesize the existing evidence in adults.
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31 Understanding the mechanisms linking physical activity with psychiatric symptoms
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33 may help to explain, predict, and intervene more effectively, which could stimulate the
34
35 identification of cost-efficient alternative therapies for preventing and treating mental illness at
36
37 all ages. To establish this evidence-based, it is imperative to synthesize and update all relevant
38
39 literature mapping the mechanisms through which physical activity reduces psychiatric
40
41 symptoms across the lifespan.
42

43 **Objective**

44
45 We aim to conduct a systematic review to explore the underlying mechanisms linking physical
46
47 activity with psychiatric symptoms in humans of all ages.
48

49 **Review questions**

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51 How does physical activity affect/associate with psychiatric symptoms via psychosocial,
52
53 neurobiological, and behavioral pathways across the lifespan?
54

55 **METHODS**

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57 The present protocol follows the PRISMA-P guideline for systematic review and meta-analysis
58
59 protocols¹⁸.
60

Patient and public involvement

Patients and the public were not involved in the design, development, conduct, reporting or dissemination of this study.

Eligibility criteria

We will include studies based on predefined criteria as summarized in **Table 1** and the text below¹⁹.

Population

We will include human studies including participants of all ages. Studies including individuals with physical or psychological disorders diagnosed by medical records, elite athletes, and animals will be excluded.

Intervention

We will include any observational studies, which have explored the mechanisms through which physical activity is associated with psychiatric symptoms. Intervention studies examining the mechanisms through which physical activity affects psychiatric symptoms will be also included. Studies in which physical fitness (i.e., capacity to perform physical activity, which refers to a full range of physiological and psychological qualities)²⁰, or sedentary behavior (i.e., any waking behavior characterized by an energy expenditure ≤ 1.5 METs, while in a sitting, reclining or lying posture)²¹ are the independent variables instead of physical activity (i.e., any bodily movement produced by skeletal muscle that results in energy expenditure)²² will be excluded. Additionally, multiple health behavior intervention studies (e.g., co-interventions such as a dietary program combined with physical activity) will be excluded because they preclude drawing conclusions on the isolated effect of physical activity or sedentary behavior on psychiatric symptoms.

Outcomes

We will include the subscales of internalizing (i.e., depression, anxiety, somatic symptoms) and externalizing (i.e., conduct problems, rule-breaking behavior, attention deficit/hyperactivity problems) disorders.

Study designs

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3 Intervention studies (randomized controlled trials [RCT], non-RCTs), prospective longitudinal
4 and cross-sectional studies will be included. We will not include conference proceedings and
5 other types of grey literature since risk of bias for these studies cannot be adequately assessed²³.
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8 9 *Potential mechanisms*

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11 Studies will be included if they explored the role of any potential neurobiological, psychosocial,
12 and behavioral mechanisms in the relationship between physical activity and psychiatry
13 symptoms.
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16 17 *Further restrictions*

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19 No language and publication date restriction will be applied. All databases will be searched
20 from their date of inception, and we will include every study that meets the above-mentioned
21 criteria regardless of the language.
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25 26 **Search strategy for identifying relevant studies**

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28 With the assistance of a biomedical information specialist, we will develop a systematic search
29 strategy based on the predetermined research question in the following electronic databases:
30 MEDLINE Ovid, Embase.com, Web of Science Core Collection, Cochrane CENTRAL register
31 of Trials, and PsycINFO Ovid. First, we will search for potentially relevant studies based on a
32 search strategy that is the combination of Medical Subject Headings (MeSH) terms for Medline
33 and Emtree terms for Embase and free text search. Our research team, including a librarian who
34 is specialized in search strategy development, has developed this search strategy. Search terms
35 are personalized to each database (see **Online supplemental appendix**). Search terms include
36 four parts: (1) terms to identify our independent variable (i.e., physical activity); (2) terms to
37 identify our mediating variables (i.e., neurobiological, psychosocial, behavioral mechanisms);
38 (3) terms to identify our outcome (i.e., psychiatric symptoms); and (4) terms to exclude articles
39 that match our exclusion criteria. An additional search for studies will be performed by
40 screening reference lists of included studies and their citations through Google Scholar. Third,
41 we will contact experts in the field to identify additional studies that may have been missed and
42 any relevant ongoing or unpublished studies.
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60 **Study records**

Data management

First, we will extract all studies identified by the different sources into an EndNote Library. Second, we will use a published method that uses this software to automatically eliminate the duplicate studies²⁴. In our final report, we will note the number of duplicates in the PRISMA flow diagram (see **Figure 1**).

Selection process

First, two independent researchers (PTNH and THPB) will screen titles and the abstracts for eligibility. When disagreements emerge between the two independent researchers, consensus will be obtained through discussion or when required, the opinion of a third researcher (MR-A) will be considered. Second, we will then obtain the full-text reports of studies that may fit eligibility criteria based on this assessment. Afterward, the same two independent researchers (PTNH and THPB) will assess eligibility based on the full texts. Any discrepancies will be again resolved after discussion with a third researcher (MR-A).

Data extraction process

Two researchers (PTNH and TT) will independently extract data from the included studies to a customized data extraction form developed a priori that has been piloted using one eligible study (see **Table 2**). Again, any discrepancies will be resolved after discussion with a third researcher (MR-A). We will contact authors for any relevant missing data.

From eligible studies, we will extract the following items: study background (name of the first author, year, and study location), sample characteristics (number of participants, age of participants, and percentage of female participants), design (intervention [RCT or non-RCT], or observational [cross-sectional or longitudinal]), independent variables, dependent variables, mediating variables, instruments used to assess the variables, statistical analyses and software, confounders, and main findings. For intervention studies (RCTs and non-RCTs), we also extract weeks of intervention, description of the program, intensity, duration, and frequency. For longitudinal studies, we also extract years of follow-up.

Risk of bias and quality of the evidence

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3 The risk of bias will be evaluated independently by two researchers (PTNH and TT) and
4 disagreements were solved in a consensus meeting with the same third researcher (MR-A). The
5 risk of bias will be evaluated using the Joanna Briggs Institute Critical Appraisal Tool for
6 Systematic Reviews (<https://jbi.global/critical-appraisal-tools>). This tool has already been used
7 by other authors in the field^{25,26}. In brief, this tool includes four specific checklists depending on
8 the study design (i.e., cross-sectional studies, longitudinal studies, RCTs and non-RCT). There
9 are four possible answers for each category: “yes” (criterion met), “no” (criterion not met),
10 “unclear” or “not applicable”. The specific tools include: eight items for cross-sectional studies,
11 11 items for longitudinal studies, nine items for non-RCTs and thirteen items for RCTs. Studies
12 will be categorized as “high risk” or “low risk”. Specifically, the studies will be considered as
13 “low risk” if at least 75% of the applicable items are scored as “yes” (criterion met). In contrast,
14 articles will be considered “high risk” when less than 75% of the applicable items were scored
15 as “yes”. This classification has been previously employed by Molina-Garcia et al.²⁷.

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Lastly, the Grading of Recommendations Assessment, Development and Evaluation framework will be used to assess the quality of the evidence across studies.

Data synthesis and analysis

In case overlapping populations are analyzed in multiple studies, we will include according to the following hierarchy the study that (1) has the lowest risk of bias, or (2) incorporates the largest sample size. In the case when a study reports multiple effect estimates for overlapping populations, we will select according to the following hierarchy: (1) the most adjusted model, (2) the closest time-point to the end of the intervention, or (3) the largest treatment group. Findings from observational and intervention studies will be rated using the method first employed by Sallis et al.²⁵, and more recently by Lubans et al.¹³, and Rodriguez-Ayllon et al.⁷. If 0–33% of studies reported a statistically significant mediation (e.g., self-esteem) between the independent (e.g., physical activity) and dependent variable (e.g., depressive symptoms), the result will be classified as no association (\emptyset); if 34–59% of studies reported a significant mediation, or if fewer than four studies reported on the outcome, the result will be classified as

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3 being inconsistent/uncertain (?); and if $\geq 60\%$ of studies found a statistically significant
4 mediation, the result will be classified as significant (\checkmark).
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7 **Ethics and dissemination**

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9 We will communicate our findings to researchers, pediatricians, health professionals, and
10 lectures through scientific seminars and conferences. Additionally, we will disseminate our
11 results using different approaches. Specifically, we will publish press articles in public journals
12 and magazines, do radio and television interviews, and publish our findings in a scientific peer-
13 review journal. We will also present our main results to policymakers and healthcare providers,
14 which might impact policy and healthcare practice.
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22 **Funding**

23
24 This work was supported by the Ramón Areces Foundation.
25

26 **Disclaimer**

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28 The funders of the present study did not have any role in the design, decision to publish or
29 preparation of the protocol.
30
31

32 **Competing interests**

33
34 None declared.
35

36 **Patient consent**

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38 Not required.
39

40 **Ethics approval**

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42 As systematic reviews use publicly available data, no formal ethical review and approval are
43 needed.
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47 **Provenance and peer review**

48
49 Not commissioned, externally peer reviewed.
50

51 **Open access**

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7 **Authors' contributions**

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9 MR-A, PTNH designed and drafted the protocol. WMB performed the search strategy. MR-A,
10 PTNH, THPB, TT, AH, DRL, MV revised and approved the final version of the manuscript.

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13 MR-A will be the guarantor of the review.

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15 **Word count**

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Table 1. Inclusion criteria based on PICOS strategy.

PICOS	Inclusion criteria	Exclusion criteria
Population	<p>1. All ages across the lifespan: infancy and toddlerhood (birth to age 2), preschoolers (2–5 years), children (6–11 years), adolescents (12–18 years), young and middle adults (18– 65), late adulthood (+65).</p> <p>2. Human studies.</p>	<p>1. Studies including individuals with physical or psychological disorders diagnosed by medical records.</p> <p>2. Elite athletes.</p> <p>3. Animal studies.</p>
Intervention	<p>1. Observational studies, which explored the mechanisms through which physical activity is associated with psychiatry symptoms.</p> <p>2. Studies examining the mechanisms through which physical activity has a positive effect on psychiatry symptoms.</p>	<p>1. Multiple health behavior intervention studies (e.g., co-interventions such as a dietary program combined with physical activity).</p> <p>2. Studies in which physical fitness (i.e., capacity to perform physical activity, which refers to a full range of physiological and psychological qualities)²⁰, or sedentary behavior (i.e., any waking behavior characterized by an energy expenditure \leq 1.5 METs, while in a sitting, reclining or lying posture)²¹ are the independent variables instead of physical activity (i.e., any bodily movement produced by skeletal muscle that results in energy expenditure)²².</p>
Comparison	1. Not applicable	
Outcomes	1. The subscales of internalizing symptoms (i.e., depression, anxiety, somatic symptoms) and externalizing symptoms (i.e., conduct problems, rule-breaking behavior, attention deficit/hyperactivity problems).	
Study design	1. Intervention studies (randomized controlled trials, non-randomized control trials), prospective longitudinal studies and cross-sectional studies.	<p>1. Conference proceedings and other types of grey literature.</p> <p>2. Narrative reviews, systematic reviews, or meta-analyses.</p>

Table 2. Summary of research investigating the mechanisms linking physical activity with psychiatric symptoms (n = 7).

Authors, year (country)	n sample (mean age ± SD, % females)	Design; target population	Independent variable (instrument)	Mediating variable (instrument)	Dependent variable (instrument)	Statistical analysis; software	Confounders	Main findings

SD= Standard deviation.

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3 **Figure 1.** Flow diagram for study selection.
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For peer review only

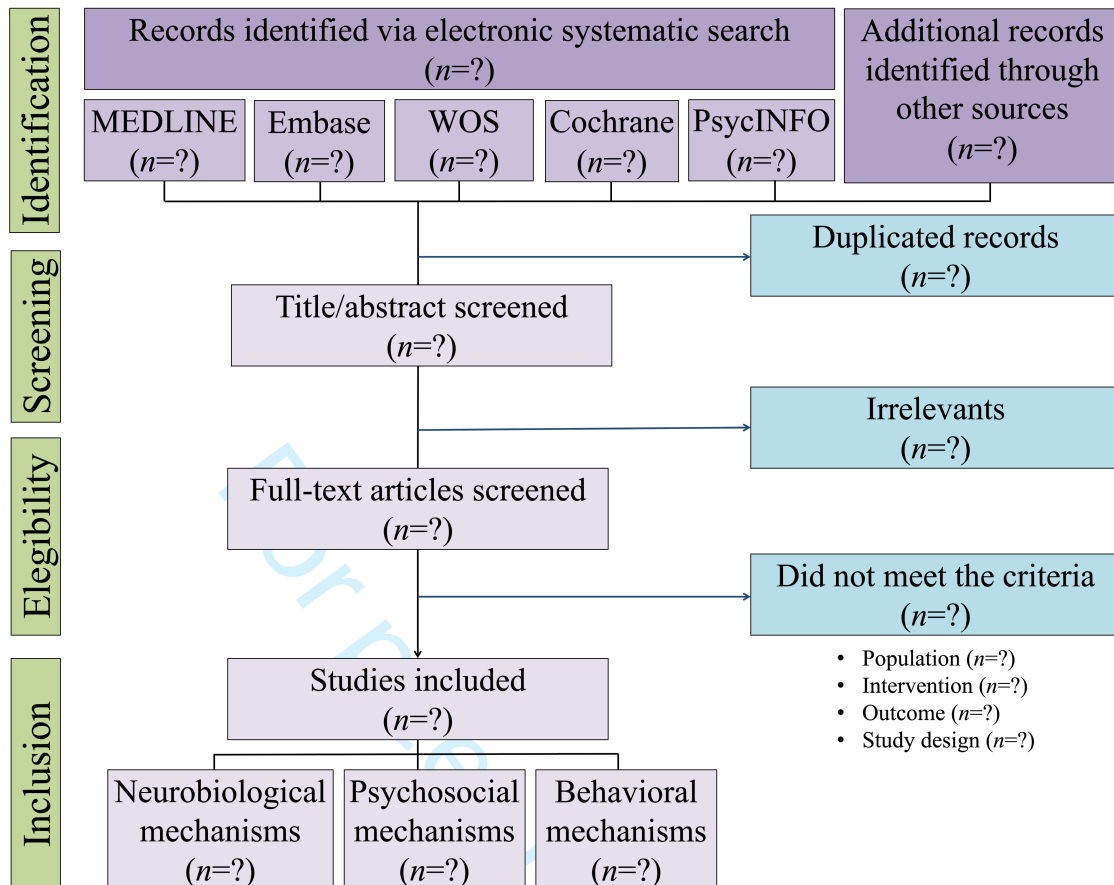


Figure 1. Flow diagram for study selection.

ONLINE SUPPLEMENTAL APPENDIX

Database searched	via	Years of coverage
Embase	Embase.com	1971 - Present
Medline ALL	Ovid	1946 - Present
Web of Science Core Collection*	Web of Knowledge	1975 - Present
Cochrane Central Register of Controlled Trials	Wiley	1992 - Present
PsycINFO	Ovid	1806 - Present

*Science Citation Index Expanded (1975-present) ; Social Sciences Citation Index (1975-present); Arts & Humanities Citation Index (1975-present) ; Conference Proceedings Citation Index- Science (1990-present); Conference Proceedings Citation Index- Social Science & Humanities (1990-present) ; Emerging Sources Citation Index (2015-present)

Embase.com

(exercise/exp OR 'physical activity'/de OR Climbing/exp OR running/exp OR walking/exp OR 'cycling'/de OR 'fighting'/de OR 'jogging'/de OR 'jumping'/de OR 'lifting effort'/de OR 'nordic walking'/de OR 'racewalking'/de OR 'stretching'/de OR 'swimming'/de OR 'weight bearing'/de OR 'weight lifting'/de OR sport/exp OR 'motor activity'/de OR 'psychomotor activity'/de OR 'physical education'/de OR locomotion/de OR swimming/de OR walking/exp OR (((physical* OR motor* OR psychomotor*) NEAR/3 (activit*)) OR exercise* OR sport* OR (physical NEAR/3 (education OR training)) OR locomotion* OR (Endurance NEAR/3 Training) OR walking OR running OR jogging OR yoga OR taichi OR tai-chi OR martial-art* OR qigong OR ((aerobic OR resistance OR physical*) NEAR/3 training)):ab,ti) AND (depression/exp OR 'anxiety disorder'/exp OR anxiety/de OR 'somatic symptom'/de OR 'attention deficit disorder'/de OR 'internalizing disorder'/de OR 'internalization (behavior)'/de OR 'externalizing disorder'/de OR 'externalization (behavior)'/de OR 'conduct disorder'/de OR 'rule breaking behavior'/de OR 'disruptive behavior'/exp OR (depressi* OR anxiet* OR (somatic* NEAR/3 symptom*) OR (attention NEAR/3 deficit NEAR/3 (disorder* OR hyperactiv* OR problem*)) OR (hyperactivit* NEAR/3 problem*) OR adhd OR internalizing OR internalization* OR internalising OR internalisation* OR externalizing OR externalization* OR externalising OR externalisation* OR (conduct NEAR/3 (disorder* OR problem*)) OR (rule* NEAR/3 breaking NEAR/3 behav*) OR ((disrupt* OR problem*) NEAR/3 behav*)):ab,ti) AND ('nuclear magnetic resonance imaging'/exp OR 'diffusion tensor imaging'/exp OR electroencephalography/exp OR electroencephalogram/exp OR 'gray matter'/exp OR 'white matter'/exp OR 'nervous system development'/exp OR 'nerve cell plasticity'/exp OR 'biological marker'/de OR marker/de OR hormone/exp OR peptide/exp OR protein/exp OR neurotransmitter/de OR opiate/de OR serotonin/de OR 'serotonin level'/exp OR noradrenalin/de OR dopamine/de OR monoamine/de OR endorphin/de OR neuroimmunology/de OR 'growth factor'/exp OR 'brain derived neurotrophic factor'/de OR 'neurotrophin gene'/de OR vasculotropin/de OR 'BOLD signal'/de OR volumetry/de OR 'brain function'/de OR 'functional connectivity'/de OR 'brain asymmetry'/de OR 'brain metabolism'/de OR 'brain structure'/de OR 'inflammatory marker'/de OR 'event related brain potential'/de OR 'emotional intelligence'/de OR 'social interaction'/de OR 'self esteem'/exp OR 'self control'/exp OR 'social connectedness'/exp OR 'self acceptance'/exp OR 'personal autonomy'/de OR belongingness/de OR confidence/de OR 'self confidence'/de OR 'self concept'/de OR (mri OR (magnetic NEAR/3 resonance) OR (diffusion NEAR/3 tensor NEAR/3 imag*) OR electroencephalogra* OR eeg OR ((grey OR gray OR white) NEXT/1 matter*) OR (nervous-system* NEAR/3 development*) OR neurogenesis* OR ((nerv*-cell* OR Neuron*) NEAR/3 plasticit*) OR hormon* OR peptide* OR protein* OR neurotransmitter* OR opiate* OR opioid* OR serotonin* OR noradrenalin* OR norepinephrin* OR dopamin* OR monoamin* OR endorphin* OR neuroimmunolo* OR neuro-immunolo* OR growth-factor* OR (brain-deriv* NEAR/3 neurotroph*-factor*) OR neurotrophin*-gene* OR IGF1 OR IGF-1 OR vasculotropin* OR VEGF OR BDNF OR VBM OR BOLD-signal* OR (blood-oxygen NEAR/3 level* NEAR/3

dependent*) OR volumetr* OR (brain NEAR/3 (function* OR asymmetry* OR metabol* OR structure*)) OR (functional* NEAR/3 connectiv*) OR (event-related NEAR/3 brain-potential*) OR ((emotion* OR psycholog*) NEAR/3 (intelligen* OR adjustment* OR regulation*)) OR (social* NEAR/3 (interacti* OR connected*)) OR (self NEXT/1 (esteem OR control* OR acceptan* OR awareness* OR concept OR efficac*)) OR (psychologic* NEAR/3 need*) OR autonom* OR belongingness* OR (perceived NEAR/3 abilit*) OR (confidence NOT (confidence-interval*)):ab,ti) AND ('intervention study'/de OR 'clinical trial'/exp OR randomization/exp OR 'prospective study'/exp OR 'longitudinal study'/exp OR 'cohort analysis'/de OR 'follow up'/de OR 'cross-sectional study'/de OR 'major clinical study'/de OR (intervention* OR trial* OR random* OR rct OR prospective* OR longitudinal* OR cohort* OR follow-up* OR cross-section*):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT (patient/exp/mj OR athlete/exp/mj OR 'breathing exercise'/mj OR 'degenerative disease'/exp/mj OR neoplasm/exp/mj OR 'cerebrovascular disease'/exp/mj OR 'cardiovascular disease'/exp/mj OR 'musculoskeletal disease'/exp/mj OR pain/exp/mj OR surgery/exp/mj OR survivor/exp/mj OR diabetes/exp/mj OR (patient* OR athlete* OR breathing OR disease* OR Alzheimer* OR Parkinson* OR osteoarthritis* OR cancer OR neoplas* OR stroke OR cva OR cerebrovascular OR cardiovascular OR musculoskeletal OR pain OR disorder* OR surger* OR transplant* OR survivor* OR diabet* OR injur*):ti) NOT [conference abstract]/lim NOT ('systematic review'/de OR 'meta analysis'/de OR 'case report'/de OR ((systematic* NEAR/3 review*) OR meta-analys* OR case-report*):Ab,ti)

Medline ALL Ovid

(Exercise/ OR Climbing/ OR Running/ OR Walking/ OR Bicycling/ OR Jogging/ OR Weight-Bearing/ OR Weight Lifting/ OR exp Sports/ OR Motor Activity/ OR "Physical Education and Training"/ OR Locomotion/ OR Swimming/ OR (((physical* OR motor* OR psychomotor*) ADJ3 (activit*)) OR exercise* OR sport* OR (physical ADJ3 (education OR training)) OR locomotion* OR (Endurance ADJ3 Training) OR walking OR running OR jogging OR yoga OR taichi OR tai-chi OR martial-art* OR qigong OR ((aerobic OR resistance OR physical*) ADJ3 training)).ab,ti.) AND (exp Depressive Disorder/ OR Depression/ OR exp Anxiety Disorders/ OR Anxiety/ OR Medically Unexplained Symptoms/ OR exp "Attention Deficit and Disruptive Behavior Disorders"/ OR Conduct Disorder/ OR Problem Behavior/ OR (depressi* OR anxiet* OR (somatic* ADJ3 symptom*) OR (attention ADJ3 deficit ADJ3 (disorder* OR hyperactiv* OR problem*)) OR (hyperactivit* ADJ3 problem*) OR adhd OR internalizing OR internalization* OR internalising OR internalisation* OR externalizing OR externalization* OR externalising OR externalisation* OR (conduct ADJ3 (disorder* OR problem*)) OR (rule* ADJ3 breaking ADJ3 behav*) OR ((disrupt* OR problem*) ADJ3 behav*)):ab,ti.) AND (exp Magnetic Resonance Imaging/ OR exp Diffusion Tensor Imaging/ OR Electroencephalography/ OR Gray Matter/ OR White Matter/ OR Biomarkers/ OR Hormones/ OR Peptides/ OR Proteins/ OR Neurotransmitter Agents/ OR Opiate Alkaloids/ OR Serotonin/ OR Norepinephrine/ OR Dopamine/ OR Endorphins/ OR Opioid Peptides/ OR Intercellular Signaling Peptides and Proteins/ OR Brain-Derived Neurotrophic Factor/ OR Vascular Endothelial Growth Factor A/ OR BOLD signal/ OR Emotional Intelligence/ OR Social Interaction/ OR Self-Control/ OR Personal Autonomy/ OR Self Concept/ OR (mri OR (magnetic ADJ3 resonance) OR (diffusion ADJ3 tensor ADJ3 imag*) OR electroencephalogra* OR eeg OR ((grey OR gray OR white) ADJ matter*) OR (nervous-system* ADJ3 development*) OR neurogenesis* OR ((nerv*-cell* OR Neuron*) ADJ3 plasticit*) OR hormon* OR peptide* OR protein* OR neurotransmitter* OR opiate* OR opioid* OR serotonin* OR noradrenalin* OR norepinephrin* OR dopamin* OR monoamin* OR endorphin* OR neuroimmunolo* OR neuro-immunolo* OR growth-factor* OR (brain-deriv* ADJ3 neurotroph*-factor*) OR neurotrophin*-gene* OR IGF1 OR IGF-1 OR vasculotropin* OR VEGF OR BDNF OR VBM OR BOLD-signal* OR (blood-oxygen ADJ3 level* ADJ3 dependent*) OR volumetr* OR (brain ADJ3 (function* OR asymmetry* OR metabol* OR structure*)) OR (functional* ADJ3 connectiv*) OR (event-related ADJ3 brain-potential*) OR ((emotion* OR psycholog*) ADJ3 (intelligen* OR adjustment* OR regulation*)) OR (social* ADJ3 (interacti* OR connected*)) OR (self ADJ (esteem OR control* OR acceptan*

OR awareness* OR concept OR efficac*) OR (psychologic* ADJ3 need*) OR autonom* OR belongingness* OR (perceived ADJ3 abilit*) OR (confidence NOT (confidence-interval*)).ab,ti.) AND (exp Clinical Trial/ OR Random Allocation/ OR exp Cohort Studies/ OR Cross-Sectional Studies/ OR (intervention* OR trial* OR random* OR rct OR prospective* OR longitudinal* OR cohort* OR follow-up* OR cross-section*).ab,ti.) NOT (exp animals/ NOT humans/) NOT (exp * Patients/ OR exp * Athletes/ OR * Breathing Exercises/ OR exp * Neoplasms/ OR exp * Cerebrovascular Disorders/ OR exp * Cardiovascular Diseases/ OR exp * Musculoskeletal Diseases/ OR *exp Pain/ OR exp * Surgical Procedures, Operative/ OR exp * Survivors/ OR *exp Diabetes Mellitus/ OR (patient* OR athlete* OR breathing OR disease* OR Alzheimer* OR Parkinson* OR osteoarthritis* OR cancer OR neoplas* OR stroke OR cva OR cerebrovascular OR cardiovascular OR musculoskeletal OR pain OR disorder* OR surgeon* OR transplant* OR survivor* OR diabet* OR injur*).ti.) NOT (Systematic Review/ OR Meta-Analysis/ OR case report/ OR ((systematic* ADJ3 review*) OR meta-analys* OR case-report*).ab,ti.)

PSycINFO ALL Ovid

(exp Exercise/ OR Physical Activity/ OR exp Sports/ OR (((physical* OR motor* OR psychomotor*) ADJ3 (activit*)) OR exercise* OR sport* OR (physical ADJ3 (education OR training)) OR locomotion* OR (Endurance ADJ3 Training) OR walking OR running OR jogging OR yoga OR taichi OR tai-chi OR martial-art* OR qigong OR ((aerobic OR resistance OR physical*) ADJ3 training)).ab,ti.) AND (exp Major Depression/ OR "Depression (Emotion)"/ OR exp Anxiety Disorders/ OR Anxiety/ OR exp Attention Deficit Disorder with Hyperactivity / OR Conduct Disorder/ OR Behavior Problems / OR (depressi* OR anxiet* OR (somatic* ADJ3 symptom*) OR (attention ADJ3 deficit ADJ3 (disorder* OR hyperactiv* OR problem*)) OR (hyperactivit* ADJ3 problem*) OR adhd OR internalizing OR internalization* OR internalising OR internalisation* OR externalizing OR externalization* OR externalising OR externalisation* OR (conduct ADJ3 (disorder* OR problem*)) OR (rule* ADJ3 breaking ADJ3 behav*) OR ((disrupt* OR problem*) ADJ3 behav*).ab,ti.) AND (exp Magnetic Resonance Imaging/ OR exp Diffusion Tensor Imaging/ OR Electroencephalography/ OR Gray Matter/ OR White Matter/ OR Biological Markers / OR Hormones/ OR Peptides/ OR Proteins/ OR Neurotransmitters / OR Opiates / OR Serotonin/ OR Norepinephrine/ OR Dopamine/ OR Endorphins/ OR Brain Derived Neurotrophic Factor / OR Emotional Intelligence/ OR Social Interaction/ OR Self-Control/ OR Autonomy/ OR Self-Concept/ OR (mri OR (magnetic ADJ3 resonance) OR (diffusion ADJ3 tensor ADJ3 imag*) OR electroencephalogra* OR eeg OR ((grey OR gray OR white) ADJ3 matter*) OR (nervous-system* ADJ3 development*) OR neurogenesis* OR ((nerv*-cell* OR Neuron*) ADJ3 plasticit*) OR hormon* OR peptide* OR protein* OR neurotransmitter* OR opiate* OR opioid* OR serotonin* OR noradrenalin* OR norepinephrin* OR dopamin* OR monoamin* OR endorphin* OR neuroimmunolo* OR neuro-immunolo* OR growth-factor* OR (brain-deriv* ADJ3 neurotroph*-factor*) OR neurotrophin*-gene* OR IGF1 OR IGF-1 OR vasculotropin* OR VEGF OR BDNF OR VBM OR BOLD-signal* OR (blood-oxygen ADJ3 level* ADJ3 dependent*) OR volumetr* OR (brain ADJ3 (function* OR asymmetry* OR metabol* OR structure*)) OR (functional* ADJ3 connectiv*) OR (event-related ADJ3 brain-potential*) OR ((emotion* OR psycholog*) ADJ3 (intelligen* OR adjustment* OR regulation*)) OR (social* ADJ3 (interacti* OR connected*)) OR (self ADJ3 (esteem OR control* OR acceptan* OR awareness* OR concept OR efficac*)) OR (psychologic* ADJ3 need*) OR autonom* OR belongingness* OR (perceived ADJ3 abilit*) OR (confidence NOT (confidence-interval*)).ab,ti.) AND (exp Clinical Trials / OR exp Cohort Analysis / OR (intervention* OR trial* OR random* OR rct OR prospective* OR longitudinal* OR cohort* OR follow-up* OR cross-section*).ab,ti.) NOT (exp animals/ NOT humans/) NOT (exp * Patients/ OR exp * Athletes/ OR exp * Neoplasms/ OR exp * Cerebrovascular Disorders/ OR exp * Cardiovascular Disorders / OR exp * Musculoskeletal Disorders / OR *exp Pain/ OR exp * Surgery / OR exp * Survivors/ OR *exp Diabetes Mellitus/ OR (patient* OR athlete* OR breathing OR disease* OR Alzheimer* OR Parkinson* OR osteoarthritis* OR cancer OR neoplas* OR stroke OR cva OR cerebrovascular OR cardiovascular OR musculoskeletal OR pain OR disorder* OR surgeon* OR

transplant* OR survivor* OR diabet* OR injur*).ti.) NOT ("Systematic Review"/ OR Meta Analysis/ OR case report/ OR ((systematic* ADJ3 review*) OR meta-analys* OR case-report*).ab,ti.)

Cochrane CENTRAL register of Trials

(((((physical* OR motor* OR psychomotor*) NEAR/3 (activit*)) OR exercise* OR sport* OR (physical NEAR/3 (education OR training)) OR locomotion* OR (Endurance NEAR/3 Training) OR walking OR running OR jogging OR yoga OR taichi OR tai NEXT chi OR martial NEXT art* OR qigong OR ((aerobic OR resistance OR physical*) NEAR/3 training)):ab,ti) AND ((depressi* OR anxiet* OR (somatic* NEAR/3 symptom*) OR (attention NEAR/3 deficit NEAR/3 (disorder* OR hyperactiv* OR problem*)) OR (hyperactivit* NEAR/3 problem*) OR adhd OR internalizing OR internalization* OR internalising OR internalisation* OR externalizing OR externalization* OR externalising OR externalisation* OR (conduct NEAR/3 (disorder* OR problem*)) OR (rule* NEAR/3 breaking NEAR/3 behav*) OR ((disrupt* OR problem*) NEAR/3 behav*)):ab,ti) AND ((mri OR (magnetic NEAR/3 resonance) OR (diffusion NEAR/3 tensor NEAR/3 imag*) OR electroencephalogra* OR eeg OR ((grey OR gray OR white) NEXT/1 matter*) OR (nervous NEXT system* NEAR/3 development*) OR neurogenesis* OR ((nerv* NEXT cell* OR Neuron*) NEAR/3 plasticit*) OR hormon* OR peptide* OR protein* OR neurotransmitter* OR opiate* OR opioid* OR serotonin* OR noradrenalin* OR norepinephrin* OR dopamin* OR monoamin* OR endorphin* OR neuroimmunolo* OR neuro NEXT immunolo* OR growth NEXT factor* OR (brain NEXT deriv* NEAR/3 neurotroph* NEXT factor*) OR neurotrophin* NEXT gene* OR IGF1 OR IGF NEXT 1 OR vasculotropin* OR VEGF OR BDNF OR VBM OR BOLD NEXT signal* OR (blood NEXT oxygen NEAR/3 level* NEAR/3 dependent*) OR volumetr* OR (brain NEAR/3 (function* OR asymmetry* OR metabol* OR structure*)) OR (functional* NEAR/3 connectiv*) OR (event NEXT related NEAR/3 brain NEXT potential*) OR ((emotion* OR psycholog*) NEAR/3 (intelligen* OR adjustment* OR regulation*)) OR (social* NEAR/3 (interacti* OR connected*)) OR (self NEXT/1 (esteem OR control* OR acceptan* OR awareness* OR concept OR efficac*)) OR (psychologic* NEAR/3 need*) OR autonom* OR belongingness* OR (perceived NEAR/3 abilit*) OR (confidence NOT (confidence NEXT interval*)):ab,ti) NOT (patient* OR athlete* OR breathing OR disease* OR Alzheimer* OR Parkinson* OR osteoarthritis* OR cancer OR neoplas* OR stroke OR cva OR cerebrovascular OR cardiovascular OR musculoskeletal OR pain OR disorder* OR surger* OR transplant* OR survivor* OR diabet* OR injur*):ti

Web of Science Core Collection

TS=(((physical* OR motor* OR psychomotor*) NEAR/2 (activit*)) OR exercise* OR sport* OR (physical NEAR/2 (education OR training)) OR locomotion* OR (Endurance NEAR/2 Training) OR walking OR running OR jogging OR yoga OR taichi OR tai-chi OR martial-art* OR qigong OR ((aerobic OR resistance OR physical*) NEAR/2 training))) AND ((depressi* OR anxiet* OR (somatic* NEAR/2 symptom*) OR (attention NEAR/2 deficit NEAR/2 (disorder* OR hyperactiv* OR problem*)) OR (hyperactivit* NEAR/2 problem*) OR adhd OR internalizing OR internalization* OR internalising OR internalisation* OR externalizing OR externalization* OR externalising OR externalisation* OR (conduct NEAR/2 (disorder* OR problem*)) OR (rule* NEAR/2 breaking NEAR/2 behav*) OR ((disrupt* OR problem*) NEAR/2 behav*))) AND ((mri OR (magnetic NEAR/2 resonance) OR (diffusion NEAR/2 tensor NEAR/2 imag*) OR electroencephalogra* OR eeg OR ((grey OR gray OR white) NEAR/1 matter*) OR (nervous-system* NEAR/2 development*) OR neurogenesis* OR ((nerv*-cell* OR Neuron*) NEAR/2 plasticit*) OR hormon* OR peptide* OR protein* OR neurotransmitter* OR opiate* OR opioid* OR serotonin* OR noradrenalin* OR norepinephrin* OR dopamin* OR monoamin* OR endorphin* OR neuroimmunolo* OR neuro-immunolo* OR growth-factor* OR (brain-deriv* NEAR/2 neurotroph*-factor*) OR neurotrophin*-gene* OR IGF1 OR IGF-1 OR vasculotropin* OR VEGF OR BDNF OR VBM OR BOLD-signal* OR (blood-oxygen NEAR/2 level* NEAR/2 dependent*) OR volumetr* OR (brain NEAR/2 (function* OR asymmetry* OR metabol* OR

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3 structure*)) OR (functional* NEAR/2 connectiv*) OR (event-related NEAR/2 brain-potential*)
4 OR ((emotion* OR psycholog*) NEAR/2 (intelligen* OR adjustment* OR regulation*)) OR
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6 acceptan* OR awareness* OR concept OR efficac*)) OR (psychologic* NEAR/2 need*) OR
7 autonom* OR belongingness* OR (perceived NEAR/2 abilit*) OR (confidence NOT
8 (confidence-interval*))) AND ((intervention* OR trial* OR random* OR rct OR prospective*
9 OR longitudinal* OR cohort* OR follow-up* OR cross-section*)) NOT TI=(patient* OR
10 athlete* OR breathing OR disease* OR Alzheimer* OR Parkinson* OR osteoarthritis* OR cancer
11 OR neoplas* OR stroke OR cva OR cerebrovascular OR cardiovascular OR musculoskeletal OR
12 pain OR disorder* OR surger* OR transplant* OR survivor* OR diabet* OR injur* OR
13 (systematic* NEAR/3 review*) OR meta-analys* OR case-report*) AND DT=(article) AND
14 LA=(english)
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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review (Page 1)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such (Page 1)
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number (Page 2)
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author (Page 1)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review (Page 10)
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments (No it does not present amendments)
Support:		
Sources	5a	Indicate sources of financial or other support for the review (Page 10)
Sponsor	5b	Provide name for the review funder and/or sponsor (Page 10)
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol (Page 10)
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known (Pages 4-5)
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) (Page 5)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review (Pages 5-7)
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage (Pages 7-8)
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated (Pages 16-20)
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review (Pages 7-8)

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) (Pages 7-8)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators (Pages 7-8)
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications (Page 13)
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale (Page 6)
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis (Pages 8-9)
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised (Page 9)
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) (Page 9)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Mechanisms linking physical activity with psychiatric symptoms across the lifespan: a protocol for a systematic review

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-058737.R1
Article Type:	Protocol
Date Submitted by the Author:	02-Mar-2022
Complete List of Authors:	Nguyen Ho, Phuong ; Erasmus University Rotterdam Ha, Tram ; The University of Danang Tong, Thao ; Erasmus Universiteit Rotterdam Bramer, Wichor; Erasmus MC, Medical Library Hofman, Amy; Erasmus MC Lubans, David; University of Newcastle, School of Education Vernooij, Meike; Erasmus MC Rodriguez-Ayllon, María; Erasmus Medical Center, Epidemiology
Primary Subject Heading:	Sports and exercise medicine
Secondary Subject Heading:	Mental health
Keywords:	Adult psychiatry < PSYCHIATRY, Child & adolescent psychiatry < PSYCHIATRY, SPORTS MEDICINE, MENTAL HEALTH

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Manuscripts

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3 **1 Mechanisms linking physical activity with psychiatric symptoms across the lifespan: a**
4 **2 protocol for a systematic review.**

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7 3 Phuong Thuy Nguyen Ho¹, Tram Ha Pham Bich², Thao Tong¹, Wichor M Bramer³, Amy
8 Hofman⁴, David R Lubans⁵, Meike W. Vernooij^{4,6*}, María Rodríguez-Ayllon⁴.

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2
3 **1 ABSTRACT**
4

5 **2 Introduction:** Persistent psychiatric symptomatology during childhood and adolescence predicts
6
7 vulnerability to experience mental illness in adulthood. Physical activity is well-known to provide
8
9 mental health benefits across the lifespan. However, the underlying mechanisms linking physical
10
11 activity and psychiatric symptoms remain underexplored. In this context, we aim to
12
13 systematically synthesize evidence focused on the mechanisms through which physical activity
14
15 might reduce psychiatric symptoms across all ages.
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17

18 **8 Methods and analysis:** With the aid of a biomedical information specialist, we will develop a
19
20 systematic search strategy based on the predetermined research question in the following
21
22 electronic databases: MEDLINE, Embase, Web of Science, Cochrane, and PsycINFO. Two
23
24 independent reviewers will screen and select studies, extract data, and assess the risk of bias. In
25
26 case of inability to reach a consensus, a third person will be consulted. We will not apply any
27
28 language restriction, and we will perform a qualitative synthesis of our findings as we anticipate
29
30 that studies are scarce and heterogeneous.
31
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33 **15 Ethics and dissemination:** Only data that has already been published will be included. Then,
34
35 ethical approval is not required. Findings will be published in a peer-reviewed journal and
36
37 presented at conferences. Additionally, we will communicate our findings to healthcare providers
38
39 and other sections of society (e.g., through regular channels, including social media).
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41 **19 PROSPERO registration number:** CRD42021239440
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1 **Strengths and limitations of this study**

- 2 • This protocol has been designed according to the Preferred Reporting Items for
3 Systematic Reviews and Meta Analyses for Protocols (PRISMA-P) guidelines and
4 guidelines of the Cochrane Effective Practice and Organisation of Care.
- 5 • This protocol presents a cautiously designed search strategy, inclusion and exclusion
6 criteria, and timespan and age-range coverage.
- 7 • A possible limitation is that included studies might be heterogeneous in the study design,
8 data collection methods, and data analysis which might limit the ability to synthesize the
9 results using a meta-analysis.
- 10 • The value of this systematic review depends on the quality and availability of the
11 evidence on the topic.

1 INTRODUCTION

2 Persistent psychiatric symptomatology in childhood and adolescence predicts vulnerability to
3 experience mental illness later in life¹. Specifically, individuals with mental illness have a
4 decreased life expectancy of 10–15 years² and a lower quality of life³ than individuals from the
5 general population. Psychiatric symptoms are typically grouped into two broad categories (i.e.,
6 internalizing/emotional, and externalizing/behavioral)⁴. Specifically, the externalizing problems
7 include a variety of disinhibited/externally-focused behavioral symptoms such as conduct
8 problems, rule-breaking behavior, attention-deficit/hyperactivity problems. On the contrary, the
9 internalizing disorder include a variety of over-inhibited/internally-focused symptoms, such as
10 depression, anxiety, or somatic symptoms. Several risk factors for psychiatric symptoms have
11 been well established in childhood (e.g., poverty and social disadvantage)⁵ and adulthood (e.g.,
12 level of education and physical illness)⁶. However, less is known about the protective factors (e.g.,
13 physical activity) that might contribute to decreasing both child and adult psychopathology.

14 There is a growing body of literature suggesting that physical activity has a small-to-
15 moderate positive effect on psychiatric symptoms in children and adolescents^{7–9}, but also adults
16 and older adults^{10,11}. However, most of the studies have focused on exploring the effect size of
17 the association or effect in terms of dose-response, while the mechanisms underlying this
18 relationship or effect remain underexplored. In 2016, Lubans et al.¹² published a systematic
19 review of the mechanisms linking physical activity and psychiatric symptoms in children and
20 adolescents. They proposed a conceptual model, which postulated three distinct yet intertwined
21 potential groups of mechanisms (i.e., neurobiological, psychosocial, and behavioral mechanisms).
22 In brief, they identified a lack of available evidence for the specific mechanisms responsible for
23 the effect of physical activity on mental and cognitive health in young people. Additionally, they
24 only included intervention studies, and although this type of design can provide evidence for
25 cause and effect, observational studies can also provide complementary information, particularly
26 when there is a lack of evidence on the topic.

27 In adults, only narrative reviews^{13–15}, mainly focused on cognition¹³ and depression^{14,15},
28 have explored the potential mechanisms that might link physical activity with psychiatric

1 symptoms in adulthood. For instance, Stillman et al.¹³ suggested that physical activity might
2 reduce depression and anxiety via psychosocial pathways (e.g., mood). Additionally, Kandola et
3 al.¹⁴ presented a conceptual framework of the key biological and psychosocial mechanisms
4 underlying the relationship between physical activity and depressive symptoms in adults.
5 However, no previous systematic reviews have been performed to synthesize the existing
6 evidence in adults.

7 Understanding the mechanisms linking physical activity with psychiatric symptoms may
8 help to explain, predict, and intervene more effectively, which could stimulate the identification
9 of cost-efficient alternative therapies for preventing and treating mental illness at all ages. To
10 establish this evidence-based, it is imperative to synthesize and update all relevant literature
11 mapping the mechanisms through which physical activity reduces psychiatric symptoms across
12 the lifespan.

13 **Objective**

14 We aim to conduct a systematic review to explore the underlying mechanisms linking physical
15 activity with psychiatric symptoms in humans of all ages.

16 **Review questions**

17 How does physical activity affect/associate with psychiatric symptoms via psychosocial,
18 neurobiological, and behavioral pathways across the lifespan?

19 **METHODS**

20 The present protocol follows the PRISMA-P guideline for systematic review and meta-analysis
21 protocols¹⁶. We will perform the search in March 2022, and we are planning to finish the
22 systematic review in June 2022.

23 **Patient and public involvement**

24 Patients and the public were not involved in the design, development, conduct, reporting or
25 dissemination of this study.

26 **Eligibility criteria**

27 We will include studies based on predefined criteria as summarized in **Table 1** and the text
28 below¹⁷.

1
2
3 1 *Population*
4

5 2 We will include human studies including participants of all ages. Studies including individuals
6
7 3 with physical or psychological disorders diagnosed by medical records, elite athletes, and animals
8
9 4 will be excluded.
10

11 5 *Intervention*
12

13 6 We will include all observational studies, which have explored the mechanisms through which
14
15 7 physical activity is associated with psychiatric symptoms. Intervention studies examining the
16
17 8 mechanisms through which physical activity affects psychiatric symptoms will be also included.
18
19 9 Studies in which physical fitness (i.e., capacity to perform physical activity, which refers to a full
20
21 10 range of physiological and psychological qualities)¹⁸, or sedentary behavior (i.e., any waking
22
23 11 behavior characterized by an energy expenditure ≤ 1.5 METs, while in a sitting, reclining or lying
24
25 12 posture)¹⁹ are the independent variables instead of physical activity (i.e., any bodily movement
26
27 13 produced by skeletal muscle that results in energy expenditure)²⁰ will be excluded. Additionally,
28
29 14 multiple health behavior intervention studies (e.g., co-interventions such as a dietary program
30
31 15 combined with physical activity) will be excluded because they preclude drawing conclusions on
32
33 16 the isolated effect of physical activity or sedentary behavior on psychiatric symptoms.
34
35

36 17 *Outcomes*
37

38 18 We will include the subscales of internalizing (i.e., depression, anxiety, somatic symptoms) and
39
40 19 externalizing (i.e., conduct problems, rule-breaking behavior, attention deficit/hyperactivity
41
42 20 problems) disorders.
43
44

45 21 *Study designs*
46

47 22 Intervention studies (randomized controlled trials [RCT], non-RCTs), prospective longitudinal
48
49 23 and cross-sectional studies will be included. We will not include conference proceedings and
50
51 24 other types of grey literature since risk of bias for these studies cannot be adequately assessed²¹.
52

53 25 *Potential mechanisms*
54

55 26 Studies will be included if they explored the role of any potential neurobiological, psychosocial,
56
57 27 or behavioral mechanisms in the relationship between physical activity and psychiatric
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59 28 symptoms. We will refer to the variables used to explore the potential mechanisms as “mediating
60

1 variables”, but we will include any study exploring the mechanisms linking physical activity and
2 psychiatric symptoms and not only those that used a mediation analysis.

3 *Further restrictions*

4 No language and publication date restriction will be applied. All databases will be searched from
5 their date of inception, and we will include every study that meets the above-mentioned criteria
6 regardless of the language.

7 **Search strategy for identifying relevant studies**

8 With the assistance of a biomedical information specialist, we will develop a systematic search
9 strategy based on the predetermined research question in the following electronic databases:
10 MEDLINE Ovid, Embase.com, Web of Science Core Collection, Cochrane CENTRAL register
11 of Trials, and PsycINFO Ovid. First, we will search for potentially relevant studies based on a
12 search strategy that is the combination of Medical Subject Headings (MeSH) terms for Medline
13 and Emtree terms for Embase and free text search. Our research team, including a librarian who
14 is specialized in search strategy development, has developed this search strategy. Search terms
15 are personalized to each database (see **Online supplemental appendix**). Search terms include
16 four parts: (1) terms to identify our independent variable (i.e., physical activity); (2) terms to
17 identify our mechanisms (i.e., neurobiological, psychosocial, behavioral mechanisms); (3) terms
18 to identify our outcome (i.e., psychiatric symptoms); and (4) terms to exclude articles that match
19 our exclusion criteria. An additional search for studies will be performed by screening reference
20 lists of included studies and their citations through Google Scholar. Third, we will contact experts
21 in the field to identify additional studies that may have been missed and any relevant ongoing or
22 unpublished studies.

23 **Study records**

24 *Data management*

25 First, we will extract all studies identified by the different sources into an EndNote Library.
26 Second, we will use a published method that uses this software to automatically eliminate the
27 duplicate studies²². In our final report, we will note the number of duplicates in the PRISMA flow
28 diagram (see **Figure 1**).

1 *Selection process*

2 First, two independent researchers (PTNH and THPB) will screen titles and the abstracts for
3 eligibility. When disagreements emerge between the two independent researchers, consensus will
4 be obtained through discussion or when required, the opinion of a third researcher (MR-A) will
5 be considered. Second, we will then obtain the full-text reports of studies that may fit eligibility
6 criteria based on this assessment. Afterward, the same two independent researchers (PTNH and
7 THPB) will assess eligibility based on the full texts. Any discrepancies will be again resolved
8 after discussion with a third researcher (MR-A).

9 **Data extraction process**

10 Two researchers (PTNH and TT) will independently extract data from the included studies to a
11 customized data extraction form developed a priori that has been piloted using one eligible study
12 (see **Table 2**). Again, any discrepancies will be resolved after discussion with a third researcher
13 (MR-A). We will contact authors for any relevant missing data.

14 From eligible studies, we will extract the following items: study background (name of
15 the first author, year, and study location), sample characteristics (number of participants, age of
16 participants, and percentage of female participants), design (intervention [RCT or non-RCT], or
17 observational [cross-sectional or longitudinal]), independent variables, dependent variables,
18 mediating variables, instruments used to assess the variables, statistical analyses and software,
19 confounders, and main findings. For intervention studies (RCTs and non-RCTs), we also extract
20 weeks of intervention, description of the program, intensity, duration, and frequency. For
21 longitudinal studies, we also extract years of follow-up.

22 **Risk of bias and quality of the evidence**

23 The risk of bias will be evaluated independently by two researchers (PTNH and TT) and
24 disagreements were solved in a consensus meeting with the same third researcher (MR-A). The
25 risk of bias will be evaluated using the Joanna Briggs Institute Critical Appraisal Tool for
26 Systematic Reviews (<https://jbi.global/critical-appraisal-tools>). This tool has already been used
27 by other authors in the field^{23,24}. In brief, this tool includes four specific checklists depending on
28 the study design (i.e., cross-sectional studies, longitudinal studies, RCTs and non-RCT). There

1 are four possible answers for each category: “yes” (criterion met), “no” (criterion not met),
2 “unclear” or “not applicable”. The specific tools include: eight items for cross-sectional studies,
3 11 items for longitudinal studies, nine items for non-RCTs and thirteen items for RCTs. Studies
4 will be categorized as “high risk” or “low risk”. Specifically, the studies will be considered as
5 “low risk” if at least 75% of the applicable items are scored as “yes” (criterion met). In contrast,
6 articles will be considered “high risk” when less than 75% of the applicable items were scored as
7 “yes”. This classification has been previously employed by Molina-Garcia et al.²⁵.

8 Lastly, the Grading of Recommendations Assessment, Development and Evaluation
9 framework will be used to assess the quality of the evidence across studies.

10 **Data synthesis and analysis**

11 In case overlapping populations are analyzed in multiple studies, we will include according to the
12 following hierarchy the study that (1) has the lowest risk of bias, or (2) incorporates the largest
13 sample size. In the case when a study reports multiple effect estimates for overlapping
14 populations, we will select according to the following hierarchy: (1) the most adjusted model, (2)
15 the closest time-point to the end of the intervention, or (3) the largest treatment group. Findings
16 from observational and intervention studies will be rated using the method first employed by
17 Sallis et al.²⁶, and more recently by Lubans et al.¹², and Rodriguez-Ayllon et al.⁹. If 0–33% of
18 studies reported a statistically significant mediation (e.g., self-esteem) between the independent
19 (e.g., physical activity) and dependent variable (e.g., depressive symptoms), the result will be
20 classified as no association (\emptyset); if 34–59% of studies reported a significant mediation, or if fewer
21 than four studies reported on the outcome, the result will be classified as being
22 inconsistent/uncertain (?); and if $\geq 60\%$ of studies found a statistically significant mediation, the
23 result will be classified as significant (\checkmark).

24 **Ethics and dissemination**

25 We will communicate our findings to researchers, pediatricians, health professionals, and lectures
26 through scientific seminars and conferences. Additionally, we will disseminate our results using
27 different approaches. Specifically, we will publish press articles in public journals and magazines,
28 do radio and television interviews, and publish our findings in a scientific peer-review journal.

1 We will also present our main results to policymakers and healthcare providers, which might
2 impact policy and healthcare practice.

3 **Funding**

4 This work was supported by the Ramón Areces Foundation.

5 **Disclaimer**

6 The funders of the present study did not have any role in the design, decision to publish or
7 preparation of the protocol.

8 **Competing interests**

9 None declared.

10 **Patient consent**

11 Not required.

12 **Ethics approval**

13 As systematic reviews use publicly available data, no formal ethical review and approval are
14 needed.

15 **Provenance and peer review**

16 Not commissioned, externally peer reviewed.

17 **Open access**

18 This is an open access article distributed in accordance with the Creative Commons Attribution
19 Non-Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build
20 upon this work non-commercially, and license their derivative works on different terms, provided
21 the original work is properly cited, appropriate credit is given, any changes made indicated, and
22 the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

23 **Authors' contributions**

24 MR-A, PTNH designed and drafted the protocol. WMB performed the search strategy. MR-A,
25 PTNH, THPB, TT, AH, DRL, MV revised and approved the final version of the manuscript. MR-
26 A will be the guarantor of the review.

27 **Word count**

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Table 1. Inclusion criteria based on PICOS strategy.

PICOS	Inclusion criteria	Exclusion criteria
Population	<ol style="list-style-type: none"> All ages across the lifespan: infancy and toddlerhood (birth to age 2), preschoolers (2–5 years), children (6–11 years), adolescents (12–18 years), young and middle adults (18– 65), late adulthood (+65). Human studies. 	<ol style="list-style-type: none"> Studies including individuals with physical or psychological disorders diagnosed by medical records. Elite athletes. Animal studies.
Intervention	<ol style="list-style-type: none"> Observational studies, which explored the mechanisms through which physical activity is associated with psychiatric symptoms. Studies examining the mechanisms through which physical activity has a positive effect on psychiatric symptoms. 	<ol style="list-style-type: none"> Multiple health behavior intervention studies (e.g., co-interventions such as a dietary program combined with physical activity). Studies in which physical fitness (i.e., capacity to perform physical activity, which refers to a full range of physiological and psychological qualities)¹⁸, or sedentary behavior (i.e., any waking behavior characterized by an energy expenditure ≤ 1.5 METs, while in a sitting, reclining or lying posture)¹⁹ are the independent variables instead of physical activity (i.e., any bodily movement produced by skeletal muscle that results in energy expenditure)²⁰.
Comparison	<ol style="list-style-type: none"> Not applicable 	
Outcomes	<ol style="list-style-type: none"> The subscales of internalizing symptoms (i.e., depression, anxiety, somatic symptoms) and externalizing symptoms (i.e., conduct problems, rule-breaking behavior, attention deficit/hyperactivity problems). 	
Study design	<ol style="list-style-type: none"> Intervention studies (randomized controlled trials, non-randomized control trials), prospective longitudinal studies and cross-sectional studies. 	<ol style="list-style-type: none"> Conference proceedings and other types of grey literature. Narrative reviews, systematic reviews, or meta-analyses.

Table 2. Summary of research investigating the mechanisms linking physical activity with psychiatric symptoms (n = 7).

Authors, year (country)	n sample (mean age ± SD, % females)	Design; target population	Independent variable (instrument)	Mediating variable (instrument)	Dependent variable (instrument)	Statistical analysis; software	Confounders	Main findings

SD= Standard deviation.

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Figure 1. Flow diagram for study selection.

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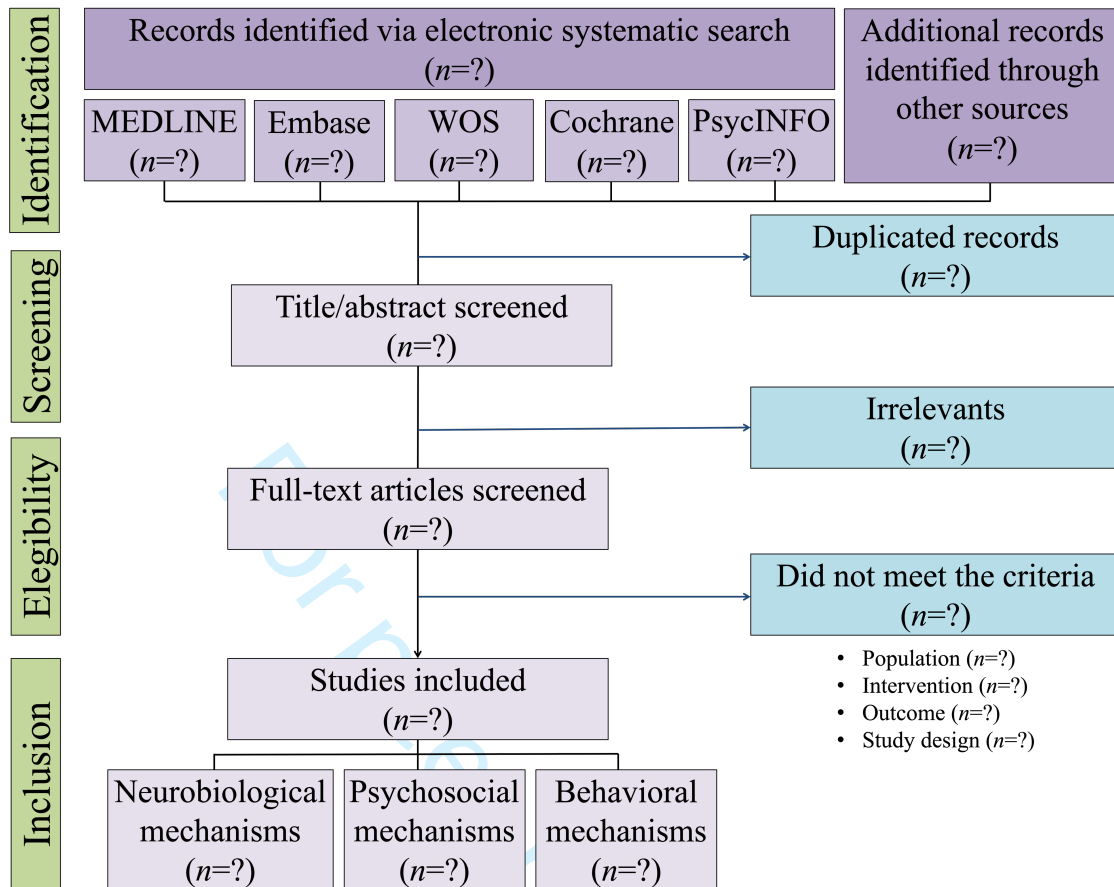


Figure 1. Flow diagram for study selection.

ONLINE SUPPLEMENTAL APPENDIX

Database searched	via	Years of coverage
Embase	Embase.com	1971 - Present
Medline ALL	Ovid	1946 - Present
Web of Science Core Collection*	Web of Knowledge	1975 - Present
Cochrane Central Register of Controlled Trials	Wiley	1992 - Present
PsycINFO	Ovid	1806 - Present

*Science Citation Index Expanded (1975-present) ; Social Sciences Citation Index (1975-present); Arts & Humanities Citation Index (1975-present) ; Conference Proceedings Citation Index- Science (1990-present); Conference Proceedings Citation Index- Social Science & Humanities (1990-present) ; Emerging Sources Citation Index (2015-present)

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(exercise/exp OR 'physical activity'/de OR Climbing/exp OR running/exp OR walking/exp OR 'cycling'/de OR 'fighting'/de OR 'jogging'/de OR 'jumping'/de OR 'lifting effort'/de OR 'nordic walking'/de OR 'racewalking'/de OR 'stretching'/de OR 'swimming'/de OR 'weight bearing'/de OR 'weight lifting'/de OR sport/exp OR 'motor activity'/de OR 'psychomotor activity'/de OR 'physical education'/de OR locomotion/de OR swimming/de OR walking/exp OR (((physical* OR motor* OR psychomotor*) NEAR/3 (activit*)) OR exercise* OR sport* OR (physical NEAR/3 (education OR training)) OR locomotion* OR (Endurance NEAR/3 Training) OR walking OR running OR jogging OR yoga OR taichi OR tai-chi OR martial-art* OR qigong OR ((aerobic OR resistance OR physical*) NEAR/3 training)):ab,ti) AND (depression/exp OR 'anxiety disorder'/exp OR anxiety/de OR 'somatic symptom'/de OR 'attention deficit disorder'/de OR 'internalizing disorder'/de OR 'internalization (behavior)'/de OR 'externalizing disorder'/de OR 'externalization (behavior)'/de OR 'conduct disorder'/de OR 'rule breaking behavior'/de OR 'disruptive behavior'/exp OR (depressi* OR anxiet* OR (somatic* NEAR/3 symptom*) OR (attention NEAR/3 deficit NEAR/3 (disorder* OR hyperactiv* OR problem*)) OR (hyperactivit* NEAR/3 problem*) OR adhd OR internalizing OR internalization* OR internalising OR internalisation* OR externalizing OR externalization* OR externalising OR externalisation* OR (conduct NEAR/3 (disorder* OR problem*)) OR (rule* NEAR/3 breaking NEAR/3 behav*) OR ((disrupt* OR problem*) NEAR/3 behav*)):ab,ti) AND ('nuclear magnetic resonance imaging'/exp OR 'diffusion tensor imaging'/exp OR electroencephalography/exp OR electroencephalogram/exp OR 'gray matter'/exp OR 'white matter'/exp OR 'nervous system development'/exp OR 'nerve cell plasticity'/exp OR 'biological marker'/de OR marker/de OR hormone/exp OR peptide/exp OR protein/exp OR neurotransmitter/de OR opiate/de OR serotonin/de OR 'serotonin level'/exp OR noradrenalin/de OR dopamine/de OR monoamine/de OR endorphin/de OR neuroimmunology/de OR 'growth factor'/exp OR 'brain derived neurotrophic factor'/de OR 'neurotrophin gene'/de OR vasculotropin/de OR 'BOLD signal'/de OR volumetry/de OR 'brain function'/de OR 'functional connectivity'/de OR 'brain asymmetry'/de OR 'brain metabolism'/de OR 'brain structure'/de OR 'inflammatory marker'/de OR 'event related brain potential'/de OR 'emotional intelligence'/de OR 'social interaction'/de OR 'self esteem'/exp OR 'self control'/exp OR 'social connectedness'/exp OR 'self acceptance'/exp OR 'personal autonomy'/de OR belongingness/de OR confidence/de OR 'self confidence'/de OR 'self concept'/de OR (mri OR (magnetic NEAR/3 resonance) OR (diffusion NEAR/3 tensor NEAR/3 imag*) OR electroencephalogra* OR eeg OR ((grey OR gray OR white) NEXT/1 matter*) OR (nervous-system* NEAR/3 development*) OR neurogenesis* OR ((nerv*-cell* OR Neuron*) NEAR/3 plasticit*) OR hormon* OR peptide* OR protein* OR neurotransmitter* OR opiate* OR opioid* OR serotonin* OR noradrenalin* OR norepinephrin* OR dopamin* OR monoamin* OR endorphin* OR neuroimmunolo* OR neuro-immunolo* OR growth-factor* OR (brain-deriv* NEAR/3 neurotroph*-factor*) OR neurotrophin*-gene* OR IGF1 OR IGF-1 OR vasculotropin* OR VEGF OR BDNF OR VBM OR BOLD-signal* OR (blood-oxygen NEAR/3 level* NEAR/3

dependent*) OR volumetr* OR (brain NEAR/3 (function* OR asymmetry* OR metabol* OR structure*)) OR (functional* NEAR/3 connectiv*) OR (event-related NEAR/3 brain-potential*) OR ((emotion* OR psycholog*) NEAR/3 (intelligen* OR adjustment* OR regulation*)) OR (social* NEAR/3 (interacti* OR connected*)) OR (self NEXT/1 (esteem OR control* OR acceptan* OR awareness* OR concept OR efficac*)) OR (psychologic* NEAR/3 need*) OR autonom* OR belongingness* OR (perceived NEAR/3 abilit*) OR (confidence NOT (confidence-interval*)):ab,ti) AND ('intervention study'/de OR 'clinical trial'/exp OR randomization/exp OR 'prospective study'/exp OR 'longitudinal study'/exp OR 'cohort analysis'/de OR 'follow up'/de OR 'cross-sectional study'/de OR 'major clinical study'/de OR (intervention* OR trial* OR random* OR rct OR prospective* OR longitudinal* OR cohort* OR follow-up* OR cross-section*):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT (patient/exp/mj OR athlete/exp/mj OR 'breathing exercise'/mj OR 'degenerative disease'/exp/mj OR neoplasm/exp/mj OR 'cerebrovascular disease'/exp/mj OR 'cardiovascular disease'/exp/mj OR 'musculoskeletal disease'/exp/mj OR pain/exp/mj OR surgery/exp/mj OR survivor/exp/mj OR diabetes/exp/mj OR (patient* OR athlete* OR breathing OR disease* OR Alzheimer* OR Parkinson* OR osteoarthritis* OR cancer OR neoplas* OR stroke OR cva OR cerebrovascular OR cardiovascular OR musculoskeletal OR pain OR disorder* OR surger* OR transplant* OR survivor* OR diabet* OR injur*):ti) NOT [conference abstract]/lim NOT ('systematic review'/de OR 'meta analysis'/de OR 'case report'/de OR ((systematic* NEAR/3 review*) OR meta-analys* OR case-report*):Ab,ti)

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(Exercise/ OR Climbing/ OR Running/ OR Walking/ OR Bicycling/ OR Jogging/ OR Weight-Bearing/ OR Weight Lifting/ OR exp Sports/ OR Motor Activity/ OR "Physical Education and Training"/ OR Locomotion/ OR Swimming/ OR (((physical* OR motor* OR psychomotor*) ADJ3 (activit*)) OR exercise* OR sport* OR (physical ADJ3 (education OR training)) OR locomotion* OR (Endurance ADJ3 Training) OR walking OR running OR jogging OR yoga OR taichi OR tai-chi OR martial-art* OR qigong OR ((aerobic OR resistance OR physical*) ADJ3 training)).ab,ti.) AND (exp Depressive Disorder/ OR Depression/ OR exp Anxiety Disorders/ OR Anxiety/ OR Medically Unexplained Symptoms/ OR exp "Attention Deficit and Disruptive Behavior Disorders"/ OR Conduct Disorder/ OR Problem Behavior/ OR (depressi* OR anxiet* OR (somatic* ADJ3 symptom*) OR (attention ADJ3 deficit ADJ3 (disorder* OR hyperactiv* OR problem*)) OR (hyperactivit* ADJ3 problem*) OR adhd OR internalizing OR internalization* OR internalising OR internalisation* OR externalizing OR externalization* OR externalising OR externalisation* OR (conduct ADJ3 (disorder* OR problem*)) OR (rule* ADJ3 breaking ADJ3 behav*) OR ((disrupt* OR problem*) ADJ3 behav*)):ab,ti.) AND (exp Magnetic Resonance Imaging/ OR exp Diffusion Tensor Imaging/ OR Electroencephalography/ OR Gray Matter/ OR White Matter/ OR Biomarkers/ OR Hormones/ OR Peptides/ OR Proteins/ OR Neurotransmitter Agents/ OR Opiate Alkaloids/ OR Serotonin/ OR Norepinephrine/ OR Dopamine/ OR Endorphins/ OR Opioid Peptides/ OR Intercellular Signaling Peptides and Proteins/ OR Brain-Derived Neurotrophic Factor/ OR Vascular Endothelial Growth Factor A/ OR BOLD signal/ OR Emotional Intelligence/ OR Social Interaction/ OR Self-Control/ OR Personal Autonomy/ OR Self Concept/ OR (mri OR (magnetic ADJ3 resonance) OR (diffusion ADJ3 tensor ADJ3 imag*) OR electroencephalogra* OR eeg OR ((grey OR gray OR white) ADJ matter*) OR (nervous-system* ADJ3 development*) OR neurogenesis* OR ((nerv*-cell* OR Neuron*) ADJ3 plasticit*) OR hormon* OR peptide* OR protein* OR neurotransmitter* OR opiate* OR opioid* OR serotonin* OR noradrenalin* OR norepinephrin* OR dopamin* OR monoamin* OR endorphin* OR neuroimmunolo* OR neuro-immunolo* OR growth-factor* OR (brain-deriv* ADJ3 neurotroph*-factor*) OR neurotrophin*-gene* OR IGF1 OR IGF-1 OR vasculotropin* OR VEGF OR BDNF OR VBM OR BOLD-signal* OR (blood-oxygen ADJ3 level* ADJ3 dependent*) OR volumetr* OR (brain ADJ3 (function* OR asymmetry* OR metabol* OR structure*)) OR (functional* ADJ3 connectiv*) OR (event-related ADJ3 brain-potential*) OR ((emotion* OR psycholog*) ADJ3 (intelligen* OR adjustment* OR regulation*)) OR (social* ADJ3 (interacti* OR connected*)) OR (self ADJ (esteem OR control* OR acceptan*

OR awareness* OR concept OR efficac*) OR (psychologic* ADJ3 need*) OR autonom* OR belongingness* OR (perceived ADJ3 abilit*) OR (confidence NOT (confidence-interval*)).ab,ti.) AND (exp Clinical Trial/ OR Random Allocation/ OR exp Cohort Studies/ OR Cross-Sectional Studies/ OR (intervention* OR trial* OR random* OR rct OR prospective* OR longitudinal* OR cohort* OR follow-up* OR cross-section*).ab,ti.) NOT (exp animals/ NOT humans/) NOT (exp * Patients/ OR exp * Athletes/ OR * Breathing Exercises/ OR exp * Neoplasms/ OR exp * Cerebrovascular Disorders/ OR exp * Cardiovascular Diseases/ OR exp * Musculoskeletal Diseases/ OR *exp Pain/ OR exp * Surgical Procedures, Operative/ OR exp * Survivors/ OR *exp Diabetes Mellitus/ OR (patient* OR athlete* OR breathing OR disease* OR Alzheimer* OR Parkinson* OR osteoarthritis* OR cancer OR neoplas* OR stroke OR cva OR cerebrovascular OR cardiovascular OR musculoskeletal OR pain OR disorder* OR surgeon* OR transplant* OR survivor* OR diabet* OR injur*).ti.) NOT (Systematic Review/ OR Meta-Analysis/ OR case report/ OR ((systematic* ADJ3 review*) OR meta-analys* OR case-report*).ab,ti.)

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(exp Exercise/ OR Physical Activity/ OR exp Sports/ OR (((physical* OR motor* OR psychomotor*) ADJ3 (activit*)) OR exercise* OR sport* OR (physical ADJ3 (education OR training)) OR locomotion* OR (Endurance ADJ3 Training) OR walking OR running OR jogging OR yoga OR taichi OR tai-chi OR martial-art* OR qigong OR ((aerobic OR resistance OR physical*) ADJ3 training)).ab,ti.) AND (exp Major Depression/ OR "Depression (Emotion)"/ OR exp Anxiety Disorders/ OR Anxiety/ OR exp Attention Deficit Disorder with Hyperactivity / OR Conduct Disorder/ OR Behavior Problems / OR (depressi* OR anxiet* OR (somatic* ADJ3 symptom*) OR (attention ADJ3 deficit ADJ3 (disorder* OR hyperactiv* OR problem*)) OR (hyperactivit* ADJ3 problem*) OR adhd OR internalizing OR internalization* OR internalising OR internalisation* OR externalizing OR externalization* OR externalising OR externalisation* OR (conduct ADJ3 (disorder* OR problem*)) OR (rule* ADJ3 breaking ADJ3 behav*) OR ((disrupt* OR problem*) ADJ3 behav*).ab,ti.) AND (exp Magnetic Resonance Imaging/ OR exp Diffusion Tensor Imaging/ OR Electroencephalography/ OR Gray Matter/ OR White Matter/ OR Biological Markers / OR Hormones/ OR Peptides/ OR Proteins/ OR Neurotransmitters / OR Opiates / OR Serotonin/ OR Norepinephrine/ OR Dopamine/ OR Endorphins/ OR Brain Derived Neurotrophic Factor / OR Emotional Intelligence/ OR Social Interaction/ OR Self-Control/ OR Autonomy/ OR Self-Concept/ OR (mri OR (magnetic ADJ3 resonance) OR (diffusion ADJ3 tensor ADJ3 imag*) OR electroencephalogra* OR eeg OR ((grey OR gray OR white) ADJ3 matter*) OR (nervous-system* ADJ3 development*) OR neurogenesis* OR ((nerv*-cell* OR Neuron*) ADJ3 plasticit*) OR hormon* OR peptide* OR protein* OR neurotransmitter* OR opiate* OR opioid* OR serotonin* OR noradrenalin* OR norepinephrin* OR dopamin* OR monoamin* OR endorphin* OR neuroimmunolo* OR neuro-immunolo* OR growth-factor* OR (brain-deriv* ADJ3 neurotroph*-factor*) OR neurotrophin*-gene* OR IGF1 OR IGF-1 OR vasculotropin* OR VEGF OR BDNF OR VBM OR BOLD-signal* OR (blood-oxygen ADJ3 level* ADJ3 dependent*) OR volumetr* OR (brain ADJ3 (function* OR asymmetry* OR metabol* OR structure*)) OR (functional* ADJ3 connectiv*) OR (event-related ADJ3 brain-potential*) OR ((emotion* OR psycholog*) ADJ3 (intelligen* OR adjustment* OR regulation*)) OR (social* ADJ3 (interacti* OR connected*)) OR (self ADJ3 (esteem OR control* OR acceptan* OR awareness* OR concept OR efficac*)) OR (psychologic* ADJ3 need*) OR autonom* OR belongingness* OR (perceived ADJ3 abilit*) OR (confidence NOT (confidence-interval*)).ab,ti.) AND (exp Clinical Trials / OR exp Cohort Analysis / OR (intervention* OR trial* OR random* OR rct OR prospective* OR longitudinal* OR cohort* OR follow-up* OR cross-section*).ab,ti.) NOT (exp animals/ NOT humans/) NOT (exp * Patients/ OR exp * Athletes/ OR exp * Neoplasms/ OR exp * Cerebrovascular Disorders/ OR exp * Cardiovascular Disorders / OR exp * Musculoskeletal Disorders / OR *exp Pain/ OR exp * Surgery / OR exp * Survivors/ OR *exp Diabetes Mellitus/ OR (patient* OR athlete* OR breathing OR disease* OR Alzheimer* OR Parkinson* OR osteoarthritis* OR cancer OR neoplas* OR stroke OR cva OR cerebrovascular OR cardiovascular OR musculoskeletal OR pain OR disorder* OR surgeon* OR

transplant* OR survivor* OR diabet* OR injur*).ti.) NOT ("Systematic Review"/ OR Meta Analysis/ OR case report/ OR ((systematic* ADJ3 review*) OR meta-analys* OR case-report*).ab,ti.)

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(((((physical* OR motor* OR psychomotor*) NEAR/3 (activit*)) OR exercise* OR sport* OR (physical NEAR/3 (education OR training)) OR locomotion* OR (Endurance NEAR/3 Training) OR walking OR running OR jogging OR yoga OR taichi OR tai NEXT chi OR martial NEXT art* OR qigong OR ((aerobic OR resistance OR physical*) NEAR/3 training)):ab,ti) AND ((depressi* OR anxiet* OR (somatic* NEAR/3 symptom*) OR (attention NEAR/3 deficit NEAR/3 (disorder* OR hyperactiv* OR problem*)) OR (hyperactivit* NEAR/3 problem*) OR adhd OR internalizing OR internalization* OR internalising OR internalisation* OR externalizing OR externalization* OR externalising OR externalisation* OR (conduct NEAR/3 (disorder* OR problem*)) OR (rule* NEAR/3 breaking NEAR/3 behav*) OR ((disrupt* OR problem*) NEAR/3 behav*)):ab,ti) AND ((mri OR (magnetic NEAR/3 resonance) OR (diffusion NEAR/3 tensor NEAR/3 imag*) OR electroencephalogra* OR eeg OR ((grey OR gray OR white) NEXT/1 matter*) OR (nervous NEXT system* NEAR/3 development*) OR neurogenesis* OR ((nerv* NEXT cell* OR Neuron*) NEAR/3 plasticit*) OR hormon* OR peptide* OR protein* OR neurotransmitter* OR opiate* OR opioid* OR serotonin* OR noradrenalin* OR norepinephrin* OR dopamin* OR monoamin* OR endorphin* OR neuroimmunolo* OR neuro NEXT immunolo* OR growth NEXT factor* OR (brain NEXT deriv* NEAR/3 neurotroph* NEXT factor*) OR neurotrophin* NEXT gene* OR IGF1 OR IGF NEXT 1 OR vasculotropin* OR VEGF OR BDNF OR VBM OR BOLD NEXT signal* OR (blood NEXT oxygen NEAR/3 level* NEAR/3 dependent*) OR volumetr* OR (brain NEAR/3 (function* OR asymmetry* OR metabol* OR structure*)) OR (functional* NEAR/3 connectiv*) OR (event NEXT related NEAR/3 brain NEXT potential*) OR ((emotion* OR psycholog*) NEAR/3 (intelligen* OR adjustment* OR regulation*)) OR (social* NEAR/3 (interacti* OR connected*)) OR (self NEXT/1 (esteem OR control* OR acceptan* OR awareness* OR concept OR efficac*)) OR (psychologic* NEAR/3 need*) OR autonom* OR belongingness* OR (perceived NEAR/3 abilit*) OR (confidence NOT (confidence NEXT interval*)):ab,ti) NOT (patient* OR athlete* OR breathing OR disease* OR Alzheimer* OR Parkinson* OR osteoarthritis* OR cancer OR neoplas* OR stroke OR cva OR cerebrovascular OR cardiovascular OR musculoskeletal OR pain OR disorder* OR surger* OR transplant* OR survivor* OR diabet* OR injur*):ti)

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TS=((((physical* OR motor* OR psychomotor*) NEAR/2 (activit*)) OR exercise* OR sport* OR (physical NEAR/2 (education OR training)) OR locomotion* OR (Endurance NEAR/2 Training) OR walking OR running OR jogging OR yoga OR taichi OR tai-chi OR martial-art* OR qigong OR ((aerobic OR resistance OR physical*) NEAR/2 training))) AND ((depressi* OR anxiet* OR (somatic* NEAR/2 symptom*) OR (attention NEAR/2 deficit NEAR/2 (disorder* OR hyperactiv* OR problem*)) OR (hyperactivit* NEAR/2 problem*) OR adhd OR internalizing OR internalization* OR internalising OR internalisation* OR externalizing OR externalization* OR externalising OR externalisation* OR (conduct NEAR/2 (disorder* OR problem*)) OR (rule* NEAR/2 breaking NEAR/2 behav*) OR ((disrupt* OR problem*) NEAR/2 behav*))) AND ((mri OR (magnetic NEAR/2 resonance) OR (diffusion NEAR/2 tensor NEAR/2 imag*) OR electroencephalogra* OR eeg OR ((grey OR gray OR white) NEAR/1 matter*) OR (nervous-system* NEAR/2 development*) OR neurogenesis* OR ((nerv*-cell* OR Neuron*) NEAR/2 plasticit*) OR hormon* OR peptide* OR protein* OR neurotransmitter* OR opiate* OR opioid* OR serotonin* OR noradrenalin* OR norepinephrin* OR dopamin* OR monoamin* OR endorphin* OR neuroimmunolo* OR neuro-immunolo* OR growth-factor* OR (brain-deriv* NEAR/2 neurotroph*-factor*) OR neurotrophin*-gene* OR IGF1 OR IGF-1 OR vasculotropin* OR VEGF OR BDNF OR VBM OR BOLD-signal* OR (blood-oxygen NEAR/2 level* NEAR/2 dependent*) OR volumetr* OR (brain NEAR/2 (function* OR asymmetry* OR metabol* OR

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3 structure*)) OR (functional* NEAR/2 connectiv*) OR (event-related NEAR/2 brain-potential*)
4 OR ((emotion* OR psycholog*) NEAR/2 (intelligen* OR adjustment* OR regulation*)) OR
5 (social* NEAR/2 (interacti* OR connected*)) OR (self NEAR/1 (esteem OR control* OR
6 acceptan* OR awareness* OR concept OR efficac*)) OR (psychologic* NEAR/2 need*) OR
7 autonom* OR belongingness* OR (perceived NEAR/2 abilit*) OR (confidence NOT
8 (confidence-interval*)) AND ((intervention* OR trial* OR random* OR rct OR prospective*
9 OR longitudinal* OR cohort* OR follow-up* OR cross-section*)) NOT TI=(patient* OR
10 athlete* OR breathing OR disease* OR Alzheimer* OR Parkinson* OR osteoarthritis* OR cancer
11 OR neoplas* OR stroke OR cva OR cerebrovascular OR cardiovascular OR musculoskeletal OR
12 pain OR disorder* OR surger* OR transplant* OR survivor* OR diabet* OR injur* OR
13 (systematic* NEAR/3 review*) OR meta-analys* OR case-report*) AND DT=(article) AND
14 LA=(english)
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For peer review only

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review (Page 1)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such (Page 1)
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number (Page 2)
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author (Page 1)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review (Page 10)
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments (No it does not present amendments)
Support:		
Sources	5a	Indicate sources of financial or other support for the review (Page 10)
Sponsor	5b	Provide name for the review funder and/or sponsor (Page 10)
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol (Page 10)
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known (Pages 4-5)
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) (Page 5)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review (Pages 5-7)
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage (Pages 7-8)
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated (Pages 16-20)
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review (Pages 7-8)

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) (Pages 7-8)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators (Pages 7-8)
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications (Page 13)
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale (Page 6)
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis (Pages 8-9)
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised (Page 9)
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) (Page 9)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.