







BMJ Open Mechanisms linking physical activity with psychiatric symptoms across the lifespan: a protocol for a 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 synthesise 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 have 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 (eg, through regular channels, including social media).

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INTRODUCTION

Persistent psychiatric symptomatology in childhood and adolescence predicts vulnerability to experience mental illness later in life.¹ For instance, It is known that 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 (ie, internalising/emotional and externalising/behavioural).⁴ Specifically, the externalising

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 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 time-span 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 synthesise the results using a meta-analysis.
- The value of this systematic review depends on the quality and availability of the evidence on the topic.

problems include a variety of disinhibited/externally focused behavioural symptoms such as conduct problems, rule-breaking behaviour, attention-deficit/hyperactivity problems. On the contrary, the internalising disorder include a variety of overinhibited/internally focused symptoms, such as depression, anxiety or somatic symptoms. Several risk factors for psychiatric symptoms have been well established in childhood (eg, poverty and social disadvantage)⁵ and adulthood (eg, level of education and physical illness).⁶ However, less is known about the protective factors (eg, physical activity) that might contribute to decreasing both child and adult psychopathology.

There is a growing body of literature suggesting that physical activity has a small-to-moderate positive effect on psychiatric symptoms in children and adolescents,^{7–9} and in adults and older adults.^{10 11} However, most of the studies have focused on exploring the effect size of the association or effect in terms

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 years), late adulthood (+65 years). 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 behaviour intervention studies (eg, co-interventions such as a dietary programme combined with physical activity). Studies in which physical fitness (ie, capacity to perform physical activity, which refers to a full range of physiological and psychological qualities),¹⁸ or sedentary behaviour (ie, any waking behaviour characterised by an energy expenditure ≤ 1.5 METs, while in a sitting, reclining or lying posture)¹⁹ are the independent variables instead of physical activity (ie, any bodily movement produced by skeletal muscle that results in energy expenditure).²⁰
Comparison	1. Not applicable.	
Outcomes	1. The subscales of internalising symptoms (ie, depression, anxiety, somatic symptoms) and externalising symptoms (ie, conduct problems, rule-breaking behaviour, attention-deficit/hyperactivity problems).	
Study design	1. Intervention studies (randomised controlled trials, non-randomised controlled 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.

MET, metabolic equivalent of task.

of dose-response, while the mechanisms underlying this relationship or effect remain underexplored. In 2016, Lubans *et al*¹² 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 (ie, neurobiological, psychosocial and behavioural 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, they only included intervention studies, and although this type of design can provide evidence for cause and effect, observational studies can also provide complementary information, particularly when there is a lack of evidence on the topic.

In adults, only narrative reviews,^{13–15} mainly focused on cognition¹³ and depression,^{14 15} have explored the potential mechanisms that might link physical activity with psychiatric symptoms in adulthood. For instance, Stillman *et al*¹³ suggested that physical activity might reduce depression and anxiety via psychosocial pathways (eg, mood). Additionally, Kandola *et al*¹⁴ presented a conceptual framework of the key biological and psychosocial mechanisms underlying the relationship between physical activity and depressive symptoms in adults. However, no previous systematic reviews have been performed to synthesise the existing evidence in adults.

Understanding the mechanisms linking physical activity with psychiatric symptoms may help to explain, predict and intervene more effectively, which could stimulate the identification of cost-efficient alternative therapies for preventing and treating mental illness at all ages. To establish this

evidence-based, it is imperative to synthesise and update all relevant literature mapping the mechanisms through which physical activity reduces psychiatric symptoms across the lifespan.

Objective

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

Review questions

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

METHODS

The present protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for Protocols guideline for systematic review and meta-analysis protocols.¹⁶ We will perform the search in March 2022, and we are planning to finish the systematic review in June 2022.

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 summarised in [table 1](#) and the text.¹⁷

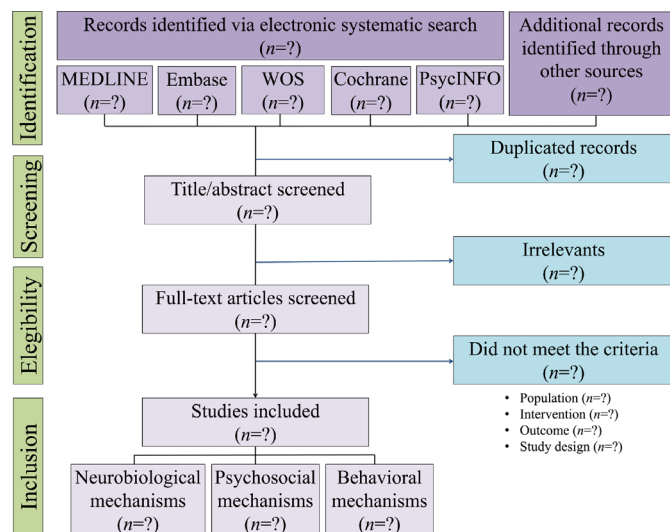


Figure 1 Flow diagram for study selection. WOS, Web of Science.

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 all 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 (ie, capacity to perform physical activity, which refers to a full range of physiological and psychological qualities),¹⁸ or sedentary behaviour (ie, any waking behaviour characterised by an energy expenditure ≤ 1.5 METs, while in a sitting, reclining or lying posture)¹⁹ are the independent variables instead of physical activity (ie, any bodily movement produced by skeletal muscle that results in energy expenditure)²⁰ will be excluded. Additionally, multiple health behaviour intervention studies (eg, co-interventions such as a dietary programme combined with physical activity) will be excluded because they preclude drawing conclusions on the isolated effect of physical activity or sedentary behaviour on psychiatric symptoms.

Outcomes

We will include the subscales of internalising (ie, depression, anxiety, somatic symptoms) and externalising (ie, conduct problems, rule-breaking behaviour, attention-deficit/hyperactivity problems) disorders.

Study designs

Intervention studies (randomised controlled trials (RCTs), non-RCTs), prospective longitudinal and cross-sectional studies will be included. We will not include conference

proceedings and other types of grey literature since risk of bias for these studies cannot be adequately assessed.²¹

Potential mechanisms

Studies will be included if they explored the role of any potential neurobiological, psychosocial or behavioural mechanisms in the relationship between physical activity and psychiatric symptoms. We will refer to the variables used to explore the potential mechanisms as ‘mediating variables’, but we will include any study exploring the mechanisms linking physical activity and psychiatric symptoms and not only those that used a mediation analysis.

Further restrictions

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

Search strategy for identifying relevant studies

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

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 studies.²² In our final report, we will note the number of duplicates in the PRISMA flow diagram (figure 1).

Selection process

First, two independent researchers (PTNH and TPBH) will screen titles and the abstracts for eligibility. When disagreements emerge between the two independent

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

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
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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. Afterwards, the same two independent researchers (PTNH and TPBH) 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 customised 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 programme, intensity, duration and frequency. For longitudinal studies, we also extract years of follow-up.

Risk of bias and quality of the evidence

The risk of bias will be evaluated independently by two researchers (PTNH and TT) and disagreements were solved in a consensus meeting with the same third researcher (MR-A). The risk of bias will be evaluated using the Joanna Briggs Institute Critical Appraisal Tool for Systematic Reviews (<https://jbi.global/critical-appraisal-tools>). This tool has already been used by other authors in the field.^{23 24} In brief, this tool includes four specific checklists depending on the study design (ie, cross-sectional studies, longitudinal studies, RCTs and non-RCTs). There are four possible answers for each category: 'yes' (criterion met), 'no' (criterion not met), 'unclear' or 'not applicable'. The specific tools include: 8 items for cross-sectional studies, 11 items for longitudinal studies, 9 items for non-RCTs and 13 items for RCTs. Studies will be categorised as 'high risk' or 'low risk'. Specifically, the studies will be considered as 'low risk' if at least 75% of

the applicable items are scored as 'yes' (criterion met). In contrast, articles will be considered 'high risk' when <75% of the applicable items were scored as 'yes'. This classification has been previously employed by Molina-Garcia *et al.*²⁵

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 analysed 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.*²⁶ and more recently by Lubans *et al.*¹² and Rodriguez-Ayllon *et al.*⁹ If 0%–33% of studies reported a statistically significant mediation (eg, self-esteem) between the independent (eg, physical activity) and dependent variable (eg, depressive symptoms), the result will be classified as no association (Ø); 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 being inconsistent/uncertain (?) and if ≥60% of studies found a statistically significant mediation, the result will be classified as significant (✓).

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

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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 (hyperactiv* 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 internalisation* OR internalising OR externalisation* OR externalizing 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) 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 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 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 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 surgery* 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

structure*)) OR (functional* NEAR/2 connectiv*) OR (event-related NEAR/2 brain-potential*) OR ((emotion* OR psycholog*) NEAR/2 (intelligen* OR adjustment* OR regulation*)) OR (social* NEAR/2 (interacti* OR connected*)) OR (self NEAR/1 (esteem OR control* OR acceptan* OR awareness* OR concept OR efficac*)) OR (psychologic* NEAR/2 need*) OR autonom* OR belongingness* OR (perceived NEAR/2 abilit*) OR (confidence NOT (confidence-interval*)))) AND ((intervention* OR trial* OR random* OR rct OR prospective* OR longitudinal* OR cohort* OR follow-up* OR cross-section*)) NOT TI=(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* OR (systematic* NEAR/3 review*) OR meta-analys* OR case-report*) AND DT=(article) AND LA=(english)