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The Effectiveness of Lifestyle Interventions for Improving the Physical Health of Children and Adolescents Taking Antipsychotic Medications: Protocol for a Systematic Review and Meta-Analysis.

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The Effectiveness of Lifestyle Interventions for Improving the Physical Health of Children and Adolescents Taking Antipsychotic Medications: Protocol for a Systematic Review and Meta-Analysis.

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Keywords: Child; Adolescent; Antipsychotic Agents; Metabolic Syndrome; Weight Gain; Psychosocial Intervention.

Word Count: 2,679

AMENTDMENTS TO PROTOCOL

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale, listed in Table 1.

Table 1: Amendments to the Systematic Review Protocol.

Document Version	Amendment	Rationale
1.0	N/A- First draft.	N/A- First draft.
1.1	**Amendment 1:** Modified inclusion/exclusion criteria. No longer including systematic reviews of RCTs. **Amendment 2:** Modified dates (pushed back deadlines and key deliverable dates by 2 months). **Amendment 3:** Modified search terms.	Amendment 1 made in line with comments from authors and advice received by UNSW academic librarians. Amendment 2 made in line with project delays. Amendment 3 made in line with feedback from authors and advice from UNSW academic librarians.
1.2	**Amendment 1:** Updated section: Background and Rationale.	Amendments implemented in line with feedback from KW.
1.3	**Amendment 1:** Proofing throughout.	Amendments implemented in line with feedback from TYW.

STUDY TIMELINE

October 2022 - March 2023: Preparation of protocol document & Prospero.

March 2023 – September 2023: Searches for published and unpublished studies (ongoing).

November 2022 – March 2023: Pilot test of eligibility criteria.

December 2022 – September 2023: Inclusion assessments and article screening.

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December 2022 – November 2023: Data collection & data entry.

April 2023 – December 2023: Follow-up missing information from papers.

September 2023 – November 2023: Data synthesis and analysis.

October 2022 – December 2023: Preparation of manuscript.

February 2024: Submission to journal for peer review.

ABSTRACT

Introduction: Children and adolescents are increasingly prescribed antipsychotic medications off-label in the treatment of behavioural disorders. While antipsychotic medications are effective in managing behavioural issues, they carry a significant risk of adverse events which compromises ongoing physical health. Of particular concern is the negative impact antipsychotic medications have on cardiometabolic health. Interventions which aim to modify lifestyle habits have the potential to alleviate the adverse effects of antipsychotic medication by enhancing weight management, increasing physical activity, promoting better nutritional practices, improving dietary habits, and promoting healthier sleep patterns and sleep hygiene. However, a comprehensive review has not been performed to ascertain the effectiveness of lifestyle interventions for children and adolescents who are at increased risk of antipsychotic-induced compromises to their physical health.

Methods and analysis: This systematic review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Four databases will be searched without any year constraints, to identify randomised controlled trials which are published in the English language and report a lifestyle intervention compared to usual care with any physical health outcome measure. Trial registers and results repositories will be scoured to identify additional studies. Two reviewers will independently conduct screening, data extraction, and quality assessment, and compare results. Quantitative data will be synthesized, where appropriate, through a random-effects meta-analysis model. Otherwise, data will be reported in a qualitative (narrative) synthesis. Heterogeneity will be quantified using the I^2 statistic. The Cochrane Risk of Bias 2 tool be used for risk of bias assessment. The Grading of Recommendations, Assessment, Development, and Evaluation system will be used to evaluate the cumulative body of evidence.

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Ethics and Dissemination: Ethics approval not required. Publication plan will target high-impact, peer reviewed journals which fall under the scope of Psychiatry & Mental Health.

Trial Registration: Registered with PROSPERO (CRD42022380277).

ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS OF THIS STUDY

- By combining data from multiple studies, this systematic review is expected to provide greater statistical power to detect differences between intervention and control groups than individual studies alone.
- By analysing the existing evidence base on lifestyle interventions, this systematic review can identify gaps where further research is needed to address unanswered questions or resolve conflicting findings.
- A potentially limiting factor of this study is the heterogeneity of lifestyle interventions, which could hinder the ability to reach definitive conclusions about their effectiveness.
- A potential limitation of this study is that the quality of included studies may vary significantly, potentially impacting the robustness of the findings.

INTRODUCTION

While antipsychotic medications are efficacious in treating a range of complex psychiatric disorders, the utility of these drugs is hampered by their tendency to elicit a range of adverse effects which compromises ongoing health.[1] Interventions which aim to modify lifestyle habits have the potential to alleviate the adverse effects of antipsychotic medication by enhancing weight management, increasing physical activity, promoting better nutritional practices, improving dietary habits, and promoting healthier sleep patterns and sleep hygiene.[2] The effectiveness of lifestyle interventions for reducing weight gain has been comprehensively studied in adult populations with serious mental illness (SMI) who take antipsychotic medications.[2-5] Adults with SMI are at increased risk of weight gain due to a combination of factors related to impaired functioning and motivation, but particularly due to antipsychotic treatment initiation.[6] During intervention periods, different components of lifestyle

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interventions can improve anthropometric measures (weight, body mass index (BMI), and waist circumference), reduce diastolic blood pressure, pressure, reduce blood sugar, improve physical fitness, and improve dietary habits for adults with SMI.[2-5,7] However, a comprehensive evaluation of lifestyle interventions for children and adolescents who take antipsychotic medications is lacking.

Select antipsychotic medications are approved to treat child psychiatric disorders including childhood schizophrenia and bipolar mania,[8] Tourette's Syndrome,[9] and aggression and irritability in children with autism spectrum disorder (ASD).[10,11] Antipsychotic medications are also prescribed off-label to children and adolescents, including those with neurodevelopmental disorders, to manage disruptive behaviour resistant to other forms of treatment.[1,12] In fact, the most common use of antipsychotic medications in paediatrics is to treat disruptive behaviours and not psychotic disorders.[13]

While there is some evidence that short term antipsychotic use may reduce aggression and conduct problems in children and adolescents with disruptive behaviour disorders,[12,14-17] antipsychotic medications carry a significant risk of adverse events which compromise ongoing health.[1,12,18] These adverse events include metabolic disturbances, sedation/somnolence, prolactin elevation, sexual dysfunction, cardiological and haematological adverse events, neurological adverse events, and even behavioural adverse events, including psychomotor retardation, anorexia, agitation, or lack of spontaneity.[1,18] Cardiometabolic disturbances are the most clinically significant in this population, due to the propensity for continued complications in adulthood and long-term morbidity costs.[19] Common cardiometabolic complications from antipsychotic medication use includes weight gain, dyslipidaemia, elevated blood pressure, and increased risk of type-2 diabetes.[20-22] There is increasing evidence to suggest that compared to adults, children and adolescents are more susceptible to developing cardiometabolic complications from antipsychotic use,[1,23-27] particularly children with ASD.[23,28] Antipsychotic prescription to children and adolescents is increasing internationally.[29-32]

Given that most lifestyle interventions targeting the physical health impact of antipsychotics have been conducted in adults with SMI, the effectiveness of these interventions in children and adolescents taking antipsychotics is unknown. Children and adolescents represent a unique cohort due to their relatively early stage of development which promotes susceptibility to the adverse cardiometabolic effects of antipsychotics.[1,23-27] Due to recurrent disruptive behaviour,

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children and adolescents who are started on psychotropic medicines tend to continue taking them for prolonged periods.[33] While several guidelines exist recommending psychological and environmental interventions as the first-line treatment for disruptive behaviours (e.g., UK NICE guidelines, Frith Prescribing Guidelines, STOMP), their implementation in practice is inadequate.[33-35] Hence, early lifestyle interventions targeted at children and adolescents prescribed antipsychotics have the opportunity to mitigate poor physical health outcomes during critical health periods and reduce the translation to overweight, obesity, and other cardiometabolic risk factors to adulthood. By reducing the negative effects of antipsychotic medications, it may be possible to sustain their usage, leading to the optimization of critical learning and developmental periods.

OBJECTIVES

The purpose of this systematic review is to evaluate the effectiveness of lifestyle interventions for improving the physical health of children and adolescents (aged 6 to 17 years) who are taking antipsychotic medications. Specifically, the proposed study will aim to answer the following research questions:

1. *For children and adolescents taking antipsychotic medications, do lifestyle interventions reduce the risk of compromised physical health (see Table 2 for the list of physical health outcome measures) compared to treatment as usual (i.e., participants who receive standard medical care services but no specific intervention for lifestyle support)?*
2. *Which individual or combined components of a lifestyle intervention are the most effective in reducing the risk of physical health decline?*

Primary Outcome Measure

While all relevant physical health outcomes will be considered (see Table 2), the primary outcome measure will be the difference in body mass index (BMI) between control and intervention groups. BMI was selected as the primary outcome measure as it is the most robust indicator to identify individuals whose excess adiposity puts them at increased

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cardiometabolic risk.[36] Where other measures of physical health are reported, they will be included (see Table 2).

METHODS AND ANALYSIS

This systematic review protocol was developed with the PRISMA-P reporting guidelines (see Appendix 2).[37]

ELIGIBILITY CRITERIA

The eligibility criteria are described in Table 2, below.

Table 2: Eligibility criteria organised in accordance with the population, interventions, comparisons, outcomes, setting, and study design (PICOS) reporting structure.

Population	Youth aged 6 to 17 years who are taking antipsychotic medications. Youth most likely to be taking antipsychotic medications include those diagnosed with a neurodevelopmental disorder (i.e., ID, ASD, ADHD, TS) and comorbid disruptive behaviour disorder/behavioural issues, or youth with first-episode psychosis, childhood schizophrenia or bipolar mania. Study will be eligible for inclusion if ≥70% of the sample is taking antipsychotic medications.
Interventions	All interventions which incorporate a 'lifestyle' intervention component and aim to improve physical health outcomes will be eligible. This includes any educational, psychotherapeutic, social, and behavioural intervention which aims to increase exercise or physical activity, optimise dietary intake, aid smoking cessation, or improve sleep quality and duration.
Comparisons	All relevant control interventions will be included (i.e., treatment as usual/usual care, placebo, no treatment, waiting list).
Outcomes	Physical health outcomes which will be **included**: 1) Anthropometric measures, including weight, height, waist circumference, or BMI percentile. 2) Blood pressure. 3) Metabolic or biological markers, including glucose and lipid levels, haemoglobin A1c (HbA1c), C-reactive protein or other relevant blood and serum markers. 4) Presence of cardiovascular or respiratory disease.

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	5) Physical health behaviour, including physical activity levels, smoking behaviour, dietary intake, sleep quality and duration, engagement in treatment and attendance. 6) Indicators of physical fitness, including aerobic capacity (i.e., VO_2 Max), and muscle strength. 7) Physical health-related quality of life. 8) Side effects of antipsychotics, including adverse drug reactions. Physical health outcomes which will be **excluded**: 1) Motor development.
Setting	All settings will be included: primary and secondary care, hospital (inpatient or outpatient), community and school-based service provisions, or remote (digital application-based or telehealth/web health services).
Study Design & Characteristics	Applicable RCTs published in the English language will be included. All years will be considered, and no date restrictions will be applied. Pseudorandomised control trials, comparative studies with concurrent controls, case series and cohort studies will be excluded. Conference abstracts, dissertations/theses, papers which are not peer-reviewed, and papers published in a language other than English will be excluded.

INFORMATION SOURCES

The literature search will be executed using MeSH terms and keywords related to lifestyle interventions in the population under investigation (as outlined in Table 2). Four databases, including MEDLINE (via PubMed), EMBASE (via Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL), and PsycINFO, will be searched without any year constraints. The results will be restricted to studies published in English and employing a randomized controlled trial (RCT) design. The search process will be guided by the Cochrane Handbook for Systematic Reviews to determine the most appropriate RCT design filter for each database. To ensure literature saturation, the reference lists of included studies will be scanned to identify additional relevant articles. Google Scholar's 'cited by' function will be used to search for relevant articles which cite the included studies. Trial registers and results repositories will be scoured, including ClinicalTrials.gov and the World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) portal, in accordance with the Cochrane guidelines.[38] To account for the emergence of new studies published in the period after initial searches were performed, searches will be re-run before final data analysis.

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SEARCH STRATEGY

The development of the search strategies for each database will be conducted with the oversight of a Medicine & Health academic librarian who possesses expertise in systematic review searching. The project team will contribute to the development of the strategies, which will be peer-reviewed by the academic librarian. The draft strategy for MEDLINE is presented in Appendix 1. After finalising the MEDLINE strategy, it will be adapted to the syntax and MeSH terms/subject headings of the other databases. The validity of the search strategies will be evaluated to ensure a high yield of eligible studies from all relevant databases.

STUDY RECORDS

Literature search results from electronic databases will be uploaded to Covidence software for systematic reviews.[39] Two reviewers will independently screen the title and abstract of each study to determine eligibility. The full text of eligible studies will be obtained and screened against the inclusion criteria. The data from the included studies will be extracted and entered into Covidence by two independent reviewers. Duplicate entries will be removed and discrepancies between the two reviewers' data will be resolved through discussion and consensus. Any unresolved conflicts between the two primary reviewers will be settled by a third reviewer. The data will be regularly backed up to ensure data integrity and to prevent loss of information. Access to the data will be restricted to authorized personnel and will be protected by secure passwords. The data collected for the systematic review will be retained for a minimum of 5 years after publication of the review, as per UNSW's recommended retention periods for research data and records. Upon finalization of results, the data will be securely uploaded to a suitable repository.

DATA ITEMS AND OUTOMES

All outcomes which relate to physical health will be extracted for analysis, including the following: (1) Anthropometric measures, including weight, height, waist circumference, or BMI percentile; (2) Blood pressure; (3) Indicators of physical fitness, including aerobic capacity (i.e., VO2 Max), and muscle strength; (4) Metabolic or biological markers, including glucose and lipid levels, proportion with abnormal glucose or lipid parameters, haemoglobin A1c (HbA1c), C-reactive protein or other relevant blood and serum markers; (5) Presence of

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cardiovascular illness, including myocardial infarction, stroke, transient ischemic attack, and pulmonary embolism; (6) Presence of respiratory illness, including lung cancer and chronic obstructive pulmonary disease (COPD); (7) Physical health behaviour, including physical activity levels, smoking behaviour, dietary intake, sleep habits, and appointment attendance; (8) Physical health-related quality of life; and (9) Side effects, including adverse drug reactions.

Missing Data

To ensure that all relevant data is included in the meta-analysis, authors of included studies will be contacted to request any missing data. For initial contact, a polite and respectful email will be sent to the corresponding author of each study, introducing the meta-analysis and the purpose of the request for missing data. If there is no response to the initial email, a follow-up email or phone call will be made after two weeks. If there is still no response after the follow-up, a final reminder will be sent after one week, highlighting the importance of the missing data and its impact on the meta-analysis results. All attempts to contact the investigators and the responses received will be documented in the meta-analysis study protocol.

RISK OF BIAS ASSESSMENT

The risk of bias will be assessed using the Cochrane Risk of Bias Tool for RCTs (RoB 2)[40]. Rob 2 assesses bias in five domains, which each incorporate one or more signalling questions that leads to judgements of “low risk of bias”, “some concerns,” or “high risk of bias”. These judgements lead to an overall risk-of-bias judgement for the included studies, enabling users to stratify meta-analyses bias according to the risk of bias of individual studies.[40] To ensure rigour, two reviewers will independently perform quality assessment and compare results. A third reviewer will be available to settle any disagreement between the two reviewers.

DATA

SYNTHESIS

Data on relevant outcome measures will be extracted from articles using a standardised data extraction form. Quantitative data will be synthesized, where appropriate, through a random-effects meta-analysis model. Effect size data will be extracted with 95% confidence intervals

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(CI) for relevant outcomes, in addition to the number of participants (*n*) in the lifestyle intervention or control group for each effect size. Where not possible to extract effect size data for the meta-analysis, data will be reported in a qualitative (narrative) synthesis. Effect size data with 95% CI for relevant outcomes will be recalculated as a standardised mean difference (SMD), to express the mean difference between groups in standard deviation (*SD*) units with a 95% CI. SMDs of less than 0.2 will be considered negligible, SMD between 0.2 and < 0.5 small, SMD between 0.5 and <0.8 medium, and SMD ≥0.8 large.[41] Risk ratios (RRs) will be used for categorical outcomes. Odds ratios will be recalculated as RRs. Heterogeneity will be quantified using the I^2 statistic, with scores of <25%, 25-50% and >50% indicating low, moderate, and high heterogeneity, respectively. Forest plots will be generated to show SMD with CIs for each study and the overall random pooled effects estimate. Analyses will be performed using R statistical analysis software.[42]

Subgroup Analysis

To explore potential sources of variability in the data, subgroup analyses will be conducted based on the following variables:

1. Patient demographics (age, gender, and diagnosis) will be considered, and categorical or meta-regression analysis will be employed to examine the relationship between mean age and SMD for continuous variables.
2. Type of antipsychotic medication.
3. Duration of lifestyle intervention treatment.
4. Length of follow-up period (3, 6, and 12 months).

Sensitivity Analysis

Sensitivity analyses will be conducted to assess the robustness of the results and to identify any sources of heterogeneity in the data. This will be performed by excluding studies with a high risk of bias, as well as by excluding studies with specific characteristics (e.g., short follow-up period, small sample size, etc.).

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META-BIAS(ES)

The systematic review will include an assessment of meta-bias to ensure the validity of the results. As described, to ensure a robust assessment of individual RCTs, the review team will utilize the Cochrane RoB 2 tool.[40] Sensitivity analysis will allow assessment of the robustness of results and identification of any sources of heterogeneity in the data.

Additional Assessments of Meta-Bias

The evaluation of outcome reporting bias within the included studies will be conducted through a comparison of the reported data to the data outlined in the original study protocol or registry, if available. This will promote transparency in the reporting of all relevant data. Funnel plot analysis will be performed to assess the presence of publication bias. The funnel plot will be created using the standard error of each study's effect size, and the symmetry of the plot will be visually inspected to assess the presence of publication bias. Additionally, formal tests of funnel plot asymmetry, such as Egger's regression test or the Begg's test, will be performed to provide a statistical evaluation of funnel plot asymmetry. The results of the analysis will provide an indication of the likelihood of publication bias and inform the interpretation of the overall results of the meta-analysis. In addition, the results of this systematic review will be compared with other relevant systematic reviews to ensure that the findings are in line with previous research. Any discrepancies will be investigated to identify any potential sources of meta-bias.

Confidence in Cumulative Evidence

The present systematic review and meta-analysis will utilize the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system [43] for assessing the strength of the body of evidence. The GRADE system offers a transparent and standardized method for evaluating the strength of the evidence, providing a basis for informed decision making. The quality of evidence will be classified into one of four levels- high, moderate, low, or very low- based on the anticipated impact of further research on the confidence in the estimate of effect. GRADE will be applied to three anthropometric assessments of cardiometabolic health (BMI, waist circumference, and blood pressure). The GRADE system

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is widely recognized as a credible and validated approach in systematic reviews and meta-analyses, with extensive validation and usage in the field.[43]

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AUTHORS' CONTRIBUTIONS

PH conceptualised and designed the systematic review with input from JB, CM, TYW, KW, AW, VA, , BT, PW, ES, MB, TS, and VE. CM, VE, and PW supervised the project.

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COMPETING INTERESTS STATEMENT

Authors have no competing interests to declare.

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Appendix 1: Example Search Strategy for MEDLINE (via PubMed).

Concept	Search Strategy	Actions
Children and adolescents	"Child"[MeSH Terms] OR "Adolescent"[MeSH Terms] OR "youth"[Text Word] OR "infant"[Text Word] OR "juvenile"[Text Word] OR "minor"[Text Word] OR "young person"[Text Word] OR "youngster"[Text Word] OR "kid"[Text Word] OR "kids"[Text Word] OR "child*"[Text Word] OR "adolesc*"[Text Word] OR "teen*"[Text Word]	Add
Population (diagnosis of mental health illness likely to be prescribed antipsychotic medications).	"Neurodevelopmental Disorders"[MeSH Terms:noexp] OR "Attention Deficit Disorder with Hyperactivity"[MeSH Terms] OR "Developmental Disabilities"[MeSH Terms] OR "Intellectual Disability"[MeSH Terms:noexp] OR “intellectual disabilit*”[Text Word] OR “intellectual impairment*”[Text Word] OR “intellectual delay*”[Text Word] OR “learning disabilit*”[Text Word] OR “learning impairment*”[Text Word] OR “learning delay*”[Text Word] OR “developmental disabilit*”[Text Word] OR “developmental delay”[Text Word] OR "Child Development	Add with AND

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	Disorders, Pervasive"[Mesh] OR "schizophrenia, childhood"[MeSH Terms] OR "Tic Disorders"[MeSH Terms] OR "autism*"[Text Word] OR "autistic*"[Text Word] OR "Kanner's Syndrome"[Text Word] OR "neurodevelopmental*"[Text Word] OR "ADHD"[Text Word] OR "attention defici*"[Text Word] OR "pervasive developmental disorder"[Text Word] OR "developmental disabilit*"[Text Word] OR "intellectual disabilit*"[Text Word] OR "schizophrenia"[Text Word] OR "psychosis"[Text Word] OR "tourette*"[Text Word] OR "tic disorder"[Text Word] OR “asperger*”[Text Word] OR "Bipolar and Related Disorders"[Mesh] OR “bipolar*”[Text Word]	
Population (people taking antipsychotic medications).	"antipsychotic*"[Text Word] OR "Antipsychotic Agents"[MeSH Terms] OR "second generation antipsychotic*"[Text Word]	Add with OR
Lifestyle intervention (general)	"life style"[Text Word] OR "lifestyle*"[Text Word] OR "non pharmacologic*"[Text Word] OR "self management"[Text Word] OR "Patient Education as Topic"[MeSH Terms:noexp] OR	Add with AND

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	"community based intervention*"[Text Word] OR "psychosocial*"[Text Word] OR "stress management"[Text Word] OR "personalised medicine"[Text Word] OR "personalized medicine"[Text Word] OR "integrat*"[Text Word] OR "healthy living"[Text Word] OR "physical activity"[Text Word] OR "behavioural change"[Text Word] OR "behavioral change"[Text Word] OR “behaviour change”[Text Word] OR “behavior change”[Text Word] OR “behaviour modification”[Text Word] OR “behavior modification”[Text Word] OR “behavioural modification”[Text Word] OR“behavioral modification”[Text Word] OR "patient education"[Text Word] OR “weight management”[Text Word]	
Specific components of lifestyle interventions (exercise, diet, nutrition, sleep, smoking cessation).	"Smoking Cessation"[MeSH Terms] OR "Smoking Cessation"[Text Word] OR "sleep*"[Text Word] OR "Sleep"[Mesh:NoExp] OR "Diet Therapy"[MeSH Terms:noexp] OR "nutrition*"[Text Word] OR "Nutrition	Add with OR

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	Therapy"[Mesh:NoExp] OR "diet*"[Text Word] OR "fitness*"[Text Word] OR "exercise*"[Text Word] OR "Exercise"[Mesh:NoExp] OR "physical therapy"[Text Word] OR "physical activity"[Text Word]	
Randomised controlled trial (Cochrane sensitivity and specificity maximising filter)	("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms:noexp] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])	Add with AND

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Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1

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Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	1 & 16
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	2
Support			
Sources	#5a	Indicate sources of financial or other support for the review	16
Sponsor	#5b	Provide name for the review funder and / or sponsor	16
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	16
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6-8
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	7-8
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	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	n/a - Provided in Appendix 1

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Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-10
Study records - 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)	9-10
Study records - 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	9-10
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	9-10
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6-8, 9-10
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	10
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	10-11
Data synthesis	#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 I2, Kendall's τ)	10-11
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10-11
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10-11
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12

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Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12-13

Notes:

- 10: n/a - Provided in Appendix 1 The PRISMA-P elaboration and explanation paper is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 21. March 2023 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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The Effectiveness of Lifestyle Interventions for Improving the Physical Health of Children and Adolescents Taking Antipsychotic Medications: Protocol for a Systematic Review and Meta-Analysis.

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Manuscripts

The Effectiveness of Lifestyle Interventions for Improving the Physical Health of Children and Adolescents Taking Antipsychotic Medications: Protocol for a Systematic Review and Meta-Analysis.

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Keywords: Child; Adolescent; Antipsychotic Agents; Metabolic Syndrome; Weight Gain; Psychosocial Intervention.

Word Count: 2,833

ABSTRACT

Introduction: Children and adolescents are increasingly prescribed antipsychotic medications off-label in the treatment of behavioural disorders. While antipsychotic medications are effective in managing behavioural issues, they carry a significant risk of adverse events which compromises ongoing physical health. Of particular concern is the negative impact antipsychotic medications have on cardiometabolic health. Interventions which aim to modify lifestyle habits have the potential to alleviate the adverse effects of antipsychotic medication by enhancing weight management, increasing physical activity, promoting better nutritional practices, improving dietary habits, and promoting healthier sleep patterns and sleep hygiene. However, a comprehensive review has not been performed to ascertain the effectiveness of lifestyle interventions for children and adolescents who are at increased risk of antipsychotic-induced compromises to their physical health.

Methods and analysis: This systematic review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Four databases will be searched without any year constraints, to identify randomised controlled trials which are published in the English language and report a lifestyle intervention compared to usual care with any physical health outcome measure. Trial registers and results repositories will be scoured to identify additional studies. Two reviewers will independently conduct screening, data extraction, and quality assessment, and compare results. Quantitative data will be synthesized, where appropriate, through a random-effects meta-analysis model. Otherwise, data will be reported in a qualitative (narrative) synthesis. Heterogeneity will be quantified using the I^2 statistic. The Cochrane Risk of Bias 2 tool be used for risk of bias assessment. The Grading of Recommendations, Assessment, Development, and Evaluation system will be used to evaluate the cumulative body of evidence.

Ethics and Dissemination: Ethics approval not required. Publication plan will target high-impact, peer reviewed journals which fall under the scope of Psychiatry & Mental Health.

Trial Registration: Registered with PROSPERO (CRD42022380277).

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- By combining data from multiple studies, this systematic review is expected to provide greater statistical power to detect differences between intervention and control groups than individual studies alone.
- By analysing the existing evidence base on lifestyle interventions, this systematic review can identify gaps where further research is needed to address unanswered questions or resolve conflicting findings.
- A potentially limiting factor of this study is the heterogeneity of lifestyle interventions, which could hinder the ability to reach definitive conclusions about their effectiveness.
- A potential limitation of this study is that the quality of included studies may vary significantly, potentially impacting the robustness of the findings.

INTRODUCTION

While antipsychotic medications are efficacious in treating a range of complex psychiatric disorders, the utility of these drugs is hampered by their tendency to elicit a range of adverse effects which compromises ongoing health.(1) Interventions which aim to modify lifestyle habits have the potential to alleviate the adverse effects of antipsychotic medication by enhancing weight management, increasing physical activity, promoting better nutritional practices, and improving dietary habits.(2) Recent work suggests that broadening intervention scope beyond diet and exercise, specifically those that incorporate sleep improvement and nicotine reduction programs, could effectively improve metabolic parameters and lower cardiovascular risk of individuals who take antipsychotic medications.(3, 4)

The effectiveness of lifestyle interventions for reducing weight gain has been comprehensively studied in adult populations with serious mental illness (SMI) who take antipsychotic medications.(2, 5-7) Adults with SMI are at increased risk of weight gain due to a combination of factors related to impaired functioning and motivation, but particularly due to antipsychotic treatment initiation.(8) During intervention periods, different components of lifestyle interventions can improve anthropometric measures (weight, body mass index (BMI), and waist circumference), reduce diastolic blood pressure, pressure, reduce blood sugar, improve

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physical fitness, and improve dietary habits for adults with SMI.(2, 5-7, 9) However, a comprehensive evaluation of lifestyle interventions for children and adolescents who take antipsychotic medications is lacking.

Select antipsychotic medications are approved to treat child psychiatric disorders including childhood schizophrenia and bipolar mania,(10) Tourette's Syndrome,(11) and aggression and irritability in children with autism spectrum disorder (ASD).(12, 13) Antipsychotic medications are also prescribed off-label to children and adolescents, including those with neurodevelopmental disorders, to manage disruptive behaviour resistant to other forms of treatment.(1, 14) In fact, the most common use of antipsychotic medications in paediatrics is to treat disruptive behaviours and not psychotic disorders.(15)

While there is some evidence that short term antipsychotic use may reduce aggression and conduct problems in children and adolescents with disruptive behaviour disorders,(14, 16-19) antipsychotic medications carry a significant risk of adverse events which compromise ongoing health.(1, 14, 20) These adverse events include metabolic disturbances, sedation/somnolence, prolactin elevation, sexual dysfunction, cardiological and haematological adverse events, neurological adverse events, and even behavioural adverse events, including psychomotor retardation, anorexia, agitation, or lack of spontaneity.(1, 20) Cardiometabolic disturbances are the most clinically significant in this population, due to the propensity for continued complications in adulthood and long-term morbidity costs.(21) Common cardiometabolic complications from antipsychotic medication use includes weight gain, dyslipidaemia, elevated blood pressure, and increased risk of type-2 diabetes.(22-24) There is increasing evidence to suggest that compared to adults, children and adolescents are more susceptible to developing cardiometabolic complications from antipsychotic use,(1, 25-29) particularly children with ASD.(25, 30) Antipsychotic prescription to children and adolescents is increasing internationally.(31-34)

Given that most lifestyle interventions targeting the physical health impact of antipsychotics have been conducted in adults with SMI, the effectiveness of these interventions in children and adolescents taking antipsychotics is unknown. Children and adolescents represent a unique cohort due to their relatively early stage of development which promotes susceptibility to the adverse cardiometabolic effects of antipsychotics.(1, 25-29) Those with neurodevelopmental disorders may have specific lifestyle challenges such as heightened sedentary behaviour,(35) poor diet and nutrition,(36, 37) disrupted sleep,(38) and frequent tobacco use.(39, 40) A distinct

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subset of this group are those prescribed antipsychotic medications. They typically present with severely disruptive behaviours and have a high likelihood of comorbid mental health diagnoses.(15) Moreover, antipsychotic medications themselves may impose changes to lifestyle such as dysregulated appetite control(8, 41) or altered sleep patterns.(42) Hence, this cohort requires an individualised strategy, one that may not be generalisable to a wider child and adolescent cohort. Such strategies should cater to their unique needs and may involve the participation of caregivers and families, or be adapted according to the developmental age and communication style of the young person.

Due to recurrent disruptive behaviour, children and adolescents who are started on psychotropic medicines tend to continue taking them for prolonged periods.(43) While several guidelines exist recommending psychological and environmental interventions as the first-line treatment for disruptive behaviours (e.g., UK NICE guidelines, Frith Prescribing Guidelines, STOMP), their implementation in practice is inadequate.(43-45) Given the potential impacts on long-term cardiometabolic health, an intervention strategy should be co-provided with antipsychotic pharmacotherapy for youth identified at risk of physical health deterioration. Hence, it should be investigated whether early lifestyle interventions targeted at children and adolescents prescribed antipsychotics can mitigate poor physical health outcomes during critical health periods and reduce the translation to overweight, obesity, and other cardiometabolic risk factors to adulthood.

OBJECTIVES

The purpose of this systematic review is to evaluate the effectiveness of lifestyle interventions for improving the physical health of children and adolescents (aged 6 to 17 years) who are taking antipsychotic medications. Specifically, the proposed study will aim to answer the following research questions:

1. *For children and adolescents taking antipsychotic medications, do lifestyle interventions reduce the risk of compromised physical health (see Table 1 for the list of physical health outcome measures) compared to treatment as usual (i.e., participants who receive standard medical care services but no specific intervention for lifestyle support)?*
2. *Which individual or combined components of a lifestyle intervention are the most effective in reducing the risk of physical health decline?*

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Primary Outcome Measure

While all relevant physical health outcomes will be considered (see Table 1), the primary outcome measure will be the difference in body mass index (BMI) between control and intervention groups. BMI was selected as the primary outcome measure as it is the most robust indicator to identify individuals whose excess adiposity puts them at increased cardiometabolic risk.(46) Where other measures of physical health are reported, they will be included (see Table 1).

METHODS AND ANALYSIS

This systematic review protocol was developed with the PRISMA-P reporting guidelines (see Appendix 1).(47)

Patient and Public Involvement

No patients involved.

ELIGIBILITY CRITERIA

The eligibility criteria are described in Table 1, below.

Table 1: Eligibility criteria organised in accordance with the population, interventions, comparisons, outcomes, setting, and study design (PICOS) reporting structure.

Population	Youth aged 6 to 17 years who are taking antipsychotic medications. Youth most likely to be taking antipsychotic medications include those diagnosed with a neurodevelopmental disorder (i.e., ID, ASD, ADHD, TS) and comorbid disruptive behaviour disorder/behavioural issues, or youth with first-episode psychosis, childhood schizophrenia or bipolar mania. Study will be eligible for inclusion if ≥70% of the sample is taking antipsychotic medications.
Interventions	All interventions which incorporate a 'lifestyle' intervention component and aim to improve physical health outcomes will be eligible. This includes any educational, psychotherapeutic, social, and behavioural intervention which aims to increase exercise or physical activity, optimise dietary intake, aid nicotine cessation, or improve sleep quality and duration.

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Comparisons	All relevant control interventions will be included (i.e., treatment as usual/usual care, placebo, no treatment, waiting list).
Outcomes	Physical health outcomes which will be **included**: 1) Anthropometric measures, including weight, height, waist circumference, or BMI percentile. 2) Blood pressure. 3) Metabolic or biological markers, including glucose and lipid levels, haemoglobin A1c (HbA1c), C-reactive protein or other relevant blood and serum markers. 4) Presence of cardiovascular or respiratory disease. 5) Physical health behaviour, including physical activity levels, smoking/vaping behaviour, dietary intake, sleep quality and duration, engagement in treatment and attendance. 6) Indicators of physical fitness, including aerobic capacity (i.e., VO_2 Max), and muscle strength. 7) Physical health-related quality of life. 8) Side effects of antipsychotics, including adverse drug reactions. Physical health outcomes which will be **excluded**: 1) Motor development.
Setting	All settings will be included: primary and secondary care, hospital (inpatient or outpatient), community and school-based service provisions, or remote (digital application-based or telehealth/web health services).
Study Design & Characteristics	Applicable RCTs published in the English language will be included. All years will be considered, and no date restrictions will be applied. Pseudorandomised control trials, comparative studies with concurrent controls, case series and cohort studies will be excluded. Conference abstracts, dissertations/theses, papers which are not peer-reviewed, and papers published in a language other than English will be excluded.

INFORMATION SOURCES

The literature search will be executed using MeSH terms and keywords related to lifestyle interventions in the population under investigation (as outlined in Table 1). Four databases, including MEDLINE (via PubMed), EMBASE (via Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL), and PsycINFO, will be searched without any year constraints. The results will be restricted to studies published in English and employing a randomized

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controlled trial (RCT) design. The search process will be guided by the Cochrane Handbook for Systematic Reviews to determine the most appropriate RCT design filter for each database. To ensure literature saturation, the reference lists of included studies will be scanned to identify additional relevant articles. Google Scholar's 'cited by' function will be used to search for relevant articles which cite the included studies. Trial registers and results repositories will be scoured, including ClinicalTrials.gov and the World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) portal, in accordance with the Cochrane guidelines.(48) To account for the emergence of new studies published in the period after initial searches were performed, searches will be re-run before final data analysis.

SEARCH STRATEGY

The development of the search strategies for each database will be conducted with the oversight of a Medicine & Health academic librarian who possesses expertise in systematic review searching. The project team will contribute to the development of the strategies, which will be peer-reviewed by the academic librarian. The draft strategy for MEDLINE is presented in Appendix 2. After finalising the MEDLINE strategy, it will be adapted to the syntax and MeSH terms/subject headings of the other databases. The validity of the search strategies will be evaluated to ensure a high yield of eligible studies from all relevant databases.

STUDY RECORDS

Literature search results from electronic databases will be uploaded to Covidence software for systematic reviews.(49) Two reviewers will independently screen the title and abstract of each study to determine eligibility. The full text of eligible studies will be obtained and screened against the inclusion criteria. The data from the included studies will be extracted and entered into Covidence by two independent reviewers. Duplicate entries will be removed and discrepancies between the two reviewers' data will be resolved through discussion and consensus. Any unresolved conflicts between the two primary reviewers will be settled by a third reviewer. The data will be regularly backed up to ensure data integrity and to prevent loss of information. Access to the data will be restricted to authorized personnel and will be protected by secure passwords. The data collected for the systematic review will be retained for a minimum of 5 years after publication of the review, as per UNSW's recommended retention periods for research data and records. Upon finalization of results, the data will be securely uploaded to a suitable repository.

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DATA ITEMS AND OUTOMES

All outcomes which relate to physical health will be extracted for analysis, including the following: (1) Anthropometric measures, including weight, height, waist circumference, or BMI percentile; (2) Blood pressure; (3) Indicators of physical fitness, including aerobic capacity (i.e., VO2 Max), and muscle strength; (4) Metabolic or biological markers, including glucose and lipid levels, proportion with abnormal glucose or lipid parameters, haemoglobin A1c (HbA1c), C-reactive protein or other relevant blood and serum markers; (5) Presence of cardiovascular illness, including myocardial infarction, stroke, transient ischemic attack, and pulmonary embolism; (6) Presence of respiratory illness, including lung cancer and chronic obstructive pulmonary disease (COPD); (7) Physical health behaviour, including physical activity levels, smoking/vaping behaviour, dietary intake, sleep habits, and appointment attendance; (8) Physical health-related quality of life; and (9) Side effects, including adverse drug reactions.

Missing Data

To ensure that all relevant data is included in the meta-analysis, authors of included studies will be contacted to request any missing data. For initial contact, a polite and respectful email will be sent to the corresponding author of each study, introducing the meta-analysis and the purpose of the request for missing data. If there is no response to the initial email, a follow-up email or phone call will be made after two weeks. If there is still no response after the follow-up, a final reminder will be sent after one week, highlighting the importance of the missing data and its impact on the meta-analysis results. All attempts to contact the investigators and the responses received will be documented in the meta-analysis study protocol.

RISK OF BIAS ASSESSMENT

The risk of bias will be assessed using the Cochrane Risk of Bias Tool for RCTs (RoB 2)(50). Rob 2 assesses bias in five domains, which each incorporate one or more signalling questions that leads to judgements of “low risk of bias”, “some concerns,” or “high risk of bias”. These judgements lead to an overall risk-of-bias judgement for the included studies, enabling users

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to stratify meta-analyses bias according to the risk of bias of individual studies.(50) To ensure rigour, two reviewers will independently perform quality assessment and compare results. A third reviewer will be available to settle any disagreement between the two reviewers.

DATA

SYNTHESIS

Data on relevant outcome measures will be extracted from articles using a standardised data extraction form. Quantitative data will be synthesized, where appropriate, through a random-effects meta-analysis model. Effect size data will be extracted with 95% confidence intervals (CI) for relevant outcomes, in addition to the number of participants (*n*) in the lifestyle intervention or control group for each effect size. Where not possible to extract effect size data for the meta-analysis, data will be reported in a qualitative (narrative) synthesis. Effect size data with 95% CI for relevant outcomes will be recalculated as a standardised mean difference (SMD), to express the mean difference between groups in standard deviation (*SD*) units with a 95% CI. SMDs of less than 0.2 will be considered negligible, SMD between 0.2 and < 0.5 small, SMD between 0.5 and <0.8 medium, and SMD ≥0.8 large.(51) Risk ratios (RRs) will be used for categorical outcomes. Odds ratios will be recalculated as RRs. Heterogeneity will be quantified using the I^2 statistic, with scores of <25%, 25-50% and >50% indicating low, moderate, and high heterogeneity, respectively. Forest plots will be generated to show SMD with CIs for each study and the overall random pooled effects estimate. Analyses will be performed using R statistical analysis software.(52)

Subgroup Analysis

To explore potential sources of variability in the data, subgroup analyses will be conducted based on the following variables:

1. Patient demographics (age, gender, and diagnosis) will be considered, and categorical or meta-regression analysis will be employed to examine the relationship between mean age and SMD for continuous variables.
2. Type of antipsychotic medication.
3. Duration of lifestyle intervention treatment.

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4. Length of follow-up period (3, 6, and 12 months).

Sensitivity Analysis

Sensitivity analyses will be conducted to assess the robustness of the results and to identify any sources of heterogeneity in the data. This will be performed by excluding studies with a high risk of bias, as well as by excluding studies with specific characteristics (e.g., short follow-up period, small sample size, etc.).

META-BIAS(ES)

The systematic review will include an assessment of meta-bias to ensure the validity of the results. As described, to ensure a robust assessment of individual RCTs, the review team will utilize the Cochrane RoB 2 tool.(50) Sensitivity analysis will allow assessment of the robustness of results and identification of any sources of heterogeneity in the data.

Additional Assessments of Meta-Bias

The evaluation of outcome reporting bias within the included studies will be conducted through a comparison of the reported data to the data outlined in the original study protocol or registry, if available. This will promote transparency in the reporting of all relevant data. Funnel plot analysis will be performed to assess the presence of publication bias. The funnel plot will be created using the standard error of each study's effect size, and the symmetry of the plot will be visually inspected to assess the presence of publication bias. Additionally, formal tests of funnel plot asymmetry, such as Egger's regression test or the Begg's test, will be performed to provide a statistical evaluation of funnel plot asymmetry. The results of the analysis will provide an indication of the likelihood of publication bias and inform the interpretation of the overall results of the meta-analysis. In addition, the results of this systematic review will be compared with other relevant systematic reviews to ensure that the findings are in line with previous research. Any discrepancies will be investigated to identify any potential sources of meta-bias.

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Confidence in Cumulative Evidence

The present systematic review and meta-analysis will utilize the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system(53) for assessing the strength of the body of evidence. The GRADE system offers a transparent and standardized method for evaluating the strength of the evidence, providing a basis for informed decision making. The quality of evidence will be classified into one of four levels- high, moderate, low, or very low- based on the anticipated impact of further research on the confidence in the estimate of effect. GRADE will be applied to three anthropometric assessments of cardiometabolic health (BMI, waist circumference, and blood pressure). The GRADE system is widely recognized as a credible and validated approach in systematic reviews and meta-analyses, with extensive validation and usage in the field.(53)

AUTHORS' CONTRIBUTIONS

PH conceptualised and designed the systematic review with input from JB, CM, TYW, KW, AW, VA, PL, BT, PW, ES, MB, TS, and VE. CM, VE, and PW supervised the project.

COMPETING INTERESTS STATEMENT

Authors have no competing interests to declare.

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Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1

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Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	1 & 16
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	2
Support			
Sources	#5a	Indicate sources of financial or other support for the review	16
Sponsor	#5b	Provide name for the review funder and / or sponsor	16
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	16
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6-8
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	7-8
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	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	n/a - Provided in Appendix 1

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Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-10
Study records - 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)	9-10
Study records - 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	9-10
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	9-10
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6-8, 9-10
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	10
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	10-11
Data synthesis	#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 I2, Kendall's τ)	10-11
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10-11
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10-11
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12

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Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12-13

Notes:

- 10: n/a - Provided in Appendix 1 The PRISMA-P elaboration and explanation paper is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 21. March 2023 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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Appendix 2: Example Search Strategy for MEDLINE (via PubMed).

Concept	PubMed	Central	Embase (Ovid)	PsycINFO (Ovid)
Children and adolescents #1	"Child"[MeSH Terms] OR "Adolescent"[MeSH Terms] OR "youth"[Text Word] OR "infant"[Text Word] OR "juvenile"[Text Word] OR "minor"[Text Word] OR "young person"[Text Word] OR "youngster"[Text Word] OR "kid"[Text Word] OR "kids"[Text Word] OR "child*"[Text Word] OR "adolesc*"[Text Word] OR "teen*"[Text Word]	"youth" or "infant" or "juvenile" or "minor" or "young person" or "youngster" or "kid" or "kids" or "child*" or "adolesc* or teen*"	"youth" or "infant" or "juvenile" or "minor" or "young person" or "youngster" or "kid" or "kids" or "child*" or "adolesc* or teen*"	"youth" or "infant" or "juvenile" or "minor" or "young person" or "youngster" or "kid" or "kids" or "child*" or "adolesc* or teen*"
Population (diagnosis of mental health illness likely to be prescribed antipsychotic medications). #2	"Neurodevelopmental Disorders"[MeSH Terms:noexp] OR "Attention Deficit Disorder with Hyperactivity"[MeSH Terms] OR "Developmental Disabilities"[MeSH Terms] OR "Intellectual Disability"[MeSH Terms:noexp] OR “intellectual disabilit*”[Text Word] OR “intellectual impairment*”[Text Word] OR “intellectual delay*”[Text Word] OR “learning disabilit*”[Text Word] OR “learning impairment*”[Text Word] OR “learning delay*”[Text Word] OR “developmental disabilit*”[Text Word] OR “developmental delay”[Text Word] OR "Child Development Disorders, Pervasive"[Mesh] OR "schizophrenia, childhood"[MeSH Terms] OR "Tic	"intellectual disabilit*" or "intellectual impairment*" or "intellectual delay*" or "learning disabilit*" or "learning impairment*" or "learning delay*" or "developmental disabilit*" or "developmental delay" or "autism*" or "autistic*" or "Kanners Syndrome" or "neurodevelopmental*" or "ADHD" or "attention defici*" or "pervasive developmental	"intellectual disabilit*" or "intellectual impairment*" or "intellectual delay*" or "learning disabilit*" or "learning impairment*" or "learning delay*" or "developmental disabilit*" or "developmental delay" or "autism*" or "autistic*" or "Kanners Syndrome" or "neurodevelopmental*" or "ADHD" or "attention defici*" or "pervasive developmental disorder" or "developmental disabilit*" or "intellectual disabilit*" or "schizophrenia" or "psychosis" or "tourette*" or "tic disorder" or "asperger*" or "bipolar*"	"intellectual disabilit*" or "intellectual impairment*" or "intellectual delay*" or "learning disabilit*" or "learning impairment*" or "learning delay*" or "developmental disabilit*" or "developmental delay" or "autism*" or "autistic*" or "Kanners Syndrome" or "neurodevelopmental*" or "ADHD" or "attention defici*" or "pervasive developmental

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	Disorders"[MeSH Terms] OR "autism*"[Text Word] OR "autistic*"[Text Word] OR "Kanner's Syndrome"[Text Word] OR "neurodevelopmental*"[Text Word] OR "ADHD"[Text Word] OR "attention defici*"[Text Word] OR "pervasive developmental disorder"[Text Word] OR "developmental disabilit*"[Text Word] OR "intellectual disabilit*"[Text Word] OR "schizophrenia"[Text Word] OR "psychosis"[Text Word] OR "tourette*"[Text Word] OR "tic disorder"[Text Word] OR "asperger*"[Text Word] OR "Bipolar and Related Disorders"[Mesh] OR "bipolar*"[Text Word]	disorder" or "developmental disabilit*" or "intellectual disabilit*" or "schizophrenia" or "psychosis" or "tourette*" or "tic disorder" or "asperger*" or "bipolar*"		disorder" or "developmental disabilit*" or "intellectual disabilit*" or "schizophrenia" or "psychosis" or "tourette*" or "tic disorder" or "asperger*" or "bipolar*"
Population (people taking antipsychotic medications). #3	"antipsychotic*"[Text Word] OR "Antipsychotic Agents"[MeSH Terms] OR "second generation antipsychotic*"[Text Word]	"antipsychotic*" or "second generation antipsychotic*"	"antipsychotic*" or "second generation antipsychotic*"	"antipsychotic*" or "second generation antipsychotic*"
#2 OR #3				
#1 AND #4				

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Lifestyle intervention (general) #6	“lifestyle intervention”[Text Word] OR “healthy living”[Text Word] OR “healthy lifestyle”[Text Word] OR “lifestyle education”[Text Word] OR “behavioral intervention”[Text Word] OR “behavioural intervention”[Text Word] OR "Behavior Therapy"[Mesh:NoExp]OR "behavioural change"[Text Word] OR "behavioral change"[Text Word] OR “behaviour change”[Text Word] OR “behavior change”[Text Word] OR “behaviour modification”[Text Word] OR “behavior modification”[Text Word] OR “behavioural modification”[Text Word] OR“behavioral modification”[Text Word] OR “physical activity”[Text Word] OR “dietary modification”[Text Word] OR “nutrition therapy”[Text Word] OR “physical therapy”[Text Word] OR “nutrition intervention”[Text Word] OR "Diet Therapy"[Mesh:NoExp] OR “weight loss”[Text Word]	"lifestyle intervention" or "healthy living" or "healthy lifestyle" or "lifestyle education" or "behavioral intervention" or "behavioural intervention" or "behavioural change" or "behavioral change" or "behaviour change" or "behavior change" or "behaviour modification" or "behavior modification" or "behavioural modification" or "behavioral modification" or "physical activity" or "dietary modification" or "nutrition therapy" or "physical therapy" or "nutrition intervention" or "weight loss"	"lifestyle intervention" or "healthy living" or "healthy lifestyle" or "lifestyle education" or "behavioral intervention" or "behavioural intervention" or "behavioural change" or "behavioral change" or "behaviour change" or "behavior change" or "behaviour modification" or "behavior modification" or "behavioural modification" or "behavioral modification" or "physical activity" or "dietary modification" or "nutrition therapy" or "physical therapy" or "nutrition intervention" or "weight loss"	"lifestyle intervention" or "healthy living" or "healthy lifestyle" or "lifestyle education" or "behavioral intervention" or "behavioural intervention" or "behavioural change" or "behavioral change" or "behaviour change" or "behavior change" or "behaviour modification" or "behavior modification" or "behavioural modification" or "behavioral modification" or "physical activity" or "dietary modification" or "nutrition therapy" or "physical therapy" or "nutrition intervention" or "weight loss"

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Randomised controlled trial (Cochrane sensitivity and specificity maximising filter) #7	("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms:noexp] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])		(Randomized controlled trial/ or Controlled clinical study/ or random$.ti,ab. or randomization/ or intermethod comparison/ or placebo.ti,ab. or (compare or compared or comparison).ti. or ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. or (open adj label).ti,ab. or ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. or double blind procedure/ or parallel group$1.ti,ab. or (crossover or cross over).ti,ab. or ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. or (assigned or allocated).ti,ab. or (controlled adj7 (study or design or trial)).ti,ab. or (volunteer or volunteers).ti,ab. or human experiment/ or trial.ti.) not (((random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)) or (Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)) or (((case adj control$) and random$) not randomi?ed controlled).ti,ab. or (Systematic review not (trial or study)).ti. or (nonrandom$ not random$).ti,ab. or "Random field$".ti,ab. or (random cluster adj3 sampl$).ti,ab. or ((review.ab. and review.pt.) not trial.ti.) or ("we searched".ab. and (review.ti. or review.pt.)) or "update review".ab. or (databases adj4 searched).ab. or ((rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/) or (Animal experiment/ not (human experiment/ or human/)))	(double-blind or random: assigned or control).tw.
#5 and #6 and #7				

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