BMJ Open

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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To cite: Hawker P, Bellamy J, McHugh C, *et al*. Effectiveness of lifestyle interventions for improving the physical health of children and adolescents taking antipsychotic medications: protocol for a systematic review and meta-analysis. *BMJ Open* 2023;**13**:e073893. doi:10.1136/bmjopen-2023-073893

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-073893).

Received 21 March 2023
Accepted 04 October 2023

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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 that compromise ongoing physical health. Of particular concern is the negative impact antipsychotic medications have on cardiometabolic health. Interventions that 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-Analysis guidelines. Four databases will be searched without any year constraints to identify randomised controlled trials that are published in the English language and report a lifestyle intervention compared with 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 the results. Quantitative data will be synthesised, 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 will 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 is not required. The publication plan will target high-impact, peer-reviewed journals that fall under the scope of Psychiatry and Mental Health.

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 based 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 the included studies may vary significantly, potentially impacting the robustness of the findings.

PROSPERO registration number CRD42022380277.

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 that compromise ongoing health.[1] Interventions that 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

programmes, could effectively improve metabolic parameters and lower the 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, 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, reduce blood sugar, improve 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 that 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 a 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 include weight gain, dyslipidaemia, elevated blood pressure, and an increased risk of type 2 diabetes.[22–24] There is increasing evidence to suggest that, compared with adults, children and adolescents are more susceptible to developing cardiometabolic complications from antipsychotic use,[1 25–29] particularly children with ASD.[25 30] Antipsychotic prescriptions to children and adolescents are 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 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 (eg, UK National Institute for Health and Care Excellence guidelines, Frith Prescribing Guidelines, stopping over medication of people with a learning disability, autism or both with psychotropic medicines), 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 as 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 of 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 6–17 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 with treatment as usual (ie, 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?

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

Population	Youth aged 6–17 years who are taking antipsychotic medications. Youth most likely to be taking antipsychotic medications include those diagnosed with a neurodevelopmental disorder (ie, intellectual disability, autism spectrum disorder, attention-deficit/hyperactivity disorder, Tourette syndrome) 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 that incorporate a 'lifestyle' intervention component and aim to improve physical health outcomes will be eligible. This includes any educational, psychotherapeutic, social and behavioural intervention that aims to increase exercise or physical activity, optimise dietary intake, aid nicotine cessation or improve sleep quality and duration.
Comparisons	All relevant control interventions will be included (ie, treatment as usual/usual care, placebo, no treatment, waiting list).
Outcomes	Physical health outcomes that will be included: 1. Anthropometric measures, including weight, height, waist circumference or body mass index percentile. 2. Blood pressure. 3. Metabolic or biological markers, including glucose and lipid levels, haemoglobin A1c, 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 (ie, maximal oxygen consumption), and muscle strength. 7. Physical health-related quality of life. 8. Side effects of antipsychotics, including adverse drug reactions. Physical health outcomes that will be excluded: 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 and characteristics	Applicable randomised controlled trials 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 that are not peer-reviewed and papers published in a language other than English will be excluded.

Primary outcome measure

While all relevant physical health outcomes will be considered (see table 1), the primary outcome measure will be the difference in BMI between the 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 Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol reporting guidelines (see online supplemental appendix 1).[47]

Patient and public involvement

No patients were involved.

Eligibility criteria

The eligibility criteria are described in table 1.

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 Trialsand PsycINFO, will be searched without any year constraints. The results will be restricted to studies published in English and employing a randomised 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 that cite the included studies. Trial registers and results repositories will be scoured, including ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform 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 rerun before final data analysis.

Search strategy

The development of the search strategies for each database will be conducted with the oversight of a Medicine and 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 the online supplemental 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 prevent loss of information. Access to the data will be restricted to authorised 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. On finalisation of the results, the data will be securely uploaded to a suitable repository.

Data items and outcomes

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 (ie, maximal oxygen consumption), and muscle strength[4]; metabolic or biological markers, including glucose and lipid levels, proportion with abnormal glucose or lipid parameters, haemoglobin A1c, C-reactive protein or other relevant blood and serum markers[5]; presence of cardiovascular illness, including myocardial infarction, stroke, transient ischaemic attack and pulmonary embolism[6]; presence of respiratory illness, including lung cancer and chronic obstructive pulmonary disease[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, the authors of the 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 2 weeks. If there is still no response after the follow-up, a final reminder will be sent after 1 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 lead 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.[50] To ensure rigour, two reviewers will independently perform quality assessments and compare the 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 synthesised, where appropriate, through a random-effects meta-analysis model. Effect size data will be extracted with 95% CI for relevant outcomes, in addition to the number of participants (n) in the lifestyle intervention or control group for each effect size. Where it is not possible to extract effect size data for the meta-analysis, the data will be reported in a qualitative (narrative) synthesis. Effect size data with a 95% CI for relevant outcomes will be recalculated as a standardised mean difference (SMD) to express the mean difference between groups in SD units with a 95% CI. SMDs of less than 0.2 will be considered negligible, SMDs between 0.2

and <0.5 as small, SMDs between 0.5 and <0.8 as medium and SMDs ≥0.8 as large.[51] Risk ratios (RRs) will be used for categorical outcomes. ORs 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.
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 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 (eg, a short follow-up period, a 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 use 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 SE 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 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 use the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE system[53] for assessing the strength of the body of evidence. The GRADE system offers a transparent and standardised 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 recognised as a credible and validated approach in systematic reviews and meta-analyses, with extensive validation and usage in the field.[53]

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Acknowledgements We express our gratitude to Samantha Bowen (UNSW), for her valuable review and insightful evaluation of our search strategy. We also extend our appreciation to Nancy Briggs (UNSW) for her thorough examination and constructive input on our data synthesis approach.

Contributors PH conceptualised and designed the systematic review with input from JB, CM, TYW, KW, AW, VA, P-IL, BJT, PW, ES, MAB, TS and VE. CM, VE and PW supervised the project.

Funding This systematic review is funded by Growing Minds Australia via the National Health and Medical Research Council (NHMRC; Grant ID: MRF2006438 (2020 MRFF Million Minds Mission) and sponsored by the University of New South Wales (UNSW), Sydney. The funding source (NHMRC Million Minds Mission) has no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data or decision to submit results.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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