Double-blind, randomised placebo-controlled clinical trial of metformin as an adjunct to a sleep–wake, activity and metabolically focused behavioural intervention to improve cardiometabolic outcomes and mood symptoms in youth with major mood syndromes: study protocol

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ABSTRACT

Introduction Metformin is a medication likely to improve measures of cardiometabolic disturbance in young people with mental illness. Evidence also suggests metformin may improve depressive symptoms. This 52-week double-blind randomised control trial (RCT) aims to investigate the efficacy of metformin pharmacotherapy as an adjunct to a healthy lifestyle behavioural intervention in improving cardiometabolic outcomes, and depressive, anxiety and psychotic symptoms in youth with clinically diagnosed major mood syndromes.

Methods and analysis At least 266 young people aged 16–25 presenting for mental healthcare for major mood syndromes who are also at risk for poor cardiometabolic outcomes will be invited to participate in this study. All participants will engage in a 12-week sleep–wake, activity and metabolically focused behavioural intervention programme. As an adjunctive intervention, participants will receive either metformin (500–1000 mg) or placebo pharmacotherapy for 52 weeks. Participants will undergo a series of assessments including: (1) self-report and clinician-administered assessments; (2) blood tests; (3) anthropometric assessments (height, weight, waist circumference and blood pressure); and (4) actigraphy. Univariate and multivariate tests (generalised mixed-effects models) will be used to examine changes in primary and secondary outcomes (and associations with predetermined predictor variables).

Ethics and dissemination This study has been approved by the Sydney Local Health District Research Ethics and Governance Office (X22-0017). The results of this double-blind RCT will be disseminated into the scientific and broader community through peer-reviewed journals, conference presentations, social media and university websites.

Trial registration number Australian New Zealand Clinical Trials Registry (ANZCTR) Number: ACTRN12619001559101p, 12 November 2019.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This double-blind randomised control trial tests whether a medication (metformin) delivers long-term benefits beyond those achieved by behavioural intervention.
⇒ A range of physical and mental health outcomes are assessed, including cardiometabolic, anthropometric, sleep–wake and depressive symptoms.
⇒ The use of HOMA2-IR as the primary outcome measurement, may be a more sensitive indicator of metabolic abnormality in this cohort, compared with traditional measures (body mass index).
⇒ As all participants receive a sleep–wake, activity and metabolically focused behavioural intervention programme, there is no comparison of this behaviour intervention to a control group.
⇒ The behavioural intervention component of the study runs for 12 weeks whereas the medication period is 52 weeks. As such, the behavioural intervention may not be sufficient to instil long-term metabolic changes.

INTRODUCTION

Youth with major mental illness often present with emerging cardiometabolic risk factors...
including insulin resistance and obesity. The high prevalence of cardiometabolic abnormalities in youth with severe mental disorders is of concern as they are thought to be the leading contributor to the premature mortality and morbidity of individuals presenting with severe mental disorders. While these cardiometabolic risk factors may emerge early on in care, there is some evidence emerging to suggest there may be some bidirectional relationships. For example, research suggests that those with depression are more likely to develop obesity over time. Another longitudinal study found that high fasting insulin levels in childhood are associated with increased risk for psychosis at age 24, and that increases in body mass index (BMI) during puberty are associated with a greater risk for depression at 24 years old. The development of these cardiometabolic risk factors so early in the course of care for young people presenting with mental disorders is especially concerning. Thus, a significant challenge for clinicians is to target and develop interventions to manage and prevent the development of these cardiometabolic risk factors in young people with mental disorders.

Key modifiable risk factors linked to the development of cardiometabolic abnormalities in this cohort include physical inactivity, poor dietary habits, and poor sleep–wake cycle regulation. Additionally, some psychotropic medication given to treat psychotic or affective symptoms are associated with weight gain, elevated blood lipids and insulin resistance. Metformin is an oral biguanide approved for the treatment of type 2 diabetes mellitus (T2DM) as monotherapy in children from 10 years of age and adolescents by the Australian Register of Therapeutic Goods. Metformin is expected to reduce hepatic glucose production, reduce intestinal absorption of glucose and enhance insulin sensitivity. In non-psychiatric children and adolescents with obesity, meta-analytic evidence has shown that whether implemented in isolation or in combination with lifestyle interventions, metformin is associated with improvement in markers of BMI, triglycerides, fasting glucose, low-density lipoprotein (LDL)-cholesterol, total cholesterol, and T2DM. There does however appear to be mixed evidence on the effect of metformin treatment on insulin resistance measures in non-psychiatric samples of adolescents, either showing some or no improvement. Most studies on youth with psychiatric diagnoses have found that metformin improves weight or BMI. However, less research has been conducted on other cardiometabolic risk factors in youth with psychiatric conditions.

Furthermore, metformin has been suggested as a potential medication adjunct in youth mental illness, to manage some of the side effects associated with psychotropic medication usage including, elevated lipids and insulin resistance. Metformin has also been linked to improved depressive and anxiety symptoms in young women with polycystic ovarian syndrome, and improved mood symptoms in adults with major depressive disorder. Additionally, evidence is beginning to emerge of the benefits of metformin pharmacotherapy on affective symptoms. Specifically, metformin prescription has been linked to improved depressive and anxiety symptoms in female youths with polycystic ovarian syndrome. Due to its link with neurogenesis, metformin may also have the potential to improve mood states in those with major mood disorders. However, with limited research in this field, the utility of long-term metformin to improve both cardiometabolic abnormalities and mood symptoms in youth mental disorders has not been explored to its full potential and warrants further investigation.

Lifestyle interventions are an effective non-pharmacological intervention option to manage drug-induced cardiometabolic disturbances in patients with psychiatric disorders and should be available pre-emptively to protect cardiometabolic health from the first presentation of illness. Psychoeducational or behavioural interventions focusing on healthy lifestyle habits including nutrition, physical activity and sleep practices have been shown to ameliorate both the physical and mental health concerns of young people with psychiatric disorders. Several studies have administered metformin together with a comprehensive lifestyle intervention containing structured physical activity, nutritional advice or motivational support. Results from these studies indicate that lifestyle interventions combined with metformin is superior to either intervention alone in reducing weight and BMI.

However, lifestyle behavioural interventions alone may not sufficiently alleviate and prevent the poor cardiometabolic outcomes in young people with mood and psychotic syndromes. In fact, pharmacological cotherapies have already been shown to produce more meaningful clinical improvements above and beyond that of lifestyle interventions in alleviating and improving the cardiometabolic risk factors in youth. For example, in studies on overweight and obese youth, several of the studies involved receiving metformin together with a comprehensive lifestyle intervention involving structured physical activity, diet advice or motivational support. Results from these studies indicate that lifestyle intervention combined with metformin is superior to either interventions alone in reducing measures of weight and BMI. Compared with lifestyle interventions, metformin also appears to produce greater benefits in reducing fasting insulin levels and homeostatic model assessment of insulin resistance (HOMA1-IR) levels at 6, 12 and 24 months in overweight/obese non-diabetic children and adolescents. Thus, metformin pharmacotherapy may assist in producing more clinically meaningful improvements in several cardiometabolic risk factors of concern in young people with clinically diagnosed mood and psychotic syndromes, however, further research is needed to understand the relationship between these factors over time.

There is also evidence to indicate that the updated HOMA2-IR may be a more sensitive indicator of metabolic abnormality in this cohort. By examining
HOMA2-IR longitudinally, along with other cardiometabolic outcomes in this cohort, we may be able to demonstrate a more sensitive measure of cardiometabolic risk than previously recognised measures. Additionally, no studies have yet examined the effects of metformin pharmacotherapy on depressive, anxiety or psychotic symptoms in young people with major mood syndromes.

Overall, this study aims to investigate the efficacy of metformin as an adjunct to a sleep–wake, activity and metabolically focused behavioural intervention programme targeted towards improving cardiometabolic outcomes and affective symptoms in young people presenting for mental healthcare for major mood syndromes. As a superiority trial, we also aim to determine whether the combined metformin pharmacotherapy and behavioural intervention is clinically better than the behavioural intervention in isolation.

METHODS AND ANALYSIS

Patient and public involvement

The study design, conduct and behavioural intervention module content was developed in consultation with representatives from the Brain and Mind Centre Youth Lived Experienced Working Group. Specifically, the module content was presented to the lived experience working group in a collaborative workshop, where module content was modified and optimised to ensure the suitability and relevance for this cohort. Patients or the public were not involved in the recruitment, conduct or dissemination plans of our research.

Design and structure

This is a phase IV double-blind randomised control trial (RCT), where participants are randomised to an adjunct medication with metformin or placebo. All participants will receive 52 weeks of metformin or placebo treatment along with a sleep–wake, activity and metabolically focused behavioural intervention programme in the first 12 weeks of the study. This behavioural intervention programme will involve structured nutritional, physical activity, sleep–wake and general healthy lifestyle information based on the Australian Guidelines of Physical Activity, the Australian Guide to Healthy Eating and published circadian research findings specific to youth mental illness.49–52 This information will be delivered for approximately 1 hour each fortnight over six online or face-to-face modules (week 1, 3, 5, 7, 9 and 11). These modules will cover the topics shown in Table 1. From weeks 1–12, participants will receive a weekly monitoring phone call to aid their engagement and ongoing participation. After week 12, participants will receive monthly

Table 1  Sleep–wake, activity and metabolically focused behavioural intervention modules

<table>
<thead>
<tr>
<th>Session</th>
<th>Topics to be covered</th>
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<tbody>
<tr>
<td>1. Body clock and sleep–wake cycle regulation for mental health (part 1)</td>
<td>Establishing a healthy mindset and goal setting</td>
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<td></td>
<td>How the brain and body are connected</td>
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<td>Role of melatonin</td>
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<td>Importance of the brain and body clock and sleep–wake cycle regulation</td>
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<td>How the brain and body clock coordinates all the biological systems</td>
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<td>How to regulate the sleep–wake cycle for example, via gradual sleep–wake rescheduling</td>
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<tr>
<td>2. Body clock and sleep–wake cycle regulation for mental health (part 2)</td>
<td>Healthy sleep–wake behaviours</td>
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<td>How lifestyle factors and behaviours influence the brain and body clock for example, exercise, light exposure, sleep environment, sleep regularisation, naps, foods, stress, anxiety and mood</td>
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<td>Sleep wake–cycle regulation tip for example, consistent sleep–wake times, avoiding naps and exercise regularly</td>
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<td>Limiting screen time in the evening</td>
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<td></td>
<td>Creating a sleep routine</td>
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<td>3. Physical activity for mental health (part 1)</td>
<td>Benefits of physical activity for physical and mental health</td>
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<td></td>
<td>Outline of Australian Physical Activity Guidelines</td>
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<td>Identifying and challenging barriers to engaging in physical activity</td>
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<td>Timing of physical activity</td>
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<td></td>
<td>Tips for starting exercise</td>
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<td>Increasing incidental activity, reducing sitting time</td>
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<td>Establishing an activity schedule</td>
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<tr>
<td>4. Physical activity for mental health (part 2)</td>
<td>Working out anywhere</td>
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<td>Fitting in exercise throughout your day</td>
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<td>Finding the motivation</td>
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<td>Concept of energy in vs energy out</td>
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<tr>
<td>5. Nutrition for mental health (part 1)</td>
<td>Energy in vs energy out and creating a healthy balance</td>
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<td>Outline of Australian Dietary Guidelines</td>
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<td>Creating a healthy eating plate</td>
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<td>Standard serving sizes/portion sizes</td>
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<td>Alcohol and mental health</td>
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<tr>
<td>6. Nutrition for mental health (part 2)</td>
<td>Timing of meals</td>
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<td>Healthy snacking</td>
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<td>Meal preparation</td>
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<td>Making healthy choices when eating out at restaurants</td>
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<td>Managing comfort eating</td>
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<td>Making sustainable choices</td>
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phone calls to monitor symptoms and medication adherence. Participants will also receive a summary sheet containing the information from the modules that they can refer to throughout the remainder of the trial. As such, the information from the behavioural intervention will not be repeated across the remainder of the intervention, however participants will be given the opportunity to discuss their behavioural changes and goals within the ongoing monthly phone calls.

Participants will be asked to wear an actigraph (GENEActiv; Activinsights, Kimbolton, UK) on the non-dominant wrist to collect 24-hour sleep–wake and physical activity parameters during weeks 1–2, 11–12, 25–26, 37–38 and 51–52. In weeks 1, 12, 26, 38 and 52, the following will also be collected: fasting blood tests to measure metabolic, immune and hormonal markers, anthropometric assessments (blood pressure, height, weight and waist circumference), self-report and clinician-administered assessments to assess various mental illness symptoms and physical activity engagement. Blood tests for genetic analysis will be collected in week 1 only. All assessments including the self-report questionnaires and clinician-rated assessments are expected to take approximately 2 hours at each time point.

Most of these self-report and clinician-administered assessments are part of the standardised assessment battery developed for the Youth Mental Health Tracker as part of the Brain and Mind Centre (BMC) multidimensional research framework.53 The multidimensional outcome framework was developed to assess a comprehensive range of measures in individuals presenting to care across a range of domains important to mental health outcomes. All observational and interventional youth mental health research at the BMC uses a standardised set of measures within this framework. These assessments are part of an ongoing larger study for all young people presenting for mental healthcare to improve the outcomes of their clinical care. The schedule of enrolment, interventions and assessment time points can be seen in Table 2. The participant will begin the trial the day they are enrolled (week 1), and will cease the trial after Week 52.

### Randomisation, dosage and treatment arms

The participants will be prerandomised in a 1:1 ratio via a block randomisation sequence of four and allocated to one of the two treatment arms: oral metformin (500 mg–1000 mg daily) or placebo. The packaging of the study medication will be prerandomised and contain a randomisation number. This dosage is based on previous studies with similar cohorts20 and guidelines on metformin prescription in youth.54 55 After 2 weeks, the participant’s tolerability (especially gastrointestinal side effects) will be assessed by the study doctor and where appropriate the dosage will be titrated up to 1000 mg per day. Participants, their healthcare practitioners (psychiatrists, psychologists, general practitioners, exercise physiologists and/or social workers) and research staff will be masked to the treatment allocation.

### Blinding

Participants, their healthcare providers and research staff (including outcome assessors) will be masked to

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Schedule of enrolment, interventions and assessment time points</th>
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<tr>
<td><strong>Study phase</strong></td>
<td><strong>Prerandomisation</strong></td>
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<tr>
<td><strong>Screening</strong></td>
<td>x</td>
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<tr>
<td><strong>Enrolment (week 1)</strong></td>
<td>x</td>
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<tr>
<td><strong>Actigraphy</strong></td>
<td>x</td>
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<tr>
<td><strong>Metformin/placebo</strong></td>
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<tr>
<td><strong>Psychoeducation sessions</strong></td>
<td>x</td>
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<tr>
<td><strong>Self-report questionnaires</strong></td>
<td>x</td>
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<tr>
<td><strong>Clinician-administered assessments</strong></td>
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<tr>
<td><strong>Genetic testing</strong></td>
<td>x</td>
</tr>
<tr>
<td><strong>Psychological assessments</strong></td>
<td>x</td>
</tr>
<tr>
<td><strong>Physical/blood assessments</strong></td>
<td>x*</td>
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</table>

*Physical assessments and/or blood tests may need to be conducted to confirm selection criteria.
treatment allocation. Unblinding of study medication may occur in the instance of a serious adverse event and for safety reasons. The decision to unblind is at the discretion of the principal investigator. The dispensing clinician will then be able to inform study staff whether the participant was on the active or placebo at the time.

Setting, recruitment and informed consent
This is a single-site, double-blind RCT, conducted at the BMC (including headspace Camperdown and Early Intervention and High Intensity Services) at the University of Sydney (Sydney, Australia). These clinics comprise a mix of primary-level mental healthcare as well as more specialised services. As such, these clinics attract young people with a range of mental health problems including those with subthreshold and full-threshold mental disorders.

All treating clinicians will be made aware of the study and eligibility criteria and will inform all suitable young people presenting for care at these services to participate in the study. Research staff will obtain written informed consent from interested young persons to participate in the sleep–wake, activity and metabolically focused behavioural intervention programme. The research team will make explicit to any potential participants both verbally and in writing (in the participant information and consent form) that participation is voluntary. They will be assured that their decision whether to participate will not affect their current or future relationship with the researchers or anyone else at The University of Sydney nor their current or future involvement with the mental health service. Participants will also be made aware that they are free to withdraw from the study at any time by contacting research staff.

Selection criteria
Young people will be invited into the double-blind RCT, based on the following inclusion criteria:
1. aged between 16 and 25;
2. a current diagnosis of a major mood syndrome (including anxiety, depression, bipolar disorder and affective psychosis) according to the Diagnostic and Statistical Manual of Mental Disorders, version V (DSM-V) criteria using the Structured Clinical Interview for DSM-V (SCID).
3. BMI ≥25;
and at least one (≥1) of the following conditions:
1. HOMA2-IR value ≥1.5;
2. currently on and/or commencing psychotropic medication (antipsychotics, antidepressants, mood stabilisers) under psychiatric supervision and/or mental illness has reached Stage 2 ‘Discrete Disorders’ in the clinical staging model framework for mood and psychotic syndromes.\textsuperscript{56,57}

The exclusion criteria are:

i. lifetime use of metformin or any other glucose lowering medication;
i. lifetime diagnosis of T1 or T2DM diabetes (gestational diabetes accepted);
iii. intellectual disability (at the discretion of a clinical psychologist or psychiatrist);
iv. major neurological disorder, medical illness which impacts on cognition, and/or a history of sustained head injury;
v. inadequate English language skills;
vi. a current alcohol or substance use disorder that impairs the individual’s ability to give informed consent and/or requires acute clinical treatment;
vii. a risk of serious self-harm (as assessed by the study doctor);
viii. an acute psychotic or manic episode that impairs the individual’s ability to give informed consent; or
ix. any contraindications to metformin treatment (described below).

Participants will not be allowed to enter the study if they possess any of the following contraindications to metformin treatment:

i. juvenile diabetes mellitus that is uncomplicated and well-regulated on insulin;
ii. diabetes mellitus regulated by diet alone;
iii. during or immediately following surgery where insulin is essential;
iv. hypersensitivity to metformin or any of its ingredients;
v. hypersensitivity to biguanides;
vi. diabetic ketoacidosis, diabetic pre-coma;
vii. renal failure or renal dysfunction (creatinine clearance<60 mL/min);
viii. acute conditions with the potential to alter renal function such as dehydration, severe infection, shock or intravascular administration of iodinated contrast agents;
ix. acute or chronic disease which may cause tissue hypoxia such as cardiac failure, recent myocardial infarction, respiratory failure, pulmonary embolism, shock, acute significant blood loss, sepsis, gangrene or pancreatitis;
x. elective major surgery;
xii. severe hepatic insufficiency;
xiii. intellectual disability (at the discretion of a clinical psychologist or psychiatrist);
xiv. a current alcohol or substance use disorder that impairs the individual’s ability to give informed consent; or
xv. an acute psychotic or manic episode that impairs the individual’s ability to give informed consent; or
xvi. any contraindications to metformin treatment (described below).

Study discontinuation and safety
Participants will be monitored for exclusion criteria and contraindications to metformin treatment in weeks 12, 26, 38 and 52. Where the participant meets any of the exclusion criteria throughout the trial, or they experience any contraindications to metformin prescription, they will be withdrawn from the study immediately, discontinued treatment and followed up by the study doctor. The participants general medicine practitioner will be notified (with consent, via email) and where necessary, counselling or other mental health support will be made available to support the young person. The principal investigator will ensure that follow-up of the participant is appropriate to the nature of any event, and that it continues until resolution. Participants who prematurely withdraw from the study or are discontinued from the study treatment will not be replaced.
An independent Data and Safety Monitoring Committee (DSMC) has been assembled to monitor the progress, safety, adverse events and efficacy of this clinical trial and provide critical evaluation and recommendations to principal investigators and all sponsors of this trial. The DSMC will meet every 6 months throughout this trial and review cumulative study data to evaluate study conduct, the scientific validity and data integrity of the study including safety of this trial.

**Study objectives**

**Primary**
To assess the efficacy of metformin pharmacotherapy as an adjunct to a healthy lifestyle sleep–wake, activity and metabolically focused behavioural intervention programme in improving HOMA2-IR scores of young people seeking treatment for mental health-related issues.

**Secondary**
To assess if changes in cardiometabolic health risk factors (fasting insulin, fasting glucose, triglycerides, HOMA2-IR, cholesterol, blood pressure, BMI and waist circumference) are observed throughout this trial and report cumulative study data to evaluate study conduct, the scientific validity and data integrity of the study including safety of this trial.

**Table 3 Outcome measures**

<table>
<thead>
<tr>
<th>Measures</th>
<th>Primary</th>
<th>Secondary</th>
<th>Tertiary</th>
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<tbody>
<tr>
<td>Measures</td>
<td>HOMA2-IR</td>
<td>Fasting glucose, Fasting insulin, Triglycerides, HDL cholesterol level, LDL cholesterol, Total cholesterol, HbA1c, Inflammatory markers (IL-1β, IL-2, IL-6, C reactive proteins, IFN-γ, TNF-α), Hormonal markers (prolactin, oestradiol, DHEAS, testosterone, LH, FSH, SHBG, AMH, serum cortisol and 17OHP), Blood pressure, BMI, Waist circumference measurement</td>
<td>The Brief Psychiatric Rating Scale (BPRS), Kessler Psychological Distress Scale (K-10), Quick Inventory of Depressive Symptomatology-self-report (QIDS-SR), Overall Anxiety Severity Impairment Scale (OASIS)</td>
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AMH, anti-mullerian hormone; DHEAS, dehydroepiandrosterone sulfate; FSH, follicle stimulating hormone; HDL, high-density lipoprotein; HOMA2-IR, homeostatic model assessment of insulin resistance; IFN, interferon; IL, interleukin; LDL, low-density lipoprotein; LH, luteinizing hormone; SHBG, sex hormone binding globulin; TNF, tissue necrosis factor.
circumference) are associated with changes in affective (depressive and anxiety) symptom severity.

**Tertiary**

To assess if changes in mood symptoms or changes in cardiometabolic parameters following adjunctive metformin treatment are associated with a range of multidimensional outcome measures in young people seeking treatment for mental health concerns. This includes mental illness symptoms, self-harm and suicidal thoughts and behaviours, physical health parameters, alcohol and substance use, inflammatory markers, hormonal response and genetic markers.

**Measures**

The following measures have been described in more extensive detail in our previous protocol outlining the pilot study of the behavioural intervention component. Key outcome measures targeted for this study are highlighted in **bold type**. Please refer to **table 3** which summarises the primary, secondary and tertiary outcome measures.

**Clinician-rated assessments**

1. **Diagnostic assessment** The SCID-5 will be used to identify any DSM-V disorders.
2. **Physical health, mental health, family health and treatment history** current and past medical history will be assessed including current medication and any changes in physical and/or mental health treatment being received throughout the trial.
3. **The Brief Psychiatric Rating Scale (BPRS)** the BPRS is used to assess psychiatric symptoms including depression, anxiety, hallucinations, delusions and unusual behaviour.
4. **Clinical staging** this framework classifies individuals according to the presentation of their mental illness in three stages—those in the earliest phases with non-specific clinical presentations (Stage 1a ‘seeking help’), those at greater-risk with more specific, subthreshold presentations (Stage 1b ‘attenuated syndromes’) and those who have already reached a threshold for a progressive or recurrent disorder meeting diagnostic criteria (Stage 2, 3 or 4).
5. **Pathophysiological mechanism** the pathophysiological model suggests three putative pathways of illness: (i) neurodevelopmental psychosis, (ii) circadian-bipolar spectrum, or (iii) hyperarousal-anxious depression subtypes.
6. **Clinical Global Impression (CGI)**: the CGI assesses a young person’s global functioning in context of their history, psychosocial circumstances, symptoms and behaviour.
7. **The Young Mania Rating Scale (YMRS)**: the YMRS is an 11-item questionnaire measuring manic episode symptom severity.
8. **The Simple Physical Activity Questionnaire (SIMPAQ)** the SIMPAQ is a 5-item clinical tool designed to assess physical activity levels.
9. **Suicidal ideation and behaviour** acute suicidal behaviour will be assessed by item 7.3 of the Comprehensive Assessment of At-Risk Mental States (CAARMS).
10. **Social and Occupational Assessment Scale (SOFAS)** the SOFAS is an assessment of the participant’s current social and occupational functioning. Scores range from 0 to 100, with lower scores indicating poorer functioning.

**Self-report questionnaires**

1. **Demographics** basic demographic information will be collected including details of work and education, ethnicity, living circumstances, relationship status and physical health (height, weight and waist circumference).
2. **Kessler Psychological Distress Scale (K-10)**: this 10-item scale provides a global measure of anxiety and depressive symptoms over a 4-week period.
3. **International Physical Activity Questionnaire (IPAQ)-short version** the short version of the International Physical Activity Questionnaires (IPAQ) is a 7-item questionnaire calculates the amount of time spent engaging in various intensities of physical activity.
4. **Somatic and Psychological Health Report (SPHERE 12)**: the SPHERE 12 assesses six psychological (PSYCH subscale), and six physical and fatigue symptoms (SOMA subscale) to identify anxiety, depression and somatisation symptoms.
5. **Sleep–wake cycle and chronotype** six questions will be asked concerning sleeping patterns and feelings when waking up based on the Pittsburgh Sleep Quality Index (PSQI) and Munich Chrono Type Questionnaire (MCTQ).
6. **Pittsburgh Sleep Quality Index (PSQI)** he PSQI is a 24-item self-report questionnaire assessing sleep quality and patterns of sleep.
7. **The Insomnia Severity Attributes Scale (ISI)** this 7-item questionnaire assesses sleep problems, daily functioning and impairment attributed to the sleep problem, and the degree of distress or concern caused by the sleep problem.
8. **Suicidal Ideation Attributes Scale (SIDAS)** the SIDAS is a 5-item self-report questionnaire assessing suicidal ideology over the last month.
9. **Quick Inventory of Depressive Symptomatology-self-report (QIDS-SR)** the QIDS assesses symptoms of a major depressive episode.
10. **Overall Anxiety Severity Impairment Scale (OASIS)** the OASIS is a 5-item self-report measure used to assess the frequency and intensity of anxiety symptoms.
11. **WHO Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST)** the ASSIST (V.3.1) is an 8-item questionnaire screening for use of drugs and alcohol.
12. Alcohol Use Disorders Identification Test-Consumption (AUDIT-C)\(^82\): the AUDIT-C is a 3-item scale measuring alcohol consumption.

13. Eating Disorder Examination (EDE)\(^83\)\(^84\): this self-report questionnaire assesses current eating disorder behaviours, including binge eating, purging and strict dieting or fasting.

14. Rosenberg Self-Esteem Scale (RSES)\(^85\): the RSES is a 10-item self-report measure of self-esteem, self-worth or self-acceptance designed specifically for use in adolescent populations.

15. Client Satisfaction Questionnaire-8 (CSQ-8)\(^86\): the CSQ assesses level of satisfaction with care.

16. Feedback Questionnaire: this is an investigator-developed questionnaire specifically relating to the feasibility and acceptability of the sleep–wake, activity and metabolically focused behavioural intervention programme and the overall metformin treatment programme.

**Blood markers**

Blood samples are to be collected in a fasting state between 8:00 am and 10:00 am by a trained phlebotomist at weeks 1, 12, 26, 38 and 52. Metabolic variables of interest include fasting glucose; fasting insulin, and blood lipids (including triglycerides and total, high-density lipoprotein (HDL) and LDL cholesterol levels). Insulin resistance will be estimated using the updated homeostatic model assessment (HOMA2-IR) using iHOMA2 software V.8.8\(^87\) from fasting blood test results.

Hormonal markers measured include progesterone, prolactin, oestradiol, dehydroepiandrosterone sulfate, testosterone, leutenising hormone, follicle stimulating hormone, sex hormone binding globulin, anti-mullerian hormone, serum cortisol and 17-hydroxypregesterone. Inflammatory markers measured include interleukin (IL)-1\(\beta\), IL-2, IL-6, interferon (IFN)-\(\gamma\), tissue necrosis factor (TNF)-\(\alpha\) and C reactive protein.

Other blood measures to be collected for monitoring purposes include HbA1c, full blood count, urea, electrolytes, liver function test, CRP, erythrocyte sedimentation rate, antinuclear antibodies, antineutrophil cytoplasmic antibodies, thyroid autoantibodies, free T4 markers, vitamin D, vitamin B\(_{12}\), folate, iron, thyroid stimulating hormone, calcium (Ca), magnesium (Mg) and phosphate (PO\(_4\)) levels.

**Genetic variants**

In week 1, genetic material will be obtained from a sample of whole blood to extract DNA for genetic analysis. These samples will be collected by clinical research staff and processed at the Institute for Molecular Biosciences, University of Queensland to identify single-nucleotide polymorphisms associated with psychiatric and/or cardiometabolic traits. Genetic information will be analysed to examine associations between genetic risk variants and cardiometabolic outcomes.

**Anthropometric assessments**

Measures of blood pressure, height and weight will be collected in weeks 1, 12, 26, 38 and 52 via direct measurement by a clinician or research staff. BMI will be calculated using the formula: weight(kg) ÷ height(m)\(^2\).\(^9\) Waist circumference is measured with the participant standing up, to the nearest 1 cm with a measuring tape at the midpoint between the bottom of the rib cage and above the top of the iliac crest (hip bone) at the end of the participant’s normal respiration.

**24-Hour sleep–wake and physical activity profiling**

All participants will wear wrist-mounted actigraphy recording devices (GENEActiv Sleep device; ActiLife, Kimbolton, UK) to record motor activity over a 2-week period during weeks 1–2, 12–13, 26–27, 38–39 and 51–52. The data collected from these devises will provide an estimation of sleep and physical activity patterns based on validated algorithms.\(^88\) Key measures include sleep onset time, sleep offset time, sleep midpoint, sleep efficiency, wake after sleep onset (number of minutes during the sleep period scored as awake) and total sleep time (number of minutes during the sleep period scored as sleep).

Physical activity levels will be assessed through the GENEActiv devices calculates as gross motor activity per day (milli-gravity (mg), 1g=9.81m/s\(^2\)) and minutes of moderate-to-vigorous physical activity per day (defined as the sum of 1-minute epochs in which gross motor activity is larger than 125mg) as described in other studies.\(^89\) The GENEActiv devices have been used widely in clinical research and validated against several types of accelerometry-based activity monitors\(^90\)\(^92\) as well as for sleep–wake scoring.\(^93\)\(^94\)

**Sample size/power calculation**

One study investigating the effect of metformin on HOMA1-IR levels in adolescents found an effect size of 0.68 after 12 months of treatment.\(^46\) We conservatively estimated that the correlation coefficient would be smaller, around 0.40 (ie, a medium effect size), taking into account the effects of the sleep–wake, activity, and metabolically focused behavioural intervention. Assuming the following parameters (power analyses completed in G*Power V.3.1.9.4): two-tailed, difference between two independent means model with a power of 0.90, an effect size of 0.4 and an alpha level of 0.05, sample size of 266 (133 in each group) will be sufficient to detect an effect.

**Data analysis plan**

All data will be deidentified and entered into a secure password-protected database accessible only by authorized study staff. Statistical analyses were conducted using R statistical software.

**Univariate analyses**

Change in HOMA2-IR score (primary objective) will be analysed via a change in mean score between the metformin and placebo groups via an independent samples t-test, with
significance set at $\alpha=0.05$. Similarly, changes in cardiometabolic measures (blood pressure, fasting glucose, fasting insulin, HOMA2-IR, cholesterol levels, BMI and waist circumference) and depressive, anxiety and psychotic symptoms (secondary objective) will be assessed via independent samples t-tests, with significance set at $\alpha=0.05$. Differences in cardiometabolic outcome change scores according to psychiatric diagnosis will be assessed via analysis of variance, with significance levels set at $\alpha=0.05$.

Finally, correlations will be examined between cardiometabolic parameters and the following (tertiary objective): depressive, anxiety and psychotic symptoms, mental illness symptoms, self-harm and suicidal thoughts and behaviours, physical health parameters, alcohol and substance use, inflammatory markers, hormonal response and genetic markers, via Pearson’s or Spearman’s correlations tests based on normative or non-normative data distribution respectively.

**Multivariate analyses**

Generalised linear mixed-effects models (using the R package nlme or lme4) will be used to examine changes in primary and secondary outcomes measures over the trial. Models will be fitted iteratively, starting first with an unconditional ‘base’ model (testing both linear and quadratic trends for longitudinal outcomes), and building in complexity towards a random intercepts and random effects model (with goodness-of-fit checks (eg, likelihood ratio test) to ensure model structural changes provide an improved fit to the data). An intention-to-treat analysis will be adopted to use all available data (including for participants that drop out); missing follow-up data will be handled using maximum-likelihood estimation. Conditional models will examine potential interindividual differences in both intercepts and slopes (ie, rate of change) as a function of several predetermined factors (age, sex, randomisation group, cardiometabolic factors, psychiatric diagnosis, clinical stage, psychotropic medication, depressive, anxiety and psychotic symptoms). Model coefficients will be presented with 95% CIs and parameter-specific p-values.

**Ethics and dissemination**

The Sydney Local Health District (RPAH Division) Human Research Ethics Committee (HREC) Committee has approved this study (X22-0017). The study will be conducted in compliance with all stipulations of the protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research and the Good Clinical Practice guidelines.

The metformin treatment and behavioural intervention programme is designed as an adjunct, not an alternative, to standard clinical treatments offered by the youth mental health services. As such, all participants are encouraged to continue to follow the healthcare advice of their treating clinicians and to remain in their care, as well as participating in the sleep–wake, activity and metabolically focused behavioural intervention sessions. This standard treatment may include medication, counselling, psychological therapy and/or referrals to a range of specialist mental health treatments or services.

The results of this study will be disseminated as widely as possible into the scientific and broader community. This may include publication in peer-reviewed journals, scholarly book chapters, presentation at conferences and publication in conference proceedings. In accordance with NHMRC policy, publications arising from this study will be deposited into an open access institutional repository, where possible. It is also intended for results to be disseminated into the wider community in a format appropriate for a lay audience, through links including the BMC website and social media, as well as newsletters.

**Trial status**

The trial has not yet begun recruitment.

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**Contributors**

CW has developed this pilot clinical trial as part of her PhD research project and drafted this original manuscript with input from other authors. IBH assisted with the design of the study. AN, NZ, JSC, YJCS, CM, BH, JCC, SH, DK and EMS were all involved with modifications to the design of the study and with drafting of this paper. All authors have read and approved the final manuscript.

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**Competing interests**

Professor IBH was an inaugural Commissioner on Australia’s National Mental Health Commission (2012–2018). He is the Co-Director, Health and Policy at the Brain and Mind Centre (BMC) University of Sydney. The BMC operates early-intervention youth services at Camperdown under contract to headspace. He is the Chief Scientific Advisor to, and a 5% equity shareholder in, InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the $30M Australian Government-funded Project Synergy (2017–2020; a 3-year program for the transformation of mental health services) and to lead transformation of mental health services internationally through the use of innovative technologies. A/Prof EMS is Principal Research Fellow at the Brain and Mind Centre, The University of Sydney. She is Discipline Leader of Adult Mental Health, School of Medicine, University of Notre Dame, and a Consultant Psychiatrist. She was the Medical Director, Young Adult Mental Health Unit, St Vincent’s Hospital Darlinghurst until January 2021. She has received honoraria for educational seminars related to the clinical management of depressive disorders supported by Servier and Eli-Lilly pharmaceuticals. She has participated in a national advisory board for the antidepressant compound Prestiq, manufactured by Pfizer. She was the National Coordinator of an antidepressant trial sponsored by Servier.

**Patient and public involvement**

Patients and/or the public were involved in the design, conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication**

Not applicable.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

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