BMJ Open

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

Chloe Wilson, Joanne Sarah Carpenter, Alissa Nichles, Natalia Zmicerevska, Yun Ju Christine Song, Catherine McHugh, Blake Hamilton, Samuel Hockey, Jacob Crouse, Dagmar Koethe, Elizabeth M Scott, Ian B Hickie

To cite: Wilson C, Carpenter JS, Nichles A, *et al*. 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. *BMJ Open* 2023;**13**:e064682. doi:10.1136/bmjopen-2022-064682

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-064682).

Received 12 July 2022
Accepted 27 January 2023

For numbered affiliations see end of article.

Correspondence to
Chloe Wilson;
chloe.wilson@sydney.edu.au

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 behavioural 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.[1–4] 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.[5 6] While these cardiometabolic risk factors may emerge early on in care,[1–4 7 8] 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.[9] 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.[10] 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,[11] poor dietary habits[12] and poor sleep–wake cycle regulation.[13] Additionally, some psychotropic medication given to treat psychotic or affective symptoms are associated with weight gain, elevated blood lipids and insulin resistance.[14]

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.[15] 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,[16] triglycerides,[16] fasting glucose,[17] low-density lipoprotein (LDL)-cholesterol,[17] total cholesterol[16 18] and T2DM.[19] There does however appear to be mixed evidence on the effect of metformin treatment on insulin resistance measures in non-psychiatric samples of adolescents,[17] either showing some or no improvement. Most studies on youth with psychiatric diagnoses have found that metformin improves weight or BMI.[20–22] 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[23] including, elevated lipids[24] and insulin resistance.[21 25] Metformin has also been linked to improved depressive and anxiety symptoms in young women with polycystic ovarian syndrome,[26] and improved mood symptoms in adults with major depressive disorder.[27]

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.[26] Due to its link with neurogenesis,[28] 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.[29–34] Several studies have administered metformin together with a comprehensive lifestyle intervention containing structured physical activity, nutritional advice or motivational support.[22 35–43] Results from these studies indicate that lifestyle interventions combined with metformin is superior to either intervention alone in reducing weight and BMI.[16 22 44 45]

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.[35–43] Results from these studies indicate that lifestyle intervention combined with metformin is superior to either interventions alone in reducing measures of weight and BMI.[16 22 44 45] 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.[46] 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.[3] 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,[47] the Australian Guide to Healthy Eating[48] 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

Session	Topics to be covered
1. Body clock and sleep–wake cycle regulation for mental health (part 1)	▶ Establishing a healthy mindset and goal setting ▶ How the brain and body are connected ▶ Role of melatonin ▶ Importance of the brain and body clock and sleep–wake cycle regulation ▶ How the brain and body clock coordinates all the biological systems ▶ How to regulate the sleep–wake cycle for example, via gradual sleep–wake rescheduling
2. Body clock and sleep–wake cycle regulation for mental health (part 2)	▶ Healthy sleep–wake behaviours ▶ 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 ▶ Sleep wake–cycle regulation tip for example, consistent sleep–wake times, avoiding naps and exercise regularly ▶ Limiting screen time in the evening ▶ Creating a sleep routine
3. Physical activity for mental health (part 1)	▶ Benefits of physical activity for physical and mental health ▶ Outline of Australian Physical Activity Guidelines ▶ Identifying and challenging barriers to engaging in physical activity ▶ Timing of physical activity ▶ Tips for starting exercise ▶ Increasing incidental activity, reducing sitting time ▶ Establishing an activity schedule
4. Physical activity for mental health (part 2)	▶ Working out anywhere ▶ Fitting in exercise throughout your day ▶ Finding the motivation ▶ Concept of energy in vs energy out
5. Nutrition for mental health (part 1)	▶ Energy in vs energy out and creating a healthy balance ▶ Outline of Australian Dietary Guidelines ▶ Creating a healthy eating plate ▶ Standard serving sizes/portion sizes ▶ Alcohol and mental health
6. Nutrition for mental health (part 2)	▶ Timing of meals ▶ Healthy snacking ▶ Meal preparation ▶ Making healthy choices when eating out at restaurants ▶ Managing comfort eating ▶ Making sustainable choices

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 cohorts[20] 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 2 Schedule of enrolment, interventions and assessment time points

	Study phase											
	Prerandomisation		Behavioural intervention week						Post-trial week			
	Screening	Enrolment (week 1)	1	3	5	7	9	11	12	26	38	52
Study procedures												
Phone screening	x											
Informed consent		x										
Meet inclusion criteria		x										
Randomization allocation		x										
Intervention phases												
Actigraphy				x		x			x		x	x	x
Metformin/placebo					◆	———	———	———	———	———	◆	
Psychoeducation sessions			x	x	x	x	x	x				
Self-report questionnaires												
Self-report questionnaires			x			x		x	x	x		
Clinician-administered assessments												
Genetic testing			x									
Psychological assessments			x			x			x	x	x	x
Physical/blood assessments	x*		x			x			x	x	x	x

*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.[56 57]

The exclusion criteria are:

i. lifetime use of metformin or any other glucose lowering medication;
ii. 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;
xi. severe hepatic insufficiency;
xii. acute alcohol intoxication or alcoholism; or
xiii. lactation.

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 the efficacy of metformin pharmacotherapy as an adjunct to a healthy lifestyle sleep–wake, activity and metabolically focused behavioural intervention programme in improving cardiometabolic health measurements (blood pressure, fasting glucose, triglycerides, cholesterol levels, BMI and waist circumference), and depressive, anxiety and psychotic symptoms of young people seeking treatment for mental health-related issues.

To assess if changes in cardiometabolic health risk factors (fasting insulin, fasting glucose, triglycerides, HOMA2-IR, cholesterol, blood pressure, BMI and waist

Table 3 Outcome measures

	Measures
Primary	► HOMA2-IR
Secondary	► 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
	► 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)
Tertiary	► Diagnostic assessment ► Clinical staging ► Pathophysiological mechanisms ► Clinical global impression (CGI) ► The Young Mania Rating Scale (YMRS) ► Social and Occupational Assessment Scale (SOFAS) ► Comprehensive Assessment of At-Risk Mental States (CAARMS) ► Somatic and Psychological Health Report (SPHERE 12) ► Pittsburgh Sleep Quality Index (PSQI) ► The Insomnia Severity Index (ISI) ► International Physical Activity Questionnaire (IPAQ) ► Suicidal Ideation Attributes Scale (SIDAS) ► WHO Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST) ► Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) ► Eating disorder examination (EDE) ► Rosenberg Self-Esteem Scale (RSES) ► Client Satisfaction Questionnaire-8 (CSQ-8) ► The Simple Physical Activity Questionnaire (SIMPAQ) ► Genetic variance via blood test ► Hormonal markers (prolactin, oestradiol, DHEAS, testosterone, LH, FSH, SHBG, AMH, serum cortisol and 17OHP) measured via the fasting metabolic blood test ► Actigraphy parameters via wrist-worn GENEActiv actigraph for a range of sleep–wake parameters including sleep onset time, sleep offset time, total sleep time (duration), wake after sleep onset, sleep efficiency, intra-daily stability/variability and total number of minutes moderate activity, total number of minutes vigorous activity and total number of sedentary minutes ► Programme feedback questionnaire

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.[58] 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[59] 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)*[60]: the BPRS is used to assess psychiatric symptoms including depression, anxiety, hallucinations, delusions and unusual behaviour.
4. *Clinical staging* [57]: 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).[57 61–63]
5. *Pathophysiological mechanisms*[64]: 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*[65]*)*: 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)*[66]: the YMRS is an 11-item questionnaire measuring manic episode symptom severity.
8. *The Simple Physical Activity Questionnaire (SIMPAQ)*[67]: 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).[68]
10. *Social and Occupational Assessment Scale (SOFAS)*[38]: 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)*[69 70]: 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*[71 72]: 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)*[73]: 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),[74] and Munich Chrono Type Questionnaire (MCTQ).[75]
6. *Pittsburgh Sleep Quality Index (PSQI)*[74]: he PSQI is a 24-item self-report questionnaire assessing sleep quality and patterns of sleep.
7. *The Insomnia Severity Index (ISI)*[76]: 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)*[77]: 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)*[78]*:* the QIDS assesses symptoms of a major depressive episode.
10. *Overall Anxiety Severity Impairment Scale (OASIS)*[79]: 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)*[80 81]: 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-hydroxyprogesterone. Inflammatory markers measured include interleukin (IL)-1β, IL-2, IL-6, interferon (IFN)-γ, tissue necrosis factor (TNF)-α 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] **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; Activinsights, 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=9.81 m/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 125 mg) as described in other studies.[88] The GENEActiv devices have been used widely in clinical research and validated against several types of accelerometry-based activity monitors[89–92] 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 authorised study staff. Statistical analyses were conducted usin 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 α=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 α=0.05. Differences in cardiometabolic outcome change scores according to psychiatric diagnosis will be assessed via analysis of variance, with significance levels set at α=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.

Author affiliations
Brain and Mind Centre, The University of Sydney, Camperdown, New South Wales, Australia

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.

Funding This project is an investigator-initiated study, sponsored by the University of Sydney and supported by philanthropic funding, for which donor(s) are families affected by mental illness who wish to remain anonymous. This study was also partially funded by a philanthropic PhD scholarship (The Liu McCabe Family Scholarship awarded to CW), a National Health & Medical Research Council Australia Fellowship (No. 511921, awarded to IBH), a National Health & Medical Research Council Emerging Leadership Fellowship (awarded to JJC) and a philanthropic fellowship (the Caroline Quinn Research Grant awarded to JSC). The funders of this study had no involvement in the: study design; collection, analysis and reporting of the data; writing of the report; or decision to submit the paper for publication.

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 Pristiq, 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, or 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.

ORCID iDs
Chloe Wilson http://orcid.org/0000-0001-6539-423X
Joanne Sarah Carpenter http://orcid.org/0000-0002-9766-6700
Alissa Nichles http://orcid.org/0000-0001-6404-7199
Natalia Zmicerevska http://orcid.org/0000-0001-7649-4711
Catherine McHugh http://orcid.org/0000-0002-4891-4966
Jacob Crouse http://orcid.org/0000-0002-3805-2936

REFERENCES

1 Chao AM, Wadden TA, Berkowitz RI. Obesity in adolescents with psychiatric disorders. *Curr Psychiatry Rep* 2019;21:3.
2 Scott EM, Hermens DF, White D, *et al*. Body mass, cardiovascular risk and metabolic characteristics of young persons presenting for mental healthcare in Sydney, Australia. *BMJ Open* 2015;5:e007066.
3 Scott EM, Carpenter JS, Iorfino F, *et al*. What is the prevalence, and what are the clinical correlates, of insulin resistance in young people presenting for mental health care? A cross-sectional study. *BMJ Open* 2019;9:e025674.
4 Kim HJ, Wilson C, Van Deusen T, *et al*. Metabolic syndrome in child and adolescent psychiatry. *Psychiatric Annals* 2020;50:326–33.
5 Firth J, Siddiqi N, Koyanagi A, *et al*. The lancet psychiatry commission: a blueprint for protecting physical health in people with mental illness. *Lancet Psychiatry* 2019;6:675–712.
6 Iturralde E, Slama N, Kline-Simon AH, *et al*. Premature mortality associated with severe mental illness or substance use disorder in an integrated health care system. *Gen Hosp Psychiatry* 2021;68:1–6.
7 Carney R, Firth J, Pedley R, *et al*. The clinical and behavioral cardiometabolic risk of children and young people on mental health inpatient units: a systematic review and meta-analysis. *Gen Hosp Psychiatry* 2021;70:80–97.
8 Smith J, Griffiths LA, Band M, *et al*. Cardiometabolic risk in first episode psychosis patients. *Front Endocrinol (Lausanne)* 2020;11:564240.
9 Mannan M, Mamun A, Doi S, *et al*. Prospective associations between depression and obesity for adolescent males and females- a systematic review and meta-analysis of longitudinal studies. *PLoS One* 2016;11:e0157240.
10 Perry BI, Stochl J, Upthegrove R, *et al*. Longitudinal trends in childhood insulin levels and body mass index and associations with risks of psychosis and depression in young adults. *JAMA Psychiatry* 2021;78:416–25.
11 Vancampfort D, Firth J, Schuch FB, *et al*. Sedentary behavior and physical activity levels in people with schizophrenia, bipolar disorder and major depressive disorder: a global systematic review and meta-analysis. *World Psychiatry* 2017;16:308–15.
12 Teasdale SB, Ward PB, Samaras K, *et al*. Dietary intake of people with severe mental illness: systematic review and meta-analysis. *Br J Psychiatry* 2019;214:251–9.
13 Wilson CE, Carpenter JS, Song Y, *et al*. Associations between 24-h sleep–wake patterns and cardiometabolic risk factors in youth seeking mental health care. *Sleep Biol Rhythms* 2021;19:337–40.
14 Correll CU, Manu P, Olshanskiy V, *et al*. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA* 2009;302:1765–73.
15 Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. *Diabetologia* 2017;60:1577–85.
16 McDonagh MS, Selph S, Ozpinar A, *et al*. Systematic review of the benefits and risks of metformin in treating obesity in children aged 18 years and younger. *JAMA Pediatr* 2014;168:178–84.
17 Sun J, Wang Y, Zhang X, *et al*. The effects of metformin on insulin resistance in overweight or obese children and adolescents: a PRISMA-compliant systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2019;98:e14249.
18 Park MH, Kinra S, Ward KJ, *et al*. Metformin for obesity in children and adolescents: a systematic review. *Diabetes Care* 2009;32:1743–5.
19 Lentferink YE, Knibbe CAJ, van der Vorst MMJ. Efficacy of metformin treatment with respect to weight reduction in children and adults with obesity: a systematic review. *Drugs* 2018;78:1887–901.
20 Correll CU, Sikich L, Reeves G, *et al*. Metformin add-on vs. antipsychotic switch vs. continued antipsychotic treatment plus healthy lifestyle education in overweight or obese youth with severe mental illness: results from the impact trial. *World Psychiatry* 2020;19:69–80.
21 Levy-Shraga Y, Madi LR, Shalev M, *et al*. Effectiveness of metformin for weight reduction in children and adolescents treated with mixed dopamine and serotonin receptor antagonists: a naturalistic cohort study. *J Child Adolesc Psychopharmacol* 2021;31:376–80.
22 Wu R-R, Zhao J-P, Guo X-F, *et al*. Metformin addition attenuates olanzapine-induced weight gain in drug-naive first-episode schizophrenia patients: a double-blind, placebo-controlled study. *Am J Psychiatry* 2008;165:352–8.
23 Ellul P, Delorme R, Cortese S. Metformin for weight gain associated with second-generation antipsychotics in children and adolescents: a systematic review and meta-analysis. *CNS Drugs* 2018;32:1103–12.
24 Shin L, Bregman H, Breeze JL, *et al*. Metformin for weight control in pediatric patients on atypical antipsychotic medication. *J Child Adolesc Psychopharmacol* 2009;19:275–9.
25 Vancampfort D, Firth J, Correll CU, *et al*. The impact of pharmacological and non-pharmacological interventions to improve physical health outcomes in people with schizophrenia: a meta-review of meta-analyses of randomized controlled trials. *World Psychiatry* 2019;18:53–66.
26 Erensoy H, Niafar M, Ghafarzadeh S, *et al*. A pilot trial of metformin for insulin resistance and mood disturbances in adolescent and adult women with polycystic ovary syndrome. *Gynecol Endocrinol* 2019;35:72–5.
27 Guo M, Mi J, Jiang Q-M, *et al*. Metformin may produce antidepressant effects through improvement of cognitive function among depressed patients with diabetes mellitus. *Clin Exp Pharmacol Physiol* 2014;41:650–6.
28 Kulkarni AS, Gubbi S, Barzilai N. Benefits of metformin in attenuating the hallmarks of aging. *Cell Metabolism* 2020.
29 Bersani FS, Biondi M, Coviello M, *et al*. Psychoeducational intervention focused on healthy living improves psychopathological severity and lifestyle quality in psychiatric patients: preliminary findings from a controlled study. *J Ment Health* 2017;26:271–5.
30 De Rosa C, Sampogna G, Luciano M, *et al*. Improving physical health of patients with severe mental disorders: a critical review of lifestyle psychosocial interventions. *Expert Review of Neurotherapeutics* 2017;17:667–81.
31 Rönngren Y, Björk A, Audulv Å, *et al*. Educational nurse-led lifestyle intervention for persons with mental illness. *Int J Ment Health Nurs* 2018;27:1022–31.
32 Fiorillo A, Pompili M, Luciano M, *et al*. Reducing the mortality gap in people with severe mental disorders: the role of lifestyle psychosocial interventions. *Front Psychiatry* 2019;10.
33 Taylor CI, Tompsett C, Sanders R, *et al*. The effectiveness of structured exercise programmes on psychological and physiological outcomes for patients with psychotic disorders: a systematic review and meta-analysis. *Int J Sport Exerc Psychol* 2020;18:336–61.
34 Goracci A, Rucci P, Forgione RN, *et al*. Development, acceptability and efficacy of a standardized healthy lifestyle intervention in recurrent depression. *J Affect Disord* 2016;196:20–31.
35 Atabek ME, Pirgon O. Use of metformin in obese adolescents with hyperinsulinemia: a 6-month, randomized, double-blind, placebo-controlled clinical trial. *J Pediatr Endocrinol Metab* 2008;21:339–48.
36 Clarson CL, Mahmud FH, Baker JE, *et al*. Metformin in combination with structured lifestyle intervention improved body mass index in obese adolescents, but did not improve insulin resistance. *Endocrine* 2009;36:141–6.
37 Clarson CL, Brown HK, De Jesus S, *et al*. Effects of a comprehensive, intensive lifestyle intervention combined with metformin extended release in obese adolescents. *Int Sch Res Notices* 2014;2014:659410.
38 Love-Osborne K, Sheeder J, Zeitler P. Addition of metformin to a lifestyle modification program in adolescents with insulin resistance. *J Pediatr* 2008;152:817–22.
39 Mauras N, DelGiorno C, Hossain J, *et al*. Metformin use in children with obesity and normal glucose tolerance -- effects on cardiovascular markers and intrahepatic fat. *J Pediatr Endocrinol Metab* 2012;25:33–40.
40 Wiegand S, l'Allemand D, Hübel H, *et al*. Metformin and placebo therapy both improve weight management and fasting insulin in obese insulin-resistant adolescents: a prospective, placebo-controlled, randomized study. *Eur J Endocrinol* 2010;163:585–92.
41 Warnakulasuriya LS, Fernando MMA, Adikaram AVN, *et al*. Metformin in the management of childhood obesity: a randomized control trial. *Child Obes* 2018;14:553–65.
42 Wilson DM, Abrams SH, Aye T, *et al*. Metformin extended release treatment of adolescent obesity: a 48-week randomized, double-blind, placebo-controlled trial with 48-week follow-up. *Arch Pediatr Adolesc Med* 2010;164:116–23.
43 van der Aa MP, Elst MAJ, van de Garde EMW, *et al*. Long-term treatment with metformin in obese, insulin-resistant adolescents:

results of a randomized double-blinded placebo-controlled trial. *Nutr Diabetes* 2016;6:e228.
44 Fu J-F, Liang L, Zou C-C, *et al*. Prevalence of the metabolic syndrome in zhejiang Chinese obese children and adolescents and the effect of metformin combined with lifestyle intervention. *Int J Obes (Lond)* 2007;31:15–22.
45 Hui F, Zhang Y, Ren T, *et al*. Role of metformin in overweight and obese people without diabetes: a systematic review and network meta-analysis. *Eur J Clin Pharmacol* 2019;75:437–50.
46 Marques P, Limbert C, Oliveira L, *et al*. Metformin effectiveness and safety in the management of overweight/obese nondiabetic children and adolescents: metabolic benefits of the continuous exposure to metformin at 12 and 24 months. *Int J Adolesc Med Health* 2016;29.
47 Health AGDo. Physical activity and exercise guidelines for all australians. 2021. Available: https://www.health.gov.au/health-topics/physical-activity-and-exercise/physical-activity-and-exercise-guidelines-for-all-australians
48 Australian Government Department of Health and Ageing. *Australian guide to healthy eating*. 2017.
49 Robillard R, Hermens DF, Naismith SL, *et al*. Ambulatory sleep-wake patterns and variability in young people with emerging mental disorders [In Press]. *J Psychiatry Neurosci* 2014.
50 Harvey AG, Mullin BC, Hinshaw SP. Sleep and circadian rhythms in children and adolescents with bipolar disorder. *Dev Psychopathol* 2006;18:1147–68.
51 Cousins JC, Whalen DJ, Dahl RE, *et al*. The bidirectional association between daytime affect and nighttime sleep in youth with anxiety and depression. *J Pediatr Psychol* 2011;36:969–79.
52 Minassian A, Henry BL, Geyer MA, *et al*. The quantitative assessment of motor activity in mania and schizophrenia. *J Affect Disord* 2010;120:200–6.
53 Rohleder C, Song YJC, Crouse JJ, *et al*. Youth mental health tracker: protocol to establish a longitudinal cohort and research database for young people attending Australian mental health services. *BMJ Open* 2020;10:e035379.
54 Soliman A, De Sanctis V, Alaaraj N, *et al*. The clinical application of metformin in children and adolescents: a short update. *Acta Biomed* 2020;91:e2020086.
55 Fitzgerald I, O'Connell J, Keating D, *et al*. Metformin in the management of antipsychotic-induced weight gain in adults with psychosis: development of the first evidence-based guideline using grade methodology. *Evid Based Ment Health* 2022;25:15–22.
56 McGorry PD, Purcell R, Hickie IB, *et al*. Clinical staging: a heuristic model for psychiatry and youth mental health. *Med J Aust* 2007;187:S40–2.
57 Hickie IB, Scott EM, Hermens DF, *et al*. Applying clinical staging to young people who present for mental health care. *Early Interv Psychiatry* 2013;7:31–43.
58 Wilson C, Nichles A, Zmicerevska N, *et al*. Effect of an online healthy lifestyle psychoeducation programme to improve cardiometabolic outcomes and affective symptoms in youth receiving mental health care: study protocol for a pilot clinical trial. *BMJ Open* 2021;11:e044977.
59 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th ed. Arlington, 2013.
60 Overall JE, Gorham DR. The brief psychiatric rating scale. *Psychol Rep* 1962;10:799–812.
61 McGorry PD, Hickie IB, Yung AR, *et al*. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. *Aust N Z J Psychiatry* 2006;40:616–22.
62 Scott J, Leboyer M, Hickie I, *et al*. Clinical staging in psychiatry: a cross-cutting model of diagnosis with heuristic and practical value. *Br J Psychiatry* 2013;202:243–5.
63 Hickie IB, Scott J, McGorry PD. Clinical staging for mental disorders: a new development in diagnostic practice in mental health. *Med J Aust* 2013;198:461–2.
64 Hickie IB, Hermens DF, Naismith SL, *et al*. Evaluating differential developmental trajectories to adolescent-onset mood and psychotic disorders. *BMC Psychiatry* 2013;13:303.
65 Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry (Edgmont)* 2007;4:28–37.
66 Young RC, Biggs JT, Ziegler VE, *et al*. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry* 1978;133:429–35.
67 Rosenbaum S, Ward PB, International Working Group. The simple physical activity questionnaire. *Lancet Psychiatry* 2016;3:e1.
68 Yung AR, Yuen HP, McGorry PD, *et al*. Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. *Aust N Z J Psychiatry* 2005;39:964–71.
69 Kessler RC, Andrews G, Colpe LJ, *et al*. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. *Psychol Med* 2002;32:959–76.
70 Andrews G, Slade T. Interpreting scores on the kessler psychological distress scale (K10). *Aust N Z J Public Health* 2001;25:494–7.
71 Craig CL, Marshall AL, Sjöström M, *et al*. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003;35:1381–95.
72 Booth M. Assessment of physical activity: an international perspective. *Res Q Exerc Sport* 2000;71 Suppl 2:114–20.
73 Berryman C, McAuley JH, Moseley LG. Sphere 12 screening questionnaire. *J Physiother* 2012;58:273.
74 Smyth C. The Pittsburgh sleep quality index (PSQI). *J Gerontol Nurs* 1999;25:10–1.
75 Shahid A, Wilkinson K, Marcu S, *et al*. *Munich chronotype questionnaire (MCTQ). STOP, THAT and one hundred other sleep scales*. Springer, 2011: 245–7.
76 Morin CM. *Insomnia: psychological assessment and management*. Guilford press, 1993.
77 van Spijker BAJ, Batterham PJ, Calear AL, *et al*. The suicidal ideation attributes scale (SIDAS): community-based validation study of a new scale for the measurement of suicidal ideation. *Suicide Life Threat Behav* 2014;44:408–19.
78 Rush AJ, Trivedi MH, Ibrahim HM, *et al*. The 16-item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry* 2003;54:573–83.
79 Norman SB, Cissell SH, Means-Christensen AJ, *et al*. Development and validation of an overall anxiety severity and impairment scale (OASIS). *Depress Anxiety* 2006;23:245–9.
80 Humeniuk R, Ali R, Babor TF, *et al*. Validation of the alcohol, smoking and substance involvement screening test (assist). *Addiction* 2008;103:1039–47.
81 Group WAW. The alcohol, smoking and substance involvement screening test (assist): development, reliability and feasibility. *Addiction* 2002;97:1183–94.
82 Bush K, Kivlahan DR, McDonell MB, *et al*. The audit alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. ambulatory care quality improvement project (ACQUIP). alcohol use disorders identification test. *Arch Intern Med* 1998;158:1789–95.
83 Hay PJ, Mond J, Buttner P, *et al*. Eating disorder behaviors are increasing: findings from two sequential community surveys in South Australia. *PLoS ONE* 2008;3:e1541.
84 Mitchison D, Hay P, Slewa-Younan S, *et al*. The changing demographic profile of eating disorder behaviors in the community. *BMC Public Health* 2014;14:943.
85 Rosenberg M. Rosenberg self-esteem scale (RSE). In: *Acceptance and commitment therapy Measures package, 61*. 1965: 18.
86 Larsen DL, Attkisson CC, Hargreaves WA, *et al*. Assessment of client/patient satisfaction: development of a general scale. *Eval Program Plann* 1979;2:197–207.
87 Hill NR, Levy JC, Matthews DR. Expansion of the homeostasis model assessment of β-cell function and insulin resistance to enable clinical trial outcome modeling through the interactive adjustment of physiology and treatment effects: ihoma2. *Diabetes Care* 2013;36:2324–30.
88 Difrancesco S, Lamers F, Riese H, *et al*. Sleep, circadian rhythm, and physical activity patterns in depressive and anxiety disorders: a 2-week ambulatory assessment study. *Depress Anxiety* 2019;36:975–86.
89 Schaefer CA, Nigg CR, Hill JO, *et al*. Establishing and evaluating wrist cutpoints for the geneactiv accelerometer in youth. *Med Sci Sports Exerc* 2014;46:826–33.
90 Hildebrand M, VAN Hees VT, Hansen BH, *et al*. Age group comparability of raw accelerometer output from wrist- and hip-worn monitors. *Med Sci Sports Exerc* 2014;46:1816–24.
91 Esliger DW, Rowlands AV, Hurst TL, *et al*. Validation of the GENEA accelerometer. *Med Sci Sports Exerc* 2011;43:1085–93.
92 van Hees VT, Gorzelniak L, Dean León EC, *et al*. Separating movement and gravity components in an acceleration signal and implications for the assessment of human daily physical activity. *PLoS ONE* 2013;8:e61691.
93 te Lindert BHW, Van Someren EJW. Sleep estimates using microelectromechanical systems (MEMS). *Sleep* 2013;36:781–9.
94 van Hees VT, Sabia S, Anderson KN, *et al*. A novel, open access method to assess sleep duration using A wrist-worn accelerometer. *PLoS ONE* 2015;10:e0142533.