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The effect of an online healthy lifestyle psychoeducation program to improve cardiometabolic outcomes and affective symptoms in youth receiving mental health care: study protocol for a clinical trial.

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Title: The effect of an online healthy lifestyle psychoeducation program to improve cardiometabolic outcomes and affective symptoms in youth receiving mental health care: study protocol for a clinical trial.

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Abstract

Introduction

Worsened cardiometabolic profiles in youth with mental ill-health have been associated with a number of modifiable lifestyle risk factors. It is becoming increasingly evident that clinical interventions need to be multi-modal in focus to improve not only mental health symptoms, but also the physical health symptoms in this already at-risk cohort.

Methods and Analysis:

This 12-week clinical trial examines the efficacy of an adjunctive online psychoeducation program for improving cardiometabolic risk parameters and affective symptoms in a transdiagnostic sample of at least 44 young people aged 16-30 who are concurrently receiving standard clinical care for clinically diagnosed anxiety, affective and/or psychotic disorders. Individuals will be invited to participate in a structured online psychoeducation program incorporating nutritional, physical activity, sleep-wake and healthy lifestyle information, delivered fortnightly over 6 online modules. Participants will undergo a series of assessments including: (1) blood tests to assess metabolic markers; (2) anthropometric assessments (blood pressure, height, weight and waist circumference); (3), self-report and clinician administered assessments determining diagnosis and symptomatology; and (4) sleep-wake behaviours and circadian rhythm assessments. Correlations and change in mean scores for all of the cardiometabolic and affective measures will be assessed after completion of the clinical trial via paired samples t-tests and Pearson's correlations.

Ethics and Dissemination

xf The results of this clinical trial will be disseminated into the scientific and broader community through peer-reviewed journals and conference presentations.

Trial Registration

Australian New Zealand Clinical Trials Registry (ANZCTR) Number: ACTRN12620000772943, Date 28 August, 2020.

Strengths and Limitations of this Study

- Young people receiving mental health care can participate in this clinical trial assessing the effect of an adjunctive online psychoeducation program for improving cardiometabolic risk parameters and affective symptoms.
- The psychoeducation program involves structured nutrition, physical activity, sleep-wake and healthy lifestyle information.
- Participants will be assessed on a range of metabolic, anthropometric, sleep-wake and mental health symptoms throughout the trial.
- Online psychoeducation modules allow participants to access the information remotely.

Keywords:

Mental ill-health, psychoeducation, cardiometabolic improvement, physical activity.

Introduction

Premature mortality in those with severe mental illness has been well documented [1-6], with diabetes and premature cardiovascular disease comprising some of the leading causes of premature mortality and morbidity in this cohort. Increased body mass index (BMI) and weight gain have been identified as key modifiable risk factors causing premature mortality and morbidity in young people with mood disorders, along with poor sleep-wake cycle regulation [7-9], physical inactivity [10-16], poor dietary habits [10 17-20] and smoking [21-26].

Whilst many mental disorders can be managed with psychotherapy alone, psychotropic medications including antipsychotics, antidepressants and mood stabilisers are used for the treatment of a number of psychotic, mood and behavioural disorders in youth [27 28]. Adolescents initiating psychotropic medications may display heterogeneous side effects with some very complex long-term cardiometabolic side effects [29-32]. Of particular concern, is the weight-gain associated with second-generation antipsychotic (SGA) usage [29 33-37] which is acute and can often be observed within 12 weeks of medication initiation [38-43]. Children and adolescents appear to be at a greater risk of psychotropic-induced weight gain than adults [44 45] and the younger the age of the child, the higher the mitigating risk [37]. Psychotropic medication induced weight gain is a noteworthy adverse drug reaction as it mediates the development of other more severe cardiometabolic outcomes [38-43].

Lifestyle interventions are an effective non-pharmacological intervention option to manage drug-induced cardiometabolic disturbances in patients with psychiatric disorders. The World Health Organisation guidelines recommend lifestyle behavioural

interventions as a first-line treatment for physical health symptoms (including the cardiometabolic health) of adults with severe mental illness [46]. The benefits of lifestyle and behavioural interventions on weight loss in obesity and for prevention of Type II Diabetes Mellitus (T2DM) are well-established [47 48]. Additionally, psychoeducational interventions focusing on healthy lifestyle habits including diet, physical activity and sleep-wake practices have been shown to ameliorate both the physical and mental health concerns of young people with psychiatric disorders [49-53].

Face-to-face psychoeducation interventions for adults with severe mental illness are able to demonstrate significant improvements in weight [54]; depressive symptoms, sleep quality and nutrition; [55] and other cardiometabolic risk factors [56]. Existing web-based psychoeducation intervention studies on adults with mental illness have demonstrated improvements in depression and anxiety symptoms [57], and increases in objective physical activity levels [58], however have not measured cardiometabolic risk factors objectively. In youth, the literature in this field is more limited, with existing or planned studies in youth cohorts measuring psychological symptom improvements only [59-61].

We are seeking to investigate the effect of an online healthy lifestyle pscyhoeducation program targeted towards improving objective cardiometabolic outcomes in young people with clinically diagnosed affective or psychotic disorders. Web-based interventions provide an alternative to traditional face-to-face interventions. The need for online programs is especially evident with the COVID-19 global pandemic impeding on young people's ability to seek face-to-face support. This has given rise to a need to develop more comprehensive resources tailored to the specific risk-factors of this

cohort in an easily accessible online format. Where effective, it would allow the program to be implemented remotely, to many individuals who may not be able to access in-person services.

Methods and Analysis

Design and Structure

This is a one-arm longitudinal clinical trial. The duration of the clinical trial is 12 weeks. All participants will engage in a self-directed online 12-week psychoeducation program. This psychoeducation program 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 previously published research, delivered for approximately 1 hour each fortnight over 6 online workshops (week 1, 3, 5, 7, 9, and 11). The modules have been developed in conjunction with those with a lived experience of mental illness to ensure the suitability and relevance for this cohort. Participants will be given a link to access the online psychoeducation modules in their own time. These modules will cover the topics shown in Table 1.

Table 1. Psychoeducation modules

Session	Topics to be covered
1. Brain and Body Connection	– How the brain and body are connected – Establishing a healthy mindset
2. Body Clock and Sleep-Wake Cycle Regulation for mental health	– Importance of the brain and body clock and sleep-wake cycle regulation – How the brain and body clock coordinates all the biological systems – Healthy sleep-wake behaviours – How lifestyle factors and behaviours influence the brain and body clock e.g. exercise, light exposure, sleep environment, sleep regularisation, naps, foods, stress, anxiety, mood.
3. Physical activity for mental health (part 1)	– Benefits of physical activity for physical and mental health – Outline of Australian Physical Activity Guidelines – Barriers to engaging in physical activity – Increasing incidental activity, reducing sitting time
4. Physical activity for mental health (part 2)	– Working out anywhere – Finding the motivation – Concept of energy in vs energy out
5. Nutrition for mental health (part 1)	– Energy in vs energy out and introducing the concept of a calorie – Outline of Australian Dietary Guidelines – Standard serving sizes/portion sizes
6. Nutrition for mental health (part 2)	– Timing of meals – Snacking – Meal preparation – Making healthy choices when eating out at restaurants – Managing comfort eating.

During week 6, participants will receive a monitoring phone call to help in the participant's engagement and ongoing participation. At the completion of all 6 modules the participant will be asked to provide feedback about the program and to share their overall satisfaction with the program via an online questionnaire.

Participants will be asked to wear an actigraph (GENEActiv Sleep device; Activinsights, Kimbolton, UK) on the non-dominant wrist to collect 24-hour sleep-wake and physical activity parameters during weeks 1-2, 6-7 and 10-12. Blood tests to measure metabolic 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 will be conducted in weeks 1 and 12. 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 multidimensional framework [62]. The schedule of enrolment, interventions and assessment time points can be seen in Table 2.

Table 2. Schedule of enrolment, interventions and assessment time points.

Study Procedures	Study Week								
	1	2	3	5	6	7	9	11	12
Informed Consent	x								
Enrolment	x								
Psychoeducation Session	x		x	x		x	x	x	
Actigraphy	x				x			x	
Self-Report Questionnaires	x								x
Clinician Administered Questionnaires	x								x
Blood Collection	x								x
Anthropometrics	x								x

Setting, Recruitment and Informed Consent

This is a multi-site, transdiagnostic intervention study, with the Brain and Mind Centre (including *headspace* Camperdown, and Early Intervention and High Intensity Services; public health organisation) at the University of Sydney (Sydney, Australia), being the lead site for this study. Further, St Vincent's Private Hospital (USpace) (private health organisation) will be another participating site in Sydney, Australia. Thus, this study involves both specialist (USpace) and enhanced primary-care (*headspace* Camperdown, and Early Intervention and High Intensity Services) youth mental health services.

Potential participants will be identified as young people aged between 16 and 30 years of age presenting to youth mental health clinics. Treating clinicians will be made aware

of the study and eligibility criteria and will identify patients presenting for care at these services who may be eligible for the study. With the patient's permission, the clinicians will pass on the contact details to the study research team, who will make further contact and initiate the informed consent process. The study staff will then obtain written informed consent from the young person to participate in the psychoeducation program.

Selection Criteria

Young people will be invited into the trial based on the following inclusion criteria: (i) aged between 16 and 30; (ii) receiving mental health care at one of the participating sites; (iii) body mass index (BMI) ≥25; (iv) willing and able to give independent written informed consent to participate in the study.

The exclusion criteria are: (i) current diagnosis or history of an eating disorder (via the Structured Clinical Interview for DSM-V Disorders (SCID)[63]); (ii) intellectual disability (at the discretion of a clinical psychologist or psychiatrist); (iii) major neurological disorder, medical illness which impacts on cognition, and/or a history of sustained head injury; (iv) not proficient in English; or (v) acute psychotic or manic episode that impairs the individual's ability to give informed consent and/or requires acute clinical treatment.

Study Objectives

Primary To determine the efficacy of an online 12-week healthy lifestyle psychoeducation program in improving cardiometabolic parameters (fasting insulin, fasting glucose, the updated homeostatic model assessment (HOMA2 IR), cholesterol, blood pressure, BMI and waist circumference) of young people seeking treatment for mental health related issues.

Secondary To determine the efficacy of an online 12-week healthy lifestyle psychoeducation program in improving affective symptoms of young people seeking treatment for mental health related issues.

Tertiary To determine if changes in cardiometabolic health risk factors are associated with changes in depressive and anxiety symptom severity.

Measures

Primary and secondary outcome measures have been established as follows:

Primary Outcome Measures

i. *Insulin resistance*: Insulin resistance will be estimated using the updated homeostatic model assessment (HOMA2-IR) using iHOMA2 software V.8.8 [64] from fasting blood test results.

Secondary Outcome Measures

Clinician Rated Assessments

i. *Diagnostic Assessment:* The presence of any DSM-V Disorders will be assessed using the Structured Clinical Interview for DSM-V Disorders (SCID)[63].

ii. *Physical Health, Mental Health, Family Health and Treatment History:* Current and past health history will be assessed and recorded by trained researchers and study doctors.

iii. *The Brief Psychiatric Rating Scale (BPRS) [65]:* The BPRS measures psychiatric symptoms including depression, anxiety, hallucinations and unusual behaviour. This scale is one of the most widely used scales to measure psychotic symptoms [66].

iv. *Clinical Staging* [67]: This framework classifies individuals according to the presentation of their mental illness from those in the earliest phases with non-specific clinical presentations (stages 1a 'seeking help'), those at greater-risk with more specific, sub-threshold 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) [67-70].

v. *Pathophysiological Mechanisms* [71]: The pathophysiological model suggests three possible pathways of illness: (i) neuro-developmental impairments, (ii) circadian dysregulation, and (iii) heightened sensitivity (i.e., stress-reactivity) in the "fear" circuitry. Based on these pathways, three clinical phenotype labels will be assigned to the individual: (i) developmental-psychotic, (ii) mania-fatigue, and (iii) anxiety-depression subtypes.

vi. *Clinical Global Impression (CGI* [72]*):* The CGI provides an indication of the patient's ability to function in context of their history, psychosocial circumstances, symptoms, and behaviour. The CGI comprises two one-item measures evaluating the severity of psychopathology from 1 to 7 (CGI-Severity, CGI-S) and the change from the initiation of treatment on a similar seven-point scale (CGI-Improvement, CGI-I).

vii. *The Young Mania Rating Scale (YMRS)* [73]*:* The YMRS is an eleven-item questionnaire measuring manic episode severity based on patient subjective report and clinical observations during the clinical interview.

viii. *The Simple Physical Activity Questionnaire (SIMPAQ)*[74]*:* The SIMPAQ is a five-item clinical tool designed to assess the degree of physical activity in cohorts at high risk of sedentary behaviour. This measure has been used in

over 23 countries and can be reliability and validly administered by health professionals [75].

ix. *Suicidal ideation and behaviour:* Acute suicidal behaviour will be assessed by item 7.3 of the Comprehensive Assessment of At-Risk Mental States (CAARMS) [76]. The CAARMS is a semi-structured assessment tool designed to evaluate those at ultra-high risk for psychosis. This assessment is only to be administered as a safety measure where the self-report Suicidal Ideation Attributes Scale (SIDAS) score reaches the cut off score of ≥ 21 indicating a high risk of suicidal behaviour.

x. *Social and Occupational Assessment Scale (SOFAS) (38)*: The SOFAS is a global rating of the participant's current social and occupational functioning, independent of the overall severity of the individual's psychological symptoms, ranging from 0 to 100, with lower scores indicating poorer functioning. The SOFAS has been used extensively in clinical research and practice and has good construct validity, interrater reliability, and predictive validity [77 78].

xi. *Eating Disorder Examination (EDE) [79 80]*: This structured interview assesses a range of current regular use of eating disorder behaviours, namely binge eating, purging and strict dieting or fasting. This interview has demonstrated good internal consistency and construct validity [81].

Self-Report Questionnaires:

i. *Demographics:* This questionnaire will comprise details on basic demographics (including details of work and education, ethnicity, living

circumstances, relationship status), and physical health (height, weight and waist circumference).

ii. *Kessler Psychological Distress Scale (K-10)* [82 83]*:* The K-10 is a 10-item version of the Kessler scale that provides a global measure of distress based on anxiety and depressive symptoms over a four-week period. It has high predictive validity and reliability [84].

iii. *International Physical Activity Questionnaire (IPAQ) - short version* [85 86]*:* The short version of the International Physical Activity Questionnaires (IPAQ) is a seven-item questionnaire calculating the amount of time spent engaging in sedentary activity; mild, moderate, or vigorous-intensity physical activity. The original IPAQ has been tested across populations and broad age groups and demonstrates good reliability and validity [85].

iv. *Somatic and Psychological Health Report (SPHERE 12)* [87]*:* The SPHERE 12 is a 12-item self-report questionnaire that assesses six psychological (PSYCH subscale) and six physical symptoms (SOMA subscale) to identify anxiety, depression, and somatisation symptoms in primary care. The SPHERE-12 has been demonstrated to have high reliability and validity in populations over the age of 16 [87].

v. *Sleep-wake cycle and chronotype:* Six questions will be asked concerning time falling asleep, waking up during weekdays and weekends, hours of sleep, feelings when waking up. Sleep timing items are based on the Pittsburgh Sleep Quality Index (PSQI)[88], and Munich Chrono Type Questionnaire (MCTQ) [89], while sleep quality items were developed based on expert agreement in existing literature.

vi. *Pittsburgh Sleep Quality Index (PSQI)[88]:* The PSQI is a 24-item self-report questionnaire measuring the quality and patterns of sleep. Seven domains are assessed including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month. This scale has good internal consistency and construct validity [90 91].

vii. *The Insomnia Severity Index (ISI)[92]:* The ISI comprises seven items assessing the perceived severity of difficulties in initiating sleep, staying asleep, early morning awakenings, satisfaction with current sleep pattern, interference with daily functioning, noticeability of impairment attributed to the sleep problem, and degree of distress or concern caused by the sleep problem. This scale has been used widely in clinical research with high internal consistency and convergent validity [93].

viii. *Suicidal Ideation Attributes Scale (SIDAS) [94]:* The SIDAS is a five-item self-report questionnaire assessing the frequency, controllability, closeness to attempt, distress, and interference with daily activities over the past month. The SIDAS has demonstrated high internal consistency and good convergent validity [95].

ix. *Quick Inventory of Depressive Symptomatology – self-report (QIDS-SR) [96]:* The QIDS is a rating scale that assesses the nine criterion symptom domains (sleep, sad mood, appetite/weight, concentration/ decision making, self-view, thoughts of death or suicide, general interest, energy level, and restlessness/agitation) designated by the DSM-IV to diagnose a major depressive episode. This scale has high internal consistency and good predictive and concurrent validity [97].

x. *Overall Anxiety Severity Impairment Scale (OASIS)* [98]*:* The OASIS is a five-item self-report measure used to assess the frequency and intensity of anxiety symptoms and the functional impairment associated with any anxiety disorder or multiple anxiety disorders. This scale has excellent test-retest reliability, and convergent and discriminant validity [99].

xi. *World Health Organisation (WHO) Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST)* [100 101]*:* The ASSIST (version 3.1) is an eight-item questionnaire screening for use of tobacco products, alcohol, cannabis, cocaine, amphetamine-type stimulants (ATS), sedatives and sleeping pills (benzodiazepines), hallucinogens, inhalants, opioids, 'other' drugs. This scale has demonstrated good validity [102] and reliability [103].

xii. *Alcohol Use Disorders Identification Test – Consumption (AUDIT-C)* [104]*:* The AUDIT-C has three short questions to estimate alcohol consumption in a standard, meaningful and non-judgemental manner. This scale has shown good reliability and validity in adolescent sample groups [105].

xiii. *Rosenberg Self-Esteem Scale (RSES)* [106]*:* The RSES is a 10-item self-report measure of self-esteem, self-worth or self-acceptance designed specifically for use in adolescent populations. Higher scores on this scale indicate higher levels of global self-esteem. This scale has extremely high internal consistency and demonstrated construct validity with other measures of self-esteem [107 108].

xiv. *Client Satisfaction Questionnaire-8 (CSQ-8)* [109]*:* The CSQ is a structured survey used to assess level of satisfaction with care. The CSQ-8 has been

found to have high internal consistency and concurrent validity in mental health outpatient settings [109].

xv. *Feedback Questionnaire.* This is an investigator-developed questionnaire specifically relating to the efficacy of the psychoeducation program and whether the participants have any feedback or suggestions for improvement to the online psychoeducation program.

Blood Markers

Participants will be required to undergo blood sample collection at baseline and week 12 to determine variables of interest including fasting glucose; fasting insulin, and blood lipids (including total, high density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol levels). Other blood measures to be collected for monitoring purposes include HbA1c, full blood count, urea, electrolytes, liver function test, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA), vitamin D, vitamin B12, folate, iron, thyroid stimulating hormone, calcium (Ca), magnesium (Mg) and phosphate (PO4) levels. Blood samples are to be collected in a fasting state by a trained phlebotomist.

Anthropometric assessments

Measures of blood pressure, height and weight will be collected from direct measurement by a clinician or research staff. Body mass index (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. Where the patient is unable to visit the

Brain and Mind Centre for an anthropometric assessment, the participant will be required to self-report height and weight and will be instructed how to gather waist circumference measurements.

24-hour sleep-wake and physical activity profiling

All participants will wear wrist mounted actigraphy recording devices (GENEActiv Sleep device; Activinsights, Kimbolton, UK) to estimate sleep and physical activity patterns based on validated algorithms. Measurements include sleep onset time, sleep offset time, sleep midpoint, sleep efficiency, wake after sleep onset (WASO: number of minutes during the sleep period scored as awake), and total sleep time (TST; number of minutes during the sleep period scored as sleep).

Physical activity will be assessed through the GENEActiv devices as gross motor activity per day (milli-gravity [mg], 1g = 9.81 m/s2) and minutes in moderate-to-vigorous physical activity per day (objective minutes in moderate-to-vigorous physical activity per day defined as the sum of 1-min epochs in which gross motor activity was larger than 125 mg) as described in other studies [110]. The GENEActiv devices have been used widely in clinical research and validated against several types of accelerometry-based activity monitors [111-114] as well as for sleep-wake scoring [115 116].

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Sample Size/ Power Calculation

The proposed sample size calculation of at least 44 participants is based on specific power analysis parameters (power analyses completed in G*Power Version 3.1.9.4), notably difference in means in HOMA2-IR scores of one sample with a power of 0.90, an effect size of 0.5, and an alpha level of 0.05. Whilst this is a feasibility study, and a sample size has been estimated, this pilot data will be used to inform power calculations for future studies investigating similar outcome measures in this specific cohort.

Data Analysis Plan

All data will be entered into a secure database and statistical analyses conducted in R statistical software. The primary and secondary objectives will be analysed by a change in mean scores of all outcome measures after completion of the 12-week online psychoeducation program via a paired samples t-test, with significance levels set at α=.05. To assess the tertiary outcome measure, correlations will be performed between all cardiometabolic change scores and affective outcome change scores via Pearson's or Spearman's correlations tests based on normative or non-normative data distribution; with a significance level set at α=.05.

Ethics and Dissemination

The Sydney Local Health District (RPAH Division) Human Ethics Research (HREC) Committee has approved this study (X20-0228). The online psychoeducation program

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 online psychoeducation sessions. This standard treatment may include medication, counselling, psychological therapy and/or referrals to a range of specialist mental health treatments or services.

In accordance with the guidelines stipulated by the funding bodies, the results of this study will be disseminated as widely as possible into the scientific and broader community. This will 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. Results will also 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.

Discussion

This trial plans to examine the efficacy of an online psychoeducation program on several cardiometabolic risk factors and affective symptoms in youth seeking treatment for mental ill-health. The modules feature a youth-friendly format, with input from those with lived experience, to maximise engagement by young people. If the findings of this exploratory trial demonstrate benefits in the targeted domains, it will be used as a basis for further clinical trials incorporating more intensive psychoeducation combined with pharmacological therapies. Due to the online nature of the psychoeducation program, there is also potential for a larger-scale study to be

implemented across a number of centres nationally, allowing individuals to access the program remotely and regionally.

Trial Status

The trial has not begun recruitment.

Funding

This project is an investigator-initiated study 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 C.E.W), a National Health & Medical Research Council Australia Fellowship (No. 511921, awarded to I.B.H) and a philanthropic fellowship (the Caroline Quinn Research Grant awarded to J.S.C). 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.

Author's Contributions

C.E.W. has developed this clinical trial as part of her PhD research project and drafted this original manuscript with input from other authors. I.B.H assisted with the design of the study. A.N., N.Z., J.S.C., Y.S., C.M., B.H., and E.S. 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.

Competing Interests Statement

Professor Ian Hickie was an inaugural Commissioner on Australia's National Mental Health Commission (2012-18). 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 (2017-20; a three-year program for the transformation of mental health services) and to lead transformation of mental health services internationally through the use of innovative technologies.

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The effect of an online healthy lifestyle psychoeducation program to improve cardiometabolic outcomes and affective symptoms in youth receiving mental health care: study protocol for a clinical trial.

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Title: The effect of an online healthy lifestyle psychoeducation program to improve cardiometabolic outcomes and affective symptoms in youth receiving mental health care: study protocol for a clinical trial.

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Abstract

Introduction

Worsened cardiometabolic profiles in youth with mental ill-health have been associated with a number of modifiable lifestyle risk factors. It is becoming increasingly evident that clinical interventions need to be multi-modal in focus to improve not only mental health symptoms, but also the physical health symptoms in this already at-risk cohort.

Methods and Analysis:

This 12-week clinical pilot trial examines the efficacy, feasibility and acceptability of an adjunctive online psychoeducation program for improving cardiometabolic risk parameters and affective symptoms in a transdiagnostic sample of at least 44 young people aged 16-25 presenting for mental health care for mood and/or psychotic syndromes (including anxiety, depression, bipolar disorder and psychosis). Individuals will be invited to participate in a clinical pilot trial for a structured online psychoeducation program incorporating nutritional, physical activity, sleep-wake and healthy lifestyle information, delivered fortnightly over 6 online modules. Participants will undergo a series of assessments including: (1) self-report and clinician administered assessments determining mental health symptomatology; (2) blood tests to assess cardiometabolic markers (fasting insulin, fasting glucose, blood lipids); (3) anthropometric assessments (height, weight, waist circumference and blood pressure); and (4) sleep-wake behaviours and circadian rhythm assessments. Changes in scores for all cardiometabolic and affective measures will be assessed via paired samples t-tests, and correlations between change scores will be assessed via Pearson's correlations.

Ethics and Dissemination

This clinical trial has been approved by the Sydney Local Health District Research Ethics and Governance Office (X20-0228 & 2020/ETH01201). The results of this clinical trial will be disseminated into the scientific and broader community through peer-reviewed journals, conference presentations, social media and university websites.

Trial Registration

Australian New Zealand Clinical Trials Registry (ANZCTR) Number: ACTRN12620000772943, Date 28 August, 2020.

Keywords:

Youth mental ill-health, psychoeducation, cardiometabolic improvement, physical activity, sleep-wake cycle regulation.

Strengths and Limitations of this Study

- This clinical trial evaluates a multidisciplinary online psychoeducation program (involving structured nutrition, physical activity, sleep-wake and healthy lifestyle information) for improving cardiometabolic risk parameters and affective symptoms, in a transdiagnostic group of young people receiving mental health care.
- A range of cardiometabolic, anthropometric, sleep-wake and mental health symptoms are assessed throughout the trial to determine whether these factors influence each other.
- Online delivery of psychoeducation modules will allow participants to access the information remotely.
- As this is a single-arm study, it cannot determine the efficacy of the intervention compared to other behavioural interventions in the same cohort.
- This pilot study will provide important information about how multidisciplinary behavioural modification programs may help to manage the immediate cardiometabolic and affective symptoms of young people receiving mental health care however cannot draw conclusions about the long-term effects of these lifestyle changes.

Background

Premature mortality in those with severe mental illness has been well documented [1-6], with diabetes and premature cardiovascular disease comprising some of the leading causes of premature mortality and morbidity in this cohort. Increased body mass index (BMI) and weight gain have been identified as key modifiable risk factors causing premature mortality and morbidity in young people with severe mental illness, along

with poor sleep-wake cycle regulation [7-9], physical inactivity [10-16], poor dietary habits [10 17-20] and smoking [21-26].

Whilst many mental disorders can be managed with psychotherapy alone, psychotropic medications including antipsychotics, antidepressants and mood stabilisers are sometimes used for the treatment of a number of psychotic, affective and behavioural disorders in youth [27 28]. Adolescents initiating psychotropic medications may display heterogeneous side effects with some very complex long-term cardiometabolic side effects [29-32]. Of particular concern, is the weight-gain associated with second-generation antipsychotic (SGA) usage [29 33-37] which is acute and can often be observed within 12 weeks of medication initiation [38-43]. Children and adolescents appear to be at a greater risk of psychotropic-induced weight gain than adults [44 45] and the younger the age of the child, the higher the mitigating risk [37]. Psychotropic medication induced weight gain is a noteworthy adverse drug reaction as it mediates the development of other more severe cardiometabolic outcomes [38-43].

Lifestyle interventions can be an effective alternative to pharmacological interventions to manage the physical and mental health symptoms of patients with psychiatric disorders [46]. The World Health Organisation guidelines recommend lifestyle behavioural interventions as a first-line treatment for physical health symptoms (including the cardiometabolic health) of adults with severe mental illness [47]. The benefits of lifestyle and behavioural interventions on weight loss in obesity and for prevention of Type II Diabetes Mellitus (T2DM) are well-established [48 49]. Additionally, psychoeducation interventions focusing on healthy lifestyle habits including diet,

physical activity and sleep-wake practices have been shown to ameliorate both the physical and mental health concerns of young people with psychiatric disorders [50-54].

Face-to-face psychoeducation interventions for adults with severe mental illness are able to demonstrate significant improvements in weight [55]; depressive symptoms, sleep quality and nutrition [56]; and other cardiometabolic risk factors [57]. Existing web-based psychoeducation intervention studies on adults with mental illness have demonstrated improvements in depression and anxiety symptoms [58], with mixed evidence on the effect of psychotic symptoms [56 59], and increases in objective physical activity levels [60], however have not measured cardiometabolic risk factors objectively. In youth, the literature in this field is more limited, with existing or planned studies in youth cohorts measuring affective symptom improvements only [61-63]. Evidence on the effect of healthy lifestyle psychoeducation programs on psychotic symptoms in youth is non-existent to our knowledge.

We are seeking to investigate the efficacy, feasibility and acceptability of a pilot clinical trial implementing an online healthy lifestyle psychoeducation program targeted towards improving objective cardiometabolic outcomes and affective symptoms in young people presenting for mental health care for mood or psychotic syndromes (including anxiety, depression, bipolar disorder and psychosis). Web-based interventions provide an alternative to traditional face-to-face interventions. The need for online programs is especially evident with the COVID-19 global pandemic impeding on young people's ability to seek face-to-face support. This has given rise to a need to develop more comprehensive resources tailored to the specific risk-factors of this cohort in an easily accessible online format. Where effective, it would allow the

program to be implemented remotely, to many individuals who may not be able to access in-person services.

Methods and Analysis

Patient and Public Involvement

The study design, conduct and psychoeducation module content was developed in consultation with a representative from the Brain and Mind Centre Youth Lived Experienced Working Group. Patients or the public were not involved in the reporting, or dissemination plans of our research.

Design and Structure

This is a one-arm longitudinal pilot clinical trial. The duration of the pilot clinical trial is 12 weeks. All participants will engage in an online 12-week psychoeducation program. This psychoeducation program 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 [64-67]. This information will be delivered for approximately 1 hour each fortnight over 6 online modules (week 1, 3, 5, 7, 9, and 11). The modules and study design have been developed in conjunction with mental health experts and those with a lived experience of mental ill health, specifically by presenting module material to a lived experience researcher and tailoring module content and delivery modes to ensure the suitability and relevance for this cohort. Participants will be given a link to access the online psychoeducation modules in their own time, or the opportunity to attend a live online module session. These modules will cover the topics shown in Table 1.

Table 1. Psychoeducation modules

Session	Topics to be covered
1. Body Clock and Sleep-Wake Cycle Regulation for mental health (part 1)	– How the brain and body are connected – Establishing a healthy mindset – Importance of the brain and body clock and sleep-wake cycle regulation – How the brain and body clock coordinates all the biological systems
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 e.g. exercise, light exposure, sleep environment, sleep regularisation, naps, foods, stress, anxiety, mood.
3. Physical activity for mental health (part 1)	– Benefits of physical activity for physical and mental health – Outline of Australian Physical Activity Guidelines – Barriers to engaging in physical activity – Increasing incidental activity, reducing sitting time
4. Physical activity for mental health (part 2)	– Working out anywhere – Finding the motivation – Concept of energy in vs energy out
5. Nutrition for mental health (part 1)	– Energy in vs energy out and introducing the concept of a calorie – Outline of Australian Dietary Guidelines – Standard serving sizes/portion sizes
6. Nutrition for mental health (part 2)	– Timing of meals – Snacking – Meal preparation – Making healthy choices when eating out at restaurants – Managing comfort eating.

Every week, participants will receive a monitoring phone call to help in the participant's engagement and ongoing participation. At the completion of all 6 modules the participant will be asked to provide feedback about the program and to share their overall satisfaction with the program via an online questionnaire. This questionnaire will provide important information about the acceptability and feasibility of the psychoeducation program in this cohort.

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, 6-7 and 11-12. Blood tests to measure metabolic 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 will be conducted in weeks

1 and 12. 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 [68]. 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.

The schedule of enrolment, interventions and assessment time points can be seen in Table 2.

Table 2. Schedule of enrolment, interventions and assessment time points.

Study Procedures	Study Week											
	1	2	3	4	5	6	7	8	9	10	11	12
Informed Consent	x											
Enrolment	x											
Psychoeducation Session	x		x		x		x		x		x	
Actigraphy	x					x					x	
Self-Report Questionnaires	x											x
Clinician Administered Questionnaires	x											x
Blood Collection	x											x
Anthropometrics	x											x

Setting, Recruitment and Informed Consent

This is a single-site, transdiagnostic intervention study, conducted at the BMC (including *headspace* Camperdown, and Early Intervention and High Intensity Services) at the University of Sydney (Sydney, Australia).

Potential participants will be identified as young people aged between 16 and 25 years of age presenting for mental health care, who are at risk for poor cardiometabolic outcomes due to being overweight or obese. Treating clinicians will be made aware of the study and eligibility criteria and will identify patients presenting for care at these services who may be eligible for the study. With the patient's permission, the clinicians will pass on the contact details to the study research team, who will make further contact and initiate the informed consent process. The study staff will then obtain written informed consent from the young person to participate in the psychoeducation program. Each participant will have a participant ID that links the participant to the research database in a confidential and de-identified manner for the purpose of research.

Participants are free to withdraw from the study at any time by contacting research staff. 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. If participants withdraw from the study, all future data (i.e., from thereon) will not be stored or used for research purposes.

Selection Criteria

Young people will be invited into the trial based on the following inclusion criteria: (i) aged between 16 and 25; (ii) receiving mental health care treatment at the participating sites; (iii) body mass index (BMI) ≥25; (iv) willing and able to give independent written informed consent to participate in the study.

The exclusion criteria are: (i) intellectual disability (at the discretion of a clinical psychologist or psychiatrist); (ii) major neurological disorder, medical illness which

impacts on cognition, and/or a history of sustained head injury; (iv) not fluent in English; or (v) an acute psychotic or manic episode that impairs the individual's ability to give informed consent and/or requires acute clinical treatment.

Study Objectives

Primary To assess the efficacy of an online 12-week healthy lifestyle psychoeducation program in improving cardiometabolic parameters (fasting insulin, fasting glucose, the updated homeostatic model assessment (HOMA2 IR), cholesterol, triglycerides, blood pressure, BMI and waist circumference) of young people seeking treatment for mental health related issues.

Secondary To assess the efficacy of an online 12-week healthy lifestyle psychoeducation program in improving affective (depressive and anxiety) symptoms of young people seeking treatment for mental health related issues.

Tertiary To assess if changes in cardiometabolic health risk factors (fasting insulin, fasting glucose, triglycerides, HOMA2-IR, cholesterol, blood pressure, BMI and waist circumference) are associated with changes in affective (depressive and anxiety) symptom severity.

To assess the feasibility and acceptability of the psychoeducation program in a cohort of young people seeking treatment for mental health related issues.

Measures

Key outcome measures targeted for this study are highlighted in **bold type**.

Clinician Rated Assessments

i. *Diagnostic Assessment:* The presence of any DSM-V Disorders will be assessed using the Structured Clinical Interview for DSM-V Disorders (SCID)[69].

ii. *Physical Health, Mental Health, Family Health and Treatment History:* Current and past health history will be assessed and recorded by trained researchers and study doctors. This includes current medication and any changes in physical and/or mental health treatment being received throughout the trial.

iii. ***The Brief Psychiatric Rating Scale (BPRS) [70]:*** The BPRS measures psychiatric symptoms including depression, anxiety, hallucinations and unusual behaviour. This scale is one of the most widely used scales to measure psychotic symptoms [71].

i. *Clinical Staging [72]*: This framework classifies individuals according to the presentation of their mental illness from those in the earliest phases with non-specific clinical presentations (stages 1a 'seeking help'), those at greater-risk with more specific, sub-threshold 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) [72-75].

ii. *Pathophysiological Mechanisms [76]:* The pathophysiological model suggests three possible pathways of illness: (i) neuro-developmental impairments, (ii) circadian dysregulation, and (iii) heightened sensitivity (i.e., stress-reactivity) in the "fear" circuitry. Based on these pathways, three clinical phenotype labels will be assigned to the individual: (i) developmental-psychotic, (ii) mania-fatigue, and (iii) anxiety-depression subtypes.

iii. *Clinical Global Impression (CGI [77]):* The CGI provides an indication of the patient's ability to function in context of their history, psychosocial circumstances, symptoms, and behaviour. The CGI comprises two one-item measures evaluating the severity of psychopathology from 1 to 7 (CGI-Severity, CGI-S) and the change from the initiation of treatment on a similar seven-point scale (CGI-Improvement, CGI-I).

iv. ***The Young Mania Rating Scale (YMRS) [78]:*** The YMRS is an eleven-item questionnaire measuring manic episode severity based on patient subjective report and clinical observations during the clinical interview.

v. ***The Simple Physical Activity Questionnaire (SIMPAQ)[79]:*** The SIMPAQ is a five-item clinical tool designed to assess the degree of physical activity in cohorts at high risk of sedentary behaviour. This measure has been used in over 23 countries and can be reliability and validly administered by health professionals [80].

i. ***Suicidal ideation and behaviour:*** Acute suicidal behaviour will be assessed by item 7.3 of the Comprehensive Assessment of At-Risk Mental States (CAARMS) [81]. The CAARMS is a semi-structured assessment tool designed to evaluate those at ultra-high risk for psychosis. This assessment is only to be administered as a safety measure where the self-report Suicidal Ideation Attributes Scale (SIDAS) score reaches the cut off score of ≥ 21 indicating a high risk of suicidal behaviour.

ii. ***Social and Occupational Assessment Scale (SOFAS) (38)*:** The SOFAS is a global rating of the participant's current social and occupational functioning, independent of the overall severity of the individual's psychological symptoms, ranging from 0 to 100, with lower scores indicating

poorer functioning. The SOFAS has been used extensively in clinical research and practice and has good construct validity, interrater reliability, and predictive validity [82 83].

iii. *Eating Disorder Examination (EDE)* [84 85]: This structured interview assesses a range of current regular use of eating disorder behaviours, namely binge eating, purging and strict dieting or fasting. This interview has demonstrated good internal consistency and construct validity [86].

Self-Report Questionnaires:

i. *Demographics:* This questionnaire will comprise details on basic demographics (including details of work and education, ethnicity, living circumstances, relationship status), and physical health (height, weight and waist circumference).

iv. ***Kessler Psychological Distress Scale (K-10)*** [87 88]***:*** The K-10 is a 10-item version of the Kessler scale that provides a global measure of distress based on anxiety and depressive symptoms over a four-week period. It has high predictive validity and reliability [89].

v. ***International Physical Activity Questionnaire (IPAQ) - short version*** [90 91]***:*** The short version of the International Physical Activity Questionnaires (IPAQ) is a seven-item questionnaire calculating the amount of time spent engaging in sedentary activity; mild, moderate, or vigorous-intensity physical activity. The original IPAQ has been tested across populations and broad age groups and demonstrates good reliability and validity [90].

vi. ***Somatic and Psychological Health Report (SPHERE 12)*** [92]***:*** The SPHERE 12 is a 12-item self-report questionnaire that assesses six

psychological (PSYCH subscale) and six physical symptoms (SOMA subscale) to identify anxiety, depression, and somatisation symptoms in primary care. The SPHERE-12 has been demonstrated to have high reliability and validity in populations over the age of 16 [92].

vii. ***Sleep-wake cycle and chronotype:*** Six questions will be asked concerning time falling asleep, waking up during weekdays and weekends, hours of sleep, feelings when waking up. Sleep timing items are based on the Pittsburgh Sleep Quality Index (PSQI)[93], and Munich Chrono Type Questionnaire (MCTQ) [94], while sleep quality items were developed based on expert agreement in existing literature.

viii. ***Pittsburgh Sleep Quality Index (PSQI)[93]:*** The PSQI is a 24-item self-report questionnaire measuring the quality and patterns of sleep. Seven domains are assessed including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month. This scale has good internal consistency and construct validity [95 96].

ix. ***The Insomnia Severity Index (ISI)[97]:*** The ISI comprises seven items assessing the perceived severity of difficulties in initiating sleep, staying asleep, early morning awakenings, satisfaction with current sleep pattern, interference with daily functioning, noticeability of impairment attributed to the sleep problem, and degree of distress or concern caused by the sleep problem. This scale has been used widely in clinical research with high internal consistency and convergent validity [98].

x. ***Suicidal Ideation Attributes Scale (SIDAS) [99]:*** The SIDAS is a five-item self-report questionnaire assessing the frequency, controllability, closeness

to attempt, distress, and interference with daily activities over the past month. The SIDAS has demonstrated high internal consistency and good convergent validity [100].

xi. ***Quick Inventory of Depressive Symptomatology – self-report (QIDS-SR) [101]:*** The QIDS is a rating scale that assesses the nine criterion symptom domains (sleep, sad mood, appetite/weight, concentration/ decision making, self-view, thoughts of death or suicide, general interest, energy level, and restlessness/agitation) designated by the DSM-IV to diagnose a major depressive episode. This scale has high internal consistency and good predictive and concurrent validity [102].

xii. ***Overall Anxiety Severity Impairment Scale (OASIS) [103]:*** The OASIS is a five-item self-report measure used to assess the frequency and intensity of anxiety symptoms and the functional impairment associated with any anxiety disorder or multiple anxiety disorders. This scale has excellent test-retest reliability, and convergent and discriminant validity [104].

xiii. *World Health Organisation (WHO) Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST) [105 106]:* The ASSIST (version 3.1) is an eight-item questionnaire screening for use of tobacco products, alcohol, cannabis, cocaine, amphetamine-type stimulants (ATS), sedatives and sleeping pills (benzodiazepines), hallucinogens, inhalants, opioids, 'other' drugs. This scale has demonstrated good validity [107] and reliability [108].

xiv. *Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) [109]:* The AUDIT-C has three short questions to estimate alcohol consumption in a

standard, meaningful and non-judgemental manner. This scale has shown good reliability and validity in adolescent sample groups [110].

xv. ***Rosenberg Self-Esteem Scale (RSES) [111]:*** The RSES is a 10-item self-report measure of self-esteem, self-worth or self-acceptance designed specifically for use in adolescent populations. Higher scores on this scale indicate higher levels of global self-esteem. This scale has extremely high internal consistency and demonstrated construct validity with other measures of self-esteem [112 113].

xvi. ***Client Satisfaction Questionnaire-8 (CSQ-8) [114]:*** The CSQ is a structured survey used to assess level of satisfaction with care. The CSQ-8 has been found to have high internal consistency and concurrent validity in mental health outpatient settings [114].

xvii. ***Feedback Questionnaire.*** This is an investigator-developed questionnaire specifically relating to the feasibility and acceptability of the psychoeducation program and whether the participants have any feedback or suggestions for improvement to the online psychoeducation program after completion of the program.

Blood Markers

Blood samples are to be collected in a fasting state between 8:00am and 10:00am by a trained phlebotomist at baseline and week 12 to determine variables of interest including **fasting glucose; fasting insulin, and blood lipids (including triglycerides, total, high density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol levels)**. Other blood measures to be collected for monitoring purposes include HbA1c, full blood count, urea, electrolytes, liver function test, C-

reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA), vitamin D, vitamin B12, folate, iron, thyroid stimulating hormone, calcium (Ca), magnesium (Mg) and phosphate (PO4) levels. **Insulin resistance** will be estimated using the updated homeostatic model assessment **(HOMA2-IR)** using iHOMA2 software V.8.8 [115] from fasting blood test results. Metabolic blood measures will be collected by a standard pathology request, and a de-identified copy of the results will be kept in the participants' file.

Anthropometric Assessments

Measures of **blood pressure, height and weight** will be collected via direct measurement by a clinician or research staff. **Body mass index (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. Where the patient is unable to visit the Brain and Mind Centre for an anthropometric assessment, the participant will be required to self-report height and weight and will be instructed how to gather waist circumference measurements.

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 two-week period for an estimation of sleep and physical activity patterns based on validated algorithms. Measurements include **sleep onset time, sleep offset time, sleep midpoint,** sleep efficiency, wake after sleep onset (WASO: number of minutes during

the sleep period scored as awake), and total sleep time (TST; number of minutes during the sleep period scored as sleep).

Physical activity will be assessed through the GENEActiv devices as gross motor activity per day (milli-gravity [mg], 1g = 9.81 m/s2) and **minutes in moderate-to-vigorous physical activity per day** (objective minutes in moderate-to-vigorous physical activity per day defined as the sum of 1-min epochs in which gross motor activity was larger than 125 mg) as described in other studies [116]. The GENEActiv devices have been used widely in clinical research and validated against several types of accelerometry-based activity monitors [117-120] as well as for sleep-wake scoring [121 122].

Sample Size/ Power Calculation

The proposed sample size calculation of at least 44 participants is based on specific power analysis parameters (power analyses completed in G*Power Version 3.1.9.4), notably difference in means in HOMA2-IR scores of one sample with a power of 0.90, an effect size of 0.5, and an alpha level of 0.05. Whilst this is a pilot study, and a sample size has been estimated, this pilot data will be used to inform power calculations for future studies investigating similar outcome measures in this specific cohort.

Data Analysis Plan

All data will be entered into a secure password protected database and statistical analyses conducted in R statistical software. The primary and secondary objectives will be analysed by a change in mean scores of all outcome measures after completion of the 12-week online psychoeducation program via a paired samples t-test, with

significance levels set at α=.05. To assess the tertiary objectives, correlations will be performed between all cardiometabolic change scores and affective outcome change scores via Pearson's or Spearman's correlations tests based on normative or non-normative data distribution; with a significance level set at α=.05. Overall completion rates of the study will be used to assess feasibility, and the average of the CSQ-8 scores will be used to assess acceptability.

Ethics

The Sydney Local Health District (RPAH Division) Human Ethics Research (HREC) Committee has approved this study (X20-0228). The online psychoeducation program 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 online psychoeducation sessions. This standard treatment may include medication, counselling, psychological therapy and/or referrals to a range of specialist mental health treatments or services.

The headspace, Camperdown clinic is an established, specialised clinic for the youth mental health population. As such, the clinic has its own internal crisis management plans and are staffed with leading expertise in managing patient distress and unexpected occurrences for the youth mental population. As a further precaution, questions about suicidal ideation or self-harm will be asked in weeks 1, 4, 8, and 12 in the monitoring phone call. If there is an indication of suicidal intent, the CAARMS will be administered and suicidality standard operating protocol will be followed. Any adverse events will be logged into an Adverse Event Monitoring Log.

Dissemination

In accordance with the guidelines stipulated by the funding bodies, 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 Brain and Mind Centre website and social media, as well as newsletters.

Discussion

This clinical pilot trial plans to evaluate the efficacy, feasibility and acceptability of a 12 week online psychoeducation program (involving structured nutrition, physical activity, sleep-wake and healthy lifestyle information) on several cardiometabolic risk factors and affective symptoms in youth seeking treatment for mental ill-health. The multidimensional modules feature a youth-friendly format, with input from those with lived experience, to maximise engagement by young people. If the findings of this exploratory trial demonstrate benefits in each of the targeted domains, it will be used as a basis for further clinical trials incorporating more intensive psychoeducation combined with pharmacological therapies. Due to the online nature of the psychoeducation program, there is also potential for a larger-scale study to be implemented across a number of centres nationally, allowing individuals to access the program remotely and regionally.

Whilst this pilot study will provide important information about how multidisciplinary behavioural modification programs may help to manage the immediate cardiometabolic and mental health symptoms (including affective, anxiety and psychotic symptoms) of young people receiving mental health care, it cannot draw conclusions about the long-term implications of these lifestyle changes on the assessed domains. Additionally, as this is a single-arm pilot study, it cannot determine the efficacy of the intervention compared to other behavioural interventions in the same cohort. Future research should thus aim to monitor participants over longer periods of time whilst comparing to other pharmacological (for example metformin) or behavioural interventions.

Trial Status

The trial has not begun recruitment.

Funding and Sponsor

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 C.W), a National Health & Medical Research Council Australia Fellowship (No. 511921, awarded to I.B.H) and a philanthropic fellowship (the Caroline Quinn Research Grant awarded to J.C). 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.

Author's Contributions

C.E.W. has developed this clinical trial as part of her PhD research project and drafted this original manuscript with input from other authors. I.B.H assisted with the design of the study. A.N., N.Z., J.S.C., Y.S., C.M., B.H., S.H. and E.S. 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.

Competing Interests Statement

Professor Ian Hickie was an inaugural Commissioner on Australia's National Mental Health Commission (2012-18). 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 (2017-20; a three-year program for the transformation of mental health services) and to lead transformation of mental health services internationally through the use of innovative technologies.

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The effect of an online healthy lifestyle psychoeducation program to improve cardiometabolic outcomes and affective symptoms in youth receiving mental health care: study protocol for a pilot clinical trial.

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Title: The effect of an online healthy lifestyle psychoeducation program to improve cardiometabolic outcomes and affective symptoms in youth receiving mental health care: study protocol for a pilot clinical trial.

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Abstract

Introduction

Worsened cardiometabolic profiles in youth with mental ill-health have been associated with a number of modifiable lifestyle risk factors. It is becoming increasingly evident that clinical interventions need to be multi-modal in focus to improve not only mental health symptoms, but also the physical health symptoms in this already at-risk cohort.

Methods and Analysis:

This 12-week pilot clinical trial examines the efficacy, feasibility and acceptability of an adjunctive online psychoeducation program for improving cardiometabolic risk parameters and affective symptoms in a transdiagnostic sample of at least 44 young people aged 16-25 presenting for mental health care for mood and/or psychotic syndromes (including anxiety, depression, bipolar disorder and psychosis). Individuals will be invited to participate in a pilot clinical trial for a structured online psychoeducation program incorporating nutritional, physical activity, sleep-wake and healthy lifestyle information, delivered fortnightly over six online modules. Participants will undergo a series of assessments including: (1) self-report and clinician administered assessments determining mental health symptomatology; (2) blood tests to assess cardiometabolic markers (fasting insulin, fasting glucose, blood lipids); (3) anthropometric assessments (height, weight, waist circumference and blood pressure); and (4) sleep-wake behaviours and circadian rhythm assessments. Changes in scores for all cardiometabolic and affective measures will be assessed via paired samples t-tests, and correlations between change scores will be assessed via Pearson's or Spearman's correlations. Feasibility will be assessed via completion

rates and the acceptability of the program will be assessed via program satisfaction measures.

Ethics and Dissemination

This pilot clinical trial has been approved by the Sydney Local Health District Research Ethics and Governance Office (X20-0228 & 2020/ETH01201). The results of this pilot clinical trial will be disseminated into the scientific and broader community through peer-reviewed journals, conference presentations, social media and university websites.

Trial Registration

Australian New Zealand Clinical Trials Registry (ANZCTR) Number: ACTRN12620000772943, Date 28 August, 2020.

Keywords:

Youth mental ill-health, psychoeducation, cardiometabolic improvement, physical activity, sleep-wake cycle regulation.

Strengths and Limitations of this Study

- This pilot clinical trial evaluates a multidisciplinary online psychoeducation program (involving structured nutrition, physical activity, sleep-wake and healthy lifestyle information) for improving cardiometabolic risk parameters and affective symptoms, in a transdiagnostic group of young people receiving mental health care.
- A range of cardiometabolic, anthropometric, sleep-wake and mental health symptoms are assessed throughout the trial to determine whether these factors influence each other.
- Online delivery of psychoeducation modules will allow participants to access the information remotely.
- As this is a single-arm study, it cannot determine the efficacy of the intervention compared to other behavioural interventions in the same cohort.
- This pilot clinical trial will provide important information about how multidisciplinary behavioural modification programs may help to manage the immediate cardiometabolic and affective symptoms of young people receiving mental health care, however cannot draw conclusions about the long-term effects of these lifestyle changes.

Background

Premature mortality in those with severe mental illness has been well documented [1-6], with diabetes and premature cardiovascular disease comprising some of the leading causes of premature mortality and morbidity in this cohort. Increased body mass index (BMI) and weight gain have been identified as key modifiable risk factors causing premature mortality and morbidity in young people with severe mental illness, along

with poor sleep-wake cycle regulation [7-9], physical inactivity [10-16], poor dietary habits [10 17-20] and smoking [21-26].

Whilst many mental disorders can be managed with psychotherapy alone, psychotropic medications including antipsychotics, antidepressants and mood stabilisers are sometimes used for the treatment of a number of psychotic, affective and behavioural disorders in youth [27 28]. Adolescents initiating psychotropic medications may display heterogeneous side effects with some very complex long-term cardiometabolic side effects [29-32]. Of particular concern, is the weight-gain associated with second-generation antipsychotic (SGA) usage [29 33-37] which is acute and can often be observed within 12 weeks of medication initiation [38-43]. Children and adolescents appear to be at a greater risk of psychotropic-induced weight gain than adults [44 45] and the younger the age of the child, the higher the mitigating risk [37]. Psychotropic medication induced weight gain is a noteworthy adverse drug reaction as it mediates the development of other more severe cardiometabolic outcomes [38-43].

Lifestyle interventions can be an effective alternative to pharmacological interventions to manage the physical and mental health symptoms of people presenting with psychiatric disorders [46]. The World Health Organisation guidelines recommend lifestyle behavioural interventions as a first-line treatment for physical health symptoms, including the cardiometabolic health, of adults with severe mental illness [47]. The benefits of lifestyle and behavioural interventions for weight loss in obese individuals and for the prevention of Type II Diabetes Mellitus (T2DM) are well-established [48 49]. Additionally, psychoeducation interventions focusing on healthy lifestyle habits including nutrition, physical activity and sleep-wake practices have

been shown to ameliorate both the physical and mental health concerns of young people with psychiatric disorders [50-54].

Face-to-face psychoeducation interventions for adults with severe mental illness are able to demonstrate significant improvements in weight [55]; depressive symptoms, sleep quality and nutrition [56]; and other cardiometabolic risk factors [57]. Existing web-based psychoeducation intervention studies on adults with mental illness have demonstrated improvements in depression and anxiety symptoms [58], with mixed evidence on the effect of psychotic symptoms [56 59]. Other web-based psychoeducation studies on adults with mental illness haves found increases in objective physical activity levels [60], however have not measured cardiometabolic risk factors objectively. In youth, the literature in this field is more limited, with existing or planned studies in youth cohorts measuring affective symptom improvements only [61-63]. Evidence on the effect of healthy lifestyle psychoeducation programs on psychotic symptoms in youth is non-existent to our knowledge.

We are seeking to investigate the efficacy, feasibility and acceptability of a pilot clinical trial implementing an online healthy lifestyle psychoeducation program targeted towards improving objective cardiometabolic outcomes and affective symptoms in young people presenting for mental health care for mood or psychotic syndromes (including anxiety, depression, bipolar disorder and/or psychosis). Web-based interventions provide an alternative to traditional face-to-face interventions. The need for online programs is especially evident with the COVID-19 global pandemic impeding on young people's ability to seek face-to-face support. This has given rise to a need to develop more comprehensive resources tailored to the specific risk-factors of this

cohort in an easily accessible online format. Where effective, it would allow the program to be implemented remotely, to many individuals who may not be able to access in-person services.

Methods and Analysis

Patient and Public Involvement

The study design, conduct and psychoeducation module content was developed in consultation with a representative from the Brain and Mind Centre Youth Lived Experienced Working Group. Patients or the public were not involved in the reporting, or dissemination plans of our research.

Design and Structure

This is a one-arm longitudinal pilot clinical trial. The duration of the pilot clinical trial is 12 weeks. All participants will engage in an online 12-week psychoeducation program. This psychoeducation program 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 [64-67]. This information will be delivered for approximately 1 hour each fortnight over 6 online modules (week 1, 3, 5, 7, 9, and 11). The modules and study design have been developed in conjunction with mental health experts and those with a lived experience of mental ill health, specifically by presenting module material to a lived experience researcher and tailoring module content and delivery modes to ensure the suitability and relevance for this cohort. These modules are intensive and information dense, and by delivering these modules every two weeks it allows the participants enough time to absorb the

information and implement the advice into their lifestyle without becoming overwhelming.

Participants will be provided a link to access the online psychoeducation modules in their own time, or given the opportunity to attend a live online or face-to-face module session. These modules will cover the topics shown in Table 1.

Table 1. Psychoeducation modules

Session	Topics to be covered
1. Body Clock and Sleep-Wake Cycle Regulation for mental health (part 1)	– How the brain and body are connected – Establishing a healthy mindset – Importance of the brain and body clock and sleep-wake cycle regulation – How the brain and body clock coordinates all the biological systems
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 e.g. exercise, light exposure, sleep environment, sleep regularisation, naps, foods, stress, anxiety, mood.
3. Physical activity for mental health (part 1)	– Benefits of physical activity for physical and mental health – Outline of Australian Physical Activity Guidelines – Barriers to engaging in physical activity – Increasing incidental activity, reducing sitting time
4. Physical activity for mental health (part 2)	– Working out anywhere – Finding the motivation – Concept of energy in vs energy out
5. Nutrition for mental health (part 1)	– Energy in vs energy out and introducing the concept of a calorie – Outline of Australian Dietary Guidelines – Standard serving sizes/portion sizes
6. Nutrition for mental health (part 2)	– Timing of meals – Snacking – Meal preparation – Making healthy choices when eating out at restaurants – Managing comfort eating.

Every week, participants will receive a monitoring phone call to aid the participant's engagement and ongoing participation. This monitoring phone call will provide the participants with the opportunity to discuss the module content with the research staff, as well as discussing their goals and how the module content can be implemented into their lifestyle. At the completion of all 6 modules the participant will be asked to provide feedback about the program and to share their overall satisfaction with the program

via a series of online questionnaires. These questionnaires will provide important information about the acceptability and feasibility of the psychoeducation program in this cohort.

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, 6-7 and 11-12. Fasting blood tests to measure metabolic 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 will be conducted in weeks 1 and 12. All assessments including the self-report questionnaires and clinician rated assessments are expected to take approximately two 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 [68]. 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 health care to improve the outcomes of their clinical care. Other clinician administered measures have been included in this study as they are

improved and updated measures of self-report measures which are subject to bias and reporting errors.

The schedule of enrolment, interventions and assessment time points can be seen in Table 2.

Table 2. Schedule of enrolment, interventions and assessment time points.

Study Procedures	Study Week											
	1	2	3	4	5	6	7	8	9	10	11	12
Informed Consent	x											
Enrolment	x											
Psychoeducation Session	x		x		x		x		x		x	
Actigraphy	x					x					x	
Self-Report Questionnaires	x											x
Clinician Administered Questionnaires	x											x
Blood Collection	x											x
Anthropometrics	x											x

Setting, Recruitment and Informed Consent

This is a single-site, transdiagnostic intervention study, conducted at the BMC (including *headspace* Camperdown, and Early Intervention and High Intensity Services) at the University of Sydney (Sydney, Australia).

Potential participants will be identified as young people aged between 16 and 25 years of age presenting for mental health care, who are at risk for poor cardiometabolic outcomes due to being overweight or obese. To avoid recruitment bias, all treating

clinicians will be made aware of the study and eligibility criteria and will encourage all suitable young people presenting for care at these services to participate in the study.

With the young person's permission, the clinicians will pass on the contact details to the study research team, who will make further contact and initiate the informed consent process. 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. The study staff will then obtain written informed consent from the young person to participate in the psychoeducation program. Each participant will have a participant ID that links the participant to the research database in a confidential and de-identified manner for the purpose of research. Participants are free to withdraw from the study at any time by contacting research staff. 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. If participants withdraw from the study, all future data (i.e., from thereon) will not be stored or used for research purposes.

Selection Criteria

Young people will be invited into the trial based on the following inclusion criteria: (i) aged between 16 and 25; (ii) receiving mental health care treatment at the participating sites; (iii) body mass index (BMI) ≥ 25; (iv) willing and able to give independent written informed consent to participate in the study.

The exclusion criteria are: (i) intellectual disability (at the discretion of a clinical psychologist or psychiatrist); (ii) major neurological disorder, medical illness which impacts on cognition, and/or a history of sustained head injury; (iv) not fluent in

English; or (v) an acute psychotic or manic episode that impairs the individual's ability to give informed consent and/or requires acute clinical treatment.

Study Objectives

Primary To assess the efficacy of an online 12-week healthy lifestyle psychoeducation program in improving cardiometabolic parameters (fasting insulin, fasting glucose, the updated homeostatic model assessment (HOMA2 IR), cholesterol, triglycerides, blood pressure, BMI and waist circumference) of young people seeking treatment for mental health related issues.

Secondary To assess the efficacy of an online 12-week healthy lifestyle psychoeducation program in improving affective (depressive and anxiety) symptoms of young people seeking treatment for mental health related issues.

Tertiary To assess if changes in cardiometabolic health risk factors (fasting insulin, fasting glucose, triglycerides, HOMA2-IR, cholesterol, blood pressure, BMI and waist circumference) are associated with changes in affective (depressive and anxiety) symptom severity.

To assess the feasibility and acceptability of the psychoeducation program in a cohort of young people seeking treatment for mental health related issues.

Measures

Key outcome measures targeted for this study are highlighted in **bold type**.

Clinician Rated Assessments

i. *Diagnostic Assessment:* The presence of any DSM-V Disorders will be assessed using the Structured Clinical Interview for DSM-V Disorders (SCID)[69].

ii. *Physical Health, Mental Health, Family Health and Treatment History:* Current and past health history will be assessed and recorded by trained researchers and study doctors. This includes current medication and any changes in physical and/or mental health treatment being received throughout the trial.

iii. ***The Brief Psychiatric Rating Scale (BPRS) [70]:*** The BPRS measures psychiatric symptoms including depression, anxiety, hallucinations, delusions and unusual behaviour. This 24-item scale is one of the most universally used scales to measure psychotic symptoms [71].

iv. *Clinical Staging [72]*: This framework stages individuals according to the presentation of their mental illness from those in the earliest phases with non-specific clinical presentations (Stages 1a 'seeking help'), those at greater-risk with more specific, sub-threshold 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) [72-75].

v. *Pathophysiological Mechanisms [76]:* The pathophysiological model suggests three possible pathways of illness: (i) neuro-developmental impairments, (ii) circadian dysregulation, and (iii) heightened sensitivity (i.e., stress-reactivity) in the "fear" circuitry. Based on these pathways, three clinical phenotype labels will be assigned to the individual: (i) developmental-psychotic, (ii) mania-fatigue, or (iii) anxiety-depression subtypes.

vi. *Clinical Global Impression (CGI [77]):* The CGI provides an indication of the young person's ability to function in context of their history, psychosocial circumstances, symptoms, and behaviour. The CGI comprises two one-item

measures evaluating the severity of psychopathology from 1 to 7 (CGI-Severity, CGI-S) and the change from the initiation of treatment on a seven-point scale (CGI-Improvement, CGI-I).

vii. ***The Young Mania Rating Scale (YMRS)*** [78]**:** The YMRS is an eleven-item questionnaire measuring manic episode severity derived from the young person's subjective report and clinical observations during the clinical interview.

viii. ***The Simple Physical Activity Questionnaire (SIMPAQ)*** [79]**:** The SIMPAQ is a five-item clinical tool designed to assess the degree of physical activity in cohorts at high risk of sedentary behaviour. This measure has been used in over 23 countries and can be reliability and validly administered by clinicians [80].

ix. ***Suicidal ideation and behaviour:*** Acute suicidal behaviour will be assessed by item 7.3 of the Comprehensive Assessment of At-Risk Mental States (CAARMS) [81]. The CAARMS is a semi-structured assessment tool designed to identify those at ultra-high risk for psychosis. This assessment is only to be administered as a safety measure where the self-report Suicidal Ideation Attributes Scale (SIDAS) score reaches the cut off score of ≥ 21 indicating a high risk of suicidal behaviour.

x. ***Social and Occupational Assessment Scale (SOFAS) (38)*****:** The SOFAS is a global rating of the participant's current social and occupational functioning, independent of the overall severity of the individual's psychological symptoms, ranging from 0 to 100, with lower scores indicating poorer functioning. The SOFAS has been used extensively in clinical

research and practice and has good construct validity, interrater reliability, and predictive validity [82 83].

Self-Report Questionnaires:

i. *Demographics:* This questionnaire will comprise details on basic demographics (including details of work and education, ethnicity, living circumstances, relationship status), and physical health (height, weight and waist circumference).

ii. ***Kessler Psychological Distress Scale (K-10) [84 85]:*** The K-10 is a 10-item version of the Kessler scale that provides a global measure of distress derived from anxiety and depressive symptoms over a four-week period. It has high predictive validity and reliability [86].

iii. ***International Physical Activity Questionnaire (IPAQ) - short version [87 88]:*** The short version of the International Physical Activity Questionnaires (IPAQ) is a seven-item questionnaire calculating the amount of time spent engaging in sedentary activity; mild, moderate, or vigorous-intensity physical activity. The original IPAQ has been tested across populations and broad age groups and demonstrates good reliability and validity [87].

iv. ***Somatic and Psychological Health Report (SPHERE 12) [89]:*** The SPHERE 12 is a 12-item self-report questionnaire that assesses six psychological (PSYCH subscale), and six physical and fatigue symptoms (SOMA subscale) to identify anxiety, depression, and somatisation symptoms in primary care. The SPHERE-12 has been demonstrated to have high reliability and validity in populations over the age of 16 [89].

v. ***Sleep-wake cycle and chronotype:*** Six questions will be asked concerning time falling asleep, time waking up during weekdays and weekends, hours of sleep and feelings when waking up. Sleep timing items are based on the Pittsburgh Sleep Quality Index (PSQI)[90], and Munich Chrono Type Questionnaire (MCTQ) [91], while sleep quality items were developed based on expert agreement in existing literature.

vi. ***Pittsburgh Sleep Quality Index (PSQI)[90]:*** The PSQI is a 24-item self-report questionnaire measuring the quality and patterns of sleep. Seven domains are assessed including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month. This scale has good internal consistency and construct validity [92 93].

vii. ***The Insomnia Severity Index (ISI)[94]:*** This seven-item questionnaire assesses the severity of difficulties in initiating sleep, staying asleep, early morning awakenings, satisfaction with current sleep pattern, daily functioning and impairment attributed to the sleep problem, and the degree of distress or concern caused by the sleep problem. This scale has been used widely in clinical research with high internal consistency and convergent validity [95].

viii. ***Suicidal Ideation Attributes Scale (SIDAS) [96]:*** The SIDAS is a five-item self-report questionnaire assessing suicidal ideology in relation to the frequency, controllability, closeness to attempt, distress, and interference with daily activities over the last month. The SIDAS has demonstrated high internal consistency and good convergent validity [97].

ix. ***Quick Inventory of Depressive Symptomatology – self-report (QIDS-SR) [98]:*** The QIDS is a rating scale assessing nine criterion symptom domains (sleep, sad mood, appetite/weight, concentration/ decision making, self-view, thoughts of death or suicide, general interest, energy level, and restlessness/agitation) outlined by the DSM-IV to diagnose a major depressive episode. This scale has high internal consistency and good predictive and concurrent validity [99].

x. ***Overall Anxiety Severity Impairment Scale (OASIS) [100]:*** The OASIS is a five-item self-report measure used to assess the frequency and intensity of anxiety symptoms, including the functional impairment and behavioural avoidance commonly associated with any anxiety disorder or multiple anxiety disorders. This scale has excellent test-retest reliability, and convergent and discriminant validity [101].

xi. *World Health Organisation (WHO) Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST) [102 103]:* The ASSIST (version 3.1) is an eight-item questionnaire screening for use of tobacco products, alcohol, cannabis, cocaine, amphetamine-type stimulants (ATS), sedatives and sleeping pills (benzodiazepines), hallucinogens, inhalants, opioids, 'other' drugs. This scale has demonstrated good validity [104] and reliability [105].

xii. *Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) [106]:* The AUDIT-C is a three-item scale gauging alcohol consumption in a standardised manner. This scale has shown good reliability and validity in adolescent sample groups [107].

xiii. ***Eating Disorder Examination (EDE)*** [108 109]: This self-report questionnaire assesses current eating disorder behaviours, including binge eating, purging and strict dieting or fasting. This self-report questionnaire has demonstrated good internal consistency and construct validity [110].

xiv. ***Rosenberg Self-Esteem Scale (RSES)*** [111]***:*** The RSES is a 10-item self-report measure of self-esteem, self-worth or self-acceptance designed specifically for use in adolescent populations. Higher scores on this scale indicate higher levels of global self-esteem. This scale has extremely high internal consistency and demonstrated construct validity with other measures of self-esteem [112 113].

xv. ***Client Satisfaction Questionnaire-8 (CSQ-8)*** [114]***:*** The CSQ assesses level of satisfaction with care and has been found to have high internal consistency and concurrent validity in mental health outpatient settings [114].

xvi. ***Feedback Questionnaire***. This is an investigator-developed questionnaire specifically relating to the feasibility and acceptability of the psychoeducation program and whether the participants have any feedback or suggestions for improvement to the online psychoeducation program after completion of the program.

Blood Markers

Blood samples are to be collected in a fasting state between 8:00am and 10:00am by a trained phlebotomist at week 1 and week 12 to determine variables of interest including **fasting glucose; fasting insulin, and blood lipids (including triglycerides, total, high density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol levels)**. Other blood measures to be collected for monitoring

purposes include **HbA1c**, full blood count, urea, electrolytes, liver function test, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA), vitamin D, vitamin B12, folate, iron, thyroid stimulating hormone, calcium (Ca), magnesium (Mg) and phosphate (PO4) levels. **Insulin resistance** will be estimated using the updated homeostatic model assessment **(HOMA2-IR)** using iHOMA2 software V.8.8 [115] from fasting blood test results. Metabolic blood measures will be collected by a standard pathology request, and a de-identified copy of the results will be kept in the participants' file.

Anthropometric Assessments

Measures of **blood pressure, height and weight** will be collected via direct measurement by a clinician or research staff. **Body mass index (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. Where the young person is unable to visit the BMC for an anthropometric assessment, the participant will be required to self-report height and weight and will be instructed how to gather waist circumference measurements.

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 two-week period for an estimation of sleep and physical activity patterns based on validated algorithms. Measurements include **sleep onset time, sleep offset time, sleep**

midpoint, sleep efficiency, wake after sleep onset (WASO: number of minutes during the sleep period scored as awake), and total sleep time (TST; number of minutes during the sleep period scored as sleep).

Physical activity levels will be assessed through the GENEActiv devices 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 [116]. The GENEActiv devices have been used widely in clinical research and validated against several types of accelerometry-based activity monitors [117-120] as well as for sleep-wake scoring [121 122].

Sample Size/ Power Calculation

The proposed sample size calculation of at least 44 participants is based on specific power analysis parameters (power analyses completed in G*Power Version 3.1.9.4), notably difference in means in HOMA2-IR scores of one sample with a power of 0.90, an effect size of 0.5, and an alpha level of 0.05. Whilst this is a pilot study, and a sample size has been estimated, this pilot data will be used to inform power calculations for future studies investigating similar outcome measures in this specific cohort.

Data Analysis Plan

All data will be entered into a secure password protected database and statistical analyses conducted in R statistical software. The primary and secondary objectives will be analysed by a change in mean scores of all outcome measures after completion of the 12-week online psychoeducation program via a paired samples t-test, with

significance levels set at α=.05. To assess the tertiary objectives, correlations will be performed between all cardiometabolic change scores and affective outcome change scores via Pearson's or Spearman's correlations tests based on normative or non-normative data distribution; with a significance level set at α=.05. Overall completion rates of the study will be used to assess feasibility, and the average of the CSQ-8 scores will be used to assess acceptability.

Ethics and Dissemination

The Sydney Local Health District (RPAH Division) Human Ethics Research (HREC) Committee has approved this study (X20-0228). The online psychoeducation program 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 online psychoeducation sessions. This standard treatment may include medication, counselling, psychological therapy and/or referrals to a range of specialist mental health treatments or services.

The headspace, Camperdown clinic is an established, specialised clinic for the youth mental health population. As such, the clinic has its own internal crisis management plans and are staffed with leading expertise in managing distress and unexpected occurrences for the youth mental population. As a further precaution, questions about suicidal ideation or self-harm will be asked in weeks 1, 4, 8, and 12 in the monitoring phone call. If there is an indication of suicidal intent, the CAARMS will be administered and suicidality standard operating protocol will be followed. Any adverse events will be logged into an Adverse Event Monitoring Log.

In accordance with the guidelines stipulated by the funding bodies, 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.

Discussion

This pilot clinical trial plans to evaluate the efficacy, feasibility and acceptability of a 12-week online psychoeducation program (involving structured nutrition, physical activity, sleep-wake and healthy lifestyle information) on several cardiometabolic risk factors and affective symptoms in youth seeking treatment for mental ill-health. The multidimensional modules feature a youth-friendly format, with input from those with lived experience, to maximise engagement by young people. If the findings of this pilot clinical trial demonstrate benefits in each of the targeted domains, it will be used as a basis for further clinical trials incorporating more intensive psychoeducation combined with pharmacological therapies. Due to the online nature of the psychoeducation program, there is also potential for a larger-scale study to be implemented across a number of centres nationally, allowing individuals to access the program remotely and regionally.

Whilst this pilot study will provide important information about how multidisciplinary behavioural modification programs may help to manage the immediate

cardiometabolic and mental health symptoms (including affective, anxiety and psychotic symptoms) of young people receiving mental health care, it cannot draw conclusions about the long-term implications of these lifestyle changes on the assessed domains. Additionally, as this is a single-arm pilot study, it cannot determine the efficacy of the intervention compared to other behavioural interventions in the same cohort. Future research should thus aim to monitor participants over longer periods of time whilst comparing to other pharmacological (for example metformin) or behavioural interventions.

Trial Status

The trial has begun recruitment.

Funding and Sponsor

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 C.W), a National Health & Medical Research Council Australia Fellowship (No. 511921, awarded to I.B.H) and a philanthropic fellowship (the Caroline Quinn Research Grant awarded to J.C). 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.

Author's Contributions

C.E.W. has developed this pilot clinical trial as part of her PhD research project and drafted this original manuscript with input from other authors. I.B.H assisted with the design of the study. A.N., N.Z., J.S.C., Y.S., C.M., B.H., S.H. and E.S. 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.

Competing Interests Statement

Professor Ian Hickie was an inaugural Commissioner on Australia's National Mental Health Commission (2012-18). 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 (2017-20; a three-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 Elizabeth Scott 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.

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