PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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.
AUTHORS	Wilson, Chloe; Nichles, Alissa; Zmicerevska, Natalia; Carpenter, Joanne; Song, Yun; McHugh, Catherine; Hamilton, Blake; Hockey, Samuel; Scott, Elizabeth; Hickie, Ian

VERSION 1 – REVIEW

REVIEWER	Jadwiga Hamułka Department of Human Nutrition, Institute of Human Nutrition Sciences; POLAND
REVIEW RETURNED	22-Nov-2020

GENERAL COMMENTS	ear Editors, Thank you for the possibility to review this manuscript. This is a very good study with a wide range of planned analyzes and the multidisciplinary psychoeducation program online. I congratulations the Authors of the idea and planning online program in the current situation, with the COVID-19 global pandemic impeding ability to seek face-to-face support. I have marked minor remarks/comments in the attached file - the manuscript. In addition, I propose to reorganize the text and clarify what is measured by researchers and what concerns self-report. This study protocol deserves to be published quickly, in my opinion. With my best regards and health wishes,

REVIEWER	Petter Andreas Ringen Oslo University Hospital, Division of Mental Health and Addiction. Norway.
REVIEW RETURNED	21-Dec-2020

GENERAL COMMENTS	This is a well-planned and scientifically interesting study. The manuscript largely describes the study adequately, but I have some concerns outlined in the points below:

	1. It could be stated clearer in the Abstract and in the last paragraph of the Introduction/aims description that the study is designed as a feasibility/exploratory/pilot study (as is described more directly in the text under Sample size and Discussion) 2. Under Strengths and Limitations the authors state only strengths of the interventions? It should be stated that this one-arm study cannot answer questions about efficiency of the interventions/efficacy compared to other interventions or answer questions of cause and effect. And: Are there any limitations to the interventions? 3. In the Introduction the authors state that "Lifestyle interventions are an effective non-pharmacological intervention option to manage drug-induced cardiometabolic disturbances in patients with psychiatric disorders." (p6/line54). I doubt that the current level of evidence fully supports this statement? I suggest that the phrasing should be moderated. 4. There is a somewhat confusing description of the selection criteria and the use of the terms/categories affective/anxity/depressive in the abstract, the aims-section of the Introduction (p7/line 45) and in the setting and Selection criteria in the Methods' section. It seems from the Selection criteria that the target population is persons between16 and 30 and receiving care at one of the youth mental health clinics (no diagnostic criteria?). This could be clarified throughout the manuscript. 5. In the design section it is stated that the psychoeducational program will involve "general healthy lifestyle information based on the Australian Guidelines of Physical Activity, the Australian Guide to Healthy Eating, and previously published research". Is it possible to specify what kind of lifestyle information that is meant with "previously published research"? 6. What is the rationale behind the choice of administration of the intervention (1 hour every 14 days)? 7. Are there any measures to avoid recruitment bias from the treating clinicians (e.g. emphasis on recruiting all patients regardless of clinical status, current lifestyle and motivation)? 8. The Secondary Study Objective is described as to determine of the efficacy of an online psychoeducation program in improving affective symptoms. The rationale for selecting affective symptoms specifically could be commented (e.g. why not anxiety symptoms or psychotic symptoms). 9. I find the verb "determine" in "determine efficacy" a bit on the strong side in the description of Objectives in this exploratory pilot-like study. Maybe "assess efficacy" or something similar would be more accurate? 10. Secondary outcome measures are plentiful. This makes it unclear how the measures are related to the hypotheses, increase the risk for multiple testing and makes the protocol strenuous for patients and, to smaller degree, clinicians. Further, there are several measures for the same type of outcome, eg. Activity is measures by both actigraph, self-report (IPAQ) and a clinician rated tool (SIMPAQ) and there are several measures for sleep-quality. This increases the risk for a scientific "fishing trip". Some secondary outcome measures are not clear measures of outcome (at least not when referring to the objectives), this is especially true for some diagnostic-like measures. • Could the number of secondary outcome measures be reduced? The reason for having many, partly overlapping, outcome measures should be justified. Preferably only a few non-overlapping measures should be defined outcomes.

	• It does not seem meaningful to treat treatment history and diagnostic assessment as outcomes? • What is the rationale behind including the Pathophysiological Mechanisms or Clinical Staging as outcomes? These measures do not seem to have any clear connection with the objectives and the inclusion of them is not mentioned in the Introduction? • Are there any other cardiometabolic risk outcome measures (e.g. Anthropometric assessments) than HOMA-IR? • Why have users not been involved in the design of the protocol? What is the expected time for completing the questionnaires? 11. Will there be any records of the adjunct treatment received by the participants?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Prof. Jadwiga Hamułka, Szkola Glowna Gospodarstwa Wiejskiego Comments to the Author:
Dear Editors,

Thank you for the possibility to review this manuscript.

This is a very good study with a wide range of planned analyzes and the multidisciplinary psychoeducation program online.

I congratulations the Authors of the idea and planning online program in the current situation, with the COVID-19 global pandemic impeding ability to seek face-to-face support.

I have marked minor remarks/comments in the attached file - the manuscript.

In addition, I propose to reorganize the text and clarify what is measured by researchers and what concerns self-report.

This study protocol deserves to be published quickly, in my opinion.

With my best regards and health wishes,

Thank you for the positive comments. The following changes in the attached file have been addressed as follows:

Page 5:

Changing the order of assessments.

The order of assessments have now changed to include self-report and clinician administered assessments listed first as follows:

“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."

Page 6:

Add social media and website to Ethics and Dissemination section

In line with the reviewer's suggestions, the manuscript has now been revised to say: "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."

Page 6:

More limitations of the study should be added.
Furthermore, in strengths, I suggest emphasizing the multidisciplinary nature of the project (program)

Thank you to the editor and reviewers for raising this point. Please refer to the above response on page 1 of this letter noting substantial changes to the "Strengths and Limitations of this Study" section of the manuscript.

Page 6:

Add target group to key words

Thank you for highlighting this point, we have made the key words more age-specific by changing the first key word to "youth mental ill-health".

Page 10:

In table 2 it is week 11-12 - this should be harmonized (clarified).

This has been corrected in the manuscript to include weeks 11-12.

Page 11:

I propose to add all weeks

To address this point all weeks have now been included in table 2 for clarity.

Page 12:

Maybe better blood markers as not only cholesterol will be tested

The phrase "cholesterol" has now been changed to blood lipids throughout the manuscript.

Page 19:

I propose to add conditions for blood collection and analysis

Thank you for seeking further clarification for this section of the manuscript. The following statement has been included in the blood marker section:

“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 total, high density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol levels).”

Page 22:

The discussion should be strengthened / improved.

The discussion section has been strengthened and expanded to include strengths, limitations and future directions.

Reviewer: 2

Dr. Petter Ringen, University of Oslo
Comments to the Author:

This is a well-planned and scientifically interesting study. The manuscript largely describes the study adequately, but I have some concerns outlined in the points below:

1. It could be stated clearer in the Abstract and in the last paragraph of the Introduction/aims description that the study is designed as a feasibility/exploratory/pilot study (as is described more directly in the text under Sample size and Discussion) Changes have been made to the abstract to make it clearer that the study is a pilot trial. The phrase “pilot clinical trial” has been used throughout the abstract for consistency.

Changes have also been made to the last paragraph of the introduction to include the following:

“We are seeking to investigate the acceptability and feasibility of a pilot clinical trial implementing an online healthy lifestyle psychoeducation program targeted towards improving objective cardiometabolic outcomes in young people presenting for care for mood or psychotic syndromes (including anxiety, depression, bipolar disorder and psychosis).”

2. Under Strengths and Limitations the authors state only strengths of the interventions? It should be stated that this one-arm study cannot answer questions about efficiency of the interventions/efficacy compared to other interventions or answer questions of cause and effect. And: Are there any limitations to the interventions?

Thank you to the editor and reviewers for raising this point. Please refer to the above response on page 1 of this letter noting substantial changes to the “Strengths and Limitations of this Study” section of the manuscript.

3. In the Introduction the authors state that “Lifestyle interventions are an effective non-pharmacological intervention option to manage drug-induced cardiometabolic disturbances in patients with psychiatric disorders.” (p6/line54). I doubt that the current level of evidence fully supports this statement? I suggest that the phrasing should be moderated.

In line with the reviewer’s suggestion, the phrasing of this sentence has been changed to “Lifestyle interventions can be an effective alternative to pharmacological interventions to manage drug-induced cardiometabolic disturbances in patients with psychiatric disorders.”

4. There is a somewhat confusing description of the selection criteria and the use of the terms/categories affective/anxity/depressive in the abstract, the aims-section of the Introduction (p7/line 45) and in the setting and Selection criteria in the Methods' section. It seems from the Selection criteria that the target population is persons between16 and 30 and receiving care at one of the youth mental health clinics (no diagnostic criteria?). This could be clarified throughout the manuscript.

Thank you for highlighting this and seeking clarification. Changes have been made throughout the manuscript to refer to the participants more consistently using the following terminology/phrase "youth presenting for mental health care".

5. In the design section it is stated that the psychoeducational program will involve "general healthy lifestyle information based on the Australian Guidelines of Physical Activity, the Australian Guide to Healthy Eating, and previously published research". Is it possible to specify what kind of lifestyle information that is meant with "previously published research"?

Thank you for seeking clarification, the "previously published research" refers to published circadian research findings specific to youth mental illness. The manuscript has now been revised to make this clear with added peer-reviewed references. It now reads:

"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 1-4…"

6. What is the rationale behind the choice of administration of the intervention (1 hour every 14 days)?

The timing of administration was based on consultation with collaborators conducting similar psychoeducation programs in a COVID-19 setting. The modules are intensive and information dense. By spreading out the modules over 2 weeks, it allows the participants enough time to absorb the information and implement the advice into their lifestyle without becoming overwhelming. Every week the participants will have an opportunity to discuss the content with the research staff to discuss their goals and how the information can be implemented into their lifestyle.

7. Are there any measures to avoid recruitment bias from the treating clinicians (e.g. emphasis on recruiting all patients regardless of clinical status, current lifestyle and motivation)?

To avoid recruitment bias, all clinicians will be made aware of the inclusion and exclusion criteria and will encourage all patients who meet these selection criteria to participate in the study. The research team will then screen and make explicit to any potential participants both verbally and in writing (in the participant information and consent form) that participation is voluntary and will not affect the patient's care received by the mental health service.

8. The Secondary Study Objective is described as to determine of the efficacy of an online psychoeducation program in improving affective symptoms. The rationale for selecting affective symptoms specifically could be commented (e.g. why not anxiety symptoms or psychotic symptoms).

There is existing evidence to suggest that psychoeducation programs are able to improve both affective and anxiety symptoms, however very limited evidence for improving psychotic symptoms. The papers referring to these findings have now been included in the manuscript by the following statement:

“Existing web-based psychoeducation intervention studies on adults with mental illness have demonstrated improvements in depression and anxiety symptoms 5, mixed evidence on the effect of psychotic symptoms 6 7, and increases in objective physical activity levels 8, 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 9-11. Evidence on the effect of healthy lifestyle psychoeducation programs on psychotic symptoms in youth is non-existent to our knowledge.”

Most of the patients who present for care at the headspace clinic, Camperdown, experience comorbid features of affective disorders, including affective psychosis. As such these participants are not excluded from the study, but only their affective and/or anxiety symptoms are expected to improve. Noting this, psychotic symptoms will also be examined.

9. I find the verb “determine” in “determine efficacy” a bit on the strong side in the description of Objectives in this exploratory pilot-like study. Maybe “assess efficacy” or something similar would be more accurate?

As per the reviewer’s recommendation, the verb has now been changed in the manuscript.

10. Secondary outcome measures are plentiful. This makes it unclear how the measures are related to the hypotheses, increase the risk for multiple testing and makes the protocol strenuous for patients and, to smaller degree, clinicians. Further, there are several measures for the same type of outcome, eg. Activity is measures by both actigraph, self-report (IPAQ) and a clinician rated tool (SIMPAQ) and there are several measures for sleep-quality. This increases the risk for a scientific “fishing trip”. Some secondary outcome measures are not clear measures of outcome (at least not when referring to the objectives), this is especially true for some diagnostic-like measures.

• Could the number of secondary outcome measures be reduced? The reason for having many, partly overlapping, outcome measures should be justified. Preferably only a few non-overlapping measures should be defined outcomes.

The headspace, Camperdown clinic is part of the University of Sydney campus, and as such is both a research centre and treatment facility. As such, most of the measures included are part of a standard intake assessment for all patients who enter the clinic at the beginning of their treatment part of a research patient centred care model. We have made this clearer in the manuscript by adding the following sentence on page 8 of the manuscript: “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 research framework 12. 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 BMC uses a standardised set of measures within this framework.”

These questionnaires are part of an ongoing larger study for all patients to improve the outcomes of their clinical care. Other measures (e.g. SIMPAQ) have been added as they are improved and updated measures of self-report measures which are subject to bias and reporting errors. To make it

clearer, the key outcome measures specific to this study have been highlighted in bold type throughout the manuscript.

- It does not seem meaningful to treat treatment history and diagnostic assessment as outcomes?

Thank you for highlighting this. To make it clearer, the key outcome measures specific to this study have been highlighted in bold type throughout the manuscript.

- What is the rationale behind including the Pathophysiological Mechanisms or Clinical Staging as outcomes? These measures do not seem to have any clear connection with the objectives and the inclusion of them is not mentioned in the Introduction?

These measures are part of the standardised assessment battery developed for the Youth Mental Health Tracker as part of the Brain and Mind Centre multidimensional research framework and are implemented for all patients who enter the clinic at the beginning of their treatment.

- Are there any other cardiometabolic risk outcome measures (e.g. Anthropometric assessments) than HOMA-IR?

Thank you for highlighting this, the cardiometabolic risk outcome measures are now included under the Secondary Outcome measures section within the in the “Blood Markers” and “Anthropometric assessments” sections.

- Why have users not been involved in the design of the protocol? What is the expected time for completing the questionnaires?

Thank you for raising this question and we should have included this in the content of our manuscript. The study design and psychoeducation module content was developed in consultation with the Brain and Mind Centre Youth Lived Experienced Researcher, Samuel Hockey. He has now been included as a co-author on the manuscript. We apologise for this oversight.

The following statements have now been included in the following two sections of the manuscript:
Design and Structure section:

“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.”

Patient and Public Involvement section:

“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.

All assessments including the self-report questionnaires and clinician rated assessments are expected to take approximately 2 hours at each time point.

11. Will there be any records of the adjunct treatment received by the participants?

Thank you for addressing this point. Yes, there will be ongoing records of the adjunct treatment received by each participant. Treatment as usual for this cohort includes general practitioner treatment, treatment by a psychiatrist, clinical psychologist, psychologist or social worker. This will be noted by the treating clinician or trained research staff in one of the clinical assessments. This has been clarified in manuscript by the following by the following statement:

“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.”

VERSION 2 – REVIEW

REVIEWER	Hamułka, Jadwiga Szkola Glowna Gospodarstwa Wiejskiego
REVIEW RETURNED	27-Feb-2021

GENERAL COMMENTS	The manuscript has been greatly corrected and improved. I congratulation to the Authors of the research design idea. Right now, I can fully support publishing this article. However, I suggest reviewing the text again and making minor editorial corrections e.g. in the subsection Clinician Rated Assessments - the order of enumeration

REVIEWER	Ringen, Petter University of Oslo
REVIEW RETURNED	12-Mar-2021

GENERAL COMMENTS	The manuscript has improved substantially by the revisions and may be published as is. However, I suggest some minor additions before publication, if space allows: Consider to adjust the title to “pilot clinical trial”. Consider to bring some of the information given on points 6 and 7 into the text. Consider to add this sentence (given as last answer to point 10) : "All assessments including the self-report questionnaires and clinician ratedassessments are expected to take approximately 2 hours at each point".

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Prof. Jadwiga Hamułka, Szkola Glowna Gospodarstwa Wiejskiego

Comments to the Author:

The manuscript has been greatly corrected and improved.

I congratulation to the Authors of the research design idea.

Right now, I can fully support publishing this article.

However, I suggest reviewing the text again and making minor editorial corrections e.g. in the subsection Clinician Rated Assessments - the order of enumeration

With best regards

Thank you to the reviewer for noticing this editorial correction. The order of enumeration for all clinician rated and self-report questionnaires has been corrected.

Reviewer: 2

Dr. Petter Ringen, University of Oslo

Comments to the Author:

The manuscript has improved substantially by the revisions and may be published as is. However, I suggest some minor additions before publication, if space allows:

Consider to adjust the title to “pilot clinical trial”. Consider to bring some of the information given on points 6 and 7 into the text. Consider to add this sentence (given as last answer to point 10) : "All assessments including the self-report questionnaires and clinician rated assessments are expected to take approximately 2 hours at each point".

The information given in point 6 of the previous revision has now been included within the Design and Structure section of the manuscript by including the following statements: “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.” and “Every week, participants will receive a monitoring phone call to aid in 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.”

The information given in point 7 of the previous revision, referring to measures to avoid recruitment bias have been emphasised in the Setting, Recruitment and Informed Consent section of the manuscript via the following statement “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.” Additionally, the following statement was included in this section “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.”

To include the information provided in point 10 of the previous revision, under the Design and Structure section, we have included the following statement “All assessments including the self-report questionnaires and clinician rated assessments are expected to take approximately two hours at each time point.”