ISRCTN61613198 https://doi.org/10.1186/ISRCTN61613198

The ketogenic diet in bipolar disorder

Submission date	Recruitment status	[X] Prospectively registered
28/02/2022	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
02/03/2022	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
27/01/2025	Mental and Behavioural Disorders	

Plain English summary of protocol

Background and study aims
Bipolar disorder (BD) is a mental health condition that affects your moods, which can swing from one extreme to another. It is a major lifelong mental health condition that significantly impacts the quality of life of those who live with it. Our current understanding of how it develops is poor, and as such treatments are not always effective. There is some evidence that the ketogenic diet (KD), which is low in carbohydrate and high in fat, may be an effective treatment for BD, and some patients already follow this diet. To date there has been no clinical trial of the KD in BD. This study will pilot the introduction of a KD for 8 weeks in patients with BD. The aim is to find out how easy it is to do this, the main challenges, and how to address these. The acceptability of the intervention will be assessed, looking at how many people remain on the diet, what side effects they experience, and what support they require in sticking to the diet. This will provide information that will help the team design a future clinical trial.

Who can participate?
Patients aged 18-70 years with bipolar disorder who have not have had any episodes of major depression, mania or hypomania in the preceding 3 months

What does the study involve?
Participants will follow the diet for 8 weeks, with an additional 2 weeks to stop it gradually (unless they chose to continue). They will have regular support from a dietitian and psychiatrist. They will have tests performed before starting the diet and after 8 weeks at a clinical research facility. These will include questionnaires relating to their mental health, general health, finances and education and employment. They will have physical measurements taken to include blood pressure, weight and height. Blood tests and brain imaging will be performed to look at specific markers which may change on the KD. This will help with understanding how the diet might work. Participants will also monitor their ketone and glucose levels and mood state daily whilst on the KD, and wear a wrist device to record sleep and activity throughout the 10-week study period.

What are the possible benefits and risks of participating?
Potential benefits to participants include learning more about their mental state over a period of time, as recorded in an app. They will also be able to better understand their sleep and activity pattern, as a summary of data from the actigraph device will be made available to them. For participants who are overweight, a potential benefit is weight loss, a well-known effect of

the ketogenic diet.
Possible risks to participants include discomfort from blood tests, or experiencing anxiety or claustrophobia when having an MRI brain scan. Following the ketogenic diet may be intrusive and impact on participants' quality of life as it will require a completely new set of dietary rules which may impact social situations. To help with this they will have regular support from a dietitian. There are potential side effects from commencing the ketogenic diet which commonly include fatigue, irritability, hunger and altered bowel habit. These are typically mild and can be managed with diet adjustments under the guidance of a dietitian.

Where is the study run from?
This study will be run from the clinical research facility at the Royal Infirmary of Edinburgh. It will be run by the University of Edinburgh with collaboration from NHS Lothian and the University of Glasgow (UK)

When is the study starting and how long is it expected to run for?
October 2021 to April 2023

Who is funding the study?
Baszucki Brain Research Fund (USA)

Who is the main contact?
Prof. Daniel Smith
d.smith@ed.ac.uk

Study website
https://www.bipolarketostudy.com/

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
306939

ClinicalTrials.gov number
Nil known

Secondary identifying numbers

Sponsor AC21156, IRAS 306939

Study information

Scientific Title
A pilot study of the ketogenic diet in bipolar disorder

Acronym
KETOBD

Study objectives
The researchers have described in detail a novel hypothesis on the mechanism by which hyperinsulinaemia disrupts the production of energy by mitochondria in the brain, resulting in increased levels of specific biomarkers, including lactate and pyruvate. Higher levels of these metabolites have been described in bipolar disorder (BD) compared to the general population and may be linked to mood instability. The ketogenic diet (KD) can provide an alternative energy source to glucose (ketones) that can bypass this abnormal processing of energy and allow for more stable levels of energy production.

This study aims to pilot the use of the KD in people with BD for 8 weeks. This will help us to understand the feasibility and acceptability of the different aspects of compliance and monitoring that will be required in a future trial. There is no specific hypothesis as this is a pilot study without a primary outcome. In a future trial, however, the researchers will hypothesise that the use of the KD in BD will result in an improvement in mental state and a reduction in the levels of certain metabolites measured through metabolomics and magnetic resonance (MR) spectroscopy.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 24/01/2022, South East Scotland Research Ethics Committee 02 (2nd Floor, Waverley Gate, 2-4 Waterloo Place, Edinburgh, EH1 3EG, UK; +44 (0)131 536 9000; sandra.wyllie@nhslothian.scot.nhs.uk), REC ref 22/SS/0007

Study design
Single-centre non-randomized interventional pilot study with no control arm

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Home

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Bipolar disorder

Interventions
All participants will be trialled on a low-carbohydrate, high-fat ketogenic diet for a period of 8 weeks, the first two of which will be an adaptation period. Support will be via dietary supervision to check adherence to prescribed diets, problem solve and identify any adverse effects, which will mainly occur over the phone or via email. Dietitians will provide guidance and practical support around establishing and characterising the diet, using recipe cards and planning, dietary booklets and providing advice on common problems.

Prior to commencing the ketogenic diet, participants will be required to attend initial baseline assessments, including mental health and health economics questionnaires, physical parameters (height, weight, blood pressure), blood tests (for biochemistry and metabolomics) and an MRI brain scan. They will also be taught how to measure their ketone and glucose measurements and monitor their mood on a daily basis and be provided with an actigraph device to wear throughout the study.

Intervention Type
Behavioural

Primary outcome measure
The feasibility and acceptability of the ketogenic diet as an intervention for bipolar disorder for a future trial. Data will be collected on a range of parameters to understand how to make all aspects of the study workable for a subsequent trial:
1. Timeline estimates for future trial recruitment by measuring the number of interested participants and fully recruited participants from each avenue of recruitment during the estimated 4-month recruitment period
2. Participant level of compliance with dietary interventions measured using fidelity checklists at weeks 0, 2, 4, 6, and 8, and daily ketone measurements during the 8-week intervention period
3. Participant level of compliance with study assessments as recorded on the case report form at baseline and week 8
4. Participant level of compliance with continuous study assessments measured using data from the study devices and apps (actigraph device, ketomojo device and app, and ilumivu app) during the 10-week study period
5. Quality of life measured using the EQ5D-5L at baseline and week 8
6. Productivity and activity impairment measured using the Work Productivity and Activity Impairment Questionnaire at baseline and week 8
7. Participant resource use measured using a Within Trial Resource Use Questionnaire at baseline and week 8
8. Staff time and cost in delivering dietary interventions, measured by keeping contemporaneous records throughout the 10-week study period
9. Attrition rate measured using the number of participants who consent to participate who remain in the study until the end of follow-up at 10 weeks, to help inform estimation of sample size for a future trial
10. Acceptability and experience of the study participants evaluated via telephone interviews after the main study has ended as part of a process evaluation

Secondary outcome measures
1. Mood stability measured by the Affective Lability Scale (ALS18) and Beck Depression Inventory (BDI) at baseline and at 8-week follow-up
2. Hypomania/mania symptoms measured using the Young Mania Rating Scale (YMRS) at baseline and 8-week follow up
3. Glucose/ketone ratio measured using ketomojo devices daily throughout the 10 week study period
4. Identification of specific metabolic changes in glucose, ketones and tricarboxylic acid (TCA) metabolites associated with the KD that are predicted by the study hypothesis, measured using serum and brain MRI measures at baseline and week 8
5. Mood, energy, speed of thought, impulsivity and anxiety measured using visual analogue scales from 1-100 at daily ecological momentary assessments during the 10-week study period
6. Episodes of bipolar depression and hypomania/mania occurring during the study period assessed by the MINI Neuropsychiatric assessment at baseline and week 8
7. Sleep duration and circadian activity/rest rhythmicity parameters assessed by actigraphs throughout the 10-week period (to include 2 weeks of stepping down the diet)

Overall study start date
01/10/2021

Completion date
08/04/2023

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 29/04/2022:
1. Meet the Diagnostic and Statistical Manual of Mental Disorders (DSM-4) diagnostic criteria for bipolar disorder for at least 1 year, assessed using the MINI Neuropsychiatric Interview
2. Clinically stable and currently euthymic, defined as 3 months with no major mood episodes (major depression lasting at least 2 weeks or hypomania/mania lasting at least 1 week), assessed using the MINI Neuropsychiatric Interview
3. Aged 18 to 70 years
4. Able to provide informed consent to take part in the study
5. Able to speak, read and understand English to a level whereby they can understand the participant information sheet (PIS)
6. Currently living in Scotland

Previous participant inclusion criteria:
1. Meet the Diagnostic and Statistical Manual of Mental Disorders (DSM-4) diagnostic criteria for bipolar disorder for at least 1 year, assessed using the MINI Neuropsychiatric Interview
2. Clinically stable and currently euthymic, defined as 3 months with no major mood episodes (major depression lasting at least 2 weeks or hypomania/mania lasting at least 1 week), assessed using the MINI Neuropsychiatric Interview
3. Aged 18 to 70 years
4. Able to provide informed consent to take part in the study
5. Able to speak, read and understand English to a level whereby they can understand the participant information sheet (PIS)

Participant type(s)

Patient

Age group
Mixed

Sex
Both

Target number of participants
25

Total final enrolment
27

Key exclusion criteria
Current participant exclusion criteria as of 29/04/2022:
1. Pregnancy or breastfeeding (or those planning to become pregnant within 3 months)
2. Active substance misuse with alcohol or illicit drugs
3. Use of the ketogenic diet in the previous 2 months
4. Currently following a vegan diet
5. Admission to hospital within the past 3 months
6. Current involvement in another research study
7. Inability to complete baseline assessments
8. Liver or kidney disease
9. Cardiovascular disease
10. Severe hyperlipidaemia
11. Type 1 diabetes
12. Insulin dependent type 2 diabetes
13. Currently training for or undertaking very high energy requirement activities (as judged by the study dietitian)

Previous participant exclusion criteria:
1. Pregnancy or breastfeeding (or those planning to become pregnant within 3 months)
2. Active substance misuse with alcohol or illicit drugs
3. Use of the ketogenic diet in the previous 2 months
4. Currently following a vegan diet
5. Admission to hospital within the past 3 months
6. Current involvement in another research study
7. Inability to complete baseline assessments
8. Liver or kidney disease
9. Cardiovascular disease
10. Severe hyperlipidaemia
11. Type 1 diabetes

Date of first enrolment
27/04/2022

Date of final enrolment
28/10/2022

Locations

Countries of recruitment
Scotland

United Kingdom

Study participating centre
NHS Lothian
Waverley Gate
2-4 Waterloo Place
Edinburgh
United Kingdom
EH1 3EG

Study participating centre
University of Edinburgh
Old College
South Bridge
Edinburgh
United Kingdom
EH8 9YL

Study participating centre
University of Glasgow
University Avenue
Glasgow
United Kingdom
G12 8QQ

Sponsor information

Organisation
University of Edinburgh

Sponsor details
The Queen's Medical Research Institute
47 Little France Crescent
Edinburgh
Scotland
United Kingdom

EH16 4TJ
+44 (0)1312423326
resgov@accord.scot

Sponsor type
University/education

Website
http://www.ed.ac.uk/home

ROR
https://ror.org/01nrxwf90

Organisation
NHS Lothian

Sponsor details
The Queen's Medical Research Institute,
47 Little France Crescent
Edinburgh
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United Kingdom
EH16 4TJ
+44 (0)1312423325
accord@nhslothian.scot.nhs.uk

Sponsor type
Hospital/treatment centre

Website
http://www.nhslothian.scot.nhs.uk/Pages/default.aspx

ROR
https://ror.org/03q82t418

Funder(s)

Funder type
Research organisation

Funder Name
Baszucki Brain Research Fund

Results and Publications

Publication and dissemination plan

The researchers will communicate findings to academic, policy, patient and public audiences via diverse channels, including peer-reviewed scientific journals, conference presentation and publication on the trial website. The researchers will publish study protocols and results. They will ensure there is dissemination of findings to patients via patient organisations and professional groups and explore with them the opportunity for translation of findings.

Participants will be sent a patient-friendly report of the main findings/results from the study by post, once the results have been analysed. Additionally, the researchers will provide feedback sessions to Bipolar Scotland groups in an easily understandable format. A lay summary of the study results will be posted on the study website.

Intention to publish date

01/12/2023

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are not expected to be made available due to the small sample size and this being a pilot study with no primary outcome.

IPD sharing plan summary

Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 3	18/02/2022	29/04/2022	No	Yes
Participant information sheet	version 1	14/04/2022	29/04/2022	No	Yes
Protocol file	version 4	14/04/2022	29/04/2022	No	No
Protocol file	version 7	10/11/2022	26/05/2023	No	No
Preprint results		03/06/2023	05/06/2023	No	No
HRA research summary			20/09/2023	No	No
Results article		10/10/2023	11/10/2023	Yes	No
Other publications	Process evaluation	21/01/2025	27/01/2025	Yes	No