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Comparison of a ketogenic diet and NHS healthy eating guidance for bipolar depression: a randomised controlled trial

Submission date
20/07/2026

Recruitment status
Not yet recruiting

Registration date
03/08/2026

Overall study status
Ongoing

Last Edited
30/07/2026

Condition category
Mental and Behavioural Disorders

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Bipolar disorder is a mental health condition which causes repeated episodes of low and high mood. Many people with bipolar disorder also experience long-lasting symptoms of depression, which can significantly affect everyday life. The current understanding of how bipolar disorder develops remains unclear, and treatments for the depressive symptoms are not always effective and often have unwanted side effects. Some evidence suggests that changes in diet might help treat depressive symptoms in bipolar disorder, so we are doing this study to investigate this further.
We think certain diets could reduce feelings of depression, and want to know if this is something doctors should recommend in the future.

Who can participate?
Male and female adults (18+ years old) with a diagnosis of bipolar disorder and are currently experiencing bipolar depression.

What does the study involve?
We want to compare the NHS EatWell Guide to nutritional ketosis. The NHS EatWell Guide recommends eating a variety of foods for a balanced diet. Nutritional ketosis is achieved by following a 'keto' diet, which is high in fat and very low in carbohydrates, allowing the body to switch to burning fat for energy.
In this study, one group of people follow the nutritional ketosis plan for 12 weeks and the other group follow the NHS EatWell Guide for 12 weeks.
• There is an equal chance of going into each group. We aim to recruit 206 people in total (103 people in each group).
• Participants will know which group they go into.
• We will study how each group gets on to see which one is the most effective as a treatment for bipolar depression.
• We will take the following measurements:
• Height, weight and blood pressure
• Blood glucose/ketones

• Blood sample to assess different markers of physical health
• Urine test to check if pregnant (if relevant)
• A series of questionnaires, which will ask about the participants mental health and physical health
• Some of the participants in the study who are based in Edinburgh will undergo a Magnetic Resonance Spectroscopy scan of the brain.

What are the possible benefits and risks of participating?
Potential benefits of taking part in this study include:
• Learning more about your mental health and mood over the time you spend in the study, and how they relate to changes in your diet.
• Education and advice on a dietary intervention from a qualified dietitian.
• The results from this study may help us to improve treatments for people with bipolar depression in the future, and your participation could make a meaningful impact on this important area of research.
• We will reimburse participants for their time and travel expenses.
The disadvantages are that participants may find the study time-consuming, as it will last 24 weeks and require you to attend 3 to 4 face-to-face appointments depending on whether they are one of the participants who will undergo brain scans (Magnetic Resonance Spectroscopy). Appointments will include questionnaires which may take some time and ask sensitive questions about the participants personal and mental health history, which some participants may find upsetting.
Dietary changes may cause side effects including stomach upset, nausea, vomiting, changes in bowel habits (particularly constipation), hunger, thirst, tiredness, irritability, weight loss, low blood sugar (hypoglycaemia), high levels of fat in the blood (hyperlipidaemia), high levels of ketones in the blood, leg cramps, or irregular periods in women. As nutritional ketosis involves eating a high proportion of fat, it may increase levels of fat in the blood (cholesterol and triglycerides).
Blood tests may be uncomfortable or upsetting, and they may cause small bruises.
There is a small chance that blood tests or brain scans might find unexpected abnormalities.
A minority of people find Magnetic Resonance Spectroscopy brain scans anxiety-provoking and may experience a fear of small spaces (claustrophobia) during the scans.

Where is the study run from?
The University of Edinburgh and NHS Lothian (UK)

When is the study starting and how long is it expected to run for?
October 2026 to July 2030

Who is funding the study?
Wellcome Trust (UK)

Who is the main contact?
Lorna Dewar
energise-bd.trial@ed.ac.uk

Contact information

Type(s)
Principal investigator, Scientific

Contact name
Prof Daniel Smith

ORCID ID
https://orcid.org/0000-0002-2267-1951

Contact details
The Royal Infirmary of Edinburgh
51 Little France Crescent
Old Dalkeith Road
Edinburgh
Edinburgh
United Kingdom
EH16 4SA
+44 7734463270
d.smith@ed.ac.uk

Type(s)
Principal investigator, Scientific

Contact name
Prof Steven Marwaha

ORCID ID
https://orcid.org/0000-0002-0303-9942

Contact details
Birmingham and Solihull Mental NHS Foundation Trust
Birmingham
United Kingdom
B13 8QY
-
s.marwaha@bham.ac.uk

Type(s)
Public

Contact name
Miss Lorna Dewar

ORCID ID
https://orcid.org/0009-0009-7260-4165

Contact details
ECTU, Usher Building The University of Edinburgh Edinburgh BioQuarter 5-7 Little France Road
Edinburgh
United Kingdom
EH16 4UX
-
energise-bd.trial@ed.ac.uk

Type(s)
Scientific

Contact name
Prof Rebecca Reynolds

ORCID ID
https://orcid.org/0000-0001-6226-8270

Contact details
The Royal Infirmary of Edinburgh
51 Little France Crescent
Old Dalkeith Road
Edinburgh
Edinburgh
United Kingdom
EH16 4SA
-
r.reynolds@ed.ac.uk

Additional identifiers

Integrated Research Application System (IRAS)
370428

Study information

Scientific Title
Evaluating nutritional ketosis versus NHS Eatwell guide for bipolar depression: single blind randomised controlled trial

Acronym
ENERGISE-BD

Study objectives
To determine the efficacy of nutritional ketosis in comparison to the NHS EatWell guide (9) for the treatment of bipolar depression.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 08/06/2026, East Midlands – Leicester South Research Ethics Committee (Health Research Authority 3 Piccadilly Place London Road Manchester, Manchester, M1 3BN, United Kingdom; +44 207 104 8193; chris.kitchen@hra.nhs.uk), ref: 26/EM/0140

Primary study design
Interventional

Allocation

Randomized controlled trial

Masking
Blinded (masking used)

Control
Active

Assignment
Parallel

Purpose
Treatment

Study type(s)

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

Interventions
ENERGISE-BD is a single blind randomised controlled trial of nutritional ketosis versus the NHS EatWell guide for the treatment of bipolar depression.

Participants will be randomised in a 1:1 ratio to either the nutritional ketosis intervention or the NHS EatWell Guide control group using a secure online randomisation system designed and managed by the Edinburgh Clinical Trials Unit (ECTU).

Nutritional ketosis intervention: Participants will follow a modified ketogenic diet for 12 weeks, providing approximately 60–75% of estimated energy requirements from fat, 5–7% from carbohydrates, with the remaining energy provided by protein. For the first two weeks pre-prepared meals will provide the required daily calorie and macronutrient composition and will be tailored to individual dietary requirements.

NHS EatWell Guide control: Participants will follow a diet based on the NHS EatWell Guide for 12 weeks, which promotes a healthy, balanced diet comprising fruit and vegetables, starchy carbohydrates, lean sources of protein, dairy or suitable alternatives, and healthy fats, with smaller amounts of foods high in fat, salt and sugar.

The allocated dietary intervention will last for 12 weeks. Participants will attend in-person study visits at baseline, 6 weeks and 12 weeks. During the 12-week intervention, participants in both groups will have weekly remote contact with a study dietitian to provide dietary support and monitor adherence to their allocated diet. At the end of the 12-week intervention, participants will be supported during a 2-week phase-out from their allocated diet. A final follow-up appointment will be conducted remotely at 24 weeks.

Brain imaging substudy: At the Edinburgh site, approximately 72 eligible participants without contraindications to magnetic resonance (MR) scanning (approximately 36 from each treatment arm) will undergo 1-hour 3T MR scans at baseline, 6 weeks and 12 weeks. Imaging will include anatomical brain imaging for the detection of incidental pathology and positioning of magnetic resonance spectroscopy (MRS) volumes of interest.

Intervention Type
Other

Primary outcome(s)
1. Depressive symptoms measured using Patient Health Questionnaire (PHQ-9) score of 6 or more at baseline and 12 week post randomisation

Key secondary outcome(s)
1. Severity of depression symptoms measured using the Patient Health Questionnaire-9 (PHQ-9) at baseline, 12 weeks and 24 weeks post randomisation
2. Anxiety symptoms measured using the Generalised Anxiety Disorder Questionnaire (GAD-7) at baseline, 12 weeks and 24 weeks post randomisation
3. Mania symptoms measured using the Altman Self-Rating Mania Scale (ASRM) at baseline, 12 weeks and 24 weeks post randomisation
4. Health-related quality of life measured using the EuroQol EQ-5D-5L at baseline, 12 weeks and 24 weeks post randomisation
5. Functional impairment measured using the Functioning Assessment Short Test (FAST) at baseline, 12 weeks and 24 weeks post randomisation
6. Concurrent medication use (psychiatric and other medications) measured using study-recorded medication data at baseline, 12 weeks and 24 weeks post randomisation
7. Continuation of allocated diet intervention measured using study-recorded intervention adherence data at baseline, 12 weeks and 24 weeks post randomisation
8. Feasibility of collecting health economic resource use consequences and associated costs of a nutritional ketosis intervention compared to the NHS EatWell Guide for bipolar depression measured using a bespoke health economic resource use questionnaire at 12 weeks and 24 weeks post randomisation
9. Body mass index (BMI) measured using BMI calculated from measured height and weight at baseline and 12 weeks post randomisation
10. Weight change from baseline (percentage) measured using percentage change in body weight calculated from measured weight at baseline and 12 weeks post randomisation
11. Blood pressure (BP) measured using blood pressure measurement at baseline and 12 weeks post randomisation
12. Glycated haemoglobin (HbA1c) measured using an HbA1c blood test at baseline and 12 weeks post randomisation
13. Insulin resistance (C-peptide and glucose) measured using blood tests for C-peptide and glucose at baseline and 12 weeks post randomisation
14. Lipid profile (total cholesterol, triglycerides, cholesterol/HDL ratio and non-HDL cholesterol) measured using a lipid profile blood test at baseline and 12 weeks post randomisation
15. Renal function (urea and electrolytes [U&Es]) measured using a urea and electrolytes blood test at baseline and 12 weeks post randomisation
16. Liver function measured using liver function tests (LFTs) at baseline and 12 weeks post randomisation
17. Plasma lactate measured using a plasma lactate blood test at baseline and 12 weeks post randomisation
18. Blood ketone levels measured using a KetoMojo device daily from baseline to 12 weeks post randomisation
19. Blood glucose levels measured using a KetoMojo device daily from baseline to 12 weeks post randomisation
20. Magnetic Resonance Spectroscopy (MRS) markers of brain energetics: Estimated molal tissue

concentration of glutamate plus glutamine (Glx), and lactate (Lac), phosphocreatine/ATP signal ratio and intracellular pH measured using Magnetic Resonance Spectroscopy (MRS) assessments of brain metabolites at baseline, 6 weeks and 12 weeks post randomisation

Completion date
01/07/2030

Eligibility

Key inclusion criteria
1. Adults (aged 18 and over) with a primary* diagnosis of bipolar disorder (BD-I or BD-II), confirmed by the Structured Clinical Interview for DSM5 (Diagnostic and Statistical Manual of Mental Disorders, fifth edition), (SCID5)
2. Bipolar depression symptoms of at least moderate clinical severity on the PHQ-9 (defined as a score of 10 or above)
*Other comorbid psychiatric diagnoses are permitted (apart from eating disorders and substance misuse/dependence)

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
100 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Currently in need of acute inpatient, crisis resolution, or home treatment services
2. Does not have capacity to consent
3. Previous use of nutritional ketosis within 2 months
4. Current use of weight loss medications (such as semaglutide or tirzepatide)
5. Inability to complete mandatory study assessments
6. No access to a smartphone and/or unwilling to add the KetoMojo app to their smartphone
7. Specific contraindications for the nutritional ketosis intervention:
7.1. Pregnancy, breastfeeding, or planning to become pregnant within 3 months
7.2. Liver failure
7.3. Pancreatitis (acute and past history)
7.4. Chronic kidney disease
7.5. Type I diabetes
7.6. Use of SGLT-2 inhibitors

7.7. Recent stroke or myocardial infarction
7.8. Heart failure
7.9. Cardiac arrhythmias
7.10. Respiratory failure
7.11. Active infections
7.12. Cancer
7.13. Hyperuricaemia
7.14. Severe hyperlipidaemia (familial hypercholesterolaemia, severe hypertriglyceridaemia, or total cholesterol >7.5 mmol/L)
7.15. Participant-reported inborn error of metabolism affecting fatty acid transport/oxidation, including organic acidurias and mitochondrial fatty acid beta-oxidation disorders
8. Past history of an eating disorder (bulimia or anorexia)
9. Currently only eating a vegan or exclusively plant-based diet
10. Other major primary psychiatric disorder that is not bipolar disorder, or major neurological disorders
11. Harmful current use of or dependence on psychoactive substances (including alcohol)
12. Currently enrolled in an interventional research study

Date of first enrolment
01/10/2026

Date of final enrolment
01/12/2029

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Royal Infirmary of Edinburgh at Little France
51 Little France Crescent
Old Dalkeith Road
Edinburgh
Lothian
Scotland
EH16 4SA

Study participating centre
Birmingham and Solihull Mental Health NHS Foundation Trust
The Uffculme Centre
52 Queensbridge Road
Moseley

Birmingham
England
B13 8QY

Sponsor information

Organisation
University of Edinburgh and NHS Lothian

Funder(s)

Funder type

Funder Name
Wellcome

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publicly available repository: Edinburgh DataShare.

Following publication of the primary study results, anticipated approximately 9–12 months after the end of the project, de-identified participant-level data, together with relevant supporting metadata and documentation, will be made available via Edinburgh DataShare for secondary research purposes. Data will remain available in accordance with the repository’s preservation and access policies.

Imaging data, including images and spectra, are potentially re-identifiable and will therefore be stored securely on University of Edinburgh servers rather than in a publicly accessible repository. Requests to access these data, or for other data-sharing activities not specified in the protocol, will be reviewed in accordance with ECTU data-sharing procedures.

Access will be subject to participant consent and applicable ethical, legal and information governance requirements. Requests will be assessed according to factors including the proposed purpose and scientific merit, suitability of the requester, data requested and risk of re-identification. Where approved, the minimum necessary data will be shared in the least identifiable form using an appropriately secure mechanism and subject to any required agreements.

IPD sharing plan summary

Stored in publicly available repository