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Evaluating the efficacy and mechanisms of a ketogenic diet as adjunctive treatment for people with treatment-resistant depression: A protocol for a randomised controlled trial

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ABSTRACT

Background: One-third of people with depression do not respond to antidepressants, and, after two adequate courses of antidepressants, are classified as having treatment-resistant depression (TRD). Some case reports suggest that ketogenic diets (KDs) may improve some mental illnesses, and preclinical data indicate that KDs can influence brain reward signalling, anhedonia, cortisol, and gut microbiome which are associated with depression. To date, no trials have examined the clinical effect of a KD on TRD.

Methods: This is a proof-of-concept randomised controlled trial to investigate the efficacy of a six-week programme of weekly dietitian counselling plus provision of KD meals, compared with an intervention involving similar dietetic contact time and promoting a healthy diet with increased vegetable consumption and reduction in saturated fat, plus food vouchers to purchase healthier items. At 12 weeks we will assess whether participants have continued to follow the assigned diet. The primary outcome is the difference between groups in the change in Patient Health Questionnaire-9 (PHQ-9) score from baseline to 6 weeks. PHQ-9 will be measured at weeks 2, 4, 6 and 12. The secondary outcomes are the differences between groups in the change in remission of depression, change in anxiety score, functioning ability, quality of life, cognitive performance, reward sensitivity, and anhedonia from baseline to 6 and 12 weeks. We will also assess whether changes in reward sensitivity, anhedonia, cortisol awakening response and gut microbiome may explain any changes in depression severity.

Discussion: This study will test whether a ketogenic diet is an effective intervention to reduce the severity of depression, anxiety and improve quality of life and functioning ability for people with treatment-resistant depression.

1. Introduction

Globally, an estimated 5% of adults suffer from depression (Organization, 2023). Antidepressants, which influence neurotransmitters, are first-line treatments for depression. However, at least 1 in 3 patients with depression do not respond to antidepressants, and not everyone responds to or wants psychological therapy (Rush et al., 2006). Furthermore, there is a high relapse rate after psychological treatment (Ali et al., 2017). Depression reduces life expectancy by seven to ten years compared to the general population, (Chesney et al., 2014) and mortality is higher in people with more severe depression, and especially in people with treatment-resistant depression (TRD) (McIntyre et al.,

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2023). TRD is common, and, in practice, many people take long-term antidepressants that are only very partially effective (Johnson et al., 2012). Therefore, new treatment options for TRD are needed.

Case reports suggest that ketogenic diets (KDs) may improve some mental illnesses (Dietch et al., 2023). A KD is characterised by high-fat and very low-carbohydrate intake, and has been successfully used to treat refractory epilepsy and metabolic disorders that commonly co-occur with depression (Keezer et al., 2016; Martin et al., 2016). KDs lead to the production of ketone bodies from fatty acids; ketones serve as an alternative energy source to maintain normal brain cell metabolism. In fact, ketones may be an even more efficient fuel than glucose, providing more energy per unit oxygen used (Cunnane et al., 2022). By providing an alternative energy source, ketone bodies reduce glucose consumption in the brain and this can modulate the activities of neurotransmitters (García-Rodríguez and Giménez-Cassina, 2021). KDs have been associated with changes in different monoamines, including dopamine, noradrenaline and serotonin (Żarnowski et al., 2012).

In humans, GABA neurons transmit inhibitory signals, while glutamate neurones transmit excitatory signals, and together these signals maintain brain activity at optimal levels. Evidence indicates that depression may relate to the imbalance between excitatory (e.g. glutamatergic system) and inhibitory (e.g. GABA system) systems (Page and Coutellier, 2019). Some evidence reported that GABAergic neurotransmission is disrupted in depression and concentrations of GABA are significantly reduced, especially in TRD (Duman et al., 2019). KDs increase production of the inhibitory neurotransmitter GABA, and restore microglial activation and neuronal excitability in the lateral habenula, a region involved in negative reward processing (Düking et al., 2022; Guan et al., 2020; Yudkoff et al., 2005).

The mechanisms of action of KD may go beyond regulating neurotransmitters. Preclinical data suggest several other potential mechanisms of action in people with depression (Brietzke et al., 2018; Neves et al., 2021). First, KDs enhance cellular bioenergetics, reduce oxidative stress, and promote vascular brain changes (Fattal et al., 2006; Puchowicz et al., 2007; Yarar-Fisher et al., 2021). The major ketone metabolite (beta-hydroxybutyric acid) influences mitochondrial function and renders it more resilient to oxidative stress by increasing glutathione levels, a known antioxidant, reducing the production of reactive oxygen species and thereby improving mitochondrial respiration (Jarrett et al., 2008). It has been suggested that abnormalities in mitochondrial function could be responsible for impairments in neuroplasticity, synaptic function and changes in brain structure and function, which could underpin behavioural manifestations of major depression. It is thought that some antidepressants and mood stabilizers, at least partially, revert these abnormalities (Villa et al., 2017). Second, KDs influence the hypothalamic-pituitary (HPA) axis. The HPA axis is a neuroendocrine system involved in maintaining homeostasis in humans under physiological conditions and stress, and cortisol is the main hormone of the HPA axis. Cortisol secretion is often abnormal in depression, with excessive cortisol being secreted after the normal morning rise in cortisol secretion (Dziurkowska and Wesolowski, 2021). In addition, the normal morning rise in cortisol, but not evening, is elevated in depression (Zajkowska et al., 2022). There is also evidence that carbohydrate restriction in the KD diet can lower cortisol levels, as carbohydrates stimulate adrenal cortisol secretion and extra-adrenal cortisol regeneration (Guarnotta et al., 2022). A KD can lower ghrelin concentrations, a peptide produced in the stomach that has orexigenic properties (Ebbeling et al., 2018). Literature shows that ghrelin increases levels of serum cortisol and may influence cortisol secretion through this mechanism (Kärkkäinen et al., 2021). Third, KDs may change the gut microbiome. Preliminary evidence suggests that gut microbes modulate brain function, particularly in relation to mood disorders. Studies in rodents have shown that a KD reduced alpha-diversity (number of different species) of intestinal microbes but increased the abundance of Akkermancia muciniphila, a known short-chain fatty acid producer, which is associated with improved metabolic health (Attaye et al., 2021). Moreover, KDs may also improve cognition. Cognitive dysfunction represents a core diagnostic and symptomatic criterion of major depression. KDs protect the brain from oxidative stress by lowering the production of reactive oxygen species (ROS) where ROS has been suggested to be one of the major hallmarks of the aging process (Bough et al., 2006; Hallböök et al., 2012). Consequently, we plan to examine the potential mechanisms of reward sensitivity, the ability to experience pleasure (i.e. anhedonia), cortisol level, gut microbiome on the associations between KDs and changes in depression.

Despite these plausible effects and potential mechanisms of action, the evidence that KDs improve mental illnesses is limited. A 2023 systematic review of the treatment effects of KD for mood and anxiety disorders identified 12 studies examining 388 participants (9 case reports, 2 cohort studies, and 1 observational study). It reported that people with mental disorders often improved on KDs, but causality is impossible to establish with these designs (Dietch et al., 2023). Controlled clinical trials are required to investigate whether a KD is efficacious in TRD, but none are examining the efficacy of KD for TRD.

Controlled trials of dietary treatment in depression are problematic because of the placebo response. A meta-analysis of 252 trials reported that 35–40% of patients randomised to placebo are classified as responders, (Furukawa et al., 2016) meaning baseline depression scores improve by at least half. A meta-analysis of trials in TRD showed similar size large improvements in people treated with placebo (Jones et al., 2021). This could occur for at least three reasons. First, trials require participants to have a questionnaire score above threshold and regression to the mean will lead to apparent improvement. Second, depression sometimes remits without treatment. Finally, placebo responses may cause the improvement. A meta-analysis showed that patients randomised to waiting list control conditions improved while waiting, (Rutherford et al., 2012) and a further meta-analysis reported that compared with waiting for treatment, people randomised to placebo improved to a greater extent, (Fernández-López et al., 2022) suggesting that people with depression have a true placebo response. We aim to assess the efficacy of adding KDs to conventional antidepressant medication for treating symptoms of depression compared to a '*placebo*' intervention with similar intensity of dietetic support that aims to promote a healthy diet through increases in vegetable consumption and reduction in saturated fat intake. By creating a credible placebo we aim to reduce bias and to isolate the effect of a KD from that of increased contact with a therapist and a novel intervention. In addition to the primary outcome – change in depression severity, we aim to examine the impact on other outcomes that are important to patients (Alma et al., 2020).

2. Methods and analysis

2.1. Design

The study is a parallel-group, randomised, proof-of-concept trial to test whether a six-week KD is an effective treatment for treatment-resistant depression with a primary outcome at six weeks. On completion of baseline assessments, participants will be randomised 1:1 into a placebo intervention diet or a KD diet. Usual treatment for depression will continue. Participants will be followed for 12 weeks, as shown in Fig. 1.

2.2. Recruitment

The study will be advertised to the public via: 1) online social media platforms through advertisements created in collaboration with our industrial partner (Nativve Health Research: https://www.healthresearch.study/). The social media advertisements will link directly to a Nativve Health Research landing page (https://www.healthresearch.study/participate/DIME/), where eligible participants will be presented with an electronic participant information sheet (ePIS); 2) public

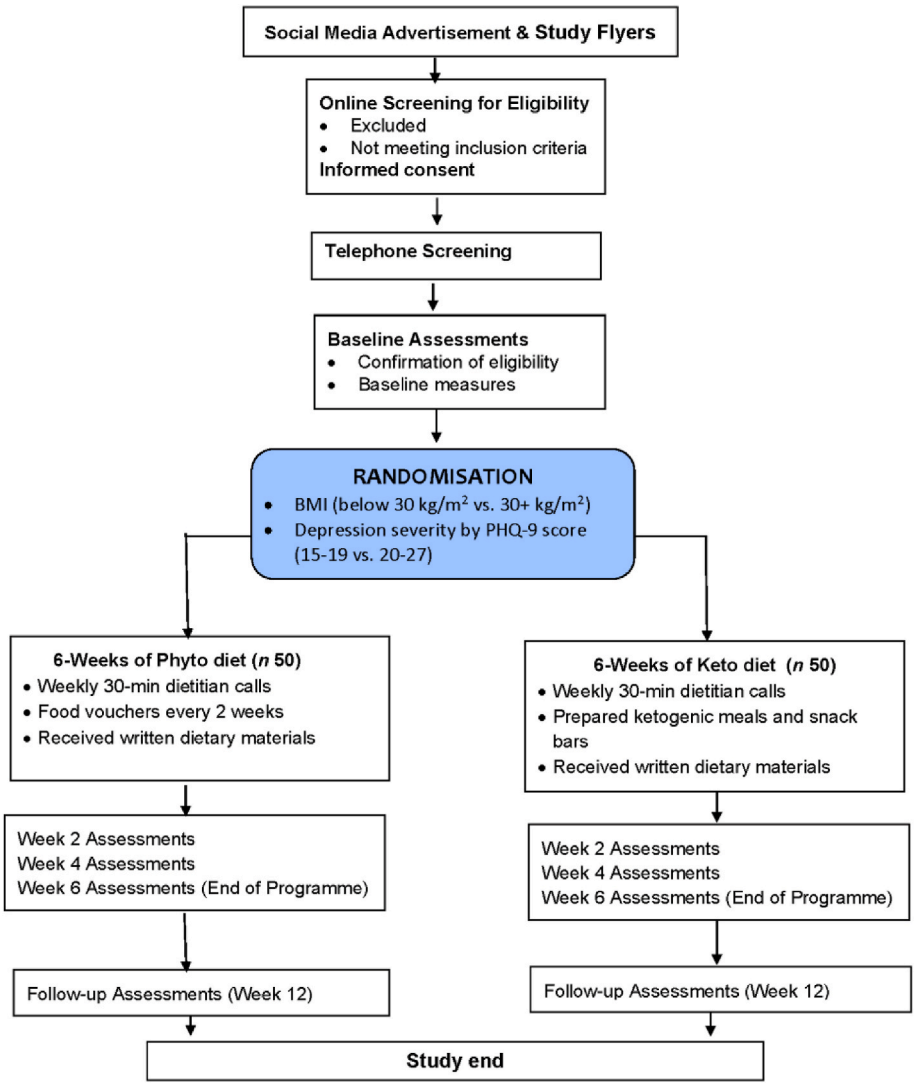

Fig. 1. Participant flow through the study.

advertisements placed in pharmacies, community centres, and other community venues. The public advertisements include a printed Nativve Health Research landing page with a QR code that can be linked to the electronic Nativve Health Research landing page.

2.3. Eligibility

Eligible participants will be adults aged 18–65 years with depression, who have been treated with at least two antidepressants in the current episode but still have moderate severity depression (≥15) as assessed by PHQ-9. The detailed inclusion and exclusion criteria are summarised in Table 1.

Eligibility will be assessed by a two-step consent process. In step 1, interested people will need to complete an online screening form to assess eligibility. In step 2, a researcher will conduct a telephone assessment to further evaluate: a) the nature of their usual diet (if applicable); b) the names, duration, and doses of antidepressants that they have been taking; c) other medical conditions diagnosed by a doctor; d) the presence of symptoms of psychosis, and e) suicide risk. The detailed information on step 2 and further assistance and monitoring suicide are in the Appendix.

2.4. Intervention group (keto diet)

We will advise participants to follow a modified KD (i.e. approximately <30 g carbohydrates per day and a moderate protein intake 15–20% energy intake) without energy restriction (Martin-McGill et al., 2019). To support adherence, we will offer participants pre-prepared KD meals (3 meals per day) and snacks from industry partners. We ask participants to test for ketosis in their morning urine at least twice a week so we can work with the participant to increase adherence if necessary. A registered dietitian will provide weekly nutritional counselling sessions, lasting up to 30 min. The dietitian will schedule appointments and assess the participant's experience with adhering to the KD diet, troubleshoot as required, give guidance on how to prevent or overcome side effects of KD diets, and keep a record of nutritional information of prepared meals and the participant's urinary ketosis level. The dietitian will also provide written information about foods that are compatible and not compatible with the diet, as well as common problems and how to overcome them. For patients who wish to stop the offered meals and have their own KD meals, we will provide written resources to support meal preparation and help them identify suitable snacks.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	
1.	Aged 18–65 years
2.	Diagnosed with depression
3.	Taken two antidepressants for at least four weeks each.
4.	PHQ-9 total score greater than or equal to 15 at baseline
5.	Able to understand and be willing to adhere to the study protocol
6.	Provision of written informed consent
7.	Have access to a tablet/computer for online assessments, follow-ups with the registered dietitian, and able to attend appointments for assessments and treatment and adhere to study procedures
8.	Have both a fridge and a freezer at home
Exclusion criteria	
9.	Currently following a low carbohydrate or ketogenic diet
10.	Currently following a diet (e.g. vegan or vegetarian) as these diets are more challenging to accommodate in a KD and adding vegetables in the control group is unlikely to be seen as helpful.
11.	Currently receiving, or have received, in-patient psychiatric treatment or electroconvulsive therapy (electric shock to the brain under brief general anaesthetic) within the past year, or scheduled to receive such treatment during the study
12.	Currently using St John's wort or other remedies for depression that were bought without a doctor's prescription
13.	Currently have suicidal ideation with intent or attempted suicide within the past two months
14.	Ever had an eating disorder, bipolar disorder, schizophrenia, or psychosis
15.	Have substance use or alcohol dependence
16.	Have epilepsy
17.	Have serious food allergies (experiencing food hypersensitivity that leads to anaphylaxis or other severe symptoms, which may require hospitalisation or are life-threatening) or otherwise require a special diet that cannot be accommodated within a KD such as phenylketonuria or lactose intolerance
18.	Treated with insulin, sulfonylureas, GLP-1 analogues, or SGLT2 inhibitors
19.	Women who are pregnant, planning pregnancy in the next three months, or breastfeeding
20.	Have a body mass index (BMI) of <18.5 kg/m2
21.	Have unstable or severe medical conditions that compromise the ability to follow the protocol or lead to marked deterioration in health state (e.g., cancer, cardiovascular, renal, lung, psychiatric, or bleeding disorders, diabetes, etc., currently receiving cancer treatment except hormonal treatment for breast cancer or non-melanoma skin cancer treatment)
22.	Have gallstones, renal tubular acidosis, kidney stones, small bowel malabsorption or a history of pancreatitis
23.	Have scheduled a major surgery in the next 3 months
24.	Taking part in other studies that may compromise this study or this study may compromise the other study/ies
25.	Have read the trial protocol or the clinical trial registration information and therefore are unblinded
26.	Live in the same household as another participant in the trial

2.5. Control group (phyto diet)

Participants in the control group will receive the same frequency and intensity of dietetic support and will be guided towards a healthier eating pattern, aiming to increase vegetable consumption and swap from saturated to unsaturated fat (i.e. from animal sources to plant sources). The novelty of the intervention is reinforced by the name (Phyto diet, meaning plant-based) with an emphasis on adding new vegetables of different colours to increase the range of phytonutrients in the diet. Likewise unsaturated fats such as olive oil are rich in Vitamin E and phytonutrients associated with general good health. Participants in the control group will receive food vouchers (£20 every two weeks) to help purchase these items. This aims to be a plausible placebo dietary treatment for depression. The dietitian will create written materials to explain the diet and suggest foods by colour with supporting recipe suggestions. There is no evidence that these manipulations will change the primary or secondary outcomes, but they may reduce cardiovascular risk and are therefore of some clinical value to the patient.

2.6. Assignment of intervention

After the baseline assessment is complete, participants will be allocated 1:1 to the KD group or control group. A non-deterministic minimisation algorithm will be used to produce treatment groups balanced for prognostic factors by minimising on (1) BMI (less than 30 kg/m^2 vs. 30+ kg/m^2), (2) depression severity (PHQ-9 score: 15–19 [moderately severe] vs. 20–27 [severe]). Allocation will be through a computer programme and concealed from trial staff until after consent and eligibility are confirmed.

All follow-ups will be remote, without trial staff, and will therefore be unbiased by staff knowledge of allocation. Following randomisation, participants will be given instructions for their respective group and a plausible reason to believe in the diet that they have been asked to follow to equalise expectations of benefit. All researchers who have contact with patients in either group will be trained to assess suicide risk and instruct patients to protect their safety. All participants will be debriefed at the end of the study about the study aims and objectives, including their assigned group allocation.

2.7. Outcomes

Participants will complete an online questionnaire. The primary outcome will be assessed by the difference between groups in the change in self-reported depression severity at week 6, using the PHQ-9 (Kroenke et al., 2001). The secondary outcome measures are remission of depression defined as PHQ-9 score $\leq$4, change in anxiety measured using the General Anxiety Disorder Scale (GAD-7), (Spitzer et al., 2006) change in anhedonia measured using the Snaith-Hamilton Pleasure Scale (SHAPS), (Snaith et al., 1995) change in cognitive impairment measured using the Perceived Deficits Questionnaire-5-item (PDQ-5), (Lam et al., 2018) change in quality of life measured using Short-Form 12 Health Survey (SF-12), (Ware et al., 1996) change in impairment of ability to work, conduct a normal social life, and maintain relationships due to mental health difficulties measured using the Work and Social Adjustment Scale (WSAS) (Mundt et al., 2002). We will also measure the adherence to KD at the intervention end and study end. We will provide a scale for participants to weigh themselves if they do not have one at home.

We will examine some possible factors that might explain the effect of KD on depression. Participants will complete an online probabilistic instrumental learning (PILT, short version) task to measure reward sensitivity (Walsh et al., 2018). Participants will provide saliva samples to measure the morning cortisol awakening response at waking, 30, 45, and 60 min after waking. Participants will also provide stool samples, which are stabilised in alcohol and returned to the laboratory to measure a global representation of the microbiome compositions, and alpha diversity using Observed Species, Whole Tree Phylogeny, and Shannon and Simpson indices. The assessments are summarised in Table 2.

2.8. Sample size

We consider a 5-point difference in PHQ-9 total score (0–27 scale) to represent a minimum clinically important difference, as suggested by Lowe et al. (Löwe et al., 2004) This study reported that the SD of the change in PHQ-9 over 3 months as 5.8 and as 6.1 over 6 months. Assuming an SD of 6 over 6 weeks would suggest a standardised effect size of 0.83 in PHQ-9 to be clinically relevant. The sample size to test differences between groups at 90% power and at a type one error rate of 5% would be 64 (32 per group). A sample size of 100 participants will be recruited in case of 35% attrition/missing data. In simulations we confirmed that this sample size remains robust under scenarios such as unequal sizes of the strata used in minimisation.

2.9. Statistical methods

Initial descriptive analysis will present the profile of the subjects by study arm without using statistical comparisons.

For the primary hypothesis, the change in PHQ-9 scores from

Table 2
Study objectives and outcome measures.

	Objectives	Outcome Measures	Time point(s)
Primary	Self-reported depression severity at post-treatment (week 6)	PHQ-9	Baseline, weeks 2, 4, 6, 12
Secondary	Anxiety	GAD-7	Baseline, weeks 2, 4, 6, 12
Secondary	The inability to experience pleasure (i.e. anhedonia)	SHAPS	Baseline, week 6, 12
Secondary	Cognitive functioning	PDQ-5	Baseline, week 6, 12
Secondary	Health-related quality of life	SF-12	Baseline, week 6, 12
Secondary	Functional outcome	WSAS	Baseline, week 6, 12
Exploratory	Anthropometric measures	BMI	Baseline, week 6, 12
Exploratory	Adherence to the assigned diet	Self-completion question on diet	Weeks 6, 12
Mechanistic	Changes in cortisol level for awakening response	Saliva sample (home test kits)	Baseline, week 6
Mechanistic	Changes in gut microbiome	Stool samples (home test kits)	Baseline, week 6
Mechanistic	Changes in reward sensitivity	PILT	Baseline, week 6
Mechanistic	Changes in the inability to experience pleasure (i.e. anhedonia)	SHAPS	Baseline, week 6, 12

Note: PHQ-9, Patient Health Questionnaire-9; GAD-7, General Anxiety Disorder Scale; SHAPS, Snaith-Hamilton Pleasure Scale; PDQ-5, Perceived deficits questionnaire-5-item; SF-12, SF Short-Form 12 Health Survey; WSAS, Work and Social Adjustment Scale; PILT, Probabilistic instrumental learning task.

baseline to week 6 will be compared between groups. A mixed effect model that includes treatment group, time and their interaction as fixed effects, and individual subjects as random effects will be fit using PHQ-9 at all available assessments. A linear contrast will be used to test the difference between groups in changes from baseline to week 6 in PHQ-9 scores. Two tailed tests and significance level of 0.05 will be used. Secondary outcomes will be analysed using analogous mixed effects generalised linear models. Pre-specified subgroup analyses of the primary outcome will be explored by baseline depression severity (severe versus moderate) and duration of depression at baseline split at the median. Differences in adverse events by study arm will be compared and presented as proportions and differences assessed using Fisher's exact test.

We will conduct an exploratory mediation analysis using methods described by Valeri & Vanderweele (Valeri and Vanderweele, 2013) to examine whether changes in gut microbiome, cortisol awakening response, reward sensitivity, and ability to experience pleasure appear to mediate changes in depression assessed by PHQ-9. We will quantify the alpha diversity and the abundance of the top ten genera at each time point and use change in these metrics in our mediation analysis. Likewise, we will use change in area under the curve for the cortisol awakening response and change in reward sensitivity as potential mediators.

The extent of missing data will be reported descriptively, including the number of participants with missing data in each group, and baseline characteristics of people with and without missing outcome data. In the primary analysis with mixed models we will use available case analysis, which assumes data are missing at random (MAR). The robustness of the conclusions to the MAR assumption will be tested in sensitivity analyses as below –

1. Sensitivity analysis assuming everyone with missing outcome data has severe depression
2. Sensitivity analysis assuming everyone with missing outcome data has no depression (included for completeness, not for plausibility)
3. Sensitivity analysis using last observation carried forwards (LOCF)
4. Sensitivity analysis using baseline observation carried forwards (BOCF)
5. Repeat main analysis with analysis restricted to (a) those with maximum of one missing observation (b) those with maximum of two missing observations

2.10. Patient and public involvement

Eight members of the public who have depression, of whom 3 had previously followed a KD diet were recruited from the Oxford Primary Care Department public panel and were involved in the study design. There was a consensus that it was important and relevant to know whether KDs can treat depression. We also engaged them to help design the methods we use in the study including the nature of the diet, the decision to use a placebo diet, the written support for participants in both arms, and the design of the social media advertising to engage participants. In particular, members of our group understood and accepted the use of the placebo diet and its value in improving health in general. Participants in the trial will be sent the results of the study upon completion, and a lay summary and infographic will be provided.

3. Discussion

There are few established and widely available treatments for people with TRD. This is the first randomised, controlled trial assessing the effects of KDs on symptoms of depression in patients with TRD. The trial has 90% power to detect large treatment effects and it is therefore possible that we will miss smaller treatment effects that may still be of value. That said, treatment effects reported in case studies and single arm trials are usually much larger than the minimally important clinical difference we are aiming to find.

We have designed this study with a form of placebo intervention. The aim is to equalise expectations of benefit from the dietary treatment and thus minimise Hawthorne treatment effects. We will debrief all participants at the end of the study and supply everyone with the results of the trial in due course.

If the treatment proves efficacious, it will create a potential new way to treat these patients. Further work will be needed to test the effectiveness of KDs in routine clinical care, where patients will not be provided with food and where many services would struggle to provide this level of support from a dietitian. That said, given the considerable morbidity imposed by TRD, there could be a case for more intensive treatment programmes such as this.

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Patient consent for publication

Not applicable.

Ethics approval

This study has been approved by the Oxford Research Ethics Committee (Ref: R87397/RE001). Trial Registration number: clinicaltrials.gov ID: NCT06091163.

Data availability statement

No data are available.

CRediT authorship contribution statement

Min Gao: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Megan Kirk:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Software, Writing – review & editing. **Eva Lash:** Project administration, Writing – review & editing. **Heather Knight:** Project administration, Writing – review & editing. **Mosch Michalopoulou:** Conceptualization, Data curation, Investigation, Resources, Writing – review & editing. **Nicola Guess:** Investigation, Methodology, Resources, Writing – review & editing. **Michael Browning:** Conceptualization, Methodology, Resources, Writing – review & editing. **Scott Weich:** Conceptualization, Methodology, Resources, Writing – review & editing. **Philip Burnet:** Resources, Writing – review & editing. **Susan A. Jebb:** Conceptualization, Methodology, Resources, Writing – review & editing. **Richard Stevens:** Formal analysis, Methodology. **Paul Aveyard:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interest

PA and SAJ are investigators on a publicly funded trial where Nestle have donated total diet replacement products to support the trial. All authors revised the manuscript critically for important intellectual content, and read and approved the final manuscript.

Acknowledgment

The trial steering committee (TSC) comprises three independent members (Ted Dinan, University College Cork; Jeff Daskalakis, University of California San Diego; Ivonne Solis-Trapala, Keele University), including expertise in psychiatry and statistics. They have no relationship to the investigators, the trial funders, nor employed by the same institution. The TSC will meet at least annually at appropriate time points to ensure the trial is conducted in accordance with clinical trial standards. The views expressed are those of the authors and not necessarily those of the UK National Health Service, NIHR or the Department of Health and Social Care.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2024.04.023.

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