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Optimising Nutritional Psychiatry Treatment: Investigating the Mediterranean Diet to Improve Symptoms of Major Depressive Disorder (OPTIMISM): A double-blind sham-controlled randomised feeding trial protocol

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Abstract

Depression is a common mental disorder and a leading cause of global disease burden. Emerging evidence supports diet as an adjunct treatment for depression. Previous studies are limited, meaning it is unclear whether improvements are directly due to dietary change. The OPTIMISM trial aims to address this gap through a sham-controlled randomised feeding trial design.

The OPTIMISM trial is a 4-week double-blind, sham-controlled, randomised feeding trial. A total of 44 participants with MDD in a current major depressive episode of moderate to severe severity will be recruited and randomised to a Mediterranean or a sham control diet, designed to reflect typical dietary intake of the general population. All food will be provided for four weeks. Participants will complete assessments and have blood and stool collected at baseline and four weeks. The primary outcome is the differential change in clinician-rated depressive severity at four weeks. Exploratory outcomes include patient-rated depressive and anxiety symptoms, and quality of life. Potential mechanisms will be evaluated through analysis of biological samples. An additional group of 22 healthy individuals without depression will also be recruited and will receive a Mediterranean diet for four weeks; their data will determine whether clinical and biological responses to the intervention are unique to depression and whether the diet treatment modulates depression-related pathology.

If the intervention diet leads to a greater reduction in depressive symptoms compared with a sham control diet, this trial will provide preliminary evidence supporting the use of a Mediterranean diet in the treatment of depression.

Keywords:

Depression, Mediterranean diet, feeding trial

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Abbreviations

AE	Adverse events
DSM-5	Diagnostic and statistical manual of mental disorders fifth edition
GAD-7	generalised anxiety disorder scale
GEE	Generalised estimation equation
GI	Gastrointestinal
MADRS	Montgomery-Åsberg depression rating scale
MDD	Major depressive disorder
MDE	Major depressive episode
MEDAS	Mediterranean diet adherence screener
NHMRC	National Health and Medical Research
PGI-I	Patient global impression-improvement score
PHQ-9	Patient health questionnaire-9
RCT	Randomised controlled trials
SCID-5-RV	Structured clinical interview for DSM disorders research version 5
SCOFF	Sick, Control, One, Fat, Food
SIMPAQ	Simple physical activity questionnaire
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SQS	Sleep quality scale
WHOQOL-BREF	World Health Organization quality of life short version scale

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Introduction

Depressive disorders are highly prevalent and a leading contributor to the global burden of disease (1). A large meta-analysis demonstrates a two-fold increase in all-cause mortality risk in people with depressive disorders compared to people without depression/general population controls. This includes markedly higher suicide risk (5.8-fold) and elevated mortality from natural causes (1.6-fold) (2). Major depressive disorder has negative impacts on quality of life and is associated with increased risk of chronic disease, including cancer and heart disease (3-5). Antidepressant treatment is suboptimal for many individuals with depression; in the STAR*D trial two-thirds of people with depression do not respond to first-line antidepressant therapy (6). A large meta-analysis of psychological treatments for depression found similar remission rates with cognitive behavioural therapy (7). There is an urgent need to identify adjunctive treatments to reduce the substantial burden of depression.

There is accumulating evidence that a healthy diet can improve symptoms of depression. A meta-analysis of 16 randomised controlled trials (RCTs) suggest that diet interventions can improve depressive symptoms across a range of healthy individual and clinical cohorts (8). All but one of the studies in this meta-analysis examined samples with nonclinical depression. As such an important research question is whether diet is effective in treating clinical depression. In a meta-analysis of a Mediterranean diet in adults with depressive disorder or subclinical depression symptoms, Mediterranean diet interventions significantly reduced depressive symptoms relative to controls (SMD = –0.53; 95% CI: –0.90 to –0.16) (9). However, there was considerable between-study heterogeneity, which could be due to differences in intervention modality (i.e., group vs. individual), intervention features (i.e., diet alone, composite or combination), intervention duration, or in the control conditions applied. For example, the three RCTs investigating a Mediterranean diet alone (i.e., without additional nutrient supplementation or lifestyle intervention) (10-12) were 3-12 weeks' duration, and were delivered one on one through dietary counselling by a dietitian or nutritionist (10, 11) or via an educational video (12). Control conditions also varied across studies; one study used unblinded habitual diet as the control condition (12) and two employed social befriending (10, 11).

The selection and design of control conditions is critically important for the precise estimation of treatment effects in dietary research. Some studies have adopted social befriending as a control. This may control for researcher interaction but does not constitute a

comparable treatment with regards to type of intervention or contextual components. For example, diet counselling typically incorporates elements such as motivational interviewing and goal setting, which may independently influence mood and therefore represent active therapeutic components in their own right. Previous critique in this field also highlights concerns regarding unequal expectancy effects and potential selection bias if study advertising and recruitment do not sufficiently obscure the trial's intent (13). Therefore, well-controlled trials are still needed to confirm whether a Mediterranean diet is efficacious beyond that accounted for by placebo, positive behaviour change or other nonspecific factors.

A feeding trial, in which all food is provided to participants, is ideal for providing proof-of-concept evidence that a specific diet has effectiveness because it maximises adherence and enables the incorporation of a placebo (sham) diet (14). Feeding trials also enable better evaluation of the effect of known quantities of foods and nutrients on physiology. Considering the methodological weaknesses of prior research, the aims of this trial were to investigate the effectiveness of a traditional Mediterranean diet on depressive symptoms in people with major depressive disorder (MDD) through a double-blind sham-controlled randomised feeding trial design and to investigate potential mechanisms. We hypothesise that a 4-week traditional Mediterranean diet will lead to a greater reduction in depressive symptoms compared with a sham diet in people with MDD experiencing a major depressive episode (MDE).

Materials and methods

Overview

This is a 4-week double-blind, sham-controlled, randomised feeding trial of a Mediterranean diet for the treatment of moderate to severe MDD. Participants will be randomised 1:1 to receive a Mediterranean diet or a sham control diet designed to reflect typical dietary intake of the general population and considered dietary intakes of individuals with depression. A sham diet was selected to facilitate a placebo control. The primary outcome is the between-group differential change in depression severity at week four measured by the Montgomery-Åsberg Depression Rating Scale (MADRS)(15). Exploratory outcomes include between-group differential change in patient-rated depression severity, anxiety and quality-of-life. Blood and stool samples will be collected to assess potential mechanisms. Twenty-two healthy individuals without depression will also be recruited and will receive a Mediterranean

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diet for four weeks. Data from healthy individuals will be used to determine whether clinical and biological responses to the intervention are unique to depression and whether the diet treatment modulates depression-related neurobiology. All participants will complete assessments and have samples collected at baseline and four weeks.

The trial is being conducted in accordance with the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research (16) and aligns with Good Clinical Practice (ICH-GCP) (17). The trial protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2025 statement, which provides a comprehensive checklist for complete and transparent clinical trial protocol reporting. Approval to conduct the trial was received from the Human Research Ethics Committees of Barwon Health (23/75), Monash University (44424) and Deakin University (2023-297). Electronic informed consent will be obtained from all participants before any assessments are administered.

Eligibility

Individuals aged 18-65 years with a diagnosis of MDD, according to the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) will be recruited. A diagnosis of MDD will be determined using the Structured Clinical Interview for DSM Disorders Research Version (SCID-5-RV) by research dietitians, following standardised training and under psychiatrists' (PH, DK) oversight. In addition, participants must be experiencing a MDE with moderate to severe depressive symptoms defined as ≥ 20 MADRS, have poor diet quality via a modified Total Diet Score (18), be willing and able to undertake and adhere to the requirements of a 4-week feeding trial and attend all trial appointments, reside in meal delivery zones, have access to a smartphone/tablet/computer with internet access and kitchen facilities (e.g., microwave or oven, freezer) and have a nominated preferred general practitioner. Antidepressant therapy and other therapies are allowed provided their frequency or dose remains unchanged throughout the intervention period.

Exclusion criteria include active suicidal ideation as assessed by self-report and by the researcher checking participant eligibility; self-reported psychiatric comorbidities, including bipolar I or II disorder, psychotic disorder, personality disorder, substance use disorder (including excess alcohol use), eating disorder or score ≥3 on the Sick, Control, One, Fat, Food (SCOFF) eating disorder screening questionnaire (19); history of a significant comorbid

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medical disorder (e.g., cancer, diabetes, dementia); history of major gastrointestinal (GI) surgery, irritable bowel syndrome, or inflammatory bowel disease. Participants will also be excluded if they are considered treatment resistant (i.e., have failed two or more trials of antidepressant therapy for the current MDE); have significant diet restrictions or allergy/intolerance, sociocultural or religious reasons that would interfere with adherence; exceed 300 min/wk of moderate or 150 min/wk vigorous activity per week; have body mass index <18.5 kg/m2 or >40 kg/m2 calculated using self-reported data or have reported unstable weight in the past 3 months (> 5% bodyweight change); are pregnant or breastfeeding; or have used probiotic, prebiotic and/or synbiotics or changed their pharmacological and/or psychological treatment for depression in the past four weeks.

Recruitment

Recruitment is being conducted at two research centres: Monash University, Alfred Campus, Melbourne, and a regional site at Deakin University, Waterfront Campus, Geelong. Participants will be recruited from the community through communication with outpatient mental health and GP services, flyers in community health services, university campuses and health services, community noticeboards, libraries and supermarkets, private clinical networks, traditional media and social media advertising. Recruitment commenced in October 2023 and is anticipated to occur over a 2-2.5-year period.

Trial procedures

Eligibility will be assessed through a three-phase screening process. Prospective participants will complete an online screening questionnaire via REDCap to assess preliminary eligibility. Eligible participants will be invited to attend a first screening call via telephone or online videoconferencing and will receive the Participant Information and Consent Form. During the first screening call, the trial requirements will be described to the participant and they will be shown an example menu plan that presented a mix of intervention and control meals (Supplementary information) by a research dietitian to facilitate a decision to participate. To be eligible, individuals must consume a habitual diet representative of average diet quality or worse, which is a score of no greater than 11 on a modified Total Diet Score (18) (Supplementary information). This criterion was included to exclude individuals already on a high quality diet. If this phase of screening is passed, informed consent will be obtained, contact details of a nominated general practitioner will be collected, and the individual will

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proceed to a second screening call in which the researcher will administer the MADRS to assess severity of depressive symptoms. If the individual meets eligibility criteria for symptom severity, a SCID will be administered to assess whether the diagnostic threshold for current MDD is met.

Eligible individuals will attend two in-person trial visits. Trial visit 1 will occur approximately one week following completion of screening to allow time to assess baseline GI symptoms and diet (see below). During trial visit 1 (baseline), participants will complete a series of assessments (Table 1) and will then be randomised to receive either a Mediterranean diet or sham control diet for four weeks. Participants will return for trial visit 2 (week 4) to complete repeat assessments and answer a blinding question to assess blinding integrity (i.e., 'Which of these diets do you think you were allocated to?': I don't know, control diet, intervention diet). They will then receive an information sheet about healthy eating for mood, be provided contact information for relevant mental health and dietary support services should they wish to seek assistance, and be reimbursed for any reasonable travel expenses associated with participation. During the following 4-week intervention period, weekly calls to participants assess for adherence, adverse events, medication changes and allow for participants to ask questions.

Randomisation and blinding

Participants with MDD will be allocated to the intervention arms using computer-generated block randomisation, with varying block sizes of 2 and 4, in a 1:1 ratio (intervention to control). The randomisation sequence is generated by a researcher not involved in data collection or participant recruitment. Randomisation will be stratified by sex and presence of current psychotherapy and/or antidepressant treatment at therapeutic dose. All participants recruited as healthy controls will receive the intervention diet and will not be randomised.

Although double-blinding is possible in a feeding trial, blinding in dietary trials is exceedingly challenging and therefore several processes and procedures will be implemented to safeguard blinding. The dietary patterns being investigated will be concealed from participants and instead participants will be told that they are taking part in a trial investigating dietary patterns and their effects on depressive symptoms. Participants and the researcher collecting clinical data will be blinded to group allocation until after analysis is completed. The success of participant and researcher blinding will be measured at trial visit 2

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using the James Blinding Index and Bang Blinding Index (20). Unblinded researchers will attend trial visits to verify diet records, coordinate meal orders and provide written instructions about the diet and conduct weekly calls. These unblinded researchers will not have any role in the collection of primary outcome data or analysis of the data.

Intervention and control diets

The design and development of intervention and control diets was undertaken by dietetic members of the research team (DT, TR, MH, HMS). Four individuals with lived experience of MDD contributed to the design of trial materials, intervention delivery and recruitment and retention strategy via a focus group in July 2023. Once the diets had been designed, they were validated by comparing with the pre-determined food group targets (Table 2) using nutrition analysis software (Foodworks Professional Version 10; Xyris Software, Australia Pty Ltd). An *a priori* variance of ±10% was deemed acceptable. Where variance exceeded 10%, adjustments were made to the menu until targets had been reached.

Participants will be provided all food and snacks for the duration of the 4-week trial and will be instructed to eat according to appetite while refraining from non-trial provided food. Provided diets are based on a 7-day rotating menu cycle, comprising a total of three meals and three snacks daily. Food will be delivered weekly with all meals provided in identical trays. Approximately half of the meals are provided ready-made from a commercial meal delivery company and the remaining provided as ingredients from a supermarket delivery for simple meal preparation. Where supermarket items are unavailable, the researcher selects alternative products that facilitate the overall diet to meet the targets for the assigned dietary pattern.

The Mediterranean diet was designed on the basis of an extensive literature search to reflect a traditional Mediterranean diet that is rich in vegetables, fruits, legumes, whole grains and nuts, has extra virgin olive oil as the principal source of dietary fat; moderate intake of fish; and low in red meat and processed foods (22,23). Specific targets for each food group is provided in Table 2.

In dietary research, an ‘inert’ placebo diet is not possible. Therefore, a sham control diet was designed to represent mean dietary intakes of Australians from the 2011-2012 National Nutrition and Physical Activity Survey which was the most recent survey at the time of menu design (24), whilst also considering the habitual dietary intake of individuals living with

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moderate to severe major depressive disorder (25) (Table 2), and to mimic the corresponding Mediterranean diet meals in appearance where possible. Extra virgin olive oil will be provided to participants separately as total oil targets for the Mediterranean diet group could not be met with bespoke frozen meals alone. Oil will be provided in opaque bottles so participants are not aware of the amount supplied. Measuring spoons will be provided to standardise quantities; 15-20 ml/d will be added in the Mediterranean diet group meals once per day and 5 ml/wk in the sham control diet (to one meal/week).

Both diets were developed for two energy levels (8mJ/day or 10mJ/day), as per previous recommendations (14), to enable the intervention to meet the nutritional needs of a range of participants, but were not designed to achieve weight loss. Diets may be adjusted based on participant hunger, activity level and bodyweight changes. Detailed written instructions for complying with the diet, coded by colour only, will be provided to each participant that include recipes for breakfast and some lunch meals, and an additional 'free food' list with examples of self-sourced foods and portion sizes that can be consumed in a given day that are in alignment with the diet targets. Instructions will be coded by colour only, and not mention the diet pattern. Beverages and seasonings will not be provided, however, a list of suitable options will be supplied. No more than four cups of tea or coffee are allowed to be consumed, and there are set limits for alcohol for each diet (Table 2). An example of a one-day menu for each diet is presented in Supplementary information.

Data collection and outcome measures

Table 1 presents outcome measures and corresponding timepoints of measurement. Demographic data including gender, age, ethnicity and education will be collected at baseline together with current medication and supplement use, medical history, bodyweight and height.

The primary outcome is between-group differential change from baseline at week four in depression severity measured using the MADRS, a clinician-administered and well validated instrument to measure depression severity (15). Exploratory outcomes include patient-rated depression severity measured using the 9-item Patient Health Questionnaire-9 (PHQ-9) (26), participants' overall perception of improvement of depressive symptoms using the Patient Global Impression-Improvement score (PGI-I) (27), anxiety symptoms measured using the Generalized Anxiety Disorder Scale (GAD-7) (28), and quality of life using the World Health

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Organization Quality of Life Short Version Scale (WHOQOL-BREF) (29). Potential mediators and effect modifiers will be measured, including sleep quality, physical activity and treatment expectation bias. These are measured using the Sleep Quality Scale (SQS)(30) and Simple Physical Activity Questionnaire (SIMPAQ)(31), and Credibility Expectancy Questionnaire (32), respectively. Bodyweight will be measured using calibrated scales (Seca 813; Seca GmbH & Co. KG, Hamburg, Germany) at trial visits and weekly bodyweight will be self-measured at home by participants. Diet acceptability will be measured using the Diet Satisfaction Score (33) and additional trial-specific food acceptability questions. GI tolerability will be measured using 3-day visual analogue scales for severity of abdominal pain, bloating, nausea, flatulence and satisfaction with bowel habits based on previously validated measures for pain (34), and stool consistency will be measured using the Bristol Stool Form Scale (35).

Fasted blood samples (18.5ml) will be collected using K2EDTA tubes and serum separator tubes at each trial visit by either an external pathology centre or a co-located health service pathology centre. Samples will be centrifuged at 1500g at 4°C for 10 minutes. Plasma and serum aliquots (250uL each) will be stored at –80˚C for subsequent analysis of circulating inflammatory cytokines, C-reactive protein, tryptophan, brain-derived neurotrophic factor, short chain fatty acids, cortisol and gut permeability markers. Participants will be advised to collect a stool sample on the morning of each trial visit and keep the sample refrigerated at 4°C until attending the research centre. Participants will be provided with instructions and a stool collection kit, including a collection container, gloves, anaerobic generator (Oxoid AnaeroGen Compact, Thermofisher Scientific) sachet and two resealable plastic bags to contain the box. A cool pack will be provided to maintain temperature when transporting the sample. If a sample is not collected prior to or at the visit, it will be collected on a subsequent day. For trial visit 1, the diet intervention will commence only after stool collection. For trial visit 2, if a sample is not able to be collected before or at the visit, the diet intervention will continue until the point of stool collection. Stool samples will be transported to the laboratory within 4 hours and processed in an anaerobic hood. Whole stool samples (2 g per vial) will be stored in sterile 2 mL O-ring screw-cap cryovials at –80˚C for subsequent analysis of gut microbiome and metabolite composition.

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Adherence

Participants will record their dietary intake using a 7-day food record at baseline and a trial-specific completion log to record consumption of the trial meals across the 4-week trial. Consumption of each meal and snack will be recorded as 'all', '3/4',1/2, ¼, none and participants are encouraged to provide notes detailing additional foods and drinks consumed, and details for why meals or snacks were not fully consumed. Participants will be classified as being adherent if ≥80% of food was consumed over the entire intervention, poorly adherent if 50-79% of food was consumed, and non-adherent if <50% of food was consumed. The Mediterranean Diet Adherence Screener (MEDAS) (36) will also be used as a supplementary measure of adherence.

Safety and adverse events

Safety protocols were developed for trial visits and weekly calls in conjunction with the team psychiatrists (PH, DK), to monitor the safety of participants throughout the trial. All participants will be advised to continue usual care from their treating clinician while participating in the trial. At weekly assessments, if a participant expresses suicidal ideation, selects mood as "much worse" or "very much worse" on the PGI-I or scores 1,2 or 3 on the PHQ-9 item 9, the principal investigator will be notified, and a suicide risk screening assessment will be administered. If the participant is assessed as high suicide risk, the rostered team mental health clinician, and emergency services where indicated, will be notified. Such participants will subsequently be withdrawn from the trial to ensure their safety.

Adverse events

All adverse events (AE) will be documented in the participant electronic trial record and will include: the onset date, duration, date of resolution (if resolved), severity (mild, moderate, or severe), seriousness, actions taken, outcome and likelihood of the relationship of the AE to the trial intervention (definitely related, probably related, possibly related, unlikely to be related and definitely unrelated). In the circumstance of a severe adverse event, participants will be encouraged to attend medical services, and the participant will be followed up until the AE resolves, stabilises, or a participant is lost to follow-up. Any treatment related to an AE will be documented. One blinded and one independent unblinded psychiatrist will review AEs every six months for the purposes of evaluating ongoing trial safety.

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Data analysis and dissemination

A sample size of 22 participants per group was selected to achieve at least 18 completers per group to meet the trial's aims regarding quantifying a treatment signal and feasibility. This sample size is in line with previously conducted feeding studies in populations with cardiometabolic diseases (37), diabetes (38) and weight management (39). A sample size of 18 per trial arm achieves 80% power to detect a standardised mean difference of one for between-group change in MADRS at the significance level of 0.05. The biostatistician and researcher conducting the analysis will be blinded to group allocation until the primary endpoint has been analysed. The primary analysis of the primary endpoint will be an intention-to-treat analysis including all randomised participants who received the intervention diet for at least one day. Additionally, a per-protocol analysis will include data from all participants who completed the trial, who were assessed for the primary outcome within ± 3 days of the 28-day timepoint, and were considered adherent to the diet.

The primary outcome (mean difference in change between MADRS scores between intervention and control groups) will be analysed using generalised estimation equation (GEE) models. The GEE for the primary outcomes includes nominal variables for follow-up timepoint, and intervention allocation, the two-way interaction between time and group allocation, and sex and presence of current antidepressant and/or psychotherapy treatment (i.e. the stratified variables). The two-way interaction measures between-group differential change from baseline at week 4 and estimates the intervention impact. All continuous exploratory outcomes will be analysed similarly. A ≥50% reduction in MADRS score will be used to classify participants into responder and non-responder categories consistent with criteria used in antidepressant drug trials (40, 41). Dietary intake will be analysed to determine adherence and to assess the integrity of the sham diet. Diet acceptability and GI tolerability will be compared between and within groups. Missing data will be imputed using appropriate multiple imputation techniques. Exploratory analysis may be conducted comparing participants receiving treatment (anti-depressant medication and/or psychotherapy) and not receiving treatment. Exploratory analyses may also be conducted to assess baseline differences between responders and non-responders. Responses from the blinding assessment will be assessed and reported using a contingency table (2x3 format). If required, subgroup analyses will be conducted to assess change in MADRS score among

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participants with incorrect/'I don't know' allocation guesses and among those with correct allocation guesses.

Biological measures will be compared between MDD and healthy individuals at baseline. The differential impact of the Mediterranean diet on biological measures will be examined in the MDD and healthy individuals. The impact of diet on microbiome-gut-brain axis signalling pathways will be evaluated including compositional and functional alterations in the gut microbiome, immune function, gastrointestinal permeability, host and microbial tryptophan metabolism and biomarkers of stress physiology including cortisol.

Data will be disseminated to participants through a plain language summary and to clinicians and researchers through conventional scientific dissemination routes (e.g. conferences, scientific publication).

Discussion

There is an urgent need to identify definitive new approaches to reduce the global burden of depressive disorders. There is accumulating evidence that diet intervention, and specifically the Mediterranean diet, has strong potential for improving symptoms of depression. However, uncertainty remains regarding whether improvements reflect change in specific dietary components, expectancy effects, or other nonspecific factors. A hypothetical example of a nonspecific factor is participation in a new diet encouraging participants to address other lifestyle issue (e.g., trying to sleep better and exercise more) which may affect their mood. Alternatively, commitment to a new diet, including planning meals, cooking, tracking food could improve mood through increased activity and routine. Previous trials have been limited by lack of blinding, inadequate controls, and minimal investigation of underlying biological mechanisms, leaving critical questions unanswered. The OPTIMISM trial will address these key gaps through investigating the effectiveness of a Mediterranean diet in clinical depression through a rigorously designed double-blind sham-controlled randomised feeding trial. By integrating comprehensive biological sampling and mechanistic analyses, this trial will also provide new insights into how diet may influence mood. In both ways, the study will advance the developing evidence that supports diet as an adjunctive approach to treat depressive symptoms in people with MDD.

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Authorship

HS conceptualised the study. DT and HS wrote the draft. All authors reviewed and approved the final manuscript.

References

1. Global Burden of Disease 2019 Diseases and injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: A systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1204-22.

2. Chan JKN, Solmi M, Lo HKY, Chan MWY, Choo LLT, Lai ETH, et al. All-cause and cause-specific mortality in people with depression: a large-scale systematic review and meta-analysis of relative risk and aggravating or attenuating factors, including antidepressant treatment. World Psychiatry. 2025;24(3):404-21.

3. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry. 2010;67(3):220-9.

4. Pinquart M, Duberstein PR. Depression and cancer mortality: a meta-analysis. Psychol Med. 2010;40(11):1797-810.

5. Correll CU, Solmi M, Veronese N, Bortolato B, Rosson S, Santonastaso P, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry. 2017;16(2):163-80.

6. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163(11):1905-17.

7. Cuijpers P, Miguel C, Harrer M, Plessen CY, Ciharova M, Ebert D, et al. Cognitive behavior therapy vs. control conditions, other psychotherapies, pharmacotherapies and

https://doi.org/10.1017/S0007114526107272 Published online by Cambridge University Press

combined treatment for depression: a comprehensive meta-analysis including 409 trials with 52,702 patients. World Psychiatry. 2023;22(1):105-15.

8. Firth J, Marx W, Dash S, Carney R, Teasdale S, Solmi M, et al. The effects of dietary improvement on symptoms of depression and anxiety: a meta-analysis of randomised controlled trials. Psychosom Med. 2019:81(3):265-280.

9. Bizzozero-Peroni B, Martínez-Vizcaíno V, Fernández-Rodríguez R, Jiménez-López E, Núñez de Arenas-Arroyo S, Saz-Lara A, et al. The impact of the Mediterranean diet on alleviating depressive symptoms in adults: a systematic review and meta-analysis of randomized controlled trials. Nutr Rev. 2025;83(1):29-39.

10. Jacka FN, O'Neil A, Opie R, Itsiopoulos C, Cotton S, Mohebbi M, et al. A randomised controlled trial of dietary improvement for adults with major depression (the 'SMILES' trial). BMC Med. 2017;15(1):23.

11. Bayes J, Schloss J, Sibbritt D. The effect of a Mediterranean diet on the symptoms of depression in young males (the "AMMEND: A Mediterranean Diet in MEN with Depression" study): a randomized controlled trial. Am J Clin Nutr. 2022;116(2):572-80.

12. Francis HM, Stevenson RJ, Chambers JR, Gupta D, Newey B, Lim CK. A brief diet intervention can reduce symptoms of depression in young adults - A randomised controlled trial. PLoS One. 2019;14(10):e0222768.

13. Molendijk ML, Fried EI, Van der Does W. The SMILES trial: do undisclosed recruitment practices explain the remarkably large effect? BMC Med. 2018;16(1):243.

14. Tien DS, Hockey M, So D, Stanford J, Clarke ED, Collins CE, et al. Recommendations for Designing, Conducting, and Reporting Feeding Trials in Nutrition Research. Adv Nutr. 2024;15(10):100283.

15. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-9.

16. National Health and Medical Research Council. National Statement on Ethical Conduct in Human Research 2025. Canberra, Australia: https://www.nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2025

https://doi.org/10.1017/S0007114526107272 Published online by Cambridge University Press

17. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). Geneva: ICH; 2016.https://database.ich.org/sites/default/files/E6_R2_Guideline.pdf

18. Russell JC, Flood VM, Sadeghpour A, Gopinath B, Mitchell P. Total Diet Score as a valid method of measuring diet quality among older adults. Asia Pac J Clin Nutr. 2017;26(2):212-9.

19. Morgan JF, Reid F, Lacey JH. The SCOFF questionnaire: assessment of a new screening tool for eating disorders. BMJ. 1999;319(7223):1467-8.

20. Petroff D, Bacak M, Dagres N, Dilk P, Wachter R. A simple blinding index for randomized controlled trials. Contemp Clin Trials Commun. 2024;42:101393.

21. Australian Guide to Health Eeating 2003 https://www.eatforhealth.gov.au/guidelines/guideline-developmentideline.

22. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013;368(14):1279-90.

23. Serra-Majem L, Tomaino L, Dernini S, Berry EM, Lairon D, Ngo de la Cruz J, et al. Updating the Mediterranean Diet Pyramid towards Sustainability: Focus on Environmental Concerns. Int J Environ Res Public Health. 2020;17(23).

24. Australian Bureau of Statistics. Australian Health Survey: Nutrition First Results - Food and Nutrients, 2011-2012. https://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/4364.0.55.007~2011-12~Main%20Features~Carbohydrate~705.

25. Opie RS, O'Neil A, Jacka FN, Pizzinga J, Itsiopoulos C. A modified Mediterranean dietary intervention for adults with major depression: Dietary protocol and feasibility data from the SMILES trial. Nutr Neurosci. 2018;21(7):487-501.

26. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606-13.

https://doi.org/10.1017/S0007114526107272 Published online by Cambridge University Press

27. Mohebbi M, Dodd S, Dean OM, Berk M. Patient centric measures for a patient centric era: Agreement and convergent between ratings on The Patient Global Impression of Improvement (PGI-I) scale and the Clinical Global Impressions - Improvement (CGI-S) scale in bipolar and major depressive disorder. Eur Psychiatry. 2018;53:17-22.

28. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166(10):1092-7.

29. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. Psychol Med. 1998;28(3):551-8.

30. Snyder E, Cai B, DeMuro C, Morrison MF, Ball W. A New Single-Item Sleep Quality Scale: Results of Psychometric Evaluation in Patients With Chronic Primary Insomnia and Depression. J Clin Sleep Med. 2018;14(11):1849-57.

31. Rosenbaum S, Morell R, Abdel-Baki A, Ahmadpanah M, Anilkumar TV, Baie L, et al. Assessing physical activity in people with mental illness: 23-country reliability and validity of the simple physical activity questionnaire (SIMPAQ). BMC Psychiatry. 2020;20(1):108.

32. Borkovec T, Nau SD. Credibility of analogue therapy rationales. JournalJournal of Behavior Therapy and Experimental Psychiatry. 1972;3(4):257-60.

33. Jospe MR, Haszard JJ, Taylor RW, Freedhoff Y. A tool for assessing the satisfaction of a diet: Development and preliminary validation of the Diet Satisfaction Score. Nutr Diet. 2020;77(2):268-73.

34. Safikhani S, Gries KS, Trudeau JJ, Reasner D, Rüdell K, Coons SJ, et al. Response scale selection in adult pain measures: results from a literature review. J Patient Rep Outcomes. 2017;2:40.

35. Heaton KW, Radvan J, Cripps H, Mountford RA, Braddon FE, Hughes AO. Defecation frequency and timing, and stool form in the general population: A prospective study. Gut. 1992;33(6):818-24.

https://doi.org/10.1017/S0007114526107272 Published online by Cambridge University Press

36. Schröder H, Fitó M, Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, et al. A short screener is valid for assessing Mediterranean diet adherence among older Spanish men and women. J Nutr. 2011;141(6):1140-5.

37. Krishnan S, Adams SH, Allen LH, Laugero KD, Newman JW, Stephensen CB, et al. A randomized controlled-feeding trial based on the Dietary Guidelines for Americans on cardiometabolic health indexes. Am J Clin Nutr. 2018;108(2):266-78.

38. Gardner CD, Landry MJ, Perelman D, Petlura C, Durand LR, Aronica L, et al. Effect of a ketogenic diet versus Mediterranean diet on glycated hemoglobin in individuals with prediabetes and type 2 diabetes mellitus: The interventional Keto-Med randomized crossover trial. Am J Clin Nutr. 2022;116(3):640-52.

39. Liu X, Zhang G, Ye X, Li H, Chen X, Tang L, et al. Effects of a low-carbohydrate diet on weight loss and cardiometabolic profile in Chinese women: a randomised controlled feeding trial. Br J Nutr. 2013;110(8):1444-53.

40. Papakostas GI, Trivedi MH, Shelton RC, Iosifescu DV, Thase ME, Jha MK, et al. Comparative effectiveness research trial for antidepressant incomplete and non-responders with treatment resistant depression (ASCERTAIN-TRD) a randomized clinical trial. Mol Psychiatry. 2024;29(8):2287-95.

41. Raison CL, Sanacora G, Woolley J, Heinzerling K, Dunlop BW, Brown RT, et al. Single-Dose Psilocybin Treatment for Major Depressive Disorder: A Randomized Clinical Trial. JAMA. 2023;330(9):843-53.

https://doi.org/10.1017/S0007114526107272 Published online by Cambridge University Press

Table 1: Schedule of assessments

Outcome	**Measure**	**Timepoint**
Clinician-rated depressive symptoms	Montgomery-Åsberg Depression Rating Scale (MADRS)	Baseline, Week 4
Patient-rated depressive symptoms	9-item Patient Health Questionnaire-9 (PHQ-9)	Baseline, Week 2, Week 4
Patient perception of global improvement	Patient Global Impression-Improvement score (PGI-I)	Weekly except baseline
Anxiety symptoms	7-item Generalised Anxiety Disorder scale (GAD-7)	Baseline, Week 4
Quality of life	World Health Organizations Quality of Life Short Version Scale (WHOQOL-BREF)	Baseline, Week 4
Diet adherence	7-day diet record Mediterranean Diet Adherence Screener (MEDAS)	Baseline, Weeks 1-4 Baseline, Week 4
Diet acceptability	Diet Satisfaction Score, Food Acceptability Questionnaire	Week 4
Gastrointestinal tolerability	3-day record assessing severity of abdominal pain, bloating, flatulence, satisfaction with bowel habits using visual analogue scales; Bristol Stool Form Scale	Baseline, Week 1, Week 4
Sleep quality	Sleep Quality Scale (SQS)	Baseline, Week 4
Physical activity	Simple Physical Activity Questionnaire (SIMPAQ)	Baseline, Week 4
Expectancy	Credibility Expectancy Questionnaire	Baseline
Inflammatory cytokines	Fasting plasma	Baseline, Week 4
Tryptophan	Fasting plasma	Baseline, Week 4
Brain-derived neurotrophic factor	Fasting serum	Baseline, Week 4
Short chain fatty acids	Fasting serum, stool	Baseline, Week 4
Gut permeability markers	Fasting plasma	Baseline, Week 4
Gut microbiome	Stool	Baseline, Week 4

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Table 2: Food group targets

Targets	**Mediterranean diet**		**Sham control diet**	
	8000kJ	10000kJ	8000kJ	10000kJ
Food Groups				
Daily target and serve size				
Fruit (150g; (350kJ)	2	3	1	1.5
Vegetables (75g;100-350kJ)	≥5	≥6	2	2.5
Wholegrains (500kJ)	≥5	≥6	2	2.5
Nuts and seeds (30g)	0.8	1	0.2	0.3
Extra virgin olive oil (60ml)	1	1	<0.1	<0.1
Dairy (500-600kJ)^	1.5	2	1.5	2
Discretionary foods (600kJ)*	≤3	≤3	5	7
Alcohol (1 standard drink)[#]	1	1	1	1
Weekly targets and serve size				
Legumes (75g)	≥5	≥6	1	1.5
Fish and seafood (100g cooked or 115g raw)	≥2	≥2	1.5	1.5
Poultry (80g cooked or 100g raw)	4	4	3	3
Lean red meat (65g cooked or 90g raw)	1	1	4	4
Eggs (1 egg)	4	6	1	2

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Nutrients				
Daily targets				
Carbohydrate (% energy)	35-40	35-40	45-50	45-50
Sugars (% energy)	<10	<10	18-20	18-20
Dietary fibre (g)	≥35	≥40	≤20	≤25
Protein (% energy)	15-20	15-20	15-20	15-20
Total fat (% energy)	35-45	35-45	30-35	30-35
Monounsaturated fatty acids (% total fat)	≥50	≥50	≤35	≤35
Saturated fatty acids (% total fat)	≤25	≤25	≥40	≥40
Polyunsaturated fatty acids (% total fat)	≤25	≤25	≤25	≤25

Serve sizes for all food groups, other than extra virgin olive oil, are taken from the Australian Guide to Healthy Eating (21)

*Examples of discretionary foods: Chocolates, chips, muffins, sweet or savoury pastries, processed meats, butter, jam

^Cheese or yoghurt preferable to milk.

[#]This was an allowance rather than a target. Applicable only for participants already consuming alcohol. Mediterranean diet-100ml red wine; Sham diet-1 standard drink (any type)

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