Development and validation of a credible control for ketogenic diet trials in depression

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Description of the initiative

Depression is a leading global public health burden associated with substantially reduced life expectancy and high healthcare costs. One-third of individuals fail to respond to standard psychological or pharmacological therapies (1) and therefore there is an urgent unmet need for innovative, accessible, and well-tolerated treatments.

The ketogenic diet is a very-low carbohydrate, high fat diet designed to mimic a fasted stated to alter metabolism via hepatic ketone body production and increased fatty acid metabolism. Pilot studies and case series suggest a ketogenic diet may improve mood in conditions including schizophrenia-spectrum and bipolar disorders (2-4), with treatment response rates of >90% after 6-12 weeks of diet therapy (2), surpassing response rates reported in first-line drug therapies. This is supported by our own qualitative data from a trial in psychosis (5) led by Dr Ruusunen (Box 1). A recent randomised controlled trial (RCT) (6) also signifies the growing interest in this approach for depression, but all studies so far lack a placebo control and adequate participant blinding. Placebo-controlled RCTs are the next step in rigorously testing this treatment so that robust evidence can be generated to support translation into practice.

The aim of this project is to develop a bespoke sham diet that mimics the appearance of a ketogenic diet, is credible and convincing as a 'special' diet, is as intensive as the ketogenic diet, but does not modify putative active components that may impact depression. We have previously successfully designed sham diets for trials of the low FODMAP diet and the Mediterranean diet (7,8), with placebo response rates equivalent to that reported in pharmaceutical interventions (Figure 1). This innovative project will enable gold standard blinded placebo controls in depression research, allowing us to distinguish true physiological benefits from non-specific and contextual effects, strengthening internal validity.

Box 1: Quotes from PsyDiet participants:

"my mood is better now"; "It's easier to be active"; "I really feel I have cheered up"; "I feel my metabolism has improved"

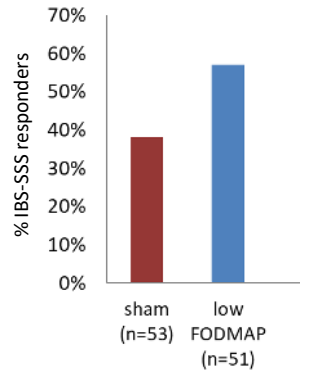


Figure 1: An example of placebo response rates in a sham-controlled dietary trial compared with an active intervention led by our team (in irritable bowel syndrome) (6)

Planned activities & deliverables

Following principles already established by the team for development and testing of a sham diet (8), we will develop and validate a sham diet for use in future ketogenic diet trials:

1. **Sham diet design & resource development (6 months):** Define macronutrient and food group targets for a diet that avoids ketosis whilst maintaining credibility as a special diet and reflects usual dietary intake of people with depression. Written participant (meal plans, recipes) and researcher resources (counselling protocols, scripts) will be developed.
2. **MOOK-Ok pilot study (6 months):** 20 healthy individuals will be recruited for a 2-week study. Individuals will receive sham dietary counselling at baseline with supporting written resources, after completion of a 3-day food record. At 2 weeks, a follow-up 3-day food record will be completed. Diet data will be analysed to evaluate whether *a priori* targets were reached (Foodworks 10, Xyris Software). Salivary ketone will be assessed via self-administered at-home salivary ketone testing we developed (10). Adherence will be defined by non-ketosis (<0.5 mmol/L BHB). Blinding success and diet acceptability will be assessed via validated questionnaires previously implemented in our research (8).
3. **Refinement: (6 months):** Diet composition, blinding, acceptability findings will determine whether diet and participant materials require iterative refinement. The resources will then be finalised.

Key deliverables Year 1: Ethics application for the pilot study, development of scientifically rigorous sham diet framework and participant and research materials, testing and validation; Year 2: Refinement of diet

References 1. Rush et al. Am J Psychiatry. 2006;163(11):1905-17 **2**. Danan et al. Front Psychiatry. 2022;13:951376 **3**. Sethi et al. Psychiatry Res. 2024;335: 115866 **4**. Campbell et al. BJPsych Open. 2025;11(2):e34 **5**. NCT03873922 **6**. Gao et al. JAMA Psych. 2026 4:e254431 **7**. Staudacher et al Gastroenterology. 2017;153(4):936-47 **8**. ACTRN12624000486527 **9**. Staudacher et al. Proc Nutr Soc. 2017;76(4):628 **10.** Kaul et al. Epilepsia. 2025; doi: 10.1111/epi.18465

Resources, enablers, budget

Our team comprises of dietitians with expertise in sham diet design (HMS), ketogenic diet (NK, AR), psychiatry (LC) and clinical trials (HMS, NK, AR, LC). Under the supervision of this expert team, a dedicated Research Dietitian will execute the first two steps of this project (Academic Level A, 0.5 FTE; €39,417). Our team will conduct the final refinement of the diet and materials. We have a engaged a network of Australian sites to be involved to pursue this program of research.

Results, expected outcomes & impact

This project will enable precise differentiation between placebo and true metabolic effects of a ketogenic diet in depression. This addresses a critical methodological gap at a time when enthusiasm for ketogenic diet therapy is accelerating ahead of high quality evidence. Findings from our research will be critical for evidence-based implementation of diet therapy in depression. This project will not only inform our understanding of ketogenic diets and the role they play as a treatment in mood and other disorders, but will also establish a sham diet paradigm that can be applied to other psychiatric and neurological conditions.

☑ **Please tick to confirm the PEN letter of endorsement is attached. Incomplete submissions will not be considered.**