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# Ketogenic metabolic therapy as a treatment for mental health disorders

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# Ketogenic metabolic therapy as a treatment for mental health disorders

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# Editorial: Ketogenic metabolic therapy as a treatment for mental health disorders

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Editorial on the Research Topic
Ketogenic metabolic therapy as a treatment for mental health disorders

For more than 75 years, biological treatments for mental illness have centered primarily around pharmaceutical interventions intended to address underlying neurotransmitter system dysfunction. This medication-oriented care model was revolutionary for its time, but unfortunately, even the most effective psychotropic medications leave the majority of people with mental illness without meaningful relief (1). Furthermore, the prevalence of mental health disorders continues to rise around the world, even in wealthy countries where most people have access to state-of-the-art psychopharmacological services (2). This alarming trend strongly suggests that environmental risk factors common to communities around the globe may be contributing to widespread declines in mental wellness.

Insulin resistance, pre-diabetes, type 2 diabetes, obesity, and other metabolic disorders are becoming increasingly commonplace around the world, and are strongly associated with mental health disorders of many kinds (3). While metabolic dysfunction negatively impacts all organ systems, the brain is arguably more vulnerable than most, because it is disproportionately metabolically demanding: despite comprising only about 2% of body weight, the brain consumes about 20% of the body's energy supply (4).

The rapidly emerging field of *metabolic psychiatry* seeks to understand and address the role metabolic dysfunction plays in mental illness, generating new scientific and clinical insights that are laying the groundwork for a 21st century paradigm shift in mental healthcare. The field urgently needs innovative treatment approaches that can address the metabolic disturbances commonly observed in mental health disorders (and mitigate the metabolic side effects of psychotropic medications), and mounting evidence suggests that ketogenic metabolic therapy has the potential to help meet both of these needs. Successfully used since the 1920s to treat epilepsy, ketogenic metabolic therapy has increasingly become the focus of researchers and clinicians seeking new approaches to a wide variety of other neuropsychiatric disorders as well. This Research Topic seeks to represent the depth and breadth of work being conducted in this new subspecialty, including theoretical perspectives, mechanistic research, case reports, and clinical trials.

Among the original clinical research papers is a retrospective qualitative analysis by Bellamy et al. of people's experiences with calorically unrestricted low-carbohydrate diets, noting benefits such as renewed purpose among those previously experiencing feelings of depression, as well as improvements in self-esteem, confidence, and other subjective measures important to quality of life not often formally assessed in metabolic research.

Calabrese et al. present a case series of three adults who achieved complete remission from both treatment-resistant major depressive disorder and generalized anxiety disorder after engaging in a 12–16 week lifestyle protocol centered around a ketogenic diet.

Edwards et al. presents the first pilot trial of the ketogenic diet in post-traumatic stress disorder, documenting acceptability and clinical benefits in two of the three individuals who completed the 4-week protocol, and highlighting challenges for future clinical trials.

Laurent details the case of a woman with bipolar disorder whose depression had responded only minimally to weekly ketamine treatments. Ketogenic metabolic therapy led to measurable improvements not only in depression, but also in anxiety and PTSD symptoms, as well as in measures of daily function, mental well-being, and quality of life. In a separate perspectives paper, Laurent encourages metabolic psychiatry researchers to collect and analyze both qualitative and quantitative data to present a fuller picture of the impact ketogenic metabolic therapy can have on the lives of people with mental illness.

Winje et al. report about a patient with type I diabetes who was able to stabilize blood glucose levels using ketogenic metabolic therapy, reducing fear of hypoglycemia as well as alleviating anxiety and depression symptoms.

Especially noteworthy is a paper by Longhitano et al. detailing the protocol they are implementing in a clinical trial involving 100 adults with schizophrenia and bipolar disorder, already under way in Australia. As this will be the world's first randomized controlled trial of the ketogenic diet in serious mental illness, their findings are eagerly anticipated.

Additional articles offer perspectives on the potential utility of ketogenic diets in the management of neuropsychiatric conditions beyond mood and psychotic disorders.

An intriguing review paper by Frank and Scolnick presents hopeful emerging evidence suggesting that properly formulated ketogenic diets, despite commonly being viewed as weight loss interventions, may support people in their recovery from anorexia nervosa, a condition with a high fatality rate and no approved biological treatment.

Ruskin et al. explore how ketosis positively influences the adenosine system, the dopamine system, and relevant factors such as inflammation, thereby representing a long-overlooked opportunity to support people suffering with addictive disorders. O'Hearn offers a conceptual analysis of the relationship between energy status, metabolic state, and sleep regulation which may help to explain the positive effect of ketosis on sleep quality. Stanton puts forth hypotheses on how well-formulated ketogenic and carnivore diets could stabilize certain factors associated with migraine headaches. Grabowska et al. point out, based on a review of 90 studies of the ketogenic diet conducted in rodent models, that behavioral health outcomes such as anxiety and depression have been less promising in these animal models than those observed in human case reports and clinical trials, a phenomenon also observed in epilepsy research (5).

Gertler and Blackford highlight the underexplored potential of ketogenic metabolic therapy in the management of pediatric mental and metabolic health disorders, particularly those that often coexist in children with epilepsy such as ADHD, autism spectrum disorder, and childhood obesity.

Diamond et al. challenge the widespread concern that ketogenic diets jeopardize cardiovascular health because they are high in fat and sometimes lead to elevations in LDL cholesterol—a persistent obstacle to wider acceptance of ketogenic diets by clinicians and patients alike.

The Centers for Disease Control estimate that more than 50% of Americans will be diagnosed with a mental health disorder in their lifetime (6), so the need for novel approaches to understanding, treating, and perhaps even preventing these burdensome conditions could not be more urgent. The papers curated for this Research Topic represent a diversity of efforts aimed at improving the lives of individuals with a range of neuropsychiatric conditions through innovative research into brain metabolism and the supervised incorporation of ketogenic metabolic therapy into clinical care. These works strengthen our understanding of the important relationship between metabolic health and mental health, and contribute to the growing sense that ketogenic metabolic therapy is emerging as a powerful, low-risk, lifestyle-based tool that could be integral in paving the path to a more hopeful future for mental health practitioners and the patients they serve.

## Author contributions

GE: Writing – original draft, Writing – review & editing. BZ-K: Writing – original draft, Writing – review & editing. SM: Writing – original draft, Writing – review & editing.

## Conflict of interest

BZ-K was employed by Ketogenic Therapies, LLC.

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## Publisher's note

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# From theory to practice: challenges and rewards of implementing ketogenic metabolic therapy in mental health

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This perspective article delves into the implementation of Ketogenic Metabolic Therapy (KMT) by a mental health counselor who attempts to bridge the gap between emerging research and real-world clinical application. Grounded in the author's clinical experiences, the article communicates the potential of KMT in mental health care, highlighting both its therapeutic promise and the insights gained from hands-on patient interactions. While the adoption of KMT necessitates adjustments in societal, emotional, and dietary domains, especially within diverse mental health contexts, these challenges are surmountable with appropriate guidance and support. The article encourages the capture of qualitative data alongside quantitative measures and advocates for an approach that considers the broader implications of improved mental well-being on families and communities. As the field advances, interdisciplinary collaborations between researchers and clinicians will be pivotal in refining and expanding the application of KMT, ultimately enhancing patient outcomes and elevating the standard of mental health care.

KEYWORDS

**ketogenic diet, metabolic psychiatry, KMT, ketogenic metabolic therapy, metabolic psychology, clinical psychology**

## Introduction

While much of the existing literature on Ketogenic Metabolic Therapy (KMT) for mental health is grounded in emerging research (1–4), the perspective of a clinician, especially one with a background in clinical psychology, offers a distinctive viewpoint. Clinicians bridge the gap between theoretical research and its real-world application, providing valuable insights from their direct interactions with patients.

The true measure of a therapeutic approach is not just its empirical evidence but how it is applied and received in everyday clinical practice. This is especially true for mental health, where individual variability is vast. Hence, a practical understanding of KMT's application, its challenges, and its real-world benefits is essential.

This leads us to the central question: "While the benefits of Ketogenic Metabolic Therapy (KMT) for mental health align well with research findings in a clinical setting, what are the practical barriers faced by patients and clinicians when attempting to implement KMT outside of research studies?"

In this perspective article, I aim to address this question primarily based on my clinical experiences. My goal is to highlight the opportunities and challenges of utilizing KMT for

mental health, with a specific focus on a mental health clinician's perspective.

## The therapeutic potential

In my clinical practice, I have been privileged to witness numerous success stories and remarkable transformations associated with Ketogenic Metabolic Therapy (KMT). These stories offer a glimpse into the immense therapeutic potential of KMT in the realm of mental health care.

One of these remarkable stories recently involved a 17-year-old who had been diagnosed with Schizoaffective disorder, suffered from both auditory and visual hallucinations, and was hospitalized for suicidal ideation. When I asked her what she wanted me to tell others about this diet, less than 8 weeks into her KMT treatment with me, she stated, "Just that this diet has been a miracle and a life changer for me." Her firsthand account emphasizes the profound impact that KMT can have on individuals grappling with complex mental health conditions. It serves as a powerful testament to the hope and promise that KMT offers, particularly in the context of challenging disorders like Schizoaffective disorder.

However, this perspective article is not about case studies. Stories such as this often lead to questions about for whom and what mental health conditions might benefit from a ketogenic intervention. This patient responded very quickly and received great and sustained benefits. But there are many confounding variables in patient populations that I have worked with that make answering that question very difficult. Still, drawing from my clinical experience, I have gained insights into the nuanced challenges and considerations that arise when implementing KMT across various patient populations.

One aspect is the interaction between KMT and existing medications or substance use that most mental health populations are on when they come to seek treatment, which might pose unique challenges for patients. For example, inadequate management of potentiation effects or titration of medications can sometimes lead to unexpected difficulties. These experiences, observed in real-world clinical settings, underscore the need for prescriber training tailored to the nuances of KMT (5, 6). As KMT gains recognition as a treatment for mental health conditions, the importance of updated and appropriate training for prescribers becomes evident. The complexities of medication management and patient expectations necessitate a nuanced approach, highlighting the importance of bridging the gap between research and practice. Prescribers untrained in ketogenic metabolic therapy (KMT) might misinterpret potentiation effects or medication withdrawal symptoms as a relapse of the patient's condition (6). For instance, a patient's re-emergence of previously resolved symptoms could lead to unnecessary medication increases. Additionally, withdrawal effects from discontinued medications might be wrongly seen as a deterioration in mental health or KMT's ineffectiveness (7–10).

It is crucial to emphasize that the field of KMT for mental health care is still evolving, and attempting to profile and determine who should or should not have access to KMT based on incomplete research findings or naïve clinical practices in the real world can be premature and potentially detrimental. Until clinical practice among prescribers working with this population matures, it becomes clear that, particularly in the context of psychiatric medications, a clear understanding of who does and does not benefit may not yet be possible (11). This will be a continued area of research as scientists attempt to discern what phenotypes and presentations of mental illness benefit most.

## Real-world challenges

### Transition challenges and emotional responses

The process of transitioning to Ketogenic Metabolic Therapy (KMT) involves significant changes in dietary habits, presenting patients with both practical and psychological challenges. Drawing from clinical experience, it's essential to consider several key aspects of this transition. Patients often grapple with the initial difficulty of envisioning a plate with very minimal carbohydrates, making this transition seem daunting. A prevailing emotional response during this phase is fear, which can manifest in various forms. Patients may experience fears related to judgment, standing out, missing out on experiences, being perceived as difficult, fearing failure or success, anticipating restrictions, and worrying about future health implications. These fears add to the emotional distress already inherent in big lifestyle changes.

### Mental health variations in transitioning

Challenges encountered during the dietary transition can vary based on specific mental health conditions. For example, individuals with depression may face struggles related to low self-efficacy and may benefit from additional emotional support. Those with health-related anxiety may need assistance in managing physical sensations without undue anxiety. Recognizing these variations is crucial for providing tailored support and interventions.

It's important to recognize that some individuals may face the added challenge of transitioning to a ketogenic diet while dealing with ultra-processed food addiction (12). Addressing this addiction alongside dietary changes is crucial for a holistic approach to their well-being. For some, particularly those with a history of processed food addiction, additional psychosocial support may be essential to facilitate a successful transition to a ketogenic diet. Recognizing this need and providing access to the necessary support can be critical for their treatment compliance and overall well-being. Future research in this area could focus on regular screening using well-established assessment instruments like the Yale Food Addiction Scale (YFAS) (13) at the beginning of diet initiation to identify subsets requiring additional psychological intervention and potentially enhance treatment outcomes.

Regardless of clinical practice orientation, the goal is to facilitate a sustainable transition. Patients benefit from assistance in planning food procurement, meal preparation, and participation in family events, fostering gradual mastery. While the initial weeks may present challenges, with effective support, patients often find that continuing with KMT becomes more manageable, leading to ongoing benefits. Patient failure to follow electrolyte supplementation instructions can result in unpleasant electrolyte imbalances. Currently, there are guidelines for electrolyte supplementation in epilepsy populations that clinicians can use in current practice when using KMT as a treatment for mental illness (14). It is not uncommon for patients to report

transient issues during the initiation phase (15) that can be clinically managed.

## Mental health fluctuations

While KMT shows promising potential as a mental health intervention, it's important to recognize that the initial phase of the diet may not be a linear journey toward improvement for all individuals. For example, patients with bipolar disorder can sometimes experience a temporary worsening of symptoms before sustained symptom improvements occur.

During this initiation phase, patients may require additional support and contact from their KMT treatment team. Prescribers, in particular, may need to make themselves more available for consultations or symptom monitoring and may need to provide bridge medications and be open to appropriate deprescription (16). Mental health professionals can play a vital role in providing ongoing support and monitoring of symptoms, which can be used to help prescribers assess the patient's needs.

As of now, further research is needed to fully elucidate the underlying mechanisms and specific patient profiles that may be more prone to these fluctuations. Nevertheless, the potential benefits of KMT, including symptom reduction and even remission of serious mental illnesses, often outweigh these temporary challenges for patients.

## Societal pressures and relationship dynamics

Individuals from diverse ethnic backgrounds, for whom family and holiday gatherings are centered around traditional foods, have highlighted the unique challenges they face in their social groups. Some have found that educating family members over an extended period and taking proactive steps, such as bringing their KMT-friendly dishes to events, can help ease the transition and maintain familial bonds (17, 18).

Different age groups and demographic backgrounds may experience these societal pressures differently. Teenagers and young adults, for example, may grapple with the desire to conform to peer dietary norms, experiencing feelings of exclusion when abstaining from certain foods. Those who frequently dine out may encounter difficulties finding restaurants with suitable menu options or may face predetermined meal choices that do not meet KMT requirements.

Patients often describe societal pressures as a notable challenge when initiating and maintaining Ketogenic Metabolic Therapy (KMT) for mental health. They recount instances where omitting carbohydrates from meals or declining carbohydrate-rich dishes leads to unexpected and sometimes distressing interactions with friends and family. These reactions can range from intrusive questioning to outright disapproval. Patients have reported clashes with prevailing notions of a well-balanced diet and warnings from misinformed individuals. Sometimes, the shift into carbohydrate restriction can strain existing friendships and family relationships. The dynamic can be similar clinically to someone with alcohol use disorder attempting abstinence and trying to find ways to connect with their social drinking circle. Patients often express uncertainty about navigating these changing dynamics.

Societal pressure and the desire to feel included in social situations can put patients at risk for symptom relapse. Within my clinical practice, this has definitely been a factor. This does not mean that the diet is "unsustainable" so much as some patients may need an extended period of check-in and support to help them both make the connection between their symptom relapse and their going off the diet and to allow them to reinitiate therapy in a supportive and non-judgmental environment. It has been my experience that often, these relapses happen after an extended period of wellness and an exit from regular psychotherapy because of symptom remission. At this point, it is unclear which patients need or would benefit from extended check-ins or support or if such extended support would lead to reduced relapse of symptoms in mental health populations using KMT.

However, while societal influences can initially pose challenges and require careful planning and the development of tools to facilitate healthy boundaries and relationship behaviors, the significant benefits that patients experience with KMT often outweigh these pressures. As patients witness improvements in their mental well-being, they frequently view societal expectations as a minor inconvenience compared to the reduction of symptoms they experience.

Overall, what I see in my practice with patients is empowerment occurs when they experience that they can take active control of their health through dietary choices. I cannot express how important this is for a population that has been told they have a chronic, debilitating lifelong illness for which, in the past, only symptom management was possible.

## Benefits observed in clinical practice

In the realm of mental health care, the implementation of Ketogenic Metabolic Therapy (KMT) has brought forth a spectrum of benefits for my patients that extend far beyond merely symptom management. As a clinician with hands-on experience using ketogenic diets as a treatment for mental illness, I've had the privilege of witnessing these transformations firsthand in populations in which I had begun not to expect significant improvement, let alone the levels of remission that occurred.

Many of my patients using this treatment report remarkable improvement in their cognitive function. Any clinician who works with mental health populations knows that patients complain of cognitive symptoms as much, if not sometimes more so, than the mood symptoms that brought them for treatment (19). Most patients I have worked with using this treatment describe heightened focus, better decision-making capabilities, and a noticeable reduction in the pervasive cognitive impairment they describe as brain fog. For these individuals, regaining their cognitive capacity played a large role in them being able to reclaim control over their lives.

Another clinical observation pertains to emotional stability. Patients who have undergone KMT often report a significant stabilization in their moods. They describe an experience in which they are able to take life as it comes and be much less overwhelmed. What my patients describe is a newfound emotional resiliency that some are rediscovering and others are experiencing for the first time in their lives. The benefit of having a predictable and balanced emotional state, along with the improvements in cognitive functioning, has had profound ripple effects on their daily lives and relationships.

Beyond addressing mental health symptoms, KMT has often led to reports by my patients of more holistic improvements in their well-being. They report increased energy levels, better sleep patterns, and restorative rest, which for many has not occurred for decades with

pharmaceutical assistance. These additional holistic benefits highlight the interconnectedness of mental and physical health and the potential that ketogenic diets hold as a comprehensive therapeutic approach for the complex populations and presentations we encounter as mental health professionals.

## The future of competent treatment teams for KMT implementation

Controlled research settings by design offer exemplary support and consideration for participants needed to establish the efficacy and safety of this therapy. Private clinicians may struggle to help patients put together competent and experienced treatment teams for their patients. Ideally, this would consist of prescribers trained in ketogenic diet-informed medication adjustment, mental health practitioners who understand their role in using their counseling skills to support diet adherence, and access to ketogenic diet-trained nutritionists and dieticians who are comfortable working with individuals suffering from mental illness. Luckily, more and more professionally accredited training programs are being developed and offered for practitioners in each of these roles, and I am of the optimistic outlook that access to professionals trained in this therapy will increase. Even one professional appropriately trained in one of these roles and encouraged in collaborative practices may be able to improve outcomes for patients using KMT as a treatment for mental illness.

## The value in capturing qualitative data

In my experience, the changes I see in my patients benefiting from this treatment are just not adequately quantifiable. While we can celebrate large quantitative differences in mood symptom checklists and objective clinical assessments as they are published in the peer-reviewed literature, I would implore researchers to also capture qualitative data in various forms. The analysis of qualitative data can help the mental health field determine many important outcome measures in terms of implementing the diet with different populations and conditions. There is valuable insight into its successful or unsuccessful implementation with different ages, diagnoses, socioeconomic status, and a variety of other variables that clinical psychologists or other qualitative researchers could mine for valuable insights (20). As the field of clinical psychology will undoubtedly attempt to incorporate KMT into biopsychosocial models of practice, further research and tailored supports are expected to emerge, offering valuable insights for specific diagnostic populations.

Researchers who do not have access to professionals in fields that specialize in qualitative analysis have a special opportunity to work together to advance clinical practice. Psychiatrists and other mental health professionals will benefit from the practical treatment knowledge that will inevitably come from such analysis with better and more targeted interventions to show for the effort made. The collection of qualitative data could even be used to project long-term benefits in terms of costs associated with the healthcare system or even quality-of-life measures within families and communities that have vast implications (21, 22) and may be of generational significance. Why would I make such a strong statement about the benefits of measuring qualitative data alongside the hard biological markers and quantitative data already being collected by eminent researchers in this field? Because due to my training in clinical psychology and human development, I understand intimately that when you improve the mood, cognitive function, and emotional capacity of a parent (23), partner, sibling, or child, the ripple effect within the well-being of that system and the community around them is exponential (24) and possibly one of our greatest challenges to measure and celebrate.

## Concluding thoughts

There is great potential for a combined effort between researchers and clinicians to advance the field of mental health. The integration of KMT into existing mental health treatment systems of care represents a significant advancement in the field. Moving forward, it is crucial that we continue conducting rigorous research, valuing the nuanced insights from individual experiences, and fostering interdisciplinary collaborations. Together, we all have significant roles to play in increasing access to patients who are suffering from symptoms of mental illness. These patients should have the right to access this form of care from the very beginning of their difficulties. It is my perspective that this should not become a treatment of last resort, reserved for those who have met the criteria as being "treatment resistant," nor should it be seen as merely an adjunctive treatment that "helps" the existing standard of care. In my clinical experience, KMT has been the intervention with the most profound and powerful treatment benefits for patients with mental illness. For that reason, our efforts in the field to study it, master it, and bring it to the masses as a standard of care become a moral and ethical imperative to a population we have inadvertently underserved for far too long (25).

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

NL: Writing – original draft.

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# Ketogenic diet and behavior: insights from experimental studies

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As a journal page for full details. The ketogenic diet (KD) has been established as a treatment for epilepsy, but more recently it has been explored as an alternative or add-on therapy for many other diseases ranging from weight loss to neurological disorders. Animal models are widely used in studies investigating the therapeutic effects of the KD as well as underlying mechanisms. Especially in the context of neurological, psychiatric, and neurodevelopmental disorders essential endpoints are assessed by behavioral and motor tests. Here we summarized research evaluating the influence of the KD on cognition, depressive and anxiety-related behaviors, and social and nutritional behaviors of laboratory rodents. Each section contains a brief description of commonly used behavioral tests highlighting their limitations. Ninety original research articles, written in English, performed on mice or rats, providing measurement of blood beta-hydroxybutyrate (BHB) levels and behavioral evaluation were selected for the review. The majority of research performed in various disease models shows that the KD positively impacts cognition. Almost an equal number of studies report a reduction or no effect of the KD on depressive-related behaviors. For anxiety-related behaviors, the majority of studies show no effect. Despite the increasing use of the KD in weight loss and its appetite-reducing properties the behavioral evaluation of appetite regulation has not been addressed in preclinical studies. This review provides an overview of the behavioral effects of nutritional ketosis addressed to a broad audience of scientists interested in the KD field but not necessarily specializing in behavioral tests.

KEYWORDS

**ketogenic diet, cognition, depressive-like behavior, anxiety-like behavior, social behavior, nutritional behavior, nutritional ketosis, animal models**

## 1 Introduction

The ketogenic diet (KD) is a very low-carbohydrate, high-fat, and adequate protein nutritional approach that induces a metabolic shift to the use of ketone bodies as an additional energy source (1, 2). In the 1920s, physicians introduced the KD as a treatment for epilepsy, especially in patients poorly responding to pharmacotherapy. By the end of the XX century, the KD resurfaced, gaining popularity with the general public mainly due

to its efficiency in treating obesity (3). Scientific interest in the KD also significantly increased, as illustrated by the fact that a PubMed search for 'ketogenic diet' shows 254 results until 2000 and 4,682 hits in the years 2000–2023. As a result of extensive research, it is now well established that, besides the well-known metabolic effects including ketosis and decreased blood glucose levels, the KD influences inflammatory processes, oxidative stress, gut microbiota, and intracellular signaling pathways (4–6). The KD also has a pleiotropic impact on brain functioning, including gene expression (7–9), neurotransmission (10), the level of neurotrophic factors (11, 12), protein phosphorylation (13), and the metabolism of amino acids (14). Due to this multifaceted effect on physiology, the KD has been increasingly investigated as an alternative or add-on therapy for many diseases (15, 16). Findings from large-scale clinical trials remain limited, and animal models are widely utilized in studies investigating the therapeutic effects of the KD as well as underlying mechanisms. Especially in the context of neurological, psychiatric, and neurodevelopmental disorders, essential endpoints are evaluated by behavioral tests, including the assessment of cognitive functions, and behaviors related to anxiety and depression. The examination of social behavior is important in studies related to Autism Spectrum Disorders (ASD). The reduction of appetite is considered crucial for the effectiveness of the KD in treating obesity in humans (17, 18). Therefore, the influence of the ketogenic diet on nutritional behavior is another interesting aspect that can be explored using animal models.

While there are several important considerations when designing behavioral experiments in animal models, one particularly crucial aspect in the KD field is the composition of the chow. Numerous variations of ketogenic chows are employed in animal research, with the most significant distinctions revolving around the macronutrient ratio, source of fat as well as macronutrient and vitamin content (19, 20). Appropriately chosen macronutrient ratio, not only carbohydrate restriction but also adequate protein content, determines the level of ketosis (21). In addition, particular fat content like medium chain triglycerides (MCT) can enhance ketone production (22–24). Since possible nutrient deficiencies resulting from a very restrictive diet are a common adverse effect of KD in humans (25), currently, a lot of attention is given to the composition of a dietary plan. The same should apply to animal models, where proper micronutrient supplementation of the ketogenic chow is critical to avoid adverse effects such as weakness and growth inhibition (26, 27).

Here, we review studies examining the influence of KD on the behavior of laboratory rodents. Included in the review were only studies that reported the level of ketosis, ensuring a minimal requirement in terms of diet composition for achieving nutritional ketosis. The article is organized into sections dedicated to cognition, depressive and anxiety-related behaviors, as well as social and nutritional behavior. Each section begins with a concise explanation of the rationale for assessing specific behaviors within the context of nutritional ketosis. Evaluation of animal behavior, interpretation of results, and translation of the findings to the clinically relevant situation require an understanding of the behavioral tests employed and inherent their limitations. Consequently, each section offers a brief overview of the available methods for evaluating the behavior in question, highlighting both limitations and potential caveats in result interpretation.

## 2 Search strategy and study selection

The term "ketogenic diet" was searched in PubMed without a year-of-publication restriction identifying 4,918. Only articles written in English were included. Articles were divided among all authors for screening of titles and abstracts in order to select full-text original papers conducted on mice or rats. In this first step of screening 880 publications were included and full texts were independently reviewed by two investigators in order to select studies showing behavioral or functional tests investigating: depressive-, and anxiety-related behaviors, cognition, and social behavior. One hundred and forty-five studies were selected for evaluation of eligibility. Separate screening was performed to identify studies reporting food intake which was discussed as an approximate of nutritional behavior.

This screening resulted in the identification of 65 articles. Only studies reporting the level of ketosis, as a measurement of blood beta-hydroxybutyrate (BHB) level, were included. Finally, 90 articles were included in the review. The last search was performed on September 26th, 2023. The flow chart illustrating the article selection process is shown in Figure 1.

## 3 Behavioral effects of KD treatment

### 3.1 Cognition

Nutritional ketosis reduces neuroinflammation, and oxidative stress, and improves mitochondrial function (28, 29). All these processes have a profound impact on brain health and in turn on neurocognitive functions. The neuroprotective properties of KDs were demonstrated in animal models of epilepsy, aging, dementia, and neurodegenerative diseases (30–32).

Cognition is a very complex construct that encompasses several aspects of intellectual functioning. Therefore, results arising from animal studies can only capture some of the meanings of this term.

Despite the availability of a variety of tests that measure slightly different, but also overlapping and interacting aspects of cognition, obtaining reliable and disease-relevant results requires careful choice of methods and usually using a combination of different paradigms.

The most commonly used behavioral test to measure impairment of cognitive functions is the Morris water maze (MWM). The MWM paradigm is designed to assess spatial learning and long-term memory by observing and recording escape latency, thigmotaxis duration, distance moved, and velocity during the time spent in the circular water tank with a hidden platform, where rodents are required to find the escape route to the platform by remembering visual cues (33). Another common test to evaluate learning and memory, particularly recognition memory, is the novel object recognition test (NOR). NOR test uses innate preference to interact with unknown objects in relation to known objects (e.g., blocks, balls) (34). Other behavioral tests used in animal studies involve modifications of maze tasks, for example, Y-maze, T-maze, V-maze, Hebb Williams Maze, or Barnes Maze. Above-described tests can be used to assess the rodents' short- and long-term memory, learning, and spatial learning (35). It is important to note that the tests evaluating cognitive functions depend on the exploratory behavior of animals and their interaction with the environment. Other parameters like locomotor activity or levels of anxiety can significantly impact the outcomes of cognitive

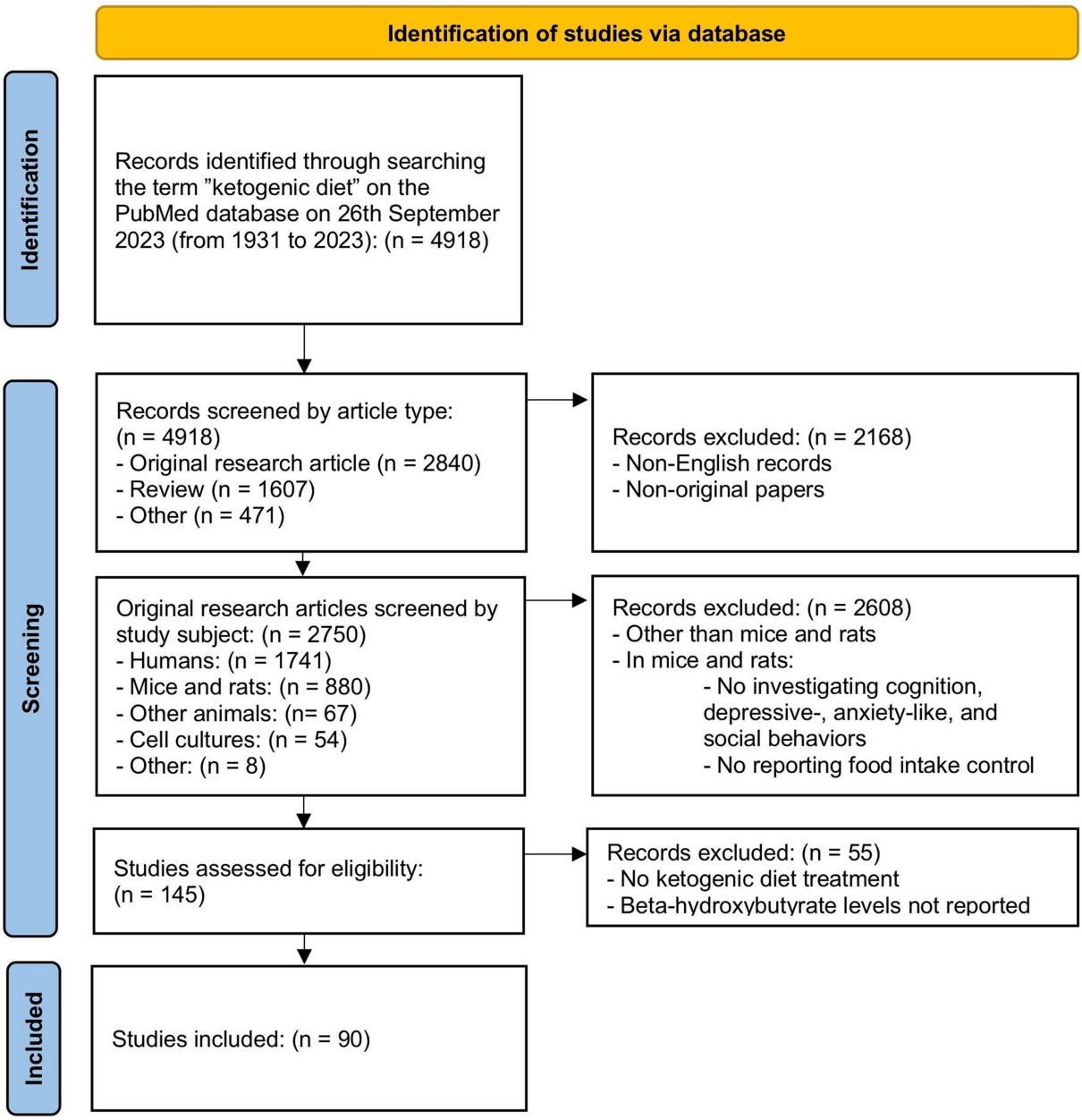


FIGURE 1
Flow chart showing the procedure of studies selection included in review.

performance during tests, in addition to cognitive abilities themselves. In some paradigms, palatable food is used as a reward for conditional learning. Using these tests when comparing animals fed with KD or standard diet requires careful consideration since the animals fed with different diets may have various levels of motivation towards obtaining food. Moreover, an inappropriately selected snack may influence the level of ketosis.

The impact of KD on cognitive functions is most commonly described in epilepsy (37–44), traumatic brain injury (TBI) (45–49), Alzheimer's disease (AD) (50–54), and also in healthy animals (55–62) especially in the context of aging (63–72).

In the animal models of epilepsy, it was reported in nine research articles (37–44). Despite the indisputable anti-seizure effects of KD, these studies do not bring unequivocal results regarding cognitive function. In different animal models of epilepsy: electrically elicited (kindled) seizures (36), spontaneously epileptic Kcna1-null mice (37), the pilocarpine-induced status epilepticus (38), and the pentylenetetrazol (PTZ)-kindled model (39) KD treatment led to improved memory functions. In the PTZ-kindled model of epilepsy KD improved spatial memory in the novel placement recognition test in rats, without changes in memory acquisition based on the MWM test results (39). Su et al. (40) drew attention to the importance of the timing of KD initiation in the pharmacological model of epilepsy, showing that early KD initiation (2 days after status epilepticus) resulted in weaker spatial learning in the MWM than observed in rats on a control diet or rats that started the KD 2 weeks after status

epilepticus. In the context of epilepsy seizure activity is a primary cause of cognitive deficits (73, 74). Therefore, it is possible that the cognition-enhancing effect of the KD observed in the models of epilepsy is an indirect result of seizure mitigation. However, despite effective seizure mitigation, no improvements in cognitive performance after KD treatment were observed in other studies in a genetic model for idiopathic epilepsy (42), kindling model of epilepsy (43), and Dravet syndrome model (44). One study conducted in the lithium pilocarpine model of epilepsy showed substantially worsened performances in the MWM of young rats treated with KD. The severe impairment in visual–spatial memory was accompanied by decreased brain growth (41). Interestingly, when applying the ketogenic chow of the same composition to rats just after weaning, we observed adverse effects such as weakness, growth inhibition, and brain undergrowth. These adverse effects were mitigated when we supplemented the diet with wheat bran (27). Similarly, other authors achieved a significant reduction in adverse effects of the same ketogenic chow through supplementation with choline or methionine (26). It is important to mention that the same ketogenic chow (Bio-Serv F3666) used in mice, for example, in spontaneously epileptic Kcna1-null mice (37), in a TBI model (47) or in naive mice, led to improved cognitive measures. These studies are discussed in the further part of this section.

In the context of aging, healthspan, and lifespan numerous studies demonstrated improved cognitive function in KD-fed animals (63–72). KD treatment introduced at both old (20 months) and young (4 months) ages, enhanced cognition across the lifespan, regardless of sex. It resulted in enhanced performance on both the elevated figure-8 maze alternation task and a cognitive dual task that involved working memory. Also, the authors noted that the observed differences in protein expression related to metabolism and vesicular transport in the prefrontal cortex and hippocampus could contribute to the development of further therapies for age-related cognitive decline (68). Zhou et al. (63) showed that KD introduced at 18 months of age improved spatial learning and memory at 26 months of age. Roberts et al. (65) showed that aged male mice fed with KD show memory improvement in the NOR test as compared to the control but also to low-carbohydrate diet-fed animals. Authors suggested that nutritional ketosis, rather than the low glycemic index, affects index lifespan and slows down age-related cognitive impairment in old mice. In aged female mice after 2 months of KD, an improvement in spatial learning but no recognition memory or short-term working memory was observed (69). Newman et al. (64) reported that long-term exposure to the cyclic KD (given every other week) reduces mid-life mortality and preserves memory in aging males. Similarly, Hernandez et al. (67) found that time-restricted access to the KD in middle-aged mice positively affected cognitive functions compared to animals fed *ad libitum* with standard chow. Additionally, there were significant differences in gut microbiome diversity and composition in both diets. Authors suggested that improved cognition was associated with an altered gut microbiome, especially lowered *Allobaculum* abundance. Observed improvement may result from time-restricted feeding paradigm rather than macronutrient composition of KD and standard chow (67). These results provide evidence that the KD may beneficially affect cognitive function in female and male rodents, especially in middle-aged and old animals, not only after long-term exposure to diet (64, 65, 67–69), but also after a few weeks of treatment (66). On the other hand, exposure to KD from postnatal day (P) 20 - P32 for at least 5 weeks may adversely impact cognition later in life in laboratory rodents (40, 41, 71). Recently, Miles and Skelton (72) reported that early-life (from P21 through young adulthood ~P90) exposure to nutritional ketosis could impair learning and memory abilities. These data may suggest that the nutritional content of a KD is not sufficient to ensure proper neurodevelopment in young animals, while other studies argue that adequate composition of the diet (in terms of micronutrients and vitamins) is crucial for the health and development of young rodents fed with KD (26, 27, 75). We have previously demonstrated that modification of commonly used ketogenic chow allows for its application in developing rats, without causing detrimental side effects (27). Importantly, no adverse effects on neurodevelopment were observed in children using a KD to treat epilepsy (41). Hence, the observed underdevelopment and reduced cognitive abilities of young rodents fed with KD seem to be associated with inadequate composition of the diet or to be species-specific.

In animal models of TBI, the beneficial effect of the KD on cognition was demonstrated in four studies (45–48) while one study reported no effect (49). The KD-fed male adolescent (45–47) or young-adult rodents (47, 48) showed significantly improved recovery after injury and spatial memory in a variety of behavioral tests (MWM, NOR, or Y-maze) compared to the injured animals fed the control diet. Besides cognitive improvement, post-TBI KD administration resulted in better neurological outcomes including decreased degeneration of neurons in the dentate gyrus (45), attenuated neuroinflammation (46, 48), white matter damage, microgliosis (46), astrogliosis (45, 46), and oligodendrocyte loss (48), and improved sensorimotor functions (46, 48). Interestingly, Appelberg et al. (47) showed that KD introduced for 1 week immediately after TBI significantly improves cognitive recovery in adolescent rats but not in adult rats, suggesting that the effectiveness of ketones as an alternative fuel after TBI may be age-dependent. However, other authors demonstrate that applying an alternative KD formulation, with a fat-to-carbohydrate plus protein ratio of 2:1, containing MCT, docosahexaenoic acid, low glycemic index carbohydrates, fibers, and leucine, extends its neuroprotective potential in TBI to adult mice (48), again pointing out the importance of diet composition. One study reported that both pre-mild TBI and post-mild TBI exposure to the KD did not affect performance in novel context mismatch test in adolescent rats of both sexes. However, other parameters like balance and motor impairments, exploratory behavior, and telomere length were improved (49).

The observation that defective insulin signaling leading to decreased glucose metabolism may contribute to the progression of AD. It may be speculated that dietary interventions improving glucose and insulin metabolism might serve as a novel therapeutic approach to AD (76). Pre-clinical studies showed that the KD can mitigate some of the molecular and cellular changes associated with AD pathophysiology, resulting from enhancement in mitochondrial function, neuroprotection, reduction in neuroinflammatory response, and the expression of apoptotic mediators (21, 31). Moreover, the KD can help to eliminate brain amyloid-beta (Aβ) plaques by increasing the concentration of low density lipoprotein receptor-related protein 1 (LRP1), glycoprotein P (P-gp), and phosphatidylinositol binding clathrin assembly protein (PICALM) (77, 78). For instance, feeding with a KD decreased astroglial response to Aβ-plaques and lowered expression of the proinflammatory cytokines in the model of familial AD (79).

KD improved cognitive deficiency in female mice in a model of sleep deprivation-induced AD and a study with APP/PS1 mice, where KD was administered for 1 or 12 months (50, 51). While in female mice carrying the "London" APP mutation (APP/V717I) feeding with KD was not able to improve cognitive measures although it reduced Aβ40 and 42 levels by 25% (52). In other studies using genetic (APP/PS1, Tg4510) or pharmacological AD models (Aβ infusions) nutritional ketosis did not rescue memory deficits in a variety of experimental paradigms, varying in the time of KD exposure or diet composition (53, 54).

In addition to the aforementioned studies, there is further evidence indicating that nutritional ketosis can affect cognitive functions in animal models of neural disorders, stress, and obesity. KD administration improved cognition accompanied by histone modification in the model of neural disorders resulting from hypoxia injury (80), and Kmt2d+/βGeo mice (model of Kabuki syndrome) (81). A similar, positive effect of KD on cognition, related to peripheral metabolism (82) and biochemical changes in the hippocampus was shown in the rat model of chronic variable stress (83). We have previously shown that obesity-induced impairment in cognitive performance was ameliorated after weight loss achieved by either calorie restriction or KD. However, rats fed with a calorie-restricted KD performed better in MWM than those fed with a calorie-restricted standard diet (84). Finally, Fukushima et al. (55) concluded that the improvement in Y-maze performance may result from KD-induced increased hippocampal expression of the AMPA receptor subunit, GluR1 of naive adult rats. Also, the administration of KD with a ketogenic ratio of 6.6:0 has been shown to improve the Y-maze performance of naive adult rats in comparison to those fed with a standard diet. While no changes were observed with a ketogenic ratio of 3.0:0 (56). No effects of KD on cognition were reported in a few studies regarding synaptic functions (57–59), social behavior (60), evaluation of hippocampal involvement in spatial-cognitive behavior (61), or behavioral profiling (62) in wild type mice and rats.

Many studies suggest that a KD has a positive impact on cognition, especially in animal models of epilepsy, TBI, and aging. These studies generally report improvements, although sometimes there is no noticeable effect. The mitigation of cognitive impairment often goes hand in hand and may be secondary to other improvements in neurological and health outcomes such as reduced seizures in epilepsy models or reduced midlife mortality and improved health in old mice (64). However, in models of AD, the effects on cognition are usually moderate or even absent, despite reductions in amyloid deposition and other processes contributing to disease progression. In naive adult rodents, six articles report no effect (57–62), while two note cognition enhancement (55, 56). Four publications show that the application of a KD directly after weaning results in cognitive impairments later in life (40, 41, 71, 72).

## 3.2 Depressive-like behavior

The potential use of a KD in the treatment of depression is explored in the literature. Mechanisms through which a KD may potentially positively influence depression symptoms involve the modulation of the glutamate-glutamine cycle, gamma-aminobutyric acid (GABA) neurotransmission and, monoamine levels (85). Additionally, the diet provides nutrients such as ω-3 fatty acids, which may contribute to improvements in depression, and it may also influence the composition of the gut microbiota (86). It was proposed that KD through modulation of gut bacteria and its metabolites improves gut dysbiosis, decreases cytokine production, and lowers overall inflammation observed in depression (87). Another important finding underlying the therapeutic potential of nutritional ketosis comes from metabolic and behavioral analysis of Dravet mice fed with KD (44). KD reduced preference for saccharin in the sucrose preference test (SPT) in wild-type and Dravet mice, however, hippocampal levels of glutamate precursor α-ketoglutarate and α-D-glucose-1-phosphate correlated positively with saccharin preference in Dravet but not in wild-type mice (44). The SPT bases on natural rodents' preference to selectively drink sweet solution when given a two-bottle free-choice regimen with access to both sucrose solution and water. A reduction in the sucrose preference ratio is indicative of anhedonia used for detection of depressive-like behavior in rodents (88).

The influence of nutritional ketosis on depressive-like behaviors and stress response was investigated in a few experimental studies (49, 57, 71, 89–96). Four studies have reported that nutritional ketosis may positively impact depressive-like behaviors (89–91, 93), as measured by the forced swim test (FST) and tail suspension test (TST), two classical behavior paradigms designed to measure depression levels, including changes observed in response to acute stress (97). The prolonged immobility in TST and FST are used for estimating depression-related behavior. Both of these models work similarly in assessing behavioral symptoms of feeling despair but not anhedonia (98).

One of the studies revealed that KD-fed rats exhibited less immobility duration in the FST when compared to those fed the standard diet (89). Additionally, the other study found that young adult CD-1 mice-offspring of mothers fed with a KD during pregnancy, exhibited reduced susceptibility to anxiety and depression (93). These observations were confirmed by Arqoub et al. (90) who observed that gestational exposure to KD reduced the expression of depressive-like behaviors in the FST. The latest study by Guan et al. (91), revealed that KD treatment decreased immobility duration in the TST and FST, and increased sucrose preference in the anhedonia-based SPT in repeated social defeat stress (R-SDS) and lipopolysaccharide (LPS) depression models. In the most recent paper by Gumus et al. (94), a combination of regular voluntary exercise with a KD decreased depressive-like behaviors in adult male mice, which was correlated with a decline of insulin and glucose or low/high-density lipoprotein (LDL/HDL) ratio and an increase of BHB levels. To the best of our knowledge, no studies are reporting the worsening of depressive-like behaviors in nutritional ketosis. No influence of KD feeding on depressive-like behaviors was reported in naive animals (57, 95), and the genetic model of Fragile X Syndrome (96).

The results from experimental studies suggest that nutritional ketosis may exhibit a beneficial influence on depressive-like behaviors. Considering the applied experimental paradigms – application of diet before acute stress or *in utero* - the effect may have a preventive character. Moreover, the differences observed in the experimental designs (e.g., the type of diet used, and time of administration), further emphasize the pressing need to investigate the underlying biological mechanisms of the anti-depression effects of the KD. Considering the positive impact of KD on depressive-like

behavior, it might be postulated that nutritional ketosis might be used in depression treatment.

## 3.3 Anxiety-like behavior

The rationale behind the potential use of KD in anxiety disorders comes from its ability to counteract pathological changes in neurotransmission that are strongly linked to anxiety. These include GABA deficiency (99, 100) and increased neuronal excitability (15). The usefulness of the KD in anxiety disorders may also arise from its impact on gut microbiota, improvement of intestinal barrier function (101), its anti-inflammatory effects (102), and reduced production of reactive oxygen species (ROS) (103). The mechanisms substantiating the potential applicability of KDs in anxiety disorders were comprehensively discussed by Zhu et al. (15) and Wlodarczyk et al. (104) while the available clinical evidence was recently systematically reviewed by Dietch et al. (105).

Numerous behavioral tests have been developed to measure anxiety in rodents (106–108). In tests like open field, dark/light compartment tests, or elevated plus maze (EPM) the assessment of anxiety relies on the fact that laboratory rodents prefer closed and dark over open and light spaces (109). Other popular type of tests, used mostly for anxiolytic screening, are "conflict" tests like the Geller-Seifter or Vogel test, in which a hungry or thirsty animal is given an option to obtain, respectively, food or water by pressing a lever that can also elicit electric shock (110, 111). Due to the nature of anxiety tests separating anxiety, exploratory, activity, and learning responses is often not possible. Therefore, for the interpretation of results and understanding of their translational potential, it is crucial to recognize that a multitude of factors influences animal behavior in those tests. The overview of most common animal tests of anxiety alongside the consideration of conceptual issues regarding methodological details, interpretation of results, and intraspecies translation is comprehensively discussed in excellent reviews that focus on anxiety evaluation in preclinical settings (106–108).

Twenty articles evaluating the influence of nutritional ketosis on anxiety-related behaviors met the eligibility criteria for this review. Most data indicate that the KD does not influence anxiety-related behaviors (39, 55, 57, 60, 64, 69, 92, 95, 96, 112–115).

Among studies performed on rats, two reported positive effects of the KD on anxiety. Both young and aged naive rats fed with a KD showed resilience against the anxiogenic open arm in the EPM test (68). KD treatment showed protective properties by reducing anxiety levels in a model of TBI. Rats exposed to the KD post-injury showed reduced anxiety- and depressive-like behaviors acutely post-TBI. While pre-injury exposure to the KD resulted in even more pronounced improvement of outcomes like reduced balance and motor impairments (49). Interestingly, one study reported increased anxiety levels and decreased locomotor activity on a KD that were reversed by environmental enrichment (71). Other studies performed on rats report no effect of a KD on anxiety-related behaviors (39, 60, 95, 112, 113).

In naive mice, one study reported that a combination of a KD and regular voluntary exercise ameliorated anxiety and depression-like behaviors (Balb/c mice) (94). However, other studies performed on naive mice did not show changes in anxiety-related behaviors (55), also in the context of aging, in male and female mice, despite improvements in other neurocognitive functions (54, 69). Gestational exposure to a KD resulted in reduced susceptibility to anxiety and depression in adulthood, alongside many neuro-anatomical differences (93). Reduced anxiety under nutritional ketosis was also reported in a study performed on a model of ASD in BTBR mice (116). Moreover, a general improvement of autism symptoms after KD treatment was observed in numerous preclinical models of ASD (10, 116–119). Other research showed that a KD supplemented with ketone monoester reduced handling-induced convulsions and anxiety-like behaviors in early alcohol withdrawal (120). The tendency toward lower anxiety-like behaviors was reported in other studies performed on mice including the model of MPC1 deficiency in adult glutamatergic neurons (114) or Fragile X Syndrome (96), but none of the studies reported anxiogenic effects of nutritional ketosis. Interestingly, a study evaluating the effects of chronic or subchronic (7 days) administration of exogenous ketones alongside a standard diet reported a reduction of anxiety assessed with EPM test in all treatment conditions (121). Summing up, studies evaluating anxiety-related behaviors in nutritional ketosis report either no effect or reduced anxiety in the majority. The latter seems to be an indirect effect originating from the mitigation of pathophysiological changes specific to the examined disease model.

## 3.4 Social behavior

Given the beneficial effect of nutritional ketosis on epilepsy, mitochondrial function, carbohydrate metabolism, and inflammation, it has been proposed that treatment with a KD has the potential to reduce some of the ASD-associated symptoms, including impaired social interactions (122). The social behavior of laboratory rodents is most commonly evaluated with a 3-chamber test which allows for assessing sociability (time spent in the chamber with mouse vs. chamber with object) and preference for social novelty (time spent with unknown vs. known mouse). Other commonly used tests include: social transmission of food preference or analysis of the social activity in a home cage where behaviors like sniffing and following are analyzed, or in the case of juvenile rodents, also play responses like evasion or rotation (123, 124). The influence of the KD on social behavior has been tested in nine experimental studies (10, 57, 60, 90, 115–119). Studies conducted in rodent models of ASD, i.e., the BTBR model (116), the prenatal valproic acid (VPA) model (117), Shank$^{3+/\Delta C}$ mice (115), *Engrailed* 2 null mice (10, 118), and the maternal immune activation model of ASD (119) reported improvement of social deficits. An increase in social activity has also been reported in wild-type rats fed with a KD (60, 117) and in offsprings of dams fed a KD during gestation (90). Only one study reported that feeding with KD has not affected sociability in naive mice (57). Despite differences in the used models, age of the animals, time of the treatment, and employed behavioral tests, most of all these studies coherently show the increased social activity of rodents fed with the KD. This suggests that the mechanism by which the KD increases social activity is independent of the alterations underlying social impairment. Another line of evidence supporting this conclusion will be the observation that KD-induced reduction in social impairment in BTBR mice is not secondary to the well-known antiepileptic properties of this diet (116). It can be hypothesized that increased social activity results from other behavioral changes like

increased arousal which translates to greater locomotor activity or reduced anxiety which leads to enhanced interest in the environment in general. However, neither reduced anxiety, increased locomotor activity nor changes in memory were reported in the studies mentioned above (10, 60). The effect is not persistent since the level of social activity is restored to control levels after the cessation of the diet (10, 60). In contrast, KD ameliorated autism-like social deficits observed in Shank$^{3+/\Delta C}$ mice, and this positive impact endured for up to 6 weeks after discontinuation of the diet (115). Most of the above-mentioned studies were conducted on male rodents, however, it has been also demonstrated that in *Engrailed* 2 null mice KD improved multiple measures of sociability in females, with limited effects in males (118). Although mechanisms underlying changes in social behavior in nutritional ketosis have not been deeply investigated, some insight was provided by Verpeut et al. (10) in the study performed on *Engrailed* 2 null mice, where immunohistochemical analysis demonstrated that groups exposed to the KD, regardless of genotype, showed increased neuronal activation in response to novel animal exposure. The KD-fed animals had more c-Fos positive cells in brain regions associated with social behaviors including the cingulate cortex, lateral septal nuclei, and anterior bed nucleus of the stria terminalis (10). This supports the idea that an increase in various aspects of sociability observed in the abovementioned studies arises from the impact of the KD on neuronal circuits controlling social behavior, independently of particular pathology underlying social impairment in used disease models.

## 3.5 Nutritional behavior

The KD is increasingly used for the treatment of obesity and as an add-on therapy in the management of type 2 diabetes (T2DM) (125). Meta-analyses comparing the effectivity of KDs to low-fat diets consistently show slightly greater weight loss, improved HDL-cholesterol, triacylglycerol (TAG), and other cardiometabolic markers but increased LDL-cholesterol (126–128). Although there is no consensus on the precise mechanism that determines the efficiency of weight loss under nutritional ketosis suppression of appetite is considered the play a leading role (17, 129, 130). Increased feeling of hunger is a common side effect of diet-induced weight loss that in the long term leads to reduced patient adherence compromising the results of the therapy and finally promoting weight regain (131, 132). Therefore understanding the mechanism of appetite suppression on a KD can significantly contribute to the improvement of weight loss therapies both in terms of lifestyle intervention as well as the development of new drugs. Studying the appetite-controlling neuroendocrine network on molecular and cellular levels is almost exclusively possible with the use of animal models. However, a question arises if animal models are suitable for studying appetite regulation under nutritional ketosis, i.e., if reduction of appetite occurs in laboratory rodents fed with the KD and how it can be measured, and finally what are the best experimental conditions to reflect the human situation. In the field of nutrition obesity on the behavior of rodents is most commonly evaluated by measuring food intake expressed in grams or in calories if different diets are compared. The most common methods for quantifying food consumption are manual weighing of the chow, but also automated chow counters, pellet dispensers, or video monitoring (133). The important factor compromising the accuracy of these methods is the fact that not the whole amount of chow leaving the food containers is consumed by animals. Especially in the case of high-fat diets (HFD) due to their consistency the chow crumbles (or is shredded by the animals) and falls into the bedding. This impacts the reliability of comparison between chows having various consistencies like standard chow and ketogenic chow. Another aspect important for methodological considerations is performing food deprivation studies or using food as a reward or reinforcement. Inappropriately chosen snack may lower the level of nutritional ketosis. Moreover, animals fed with different diets (standard and KD) may vary in their interaction with food, e.g., the motivation to obtain food, or may have different fasting tolerance. In the first couple of days after switching to a KD rodents usually reduce food/calorie intake (134–136). This reflects the need to acclimate to the type and consistency of new chow rather than a reduction of appetite since the calorie intake quickly goes back to baseline levels (134–136). After the habituation period, rodents fed with a KD usually consume less food expressed in grams but equal calories as the animals fed with standard chow. This trend was observed in wild-type animals fed with KD for up to 2 months (26, 55, 57, 83, 137–141) or longer (58, 142–145) as well as in different disease models like T2DM model (146), AD model (54), in the stress model (92), glaucoma model in both females and males (147), models of hepatic enzyme disturbances (148, 149), and in acute alcohol withdrawal symptoms (120). However, despite the equivalent caloric intake, feeding with KD often results in improved body mass (26, 83, 138, 140, 144) and metabolic health in long-term treatment (65). In some studies, rodents fed with KD consumed more calories than chow-fed controls, which was probably associated with lower energy assimilation because weight gain was not increased (44, 60, 95, 135, 150–158). One exception is a study in the model of Dravet syndrome where increased calorie intake was accompanied by increased body weight probably resulting from improvement of other disease symptoms (44). Decreased calorie intake, accompanied by decreased body weight during nutritional ketosis was reported in a couple of studies (53, 159–163). Taken together the majority of studies show that a KD, in comparison to standard chow, does not induce a spontaneous reduction in food intake. This suggests that the reduction in appetite observed in humans following a KD either does not occur in laboratory rodents, at least when compared to a standard chow, or is not detected through routine monitoring of food intake.

To answer the question of whether rodent models can be used to study mechanisms of appetite regulation under nutritional ketosis assessment of appetite could be performed in conditions where animals significantly overeat. This can be achieved by testing the changes in the appetite of diet induced obesity (DIO) animals after switching them to a standard or KD or by offering palatable snacks to animals fed with either KD or standard diet. It is a matter of ongoing discussion whether the disruption of homeostatic hunger regulation or the hedonic reward system governs overeating in rodents exposed to HFDs (164).

Therefore, experimental conditions need to be planned carefully with consideration of the underlying neuroendocrine status, choice of food/snacks, and test methods. Not only monitoring food intake but also applying behavioral tests like the food/risk competition test or food preference test would be informative (165). According to our best knowledge, such studies have not been performed so far. However, one study showed that animals previously fed with KD or HFD

preferred to obtain morecalories from HFD, than animals fed with standard chow (55).

Laboratory rodents are widely used in research exploring mechanisms of KD action. However, the aspect of appetite regulation was not addressed in those studies so far and it remains an open question whether animal models are adequate research tools in this regard. Multiple factors including the differences in feeding patterns of humans and laboratory rodents or mechanisms that govern overeating need to be taken into account. Although study design seems to be challenging, the potential benefits of understanding KD-induced changes in the neuroendocrine network controlling appetite may have implications for the treatment of obesity that go beyond the use of the KD itself.

## 4 Summary

The majority of research performed in various disease models shows that the KD positively impacts cognition, especially in the models of epilepsy, TBI, and aging but also in naive animals (Supplementary Table S1). Almost an equal number of studies reports a reduction or no effect of the KD on depressive-related behaviors.

For anxiety-related behaviors, the majority of studies show no effect of the KD treatment. The adverse influence of the KD on cognition, anxiety-, and depressive-related behaviors was rarely reported (Table 1). Beneficial effects observed in behavioral measures seem to arise from the neuroprotective properties of the KD. Since the behavioral changes are accompanied by improvements in other outcomes specific to a disease model. In contrast, the increase in social activity seems to be unspecific and independent of the underlying cause of social impairment.

Despite the growing use of the KD in the treatment of obesity, accompanied by scientifically proven efficiency and appetite-reducing properties of the KD, the aspect of nutritional behavior of KD-fed animals has not been addressed so far. It remains an open question whether animal models are adequate research tools to study appetite regulation under nutritional ketosis.

Using animal models to evaluate the influence of the KD on behavioral measures requires paying special attention to the composition of the diet. While the proper macronutrient ratio is reflected by elevated blood BHB levels, an adequate micronutrient supply must be provided to avoid malnutrition that will affect behavioral measures (26, 27, 75). A couple of studies point out that additional supplementation of the KD with, e.g., MCT, ketogenic amino acids, or exogenous ketones may impact not only physiological but also behavioral effects of the diet in laboratory animals (48, 166) but also in humans (167). Although currently, many scientists acknowledge the significance of the KD's composition in determining

TABLE 1 The behavioral effects of ketogenic diet treatment.

| | | Behavioral outcome | | | | | |
|---|---|---|---|---|---|---|---|
| | Research area | Positive effect | *n* | No effect | *n* | Negative effect | *n* |
| Cognition | Naive animals | (55, 56) | 2 | (57–62) | 6 | – | – |
| | Epilepsy | (37–39, 36) | 4 | (42–44) | 3 | (40, 41) | 2 |
| | Traumatic brain injury | (45–48) | 4 | (49) | 1 | – | – |
| | Aging | (63–70) | 8 | – | – | – | – |
| | Alzheimer's disease | (50, 51) | 2 | (52–54) | 3 | – | – |
| | Neurodevelopment | – | – | – | – | (40, 41, 71, 72) | 4 |
| | Other | (80–84) | 5 | – | – | – | – |
| Depression-related behavior | Naive animals | (71, 89) | 2 | (86, 95) | 2 | – | - |
| | Stress | (91) | 1 | (92) | 1 | – | – |
| | Prenatal exposure | (90, 93) | 2 | – | – | – | – |
| | Other | (49, 95) | 2 | (96) | 1 | – | – |
| Anxiety-related behavior | Naive animals | – | – | (55, 57, 60, 95, 112) | 5 | – | – |
| | Epilepsy | – | – | (39) | 1 | – | – |
| | Traumatic brain injury | (49) | 1 | – | - | – | – |
| | Aging | (68) | 1 | (64, 69, 113) | 3 | – | – |
| | Neurodevelopment | – | – | – | – | (71) | 1 |
| | Stress | – | – | (92) | 1 | – | – |
| | Prenatal exposure | (93) | 1 | - | - | – | – |
| | Autism spectrum disorders | (116) | 1 | (115) | 1 | – | – |
| | Other | (94, 120) | 2 | (96, 114) | 2 | – | – |
| Social behavior | Naive animals | (60, 90) | 2 | (57) | 1 | – | – |
| | Autism spectrum disorders | (10, 115–119) | 6 | – | – | – | – |

its properties, most studies primarily investigate its effects in comparison to standard rodent chow. The differences between KDs of various compositions are rarely tested. Therefore, drawing direct conclusions about the role of diet composition or the presence of a particular ingredient that would be backed by strong scientific evidence is usually not possible.

## Author contributions

KG: Investigation, Visualization, Writing – original draft. MG: Investigation, Writing – original draft. MP: Investigation, Writing – original draft. NP: Investigation, Writing – original draft. JJB: Conceptualization, Supervision, Writing – review & editing. MN-Ch: Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. DL: Conceptualization, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1322509/full#supplementary-material

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## Glossary

| | |
|---|---|
| AD | Alzheimer's disease |
| ASD | Autism spectrum disorders |
| Aβ | Amyloid-beta |
| BHB | Beta-hydroxybutyrate |
| DIO | Diet-induced obesity |
| EPM | Elevated plus maze |
| FST | Forced swim test |
| GABA | Gamma-aminobutyric acid |
| HDL | High-density lipoprotein |
| HFD | High fat diet |
| KD | Ketogenic diet |
| LDL | Low-density lipoprotein |
| LPS | Lipopolysaccharide |
| LRP1 | Low density lipoprotein receptor-related protein 1 |
| MCT | Medium chain triglycerides |
| MWM | Morris water maze |
| NOR | Novel object recognition |
| P-gp | Glycoprotein P |
| PICALM | Phosphatidylinositol binding clathrin assembly protein |
| PTZ | Pentylenetetrazol |
| R-SDS | Repeated social defeat stress |
| ROS | Reactive oxygen species |
| SPT | Sucrose preference test |
| T2DM | Type 2 diabetes |
| TAG | Triacylglycerol |
| TBI | Traumatic brain injury |
| TST | Tail suspension test |
| VPA | Valproic acid |

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# Specifically formulated ketogenic, low carbohydrate, and carnivore diets can prevent migraine: a perspective

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This article presents a hypothesis explaining the cause of migraines, suggesting that electrolyte imbalance, specifically a lack of sufficient sodium in the extracellular space of sensory neurons, leads to failed action potentials. The author argues that migraines are triggered when sodium channels fail to initiate action potentials, preventing communication between neurons. The article discusses the evolutionary perspective of the migraine brain, stating that migraineurs have a hypersensitive brain with more sensory neuronal connections, making them more reactive to environmental stimuli and in need of more minerals for the increased sensory neuronal communication. Since glucose is often used to reduce serum hypernatremia, it follows that a high carbohydrate diet reduces sodium availability for use in the brain, causing an electrolyte imbalance. Low carbohydrate diets, such as ketogenic, low carb-high fat (LCHF), and carnivore (all animal products), can be beneficial for migraineurs by reducing/eliminating carbohydrate intake, thereby increasing sodium availability. In support, many research papers and some anecdotal evidences are referred to. The article concludes by proposing lifestyle modifications, such as dietary changes and sodium intake management. These will provide migraineurs with a long-term healthy metabolic foundation helping them to maintain strong nutritional adherence and with that aiding continued proper neuronal functioning and migraine free life.

KEYWORDS

**migraine, hypersensory, ketogenic, LCHF, carbohydrate, salt, metabolic, carnivore**

## 1 Introduction

Migraine is one of the top 10 most disabling conditions, leading to much suffering and negative lifestyle consequences, including loss of work (1). Current treatments available for migraine headaches are not effective; most of them do not work, or if they do, they have very serious side effects. Migraine medications aim to reduce or prevent headache symptoms but do not stop or prevent the migraine itself. Headache is just one very common but nonessential symptom of migraines. There is no scientific consensus on the cause of migraine. Disparate research areas are heading in different directions, suggesting various mechanisms. Not only is migraine not understood, but some of the medications prescribed for it have unknown mechanisms of actions, like Flunarizine (Flumig or Sibelium) (2), Amitriptyline (Elavil) (3), Levetiracetam (Keppra) (4) and many others. Migraine is a "black box" condition. Yet interestingly these and most other drugs for migraine do tap into the same areas this paper covers, only, as the reader will see, they hinder rather than support healthy brain activity.

That migraine is little understood can be seen by the variety of studies that try to define what it is and what it is caused by. Researchers usually look to food triggers (5), environmental variables like the weather (6), vascular conditions, or hormonal changes (7), and even suggest that migraine is predominantly a "woman's disease" (8) and therefore female hormones are often blamed. While the majority of migraineurs are female, a large percent of them is menopausal or post-menopausal and, of course, how do we account for the small but still present male and child populations with migraines? And how do we account for those females who do not get migraines from their hormonal variations? In fact, in the years prior to puberty, migraine is more common among boys than girls (9), and colic is suspected to be an infant migraine presentation (10). Clearly, while hormones may make things worse in migraine, they cannot possibly be the cause of it.

While other suggestions are more general in nature, many of them can be eliminated from further consideration by the available evidence. Migraines have also been associated with anxiety and other psychiatric disorders (11), vascular disease (disease of the blood vessels), cardiovascular disease (disease involving the heart) (12, 13), MTHFR gene polymorphism (14), contraceptives (15), stroke (16), increased matrix metalloproteinase activity (17), oxidative stress (18, 19), neuropathy (20), blood-sugar level variations (21), maladaptive stress response (22), and metabolic disease (17, 23, 24). And with each field so narrowly defined, it is hard, if not impossible, for specialists within any one of these fields to look outside and find patterns of similarities and differences, so that many areas of research could be combined, and conclusions drawn.

Some researchers suggest that migraine is not inside the brain but is extracranial, and is associated with arterial dilatation (25). While extracranial dilation may or may not be associated with migraine, it most certainly is not the cause of it. Imagining studies show changes inside the brain right before or during a migraine. Examples are: cortical hypoactivity that is characterized by a decreased level of neuronal pre-activation excitability (26) or neuronal hyperexcitability (27, 28), structural abnormalities of the brain (29), brainstem dysfunction (30), white matter abnormalities and/or infarct-like lesions and/or volumetric changes in gray and white matter regions (29), neurogenic inflammatory responses from CGRP releasing trigeminovascular network of neurons (31), abnormal function of receptor channels of sensory neurons in some cortical areas that stimulate perivascular intracranial nerve fibers (32), structural and functional brain alterations (33), occipital cortex hyperexcitability (34), neurotransmitter and neuromodulator metabolic abnormalities (35), a spreading depression-like neuroelectric event during migraine aura (36) and in migraine without aura (37), hsCRP-measured cerebral white matter hyperintensities (13), and many more.

A number of research papers on migraine discuss the differences between neuronal plasticity and variations in excitatory vs. inhibitory behavior of the neurons (38, 39), as well as differences in functional connectivity between the brain of migraine sufferers and non-sufferers (40), as well as yet unexplained white matter differences (41). Migraine and seizure share many of their features. The Epilepsy Foundation suggests that those having an epileptic seizure disorder are twice as likely to also have migraines. Misdiagnoses are frequent because the symptoms are so similar (42, 43). In the case of epileptic seizures, the "seizures are generated by hyperexcitable and hypersynchronous neuronal firing that leads to the rhythmic recruitment of large populations of neurons. A seizure is triggered when a sufficient number of neurons synchronously depolarize and generate action potentials" (43), and this is quite similar to what happens in migraine, only the neurons do not depolarize synchronously but in a wave, which is referred to as Cortical Spreading Depression (CSD). Although it is still debated whether CSD even exists, and if it does, what its role may be (34), here we will emphasize the role of CSD, which we believe to be a crucial and characteristic phase of migraine. CSD is not exclusive to migraine, it is also part of seizure, brain injury, and other conditions (44).

Looking at any of the research areas, none provides a comprehensive explanation of how and why what they found occurs, and how it generates migraine with or without headache. A comprehensive theory must explain the major manifestations of the condition, must generalize the phenomena to similar or related entities, and must include hypotheses that can be supported, refuted, or improved on (45), to explain how and why a migraine starts and why it often leads to pain. It is clear that not only is the cause of migraine elusive, but also the manifestation of migraine is not understood. In addition, although migraine need not have pain accompanying it (46), it appears that almost all research is following the headache aspect of migraine, which suggests that whatever they find could not explain what "migraine" is; they only aim at preventing migraine headaches.

With little understanding of what migraine actually is, no wonder that good and reliable prevention measures or treatments are not available. I found that even the diagnostic practices are questionable. For example, migraines always come with prodromes, yet prodromes are hard to define or recognize by the migraineurs themselves. An experiment, using electroencephalogram, detected prodrome as a higher complexity of brain activity in patients who were in the preictal phase (prodrome phase) than in patients during the interictal phase (the actual migraine) (47). Understanding prodromes and helping migraineurs discover when they are in a prodrome phase can help them avoid a migraine. Doctors rarely if ever ask if the patient experiences prodromes. Ignoring this means that a doctor may diagnose some other form of headache, such as cluster, sinus, cervicogenic, stress, occipital neuralgia, optic neuritis, or idiopathic intracranial hypertension as migraine.

Existing guidelines are not clear and are also ignored or overruled by physicians. The International Headache Society is the main authority on headache types, and migraine headache is defined by it as a unilateral pain (48). Yet in a large percent of the literature and online guides—such as Medscape (49) or Merck Manual (50) and other scientific literature (51) this definition is not followed and even stated that migraine can also be bilateral. There are many other areas where confusion exists in the definition of what a migraine headache really is. Per the International Headache Society migraine is a primary headache, meaning it is not caused by any preexisting condition. Nevertheless, much literature informs us (and also reported to me by a large number of people) that doctors often diagnose any "big headache" as migraine headache, even when it is caused directly by a traumatic brain injury or some other health condition (52). There is a misdiagnosis crisis of migraines.

Many studies discuss how well epileptic seizures can be lessened and or prevented by lifestyle modifications, specifically by the ketogenic diet (53–56). Given the similar pathophysiological nature of seizure and migraine, the benefits of the ketogenic diet need to be examined, not just to see if it works to lessen migraine headache

frequency or eliminate migraines completely, but to also give us clues as to the cause of migraine. It is likely that if we can reduce the incidence of a condition by a particular treatment, the treatment itself can be reverse engineered to shed light on the cause.

As we have seen, there is no widely accepted, comprehensive definition of migraine. One of the confounding factors is that most migraineurs have multiple "types" of migraine symptoms. Literature separates migraines into "migraine types" based on symptoms and assumes that once a person is, for example, a hemiplegic migraineur, that person will have all her migraine hemiplegic. Based on the numerous cases that I have come across—including my own migraines that have contained a number of different migraine types from classic aura to scintillating scotoma, to complex migraine (without aura), to light hemiplegic (arm tingling and loss of strength, droopy eye)—I can firmly state that migraine type based on symptoms is not a stable, life-long determinant.

While this paper will cover all migraine types, after identifying the root cause, it will become clear that all migraine types are just one thing: migraine. What makes them appear different is the area of the brain being affected. The cause is the same in all migraines, no matter what their symptoms and where in the brain they start. Based on the brain differences between a migraineur and a non-migraineur, if we place them into the same room with a specific light, odor, and sound setting, they will sense a completely different environment around them. The migraineur will find the light brighter, the sound louder, and the odor stronger. What this suggests is that migraineurs are not sensitive to bright light, but they see regular light brighter, they hear regular sounds louder, and smell regular odors stronger. Their brain is more "environment adapted." As was introduced earlier, this was an evolutionary advantage in human ancestral life, but it has become a burden in our modern bright, loud, odorous lives full of excitatory stimulants that play havoc with a brain brimming with sensory neurons that overreact to them.

## 2 The cause of migraine

I first define the cause based on my hypothesis, and then proceed to show why and how it is correct. At the same time, I aim to bring up as many opposing arguments to it as I can think of.

### 2.1 The hypothesis

The cause of migraine is an electrolyte imbalance, specifically, not enough sodium in the extracellular space of the sensory neuron (s) to initiate action potential. Action potentials spread information in the nervous system to connected neurons and propagate commands to the periphery. If the action potential fails at any Node of Ranvier, the neuron's communication is stopped, and instructions never reach their intended target. The neuron moves back into resting state with voltage-gated sodium channels closed. The symptoms resulting from blocked or malfunctioning sodium channels or insufficient sodium at the channels are: seizures, altered mental status, hypotension, prolonged QRS (ventricular depolarization in the heart), a terminal R-wave in lead to aVR (57), edema, swelling of the brain, coma, death, and I argue that this list should also include migraine.

We should ask why the brain would ever be short of sodium to the extent that the neurons cannot function as a result of failed action potentials. Common causes of hyponatremia are dehydration, vomiting, diarrhea, too much fluid consumption (water toxicity), type 2 diabetes, hyperglycemia, hyperkalemia, malabsorption disorders, kidney failure, heart failure, cirrhosis, diuretics, cerebral hemorrhage, subarachnoid hemorrhage, Guillain-Barré syndrome, head injury, brain tumor, meningitis, certain medications, hypomagnesemia, hypocalcemia, vitamin D deficiency, and there are many more (58).

To ensure properly functioning osmolality in the brain the right amount of sodium, chloride, and potassium must be present. At equilibrium, extracellular osmolality equals intracellular osmolality, and the net movement of water across the cell membrane is zero. When the extracellular sodium concentration is reduced, hypo-osmolality and hypotonicity will ensue as the water flows from the extracellular space into the intracellular area. The water movement into the neuron causes its swelling. In the brain, even minimal changes in the intraneuronal volume (specifically swelling) leads to dramatic symptoms due to the lack of space (59). Neuronal adaptation to hyponatremia involves movement of electrolytes from inside the cell to the extracellular area. Within the first hours of hyponatremia, there is a significant decrease in the intracellular content of sodium, chloride, and potassium (60, 61). The kinetics of brain electrolytes depletion during acute hyponatremia have been studied and described. After 3 h of hyponatremia, brain depletion in electrolytes reaches a plateau, and the depletion of sodium is believed to be primarily from the cerebrospinal fluid, which occurs together with intracellular depletion of chloride faster than the intracellular depletion of potassium (62). In total, the brain can lose no more than 18% of its ion content (59). It is expected that by the time the mechanisms behind electrolyte loss are exhausted, severe continued hyponatremia will inevitably cause significant brain edema. Hyponatremic encephalopathy has many very similar symptoms to migraine: headache, nausea and vomiting, fatigue, confusion, and loss of balance, pointing to similar pathophysiology of the two conditions.

Furthermore, renal sodium wasting is a common feature of migraineurs. An early study showed that migraineurs excrete 50% more sodium in their urine than non-migraineurs (63). And hyponatremia is the most common cause for electrolyte imbalance in the brain (64). It is important to elaborate that the brain may suffer a hyponatremic event for reasons other than dehydration. Hyponatremia may be caused by the foods we eat as well. A study showed that for every 100 mg/dL increase in serum glucose concentration, the average decrease is serum sodium is 2.4 mEq/L (65), but this reduction in serum sodium is not linear. With the ranges of normal sodium levels of 135–145 mEq/L, a 2.4 mEq/L drop can easily tilt the person toward serious hyponatremia by simply eating lots of carbohydrates (66). In fact, mortality rate increases when serum sodium levels drop from 139 mEq/L to 132 mEq/L (67). Since hyperglycemia is a causal factor in hyponatremia, the reduction of hyperglycemia will prevent a dangerous drop in serum sodium levels.

Hypernatremia is less likely to occur, and if it does, it is less likely to cause any trouble in the brain, because it induces the movement of water across cell membranes in the opposite direction from hyponatremia (68). Hypernatremia induces hypertonicity and causes transient cellular dehydration (69, 70). Sustained hypertonicity promotes the accumulation of organic osmolytes (e.g., glutamate, taurine, and myo-inositol) and these adaptive changes thereby pull

water into the cells and restore the cell volume (71, 72). Therefore, chronic hypernatremia is much less likely to provoke neurologic symptoms.

At this point it is important to introduce the actual anatomical and physiological differences that distinguish the migraine brain from the brain of a person without migraines.

## 2.2 The evolution of the migraine brain

The sensory neurons in the brain of a migraineur have more connections (73) than in the brain of those without migraine and these connections themselves also differ from the norm (74). Migraine brain seems to always be "on," as migraineurs have only nominal changes in voltage between states of action potential and resting potential (75–77). Clearly, the brain of a migraineur is anatomically different from the brain of a non-migraineur, and as a result, it has been called the hypersensitive brain (78). The sensory neurons in mammals evolved during periods of high vulnerability levels, when vigilance was a major component of survivability, and the heightened sensory sensitivity presented a survival advantage.

Limited studies exist on the evolution of specific sensory networks in the brains of mammals (79), and these studies do not compare modern humans to other mammals in their native wilderness, where predation presents a risk to life, and where heightened sensory organs provide fitness for survival. Some studies that compare some of the human sensory organs to those of other primates conclude that humans have lost some of their ability to smell relative to other primates (80). The hypersensitive brain had to be the original standard but by now the majority of humans have adapted to a lack of danger from predatory animals and to a measure of predictability and safety of their environment. A great number of the human population have also adapted to city-dwelling and the associated noises, odors, and lights with excitation inhibition of their sensory neurons.

Why females and children are more vulnerable can also be explained by the hypothesis. Generally men were the hunters, carrying weapons, and the success rate of a predator killing a hunter was likely quite low. By contrast, women and children were left behind to gather—squatting or bending down without weapons, they are the ideal pray for a predator. As a consequence, this group developed and retained stronger sensory organ systems, especially for the time of their heightened vulnerability. Before puberty, more boys have migraines than girls (81). Boys became hunters at or shortly after puberty and correspondingly we see most boys losing their migraines after puberty (81). In our modern Western civilized world humans have no need for keen sensory organs against predators, and so it makes sense that such an energy sink would have devolved by adapting to a less sensitized human lifestyle with reduced ability to sense.

However, a group of people, the migraine sufferers, appear to lack this adaptation. Comparison studies of the sensory neurons of the sensory organs are lacking, but what we do know is that migraine is initiated by odor, light, sound, taste, and touch, suggesting that migraineurs form a subpopulation of humans who are not properly adapted to modern life full of odors, noise, light, and other potentially overstimulating factors. The explanation for this is the lack of proper neuronal inhibition that some studies do show (82–84).

It is well understood that the migraine brain responds to stimulation differently from the norm; it is easily overstimulated and has difficulty dealing with a hyperexcited state (78). Excitation in the brain is defined as communication between neurons via neurotransmitters, which move through each neuron by electricity created in the axon at each Node of Ranvier and rushes through the spike train to the axon terminals (85). An average neuron has a Node of Ranvier at about every 350 μM (86), and at each one there are approximately 700,000 voltage gated sodium channels (87). These sodium channels are responsible for the initiation of the electricity by generating action potentials, which then can move to the next Node of Ranvier by saltatory conduction (88) and all through the axon of the neuron to the axon terminals.

Neuronal excitability depends on membrane potential that can be altered by neurotransmitters released at synapses. Membrane potential is created by selectively permeable ion channels in the membrane. Altering the membrane potential creates a current across the membrane. However, every action potential is either excitatory or inhibitory. Excitatory currents are those that prompt one neuron to share information with the next neuron through an action potential that leads to the release of excitatory neurotransmitters, while inhibitory currents are action potentials that send inhibitory neurotransmitters into the synapse. In addition, the action potential itself also differs between excitatory and inhibitory release. Disruption of the balance between excitatory and inhibitory inputs is one likely cause of diseases marked by bouts of abnormal neural activity (83).

In the case of inhibition, it is an inhibiting neuron that is used for activation in order to release GABA, an inhibitory neurotransmitter. Its activity reduces the amount of neurotransmitter released into the presynaptic area, and with fewer $Ca^{2+}$ rushing into the neuron, less neurotransmitter is released into the target synapse. There is also postsynaptic inhibition, where the dendrites of the postsynaptic neuron cancel some of the incoming signals, receiving fewer average stimulus, too small to start an excitatory state.

Most of the sodium channels in the Nodes of Ranvier are Nav1.6 sodium channels. These channels are responsible for the generation of the action potentials that initiate the electricity that must move through the axon to either excite or inhibit. There is a threshold number of these sodium channels that must be met if the action potential is to be successfully generated. Presynaptic action potential failure prevents transmission to postsynaptic neuron, stopping the spike train (89, 90). Since the brain of the migraineur has altered sensory neuronal connections and more of them (33, 91) firing in what is referred to as hypersynchrony (92) or more commonly in migraine as cortical spreading depression (CSD) (93), a lot more sodium and ATP is used by the brain of a migraineur than that of a brain of an individual without migraines.

Myelin is a cholesterol and fatty acid rich substance that serves as a specialized insulation sheath around the axons in the nervous system, facilitating axon signal conduction by enabling saltatory conduction. Damage to the myelin sheath can inhibit saltatory conduction and prevent neuronal transmission. Myelin sheath damage is commonly seen on brain MRIs of migraineurs (94, 95). "Myelin can decrease the capacitance by a factor of up to 1,000" (39) suggesting that damage to the myelin increases the need for charge, necessitating a larger number of sodium ions entering through more sodium channels.

Several academic articles refer to migraine as channelopathy (96–99). Channelopathies are diseases associated with defects in ion channels, either genetic or acquired (100). A channelopathy may cause an abnormal "gain of function" (such as myokymia (101) and ptosis (102), that are commonly missed by practitioners, even though they are often associated with migraine), or an abnormal loss of function (such as weakness or numbness) depending on whether loss of channel function leads to excessive excitability or to lack of excitability (103). In the case of migraine, several ionic channels are genetic variants, including the sodium-potassium ATPase ($Na^+/K^+$/ATPase) channel, which is responsible for resetting the membrane potential to resting state (104) to rebuild the saltatory conduction. In addition, visiting the human genome database (105) and looking at the currently discovered genetic variants associated with migraine, in order of relevance of the variant to migraine, the first three most relevant variants out of 3,866 to date are the ATP1A2 ($Na^+/K^+$/ATPase Subunit Alpha 2), CACNA1A (Calcium Voltage-Gated Channel Subunit Alpha A), and SCN1A (Sodium Voltage-Gated Channel Alpha Subunit 1). These are the three main voltage-gated ionic channels whose proper functions are most critical to neuronal communication, and which are variant.

As noted earlier, an important aspect of migraine is CSD. During CSD, a large ionic shift with the redistribution of ions between intracellular and extracellular compartments takes place in the brain (106) intermixed with a pH shift (107, 108). The ionic shift appears to increase the sodium availability, and with the changes in cerebral pH a large increase in lactate is seen in the brain (107). The neurons in the brain are able to use lactate fed to them by the astrocytes instead of glucose. The reason for the increased lactate is possibly associated with a sugar crash (reactive hypoglycemia), which may follow a carbohydrate meal. Studies show that dietary carbohydrates cause fatigue and brain fog as part of reactive hypoglycemia (109). These events are described in great detail elsewhere (106), but in brief: As cells lose energy resulting from a sugar crash and/or hypoxia, voltage-gated pumps that normally move ions into and out of the cell fail or operate in reverse. These induce a rapid efflux of $K^+$ from intracellular space, causing an increase in extracellular $K^+$. The rapid rise in extracellular $K^+$ elicits neuronal excitation, followed by excessive depolarization and a period of electrical silence during which the potential at the brain surface becomes negative. $Ca^{2+}$ ions flow in as the depolarization opens voltage gated $Ca^{2+}$ channels and extracellular $Ca^{2+}$ falls to abnormally low levels. $Na^+$ and $Cl^-$ enter neurons. Water follows passively, driven by the influx of $Na^+$ and $Cl^-$, which greatly exceeds the efflux of $K^+$. The extracellular space is reduced, and local intracellular edema ensues.

In case of migraine brains, because of the hyperexcited state of the sensory neurons, more fuel is needed. The amygdala initiates a fight-or-flight response, sending a message to the adrenal glands to release epinephrine (adrenaline), which in turn triggers many functions. One of them is the release of glycogen for more energy in order to facilitate the extra work and the need for recovery of the brain. The glial cells, primarily the astrocytes, store some small amounts of glycogen to ensure constant glycogen supply in the brain in order to prevent a critical sugar crash for short amounts of time. However, as glucose enters a neuron large amount of sodium leaves (110). This causes localized extracellular edema and reduction in the intracellular $Na^+$ levels, increase in the intracellular $K^+$ levels relative to $Na^+$, closure of the voltage-gated sodium channels, and ultimately failed action potential.

And this is where we reach the state when migraine starts. To visualize the differences in response to the same stimulus by a migraineur vs. a non-migraineur, the following schematic demonstrates the summary of events. The specific stimulus elicits the conditions for a migraine (111), generating unstable excitability (112), leading to migraine following the order of events as described above (Figure 1).

Furthermore, while all people will experience similar efflux of sodium and water from neurons in response to glucose, a sodium imbalance will not trigger other conditions with similar frequency or with the same symptoms. For example, epileptic seizures may also be caused by electrolyte imbalance and reduced sodium availability (113), but the symptoms of seizures are very distinct and easy to tell from migraine. Other clinical conditions, such as dehydration, renal failure, diabetes insipidus, or sodium wasting (63), all can cause serious modifications of plasma osmolality and electrolyte imbalance, causing alterations in brain metabolism and function (114). The driving force behind the extreme sensitivity to these osmolality changes in electrolytes in migraines is associated with the anatomic differences of the sensory neurons in the brain of migraineurs. Migraineurs have excess sensory neuronal connections (73) and that means more action potential is needed to work with the incoming sensory stimulus.

One may ask about the importance of other electrolytes, such as potassium, calcium, or magnesium. How might they connect to migraines? Most of the potassium is inside the cells whereas most of the sodium is outside of the cells and potassium is not affected by glucose entering the cells because potassium is not a glucose cotransporter. Potassium levels are modulated by many conditions, such as kidney failure, diabetes mellitus, adrenal disease, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and potassium-sparing diuretics (115), but these conditions are not associated with migraines and so are not discussed in this paper. Magnesium does not leave because of glucose entering the cells and so does not affect electrolyte osmolality at all. And lastly, while more calcium is needed as a result of more neurotransmitter delivery into the synapse, calcium is not affected by glucose entering neurons either. The only mineral that is actively affected is sodium. Sodium is an active glucose cotransporter in the body as well as in the brain, where SGLT1 and SGLT3 cotransporters are used.

## 2.3 The nutrition connection

The availability and variety of nutrition for humans can be followed by moving back in the evolutionary timeline. For most of human evolution humans mostly consumed animal products if they could, with some carbohydrates mixed in as necessity or seasonally desirable. For 99% of human history, humans had a hunter-gatherer lifestyle (116). It wasn't until about 12,000–15,000 years ago that the diet of some human groups started to include larger amounts of plants filled with carbohydrates. In addition, the ancestral human lived without loud smelly cities with cars, and flashing lights, and so they did not live in a constant hyperexcited sensory state, where electrolyte imbalance is highly likely. Consequently, a diet that reduces electrolyte imbalance should be beneficial for migraine sufferers.

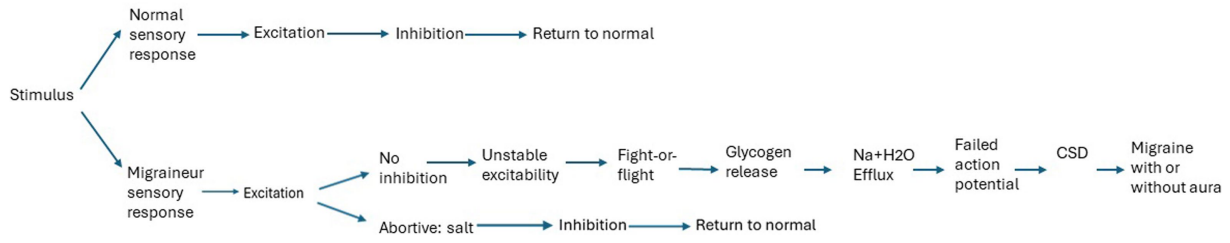


FIGURE 1
Migraine Progression.

The question then becomes, what may a migraine sufferer eat that would affect her hypersensitive sensory neuronal brain in a way that prevents the development of a migraine? Can a change in lifestyle drive a change in migraines? And if so, how does a new way of eating prevent migraine and migraine headaches?

## 2.4 Carbohydrate and migraine

As we have just concluded, the hypersensitive sensory neuronal migraine brain possesses a high number of connections, that transmit more signals because of the higher number of registered environmental excitatory inputs. As a result, the brain of a migraineur has not only increased energy requirements in terms of fuel (ATP) but also in sodium to operate the increased electrical activity of this hypersensitive brain. The brain uses glucose, lactate, and glycogen as its primary fuel for about 25% of its energy need, as these are the exclusive fuels for astrocytes. While some neurotransmitter generation do require glucose, most may be generated by the use of ketones (117).

An interesting phenomenon occurs because of increased glucose use by the mitochondria, due specifically to the pyruvate conversion process in the form of excess reactive oxygen species (ROS). A study showed a metabolic collapse in the hippocampus—the area of the increased ROS—resulting in ionic channel malfunction and CSD-like depolarization (118), which is precisely what precedes a migraine. CSD is not the exclusive property of migraine; many other neurological conditions also exhibit it, including mechanical brain damage, electrical stimulation, hypo-osmolarity, hyperthermia, chemical agents such as potassium, the neurotransmitters glutamate and acetylcholine, acute hyperexcitability, sodium pump inhibitors, hypoglycemia, hypoxia, ischemia, and it can also be induced by noxious odor challenges (119–122). CSD is a common occurrence and seeing it preceding a migraine is not surprising. One may envision CSD as a brain-driven self-rescue system to reallocate available resources to neurons across the brain. In fact, a study on rats concluded that CSD can also be induced by exercise and the CSD leads to beneficial effects in cerebrovascular system functions and increased cerebrovascular stability (123).

When the brain does not get enough glucose, the neurons will switch to ketone use. However, it is seldom discussed if a brain, given plentiful glucose and ketones at the same time, would prefer to use glucose or ketones? Since glucose is considered to be the prime fuel for the brain by most academic literature, the assumption is that as long as glucose is provided for the brain, it will use glucose. But this is incorrect. A study showed that the brain will preferentially use ketones over glucose even when both are present (124), where exogenous ketones were supplied to otherwise glucose-rich brains that had degenerative diseases caused by glucose metabolism difficulties in the brain. This paper suggests that a migraine brain seems to have glucose metabolism difficulties. This leads to the important point that it is not whether glucose is available or not, but rather can the brain metabolize glucose or not? Experiments on rats show that ATP is increased when ketones are used by the brain (125). This study further suggests that with ketone use by the brain, neuronal stability is followed.

Studies on human fetuses while in the mothers' womb show that the fetus' brain selectively uses ketones, yet clearly the fetus' brain is well endowed with the opportunity to use glucose if it wishes (126, 127). And babies retain metabolic flexibility for a number of years as they come in and out of ketosis based on their feeding schedule (128). Clearly, such stability is what the brain could benefit from in the case of migraine (and other brain-diseases) as well. And as mentioned repeatedly earlier, glucose entering neurons causes an efflux of sodium, contrary to the increased requirements, creating instability. The logical conclusion is that a reduction of carbohydrate consumption and an increase of ketones and sodium in the brain are likely beneficial for migraine prevention.

The cascade of events leading to the inability of firing action potentials can be prevented by increased sodium (129–131) and reduced carbohydrate consumption. The consumption of carbohydrates is not essential because gluconeogenesis by the liver provides the necessary glucose to all organs as needed. The primary fuel for the body is fat, not glucose (132–135). The primary preferred fuel for the brain is ketones, as demonstrated earlier. Diets low in carbohydrate, such as the ketogenic, low carb-high fat (LCHF), and carnivore diets (136, 137), as well as consumption of appropriately higher levels of sodium (130, 138) are beneficial. Studies show that fatty acid utilization for fuel in the brain is key for repairing neurodegenerative disorders (139). Ketone bodies are an efficient fatty acid fuel that can compensate for the deficient glycolytic metabolism of the migraine brain (140).

The ketogenic diet has been a much-researched approach in many neurological conditions (141, 142) because the brain is very specifically adapted to use ketones as fuel instead of glucose (143). Many studies have focused on the ketogenic diet especially for epilepsy (144) but some studies show its benefits in migraine as well (145). However, numerous concerns have been voiced because of the temporary side effects of converting from a high carbohydrate diet, where the brain

and much of the body use glucose as its primary fuel, to the ketogenic diet, where the brain's and some organs' primary fuel changes to ketones. While the brain appears to make the change from glucose to ketones quite easily (146), it is not so easy for the body for some people. There are two primary issues: the ketogenic diet is restrictive, and some people find it difficult to adhere to and there is an adaptation period that can cause discomfort for some.

While the ketogenic diet is restrictive, the extreme carbohydrate sensitivity of migraineurs gives near immediate feedback about the benefits or harms of dietary choices. If the migraineur gets a migraine each time a high carbohydrate meal is consumed and remains migraine free after a ketogenic, LCHF, or carnivore meal, the migraineur will happily accept the new regimen.

Some of the known physiological difficulties are grouped under the term "keto flu," represented by fatigue, headache, and gastrointestinal difficulties associated with the body converting to ketone use. A similar condition is referred to as "fat adaptation" in athletes who restrict carbohydrates in order to train for a competitive event a couple of weeks later, because the body using fat for fuel can become stronger and important glycogen stores are spared (147). The reason for keto flu is debated (148), but most agree that it affects a large part of the general population when starting the ketogenic diet (149). It is likely associated with the loss of fluids and electrolytes, specifically sodium, as insulin drops to lower levels in the body quite drastically after the reduction of carbohydrates. With high insulin, the kidneys recycle sodium and retain excess water correspondingly (150). It is also important to replenish lost electrolytes, because the ketogenic diet is a fasting mimicking diet (151), and the increased use of glucagon in response to fasting reduces both sodium and water (152).

Additionally, keto adaptation is not the same for each person. Some people enter the state of ketosis very soon after starting the ketogenic diet and without keto flu. Since comprehensive research is lacking in this area, we cannot forecast how long such adaptation will take and when any benefits of the ketogenic diet can be realized for a given candidate. In my limited experience I found that the benefits accrue sometimes from as little as a couple of weeks to as much as many months, depending on how long the person had migraines, what kind of medications were taken, how damaged the metabolic health of the individual is, and also the age of the individual.

A critical point is the potential interactions between certain medications and the ketogenic diet. For example, Topiramate (Topamax) label lists serious interactions with the ketogenic diet as it may lead to kidney stones. Although other drugs have not been labeled with warnings, caution must be taken, and frequent de-prescribing may be necessary. Patients on the ketogenic diet find their insulin and weight dropping very fast and medication doses correspondingly need to be reduced. The ketogenic diet has shown blood pressure reduction (153), the reversal of kidney disease (154), reduction of HbA1c and increase of HDL (155, 156) and even the reversal of type 2 diabetes (157). Many thousands of anecdotal reports point to great success with the ketogenic diet as well as with the lesser studied carnivore and LCHF diets, providing an incentive for others to try them.

Our next questions are: Can we remove carbohydrates from the diet of migraineurs safely? Can we increase the availability of sodium to the brain of migraineurs safely and what is the best way? Will these steps help reduce or prevent migraines?

## 2.5 The safety of salt

There are many research papers showing results in applying ketogenic or other low carbohydrate diets to migraine, but studies do not exist about adding extra salt. In fact, there is quite a bit of concern surrounding the increase of dietary sodium. Here I address some of the issues.

Strong anecdotal evidence suggests that increasing salt, specifically when taken with water (as opposed to eating more salt with food) in order to increase sodium availability in the blood for the use of the brain, is beneficial. Electrolyte drinks are sold in stores and research shows that they have beneficial effects in hydration over water (158). Studies show that migraineurs who consumed more salt reported fewer headaches (129). Hypertension and hypotension both are considered to be comorbid with migraine and therefore it is suggested that the cardiovascular risk profile is higher in migraineurs (159–162). However, I previously questioned the perceived cardiovascular risk aspect of migraine (163) and it is very easy to overlook that the medications migraineurs are placed on often cause cardiovascular diseases on their own. Might it be that migraineurs end up with hypertension and increased cardiovascular disease as a result of the medications they are taking for migraine? For example, NSAIDs are the choice for over-the-counter use, and they are well-known to cause cardiovascular problems (164). Propranolol (propranolol hydrochloride) is a frequently prescribed medication for migraine, although it is actually a strong heart medication with significant cardiovascular health concerns (165). Triptans are the most often prescribed medications for migraine and there are very serious concerns with respect to the cardiovascular and heart damage they cause (166). Various SSRIs and TCAs are often prescribed for migraine as well. While SSRIs are deemed safer than TCAs in terms of cardiovascular profile, they are not completely safe (167). CGRP inhibitors are the latest class of medications recommended for migraine and because they are so new, less information is available in published literature. But some academic articles point out that the cardiovascular system has CGRP receptors in order to initiate vasodilation. When the CGRP receptors are inhibited, vascular damage and associated dangers arise (168, 169). Given the many medications prescribed to migraineurs and that the evaluation of cardiovascular disease associated with migraine often does not include a questionnaire for what medications migraineurs take, I believe that it is irresponsible to suggest that migraineurs are generally more susceptible to end up with hypertension and cardiovascular disease, absent any medications.

While there is much general concern about increased dietary sodium and its association with hypertension, the physiology of sodium use by the body and the method of elimination of the excess sodium does not give rise to hypertension concern in the metabolically and thereby cardiovascular-healthy, individuals, and, in fact, the opposite is true: a reduced sodium diet leads to hypertension (170, 171). In addition, reduced sodium diets are now understood to cause insulin resistance and cardiovascular disease (172, 173). And a study showed that even in the case of subjects with salt sensitive and salt resistant hypertension, while their systolic pressure dropped minimally on a reduced sodium diet, their insulin resistance markedly increased (174). It is also interesting to note that while most people in pain tend to have an increase in blood pressure, a study showed that migraineurs suffer from hypotension before, during, and shortly after

a migraine attack (175). This is further validation that migraine is associated with hypovolemia due to electrolyte imbalance and loss of sodium. And hypovolemia is a consequence of inappropriate hydration and high carbohydrate consumption. And lastly, a study injected saline directly into the arterial vein of the brain and found that all subjects experienced significant relief, with a large percent having complete pain relief (176).

Therefore, even if the consumption of salt may increase blood pressure in some people, given the hypotension migraineurs exhibit before, during, and after a migraine episode, an increase in blood pressure would clearly be welcome. Additionally, one may ask: if salt increases blood pressure, why is intravenous saline the first line of treatment (for migraine as well as for many other conditions) in most emergency departments (177, 178)? And would not an increase in salt (an essential mineral) be safer than the taking of unsafe medications with lots of side effects?

Salt in water is an electrolyte and it heads straight to the blood since it is not "food" *per se*. And since most of the sodium in our body is in our blood and outside of the cells, drinking salt with water is the fastest and safest way to regulate the sodium amount in the blood. There are no human experiments on salt in food vs. water, but a mouse study shows that the pathways of sodium absorption are different in food from water (179). We excrete salt both via the kidneys and also via feces, although much of what is excreted in the feces is reabsorbed by the colon (180).

## 2.6 The safety of low carb diets

The low carbohydrate diets have initiated quite a controversy over the past few years. However, by now there are dozens of clinical trials associated with research on low carbohydrate diets. Not only are they safe, but these trials show them effective in helping, and in some cases reversing various illnesses, or at least putting a particular condition into remission. Specifically weight loss, cardiovascular health, type 2 diabetes, and many neurological conditions, such as epilepsy, Alzheimer's disease, Multiple Sclerosis, Parkinson's Disease, Schizophrenia, and many more conditions have been shown to strongly benefit from a low carbohydrate diet (157, 181–187).

Overwhelming anecdotal evidence suggests that the application of any of the low carbohydrate diet forms: LCHF, ketogenic, and carnivore, provided they are well-formulated for health with sufficient protein and fats, should be helpful in preventing migraine, but the reason why it is so, is often misunderstood. For example, a small trial concluded that the ketogenic diet is likely beneficial because it helps people lose weight and migraine sufferers are overweight (188). Interestingly there are many studies pointing to migraineurs being overweight (189, 190), yet my experience in working with thousands of migraine sufferers from around the world is that they are not overweight—in fact many are underweight as a result of being unable to eat while they are so often in pain. Regardless, weight loss on its own is not likely to lead to the reduction of migraine given that it is a genetic condition of ionic channel variants and the brain's glucose intolerance (191). Rather, with the help of the hypothesis laid out in this paper we can understand that it is the reduced carbohydrates in the ketogenic and other low carbohydrate diets, especially the carnivore diet, and the increased salt that provide relief for migraine sufferers.

Let me bring a couple of specific anecdotal evidences, where the benefit of the diet change and especially the use of salt in water was very specifically the cause of the migraine free life.

In one example, a marathon runner approached me for help. She was not overweight and appeared metabolically healthy but she would run 10 miles daily for practice and always end up with a migraine. She was also suffering from monthly hormonal migraines with her cycles. Knowing that estrogen recycles sodium and thereby increases body weight by retaining water, whereas progesterone does the exact opposite, and both estrogen and progesterone thereby cause an electrolyte imbalance, measuring her first morning weight daily helped us identify her need for excess salt and water for her cycle prep, which in turn got rid of the hormonal migraines. She started with the LCHF diet and moved to ketogenic once feeling stable. During her marathon practices, and later during the actual races, the sugar gel packs were replaced with butter, cheese, and salt packs, and with the reduction of water from a cup at every stand to saltwater sips once in a while, she has been able to run marathons without ending with a migraine. She recently celebrated 1 year without a migraine.[1]

In another example, a teenager presented with her mom. He had cyclical vomiting and irritable bowel syndromes. Given his strong reaction to any form of carbohydrate, he started a specifically formulated high protein medium fat carnivore diet, which he has been able to maintain now for over 5 years. He and his parents celebrated his success of passing the Marine's Crucible last year (see Footnote 1).

## 2.7 The low carbohydrate benefit

Why any of the low carbohydrate diets are beneficial is clear considering the carbohydrate sensitivity of the brain and the associated osmolality changes. As noted earlier, ketones are the preferred fuel for the brain that has glucose metabolism difficulties (192). Ketones in the brain are 3β-Hydroxybutyrate (3HB) and acetoacetate, which are fatty acids of medium chain triglycerides that can easily cross the blood brain barrier (193) and provide the fuel with great efficiency (194–196). Ketogenic diets have had great success with epileptic seizures (197), as well as Alzheimer's disease, Multiple Sclerosis, and a host of other neurodegenerative diseases. The use of ketones by most brain functions defers the use of glucose to the glial cells (198). When we reduce glucose to the brain, we are also reducing glucose to the body. The ensuing fundamental changes lead to reversal of metabolic disease and re-establishment of insulin sensitivity in general, which improves the brain's insulin sensitivity as well (181, 182, 199, 200).

The reversal and/or prevention of metabolic disease in the brain, especially in those populations whose brain cannot use glucose well as fuel, aids the healing processes of the brain. Further studies are needed in this area specifically with respect to migraine. These studies will help us to fully understand and underscore the numerous empirical success stories.

1 https://stantonmigraineprotocol.com/testimonials/

## 3 Discussion

Rather than medicating with strong brain modifying drugs in order to reduce the sensitivity of the brain of the migraineurs, why not modify the brain's environment in such a way that the migraineur's brain can retain plenty of sodium for the increased level of action potential it needs. Having enhanced sensory organs is not an absolute disadvantage. For example, we can frequently hear of stories where a migraineur smelled a gas leak, verified only by gas leak detection equipment, and saved a neighborhood. Medications blunt the hypersensory neurons of the migraine brain by blocking how the brain normally functions. While this may help reduce migraine symptoms, these medications degenerate the brain to work at a lower level of sensitivity. Instead of reducing the sensitivity, thereby dulling the senses of the migraineur, we could simply support the migraine brain with the right nutrients to reduce the chance for an electrolyte imbalance and the ensuing migraine.

The problem can be resolved by avoiding a high carbohydrate diet and by adding a sufficiently increased amount of salt to consumed water to increase blood volume, to provide enough sodium for the brain under any circumstance, so it can continuously support those important action potentials.

The ketogenic diet is specifically beneficial because it is a comfortable way of eating in a social setting, and it is also easy to remain on the ketogenic diet for a long time—perhaps for life. The production of ketones for the use of the brain has additional benefits, such as reversal of metabolic disease and the possible prevention/reversal of neurodegenerative diseases that often disproportionally afflict migraine sufferers (201, 202).

Finally, clinical trials are lacking in migraine research with nutrition. This is understandable, given how many medications migraine sufferers normally use, the subjectivity of evaluating if the diet reduced the number of migraines or migraine intensity, and the potential interactions between the many migraine medications taken and a given diet. To test the real benefit of a nutritional approach, the migraineurs would have to remain medication free during the trial and, of course, there is no placebo for food, so the control and trial groups would never be blinded, and thus inherently biased. In addition, since most migraines start in the morning hours—often the result of the dawn phenomenon blood glucose variations—the test subjects would have to be in a controlled environment for the entire length of a clinical trial. This is a hard task given that migraine prevalence is highest during childbearing and raring (203), making an in-house long-term clinical trial with meal and medication control very expensive and impractical.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Author contributions

AS: Conceptualization, Visualization, Writing – original draft, Writing – review & editing.

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## Publisher's note



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# Opinion: Are mental health benefits of the ketogenic diet accompanied by an increased risk of cardiovascular disease?

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## Introduction

Ketogenic (very low carbohydrate) diets have well-established, as well as potential, benefits in the treatment of neurological disorders. Over a century ago the ketogenic diet was adopted as an effective treatment for epilepsy (1). More recently, ketogenic diets have demonstrated promising therapeutic potential in a broad range of neurological disorders, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, ischemic stroke, migraine, major depressive disorder, bipolar disorder and psychotic illness (2–5), as well as a potential treatment for traumatic brain injury (6). This research has identified great promise in the use of the ketogenic diet to improve brain functioning, particularly in response to psychiatric disorders and injury.

The ketogenic diet, however, is not without its detractors. A concern with the ketogenic diet is that in some individuals very low carbohydrate consumption can lead to dramatic increases in the level of low-density lipoprotein cholesterol (LDL-C) (7, 8), which is considered a primary cause of cardiovascular disease (CVD) (9). Whereas the ketogenic diet is beneficial for mental health and in the treatment of neurological disorders, but for some individuals with elevated LDL-C, is that benefit obtained at the cost of increasing their risk of developing CVD? We have addressed this issue with an analysis of the benefits vs. potential harms of a ketogenic diet-induced increase in LDL-C.

## Is elevated LDL-C inherently atherogenic?

An elevated level of LDL-C has been described as "unequivocally recognized as the principal driving force in the development of (atherosclerotic cardiovascular disease)" (9) and that "the key initiating event in atherogenesis is the retention of low-density lipoprotein (LDL) cholesterol (LDL-C) … within the arterial wall" (10). The view that high LDL-C is atherogenic provides the basis for why an LCD-induced increase in LDL-C has been seen as increasing the risk for developing CVD (8, 11–18). In one example, a ketogenic diet-induced increase in LDL-C was the topic of an editorial that stated these individuals should "work closely with their doctor to implement lifestyle changes and/or medical therapy directed toward lipid lowering with the aim of reducing cardiovascular risk" (18).

Although LDL-C as a cause of CVD is the consensus of key opinion leaders, there are findings that are not supportive of this perspective. An inconsistent, and largely ignored, finding is that cardiovascular and all-cause mortality in people with familial hypercholesterolemia (FH), who have extremely high levels of LDL-C from birth, declines with advanced age, resulting in an overall normal lifespan (19–23). Moreover, people with FH exhibit an equivalent degree of aspects of cardiovascular morbidity, such as ischemic stroke (24), as the general population. These findings challenge the consensus that high LDL-C is inherently atherogenic.

What has been largely ignored in the consensus opinion of FH is that only a subset of individuals with FH die prematurely of CVD. A close assessment of this research reveals that this subset of FH individuals develop coagulopathy, independent of their LDL-C levels (25–29). In one representative study, Jansen et al. (28) reported that FH patients that developed CVD had a polymorphism for the prothrombin gene, which is also associated with premature CVD in the non-FH population (30). Sugrue et al. (31), as well, reported that FH individuals with coronary heart disease (CHD) had higher levels of clotting factors (plasma fibrinogen and factor VIII), and conversely, Sebestjen et al. (32) found reduced markers of fibrinolysis in FH individuals that experienced a myocardial infarction, both of which were independent of their LDL-C.

In complementary research, high LDL-C appears to protect against bacterial infection, which is a risk factor for CVD (33–39). The protection of individuals with high LDL-C from infection and its sequalae is manifested, in one example, by the significantly lower rate of sepsis, and sepsis-induced organ damage, in people with high LDL-C, compared to those with low LDL-C (40).

With regard to the critical factors leading to CVD susceptibility, it has long been recognized that coronary artery calcium (CAC) scoring is superior to LDL-C as the single best predictor of fatal and non-fatal coronary events (41–44). For example, approximately half of FH individuals assessed showed zero CAC, which would indicate they have a low risk for developing CVD, despite their high LDL-C levels (45). Moreover, this study demonstrated that a high CAC score and elevated fasting glucose, unlike LDL-C, were both associated with coronary events (Figure 1). Similar findings were reported by Mortensen et al. (46) in a study of non-FH individuals. These findings led Bittencourt et al. (47), to conclude that "treatment of individuals with very high LDL-C (>190 mg/dl) irrespective of their clinical risk … might not be the most prudent approach."

At a mechanistic level, concerns with a ketogenic diet-induced increase in LDL-C have not taken into account that the "total LDL-C" measure reported in a conventional lipid panel represents a heterogeneous population of different LDL particle types (48, 49), one of which is referred to as lipoprotein (a) [Lp(a)]. An elevation of Lp(a) is an independent risk factor for the development of CVD (50–54). The association of Lp(a) to CVD may be driven, in part, by its strong atherogenic effects at multiple metabolism levels, particularly in promoting thrombosis (55, 56). For example, Yang et al. (57) demonstrated that the combination of high Lp(a) and fibrinogen levels were correlated with the highest incidence of ischemic stroke in statin-treated patients, while LDL-C levels were unrelated to stroke incidence. Finally, Willeit et al. (58) showed that Lp(a) is a critical component of the association of LDL-C with CVD; without the Lp(a)component, LDL-C, alone, was not associated with CVD.

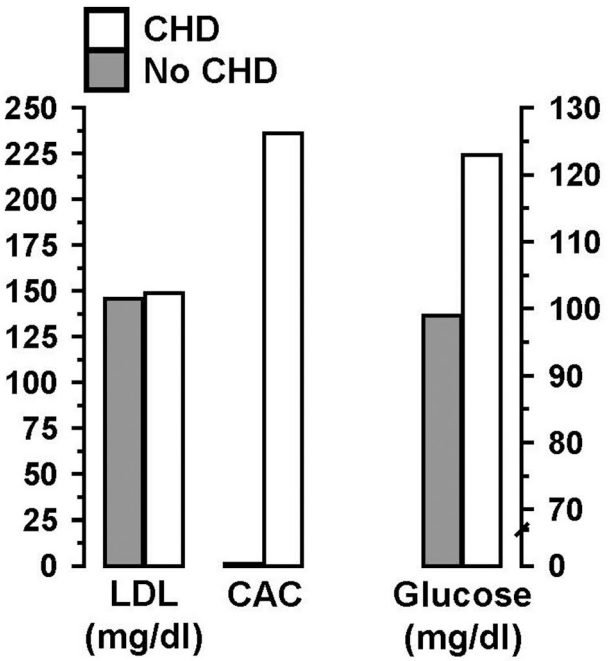


FIGURE 1
In individuals with familial hypercholesterolemia (FH), a high coronary artery calcium (CAC) score and elevated fasting glucose, unlike high low-density lipoprotein cholesterol (LDL-C), were associated with coronary heart disease (CHD). Data from Miname et al. (45).

## Insulin resistance and cardiovascular disease

Hyperinsulinemia and hyperglycemia, collectively referred to as insulin resistance (IR), are strong and independent risk factors for CVD (59–63). IR may develop into type 2 diabetes, which typically is not accompanied by an elevation of LDL-C (64), and yet it has the greatest risk for CVD (65). There are multiple mechanisms by which IR exerts an adverse effect on blood vessel structure and functioning leading to CVD (60, 61, 66–71). For example, Yu et al. (72) reported that elevated fasting plasma glucose, hemoglobin A1c and triglycerides (TG), unlike, LDL-C, were all positively correlated with the severity of coronary stenosis. Thus, IR is superior to LDL-C as a marker for CVD risk.

An important but often ignored influence on LDL-C structure and function is referred to as atherogenic dyslipidemia, in which elevated LDL-C is accompanied by elevated triglycerides and low HDL, which is a common metabolic state in people with Type 2 diabetes and obesity (73–75). Under atherogenic dyslipidemia conditions, the composition of the LDL particles (LDL-P) exhibits a shift toward a greater density of small, dense LDL-P (sdLDL) and a reduced density of large, buoyant LDL-P (lbLDL). This shift in the dominance of sdLDL over lbLDL is characteristic of a

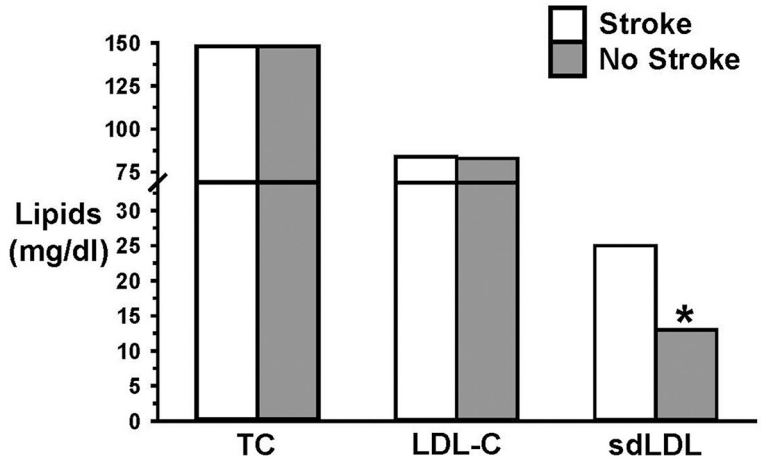


FIGURE 2
Elevated small dense LDL (sdLDL), but not LDL-C, was an independent risk factor for ischemic stroke. Data from Zhou et al. (87). * = $p < 0.05$.

pro-atherogenic state, originally described as "phenotype B" (76). Phenotype B, in contrast to those with low triglycerides, high lbLDL and high HDL (phenotype A), is strongly associated with an increased incidence of CVD (48, 56, 77–90). One example of this finding is that an elevated level of sdLDL, but not LDL-C or lbLDL, was an independent risk factor for ischemic stroke (87) (Figure 2). Numerous observational studies, as well, have shown that lbLDL is not associated with CVD (91–94).

It is therefore important to recognize that the primary reason why LDL-C is a poor marker for CVD risk is because it is a hybrid measure, composed of different sizes of LDL particles (sdLDL and lbLDL), as well as Lp(a) (discussed previously), each with a different association to metabolic health and CVD risk (90, 95) [see also Gjuladin-Hellon et al. (96) and Diamond et al. (97) for related review and discussion].

## Effects of low carbohydrate diets on cardiovascular disease risk factors

Carbohydrate restriction has been shown to improve a broad range of CVD risk factors (49, 98–122). It is notable that along with the improvement in metabolic measures, LCD reduces the need for hypoglycemic and antihypertensive medications (111, 123–132). Moreover, LCDs attenuate the atherogenic dyslipidemia risk triad (reducing TGs, sdLDL, increasing lbLDL and HDL) (49, 96, 105, 133–136). Long-term trials and case reports have demonstrated the benefits of LCD (49, 100, 102, 137–144) and in documenting improvements in numerous CVD risk biomarkers (133, 144–146).

Despite the improvements in CVD risk factors with LCD, there remain concerns about LCD because of the absence of research on individuals with diet-induced high LDL-C and coronary events. A case study on a father and son diagnosed with FH may be of value in appreciating how atherogenic dyslipidemia is expressed as CVD risk, indirectly in relation to LCD. In this study, a father and son shared the same LDL mutation which resulted in both being diagnosed with FH. Despite their equivalently high levels of total cholesterol (344 vs. 352 mg/dl; father vs. son) and LDL-C (267 vs. 271 mg/dl; father vs. son), only the son (54 years old), but not the father (84 years old), had coronary heart disease (CHD). Although dietary assessments were not provided, the authors suggested that differences in their lifestyles and diets may have been a contributing factor to their differential incidence of CHD, independent of their LDL-C. Specifically, the father's triglycerides at 124.0 mg/dl were almost half of the 230.0 mg/dl measured in his son, and the father's HDL at 54.0 mg/dl was far greater than his son's HDL at 34.8. Thus, the high triglycerides and low HDL of the son provided the basis of the authors' perspective that the son exhibited LDL subclass pattern B, which is associated with a high risk of CVD and a high carbohydrate diet (75, 76). Overall, these findings are consistent with the work of Sijbrands et al. (22), who concluded that cardiovascular outcomes in people with FH are not determined solely by high LDL-C, and instead are the result of the interactions among lipids, genetics and dietary factors.

## Discussion

We have addressed concerns regarding high LDL-C that can develop in a subset of individuals on a ketogenic diet. Our commentary has evaluated whether these concerns are justified. We have briefly summarized research which has demonstrated that LDL-C is a faulty marker of CVD risk because it is a hybrid measure composed of multiple components, each with a different association to CVD. Specifically, LDL-C includes lbLDL, sdLDL, and Lp(a), each of which can be influenced by proximal influences on CVD, such as insulin resistance, hypertension, hyperglycemia and more generally, metabolic syndrome. Thus, sdLDL and Lp(a) are not intrinsically atherogenic; each becomes an atherogenic component of the maelstrom of metabolic dysfunction that occurs in response to metabolic syndrome.

The component of LDL-C that dominates in metabolically healthy people is the lbLDL particle, which is not associated with CVD events. Observational trials and RCTs have demonstrated

that individuals with high LDL-C and a dominance of lbLDL (phenotype pattern A) and an LCD-like lipid profile (low TGs and high HDL-C), have a lower rate of coronary events than those with pattern B (high LDL-C, high TGs, and low HDL-C) (147, 148).

In summary, our review of the literature provides support for the conclusion that elevated LDL-C occurring in an individual on a ketogenic diet does not place a person at an elevated risk for CVD. Indeed, a person on a ketogenic diet would exhibit a dominance of beneficial lipid markers (low triglycerides, high HDL, high lbLDL), as well as beneficial non-lipid markers (low inflammation, blood glucose, and blood pressure). These findings support the conclusion that pharmacological or dietary interventions to reduce LDL-C in an individual on LCD are not warranted. Indeed, this favorable cluster of LCD-induced changes in biomarkers should not only result in a reduced risk of CVD, it should promote beneficial health outcomes based on the important role of LDL in optimizing immune functioning.

## Author contributions

DD: Writing – original draft, Writing – review & editing. PM: Writing – review & editing. BB: Writing – review & editing.

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# Complete remission of depression and anxiety using a ketogenic diet: case series

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**Background:** There is little data that describe the use of ketogenic metabolic therapy to achieve full remission of major depression and generalized anxiety disorder in clinical practice. We present a retrospective case series of three adults with major depression and generalized anxiety disorder with complex comorbidity, treated with personalized ketogenic metabolic therapy, who achieved complete remission of major depression and generalized anxiety disorder and improvements in flourishing, self-compassion, and metabolic health.

**Methods:** Three adults, ages 32–36, with major depression, generalized anxiety, other anxiety disorders, and comorbid psychiatric conditions were treated for 12–16 weeks with personalized whole food animal-based ketogenic metabolic therapy (1.5:1 ratio) in a specialized metabolic psychiatry practice. Interventions included twice-weekly visits with an experienced ketogenic registered dietitian; daily photo journaling and capillary blood BHB/glucose/GKI monitoring; virtual groups; family/friends support; nature walks and talks several times per week, and community building. Successful adoption of the ketogenic diet was defined as the achievement and maintenance of capillary BHB $\geq$ 0.8 mmol/L and GKI < 6. Remission was assessed by GAD-7 and PHQ-9, and quality of life was assessed subjectively and with validated scales for flourishing and self-compassion. Metabolic health was assessed by laboratories/biometric measures.

**Results:** Two patients achieved remission of major depression (PHQ-9 $\leq$ 4) and generalized anxiety (GAD-7 $\leq$ 4) within 7 weeks of therapeutic nutritional ketosis; one required 12 weeks. Anxiety responded and remitted more quickly than major depression. Flourishing and self-compassion increased steadily. Patients lost 10.9 to 14.8% of their initial body weight within 12 weeks and improved metabolically; one achieved optimal metabolic health.

**Conclusion:** Complete remission of major depression and generalized anxiety disorder occurred within 7–12 weeks of therapeutic nutritional ketosis during treatment with a personalized animal-based ketogenic diet (ratio 1.5:1) in adults with complex comorbid depression and anxiety engaged in a specialized metabolic psychiatry program.

KEYWORDS

**ketogenic metabolic therapy, KMT, ketogenic diet (KD), metabolic dysfunction, depression, anxiety, case report**

## Introduction

Emerging brain-based research in psychiatry and neurology has focused on identifying fundamental metabolic disturbances within neurons and throughout the body involving insulin resistance, inflammation, oxidative stress, and alterations of the gut microbiome (1). All four of these fundamental metabolic disturbances are present in major depression (2), and underlying anxiety disorders (3) and can be directly modulated through the use of ketogenic metabolic therapy (KMT) (4).

As psychiatric disorders have risen over the past several decades, the prevalence of metabolic syndrome has sharply increased, with only 12.2% of U.S. adults meeting the criteria for optimal metabolic health, leaving 87.8% metabolically compromised (5, 6).

Metabolic syndrome affects almost a third of individuals with major depression (7). It is a significant contributor to their morbidity and mortality (8) and is rooted in impaired glucose metabolism and utilization. Insulin resistance has been well described in many tissues, including the brain (9), where it is being investigated as a link between metabolic health and mental health conditions. Preclinical models demonstrate that glucose intolerance is directly associated with anxiety and that insulin resistance triggers depressive behaviors (9). In brain tissue, insulin resistance results in cerebral glucose hypometabolism and a vicious cycle of unmet energy needs (10). In human studies, cerebral glucose hypometabolism is a feature of major depression (11, 12) and generalized anxiety disorder (GAD) (13).

KMT, also known as the therapeutic ketogenic diet, or KD, is a low carbohydrate, moderate-protein, high-fat diet that supports a fundamental metabolic shift from glucose to ketone bodies as the primary fuel source (14). Classic KMTs are formulated with strict macronutrient ratios, most commonly 4:1 and 3:1 (fat: protein + carbohydrates), and have demonstrated efficacy in intractable epilepsy and genetic disorders. More recently, modified classic KMTs with lower macronutrient ratios of 2.5:1, 2:1, and 1.5:1 have been utilized in research and clinical practice (15, 16). These allow more variety in the diet, meet micronutrient needs except vitamin D (17), and are easier to sustain for extended periods of time.

KMT exploits the body's natural ability to produce ketone bodies (d-beta-hydroxybutyrate (BHB), acetoacetate, and acetone) in the liver from fatty acids by keeping carbohydrate consumption very low. Acute and sustained production of ketone bodies produces a fundamental shift in fuel energetics within cells, particularly neurons, which can radically re-route and quickly rely on readily available BHB and acetoacetate for cellular energy (18). Ketone bodies also increase vascular density at the blood–brain barrier, which can strikingly increase the availability of ketone bodies for brain energy metabolism by 40-fold (19). Ketones are a preferred energy source in the CNS (20) and neurons will choose ketones over glucose when available.

Nutritional ketosis (10) using a KMT is a natural, not pathological, state (21) where the body's energy and protein synthesis needs are met with a high-fat/moderate-protein/low-carbohydrate diet, resulting in sustained elevations of serum ketones and fatty acids and normal glucose without acidemia. In both acute and long-term nutritional ketosis, ketone bodies have a number of biological effects that directly change the brain's cellular energy status (15), increase mitochondrial density (22), and improve mitochondrial morphology, which has been shown to be altered in mood disorders (23, 24). Mitochondrial abnormalities have also been postulated to be responsible for changes in synaptic function and neuroplasticity, potentially associated with symptoms of depression and anxiety (19).

Recent research shows that a ketogenic diet (KD) reduces neuronal firing rates, modulates ion channels and cell signaling cascades, and stimulates the biochemical synthesis and neurotransmission of GABA by inhibiting glutamate decarboxylase, a major inhibitory neurotransmitter involved in neuronal firing and anxiogenesis (25, 26). BHB activates the transcription of antioxidant-related genes by inhibiting histone deacetylases, triggering long-term adaptive changes in gene expression. In addition, at physiologic concentrations, ketone bodies reduce neuroinflammation through direct action at G-protein coupled receptors (25). KD also favorably alters the gut microbiome (27). Perhaps most importantly, KD directly increases NAD+, which reduces reactive oxygen species and increases mitochondrial ATP production. It is also utilized as a substrate for sirtuins and PARP enzymes associated with DNA repair and longevity. A sustained increase in NAD+ may underlie the pleiomorphic benefits of KMT across multiple neuropsychiatric conditions (28). In terms of the frequent abnormal alarms set off in the amygdala during anxiety, nutritional ketosis may provide an acute and long-term intervention to reduce generalized anxiety, panic attacks, obsessive doubt, and symptoms of post-traumatic stress disorder (PTSD). For apathy, anhedonia, amotivation, and abulia seen in major depression, therapeutic nutritional ketosis may provide higher and more sustained intraneuronal energy and repair (29, 30).

There is no published data that describes the implementation and use of personalized KMT for adults in real-world clinical practice who present with major depression comorbid with GAD and complex psychiatric comorbidity.

The aim of this case series is to examine the response to the treatment of major depression and generalized anxiety with whole-food animal-based personalized KMT in adults with complex psychiatric comorbidity and varied metabolic status. We conducted a retrospective review of three cases from our Metabolic Psychiatry Registry that demonstrate a consistent response and remission of major depression and generalized anxiety among patients who are psychiatrically and metabolically complex, despite differences in the initiation and adoption of KMT, and varied metabolic dysfunction. We describe the evaluation process and prescription of KMT, baseline metabolic workup and monitoring, elements that fostered treatment engagement and adherence, and challenges encountered during 12 weeks of KMT. We correlated capillary BHB/GKI with time to the remission of major depression and GAD and the achievement of metabolic health.

## Case presentations

We present individual case descriptions with time to response and remission, clinical challenges during KMT, and metabolic outcomes. Response was assessed quantitatively using PHQ-9, GAD-7, and correlated with BHB drawn from capillary blood and glucose–ketone index (GKI) using Keto-Mojo® GK+ Blood Glucose and β-Ketone Dual Monitoring System (ketone/glucose correlation coefficients to serum of 0.9927/0.9974) to determine the length of time to response and remission. Improvement in quality of life was assessed by qualitative reports during clinical visits and quantitatively using Self-Compassion Scale (SCS) and Flourishing Scale. Additional rating

scales were used throughout treatment to assess symptomatic response during KMT to comorbid psychiatric conditions.

It is important to stress that in our therapeutic intervention (see Supplementary Data). KMT was used as a medical prescription, with a properly formulated, individualized ketogenic diet offered in conjunction with multiple clinical supports and lifestyle therapies, including sleep, circadian rhythms, movement, community building, friends, and family supports provided by the program, small group nature walks and talks with other patients, and the registered dietitian and psychiatrist, psychiatric follow-up, and metabolic monitoring. Clinician contact was frequent, in person, virtually, through digital tools, and outdoors in nature.

Metabolic health was assessed by interval measures of relevant laboratories, % body fat, visceral fat level, and blood pressure.

## Case 1

Case 1 is a 32-year-old unemployed married man. He had a lifelong history of previously unrecognized and untreated recurrent major depression, as well as GAD, obsessive-compulsive disorder, trypanophobia, and binge eating disorder. He experienced prominent inattention and distractibility since childhood; an adequate prior trial of atomoxetine 100 mg po qd for 1.5 years was somewhat effective; and lisdexamfetamine 70 mg was somewhat effective. He had long declined consideration of SRIs, SNRIs, other antidepressants, and buspirone. He was unaware of the degree to which his complex symptoms had pervasively affected his functioning and quality of life, resulting in his inability to sustain employment, financial insecurity, and adverse interpersonal relationships. Medical history was notable for hypothyroidism with negative antibodies treated with levothyroxine 25 mcg, declined treatment for known hypertension, and frequent snoring without evaluation for obstructive sleep apnea. Metabolically, he was obese (BMI 34.7 kg/m$^2$), with a percent body fat of 36.1%, with a history of muscle cramping during exercise and longstanding untreated essential hypertension (BP 138/102); labs revealed a dyslipidemic profile with TG 241 mg/dL; TG/HDL ratio was 6; and AST/ALT were elevated at 44/82 mg/dL. Fasting glucose was 82 mg/dL.

Family history was notable for anxiety, thyroid dysfunction, and hypertension in first-degree relatives.

At the initiation of KMT 1.5:1, Case 1 chose to incorporate time-restricted eating and consumed two meals per day within a 4–8 h eating window. He achieved therapeutic nutritional ketosis with a mean serum BHB of ≥0.8 mmol/L, GKI < 6 within a couple of days, and high average serum BHB levels of 4.6 mmol/L within 1 week (Figure 1), without adverse effects. He maintained adherence without the muscle cramping he had experienced with exercise before KMT, due to close attention to electrolyte needs and supplementation during KMT. Vitamin D deficiency (26 ng/mL 25-OHD3) was treated with vitamin D3/K2 5,000 IU qd. Generalized anxiety response (GAD-7 decreased from 16 to 8) within 1 week and completely remitted 6 weeks later. The initial PHQ-9 of 17 indicated moderately severe depression. Depressive symptoms completely remitted (PHQ-9 ≤ 4) within 5 weeks of consistent therapeutic nutritional ketosis. Binge eating ceased within days of KMT initiation, and he reported that he "no longer gets over hungry," and that he "no longer eat[s] without realizing [he's] eating." The SCS increased from 3 to 4.6 over 4 weeks. The Flourishing Scale increased significantly from 44 to 53 at 14 weeks; the 12-week data were missing. He reported increased mental focus, increased energy, renewed confidence, and motivation to return to work. Within 4 weeks of initiating KMT, he secured a demanding full-time position exceeding his previous experience; after 8 weeks, he was given additional responsibilities, handled them well, and began three online college courses.

At week 10, he reported fatigue during weightlifting but declined to obtain labs. Photo journaling revealed only one meal a day frequently, which was inadequate to meet his protein needs and macronutrient/micronutrient goals. The inquiry revealed he intentionally restricted his intake due to fear of slowing down his body fat loss. KMT macronutrient needs were reviewed for his current lean body mass and overall body composition, and presented in a new visually appealing way. He was reassured and he quickly increased his intake to a minimum of two meals per day with increased fats as recommended. By 12 weeks, obsessive thoughts lysed (YBOCS 1), and "anxiety was almost gone." Interpersonal relationships were improved.

Metabolically, Case 1 lost 36.9 lbs./16.8 kg over 12 weeks, BMI decreased from 34.7 to 29.6 kg/m$^2$, % body fat decreased from 36.1 to 28.7%, without loss of lean body mass, and blood pressure normalized from 136/102 to 116/81.

## Case 2

Case 2 was a 36-year-old married man with a lifelong history of mood dysregulation, irritability, and trauma from adverse childhood experiences and recent work experiences. He had a history of childhood-onset generalized anxiety, panic disorder, and PTSD, as well as recurrent major depression, which was moderately severe and persistent. His anxiety was unrecognized and untreated. Although he did not have a history of mania, hypomania, or mixed states, he had been treated throughout childhood and adolescence with sertraline 50 mg (ineffective), duloxetine 60 mg (agitation), escitalopram 20 mg (diaphoresis), lamotrigine 300 mg (poor school performance), divalproex ER 1,500 mg (tremor, sluggishness, and weight gain), oxcarbazepine 1,200 mg (fatigue), olanzapine (hunger and weight gain), methylphenidate (ineffective), amphetamine-dextroamphetamine mixed salts 20 mg, and lisdexamfetamine (tachycardia). He discontinued all psychiatric treatment at age 19, but remained symptomatic for 15 years. Recent work-related trauma was unresponsive to psychotherapy and prompted him to present for evaluation and treatment; in addition to major depression and three concurrent anxiety disorders, he met DSM-V criteria for ADHD, a combined type, which had not been previously recognized. Medical history was notable for juvenile ankylosing spondylitis, hyperlipidemia, obstructive sleep apnea, cholecystitis, vitamin B12 deficiency, and vitamin D deficiency. There were no medications other than supplemental vitamin D3 (2,000 IU po qd). Metabolically, he was overweight with a BMI of 28.7 kg/m$^2$, % body fat 26.1, elevated visceral fat level 10, HS-CRP 2.5, total cholesterol 247 mg/dL, and LDL 174 mg/dL. Fasting insulin, HOMA-IR, and blood pressure were WNL.

Family history included bipolar disorder, depression, anxiety, ADHD, hyperlipidemia, hypertension, colon cancer, and breast cancer.

He adopted KMT within less than a week, increased vitamin D3/K2 to 5,000 IU po qd, added magnesium glycinate 250–350 mg po qd, and replaced his sugar-containing electrolyte drink with one free of added sugars. However, he initially struggled to meet his daily goals

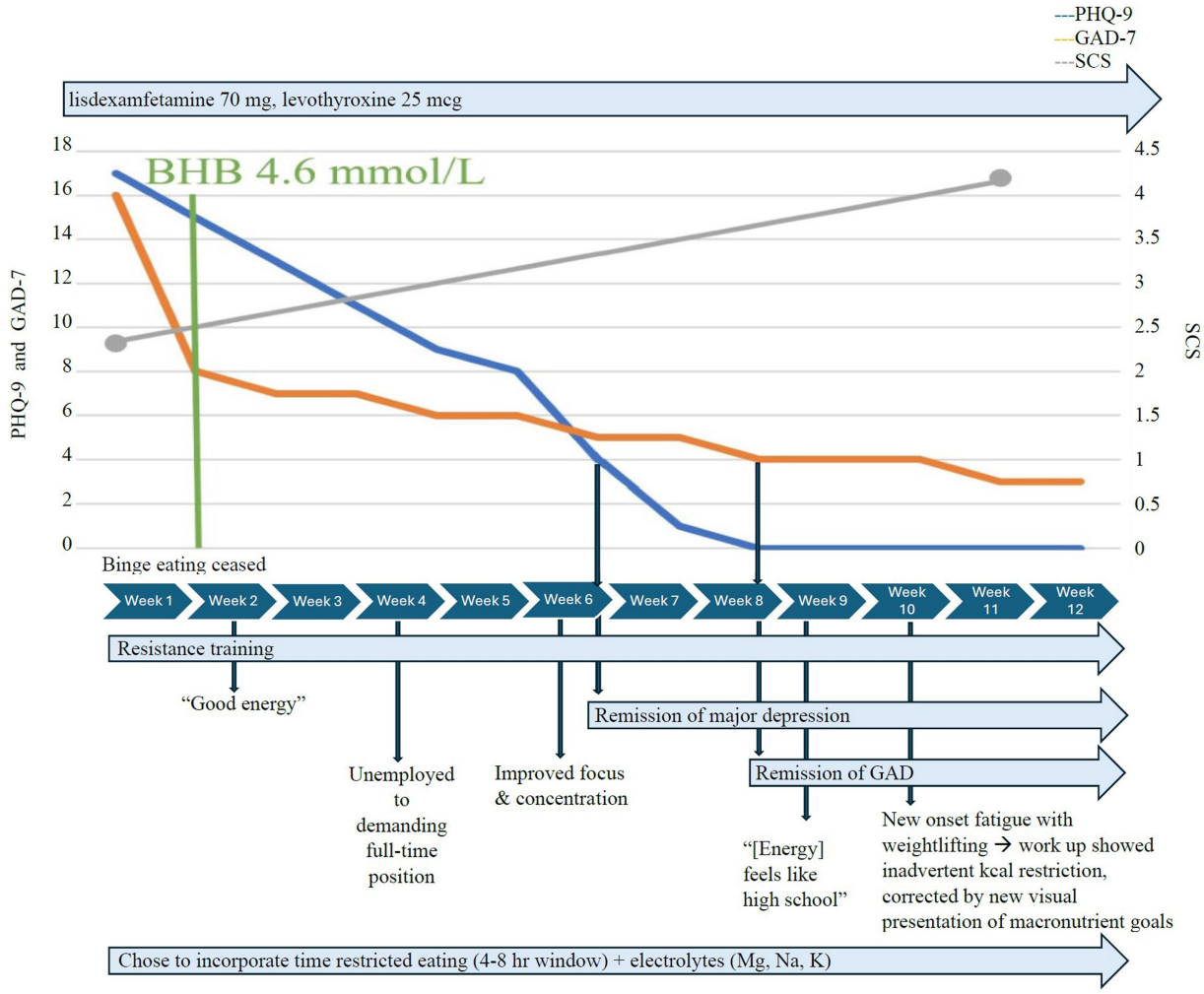


FIGURE 1
Case 1 KMT timeline.

for fat consistently, exercised heavily, and reported new-onset fatigue during exercise. Serum ketones were variable and fluctuated between 0.2 and 1.8 mmol/L throughout the first 8 weeks of KMT.

Treatment of emergent fatigue with strenuous exercise required evaluation which identified low serum carnitine. He had delayed obtaining baseline serum carnitine at initiation and, despite symptoms, delayed recommended follow-up with follow-up serum acylcarnitine and urine carnitine when ordered. He obtained a baseline serum carnitine late in KMT at 8 weeks instead of before or during week 1. Carnitine esters were 21 mmol/L and the esterified/free ratio was 0.57. Additional carnitine evaluation was ordered: a complete acylcarnitine profile showed elevated acylcarnitine, C2 19.6 nmoL/mL, and mildly elevated OH-butyrlcarnitine, C4OH (0.08 nmoL/mL), and glutarylcarnitine, C5DC (0.07 nmoL/mL); further studies of urine carnitine showed elevated urine total carnitine (522 mmol/mg Cr) and urine free carnitine (211 nmol/mg Cr). In response, we advised increased red meat consumption and supplementation with acetyl-l-carnitine 1,500 mg po bid with meals; exercise fatigue resolved within days, and he quickly achieved consistent therapeutic ketosis with capillary BHB ≥ 0.8 mmol/L (Figure 2).

Despite inconsistent capillary BHB and GKI early in treatment, GAD-7 decreased from 8 to 4 within 2 weeks of KMT initiation and to 0 after an additional 4 weeks and remained at 0. Major depression was moderately severe at the initiation of KMT (PHQ-9 = 16), responded at 5.5 weeks (PHQ-9 = 8), and fully remitted at 9 weeks, coinciding with the first week in which he achieved consistent BHB ≥ 0.8 mmol/L/GKI 6.5 and had added acetyl-L-carnitine 1,500 mg po bid. Self-compassion increased from 2.7 to 4 over 12 weeks. He reported "increased mental focus," more patience with coworkers and family, and stated he no longer felt "a general pull of anger all the time."

Case 2 achieved optimal metabolic health in 12 weeks. He lost 21 lbs./9.5 kg, his BMI decreased from 27.8 to 24.9 kg/m$^2$, % body fat decreased from 26.1% to 17.8%, his visceral fat level decreased from 10 to 6, and his HS-CRP normalized, decreasing from 2.5 to 1.

## Case 3

Case 3 was a 34-year-old single woman with a history of childhood adversity and trauma, PTSD, childhood-onset GAD,

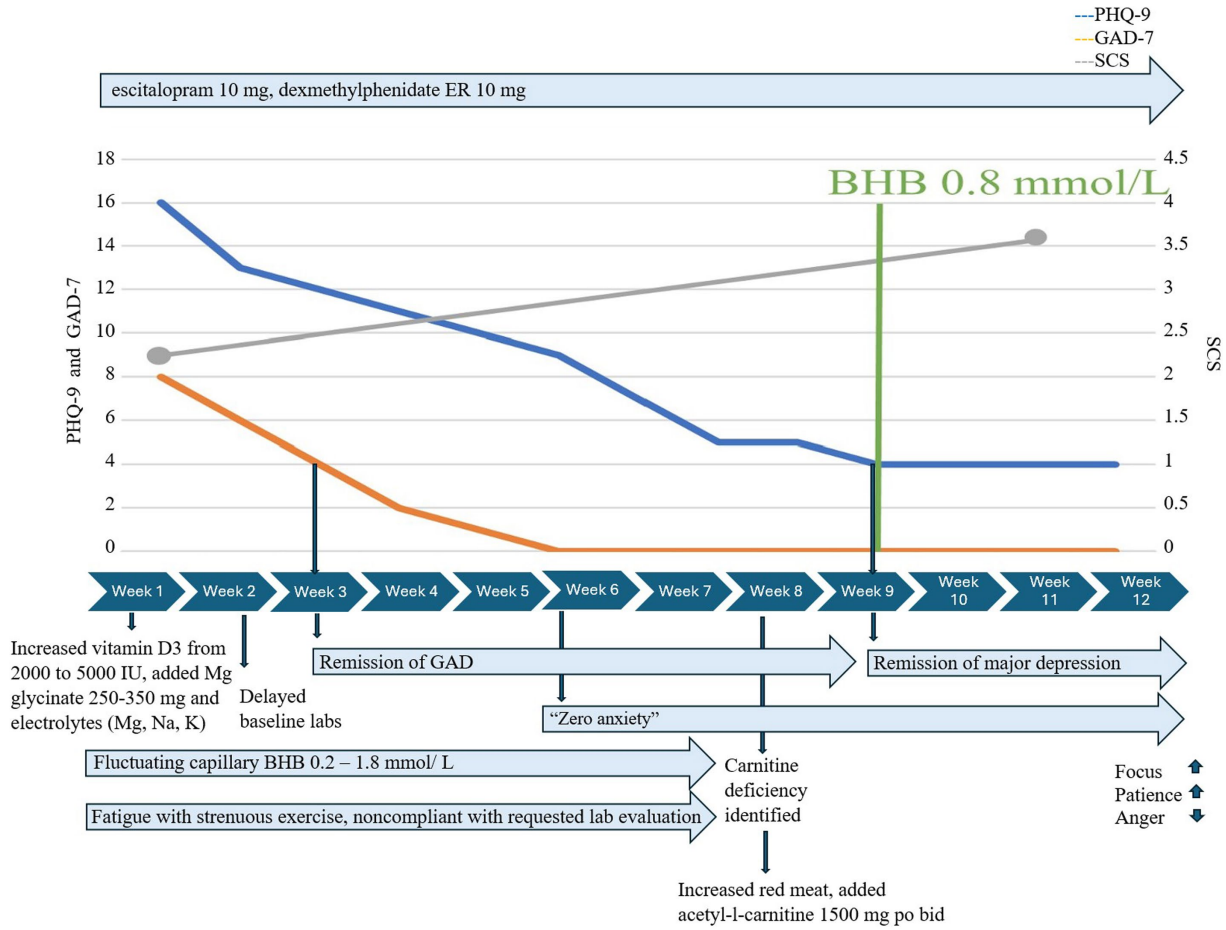


FIGURE 2
Case 2 KMT timeline.

and recurrent severe major depressive disorder. She developed anorexia in adolescence and later binge eating disorder with weight fluctuations up to 100 lbs. and reported a long history of dietary attempts at weight loss, including the use of low-carb diets. She had been previously prescribed long trials of citalopram, risperidone, and ziprasidone, all of which were ineffective. ADHD, the inattentive subtype, was treated with a long-acting methylphenidate with intermittent compliance. Her medical history included irritable bowel syndrome, hypothyroidism, obstructive sleep apnea, chronic fatigue syndrome, and cholecystectomy. Medications included bupropion XL 150 mg po qam, duloxetine 60 mg po qd, lisdexamfetamine 20 mg po qam, NP thyroid 15 mg, and levothyroxine 25 mcg po qd. She was obese with a BMI 43.7 kg/m$^2$, 52.2% body fat waist circumference > 35″, low HDL of 46, TG/HDL ratio of 2.1, elevated insulin resistance score of 67, elevated fasting insulin of 15 μIU/mL, and C-peptide of 2.08 ng/mL. HS-CRP was very high 6.4 mg/dL, with a dyslipidemic advanced lipid profile showing elevations in LDL particle number, small and medium LDL, and low and large HDL particles. BP was within normal limits.

Family history was notable for depression, generalized anxiety, and ADHD in first-degree relatives and unspecified psychosis in second-degree relatives; family medical history included obesity, type II diabetes mellitus, hyperlipidemia, and breast cancer in first-degree relatives.

She began KMT as adjunctive treatment to medication, which remained unchanged throughout 12 weeks. Initial mild transient fatigue resolved rapidly with no other adverse effects. Adherence to KMT was initially variable, affected by travel, holiday events, and family pressure to eat processed carbohydrates and desserts. She realized quickly that her lack of preparation for these events contributed to difficulties adhering to KMT and adopted simple strategies to prepare ahead. Initially, GAD-7 decreased from 12 to 6 within 2 weeks, even before consistent adherence to KMT. By week 3, when she achieved consistent therapeutic ketosis, the mean BHB was 1.4 mmol/L/GKI 4.2, and GAD-7 dropped to 4 for the first time (Figure 3). One week later, the mean BHB was 2.1 mmol/L/GKI 2.3, and she reported binge eating had stopped; she could "now ignore sugar cravings completely" and "no longer related to struggles with hunger and cravings." Notably, KMT did not precipitate a return of anorexic thoughts, body preoccupation, or behaviors. She learned to navigate social situations and restaurants more easily while maintaining KMT.

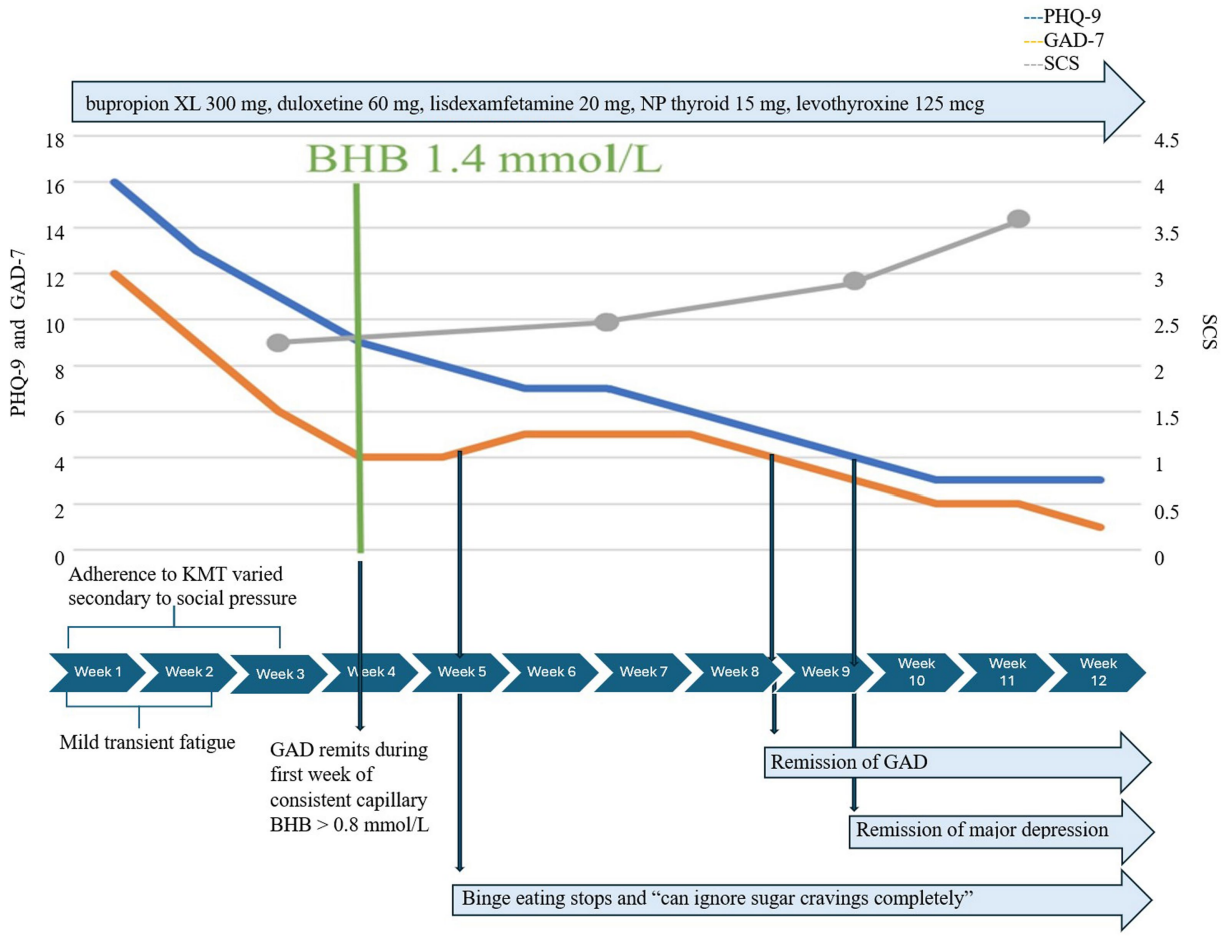


FIGURE 3
Case 3 KMT timeline.

Complete remission of depression occurred 5 weeks later, after a total of 8 weeks of consistent nutritional ketosis, and she said, "I do not have it anymore. I've just noticed I'm happy all the time, which is funny." GAD remitted sooner, 5 weeks after consistent therapeutic ketosis. SCS increased from 3 to 4 over 12 weeks, and flourishing scale increased from 47 to 53.

Metabolically, despite insulin resistance and requiring 3 weeks to achieve consistent therapeutic ketosis, Case 3 lost 28.7 1bs/13.0 kg within 12 weeks, BMI decreased from 43.7 to 37.7 kg/m$^2$, % body fat decreased from 52.2% to 48.9%, insulin resistance score decreased from 67 to 36, and hs-CRP decreased from 6.4 to 2.3.

None of these patients reported nausea, orthostasis, drowsiness, insomnia, agitation, or hypomania. There were no drug-KMT interactions identified, and none of the patients were treated with anticonvulsants, such as topiramate or zonisamide, which could have potentially increased the risk of nephrolithiasis.

## Discussion

Although KD was first shown to produce antidepressant effects and alleviate "behavioral despair" in preclinical studies more than 20 years ago (20), there is little clinical data regarding KD in major depression and anxiety disorders.

A retrospective analysis of 31 individuals with primary diagnoses of major depression ($N=7$), bipolar II disorder ($N=13$), and schizoaffective disorder ($N=12$) who had failed to respond to conventional psychiatric care was treated with KD (75%–80% fat, 15%–20% protein, 5% carbohydrate) for 12 weeks in a psychiatric hospital (31). Of these patients, 22 were voluntarily admitted for the initiation of KD, and the remainder were offered KD during their inpatient hospital course. Change in depression was measured by HAM-D and MADRS in 6 of 7 patients with major depression and 12 of 13 patients with bipolar disorder. Notably, 100% of patients given the HAM-D showed statistically significant improvement in depressive symptoms (mean HAM-D decreased from 25.4 to 7.7; mean MADRS decreased from 29.6 to 10.1). However, serum ketones were not measured; urinary ketone measures were obtained once in 28 patients during the 12-week intervention; 18 patients (64%) showed positive urine ketones (31).

Bipolar depression was included in a recent randomized controlled pilot study assessing the safety and feasibility of KMT as adjunctive therapy, and reported safety and feasibility with excellent adherence and maintenance of ketosis (mean BHB 0.88 ± 0.99 mmol/L for 12 weeks) (32).

One case report utilized KD (65% fat, 25% protein, 10% carbs) with a time-restricted feeding window in a 65-year-old woman with major depression and type II diabetes and reported remission of depression (PHQ-9 17 to 0), normalization of HbA1c, decrease in estimated average glucose from 216 to 96 mg/dL, improvement in HOMA-IR from 9.4 to 2.3, and TG/HDL ratio from 4.7 to 1.2 over 12 weeks. The only measured serum BHB reported in the case was a mean of 1.5 mmol/L by week 12 (30).

A recent meta-analysis of low carbohydrate diets used in controlled trials that evaluated symptoms of depression and anxiety, not disorders, in varied metabolic and inflammatory conditions reported that the symptomatic response of these symptoms was inconclusive (33). The conclusions may not apply to KMTs; the meta-analysis was limited by grouping varied diets with higher carb intake and higher protein intake than usually associated with diets formulated to induce nutritional ketosis; serum or capillary BHB was not reported; and primary and secondary outcomes varied across studies.

In anxiety, preclinical research shows that exogenous ketone supplementation reduces anxiety behaviors (34). There is one case report of a self-administered Atkins Diet for weight loss in a woman with panic disorder (35) but no reports of KMT in panic disorder, OCD, or PTSD. Case reports of KD addressing anxiety describe two cases of decreased anxiety symptoms in a woman with women, one with bipolar I disorder and another with unspecified mood disorder, comorbid emotional dysregulation, body dysmorphic disorder, and eating disorder (36, 37), and one case report that describes the elimination of anxiety symptoms in a man with bipolar disorder (38). Anxiety and obsessive preoccupations improved in weight-restored anorexic women, in one case report describing complete remission of anorexia (39) and in a retrospective case series where animal-based KD was adopted without dietary prescription and monitoring (2); however, ketone measures were not reported. One small pilot trial where KD was followed by ketamine infusions reported a significant lessening of obsessive preoccupations in weight-recovered women with chronic anorexia; here, ketosis was measured by breath acetone (40).

Finally, all three patients had comorbid ADHD, which may be important. Approximately 65–89% of adults with ADHD experience one or more comorbid psychiatric conditions, and ADHD often occurs comorbid with anxiety and depression (41). Preclinical studies in murine models (42) of ADHD with hyperactivity suggest that KD may improve symptoms via alteration of the gut microbiome. Preclinical studies in dogs with epilepsy displaying ADHD-like behaviors treated with a medium-chain triglyceride KD have shown decreased pathological behaviors (43). Further research exploring the effect of KMT in humans with ADHD should be considered to understand the mechanisms of action and assess short- and long-term risks and benefits.

There is little research regarding the selection, implementation, and treatment course for KMT use as adjunctive or sole treatment in individual psychiatric conditions. Given the potential benefits of therapeutic nutritional ketosis and the restoration of metabolic health (44), there is a pressing need to identify the biological underpinnings of KD in psychiatric disorders and delineate factors associated with the successful adoption and adherence of KMT and responses in common psychiatric disorders such as depression and anxiety. In clinical practice and real-world settings, where patients often present with multiple comorbidities, consideration of KD can seem daunting to clinicians.

Despite that, this case series illustrates complete remission of both major depression and GAD in three adults with complex psychiatric comorbidity and previously unrecognized metabolic dysfunction using whole-food, animal-based personalized KMT. Anxiety responded first and time to remission occurred rapidly within 7–12 weeks, despite varied challenges, including preferences for time-restricted eating, slow adoption, inconsistent monitoring, and emergent fatigue during strenuous exercise, which occurred many weeks into KMT due to low serum carnitine and spontaneous reduction of protein intake rather than keto-adaptation or "keto-flu." All patients improved metabolically, and one patient achieved optimal metabolic health (6).

These patients were representative of many adults in clinical psychiatric practice who present with persistent, serious symptoms interfering with several life domains. They each had five DSM-V psychiatric disorders: severe unipolar major depression, GAD, at least one other anxiety disorder (OCD, PTSD, and/or panic disorder), and ADHD, and two had binge eating disorder. They had all failed at least two previous adequate trials of medications and psychotherapy and were seeking relief. All had family histories of mood and anxiety disorders and documented metabolic disease in first-degree relatives. Extensive laboratory testing and bioimpedance evaluations were eye-opening because, although they were overweight, they were not aware of the extent to which they were already metabolically ill; we suspect it enhanced their motivation to adopt and maintain KMT.

This case series is limited by describing only three patients, which limits the generalizability of our results as well as the inherent selection bias, as they were interested in KMT after failing standard therapies. In addition, they were selected because their complex psychiatric comorbidity reflects the complexity seen in the majority of our outpatient psychiatric practice. This degree of complexity may limit the generalization of these findings, although it is important to note that outpatient clinical psychiatric practice as a whole has seen an increase in complex psychiatric comorbidity over the past two decades (44).

As a retrospective case series, there may be additional limiting and confounding factors, including the lack of a control group. Some rating scales and digital data are missing, which may impact the completeness of the analysis. Time to consistent nutritional ketosis and delays in obtaining necessary labs requiring intervention may have contributed to a longer time to response and remission; response and remission may occur earlier than reported here, and this deserves further research. Finally, it is not clear to what extent immersive treatment (see Supplementary material 1) and additional interventions during KMT, such as close digital monitoring, frequent clinical contact, group supports, and nature walks, contributed to the rapidity of response/remission of anxiety and depression, or to overall treatment success, independent of the biological effects of KMT, and which of these elements were most critical; more research is needed. Carefully designed prospective studies and randomized controlled trials providing higher levels of evidence are needed to examine the use of KMT and time to response and remission in individuals without comorbidity and determine the extent to which comorbidity may confound or alter these (8).

As metabolic psychiatry moves forward, we need both preclinical and larger, well-controlled clinical studies examining the pleiomorphic

effects of ketone bodies in the brain and in the body to understand how we can best leverage whole foods to optimize brain energy, enhance genetic expression, reduce neuroinflammation, optimize metabolic health, and safeguard the promise of our future.

## Patient perspectives

"I'm very pleased with my progress in weight loss and focus and there is a significant improvement in energy, which are all at the best levels that they have ever been. My energy levels are as good as they were when I was an athlete in high school." "I've been given more to handle [at work]" [Case 1].

"Sleeping well, feeling well overall, I feel a little less irritable. Something bad happened … and I handled it much more calmly than I ever would have." "My ketone levels have been more consistent and I have not had any episodes of feeling weak during exercise since I started taking carnitine [with meals]" [Case 2].

"I'm not depressed anymore." "I understand why things had gone wrong in the past with trying low carb diets on my own." "The accountability and the community support is really important for me" [Case 3].

## Data availability statement

The datasets presented in this article are not readily available because of reasons of sensitivity, but de-identified data are available from the corresponding author upon reasonable request. Requests to access the datasets should be directed to LC, drcalabrese@loricalabresemd.com.

## Ethics statement

Ethical approval was not required for the studies involving humans because this is a retrospective review of three cases from the usual course of clinical practice. All individuals provided written informed consent for the treatment intervention described, and for publication of their data. All data has been de-identified to protect confidentiality. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

## Author contributions

LC: Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. RF: Conceptualization, Data curation, Investigation, Writing – original draft, Writing – review & editing. MG: Investigation, Writing – review & editing.

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## Conflict of interest

LC is the founder of Innovative Psychiatry, LLC and Touchpoints 180™, organizations offering metabolic psychiatry consultation and ketogenic metabolic therapies for which she receives payment, provides free presentations and a free LowCarb Lifestyles Book Club. RF was employed by Innovative Psychiatry.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1396685/full#supplementary-material

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# Understanding the experiences of ketogenic metabolic therapy for people living with varying levels of depressive symptoms: a thematic analysis

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**Background:** Evidence suggests that a ketogenic diet (KD) may help to alleviate psychiatric symptoms, including depression and anxiety. Positive changes have been reported such as improvements in cognition, concentration, and sleep, a reduction in hunger, and an increase in well-being, energy, confidence, and resilience. This research aims to understand the impact of a non-calorie-restricted KD on depression and aspects of psychological well-being in those with varying degrees of depressive symptoms. Though there are a few studies directly exploring the experiences of those following a KD, this will be the first study to explore the narrative from a mental health and psychological well-being viewpoint.

**Method:** A sample of nine participants who had followed a non-calorie restricted KD intervention of 50 g of carbohydrates or less per day for at least 12 weeks were recruited. Participants were split into 'healthy adults' group who had no to low depressive symptoms and 'depressive symptoms' group who had mild to moderate depressive symptoms. A reflexive thematic analysis was considered suitable for this study.

**Findings:** Five core themes and 24 subthemes were created. These were, (1) Poor health prior to program; (2) Hunger and cravings-the food and mood connection; (3) Psychological well-being improvements; (4) It becomes a lifestyle; and (5) Implementation difficulties. Participants experienced mental health improvements such as increased self-esteem, confidence, motivation, and achievement. Some experienced more control in life and a greater sense of reward. Those with depressive symptoms who initially reported low self-worth and hopelessness later reported increased self-esteem and renewed meaning and purpose in life. The findings from this study reflect the previous reports that the diet implementation can be difficult initially, but soon becomes easy to follow and turns into a lifestyle.

**Conclusion:** In the literature, there are very few qualitative studies that explore the accounts and lived experiences of those following a KD. From the participants' accounts in this study, it appears that the benefits and positive outcomes of this diet outweigh any negative side-effects experienced. This is encouraging for those who are looking for adjunctive therapies to address and improve their depressive symptoms and overall mental health.

KEYWORDS

depression, thematic analysis, diet adherence, human, ketogenic diet, qualitative research, quality of life

## 1 Introduction

The ketogenic diet puts the body into ketosis, a metabolic state which utilizes fat and ketones as a primary fuel source (1). Evidence suggests that the KD produces significant metabolic changes in the body that influence mood and depressive symptoms (2–4). According to previous research, the presence of ketones in the body has been shown to be neuroprotective, promote mood stabilization, and may improve symptoms of depression (5–7). The theoretical basis for this is that the ketones provide an alternative energy source to the brain which can regulate many biological processes that have become dysregulated due to biological or psychological factors (8–11).

To date, many of the studies on the KD and psychiatric conditions have focused on mechanisms of action in rodents and mice, and less so in humans (12–15). Though human studies have recently been published they are predominantly case studies or initial pilot studies (6, 16–19) no randomized control trials have been carried out to investigate the impact of the ketogenic diet on psychological well-being or depressive symptoms, though they are now underway.

Studies looking at the effects of the ketogenic diet on psychiatric conditions have been published as far back as the 1960's (20). Research into the ketogenic diet's effects on bipolar depression type 1 (21) and bipolar depression type 2 (22) in the past decade has suggested that the diet has mood stabilizing effects and may reduce the need for psychiatric medications. More recently, a study using the ketogenic diet for serious mental illness in an inpatient hospital setting of 28 patients, found 43% clinical remission and 64% of patients discharged on less medication than when they started (16). Randomized controlled trials (RCTs) are in progress to investigate whether a ketogenic diet can be used as a therapeutic medical intervention for psychiatric illness. However, the research available at present is predominantly quantitative in nature.

It is important to carry out qualitative research in these populations to better understand the experiences, both positive and negative, of those following specific diets. A recent publication in the area of ketogenic metabolic therapy for mental health has called for more qualitative research to be carried out in this area. The authors state that the changes clinicians see in their patients may not always be quantifiable and therefore without a qualitative perspective, there is a risk that not all positive and negative changes are being adequately captured (23).

When reviewing the low carbohydrate and ketogenic diet literature, it is only within the last 5 years that qualitative studies on the ketogenic diet have been published. This may be a result of the ketogenic diet gaining popularity in recent years as a dietary approach to lose weight. Harvey et al. (24) looked at healthy adults, non-obese, non-diabetic, following a ketogenic diet with medium chain triglycerides (MCT) oil supplementation ($N = 28$), specifically the 'lived experience' of such individuals over 3 weeks. Participants experienced benefits in well-being, mood, and sugar cravings and these improved gradually over the duration of the study. They found that mood, energy, and cognition were low at the start of the study, most likely due to an immediate reduction in blood glucose with a slower increase in ketones, as the participants had not yet reached a state of ketosis. This was also true for satiety levels, hunger, and the desire to eat, as well as sugar cravings, all of which improved as time went on and participants achieved a state of ketosis, where ketone levels increased and provided energy for the body. Individuals who came off the diet or who were non-compliant with it, experienced negative effects in the form of a "food hangover."

Sleep quality also improved which is to be expected as research suggests that following a higher carbohydrate diet negatively impacts sleep by increasing sleep length but reducing its quality by spending more time in rapid-eye-movement (REM) compared to slow-wave sleep (SWS) (25). According to a systematic review, individuals following a low carbohydrate diet tend to spend more time in SWS and experience an increase in the duration of deep sleep (26).

Using thematic analysis, Newson and Parody (27) looked at individuals' experience of low carbohydrate diets (LCD) in those living with T2D. They found that in 10 participants who had been following a LCD for at least 5 months, they experienced a lack of hunger, gained confidence, felt resilient, calm and more energetic. Although they felt starting the LCD was difficult, it was easier over time, and soon became a lifestyle.

Wong et al. (28) looked at those with type 1 diabetes and T2D who followed a ketogenic diet for between six and 19 months ($N = 14$). Using thematic analysis, they found that individuals experienced greater glycemic control, weight loss and satiety. Participants also experienced improvements in cognition, specifically concentration, a reduction in chronic pain levels, an increase in well-being and energy, and improvements in sleep. Individuals reported no hunger and stated that the KD was easier to follow than other diets, however they did initially express difficulty getting used to the idea of eating a KD as the foods eaten are not in keeping with conventional nutritional guidelines. Individuals reported some keto flu or keto adaptation symptoms at the start of the diet such as fatigue, headaches, dizziness, and constipation but these symptoms were temporary and soon passed. These findings support the work of Bostock et al. who found that keto flu symptoms were apparent when starting the diet but that they were transient (2020).

According to Wong et al. (28), Newson and Parody (27), and Bostock et al. (29) the diet implementation can be difficult initially, but soon becomes easier to follow and progresses into a lifestyle. The findings from the current study reflect these previous reports. From this literature, it is clear that the ketogenic diet can lead to improvements in mental health and relief from psychiatric symptoms in some people. The benefits, if a patient responds to the diet, can be life changing, and the safety of the diet has been confirmed (30–33), but whether the diet is easily implemented and sustainable in the real-world within the general population is uncertain. Research is required to investigate the accounts, perspectives, and experiences of those following a ketogenic diet to better understand their journey to

improve their physical and mental health. This will help researchers to better inform care pathways and provide the right support to individuals at the right time.

Research suggests that some individuals following a ketogenic diet may experience improvements in their psychological well-being, though it is unclear which population would benefit most from this dietary intervention and what 'barriers to entry' they might face when initiating the diet (5, 18, 34).

The aim of this current study is to review the accounts of participants who have completed an online ketogenic dietary program through a remote care model and to identify any common themes relating to their journey. This study focused specifically on the health of participants prior to the start of the program, the challenges and obstacles they faced implementing the diet and any physical or psychological changes, either positive or negative, that they experienced throughout the program. Aside from directly discussing their accounts of the diet, the interviews also covered participants' overall health and well-being in a broader sense and touched on areas such as their relationship with food, their general health, and their mental and physical state prior to starting the ketogenic diet.

Through reflexive thematic analysis, the accounts and attitudes of participants following the ketogenic dietary intervention were explored. Though there are a few studies directly exploring the experiences of those following a LCD or ketogenic diet, this is the first study to explore the narrative through the lens of mental health and psychological well-being. The findings will inform future research directions into the application of a ketogenic diet and ketogenic metabolic therapy either through online programs or via healthcare professionals in clinical practice. The data gathered will also help to understand the utility of ketogenic metabolic therapy more fully for those with depressive symptoms and poor psychological well-being.

# 2 Materials and methods

## 2.1 Design

The study was nested within a randomized controlled trial (RCT) on the impact of the ketogenic diet on depression and psychological well-being. This was an interview-based research piece, carried out by the first author, using face to face semi-structured interviews of participants drawn from the RCT sample of ketogenic dieters and using Braun and Clarke's reflexive thematic analysis process to draw out, create, and analyze themes (35). Reflexive thematic analysis takes an experiential approach and was chosen to understand the views, perspectives, and perceptions of participants following the ketogenic dietary intervention (36).

## 2.2 Participants

### 2.2.1 Collaborators—Diabetes Digital Media Ltd.

Since 2007, Diabetes Digital Media Ltd. (DDM) has been providing lifestyle intervention programs and community support for those with diabetes. Their Low Carb Program currently has over 475,000 members and is the world's largest low carbohydrate intervention. DDM provided the researcher with access to their Low Carb Program. They gave the researcher access to the program and permission to create a bespoke ketogenic diet version with aligned support materials. The program included dietary recommendations to focus on unprocessed foods with the goal of reducing carbohydrates to <50 g per day, educational videos on a variety of topics including macronutrients, food swaps and ketone testing, methods to track progress and supportive forums for peer support.

### 2.2.2 Participants

A sample of nine participants who had followed the ketogenic diet intervention arm of the RCT were recruited for this study. The ketogenic diet consisted of no more than 50 g of net carbohydrates per day, with fat and protein *ad libitum* and a focus on whole foods was encouraged. The sample consisted of five participants who had been previously placed in the 'healthy adults' group for the RCT and four participants who had been placed in the 'depressive symptoms' group. Groups were determined based on participants scores on the Patient Health Questionnaire (PHQ-9) which measures the severity of their depressive symptoms (37). Those with little or no depressive symptoms (<5 on the PHQ-9) were included as the 'healthy adults' group and those with mild to moderate depressive symptoms (5–19 on the PHQ-9) were included as the 'depressive symptoms' group.

Out of the five in the 'healthy adults' group, one participant had a diagnosis of depression, and had been taking antidepressants for more than 3 weeks as defined in the RCT eligibility criteria. However, when randomized to a dietary intervention, their PHQ-9 score was three, suggesting low to no depressive symptoms and therefore they were allocated to the healthy adults group rather than the depressive symptoms group.

In the healthy adults group, there were four females and one male, and in the depressive symptoms group there were three females and one male. The mean age overall was 51 years (SD 8.12). The mean age for healthy adults was 52 years (SD 10.23) and for depressive symptoms it was 49 years (SD 5.47). All nine participants were renamed for the purpose of this analysis in order to maintain their anonymity. Reference names are seen in Table 1 along with their group allocation, age, and gender. To participate in the RCT, participants were deemed eligible based on their answers to a baseline screening questionnaire. Detailed inclusion and exclusion criteria for the RCT will be published, but an overview can be seen in Table 2.

TABLE 1 Demographics of participants, anonymized name, psych group, age, and gender.

| Participant number | Anonymized name | Psych group KD | Age | Gender |
|---|---|---|---|---|
| 1 | Amari | Healthy | 36 | Female |
| 2 | Anika | Healthy | 63 | Female |
| 3 | Diane | Healthy | 58 | Female |
| 4 | *Harriet | Healthy | 54 | Female |
| 5 | Mark | Healthy | 50 | Male |
| 6 | Jessica | Depressive | 56 | Female |
| 7 | Philip | Depressive | 43 | Male |
| 8 | Sarah | Depressive | 47 | Female |
| 9 | Whitney | Depressive | 50 | Female |

*Participant had a diagnosis of depression but showed very few depressive symptoms on the PHQ-9 and so allocated to healthy group.

TABLE 2 Criteria of inclusion and exclusion for RCT eligibility.

| Criteria | Included | Excluded |
|---|---|---|
| Age | 19–65 | <19, >65 |
| Location | UK | Outside the UK |
| Body Mass Index (BMI) | >18.5 kg/m$^2$ | <18.5 kg/m$^2$ |
| Diabetic Status | Non-Diabetic | Pre-Diabetic, T1D, T2D |
| Physical Health Status | No Physical Health Issues | Physical Health Issues |
| Pregnancy Status | Not pregnant and no plans in next 6 months | Pregnant or planning pregnancy in next 6 months |
| History of Recent Weight Loss | Less than 12.7 kg | 12.7 kg or more |
| History of Using a Low Carbohydrate or Ketogenic Diet in last 2 years | No History | History |
| Partaking in Trial Status | Not currently partaking in trial on diet or exercise | Partaking in other trial on diet or exercise |
| Mental Health Diagnosis Status | Depression and anxiety only | Any other mental health diagnosis |
| Severe Depression - High Risk Status Question 'Recently have you had thoughts that you would be better off dead or of hurting yourself in some way?' | Answered 'No' | Answered 'Yes' and referred to mental health support services |
| Antidepressant Medication Status | Taking Antidepressants for more than three weeks | Taking Antidepressants for less than three weeks |
| Patient Health Questionnaire (PHQ-9) | Scores of less than 20 | Scores of 20 or greater |

### 2.2.3 Materials and measures

For the semi-structured interviews, open ended interview questions with a series of prompts were developed by the researcher in order to extract the full journey from the eligible participants. Examples of the questions included in the interview were 'how had you been feeling psychologically and emotionally before starting this program?' and 'please can you describe your journey on the diet?', with prompts such as; 'what were reasons for joining the program?', 'how do you think diet played a part in how you felt?', 'what was your opinion of yourself?', 'how did you feel in the first few days?' and 'how has your mental state or mood changed?'

### 2.2.4 Ethical protocol

The research protocol for this qualitative investigation was approved by the University of East London, UREC 1718 87 on the 4$^{th}$ of July 2018 and interviews were carried out between April and June 2019. Participants provided their written informed consent to participate in this study and were reminded that they could withdraw from the study at any point. Participants consented to the recording of interviews, which were anonymized and transcribed. Interviews were stored on an encrypted computer, which housed all data.

### 2.2.5 Procedure

Participants must have completed 12 weeks of the trial to be eligible for this study as it was imperative that they could give a full account of the ketogenic intervention from start to finish. Thirty-three participants were identified as eligible for the study. Participants were contacted and asked if they would take part in the follow up interview. Once participants had been recruited, read, and understood the information sheet and signed the consent form, the researcher agreed a time and date to carry out the interview. Interviews were approximately 30 min long, with some a little longer based on how much the participant wanted to share. The researcher reached data saturation with nine participants. This is the point where no additional themes or insights would emerge from continued data collection.

Participants were encouraged to share their journey of following the online dietary intervention and the positive and negative effects they encountered during their dietary change. Following the interviews, all participants were debriefed and thanked for their participation in the study. Interviews were transcribed and full transcripts were then uploaded to data analysis software NVivo to assist with the qualitative analysis. Once uploaded, the audio recordings were subsequently deleted.

### 2.2.6 Epistemological position

An essentialist and realist approach to the data was taken, with the language used by participants to share their accounts of the intervention taken at face value, with no further in-depth interpretation of the meaning of language used seen as necessary. What participants say is their experience and reality (38). Then, an inductive or 'data-driven' approach was taken as there were no specific research questions and no pre-defined themes for this study. This was an exploratory analysis where the themes became analytical outputs and were reflective of the data collected and were therefore free from the researcher's analytical preconceptions (39). Themes were actively identified at the semantic level, meaning that no further interpretation of the data was carried out beyond what the participants had shared. Themes were then described and further interpreted. This position and approach are similar to that used by Newson and Parody (27) who used thematic analysis to investigate the experiences of those with T2D following a LCD. Discussions occurred between authors throughout the study process to ensure a shared understanding and agreement on the final themes.

### 2.2.7 Analysis

An inductive thematic analysis of the interview transcripts was carried out following the six-phase framework set out by Braun and Clarke (38), to review the shared accounts of participants. Transcripts were initially coded line-by-line and sorted. The researcher became familiar with the data by reading and re-reading the transcripts before generating initial codes. These preliminary codes were assigned to the data to describe the content. The researcher then searched for consistent patterns and developed themes from the codes across all interviews after a period of familiarization with the collected data which is in keeping with the work of Terry et al. (40). Once themes were constructed, they were

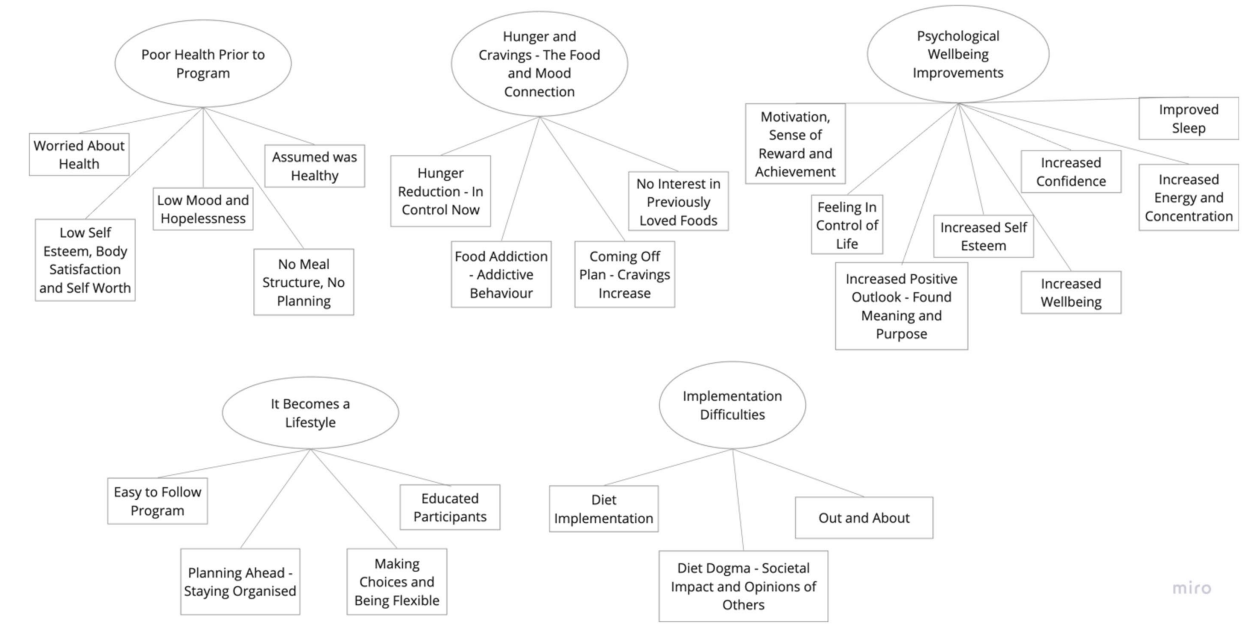


FIGURE 1
Thematic map showing five main themes.

repeatedly reviewed, defined, and renamed. There were five main evident themes with three to eight sub-themes each, see the final Figure 1. The findings were kept to five themes so that the analysis stayed coherent, and that the researcher could provide a meaningful overview of the data. This is in keeping with the guidance from Braun and Clarke (35).

# 3 Results and findings

## 3.1 Findings in relation to groups and previous research

Five core themes and 24 subthemes were created during this analysis as seen above. The five core themes in order from highest referenced to lowest referenced were, (1) Poor health prior to program; (2) Hunger and cravings—the food and mood connection; (3) Psychological well-being improvements; (4) It becomes a lifestyle; and (5) Implementation difficulties. Direct quotes from participants have been included to help illustrate each theme and subtheme and, in some cases, the group they were allocated to has been identified to better understand if a subtheme was predominantly representative of one specific group rather than another.

## 3.2 Theme 1—Poor health prior to program

This theme is characterized by participants stating that they felt generally healthy, however as the theme was refined, physical and psychological health issues arose from the data which suggested that people were not as healthy as they had initially assumed.

### 3.2.1 Subtheme—Assumed was healthy

The first question in the interview asked how the participants health was before starting the program. Four participants out of nine, "assumed they were healthy" and that they ate in a generally "healthy" way. Diane believed that her health was "pretty good in general," both now and before they started the program. Whitney stated that she could not remember the last time she purchased a ready-made meal as she always prepares her meals at home alluding to the fact that she followed a healthy diet overall. Mark shared his thoughts when grocery shopping:

> *"You know, I'd go round the supermarket and look at people's trollies and think ooh no you do not want to be eating all that crap because I thought we were, well we were, we do, eat relatively sensibly."* (Mark).

Some participants were following a standard western diet prior to starting the ketogenic diet. Other diets such as the Mediterranean diet, which is lower in processed foods, are associated with greater psychological well-being compared to the western diet (41). Perhaps some participants experienced this when moving from the standard western diet to the ketogenic diet.

### 3.2.2 Subtheme—No meal structure, no planning

Though answers to the interview questions about health varied from good to bad, the overarching observation was of poorer health prior to initiating the program. There appeared to be a lack of meal structure and little planning of food or meals in advance which led participants to graze through the day, eat on the go, or eat less healthy options based on what was available when they were faced with hunger. This was reported by two participants in the depressive symptoms group and one in the healthy group. The lack of meal structure and food planning was felt by Sarah who shared that because she only had to cook for herself, she did not, and for Harriet, she would spend the

day "eating rubbish" and skipping dinner as a result. For Whitney, a morning routine with no meals planned appeared to be normal:

> *"So, then I would not have time for breakfast so would just go to work and drink coffee…There is that, if there's biscuits going round, or cake, you would have that before your lunch."* (Whitney).

Participants appeared to have a daily self-care routine that lacked a meal structure or food planning stage. The perceived lack of time to plan meals or prepare food is associated, unsurprisingly, with a higher intake of fast and convenient food (42). On the other hand, meal planning has been linked with improved diet quality and less obesity (43) and structured meals may increase the success of weight loss (44) and therefore overall health if employed consistently.

### 3.2.3 Subtheme—Worried about health

There appeared to be an underlying feeling prior to the program, of worries about current and future health, understandably. Again, this questions how participants truly felt about their overall health prior to the program. Though just under half of the participants stated they felt generally healthy, once the researcher dug a little deeper there appeared to be ongoing health concerns among many. Philip stated that though he had not been morbidly obese, he had always been on the "wrong side of ok" and that was a concern for him. The idea that some participants needed to take medications for their ailments was also a cause for worry. Amari stated that she did not want to take the medication and it "does not make me feel nice." When participants were asked to share more about their experience of health prior to the program, it became clear that there were both significant negative physical and psychological symptoms present in their everyday lives. Physically, participants experienced extreme tiredness, fatigue, and lethargy throughout the day.

> *"I was really struggling in meetings at work, and I was constantly falling asleep, and I kept thinking, what on earth is wrong with me!"* (Harriet).

> *"Tired is an accurate word of how I would describe myself, sluggish and just tired. I did not have a lot of energy anymore, restless, you know."* (Sarah).

Prior to the dietary intervention their cognition and ability to concentrate was also impaired, they lacked focus and often experienced symptoms such as brain fog. Mark stated that he had always had a low attention span, and that he still struggles with that now. Philip shared his more debilitating experience:

> *"Whether it's a funk or fog I do not know, so this is where I sort of started, I could not really sort of keep any concentration and any focus or goal…I've always enjoyed learning, but I could not focus, I could not retain any attention to what I was doing…I was getting frustrated with myself."* (Philip).

### 3.2.4 Subtheme—Low self-esteem, body satisfaction and self-worth

Psychologically, extremely low self-esteem, poor body satisfaction and little self-worth were evident in four of the nine participants. Worthlessness is a symptom identified in the diagnosis of depression and research shows that poor body satisfaction predicts worse depression and mood outcomes (45, 46). Three participants from the depressive symptoms group stated that they felt "terrible about myself" (Jessica), that they were "feeling so rotten" (Whitney), and "my opinion of myself has never been terrific" (Philip). One participant from the healthy group shared that:

> *"I could not even look at myself in the mirror, really, really, low self-esteem."* (Amari).

This was followed by "rock bottom" confidence (Jessica), a lack of motivation, and the feeling they were "stuck in a rut." Understandably, day to day energy was limited and carrying out simple daily routines and tasks was a struggle for some participants. As Jessica put it, "I could not motivate myself to do anything." Whitney shared her thoughts:

> *"Yeah, so I suppose a lack of motivation, you just get into that rut do not you, you feel lazy so you just, you cannot get up…and just felt stuck in a rut."* (Whitney).

This lack of motivation, and low energy that participants experienced ties back to their difficulty of following a routine that supports a healthy lifestyle and may have been a contributing factor to their lack of daily structure with regards to meal timing and food planning. Whitney again shared an example of this:

> *"Not getting out of bed on time to get myself ready for work to get to work…Yeah just feeling pretty lazy actually."* (Whitney).

### 3.2.5 Subtheme—Low mood and hopelessness

For some participants, their mood was extremely low which is a symptom necessary for the diagnosis of depression (46). From the healthy group, Anika felt "quite depressed really," and from the depressive symptoms group, Philip experienced a sense of hopelessness.

> *"I was beginning to worry about, not depression itself but being in a rut if you know what I mean…I felt pretty hopeless, I wasn't suicidal, I just could not work out what was wrong with me."* (Philip).

Jessica even felt a lost sense of meaning and purpose in their life.

> *"I was just getting really down about, well where is my life going and what was there left for me to do…but I could not find my niche in life…you lose your identity really…you just think, oh well, who am I then? Where do I fit in?"* (Jessica).

These low feelings and experiences were to be expected in some participants as they showed mild to moderate depressive symptoms at the start of the study which is why they were placed in the depressive symptoms group. However, their accounts of daily life prior to the program are clearly impactful. What is interesting is that there is a positive relationship between the western diet, and major and persistent depression (47) which could in part explain their perceived low mood. The western diet is also associated with metabolic

syndrome which is associated with depression (48–50). Overall, these findings suggest that poor physical and mental health was experienced by some participants prior to starting the ketogenic diet regardless of how individuals scored on the depression scale (PHQ-9).

## 3.3 Theme 2—Hunger and cravings—the food and mood connection

The second theme from this data is Hunger and Cravings – The Food and Mood Connection. This theme starts by explaining how participants experienced hunger and cravings during this program, followed by their experience of an increase in self-awareness where they were able to make the connection between eating certain foods and the impact thereof both physically and mentally.

### 3.3.1 Subtheme—food addiction—addictive behavior

Many participants noted that consuming sugar through sweets, chocolates, or baked goods, had a negative impact on their physical and psychological health. They found that when they ate sugar or carbohydrates, they "crave it more" (Whitney). Harriet shared how her cravings could impact her behavior around sugar:

> *"If I do not have any sugar, I do not crave it but the minute I have some, then I just go off the scale again."* (Harriet).

When she attempted to eliminate the sugar from her diet, she experienced emotional withdrawal like symptoms. This may sound extreme, but sugar addiction (51) has been shown to be equally or more addictive than other substances such as cocaine (52–54) and food addiction has been recently considered a valid diagnostic construct (55). Research suggests that the western diet can promote addictive eating behaviors due to the composition of many ultra-processed convenience foods which are high in fat, salt and sugar, the combination of which is not found in natural whole foods (49). Interestingly a recent case series shows promise for treating Binge Eating Disorder and food addiction symptoms with a ketogenic diet (56). A pilot study by Rostanzo et al. (57) of five participants using the KD as a treatment for binge eating and food addiction in women found that after following a KD no cases of food addiction or binge eating were recorded, and all participants improved.

In the current data, there were three accounts from participants on their experience of sugar withdrawal.

> *"I have to go through that real craving few days where I feel like I need to be locked in a room so I cannot have any, and then I'll be fine."* (Harriet).

> *"How your brain just thinks, it makes you believe it will be ok to have one, I can account for this it will be ok, but no it will not be one, it never ever is, and even now, I know that, the sensible side of me knows that but the craving and desire was so strong."* (Harriet).

> *"I could demolish a packet of biscuits without even thinking about it, I could honestly, if the biscuits are in the house, I can eat them, they are in the house and they are there and they are calling me all the time."* (Jessica).

These accounts of sugar withdrawal are similar to the behavior effects noted in other addictions. Research suggests that highly processed foods such as sugar can trigger addiction-like symptoms and behaviors, including withdrawal when restricted or reduced in some people (58, 59). These behaviors are linked to alterations in the brain's neurochemistry, such as in the dopamine pathway, which is also altered by other addictive substances (51). In rat studies, the withdrawal symptoms from sugar were found to be similar to symptoms of morphine or nicotine withdrawal (60). Alongside this, physical symptoms of withdrawal were also experienced, and one participant could feel the impact of sugar on their blood glucose levels. Diane said:

> *"Weird headachy thing when I feel my sugar go up. You know what I mean, it's like a sugar spike kind of feeling, I feel a bit muddy headed and a bit groggy."* (Diane).

Another participant realized that they were experiencing a change in blood glucose levels post sugar intake. They realized after they had eaten some sugar, that they were experiencing the sugar spike. They had heard about it happening before and had thought "really does that exist?" (Harriet).

### 3.3.2 Subtheme—Hunger reduction—in control now

Once participants had started the ketogenic diet, hunger levels appeared to drop, cravings dissipated, and they felt more in control of their diet. This is in keeping with previous research which has shown that cravings for starchy foods and sweets disappear (61), appetite is suppressed, and satiety levels are heightened on a KD due to the physiological state of ketosis (62–64).

If the KD is implemented correctly, and ketosis is the goal, ketone bodies are produced and begin to rise, reaching 1-2 mmol/L after approximately 48–96 h of reduced carbohydrate intake (65). Ketones have appetite suppressing effects and therefore it is expected that hunger levels will drop (66, 67) once ketones begin to rise. Physical cravings should also reduce once blood sugar levels regulate and ketones rise (68, 69), leaving only emotional cravings like eating in response to negative emotions (70, 71) such as when anxious or bored, or even when happy (72).

Participants began to experience the drop in hunger and the reduction in frequent and bothersome food-related thoughts. Though they expected to be hungry following this diet, as they had been on previous diets, the hunger occurred only once or twice, if at all. This is in keeping with the findings from Newson and Parody (27) whose participants also acknowledged a reduction in hunger. Participants stated, "I just do not seem to get hungry at all" (Jessica) and "I'm actually eating less now than I was before" (Mark), and "I do not even think about food" (Harriet). Philip shared his thoughts:

> *"It seems to be really easy, it's like the simplest thing in the world is to not eat, rather than worry about it…I'm not a scientist, but I put that lack of hunger down to the lack of carbs."* (Philip).

Similar to hunger, although participants were expecting to crave certain foods, little to no cravings were experienced. Some were

experienced in the first few days as mentioned above, but not to the extent that was expected. Amari stated that:

> *"I thought I might crave, I do not know something savoury or something sweet and I really have not. It's been fine."* (Amari).

Over the duration of the program, cravings appeared to reduce with ongoing low carbohydrate intake and little sugar. One participant stated succinctly, "Because I'm not having it, I'm not craving it" (Whitney). This is to be expected as physiologically, once sugar is ingested, blood sugar rises and ketones drop (73). Blood sugar and ketone levels have an inverse relationship (74). This blood sugar spike will decrease once more and leave the individual seeking more sugar and carbohydrates to increase their blood sugar levels. This is known as postprandial hunger (75). With the reduced sugar intake, individuals can avoid this cycle of sharply rising and falling blood sugar levels.

### 3.3.3 Subtheme—no interest in previously loved foods

Three participants from the healthy group and one from the depressive symptoms group shared that as time went on, they no longer wanted or liked the taste of anything sweet, "I think my body is used to not having anything sweet in my life now" (Amari). This is in keeping with the research which shows that taste intensity can change, and that sweet receptors can become sensitized as there is no longer a frequent influx of sweet tastes (76). Harriet sums up the experience:

> *"Because I have such a sweet tooth, once I stopped that I was amazed at how I could just, I had no interest in anything sweet."* (Harriet).

Though cravings were reduced or even eliminated when following the diet, cravings could return for two reasons. Firstly, if carbohydrate filled foods were observed and looked appetizing, such as at social events, or other events where it was difficult to remove them from sight. Sarah mentioned how her workstation was surrounded by chocolate bars. Having these sugary treats around throughout the day when emotions and stresses can occur and at times overwhelm, is not ideal. Research has shown that willpower to resist sugar as a pick me up is difficult when feeling stressed or overwhelmed throughout the day (77). These foods are better off 'out of sight and out of mind'. Mark said:

> *"I think a lot of the time I'm not hungry or craving anything and then you see something, and you go hmm."* (Mark).

### 3.3.4 Subtheme—Coming off plan—cravings increase

Secondly, if participants came off plan or increased their carbohydrate intake enough to come out of ketosis, their blood glucose, cravings, and hunger would increase, and some participants felt like they were "back to square one" (Harriet).

> *"On the Saturday, we had pizza and, on the Monday, not only did I get that horrible hunger, but I was in a tetchy mood."* (Philip).

As Philip mentioned, not only did coming off plan increase his cravings and hunger again, but for some participants, their mood and physical health were negatively impacted as they likely experienced symptoms of keto flu as they moved back into a state of ketosis. Philip followed on with:

> *"I've really noticed the difference to my mood. I notice now, the next day, I'm really irritable and again I'm putting it down to eating too much or eating too much of the wrong things."* (Philip).

One participant mentioned that they experienced quite severe side effects from eating a lot of carbohydrates in one sitting at a wedding:

> *"The day after, I came out in a rash, so my eye swelled up and yeah, just dreadful and that week felt just a bit rotten really."* (Whitney).

Understandably, for most participants, their interest in previously loved foods soon decreases and they no longer miss foods they used to eat either because of how their body now responded to those foods or because their tastebuds and food preferences had changed. Wise et al. (76) reported that a reduction in sugar intake led to an increase in perceived sweetness; however, research is unclear as to whether a reduction in sugar intake changes food preferences. The draw toward foods high in sugar or carbohydrates is no longer present and participants stated that going without old favorites "does not bother me anymore" (Sarah), they have "no interest in anything sweet" (Harriet) and well, "I do not feel like it" (Whitney). Mark shared how certain he was about the dietary change:

> *"I really do not miss anything and in fact the thought of eating a plate of pasta now or potatoes fills me with dread."* (Mark).

It appears that participants have experienced a shift in their attitude toward the diet and their approach to food and the role food plays in their life. They appear to have a heightened sense of self awareness that wasn't apparent prior to starting the program. The chaos and decision fatigue around 'dieting' day to day is no longer present. Mark shared that he could go out to a restaurant and "just get on with it without making a fuss" and Jessica felt that food is no longer the be all and end all of the day, "I do not think about it like I used to," "It has been a complete revelation to me," said Whitney. The increase in self-awareness is summed up well by Philip who said:

> *"Now I can catch myself when I know I'm tetchy about nothing in particular, I'm aware of that now."* (Philip).

Overall, participants experienced a significant reduction in their hunger and cravings which only increased when tempted or if they veered off plan with higher carbohydrates either on purpose or by accident. Participants observed and were later able to identify the negative effects that increased sugar and carbohydrate intake had on their mood and psychological well-being.

## 3.4 Theme 3—Psychological well-being improvements

This theme discusses the psychological changes and improvements that participants experienced over the course of the program. Most interestingly, what appeared to be relatively low self-reported

well-being prior to the start of the program, seemed to increase over the duration of the study. This may have been due to an overall improvement in metabolic health. Evidence suggests that ketogenic metabolic therapy, and the state of ketosis, has broad positive effects across multiple metabolic pathways. This can be seen in the research, see Sethi and Ford (34) and Kraeuter et al. (78) for a review of this area.

### 3.4.1 Subtheme—Motivation, sense of reward and achievement

An increase in motivation, determination, achievement, and a sense of reward was felt by some participants. In theme 1, "poor health prior to program," participants stated that other diets had not worked for them and that they felt they lacked motivation daily. Since following the program, participants said that they were "determined" now (Sarah) and that "It's nice to feel you are doing something good for yourself" (Diane). Participant Amari shared her account of the diet:

> *"It's just worked amazing well compared to anything else I've ever tried I feel great, I feel fantastic with it."* (Amari).

### 3.4.2 Subtheme—Increased positive outlook—found meaning and purpose

It appears that the sense of hopelessness, previously described by three participants, had disappeared. A sense of meaning and purpose was found, along with increased positivity. Hopelessness has been shown to be a risk factor for suicidal ideation, which is one of the symptoms needed for a diagnosis of depression according to the DSM-V (79, 80).

Therefore, by eliminating the sense of hopelessness and finding a sense of meaning, the risk of suicidal ideation may be reduced, which in turn reduces the number of diagnostic symptoms present (46).

Participants shared that they felt "a lot more positive and cheerful overall" (Jessica) and that it has given them "more of a positive outlook and helps me focus on my objectives" (Mark). Anika's account showed the renewed sense of hope:

> *"I think my outlook on life is better on the grounds that I do not think I'm going to end up sort of in a wheelchair or whatever, so I think I do feel more energised and it's made me feel more positive."* (Anika).

These improvements suggest an increase in aspects of psychological well-being such as mental well-being and depressive symptoms. These improvements in depressive symptoms would be in keeping with the findings from Tillery et al. (81) who reported a reduction from moderately severe depressive symptoms to no symptoms in a depression case study of the ketogenic diet. These findings are also in keeping with the improvement in mental well-being found by Unwin et al. (82) and the decrease in depression found by Danan et al. (16) when following a low carbohydrate and ketogenic diet. The observed improvements also support the reports of antidepressant effects found in mice models following a ketogenic diet (15, 83).

### 3.4.3 Subtheme—Improved sleep

Sleep also improved for many participants on this diet. Some participants were struggling in meetings and were constantly falling asleep during the day. This appeared to resolve the longer they were following the diet and may also have been a result of their now stable energy levels. The literature suggests that some people experience a reduction in sleep duration when following a ketogenic diet, for example they sleep 7 h now instead of nine, but their sleep quality stays the same or improves, in that they wake up refreshed and more energized than before, therefore reducing morning sleepiness (84–88). One participant shared their sleep improvements:

> *"I'm sleeping better, I struggle with insomnia and have done for four years and I'm definitely sleeping better."* (Amari).

It is important to note that for some people, sleep may get worse before it gets better, especially in the first few weeks of the KD as the body moves into a state of ketosis (29, 89). For those with depressive symptoms or other diagnosed psychiatric illnesses this requires close monitoring as sleep deprivation or untracked sleep alterations can increase the possibility of experiencing negative psychiatric symptoms such as mania, hypomania, and psychosis (90–93). Therefore, it is important to always work alongside an experienced clinician when deciding to implement ketogenic metabolic therapy with the goal of reducing psychiatric symptoms and improving overall mental health.

### 3.4.4 Subtheme—Increased energy and concentration

Concentration and energy levels improved for some participants whereas prior to starting the program these levels had been low. One participant who had been a student and studying throughout the program stated that:

> *"I feel like I can concentrate a lot better because before I could never study on a night, it would have to be during the day because by 7 or 8 o'clock at night I was just completely drained whereas now I'm quite happy to keep reading until 9 or 10 o'clock at night. I just feel like everything is, concentration levels are much better."* (Sarah).

Four participants stated that they have more energy overall and that they "feel a lot more energised" to do day to day things like walk their dogs (Jessica) or go to yoga (Anika). One reason for this may be that energy levels when in ketosis and keto-adapted, remain stable throughout the day and do not rely on glucose to provide energy as there is a consistent supply of fat store derived ketones to use as energy (94). Campbell and Campbell (6) found that 25% of their participants experienced increased energy when following a ketogenic diet for their bipolar symptoms. Overall, this improvement in both energy and concentration is encouraging as both lack of energy and reduced concentration are symptoms that may be indicative of depression (46).

### 3.4.5 Subtheme—Increased confidence and self esteem

Alongside these improvements, some participants' confidence that was lost prior to the program, began to make a comeback and self-esteem improved also. Two participants from the depressive symptoms group mentioned that they felt better about themselves and that they feel more confident since following the program, "feeling better about myself is its own reward" (Philip). Jessica

struggled prior to the program with low confidence, and since then she shared that:

> *"When I left work my confidence was just rock bottom, I just though oh where is me gone? And now I just feel that me is coming back really."* (Jessica).

These improvements may be related to the diet change and the effect of ketones, but they may also be attributed to a sense of achievement in meeting their weight loss goals and improving their physical and mental health. These improvements are in keeping with the findings of Protogerou et al. (95) in individuals following a zero-carbohydrate diet.

### 3.4.6 Subtheme—Increased well-being and feeling in control of life

Increases in psychological well-being, a sense of calm, equilibrium, and patience were also observed among at least five participants which is in keeping with the earlier mentioned work by Harvey et al. (24). Experiencing calmness when in ketosis is not a new phenomenon and research suggests that this may be because ketones can reduce neuronal excitability (96). Perhaps this is what participants experienced when they mentioned a sense of calm, patience, and less frustration. This increased sense of calm and tranquility experienced by participants is the opposite of agitation which is a symptom that may be indicative of depression (46).

It is also possible that the routine associated with following the ketogenic diet gave participants a greater sense of control over their diet and their health. Perhaps they were able to form healthy habits as once established, routines and habits require little effort to maintain (97). This may have contributed to increased patience with others as they were less worried and experienced less frustration and decision fatigue when it came to self-care and diet choices, leading them to exhibit a sense of increased well-being.

Whitney stated that she is "no longer in the same place as when I started, much happier" and Mark summed up his heightened well-being:

> *"You know the song Park Life by Blur, where it says you should cut down on your pork pies mate get some exercise, and it talks about the birds and it giving him an enormous sense of well-being, and that always resonates with me in my head, it should be called "pork life" not park life, the enormous sense of well-being that you get."* (Mark).

Overall, improvements in psychological well-being were observed by many participants from both the healthy adults group and those with depressive symptoms. Improvements were noted in aspects of psychological well-being that were low prior to the program start, for example self-esteem, motivation, confidence, and a sense of meaning and purpose. The improvements experienced here are in keeping with the findings stated earlier from Harvey et al. (24), Newson and Parody (27), and Wong et al. (28).

These psychological improvements may have been a result of the dietary changes and ketone effects on a biological level. However, on a psychosocial level, improvements may also have been a consequence of achieving their weight loss goal, taking control of their health by following a diet, or contributing their data as part of a wider research study.

## 3.5 Theme 4—It becomes a lifestyle

This theme discusses how the diet becomes a lifestyle over time for participants. There were some initial implementation difficulties that will be discussed later, but overall, it appears that participants were able to easily follow the diet once they understood how to apply and integrate it into their life. On average it takes 66 days or 9 weeks to create an automatic habit, which suggests that for those who continued the study for the duration of the intervention (12 weeks), they may have created a new habit, of following the diet (97). Perhaps this is what helped them to turn it into a lifestyle. These findings are in keeping with the qualitative findings of Newson and Parody (27) who looked at the experience of a LCD in those with T2D. Their participants stated that the diet was difficult initially but then it became sustainable. Participants also noted that they no longer craved carbohydrates and looked at a LCD as a lifestyle.

### 3.5.1 Subtheme—Educated participants and easy program to follow

Participants shared that the diet wasn't that difficult "once you get the hang of it" (Diane), and that "it does not seem like particularly hard work" (Sarah). Over time it became a lot easier to understand what participants could and could not eat and it therefore became a lot more "instinctive" (Anika). Mark stated that:

> *"This is so easy to do, it's a no brainer and I do not know why it is not out there."* (Mark).

This is in keeping with the works of Wong et al. (28) in comparison to other diets that they had tried in the past, the KD was easier to follow, tastier, and overall, was more enjoyable.

However, in order for it to become a lifestyle, education about the diet, how it works and how to implement it was crucial. Initially, participants followed education videos provided in the program, learnt to read product labels and understand them, and calculated carbohydrates, calories and macronutrients using a notebook or an online tracker app such as MyFitnessPal or Cronometer. Over time, and with practice, the need to do this repeatedly reduced. This may be because participants had learnt the macronutrient composition of most of their foods and therefore only needed to do this when eating something that they would not usually eat, such as when out at restaurants or on holidays. Cadario et al. (98) found that in the general population, individuals tend to eat the same breakfast every day while seeking more variety for other meals. This lends to the idea that once participants found one or two suitable breakfast options, the frequency of tracking may have dropped. It is not certain, but perhaps this also happened for other meals in the day.

### 3.5.2 Subtheme—Planning ahead—staying organized

Prior to the program start, some participants mentioned that they had no meal structure or food plan and that they often ate what was in front of them at work and therefore would later skip meals. After some time following the program, many participants found that the

key to staying on track was to plan ahead and stay organized, and in some cases, cook or prepare food at home ahead of time such as making their own protein bars without sugar. Planning ahead and preparing food at home is not specific to the ketogenic diet however, as research shows that these actions are important for any dietary program to be successful (99). Meal planning and preparing food ahead of time is associated with a healthier diet overall (43).

Harriet shared that checking the menu and knowing where you will or can eat when out and about is a good way to keep this diet easy. Sarah stated that:

> *"Even going into town, having an afternoon, you cannot have your cake and your coffee, you have just got to think ahead of what you are going to eat."* (Sarah).

Eating out in restaurants and cafes was therefore no longer difficult or confusing. Participants were able to find meals on the menu that fit the ketogenic diet, or they would swap carbohydrate filled sides for leafy greens. Simple side swaps, switching a beer for a vodka and diet soda, skipping the bread, or leaving the chips behind meant that participants could still eat out and spend time with others, "you can order the food, just do not eat all of the carbs that come with it" (Diane). These findings are in keeping with the works of Wong et al. (28) who found that participants appeared to overcome these challenges over time by adjusting their routine.

### 3.5.3 Subtheme—Making choices and being flexible

But for some, flexibility was key and ultimately the choices lay with the participants. Perhaps mastering this flexibility helped to keep them on track long term. These results replicate the findings from Newson and Parody (27) whose participants also mentioned that they allowed themselves some flexibility from time to time. Having said this, this flexible approach may not be possible for everyone using a ketogenic diet or ketogenic metabolic therapy to improve their mental health, psychological well-being or certain physical health conditions. More research is necessary in this area.

Participants were able to overcome implementation difficulties and navigate social situations in order to maintain the improvements in their physical and psychological health. Initially they may have been motivated by physical appearance changes but over the long term it appears it was other physical or psychological changes that kept them on track. Participants felt the diet was worth it given the health improvements they experienced.

> *"If I'm left to my own devices, I'm absolutely fine."* (Philip).

Having a greater "Why" for following the diet after the end of the program is key. Overall, this subtheme suggests that without the pressure of others, participants were able to make personal choices and decisions in line with their health goals.

## 3.6 Theme 5—Implementation difficulties

This theme identifies and discusses three main areas where difficulties were encountered when implementing the diet. As with any new diet or way or eating, a transition period is expected with some short-term obstacles to overcome. Learning about the macronutrients of foods, what and when to eat, all of this requires time. The ketogenic diet is no different. It takes time to learn about carbohydrates and the levels of these in each food and how they affect one's individual blood glucose and ketone levels. In a study by Campbell and Campbell (6) looking at the implementation of ketosis in those with bipolar disorder, 22% of participants mentioned they encountered an adaption period before they experienced any positive effects from the diet.

### 3.6.1 Subtheme—Diet implementation

The first challenge area was initiating the diet and getting into a state of nutritional ketosis. Participants found that it took some time before they felt they knew what they were doing. This is in keeping with the works of Campbell and Campbell (6) who found that 10% of their participants had difficulties implementing the diet initially.

In the first week to 2 weeks of implementing the ketogenic diet, there is a transition into ketosis which can give rise to some negative symptoms. This is better known as "keto induction" or experiencing the "keto flu" although it bears no similarity to the viral flu. These negative symptoms are transient and do not last long with resolution of symptoms reported from day 3 up to 4 weeks (29). From the data, as expected, some participants experienced these negative symptoms. These short-term symptoms included increased hunger in the first few days, wanting to urinate more than usual, loose bowels, and reduced energy to carry out day to day tasks. These symptoms "did not last very long at all" (Jessica), and "went away on their own" (Harriet). This is in keeping with findings from the literature which states that symptoms are less severe and do not last as long as expected (28, 95).

### 3.6.2 Subtheme—Out and about

After short term symptoms subsided and participants entered a state of ketosis, the challenge participants then faced was how to fit the diet into their current lifestyle and how to overcome obstacles along the way. The second challenge area was trying to avoid carbohydrates day to day while out and about. Avoiding carbohydrates at social events was a challenge, especially as some felt they were missing out in some instances such as when others are eating dessert at a social lunch. Some participants simply did not want to come across as rude to their work colleagues. These situations eventually become easier once the lifestyle is implemented but initially it can be difficult. Many participants felt that restaurant and café meal options were predominantly carbohydrate based, which made it difficult initially to navigate the menu and choose ketogenic friendly options to enjoy. Participants mentioned that at the start of the diet, "it's not great trying to keep the carbs low" (Diane) when out, and that if you stop anywhere, "most of the things available are sandwiches and sort of carb-based foods" (Anika). Diane said that:

> *"The other options are there, it's just, everything comes with piles of carbs quite honestly."* (Diane).

This challenge also extended to holidays abroad where access to usual foods was restricted. Being "away from home was difficult" (Sarah) in the early days of the diet, for example, one participant stated that although restaurants had menus, "they are very limited" (Jessica) and "hotel options are not always all you might hope for" (Diane).

However, once participants learnt what to eat and began to plan ahead, these challenges resolved.

### 3.6.3 Subtheme—Diet dogma, societal impact and opinions of others

The third and final challenge area was overcoming societal norms and diet dogma, and this extended to the opinions of others like friends, family, and work colleagues. Though this is similar to Theme 4 - subtheme 3 "making choices and being flexible," this subtheme relates to the impact of society and the outward world on the individuals' food choices and decisions.

Following a diet that encourages the consumption of some foods that have been vilified in society (such as eggs, butter, bacon, and red meat) is difficult for some participants (100). This is understandable as mainstream nutritional advice has often been confusing and conflicting for people (101) which is not helped by the lack of adequate nutritional training for doctors to educate their patients (102). The idea of eating fat and reducing the amount of fruit in the diet was "really odd" and a "tricky thing to get your head around" (Amari). Diane had the same experience when it came to eating eggs:

> *"I'm not sure, I was concerned about the wisdom about eating quite so many eggs."* (Diane).

The pre-held beliefs about what foods to eat and not eat, as well as when to eat, extended to participants' friends, family, and colleagues too. Once the participants were able to implement the diet it became the opinions of those around them that became the challenge. One participant mentioned that they felt pressured to eat the food given to them by a friend and "it was like, back to square one" (Harriet) with regards to hunger and cravings. Mark experienced this when out with friends:

> *"They'll ask me why aren't you eating and I'll say well I'm not hungry and then I do not know if we will end up going down a rabbit hole."* (Mark).

Philip also noted that he had no issue when on his own but that:

> *"If there are other people around or if I go and see a friend or something like that, I find I'm having to say no to cheesy chips."* (Philip).

Overall, participants were able to navigate and overcome these three main challenges when implementing the diet.

Food and eating for many in society is a social occasion in the presence of other people. Eating with family in the evenings or eating with friends at the weekends has been shown to facilitate social bonding and increases satisfaction with life (103). It has been reported that individuals are influenced by what and how much those around them eat (104). For example, there is research to suggest that eating with a partner who chooses 'unhealthy' foods, may negatively influence an individual's decision to eat 'healthy' foods (105) and that societal norms can also have a negative impact on an individual's food choice and intake (106).

A study by Vue et al. (107) found eight 'need states' in which individuals eat which range from a basic need for food, to social expression, celebration or to gain recognition suggesting that individuals eat for both physical and emotional or social needs. This suggests that there are other lifestyle obstacles and motivations, outside of just food as fuel, that get in the way of following a 'healthy' diet and can derail even the most focused individuals. Attempting to follow a diet that is different to those around you can be difficult, especially during the implementation phase.

## 4 Discussion

There is a growing body of evidence in support of using ketogenic metabolic therapy, and the KD as an adjunct to standard treatment for those with varying psychiatric illnesses. Studies looking at the effects of the KD on psychiatric conditions have been published as far back as the 1960's (20) with more recent research focused on the diet's effects on bipolar disorder, depression, schizophrenia and eating disorders (16, 18, 56, 108). The purpose of the current study was to review the accounts of participants who completed a KD intervention and to identify any common themes relating to their journey.

The complete array of biological mechanisms by which the KD works is not yet known and the conclusions from the literature are mixed, however, research suggests that KDs should be further tested as an intervention for some psychiatric conditions such as bipolar disorder and depression (7, 34). As there are a host of biochemical actions and reactions observed when in a ketogenic metabolic state, there is enough research to warrant a closer look at the possible effects on affect and other aspects of psychological well-being. A review by (109) of over 3,500 RCTs suggests that the effect that psychotherapy and pharmacotherapy have on psychiatric disorders is limited and that more research is necessary to identify other novel treatments for these conditions.

In the current literature there are very few qualitative studies that explore the accounts and lived experience of those following a low carbohydrate or ketogenic diet. Only one study looked specifically at healthy, non-obese, non-diabetic participants (24) and no studies were found that looked specifically at a depressed population following a low carbohydrate or ketogenic diet.

This current explorative qualitative study is the first to examine the accounts of following a KD in both healthy participants and those with depressive symptoms. The findings from this current study show that some improvements in mental health and psychological well-being were observed. Considering the thematic analysis was carried out with an essentialist realist epistemological stance, findings from this thematic analysis may be generalizable and repeatable if conducted with a similar methodology.

Through this current qualitative study, participants stated the strengths and limitations of following a KD to improve their health. The theme 1 subthemes, "low self-esteem, body satisfaction and self-worth," and "low mood and hopelessness" were predominantly reported by those in the depressive symptoms group. In addition to this, those who experienced the theme 3 subtheme of "increased confidence and self-esteem" at the end of the intervention were also all from the depressive symptoms group. This might suggest that those with depressive symptoms experienced improvements in these areas over the duration of the

intervention. Although no qualitative studies have looked at this population in relation to the ketogenic diet, the findings are in keeping with the thematic analysis carried out by Newson and Parody (27) whose participants with T2D experienced increased confidence levels.

It is interesting to note that those who expressed the theme 2 subtheme of "food addiction – addictive behaviour," were all females. In the binge eating literature, a study by Levallius et al. (110) looking at addictive-like behaviors across genders found that 42% of females reported binge eating compared to 21% of males. To support this, a mouse study by Wei et al. (111) reported that female mice are more likely to have an addictive phenotype for sugar compared to male mice. Hussenoeder et al. (112) carried out a survey ($N = 1,474$) exploring anxiety and food addiction across genders and found that episodes of anxiety increase food addiction in females but not males. This may be because eating sweet foods in excess has been shown to reduce the effects of stress in females and not males (113). Further to this, females are more likely to report emotional eating, or eating because of anxiety compared to males (114). Perhaps the females in this current study experienced higher levels of addiction-like behavior as a result of this phenotype or in order to reduce anxiety and stress. Further research is necessary to fully understand this finding.

Overall, the accounts and obstacles that these participants faced while implementing the KD are mostly consistent with the current literature and the first author's experience supporting individuals implementing ketogenic metabolic therapy and following a KD to improve the mental health. These accounts appear to cover most, if not all, of the challenges that are to be expected when starting a KD and implementing a lifestyle change like this.

## 5 Limitations and contribution to research

From the participants' accounts in this study, it appears that the benefits and positive outcomes of this diet outweigh any negative side effects experienced. This is encouraging for those who are looking for adjunctive therapies to address and improve their depressive symptoms, or if they are simply looking to increase their overall physical and psychological well-being. However, further qualitative, and larger scale quantitative research is needed to develop a greater understanding of the challenges and obstacles that face individuals who start a ketogenic diet, for any health goal.

Further to this, understanding the individual tolerance and both the physical and mental response to the KD in the wider community, is warranted in order to design personalized approaches to dietary implementation. These tailored approaches should address, reduce, or eliminate both the personal and social challenges faced by so many when starting the KD, so as to make it easier to implement and maintain long term.

Overall, future ketogenic dietary protocols can be better informed from these results. Implementation difficulties at the commencement of the diet should be accounted for when designing new protocols. Individuals should be informed as to what to expect and support from peers, mentors or coaches should be available throughout the first few weeks at least until hunger and cravings reduce, individuals are comfortably in ketosis, and the timeframe for hypomania has passed. If individuals are using this dietary intervention to improve mental health symptoms, ongoing support by an experienced clinician is recommended.

In terms of risks for success and maintenance, the data from this study suggests that the implementation period was the most difficult to progress through. Therefore, alongside peer or mentor support, resources should be created to accompany future protocols. These resources could cover topics such as staying organized and planning ahead, eating out and about, how to manage social situations and how to overcome other lifestyle obstacles such as diet dogma.

Once participants made the KD a lifestyle, they presented as knowledgeable and educated on how to follow the diet but also were able to make personalized choices which made it easier to maintain.

From these results, it is clear that the KD can be beneficial for psychological well-being. As is known from the epilepsy and T2D research the KD can exhibit strong therapeutic effects for many illnesses. These results suggest that the KD can improve many aspects of psychological well-being. Importantly it would seem that in most individuals who might undertake it - not just those with moderate symptoms of depressive illness, but potentially those with low to no symptoms might experience enhanced well-being. This could be further explored with a broader range of well-being measures, and other mental health conditions such as ADHD, anxiety, and obsessive-compulsive disorder (OCD). Therefore, future promotion of the KD and ketogenic metabolic therapy should reflect this and be personalized to individuals who may benefit from its effects. Additionally, if the diet is presented in a personalized manner, tailored to the individual and targeting their specific symptoms, it may result in better adherence generally, but more specifically for those with poor mental well-being.

Overall, the results of this study will aid researchers to better understand how a low carbohydrate and ketogenic diet can be applied in people's daily lives either by using an online program or with the support of mentors, coaches, and health professionals such as experienced clinicians, psychologists, dietitians, and nutritionists. The benefits, drawbacks, and changes to aspects of psychological well-being that may be experienced by participants, which have been indicated but relatively undetailed throughout the literature and the quantitative arm of this work are now better understood.

## Reflexivity statement

At the time of research project design, the researcher was working in acute inpatient psychiatric services as an assistant practitioner on both male and female wards. The researcher also took the position of ketogenic nutritional consultant in a private limited company from 2017 to 2023, the duration of this research project. Here, the researcher disseminated the current ketogenic and fasting literature into layman's terms and educated the public with this information over a period of 6 years. The researcher also worked 1:1 and via groups with clients to initiate a ketogenic diet and fasting protocols, based on the scientific literature for the goals of fat loss and improved general health. The

researcher has also personally followed a ketogenic diet since 2014. The initiation of this diet is what prompted this research project. In the final year of this research project, the researcher worked with clients who were implementing the diet with the goal of improving their mental health. Overall, this experience and these events may have aided the researcher in the design of this study and may naturally have shaped how the researcher developed codes and themes for the data in this study.

## Data availability statement

The datasets presented in this article are not readily available due to the qualitative nature of this research. Participants of this study did not agree for their full transcripts to be shared publicly. No requests for datasets are permitted.

## Ethics statement

The studies involving humans were approved by the University of East London, UREC 1718 87. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

EB: Conceptualization, Formal analysis, Methodology, Writing – original draft. FH: Writing – review & editing. JW: Writing – review & editing. JB: Writing – review & editing. JT: Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Bringing nutritional ketosis to the table as an option for healing the pediatric brain

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Our core premise is that personalized variations of a ketogenic diet are likely to benefit pediatric patients with neuropsychiatric symptoms across multiple domains. Although pediatric epilepsy is currently a well-accepted indication for a strict ketogenic diet, there is a dearth of knowledge and therefore clinical guidelines upon which to recommend nutritional ketosis for pervasive pediatric conditions such as autism spectrum disorder and ADHD, even when comorbid epilepsy is present. However, there are published cohort studies and current clinical trials implementing medical ketogenic therapies for cognitive impairment, psychiatric comorbidities, motor disability, and even neuroinflammation. As holistic practitioners, it is imperative that we consider the health of a child in its entirety - and additionally offer the ketogenic diet as a therapeutic option when it may be synergistic in treating extra-neurologic diseases such as obesity. While there are uniquely pediatric potential adverse side effects such as linear growth deceleration and micronutrient deficiencies, previous trials in epilepsy and our center's experience have already proven the ketogenic diet to be a low-risk intervention when optimized with appropriate patient monitoring and support.

KEYWORDS

**ketogenic diet, pediatrics, child neurology, ADHD, autism spectrum disorder, mental health**

## Introduction

Multiple epidemiologic studies agree that the burden of pediatric mental health diagnoses is exponentially increasing (1). Commonly cited explanations are diverse, ranging from increased use of and dependence on social media, increased obesity rates, and decreased medical insurance coverage for mental health support. Yet, while additional funding and availability of psychopharmacological therapies and mental health practitioners clearly help, current evidence-based approaches are not enough. Classical medical therapies often have severe and lifelong adverse side effects, especially for the developing brain. Improvement to the desired level of independent functioning frequently demands polypharmacy, further amplifying the risk of side effects.

Use of a ketogenic diet as a medical therapy for pediatric epilepsy was first described by Dr. Russell Wilder in the Mayo Clinic Proceedings (2). Since that time, support for its efficacy at or above the level of standard antiseizure medications has solidified its keystone role (3). In conjunction with Dr. Wilder, a pediatrician Mynie Peterman noted parallel improvements in behavior and cognition on a ketogenic diet (4). However, these benefits are often seen as secondary, beneficial only as compared to the lack of an adverse outcome, or simply fortuitous.

*Our perspective is that this benefit needs to be brought front and center as a primary outcome, so that we can identify children with neurodevelopmental impairments, with or without seizures, who may require it most.*

Within the subtext of epilepsy studies, there is evidence ranging from anecdotal to statistically-significant secondary outcomes that improvements in other domains besides epilepsy are present. This is highly relevant, as ~80% of children with epilepsy have comorbid behavioral or cognitive impairment (5) and the highest risk factor for autism spectrum disorder in children with epilepsy is intellectual disability (6). Given the cascade of paradigm-shifting studies in adult psychiatric disease, it stands to reason that children may also benefit from a ketogenic diet or nutritional ketosis (7) – and given the existing expertise in pediatric epilepsy centers, pediatric practitioners are well-equipped to initiate and study this powerful intervention. We acknowledge that evidence-based use of the ketogenic diet in pediatrics is currently limited to intractable epilepsy; however, we suggest that "off-label" indications are supported by anecdotal evidence while the academic community mobilizes to initiate objective, randomized controlled trials with standardized, quantitative outcome measures to improve the standard of care for multiple common neuropsychiatric conditions. Although review of proposed mechanisms of the ketogenic diet is beyond the scope of this paper, we suggest that the multifactorial, pleiotropic effects of the ketogenic diet in different clinical contexts converge upon and pave the way for a common therapeutic improvement for an increasingly broadening range of common neuropsychiatric conditions (Figure 1).

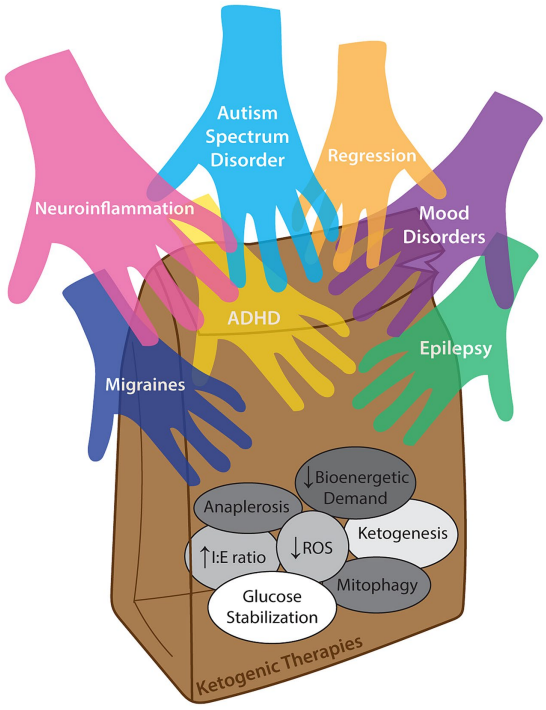


FIGURE 1
Concept illustration of multiple neuropsychiatric diagnoses which may benefit from (i.e., reaching into a lunch bag representing) ketogenic therapies. The diversity of proposed mechanisms of action that may confer different benefits across a range of clinical contexts are inside the bag, and while it is likely that different diagnoses improve secondary to varied combinations of these mechanisms, direct causation for any single disease is not definitively known. 'Anaplerosis' is refilling of TCA cycle intermediates. "Decreased bioenergetic demand" is improving mitochondrial function. "Increased I:E ratio" is a relative increase in inhibitory (e.g., GABAergic) signaling over excitatory (glutamatergic) transmission. "Decreased ROS" is reduction of radical oxygen species. "Ketogenesis" is the actual generation of ketone bodies. "Glucose stabilization" is decreasing glucose variability over time. "Mitophagy" is recycling and generation of healthier mitochondria (as reviewed by Masino and Rho (8)).

## Application of a ketogenic diet as a medical therapy for pediatric mental health

While a strict 4:1 classic ketogenic diet may be necessary for drug-resistant epilepsy (9), recent studies suggest a less-restrictive Modified Atkins Diet is often sufficient to yield demonstrable benefit (10, 11). If the goal of using a ketogenic diet is to improve a child's mental health so that they more easily socialize and learn in parallel with other children in a regular school environment, a comparatively less restrictive protocol that can be initiated at home rather than during an inpatient hospital admission is ideal. The effective and therapeutic degree of ketosis in an individual is exquisitely patient-specific and does not correlate perfectly to the ketogenic diet ratio across individuals. An intervention with a higher degree of flexibility and reduced risk for side effects is more likely to be successful in the long-term.

There are several versions of a ketogenic diet available for use. Our version of the Modified Atkins Diet (MAD), also called Modified Ketogenic Diet (MKD), consists of 40–60 g total carbohydrate per day with 1–2 tablespoons fat added to each meal. Fat sources are often butter, mayo, and oil. If feasible for patients, MCT oil is the preferred fat source and is encouraged at each meal. MCT oil will bypass the usual fat metabolism to be used more immediately for conversion to ketones, thus expediting ketogenesis by bypassing digestive enzymes and the carnitine shuttle (12). In addition, use of MCT oil may allow for a comparatively higher carbohydrate and protein intake without compromising nutritional ketosis (3).

## Uniquely pediatric indications, contraindications, and side effects

A challenge that's imperative upon all pediatric practitioners is to identify inborn errors of metabolism that benefit from specific dietary therapies as early as possible. A subset of these (e.g., phenylketonuria) are readily identified on the Newborn Screen, a primarily biochemical screening test with modest state-to-state variability. However, other syndromes are not able to be screened for in a blood spot or do not emerge until later in infancy/childhood. For example, Glut1 deficiency syndrome is a genetic-metabolic condition that impairs transport of glucose across the blood brain barrier; it is diagnosed by identification of pathogenic variants in *SLC2A1* and/or low absolute or relative glucose in the cerebrospinal fluid, in the proper clinical context. Most children do not develop symptoms until early infancy or later, and have broad phenotypic variability ranging from severe epilepsy to disruptive movement disorders and mild–moderate intellectual disability (13). Because a ketogenic diet improves not only seizure control but also cognitive development, motor function, and freedom

from disabling hemiplegic migraines, it is critical that testing is made available early in life and with minimal invasiveness when possible (i.e., genetic or blood screening rather than diagnostic lumbar puncture). Similarly, other genetic/metabolic diagnoses where a ketogenic diet is considered a potential first-line therapy because glucose supply to the brain is impaired include glycogen storage disorders (type III/Forbes' disease and type V/McArdle's disease), phosphofructokinase deficiency, pyruvate dehydrogenase complex deficiency, and some mitochondrial disorders (14). In contrast, there are specific inborn errors of metabolism where implementation of a ketogenic diet is contraindicated and would be dangerous, including: carnitine deficiency (primary), carnitine palmitoyltransferase (CPT) I or II deficiency, carnitine translocase deficiency, beta-oxidation deficiencies including medium-chain acyl dehydrogenase deficiency (MCAD), long-chain acyl dehydrogenase deficiency (LCAD), short-chain acyl dehydrogenase deficiency (SCAD), long-chain 3-hydroxyacl-CoA deficiency, medium-chain 3-hydroxyacl-CoA deficiency, pyruvate carboxylase deficiency and porphyria (15). We bring these up to suggest that a recommendation to start a ketogenic diet as well as metabolic and genetic testing should be thoughtfully considered (see Table 1 for suggested testing) by a knowledgeable healthcare team, regardless of the indication (though this often is linked to the etiology).

Parents often wish to know potential adverse effects of a ketogenic diet in parallel with feasibility considerations. During the transition period onto a ketogenic diet, common issues such as dehydration, relative hypoglycemia, nausea, and decreased energy can be addressed with increased consumption of fluid-containing electrolytes, and quickly resolve. Further corrections for abnormal electrolytes, metabolic acidosis, vitamin deficiencies, and constipation are possible. Historically, negative pediatric health outcomes have included linear growth deceleration, increased gastroesophageal reflux and constipation, and increased risk of nephrocalcinosis, with some consideration for increased risk of osteoporosis and secondary carnitine deficiency (with decreased efficacy of a ketogenic diet and/or associated cardiomegaly), and hepatotoxicity in adulthood. In our experience, these side effects are rare when the ketogenic diet is initiated as a medical therapy and followed by an experienced dietitian in even the youngest patients (16). Using a more liberal ketogenic diet, such as the MAD/MKD that brings about a lower level of nutritional ketosis, will lower the risk of potential side effects (11). As many children take liquid medication with a high carbohydrate content, dose formulation must be considered and often adjusted to crushed tablets or opened capsules; parents must also be aware of antibiotics, antipyretics, and common supplements that may be suggested by physicians and available over the counter in sugary syrups. Overall, the highest risk is perhaps parental dissatisfaction or inability to adhere to a ketogenic diet, prompting discontinuation. For example, implementation of a ketogenic diet in children with intractable epilepsy has been demonstrated to increase parental stress (17). In an ideal situation, a multidisciplinary team is able to provide parental education and support to initiate and maintain the diet with the understanding that it is a major lifestyle change impacting the entire family; an unfortunate reality is that this may not be possible for many biopsychosocial reasons in all cases where it is medically indicated.

## Existing literature in pediatric mental health

Given the number of children who have been treated with a ketogenic diet for epilepsy, what can we learn about *other* changes that they have experienced in their health in parallel? In two studies from Johns Hopkins, parental goals for starting a ketogenic diet cited improvement in cognition as the second most common reason for

TABLE 1 Recommendations for testing.

| Demographics | Serum studies | Functional studies (indication) | Tests to consider to exclude other diagnoses (symptom) |
|---|---|---|---|
| • Height<br>• Weight<br>• BMI<br>• Head circumference | • CBC<br>• BMP<br>• Magnesium<br>• Ionized calcium<br>• Lactic acid<br>• Lipid Profile<br>• Fasting Insulin<br>• BHB<br>• Carnitine level<br>• Acylcarnitine profile<br>• Vit D levels<br>• Urine fractional calcium excretion | • EEG (seizures)<br>• MR brain/spine (demyelinating, IEM)<br>• Vanderbilt survey (ADHD)<br>• PHQ9, BDI (MDD)<br>• GAD7 (GAD)<br>• Disease-specific parental questionnaires<br>• CORE-KETO outcomes | • Thiamine (B1) level (memory deficit)<br>• Vit B12 level (psychosis)<br>• Copper, ceruloplasmin (psychosis)<br>• Lead level (psychosis)<br>• Thyroid function tests (mood changes, psychosis, regression)<br>• Chromosomal microarray and/or Whole Exome Sequencing (developmental delay, autism spectrum disorder)<br>• CSF glucose and lactate (developmental delay +/− seizures and movement disorder)<br>• CSF folate, neopterin, tetrahydrobiopterin (developmental delay) |

Recommendations for testing before and concurrent with ketogenic diet initiation. Demographic information and basic measurements are indicated for following growth. Serum studies are needed to monitor electrolyte, vitamin, and hormonal changes that may indicate risk of side effects (e.g., nephrocalcinosis). Functional studies are expected to be disease-specific, but suggestions provided including clinical monitoring relevant to epilepsy, demyelinating disorders, ADHD, mood disorders, and consensus diet guidelines. Finally, dependent upon the clinical symptoms being addressed, we suggest careful survey of other causes of neuropsychiatric symptoms that are commonly missed at first assessment and would require different treatment protocols.

initiating the consult, second only to potential reduction in seizure frequency (18, 19). Remarkably, this goal was achieved in more than 50% of families. In a cohort of fifty children from the Netherlands, a positive cognitive and behavioral impact was noted in children with refractory epilepsy treated with a ketogenic diet as compared to a control group over a 4 month period, independent of any changes in seizure frequency (20). Parental questionnaires reflected lowered anxiety, mood-disturbed behavior, and higher productivity; in parallel, objective cognitive tests demonstrated improved receptive vocabulary and reaction time in the absence of any medication changes. If and when a ketogenic diet may be recommended for adolescent mood disorders is an active area of research with initial promise (21, 22). A key question moving forward is what are the optimal measures by which to quantify improved mood and cognition, as well as other non-seizure outcomes.

## ADHD

Approximately 10% of children in the US (6 million) are currently diagnosed with Attention Deficit Hyperactivity Disorder (ADHD), making it the most common neuropsychiatric condition of our time (23). ADHD is also the most common comorbid psychiatric diagnosis in children with epilepsy, affecting nearly 30% of patients (24). This overlap begs the question of whether intractable ADHD may benefit from similar therapies known to be effective in intractable epilepsy. Intriguingly, children with ADHD but not epilepsy are also noted to have more frequent interictal epileptiform discharges on sleep-deprived electroencephalograms (EEGs) (25). In children who are able to maintain a ketogenic diet for intractable epilepsy for a year, social problems and attention have been improved in parallel with seizure reduction (26).

It is worth noting that higher overall sugar consumption, especially in liquid form, is commonly thought to increase symptoms of hyperactivity and inattention and has support in primary and meta-analytic studies (27, 28), though isolating other socioeconomic and lifestyle factors that contribute to dietary choices is difficult (29). Multiple 'restrictive' diets including the DASH diet, Mediterranean diet, and a strict elimination diet offered some benefit in limited cohort samples, though sustainability remains a concern, and common elements such as reduction of processed food intake are pervasive confounding factors.

The association between multiple micronutrient deficiencies and severity of ADHD symptoms is well-documented; low magnesium, iron, and zinc levels all correlate with increased diagnosis rates and symptom severity scales, while supplementation with these as well as vitamin B6 (pyridoxine), and omega-3 fatty acids have shown benefit (30–33). Use of probiotics and avoidance of allergens triggering autoinflammatory responses continue to accumulate and are worth mentioning, though beyond the scope of this perspective. However, we propose that there is a role for tailoring a ketogenic diet to children who live with ADHD despite correction of underlying medical issues and nutritional deficiencies, school accommodations and psychosocial education, and either first-line medical management or contraindications and side effects to stimulant use.

## ASD

Approximately 20% of children with epilepsy are also diagnosed with autism spectrum disorder (ASD) (34), suggesting shared neurobiological underpinnings. Co-occurring diagnoses also introduce challenges in using certain antiseizure medications where adverse side effects such as behavioral shifts, mood changes, or hyperactivity are amplified. Excluding data from animal models, there is limited evidence thus far that nutritional ketosis can be beneficial. For example, a 6 month pilot study of a ketogenic diet using primarily MCT oil in 30 children showed improvement in a majority of them on the Childhood Autism Rating Scale (CARS), though was limited by a 40% non-compliance rate (35). Multiple anecdotal reports suggest potential improvement across cognitive, behavioral, and psychiatric domains (36, 37). However, larger-scale standardized studies are sorely needed. It is clear that antipsychotic medications commonly used to address aggression in children with autism present an increased risk of metabolic syndrome, whereas nutritional ketosis maintains or improves the cardiovascular and metabolic health of most individuals. Conceptually, if impaired neuronal metabolism contributes to symptoms, alleviating rather than exacerbating underlying metabolic stress would appear beneficial, though the data are not yet available to demonstrate this.

## Regression

Exciting data are emerging to suggest a role for the ketogenic diet in Alzheimer's Disease (AD), referred to by some as "Type III Diabetes Mellitus" given demonstration of glucose hypometabolism on PET imaging (38). We suggest that children with Down Syndrome/Trisomy 21 may warrant special consideration for a ketogenic diet, given increased expression of alpha-synuclein and a well-established genetic predisposition for early-onset dementia similar etiologically to AD. Case reports thus far are encouraging (39). Similarly, Down syndrome regression disorder (DSRD) is a syndrome in which neurological functioning across domains becomes impaired in a multifactorial yet poorly understood cascade of autoimmune, proconvulsant, and perhaps neurodegenerative reactions (40). While IVIG offers some suggested benefit, we propose a role for nutritional ketosis as a uniquely beneficial therapy because it is pleotropic (and thus likely to address multiple disease mechanisms), and is a low-risk intervention compared to long-term steroids, antipsychotic medication, or immunosuppression.

# Case studies

As we expand our practice to include a broader swathe of neuropsychiatric diagnoses, we continue to draw from our past experiences with children with intractable epilepsy. Below are case examples where other appreciable benefits of a ketogenic diet were clearly noted.

## Patient A

Patient A is a 21 year old young man with Dravet Syndrome. He presented at 5 months of age with seizure onset and subsequent diagnoses of intractable epilepsy, intellectual disability, behavioral concerns, and gait abnormalities. Initial seizures included hemi- and generalized convulsions that frequently progressed to status

epilepticus. At 9 months, he began having myoclonic jerks and absence seizures. He was trialed on 6 antiseizure medications, yet continued to have persistent daily seizures. He was started on the classic ketogenic diet as an outpatient at 19 years old, and fed by gastrostomy tube 95% of the time with small tastes by mouth. His ratio was increased slowly over a few months to a final ketogenic ratio of 2.5:1. At that time, his mother noted a slight decrease in the number of seizures, reduced use of rescue medication, and less intense convulsions; however, they were still occurring daily. Due to difficulties in obtaining the lower ratio formula, they started to use ketogenic formula in the 4:1 ratio. His seizures were reportedly better on the higher ratio and worsened when he went back on the lower ratio formula, so it was decided to maintain the 4:1 ratio. His mother reported that after several months of the higher ratio formula, cognitive improvements unexpectedly emerged; he was able to speak in full sentences and follow multiple step commands, which was not possible prior to the start of the diet therapy. *We present this case as an example where seizure improvement was modest, yet expressive and receptive language gains were remarkable.*

## Patient B

Patient B is an 11 year old boy with Angelman Syndrome, evidenced by characteristic facial features, EEG features, and a pathogenic *UBE3A* gene variant. He was diagnosed with febrile seizures in infancy, then subsequently with unprovoked, atypical absence seizures requiring an antiseizure medication. Subsequent atonic seizures prompted the addition of a second antiseizure medication. He had many improvements at this time, such as taking steps, sleeping, and improved PO intake as well as seizure remission. At 3 years old, seizures increased again, and a third antiseizure medication was required. The classic ketogenic diet was initiated at 4 years old when seizure frequency was more than 10 times per day; seizures stopped within a few days of initiation, and he is maintained on a KD at a 3:1 ratio and fully fed by mouth. While his seizures are very well controlled on KD, his parents report that he is more alert, engaged with his surroundings, and social with family and friends. *Taken together, gains in cognition and behavior have provided improved quality of life in parallel with seizure remission.*

## Patient C

Patient C is a 4 year old boy with severe intellectual disability, spastic quadriparesis, optic nerve hypoplasia, congenital hypothyroidism, and intractable multifocal epilepsy secondary to a pathogenic variant in *IMPDH2*. Seizures began at 2 months of age, prompting initiation of an antiseizure medication with subsequent developmental gains. Abnormal eye movements prompted initiation of a second antiseizure medication. With onset of status epilepticus, a third antiseizure medication was added. At this time, his parents noted an asymmetric gait with dragging of his left leg, and expressive speech regression, as he had become nonverbal and communicated only with an assistive tablet. He became easily aggravated, with hair pulling and frequent hitting his own head and others. Patient C started the classic ketogenic diet at 3 years old. He received food by mouth during the day and took water and one formula feeding by gastrostomy tube during the night. On a 3:1 ketogenic ratio, metabolic acidosis was noted on routine labs and seizures did not improve. However, his mother reported that he is more alert and active after starting the KD. His therapists noted a longer attention span and restoration of his verbal skills to near baseline. *Medications are still adjusted in conjunction with the ketogenic diet to optimize management of epilepsy as well as cognitive and motor performance.*

## Concluding remarks

In this article, we provide a rationale and supporting existing evidence for use of a ketogenic diet in pediatric neuropsychiatric conditions and provide limited case studies from our own experience where its implementation provided clear benefits. In the future, we expect nutritional ketosis to be more commonly offered and trialed given its advantageous risk–benefit profile. While epilepsy remains the primary evidence-based indication for its use in pediatric neurology, small cohort studies and open-label trials have already opened the door to its potential role as supplemental therapies in migraine headaches, demyelinating disease, and brain tumors. We expect that the widespread need for additional solutions for ADHD, ASD, and intellectual disability coupled with our existing experience and best practices in this sphere will usher in an opportunity for earlier, more frequent consideration of nutritional ketosis.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Author contributions

TG: Writing – original draft, Writing – review & editing. RB: Writing – original draft, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Retrospective case study: ketogenic metabolic therapy in the effective management of treatment-resistant depressive symptoms in bipolar disorder

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This retrospective case study assessed Ketogenic Metabolic Therapy's (KMT) efficacy in a bipolar disorder patient with treatment-resistant depressive symptoms insufficiently controlled by weekly ketamine treatments. Monitoring included relevant biomarkers of ketone production and macronutrient levels, alongside mood evaluations through the Generalized Anxiety Disorder-7 (GAD-7), Depression Anxiety Stress Scales (DASS), and PTSD Checklist for DSM-5 (PCL-5), showing mood stabilization and improved functionality. Qualitative analysis revealed sub-stantial enhancements in functioning, life quality, and mental well-being. This study enriches the metabolic psychiatry literature, emphasizing KMT's potential benefits by integrating quantitative data from recognized psychiatric assessment tools and qualitative insights.

KEYWORDS

**ketogenic diet, bipolar disorder, KMT, ketogenic metabolic therapy, metabolic psychiatry, mood disorders, treatment-refractory depression, clinical psychology**

## 1 Introduction

Bipolar II disorder is marked by significant emotional and psychological distress, characterized by periods of depressive episodes and hypomania (1). This condition not only affects an individual's psychological well-being but also has profound implications on their social and occupational functioning (2). The complexity of Bipolar II disorder, especially with treatment-resistant depressive symptoms, presents a substantial challenge in psychiatric care (3). Current treatments for Bipolar II disorder often include a combination of mood stabilizers, antidepressants, and psychotherapy. However, a notable subset of patients remains resistant to these interventions, experiencing persistent symptoms and a diminished quality of life. Even individuals with bipolar disorder undergoing treatment still spend about 19% of their time in depressive states and an additional 18% in sub-syndromal depressive states (4). This resistance underscores the urgent need for alternative strategies that can offer relief and improve patient outcomes (5).

Emerging evidence suggests that metabolic interventions, such as Ketogenic Metabolic Therapy (KMT), also known as the ketogenic diet, may offer favorable treatment outcomes for individuals with psychiatric disorders. Well established in the management of epilepsy (6), recent studies indicate that the ketogenic diet may have beneficial outcomes for individuals with bipolar disorder, with observations from case studies (7–9) and pilot studies (10–12) reporting notable improvements in symptoms.

The diet's mechanism is believed to involve the modulation of brain energy metabolism and neurotransmitter levels (13–16), providing a compelling rationale for its application in Bipolar II disorder.

This case focuses on an individual diagnosed with Bipolar II disorder, presenting with persistent depressive episodes marked by significant lethargy, low mood, and difficulty in managing daily activities despite standard treatment protocols. By employing both quantitative and qualitative methods, this case study seeks to understand better the treatment potential of KMT with patients for whom standard care has not yielded satisfactory outcomes.

# 2 Case presentation

## 2.1 Clinical background

In this case, a 53-year-old female with Bipolar II reported persistent mood instability and depressive episodes resistant to past and current conventional treatments. Psychiatric intervention at time of diet implementation consisted of weekly ketamine treatments for temporary symptom relief. Despite this intervention, the relief from depressive symptoms was short-lived, lasting only 1 to 3 days before the symptoms returned. The patient also experienced migraine headaches. Prior attempts at management included medication, psychotherapy, a Mediterranean diet, physical exercise, and consistent sleep schedules, which yielded limited improvement. Given the limited efficacy of standard treatments and the transient benefits achieved with ketamine therapy, she was open to exploring KMT as a novel intervention. Her history of psychiatric conditions began in childhood and adolescence, leading to subsequent diagnoses of Generalized Anxiety Disorder and Major Depressive Disorder before the eventual identification of Bipolar II as the most recent diagnosis. At the initiation of treatment, the participant was receiving medical care for additional chronic conditions, which included Immune Thrombocytopenia, Migraines, Hypothyroidism, and recurrent shingles (Herpes Zoster).

## 2.2 Ketogenic metabolic therapy intervention strategy

Macronutrient tracking was initiated using Cronometer, which identified an average baseline carbohydrate consumption of between 200 and 300 g per day. BMI was in a healthy range at diet commencement and remained so throughout treatment. Virtual meetings for KMT support were scheduled twice weekly for 30-min intervals over 3 months and then moved to weekly. Carbohydrate consumption was systematically reduced over 2 weeks to achieve a 30 g total intake per day. Macronutrient ratios were initially set at a 1:1 ratio and later adjusted to a 1.5:1 ratio (154 g Fat, 72 g Protein, 30 g Total Carbohydrates) to increase ketone production. Total carbohydrate measurement was chosen over net to initiate and maintain ketosis at consistent levels. Both ratios used are generally considered Modified-Atkins (MAD). The diet consisted primarily of beef, pork, chicken, eggs, dairy, and salmon, with primary fat sources being MCT oil, avocado oil, and butter. Low-carbohydrate vegetables and minimal amounts of low-carb berries complemented this.

Supplementation provided included a non-methylated B-complex, trace minerals (providing zinc, copper, manganese, chromium, molybdenum, boron, and vandyl sulfate), vitamin D, and electrolytes in the form of sodium, magnesium, and potassium. Testing compliance was 89% complete for daily ketone measures and 91% complete for daily glucose measures over the 21-week period. Blood glucose and BHB level tracking was initiated and showed nutritional ketosis was achieved at 1.0 mmol/L (Figure 1). Approximately 3.5 weeks into the process of carbohydrate restriction, lab work was received showing free carnitine at 16 µmol/L that identified hypocarnitinemia (17), prompting ongoing L-carnitine supplementation of 3,000 mg in divided doses daily.

# 3 Evaluation of intervention outcomes

## 3.1 Quantitative analysis

Mood assessments were collected at baseline, one-month, four-month, and five-month intervals. They were selected for their validity in assessing self-reported markers of mood, anxiety, stress, and PTSD symptoms. The Generalized Anxiety Disorder-7 (GAD-7), Depression Anxiety Stress Scales (DASS), and PTSD Checklist for DSM-5 (PCL-5) were used. Although no prior diagnosis of PTSD was given, the PCL-5 includes items that assess symptoms such as trouble sleeping, feeling easily startled, difficulty concentrating, and strong negative emotions, which can overlap with symptoms of Generalized Anxiety Disorder, Major Depressive Disorder, and Bipolar Disorder. As the case study participant had received these diagnoses in the past, its inclusion allowed for the detection of nuanced symptom changes potentially relevant in measuring changes in mental health status.

The Generalized Anxiety Disorder-7 (GAD-7) is a self-reported assessment measuring the severity of anxiety symptoms and is considered a dimensional indicator of Generalized Anxiety Disorder severity (18). Scores at the onset indicated mild symptoms, which decreased over the course of the intervention, ending in a normal range (Figure 2). A breakdown of these changes is presented (Supplementary Table S1), quantifying the initial severity and subsequent reductions in GAD-7 scores over the 21-week period.

The Depression Anxiety Stress Scales (DASS) is based on a dimensional rather than a categorical conception of psychological disorders and differentially assesses three negative emotional states: depression, anxiety, and stress (19, 20). Initial evaluations showed high levels of these symptoms, especially depression, indicating substantial emotional distress. The 42-item version of the DASS was administered with scores indicating a reduction in symptoms (Figure 3).

Baseline scores indicated moderate to severe levels of depression, anxiety, and stress, with reductions across all three subscales as treatment progressed. Particularly notable was the decrease in depression scores from a moderate level to a normal range. Additionally, anxiety and stress scores showed decreases, indicating a shift towards milder symptomatology (Supplementary Table S2). Differences in initial severity scores between the GAD-7 and DASS anxiety scale could be attributed to the broader assessment coverage provided by the DASS.

The PTSD Checklist for DSM-5 (PCL-5) is a self-report rating scale for assessing the 20 DSM-5 symptoms of post-traumatic stress disorder (21). Initial assessment revealed endorsement of Criterion D

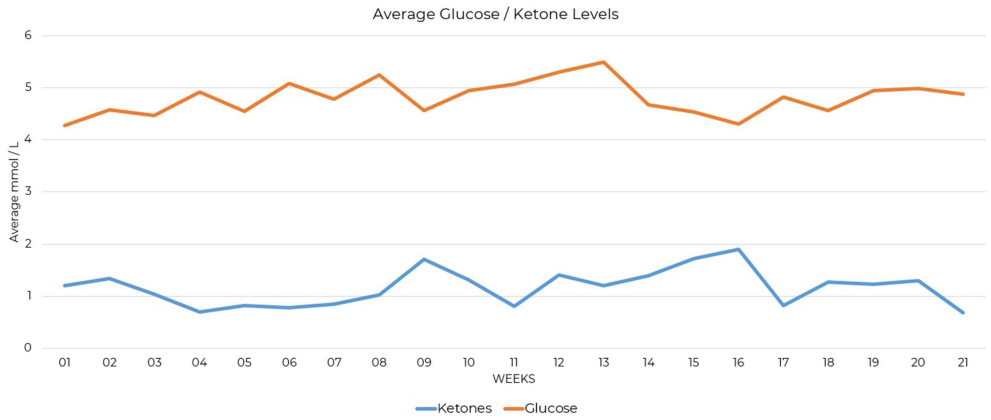


FIGURE 1
Line graph showing average glucose and ketone levels in mmol/L over 21 weeks.

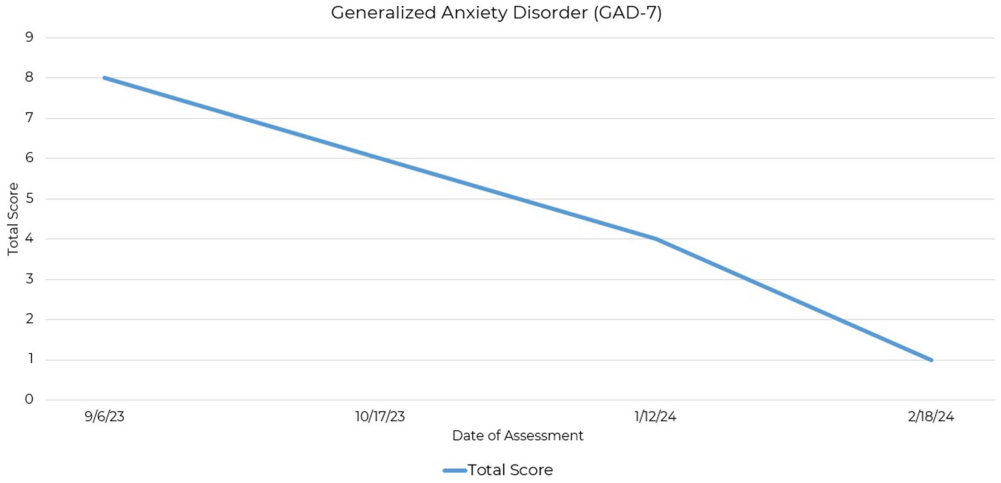


FIGURE 2
Line graph depicting the reduction in GAD-7 total scores across four assessment points over a 21-week period.

(negative alterations in cognitions and mood), initially exhibiting the highest severity, and Criterion E (alterations in arousal and activity). Subsequent assessments showed a consistent decrease in these scores, with marked improvements observed in both Criterion D and Criterion E (Figure 4).

Although there are currently no empirically derived severity ranges for the PCL-5 (22), reductions in Criteria D and E suggest improvement in mood and arousal symptoms over the assessment period. These criteria, indicative of symptoms seen also in depression and anxiety, may serve as markers of symptom improvement relevant to this case study participant (Supplementary Table S3).

## 3.2 Qualitative analysis

Qualitative analysis, as delineated by Yin and discussed in Baškarada (23), was employed to ensure the systematic collection, analysis, and interpretation of data. The qualitative component of data collection centered on the exploration of participant experience using KMT as a treatment for mental illness, recognizing that quantitative assessments may not fully encapsulate the participant's experience.

Deductive thematic analysis was applied to the case study's transcript data, focusing on four predefined themes: the personal and emotional journey with KMT, the adoption decision-making process, enhancements in quality of life, and a comparative analysis of conditions before and after KMT. Open-ended, non-leading questions encouraged unbiased responses, developed in line with the Case Report (CARE) guidelines (24) and as detailed in Supplementary Table S5. Conducted virtually after informed consent, the interview's structured approach, conducted by the case study author and guided by these themes, facilitated the categorization of the transcript via a systematic coding procedure. Deductive coding in a single case allows focus on specific theoretical constructs that enable a targeted exploration of the participant's experiences, as detailed in Supplementary Table S4, which links the coding strategy directly to the theoretical constructs addressed. Incorporating peer debriefing and soliciting participant feedback on the

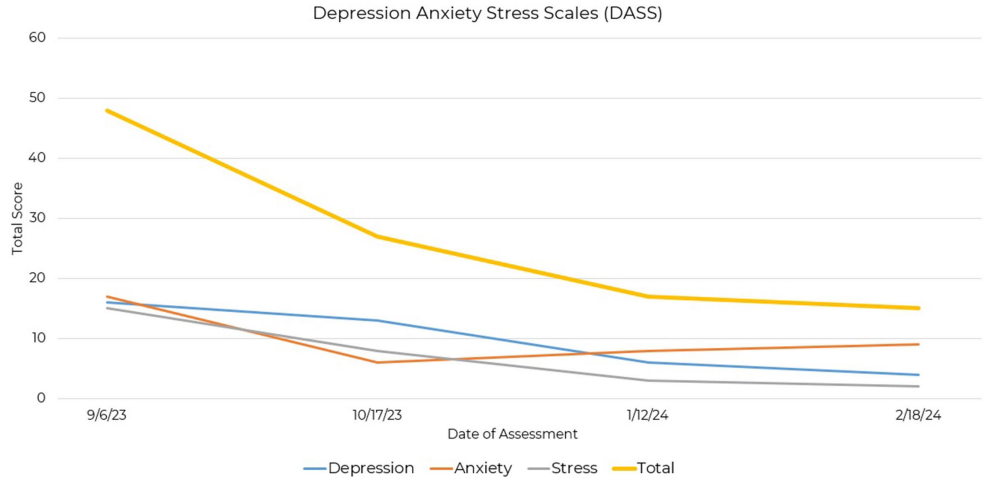


FIGURE 3
Line graph depicting the reduction in DASS total and subscale scores across four assessment points over a 21-week period.

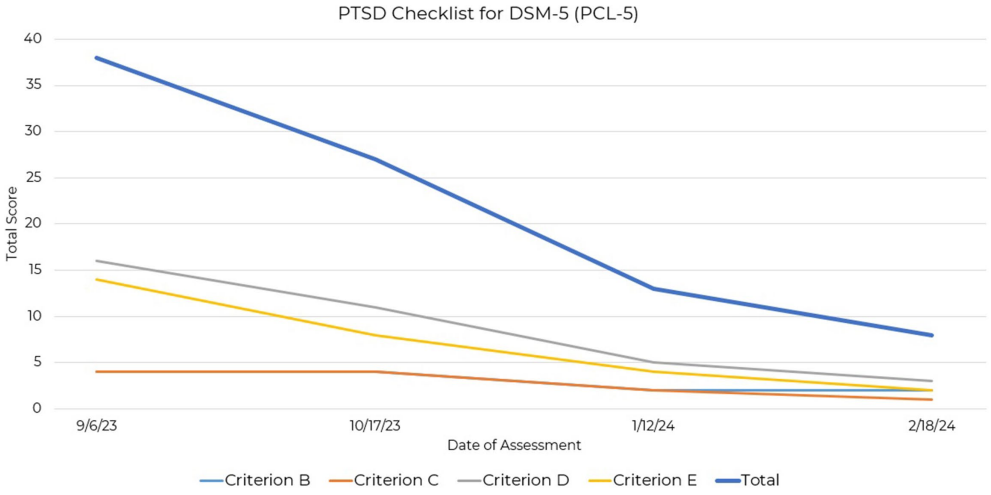


FIGURE 4
Line graph depicting the reduction in PCL-5 total and criterio subscales across four assessment points over a 21-week period.

interview's comprehensiveness and preliminary findings helped manage researcher bias, ensuring an objective qualitative examination of KMT's impact in this single case study analysis.

### 3.2.1 Personal and emotional journey with KMT

The theme 'Personal and Emotional Journey with KMT' was used to identify codes for symptom severity, emotional impact, and personal insights. These codes were utilized to document the participant's mental and physical health fluctuations, emotional responses, and self-reflections on their experience with KMT, focusing on the direct impact of KMT on the individual's life. Codes developed within this theme identified the experience of a personal and emotional journey with KMT that communicated the transition from a state of profound mental health struggles to a newfound stability and normalcy. Clinically, this reflected a significant shift in self-perception and emotional regulation, which is foundational in the therapeutic process (25, 26). The narrative revealed how, for this participant, KMT facilitated a re-engagement with life with movement from a position of vulnerability and isolation to one of agency and connectedness. An example of coded data included the patient stating, "I think everyone has to deal with some anxiety and depression. I feel like the amount that I have in my life at this point is like a normal amount."

### 3.2.2 Adoption decision-making process

The "Adoption Decision-Making Process" theme and subsequent code development investigated the participant's route to choosing the intervention. It examined past treatments, differences between expected and actual effects, factors influencing their choice, intervention tolerability, and the potential impact of earlier access. This distillation attempted clarification of the participant's decision-making framework. Actual codes applied included 'Previous Treatments,' 'Expectations vs. Reality,' 'Journey to KMT,' and 'KMT Treatment Availability.'

In this single case, the participant's decision-making process was driven by frustration with standard-of-care treatments towards the

adoption of the KMT approach. This identification of a pivotal decision-making phase was suggestive that active patient engagement in treatment choices might be indicative of the broader search for autonomy and efficacy in treatment strategies among individuals with treatment-resistant conditions. The coded narrative identified the psychological impact of finding new hope after numerous failed attempts with traditional therapies and reflected critical moments of self-determination, where the participant took an active role in their KMT treatment plan. The theme adequately captured that the participant viewed the intervention as sustainable with prolonged continuation as needed to control symptoms. The theme was further able to identify an expression of the participant that they would have preferred earlier introduction to the therapy, indicating that the current substantial relief they experienced may not have been achieved had they not discovered this treatment option on their own. This sentiment highlights the importance of early and proactive consideration of KMT by mental health and other professionals with whom they come in contact. An example of coded data included the patient stating, "I do not think if I had not stumbled upon it myself, and had just a very open and caring practitioner to discuss it with for the first time, that I would be experiencing the sense of relief that I'm experiencing today."

### 3.2.3 Enhancements in quality of life

Delineating through deductive analysis, the theme of "Enhancements in Quality of Life" focused on capturing the broad improvements in the participant's life following KMT adoption. This theme encompassed codes for 'Lifestyle Adjustments,' detailing changes in habits and routines, and 'Life Quality Improvement,' highlighting overall enhancements in life satisfaction across relationships, work, hobbies, and lifestyle. These codes detailed multifaceted benefits beyond clinical symptom alleviation to identify positive impacts on daily living and well-being.

The findings demonstrated improvements in quality of life post-KMT adoption were suggestive of the therapy's capacity to effect change beyond symptom relief, touching on aspects of daily functioning, social engagement, and overall well-being. Clinically, this theme highlights the impact of KMT, suggesting that its benefits extend into the psychosocial realm, enhancing patients' ability to engage in meaningful relationships, pursue interests, and maintain a sense of normalcy. The narratives reveal a restoration of hope and vitality, which is paramount in the recovery process. This enhancement in quality of life can possibly be attributed to the stabilizing effects of KMT on mood, which, in turn, facilitates greater emotional resilience and adaptability in facing life's challenges. An example of coded data included the patient stating, "I actually made the drive with very little fatigue, no anxiety, great energy. All the things that kind of crop up at those kind of appointments happened, but I felt like I dealt with them just so much more easily. Just easily!"

### 3.2.4 Conditions before and after KMT

The 'Conditions Before and After KMT' theme, through deductive analysis, captured the participant's experiences pre-and post-KMT adoption, employing codes for detailed comparisons and evaluation of efficacy. Codes within this theme included 'Before After Comparison' for specific contrasts in conditions and emotional states and 'Treatment Efficacy' assessing KMT's performance against prior treatments. An example of coded data included the patient stating, "I just spent a lot of time very depressed and feeling very withdrawn," to describe their prior experience. This structured analysis sought to clarify the participant's experience of the impacts of KMT on their condition and life, offering a more nuanced understanding of KMT's effectiveness and its role in altering patient outcomes.

The comparative analysis of conditions before and after implementing KMT for this participant provided a clear contrast between the debilitating effects of bipolar disorder and the empowering influence of effective management through this therapy. This theme is clinically significant as it illustrates the potential of KMT to redefine the treatment landscape for individuals with treatment-resistant bipolar disorder. The narrative highlighted a marked improvement in mood stability, cognitive function, and overall well-being, endorsing the effectiveness of KMT in addressing the complex needs of this population. The theme also reflected the broader implications of KMT for clinical practice, framing KMT as a viable approach for the management of bipolar disorder and enhancing patient outcomes.

From a clinical perspective, the analysis of data from this theme underscored the significance of KMT as a possibly viable intervention for individuals with treatment-resistant bipolar disorder. The collected narrative provided a detailed account of KMT's impact on personal well-being, decision-making processes related to treatment choices, quality of life improvements, and the condition's comparative state before and after KMT implementation. These findings offer valuable insights into the potential of KMT to augment clinical practice and patient management.

## 4 Discussion

The participant further reported that in response to significant reductions in symptoms and under the guidance of their physician, they were able to discontinue the use of some medications and reduce others previously prescribed for the aforementioned chronic conditions. In regards to mood, initial improvements were verbally reported by the patient 2 weeks after diet initiation. Improvements in mood continued and were generally maintained 5 months following the initiation of KMT, offering data on the timeline of symptom improvement. This data may be helpful for aligning the expectations of both patients and clinicians, as well as for informing the design of future research studies. Studies with extended durations or follow-ups may better capture the potential benefits of KMT as a treatment option for mental illnesses.

This participant's outcome suggests that metabolic health interventions, like ketogenic diets, could offer new directions for treating psychiatric disorders, especially where standard-of-care treatments fall short. The qualitative analysis suggests the possibility that those suffering from Bipolar II disorder may benefit from early introduction to the treatment as an option. While promising, these findings stem from a single case, urging further research to validate these results in broader clinical settings. This work supports further research on the use of KMT as a potential treatment in psychiatry.

## 5 Conclusion

In this case study, a ketogenic diet significantly improved treatment-resistant depressive symptoms in a patient with bipolar

disorder. Both mood assessments and the patient's experience showed marked improvements. Mood scores moved to normal ranges, indicating stabilized mental health. The patient's account highlighted improved functioning, better quality of life, and emotional well-being. This case study is of particular interest because it documents the longer-term feasibility of diet implementation, ketone testing compliance, and improvements in relevant symptoms reported by qualitative and quantitative methods. However, any conclusions based on this case study are severely limited by its single-participant sample size and retrospective design, highlighting the need for further research employing randomized controlled trials. Integration of both quantitative and qualitative data may be valuable to adequately represent improvements that researchers are attempting to document as a result of using KMT as a treatment for mental illness.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

Ethical approval was not required for the studies involving humans because this was a retrospective case study. After the intervention, the participant decided whether or not they wanted to contribute their experience to the research. Informed consent was obtained to use existing quantitative data and collect case study interview data for analysis. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

NL: Writing – original draft, Writing – review & editing.

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## Conflict of interest

NL is employed by and owns Family Renewal, Inc. DBA Mental Health Keto.

## Publisher's note



## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1394679/full#supplementary-material

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# The effects of ketogenic metabolic therapy on mental health and metabolic outcomes in schizophrenia and bipolar disorder: a randomized controlled clinical trial protocol

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**Background:** Schizophrenia, schizoaffective disorder, and bipolar affective disorder are debilitating psychiatric conditions characterized by a chronic pattern of emotional, behavioral, and cognitive disturbances. Shared psychopathology includes the pre-eminence of altered affective states, disorders of thoughts, and behavioral control. Additionally, those conditions share epidemiological traits, including significant cardiovascular, metabolic, infectious, and respiratory co-morbidities, resulting in reduced life expectancy of up to 25 years. Nutritional ketosis has been successfully used to treat a range of neurological disorders and preclinical data have convincingly shown potential for its use in animal models of psychotic disorders. More recent data from open clinical trials have pointed toward a dramatic reduction in psychotic, affective, and metabolic symptoms in both schizophrenia and bipolar affective disorder.

**Objectives:** to investigate the effects of nutritional ketosis via a modified ketogenic diet (MKD) over 14 weeks in stable community patients with bipolar disorder, schizoaffective disorder, or schizophrenia.

**Design:** A randomized placebo-controlled clinical trial of 100 non-hospitalized adult participants with a diagnosis of bipolar disorder, schizoaffective disorder, or schizophrenia who are capable of consenting and willing to change their diets.

**Intervention:** Dietitian-led and medically supervised ketogenic diet compared to a diet following the Australian Guide to Healthy Eating for 14 weeks.

**Outcomes:** The primary outcomes include psychiatric and cognitive measures, reported as symptom improvement and functional changes in the Positive and Negative Symptoms Scale (PANSS), Young Mania Rating Scale (YMS), Beck Depression Inventory (BDI), WHO Disability Schedule, Affect Lability Scale and the Cambridge Cognitive Battery. The secondary metabolic outcomes include changes in body weight, blood pressure, liver and kidney function tests, lipid profiles, and markers of insulin resistance. Ketone and glucose levels will be used to study the correlation between primary and secondary outcomes. Optional hair cortisol analysis will assess long-term stress and variations in fecal microbiome composition. Autonomic nervous system activity will be measured via wearable devices (OURA ring and EMBRACE wristband) in the form of skin conductance, oximetry, continuous pulse monitoring, respiratory rate, movement tracking, and sleep quality. Based on the encouraging results from established preclinical research, clinical data from other neurodevelopment disorders, and open trials in bipolar disorder and schizophrenia, we predict that the ketogenic metabolic therapy will be well tolerated and result in improved psychiatric and metabolic outcomes as well as global measures of social and community functioning. We additionally predict that a correlation may exist between the level of ketosis achieved and the metabolic, cognitive, and psychiatric outcomes in the intervention group.

KEYWORDS

**nutrition, mental health disorders, ketogenic diet, schizophrenia, randomized control trial (RCT), bipolar disorder, dietary intervention, metabolic therapy**

## 1 Introduction

Schizophrenia, schizoaffective disorder, and bipolar disorder are severe and enduring psychiatric conditions characterized by a lifelong pattern of emotional, behavioral, and cognitive symptoms (1–4). These conditions, albeit diagnostically distinct, share several clinical and epidemiological traits, including significant metabolic co-morbidity resulting in a reduction in life expectancy, ranging from 13 to 15 years (5) and up to 25 years in low-income countries (6, 7). Those suffering from chronic psychotic disorders endure the additional burden of poor metabolic health (8). Unfortunately, the currently available antipsychotic medications are only partially effective in assisting with symptom management and come with serious side effects, including diabetes, weight gain, and high blood pressure, leading to a greater prevalence of metabolic syndrome and cardiovascular disorders (9).

A major roadblock to developing better therapeutical approaches in serious mental illnesses, such as schizophrenia and bipolar disorder, is the lack of sufficient development in our understanding of disease mechanisms and the identification of potential new therapeutic targets. Since the serendipitous discovery of antipsychotics and lithium in the treatment of schizophrenia and bipolar disorder, respectively, the dominant mechanistic explanations have focussed mainly on major neurotransmitter systems, such as the dopaminergic, serotonergic, and glutamatergic neurotransmission (2, 4, 10). Targeting these systems by pharmaceutical agents has produced major improvements in managing key symptoms and the patient's quality of life. However, they have also contributed to the development of clinically significant side effects, including motor, metabolic, and endocrine disturbances, which strongly and negatively influence quality of life and life expectancy (11). Those shortcomings of traditional pharmacological approaches have in turn driven recent efforts to identify underlying disease mechanisms as putative targets for symptom improvement and better quality of life for individuals with schizophrenia and bipolar disorder. The development of human genetics and the different-omics technologies, including genomics, transcriptomics, and metabolomics, have revealed the potentially interlinked role of inflammatory/immune mechanisms and altered systemic and brain bioenergetics in the pathophysiology of these disorders (12–16) (Figure 1). Here we briefly review the basics of brain bioenergetics and its alterations in schizophrenia and bipolar disorders to provide a strong mechanistic rationale for our clinical trial.

Although constituting just 2–3% of the total body weight, the adult human brain is responsible for the consumption of a disproportionately large fraction, nearly 20%, of the human body's basal metabolic rate (17). Glucose is the main energy substrate in the brain (18). The high-energy molecule adenosine triphosphate (ATP) is produced from glucose through glycolysis, the non-oxidative breakdown of glucose to pyruvate and lactate in the cytoplasm, through the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS) in the mitochondria (18). Reversing ion movements that generate neuronal post- and pre-synaptic responses consume most of the energy from ATP (19). Glucose is not only the major source of ATP but is also used for the biosynthesis of ribose to form ribonucleic acids, fatty acids, and cholesterol (Figure 2). In addition, glucose through the pentose-phosphate pathway (PPP) is involved in the protection against oxidative stress and through the

Abbreviations: KD, Ketogenic diet; AGHE, Australian Guide to Healthy Eating; PIS, Participant information sheet; PANSS, Positive and Negative Syndrome Scale; ALS-18, Affect Liability Scale; YMRS, Young Mania Rating Scale; WHODAS – 2, WHO Disability Assessment Schedule – 2; BDI, Beck Depression Inventory; DOI, Duration of illness.

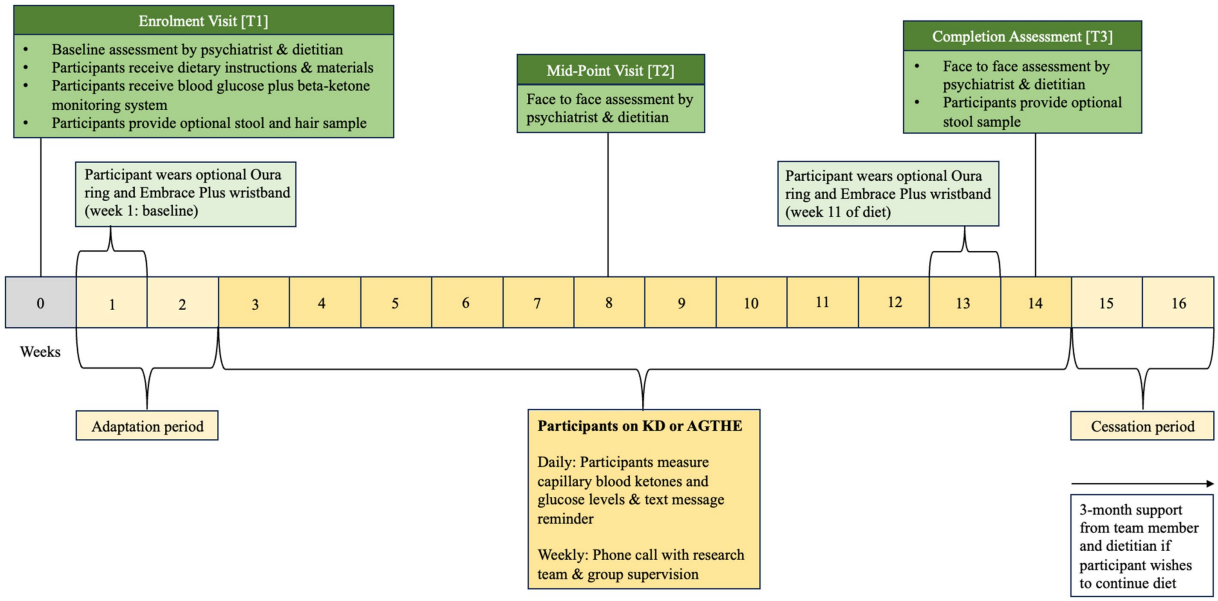


FIGURE 1
Following Enrolment at T1, participants progress to an "adaptation period" of 2 weeks followed by 6 weeks of allocated dietary intervention until they reach the Mid-Point Visit [T2]. Participants will continue through for further 6 weeks to the Completion Assessment [T3] at week 14.

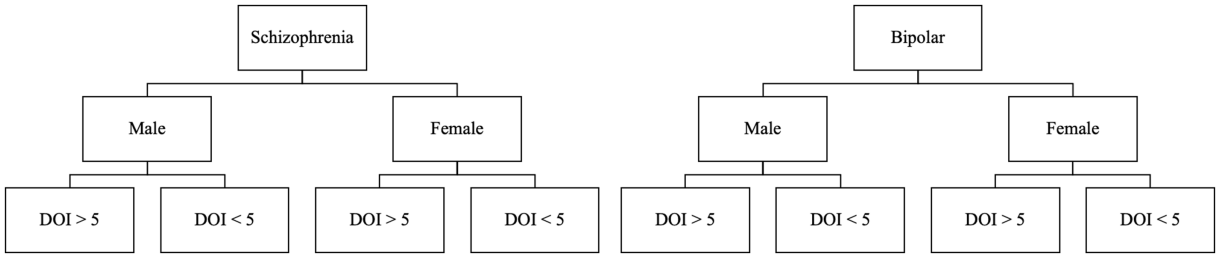


FIGURE 2
Participants will be stratified to one of 8 groups, depending on their primary diagnosis, biological sex, and duration of illness greater or less than 5 years.

TCA cycle in the production of amino acids such as glutamate and subsequently GABA (18). Neurons and glia cells cooperate in their energy production. Astrocytes take up glucose from the brain capillaries and metabolize it to lactate through glycolysis, which is transported to neurons through monocarboxylate transporters, a process called the astrocyte-neuron lactate shuttle (19). Neurons then convert lactate to pyruvate and generate ATP thought the TCA cycle and the OXPHOS (18). However, neurons are able to generate ATP directly through glycolysis, even in the presence of sufficient oxygen concentration (aerobic glycolysis), during heightened activity (18). Therefore, deficits in glucose and energy supply in neurons or in glia cells can impair the dynamic regulation of key brain circuits, ultimately resulting in abnormal brain function and behavior (20).

Systemic glucose metabolism abnormalities marked by hyperglycemia and insulin resistance have long been noted in schizophrenia, predating the advent of antipsychotic agents and in treatment-naïve, first-episode psychosis patients (21) In the brain, impairments in glucose metabolism and mitochondrial functions have been detected through diverse methodologies. Essentially, reduced expression of genes encoding various glycolytic enzymes, including the rate-limiting hexokinase, have been observed, alongside diminished levels of enzyme proteins and their activity (22), specifically in glutamatergic neurons in the dorsolateral prefrontal cortex in people with schizophrenia (23, 24). Furthermore, multiple mitochondrial impairments, including altered expression of electron transport chain enzymes, such as Complex-I and Complex-V (ATP-synthase), have been demonstrated in the brains of people with schizophrenia (25–27). Brain imaging studies have identified decreased glucose utilization in the frontal cortex (hypofrontality) and a switch to more glycolytic ATP production associated with elevated brain lactate levels (28, 29). These findings contribute to the conceptualization of schizophrenia as a disease of impaired brain bioenergetics (14).

Similarly, metabolomics and magnetic resonance spectroscopy indicate that energy dysregulation is a central feature of bipolar disorder pathophysiology (30–32). Accordingly, mania represents a condition of heightened cerebral energy metabolism facilitated by hyperglycolysis and glutaminolysis. When oxidative glucose metabolism becomes impaired in the brain, neurons can utilize

glutamate as an alternative substrate to generate energy through oxidative phosphorylation. It has been hypothesized that the upregulation of glycolysis and glutaminolysis in this manner causes the brain to enter a state of heightened metabolism and excitatory activity which may underlie the subjective experience of mania (30). Supporting this hypothesis, recent studies have identified mitochondrial abnormalities and resulting elevation of deleterious free oxygen radicals in bipolar disorder (33–35). Taken together, recent progress in the neurobiological understanding of schizophrenia and bipolar disorder points toward the mechanistically important role of abnormal brain bioenergetics in their pathophysiology.

Ketogenic metabolic therapy, achieved via the consumption of a low carbohydrate (CHO)-high fat-containing diet (ketogenic diet; KD), elevates circulating ketone bodies, such as acetoacetate and beta-hydroxybutyrate. Ketone bodies can serve as an alternative energy source for impaired glucose metabolism and support mitochondrial function (36), thus potentially counteracting the underlying bioenergetic abnormalities in schizophrenia and bipolar disorder (37, 38). Three weeks of KD or beta-hydroxybutyrate administration effectively normalized behavioral impairments in a hypo-glutamatergic animal model of schizophrenia (39–41). After highly encouraging results from case studies showing dramatic improvements in a wide range of symptoms and quality of life in patients with schizophrenia on KD (42–45), a recent single-arm clinical trial in which patients with schizophrenia and bipolar disorder consumed a medically supervised KD, showed improvements in several psychiatric symptoms and metabolic functions (46). KD was also successfully used in a recent single-arm trial in patients with bipolar disorder (47). To indicate an increasing interest in ketogenic therapeutic interventions in psychiatry a recent pilot trial protocol aims to investigate the effect of a 'ketogenic-mimicking diet' (combining supplementation of ketone esters with a low glycemic index dietary intervention) on neural network stability, mood, and biomarker outcomes in the setting of bipolar disorder (48).

Taken together, positive results from extant preclinical studies, case studies, and uncontrolled clinical trials point toward a clinically significant role for ketogenic metabolic therapy in the treatment of serious mental illness and offer hope to millions of individuals worldwide, who suffer from those conditions. However, no data from randomized controlled clinical trials exist to date. Such clinical trial ought to compare the effects of KD with another dietary intervention under circumstances that are identical for all randomly assigned trial participants in every possible aspect, such as trial management, clinician's attention, and outcome measures, to establish the specific contribution of the ketotic metabolic state on the outcomes of interest. Here we report the detailed protocol of a randomized controlled clinical trial to investigate the efficacy of ketogenic metabolic therapy on psychiatric, cognitive, and functional symptom improvement and metabolic changes in schizophrenia and bipolar disorder.

# 2 Methods

## 2.1 Study design

This randomized placebo-controlled parallel-designed clinical trial is registered with the Australian New Zealand Clinical Trials Registry (ANZCTR), the mandated online register of clinical trials being undertaken in Australia, New Zealand, and other Oceanic Nations (Reg. No: ACTRN12623000854639).

### 2.1.1 Recruitment and screening

Advertisements will be disseminated to local community mental health teams, general practitioners, general hospitals, and other health facilities. Advertisement is also broadcast via social media networks and press launches from Townville University Hospital and James Cook University. Prospective participants register via the trial website[1] and will then receive an email with information material relating to the structure and requirements of the trial. Prospective participants will then be screened for eligibility via telephone by the principal investigator, who is a senior psychiatrist. During the screening call or Timepoint 0 [T0], the principal investigator (CL) will check the prospective participant's eligibility to enroll in the trial against the inclusion and exclusion criteria (Table 1).

### 2.1.2 Assessments

Eligible participants progress to the first physical visit (Enrolment Visit at Timepoint 1 [T1]) and are asked to complete a three-day food diary before attending the appointment. During the enrolment visit [T1], formal written consent is obtained by a trial psychiatrist (CL, SG, or OS) before baseline assessments of psychiatric, cognitive, and metabolic outcome measures are taken. Participants are then randomized into either the Ketogenic Diet (KD) or the Australian Guide to Healthy Eating (AGHE) group by stratified, computer-generated blinded allocation. Following randomization, participants progress to the dietitian assessment and group-specific dietary education. Dietary education and counseling for each group are provided by a senior dietitian, including the provision of the existing evidence base for nutrition in mental health to assist in personalizing the KD or AGHE diet. Consideration will be given to their metabolic health, dietary preferences, age, sex, and physical activity level that may impact their estimated energy requirements (EER). Participants will then receive detailed dietary instructions and specific educational material to foster independent meal preparation. All participants, irrespective of their group allocation, will be instructed to complete a 2-week diet "adaptation period" where both groups progressively adjust their diet to minimize any side effects due to metabolic adaptation to the new diet and to allow participants to adjust their daily routine to the new food preparation requirements. Participants will be asked to complete daily food diaries and are provided with weekly dietetic support in the form of face-to-face consultation, and phone-, and email follow-up to increase compliance, alter individual diet prescriptions where required, and for safe cessation of the diet. In the second visit (Mid-Point Visit or Timepoint 2 [T2]), psychiatric and metabolic assessments are repeated. In the third visit (Completion Assessment or Timepoint 3 [T3]), all psychiatric, metabolic, and cognitive assessments are repeated. T1 is at baseline (week 0), T2 occurs on week 8, and T3 on week 14. The intervention is 12 weeks from week 3 to week 14, plus a 2-week washout period, for a total of 14 weeks duration (Figure 1). During the washout period, participants are instructed to progressively revert to a diet of their preference.

1 https://nqdit.com.au/

TABLE 1 Participant eligibility.

| Inclusion criteria | Exclusion criteria |
|---|---|
| To be eligible for this study, an individual must meet the following criteria:<br>• Have been diagnosed by a psychiatrist with either schizophrenia, schizoaffective disorder, or Bipolar Affective Disorder and have had the condition for at least 6 months.<br>• Being clinically stable (no episodes of hospitalization or significant treatment changes for at least 3 months)<br>• Possess the mental capacity to provide informed consent and willingness to sign a written informed consent document.<br>• Aged ≥18 years old.<br>• Able to understand the basic principles of the specific diet and follow dietary instructions as provided by the study dietitian.<br>• Willingness to adhere to all study procedures including the completion of an accurate diet and symptoms diary, daily blood glucose and ketone monitoring, and to attend the visits as scheduled. | Individuals who meet any of the following criteria will be excluded from participation in this study:<br>• Pregnant, breastfeeding, or planning to become pregnant within 3 months.<br>• Active substance misuse with alcohol or illicit drugs.<br>• Use of the ketogenic diet in the previous 2 months.<br>• Currently following a vegan diet.<br>• Admission to a mental health hospital within the past 3 months.<br>• Inability to complete visits and assessments.<br>• Uncompensated cardiovascular disease.<br>• Severe hyperlipidemia.<br>• Type 1 diabetes.<br>• History of eating disorder.<br>• BMI < 18.5 kg.<br>• On medication that can cause ketosis.<br>• Not willing to change diet or unable to change diet due to medical reasons.<br>• Active liver or kidney disease.<br>• No access to cooking facilities and ingredients to prepare recipes following the specific diet.<br>• Current involvement in another research study. |

TABLE 2 Most commonly used therapeutic Ketogenic diets.

| | Modified Atkins diet | Modified Ketogenic diet | Low glycaemic index treatment | Classic Ketogenic diet |
|---|---|---|---|---|
| Fat (%) | 65 | 75 | 60 | 90 |
| Carbohydrates (%) | 10 | 5 | 10 | 4 |
| Protein (%) | 25 | 20 | 30 | 6 |

Participants may also continue with their allocated diet, if they choose to do so.

Pre-existing psychiatric and metabolic treatment will continue as per the treating team's medical advice. Metabolic medication might be adjusted for those in the KD group in collaboration with their physician to minimize the risk of hypoglycemia. Participants in both groups will be given a blood ketone and glucose monitoring device at the end of the enrolment visit (T1) and instructed to take a daily capillary blood sample to measure glucose and ketone levels. The measurement will occur consistently every day, 2 h before their routine dinner time. Daily glucose and ketone measurements are uploaded to a team's database daily and strictly monitored to detect any emergent metabolic abnormality.

### 2.1.3 Allocation

Participants will be blinded to the study hypothesis and interact with clinicians who are kept blind to their group allocation as far as possible. Allocation will occur only after the initial psychiatrist assessment. If a psychiatrist becomes accidentally unblinded to a participant's allocation during the running of the trial, a different team psychiatrist will be asked to continue the remaining time points assessment(s) for that participant. Participants in both groups will be treated identically in all respects except for the intervention being tested.

The study is being conducted at a single site at the Translational Research Facility, Australian Institute of Tropical Health and Medicine, James Cook University at Townsville Campus, Queensland, Australia. Human Research Ethics Approval (HREC/2022/QTHS/85408) for this study was received by the Townsville University Hospital HREC board, responsible for the study population's catchment area.

## 2.2 Experimental intervention

The intervention involves a 12-week dietitian-led, medically supervised KD, designed to induce a state of nutritional ketosis. Several dietary regimes for achieving ketosis in adults exist including the Modified Atkins Diet (MAD)/ Modified Ketogenic Diet (MKD), Low Glycaemic Index Treatment (LGIT), and the Classical Ketogenic Diet (Table 2). These diets share a common principle of reducing carbohydrate (CHO) intake while increasing fat consumption. The variation in the degree of CHO reduction and fat increase distinguishes these regimes. In this trial, a MKD (2:1 ratio) will be implemented to induce ketosis in participants. The MKD was selected for its higher compliance rates (49, 50) and its allowance for greater flexibility and food variety compared to the classical ketogenic diet (4:1 ratio). The prescribed amount of macronutrient distribution will aim for approximately 75% of EER from fat, 5% from CHO, and the remaining from protein. Additionally, participants following the MKD will be recommended to supplement with a CHO-free multivitamin in accordance with best practice guidelines (49).

## 2.3 Control diet

The study's control group adheres to a 12-week regimen of dietitian-led and medically supervised nutrition, aligning with the principles outlined in the Australian Guide to Healthy Eating (AGHE). Macronutrient intake, including carbohydrates, fat, and protein, is calculated to match individual factors such as age, weight, and level of

physical activity as set out in the guidelines. Within this framework, the recommended optimal macronutrient ranges from the AGHE are encouraged, with protein comprising 11%, fats ranging from 20 to 35%, and the remainder from carbohydrates (see Table 3) (51).

# 3 Psychiatric outcome measures

## 3.1 Positive and negative syndrome scale

Positive and Negative Syndrome Scale (PANSS) is among the most-validated instruments for assessing positive, negative, and general psychopathology associated with schizophrenia. The PANSS is a standardized clinical interview that rates the presence and severity of positive and negative symptoms, as well as general psychopathology for people with schizophrenia within the past week. Of the 30 items, seven are positive symptoms, seven are negative symptoms, and 16 are general psychopathology symptoms. Symptom severity for each item is rated according to which anchoring points in the 7-point scale (1 = absent; 7 = extreme) best describe the presentation of the symptom (52). Positive and negative scales showed good inter-rater reliability and interclass correlation coefficients (ICC) of 0.72 and 0.80, respectively. Inter-rater reliability was moderate for the general psychopathology scale; ICC = 0.56 (53).

## 3.2 The young mania rating scale

The Young Mania Rating Scale (YMRS) is a clinical interview scale and is one of the most frequently utilized rating scales to assess the severity of manic states in bipolar affective disorder. The scale has 11 items and is based on the patient's subjective report of his or her clinical condition over the previous 48 h. Additional information is based on clinical observations made during the clinical interview. The items are selected based on published descriptions of the core symptoms of mania. The YMRS follows the style with each item given a severity rating. Four items are graded on a 0 to 8 scale (irritability, speech, thought content, and disruptive/aggressive behavior), while the remaining seven items are graded on a 0 to 4 scale. These four items are given twice the weight of the others to compensate for poor cooperation from severely ill patients (54).

## 3.3 World health organization disability assessment schedule, version 2

The World Health Organization Disability Assessment Schedule, version 2 (WHODAS 2.0) is the standard measure of disability promoted by the World Health Organization. WHODAS 2.0 is a patient-reported outcome instrument that uses 36 questions to assess the global health status of patients across 6 health domains, i.e., Cognition, Mobility, self-care, social interaction, life activities, and social participation. The WHODAS 2.0 is a validated and established questionnaire that can be used to assess the health status of patients irrespective of disease (55).

## 3.4 The Beck depression inventory

The Beck Depression Inventory (BDI) is one of the most widely used measures in both research and clinical practice for assessing depression. BDI is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms according to diagnostic criteria listed in the Diagnostic and Statistical Manual for Mental Disorders. BDI demonstrates high internal consistency, with alpha coefficients of 0.86 and 0.81 for psychiatric and non-psychiatric populations, respectively (56).

## 3.5 The affective lability scale 18

The Affective Lability Scale 18 (ALS-18) is a valid and reliable instrument for measuring affect lability. ALS measures individual proneness to rapid shifts from the different emotional states of anxiety, depression, anger, and hypomania (57). The ALS-18 item version is based on a three-factor model of affective lability (anxiety/depression, depression/elation, and anger), with each factor retaining at least two items from each of the original six subscale versions. ALS-18 is highly correlated with the original 54-item version ($r = 0.94$).

# 4 Assessment of cognitive function

Cognitive functioning at baseline (T0) and post-intervention (week 14, [T3]) will be assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB). CANTAB measures are a reliable, valid, sensitive way of collecting comprehensive and accurate information on cognitive functioning in a clinical sample (58). Test batteries are delivered digitally using an iPad, allowing for standardized data collection at multiple time points and automated creation of comprehensive data sets. The level of information provided by each CANTAB measure allows for in-depth analysis of highly specific components of cognitive functioning providing specific insight into intervention efficacy within the context of a much wider dataset (59, 60). A customized test battery, consisting of 7 separate neuropsychological assessments (Table 4) was designed for data collection during this clinical trial.

TABLE 3 Ketogenic diet vs. the Australian guide to healthy eating.

| Ketogenic diet | Australian guide to healthy eating |
|---|---|
| • < 50 g of carbohydrates per day<br>• Total daily calories:<br>o 70–80% fat<br>o 5–10% carbohydrates<br>o 10–20% protein | • Plenty of vegetables of different types and colors, and legumes/beans<br>• Fruit<br>• Grain (cereal) foods, mostly wholegrain and/or high cereal fiber varieties, such as<br>• breads, cereals, rice, pasta, noodles, polenta, couscous, oats, quinoa, and barley<br>• Lean meats and poultry, fish, eggs, tofu, nuts and seeds, and legumes/beans<br>• Milk, yogurt, cheese, and/or their alternatives, mostly reduced fat |

TABLE 4 CANTAB neuropsychological test aspects.

| Neuropsychological test (CANTAB) | Test variation | Administration time (Min) | Outcome measures |
|---|---|---|---|
| Motor Screening Task (MOT) | Voice | 2 | – Accuracy<br>– Difficult/speed adjustment |
| Spatial Working Memory (SWM) | Recommend Standard Tone 2.0 | 4–6 | – Errors<br>– Incorrect selection, reselection |
| Emotional Recognition Task (ERT) | Short (Caucasian) | 6–10 | – Correct recognition<br>– Response latency |
| Rapid Visual Processing (RVP) | 1 Target Tone | 7 | – Response latency<br>– Probability of false alarms<br>– sensitivity |
| Paired Associated Learning (PAL) | Recommended Standard Tone | 8 | – number of errors<br>– number of trails required<br>– memory scores<br>– stages completed |
| One Touch Stocking of Cambridge (OTS) | Short | 10 | – number solved on first choice<br>– Mean number of choices to solve<br>– Mean latencies |
| Cambridge Gambling Task (OTS) | Ascending First Shortened Tone | 12–18 | – Risk-taking<br>– Decision-making quality<br>– Decision time<br>– Risk adjustment<br>– Delay aversion<br>– Impulsivity |
| Total administration time | | 49–61 | |

## 5 Clinical laboratory measures

*Anthropometric biomarkers*: Bodyweight will be measured using an electric scale (two decimal accuracies), while the standing height will be measured by a stadiometer at baseline, week 8 and week 14. The body mass index (BMI) will be calculated using these measures.

*Cardiovascular biomarkers*: At each visit, blood pressure will be measured using an Omron HEM7 120 Blood Pressure Monitor. Blood pressure will be measured from the left arm while the participant is seated and at rest. Two readings will be collected for systolic and diastolic blood pressure. Heart rate will likewise be assessed at a resting position using the Omron HEM7 monitor.

*Metabolic biomarkers*: Fasting peripheral blood will be collected in participants at baseline, week 8, and week 14. 0.5 mL of whole blood will be transferred from the EDTA tube to a new tube and frozen until analysis. The remaining samples will be spun at 3000 rpm for 10 min. Serum and Plasma will be transferred to new tubes and frozen at −80 degrees Celsius until analysis. From the samples, the metabolic biomarkers: triglycerides, high-density lipoprotein (HDL-c), low-density lipoprotein (LDL-c), total cholesterol (TC), insulin, glucose, and HbA1c will be measured.

*Immune biomarkers*: Interleukin-6 (IL-6), IL-12, tumor-necrosis-factor (TNF) alpha, albumin, fibrinogen, and c-reactive protein (CRP) will be assessed using the collected blood.

*Neuroendocrine biomarkers*: Dehydroepiandrosterone sulfate (DHEAS) will be assessed from the collected blood samples, while cortisol concentrations will be assessed from hair samples collected at baseline and week 14 using the Salimetrics Saliva Cortisol ELISA kit.

## 6 Randomization

For this study, stratified randomization will be used. We will stratify by assuming eight groups based on the following criteria: diagnosis (schizophrenia or bipolar disorder), gender (male or female), and duration of illness (DOI; more or less than 5 years). Groups will be divided as demonstrated in Figure 2.

Each of the stratified groups will be randomly allocated into either KD or AGHE. The allocation will be concealed from the investigators and will only be known by the Clinical Research Coordinator. Each subsequent entry to each stratum will be sequentially followed, thereby creating a stratified, random allocation. Recruitment for this trial will be continuous for 18 months or until the required participation number has been reached.

## 7 Measurement tools used

### 7.1 Wearable devices

An Oura ring (Ōura, Oulu, Finland) and an Embrace wristband (Empatica, Cambridge, United States) will be offered to all participants to wear for a week during the introductory

period before starting the diet (week 1 [T1]) and during week 14, just before finishing the diet. This measurement is optional and can be selectively opted out by the participant. Sensor biomarker data including heart rate (HR), heart rate variability (HRV), and electrodermal activity (EDA) from the Oura and Embrace devices will be utilized to provide an overall autonomic nervous system (ANS) stress score, using a pre-trained machine learning model previously shown to be a reliable predictor of acute stress (61).

### 7.2 Stool collection

It will be optional for all participants to supply a stool sample at the start of the trial (prior to T1) and again at the end of the trial period (week 14) for the future analysis of changes in the fecal microbiome composition and its metabolites. The participant will be supplied with a self-collection kit during the Week 0 assessment, and they can collect the specimen at home at their earliest convenience. The kit can be posted to the research team.

### 7.3 Hair collection

It will be optional for all participants to supply a hair sample at the start of the trial (prior to T1) and again at the end of the trial period (week 14) for future analysis of cortisol to assess the cumulative impact of the biological stress response over time. The small sample (5 mg) will be taken by a researcher during the physical assessment.

### 7.4 Glucose and ketone measurement

Ketone and glucose levels will be monitored by the participants from home. A "blood glucose plus beta-ketone monitoring system" and test strips will be supplied to all participants. The participant will be required to take daily samples by finger prick (1.0 uL blood) 2 h before eating dinner. The monitor system will inform the investigators and the participants about the time spent in ketosis. During the week 0 assessment, participants will be asked a preference to inform us about their daily ketone and glucose results. This may also include a daily reminder text to the participant if they prefer. The participant can choose to either upload a photo of the result to a phone used during the trial, text-message the result to the phone or they can choose to receive a daily phone call and talk to a team member. The trial phone will be monitored by a team member 24/7.

## 8 Data analysis

### 8.1 Sample size and statistical power

The optimal sample size is calculated based on a statistical power of 90% and a significance level of 0.05 (two-tail). To calculate the sample size, we have estimated the incidence of significant improvement in primary or secondary outcome measures to be 75% in group 1 (individuals on the KD) and 40% in group 2 (individuals on the AGHE diet). We will aim for a 1:1 enrolment ratio.

Using these values, our estimated sample size is 80 individuals (40:40), however, considering a dietary intervention attrition rate of at least 20%, we will aim to recruit 100 individuals (50:50).

### 8.2 Data analysis plan

The analysis of the biological samples will be conducted by biomedical staff at James Cook University overseen by the James Cook University Specialist in Clinical Biochemistry and Clinical Research Coordinator of the Australian Institute of Tropical Health and Medicine. This will follow standard analytic pipelines established in these units.

We predict that analyses of observed data will be largely descriptions of response, adherence, and distributions of values. Simple correlations between study parameters will follow standard statistical methods and the assistance of a statistician has been sought to define the statistical plan before the research plan is finalized. Software packages will include SPSS (v28) and *R* (v4.2.1).

In line with Burgess et al. (62) and many other modern statisticians who have described the procedure of hypothesis testing on baseline characteristics as unnecessary and potentially harmful (63), we will present the distribution of baseline information of intervention groups in a simple table, allowing readers to compare the extent of similarities, each with a mean and percentage value for both treatment groups separately. Additional co-variables may likely be at play, especially socioeconomic status, BMI, and severity of illness. Therefore, a degree of covariate adjustment is expected at the statistical calculation stage. Logistic regression and Analysis of Covariance are likely going to be incorporated into the data analysis plan.

For our quantitative endpoints (e.g., on psychiatric scales and metabolic parameters), linear mixed effects (LME) models will be used to compare the intervention and control groups. If normality cannot be assumed, a logarithmic transformation of the response variable will be performed to meet the assumption of normality. Mixed-effect logistic regression will be used for binary endpoints and longitudinal data. If data normality cannot be achieved, a comparison of our variables of interest between groups will take place using non-parametric tests, e.g., the Mann–Whitney U test. All analyses will be conducted by an intention-to-treat (ITT) approach using all available data, including those who were not to complete the study. Patient data will be analyzed per their original treatment allocation. All data analyses will be performed using 5% significance levels and audited by several members of the research team to ensure accuracy before submission.

## 9 Discussion

The rationale for this randomized controlled clinical trial is based on a converging line of evidence coming from recent studies showing a variety of brain bioenergetic abnormalities in

schizophrenia and bipolar disorders, prior preclinical research demonstrating the efficacy of the ketogenic diet in animal models of schizophrenia, as well as recent encouraging results from case studies and pilot, single-arm clinical trials that indicate clear symptom improvement and better metabolic control in patients with serious mental illness on a ketogenic diet. We expect that the dietary metabolic interventions in our trial will result in beneficial changes in symptoms, everyday functioning, and overall metabolic health for our participants. The control diet, based on the AGHE guidelines, is likely superior in terms of its health effects compared to the participants' usual dietary patterns because of its focus on incorporating whole grains, dietary fiber, plant-based proteins, and unprocessed food. We expect that the ketogenic metabolic therapy, with its targeted effect on brain and systemic energy metabolism, will result in further improvements in metabolic health, controlling psychiatric symptoms and improving overall functioning, above and beyond the control diet. In addition to establishing efficacy, our design will allow the assessment of the participant's compliance with and adherence to a relatively restrictive dietary schedule that requires major deviations from their usual diet. This will be important for future dietary metabolic interventions in serious mental illness, where patients are generally perceived to be struggling with such challenges.

In case of demonstrated efficacy, it is crucial to understand the mechanism of action of this novel metabolic intervention to give informed advice to the psychiatric community on any potential change in clinical practice. Our trial will collect data from different domains, including systemic metabolism and inflammatory processes, autonomic nervous system activity, sleep patterns, and changes in the gut microbiome. Outcome measures from these systems, when correlated with improved psychiatric symptoms, cognitive functions, and overall daily functioning will inform us about the potential involvement of underlying mechanisms. With regards to mechanisms of action of dietary intervention, the possible mediating role of the gut microbiome is of primary importance as the ecosystem of the bacteria in the gastrointestinal system interacts with the consumed diet even before the different nutrients and other food-derived molecules get into the bloodstream (64–67). It is conceivable that some of the effects of the ketogenic metabolic therapy may be mediated by the gut microbiome, either directly through microbiome-derived metabolites that reach the brain or indirectly through changes in the enteric nervous system activity. We aim to establish such a role for the gut microbiome by demonstrating ketogenic diet-related changes associated with symptom improvement. Ketone bodies, beta-hydroxybutyrate, and acetoacetate are the metabolic products of the liver while on the ketogenic diet (36). Ketones have been shown to directly benefit brain bioenergetics (68, 69). The daily ketone monitoring will make it possible not only to confirm adherence to the ketogenic diet but also to correlate ketone levels with daily changes in the self-reported energy levels of the participants. Alterations in autonomic nervous system activity and sleep have been widely reported in schizophrenia (70) and bipolar disorders (71, 72). The ketogenic diet seems to be effective in influencing these functions. Therefore, the potential mechanistically important role of autonomic nervous system activity and sleep health can be uncovered by monitoring these functions using wearable devices before the introduction and at the end of the dietary intervention. Although human studies are rarely designed to include an experimental intervention that directly informs about exact mechanisms of action, the complex analysis of multiple, interacting systems will show biomarkers that are specifically modified by the treatment and associated with improvements in different symptom domains.

Our trial design has some limitations. Firstly, despite our best efforts to keep the overseeing psychiatrists blind to the dietary arm allocation of individual participants, we cannot rule out the possibility that some participants may disclose their diets during the psychiatric assessments in the middle or at the end of the trial. Also, an argument can be made that some of our motivated participants may have information about the expected benefits of the ketogenic metabolic therapy in their condition, which could conceivably introduce an expectation bias if assigned to the ketogenic arm of the trial. We will, however, obtain their daily blood ketone levels which can be correlated with the results of the psychiatric and cognitive assessment, and give an objective control measure to address the above limitations. Another possible limitation is that due to the nature of this clinical trial conducted in an outpatient setting, relying on the ability of the participant to adhere to a relatively restrictive dietary regime independently, the recruited participants will be better functioning than some other patients with serious mental illness, resulting in a self-selected study population. We acknowledge this limitation, but we argue that although we might be able to demonstrate better adherence in this self-selected group, it may be a strength of the trial to demonstrate symptom improvement in participants who may be somewhat better functioning already. Additionally, demonstrating adherence to a restrictive dietary regimen by a population with severe mental disorders in the community may in itself be regarded as a satisfactory outcome measure.

In conclusion, we expect this randomized controlled clinical trial to assess the feasibility, efficacy, and safety of ketogenic metabolic therapy in schizophrenia and bipolar disorder. To our knowledge, our proposed trial is the first of its kind worldwide. We hypothesize that this study will reveal improvements in symptoms, overall quality of life, and better metabolic functioning for our participants. Results from this trial may inform future studies on more specific mechanisms of action, as well as introduce a novel treatment modality to manage psychiatric disorders that would otherwise have been considered as long-term, debilitating conditions.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving humans were approved by the Human Research Ethics Committee of Townsville University Hospital and James Cook University [HREC/2022/QTHS/85408 and JCU (James

Cook University) C45]. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

CL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. SF: Data curation, Methodology, Project administration, Software, Writing – original draft, Writing – review & editing. IP: Data curation, Project administration, Visualization, Writing – review & editing. J-LS: Conceptualization, Data curation, Methodology, Project administration, Supervision, Writing – review & editing. FF-M: Conceptualization, Methodology, Validation, Writing – review & editing. TB: Conceptualization, Funding acquisition, Methodology, Resources, Writing – review & editing. GV: Data curation, Formal analysis, Methodology, Visualization, Writing – review & editing. DR: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing. OS: Project administration, Writing – original draft, Writing – review & editing. SG: Project administration, Writing – review & editing. MA: Formal analysis, Methodology, Software, Supervision, Writing – review & editing, Conceptualization, Data curation. IC: Conceptualization, Methodology, Resources, Validation, Writing – original draft. SS: Conceptualization, Methodology, Supervision, Validation, Writing – review & editing. CP: Conceptualization, Funding acquisition, Methodology, Supervision, Validation, Writing – original draft. ZS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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## Conflict of interest

FF-M was employed by the company FoodiQ Global.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

## Publisher's note



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# Signals of energy availability in sleep: consequences of a fat-based metabolism

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Humans can flexibly switch between two primary metabolic modes, usually distinguished by whether substrate supply from glucose can meet energy demands or not. However, it is often overlooked that when glucose use is limited, the remainder of energy needs may still be met more or less effectively with fat and ketone bodies. Hence a fat-based metabolism marked by ketosis is often conflated with starvation and contexts of inadequate energy (including at the cellular level), even when energy itself is in ample supply. Sleep and satiation are regulated by common pathways reflecting energy metabolism. A conceptual analysis that distinguishes signals of inadequate energy in a glucose-dominant metabolism from signals of a fat-based metabolism that may well be energy sufficient allows a reexamination of experimental results in the study of sleep that may shed light on species differences and explain why ketogenic diets have beneficial effects simultaneously in the brain and the periphery. It may also help to distinguish clinically when a failure of a ketogenic diet to resolve symptoms is due to inadequate energy rather than the metabolic state itself.

KEYWORDS

**adenosine, AMPK, ketogenic diets, metabolism, ROS, sleep, satiety, orexin**

## 1 Introduction

Ketogenic diets (KDs) result in a metabolic state distinct from that of non-ketogenic diets: regardless of caloric intake or exact composition, by definition a diet is ketogenic when it leads to a fat-based metabolism marked by sustained ketosis (1). The terms "fat-based metabolism" and "glucose-based metabolism" refer to the primary metabolic fuel in use, which can be measured by respiratory quotient (2). The process of shifting from a glucose-based metabolism to a fat-based one is referred to as "keto-adaptation" (3). The full complement of physiologic and metabolic differences between these states are many and still being elucidated; those most pertinent to energy signaling will be discussed below.

Although some studies and applications of KDs entail hypocaloric energy supply or even starvation, this attribute is not necessary for sustained ketosis in humans, which can be achieved in eucaloric or even hypercaloric conditions provided carbohydrate intake, and to a lesser extent protein intake, are restricted (4). The terms hypo-, hyper-, and eucaloric have an implicit assumption we would clarify, however. Typically when using these terms, experimenters establish a baseline level of intake per individual over a period of weight stability, and then assume for simplicity that this value is a fixed one for the individual. This is, of course, an oversimplification, because of metabolic adaptations, and can lead to absurdities if not phrased carefully.

For example, in a recent study of low carbohydrate, high fat diets (LCHFD) in mice (5), mice given an *ad libitum* obesogenic diet ate more and gained more weight than those on a standard control diet. Hence they were deemed "hypercaloric". However, some of them were then switched to an *ad libitum* LCHFD. Those mice continued to eat the same level of calories, but ceased to gain weight and reversed pathological symptoms. Although they were still eating food with caloric value roughly equal to the amount that was previously hypercaloric, they were technically no longer hypercaloric, but rather eucaloric at a higher caloric value than before. Critically, these isocaloric conditions both occurred *ad libitum*. That is, depending on the dietary composition, the mice ate to the point of extensive weight gain and metabolic disease in one case, but to weight stability and improved health in another.

This distinction is key for discussing satiation, since physiologically driven satiation can be determined, ultimately, only by observation of *ad libitum* intake. This means that satiation can occur independently of caloric balance, and has important implications for the success of dietary interventions. There are competing models for how food intake is regulated. The energostatic model for the control of food intake places the parameter of regulation on the cellular production of energy. As we will discuss, this model has been used to explain observations in obesity (6, 7) and further to explain connections between metabolism and sleep (8, 9). While a hypothesis directly linking satiation signals to sleep has been carefully described by Nicolaidis (10) (detailed below), what has been less explored before is the potential function of that connection. In this conceptual analysis, we attempt to show how sleep regulation by energy signals may fit into a functional theory of sleep.

Because low glucose availability implies low energy availability in the context of a glucose-based metabolism, but not in that of a fat-based metabolism, the biochemical signals corresponding to low glucose are sometimes mistaken for signals of inadequate energy despite the context of an energy adequate fat-based metabolism. The first aim of this article is therefore to describe the often overlooked differences between hypocaloric diets and eucaloric KDs, and to illustrate this with effects on sleep. Further, the model is used to reframe questions about the differential effects of sleep restriction and total sleep deprivation in human and non-human animal studies.

## 2 Ketosis and the "metabolic switch"

The phrase "metabolic switching" has been used to describe "the body's preferential shift from utilization of glucose from glycogenolysis to fatty acids and fatty acid-derived ketones" during fasting as a specialized mode that's beneficial to periodically turn on (11). Likewise, "the 'glucose switch' profile" is a description of a hysteresis-like mechanism in which hypoglycemia induces a more lipid-oxidation dependent state by reducing expression of genes that stimulate glucose use in mitochondria (12). This is argued to be beneficial for reducing or reversing the burden of diseases of aging if induced often enough to significantly reduce the lifetime exposure to glucose metabolism. However, switches by nature have multiple positions, and we might equally call a transition from a ketogenic metabolism to glucose utilization a "metabolic switch". That is, while the authors above portray a fat-based metabolism as a switch away from an implicit default, both modes are arguably valid defaults, as hysteresis works in both directions.

One reason that a glucose-based metabolism has been considered a default, is that much of what we know about the metabolic state of ketosis comes from studies in fasted humans or other animals, which makes fat-metabolism appear to be by necessity transient. While the basic biochemical profile is the same whether or not fat is being eaten, ketosis depends on a combination of low available glucose and glucose production substrate on the one hand, and high available fat on the other. In contrast to most other animals, humans have a high base level of body fat that perpetuates a ketogenic metabolism longer under starvation conditions than would otherwise occur before phase III starvation (see Box 1), characterized by higher rates of protein catabolism, sets in O'Hearn et al. (13). Nonetheless, many of the most informative current studies and reviews focus on the fasted state or otherwise calorically restricted ketogenic diets (KDs). An oft acknowledged drawback to this approach is that keto-adaptation, the full transition from glucose-based into fat-based metabolism, typically takes 2–5 days, and so conclusions drawn after only a few days of intervention may not fully characterize a ketogenic metabolism. A second disadvantage is that observations may result from low energy availability that would differ under fully fed ketogenic states.

### 2.1 Energy signals characterizing a fat-based metabolism

The biochemical profile associated with a fat-based metabolism includes, among many other differences relative to a glucose-based metabolism, elevated ketone bodies, adenosine, orexin, AMP-activated protein kinase (AMPK), and homeostatic responses to mitochondrial reactive oxygen species (ROS), including uncoupling proteins. Each of these participates in energy partitioning and signaling.

Ketone bodies have been described in different ways based on origin and function. For example, from an origin perspective, they've been called "byproducts of fat metabolism" [e.g., (14, 15)]. From a functional perspective, they are often though of as an "alternative fuel" to glucose for the brain [e.g., (16, 17)]. While these are accurate descriptions, it is more neutral to describe them as a *transport form of fat* able to cross the blood-brain barrier such that it can be used as an energy substrate *complementarily* to glucose. From a signaling perspective, ketone bodies inhibit muscle catabolism (18). When fat metabolism is high, as in phase II, endogenous glucose production can rely more on its byproducts glycerol and acetone for substrate, and lactate recycling from the Cori cycle (19). They also homeostatically regulate lipolysis (20).

Adenosine, AMKP, and orexin are considered energy sensors. Adenosine accumulates from the breakdown of adenosine triphosphate (ATP), but it is also a source of ATP (21, 22). Hence, high levels can indicate ATP being used faster than it is generated (23). Similarly, AMPK is activated by an increase in the ratio of AMP (adenosine monophosphate) to ATP, where AMP is another result of the utilization of ATP. Orexin is a neuropeptide. As

**BOX 1 Phases of starvation.**

The process of starvation has been divided into phases based on the primary fuel substrate: as repositories of each fuel type run out, metabolism shifts to catabolize the next. Assuming we start with ample glycogen stores, animals normally go through three phases: phase I, corresponding to a glucose-based metabolism; phase II, corresponding to a fat-based metabolism; and phase III, which is also glucose-based, but for which the primary source of fuel is protein from muscle catabolism.

This categorization based on primary substrate is useful even when there is no starvation. To avoid further conflation of energy inadequate and energy adequate very-low-carbohydrate conditions, we will sometimes use the hybrid terms *phase I/II/III metabolism*, which are agnostic about the whether the source is endogenous or exogenous, and have no implication of malnourishment, but still recognize the substrate type in use.

These distinctions highlight the lack of specificity of "fasting-mimicking" as a characterization of KDs.

suggested by its name, it is associated with hunger, and it is implicated in appetite, wakefulness, and energy expenditure (24). It is activated by low glucose levels (25–27). Mitochondrial ROS is a byproduct not of ATP use, but its generation, and so it also signals energy availability (see Section 6 below).

## 2.2 Mixed states

These two metabolic states, or modes, have biochemical signatures that generally reflect their complementary functions of building (anabolism) and clearing (catabolism), such that one stimulates and benefits the other. For example, brain-derived neurotrophic factor (BDNF) and fibroblast growth factor 21 (FGF21) have names and structures suggesting they are trophic factors, even though they are more expressed under a fat-based metabolism or catabolic states (28–30). In the case of BDNF, this has mechanistically been attributed to the ketone body beta-hydroxybutyrate, which increases BDNF when administered in various forms and which has also been implicated as the mediator of exercise-induced BDNF (31–35). FGF21 is more controversial in mechanism; there are mixed findings depending on species, tissue, and health of the subject (36–38). But FGF21 is consistently increased in prolonged fasting and protein insufficiency (38, 39) So these substances are stimulated by catabolic states, but functionally appear to be trophic or at least anti-catabolic (40). It has been argued that the growth itself is more stimulated by an anabolic switch, after their upregulation (11).

In general, a glucose-based metabolism reflects a more anabolic, or growth promoting phase, whereas a fat-based metabolism tends to reflect energy release from the breakdown of materials. But it must be emphasized that energy can be released from a baseline glucose-based metabolism (one does not have to be ketogenic to use fat stores, for example) and growth can happen while maintaining chronic ketosis, as evidenced by children on ketogenic diets for epilepsy or babies prior to weaning (41). This is because there can be signals of one mode within the other that don't persist long enough to fully change modes. This hysteresis is characteristic of bistable biochemical systems, which typically result from positive feedback loops or substrate inhibition cycles (42, 43). In particular, this is true of fatty-acid oxidation and glucose metabolism (43, 44). Signatures of one mode in the context of the other mode are normally transient, because if the stimulus persists, metabolism enters the other mode. Middle states are generally avoided, because metabolic regulation of gene expression exhibits hysteresis, such that states tend to attract their full expression and persist (12). Part of this is attributable to the Randle cycle, in which cellular uptake of glucose and fat tend to mutually inhibit each other (45). However, if signals remain mixed, this can be an indication of pathology. With a glucose-centric view of metabolism, this pathological mixed state is often erroneously identified with the signatures of a fat-based metabolism even when in context the signature is appropriate. Examples of this include ketosis conflated with keto-acidosis, or glucose intolerance with pathological insulin resistance (IR). Blagosklonny (46) refers to this latter phenomenon by describing fat metabolism as "benevolent pseudodiabetes".

## 2.3 Fat oxidation: low energy or high energy?

Metabolic processes associated with fatty acid oxidation (FAO) sometimes have opposing implications for energy status depending on metabolic mode. In the context of a glucose-based metabolism, relying mainly on fat oxidation is a marker of low energy status, because in order for FAO to gain prominence, the contextually primary substrate for energy, glucose, must be reduced. Relatedly, due to the fact that (long chain) fatty acids have longer carbon chains, they require more oxygen for their complete oxidation than glucose does. This is sometimes considered less efficient. When mitochondrial ATP is measured by oxygenation rate, as in Donohoe et al. (47), the spurious conclusion may be drawn that cells are in an energy deprived state, even when there is simultaneous evidence to the contrary, such as increased energy expenditure from voluntary locomotor activity. Similarly, the ratio of the oxidized and reduced forms of nicotinamide adenine dinucleotide, NAD+ and NADH, can be used as an indication of cellular energy-deprivation-derived stress (IBID.), even though it is also consistent with a switch to long chain fatty acids as a primary source of energy, with or without energy scarcity. Yet another example comes from the "energy sensor" AMPK, which increases in response to low energy availability (48). Yet under a fat-based metabolism, higher fat oxidation, ie. higher energy, is also associated with higher AMPK (49). This is further understood by noting that FGF21 stimulates AMPK (50), and FGF21 in turn can be stimulated by a variety of nutritional factors including ethanol, sucrose, and fat (51–54). Because these signals appear mixed, there have been calls for research to discover how KDs can be satiating, despite inducing hunger signals (55).

All of these examples can be reconciled by taking into account the background state. Glucose scarcity in a glucose-based metabolism stimulates signals that, if perpetuated, induce a

fat-based metabolism. The reverse is also true. As succinctly put by Mobbs et al. (12), "*a general feature of metabolic regulation is that substrates typically induce the metabolic machinery necessary for their own metabolism.*" But this also implies that high levels of circulating fat will induce features of a fat-based metabolism even when glucose remains high. This creates an important asymmetry, because the presence of glucose prevents full fat adaptation, resulting in discordant signals sometimes indicative of type 2 diabetes.

# 3 Common pathways in satiation and sleep

## 3.1 Measures vs. functions

It turns out there many common pathways in the regulation of hunger and satiation on the one hand, and sleep and waking on the other. To discuss these, it will be helpful to distinguish between a biological state, its measurable markers, and the functions that use these markers as signals (Box 2). In particular, many competing theories of hunger and of sleep differ in their proposed variable of regulation. It matters, for example, whether our theory presupposes that sleep duration is homeostatically regulated, or whether sleep duration is a consequence of some other homeostatically regulated variable. In this section, we will review evidence that the primary regulated variable in both satiety and sleep is energy availability, and that this commonality underlies their overlapping pathways.

## 3.2 Satiation, satiety, and the energostatic model

Satiation is the component of cessation of desire to continue eating attributable to physiological signals– as opposed to desires based on external factors that could supersede attention to such signals, for example, the desire to escape a predator, or the desire to curtail a meal based on belief that reduced eating will improve physical fitness. Satiety is the analogous absence of desire to begin eating again, and thus can be thought of as the persistence of satiation signals across time.

The energostatic (or ischymetric) model of satiety, originally introduced by Booth (56), uniquely acknowledges satiety regulating effects of energy production at the cellular level agnostic of source. For an in-depth explanation of this model [see Friedman (6)]. A key insight of the energostatic model is that of locating the parameter of regulation to *energy production* rather than body fat or energy balance *per se*. Hence, for example, obesity is seen not as a result of dysregulation of the homeostatic control of a fat mass set point, but of adaptation to energy production challenges. Accordingly, sensed energy, not fuel, stores, or other "potential energy" (which may or may not actually become ATP), is the mechanism leading to satiation. An important result of the focus on energy sensing is that it helps elucidate tight, bidirectional links between sleep and energy homeostasis.

## 3.3 Measures and functions of sleep

While there are many measurable aspects of sleep, we will focus on duration for each of the two main sleep stages, rapid eye movement (REM) and non-REM (NREM), and the intensity of slow wave activity (SWA) during the latter. REM is characterized by brain activity strongly resembling that of waking, and it was therefore originally called "paradoxical" sleep by Michel Jouvet in 1959 (57), whereas brain activity is reduced and differently patterned in slow wave sleep (SWS).

The drive to sleep has primarily been associated with SWA, such that its absence creates pressure for sleep that is relieved only by SWA. Increased sleep pressure leads to higher intensity of SWA, rather than longer duration. Sleep is therefore normally considered to be homeostatically regulated via SWA. Although there are at least a dozen published theories describing the relationships between NREM and REM (58), much data supports a dependence of REM on NREM suggesting that REM is at least partially homeostatically regulated by SWA (58–60) However, REM is also subject to increased drive when suppressed independently of NREM. Unlike the case with NREM, it is REM duration that appears to be regulated, such that there is a rebound of increased duration after suppression (61). The mechanisms of REM drive are not known, but there is evidence that BDNF is required to stimulate it (IBID). However, BDNF expression also increases SWA in NREM sleep (62) leaving the possibility of common causes in the regulation of both stages.

While the full complement of the functions of sleep is yet to be elucidated, the basic intuition that sleep is restorative and anabolic is at best incomplete, partly because the functions of REM and NREM evidently differ, and partly because some consequences of sleep are clearly more catabolic than anabolic. On the one hand there is evidence of protein synthesis (63). On the other, for example, during NREM sleep there is clearance of metabolites and toxins (64). There is also extensive synaptic pruning, leading to the synaptic homeostasis hypothesis (65), which proposes that continuous learning during waking periods make the brain too expensive to operate, such that synapses must be regularly pruned to allow learning to continue. Hence there is a "restoration", but the restoration is not only one of rebuilding lost tissue, but also tearing tissue down.

**BOX 2 Markers and signals.**

A marker of a biochemical process is just a consistently detectable output that thereby reliably indicates the presence or degree of that process. However, any such reliable indication can therefore carry information to other processes, hence becoming a signal. For example, the presence of high levels of ketone bodies in the bloodstream contains the information that protein derived from muscle is less required than under the same low glucose condition with lower fat oxidation as in phase III metabolism (see main text).

Benington and Heller (66) first suggested that NREM sleep may function to restore brain energy. They reasoned that the increased release of adenosine synthesized from AMP that is associated with increasing sleep intensity must either reflect compromised metabolic supply or increased metabolic demand. The latter was rejected as unlikely due to the observation that neurons are quiescent during slow wave sleep. While it is true that energy use does thus decrease, it is also notable that the onset of NREM is accompanied by a surge in ATP generation from a variety of substrates including glycogen, lactate, and adenosine accumulated during waking (67). Moreover, wakefulness and low energy supply are strongly linked, as discussed below. This link is so reliable that the following hypothesis was formed.

### 3.4 Nicolaidis' hypothesis of satiation and sleep

Based on multiple lines of experimental evidence, Nicolaidis (10) proposed the following hypothesis: "Whenever a neurosubstance is shown to induce satiety, it may also be somnogenic, and it should also increase the background metabolic rate. Conversely, whenever a neurosubstance is shown to be orexigenic, it should also promote wakefulness and, at the same time, decrease the background metabolic rate." The hypothesis is motivated by the following observations on energy balance and sleep.

## 4 Energy balance in sleep

### 4.1 Duration relationships

While short sleep is considered a risk factor in obesity (68), many studies have found a direct relationship between weight gain and sleep duration: animal studies have found increases in NREM and in some cases REM proportionate to induced weight gain (but not energy intake *per se*), and decreases during loss (69–72). In humans, it has been noted that anorectics sleep less than non-anorectics, that this reduction is rescued in recovery, and that obese people losing weight also have reductions in sleep (73). This reduction appears to effect mainly REM sleep, suggesting that while SWS is promoted by energy use, REM has a stronger requirement for energy availability. This is supported by the fact that other high REM situations are associated with fat gain, such as in infancy (74) and after high carbohydrate meals (75). It is also part of the basis of the energy allocation model of sleep (76), which posits that REM requires so much energy that it shuts down peripheral energy use, such as thermoregulation, in order to reallocate that energy for its functions while minimally affecting total expenditure.

Sleep duration is also positively related to energy intake of the previous meal (8, 9), but, importantly, this effect was not observed by these authors in fat animals under the initial days of starvation. This suggests that it is not the weight loss itself that causes short sleep, but rather the low availability of energy; animals that are able to provide adequate energy from stores do not have reduced sleep duration.

Along the same lines, a group of 80 overweight humans with chronic short sleep spontaneously ate less and lost weight when subjected to sleep extension from <6.5 to 8.5 h time in bed (77). As energy expenditure was not changed, the implication is that mild sleep restriction would likewise increase energy intake without increasing energy expenditure. Spontaneous reduction of intake is particularly interesting because it implies that there has been an increase in energy use from body stores contributing to earlier satiation. This contrasts with weight loss from caloric restriction, which may take place in the absence of physiological satiation, suggesting that energy needs are not fully compensated for by fat stores, and total energy is inadequate. Thus, Tasali et al.'s results are consistent with sleep restriction reducing the ability to use glucose via inducing a 'mixed state", hence reducing available energy from food which then must be "lost" to fat storage. These concepts are illustrated in Figures 1A–D. Like the case above in which over-fat animals did not lose sleep during the initial days of starvation because using their fat mass made up the difference in energy, in these subjects, sleep extension was associated with continued satiation, even though they ate less. These apparent counter-examples to the general association between weight loss and reduced sleep reveal a refined association by taking into account energy use: weight loss is associated with shorter sleep when it is accompanied by low energy access, but may accompany normal duration of sleep when energy access is adequate.

### 4.2 The effects of a fat-based metabolism on sleep

The effects of fasting and KDs on sleep have been reviewed previously (78). While there have been normalizations of pathological REM duration, the primary effect of a ketogenic metabolism is an increase in SWS. O'Hearn hypothesized that increased brain energy as a result of the KD is responsible for the increased SWA, and that this may be a contributing factor to the cognitive and neurological benefits of KDs. An important observation in that discussion is that orexin signals hunger and wakefulness in the context of a glucose-based metabolism, because it is a marker of low glucose, but in the context of an energy adequate KD, it is high despite satiety and normal sleep duration. Increases in adenosine were also noted (IBID). Accordingly, it was further suggested that the simultaneous increases in adenosine and orexin, which are normally in signaling opposition—adenosine signals satiety and sleep, whereas orexin signals hunger and wakefulness—permit higher levels of adenosine to accumulate with less sleep pressure, which could contribute to the anti-convulsant (79–84) and anti-depressant (85) properties of adenosine without compromising wakefulness.

## 5 Sleep deprivation and metabolism: apparently conflicting data

Sleep restriction (SR) is a form of partial sleep deprivation characterized by reduced sleep duration. SR has often been compared with total sleep deprivation (TSD). For example,

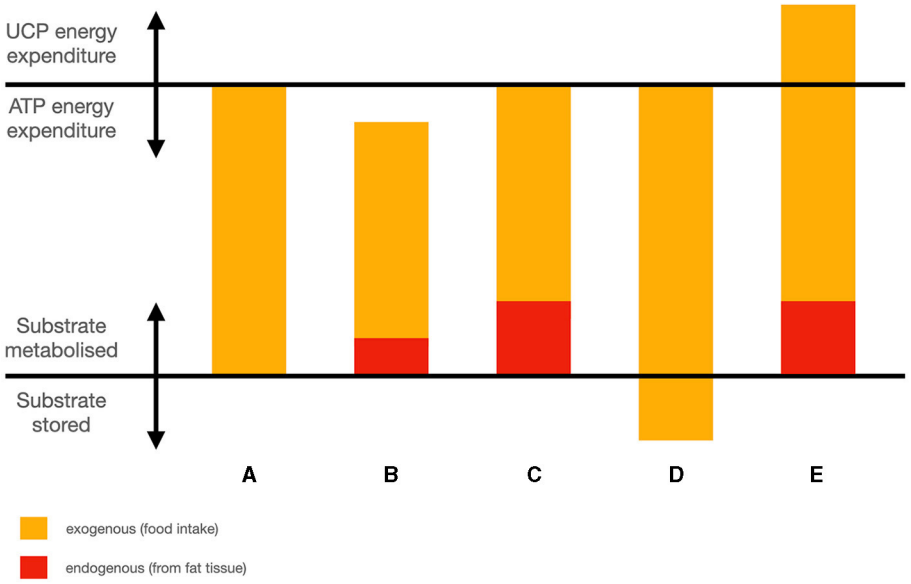


FIGURE 1
Simplified schematic of fuel partitioning components: **(A)** weight stable; **(B)** weight loss, energy inadequate; **(C)** weight loss, energy adequate; **(D)** higher intake, weight gain; **(E)** higher intake, weight loss.

Van Dongen et al. (86) compared impairment from accumulated SR to that from TSD. As those authors show, at least in some ways sleep deficit may produce a dose-response effect, with TSD inducing the most extreme rate of accumulation. This approach has been followed by others, for example, Lim et al. (87) compare them for resulting sleepiness and risk taking, Groeger et al. (88) compare them for positive and negative affect changes, and Dennis et al. (89) compare them in resulting compensatory eating. These kinds of similarities and the practical importance of SR as well as sleep fragmentation and circadian desynchrony in modern society has spurred more research comparing these types of sleep disturbances (90).

However, it is important to recognize that there can be qualitative differences between SR and TSD. For example, SR disproportionately affects REM compared to SWA (91–93). This architectural difference implies that SWA takes some priority, a finding with important implications for sleep homeostasis, as well as for the cause of behavioral and physiological impairments under SR (94). For this reason, SR and TSD must be compared with care. Also, because of this cumulative property, predictions of performance based on TSD do not translate with equal accuracy to SR without taking sleep history into account (95).

In the context of studying the potentially causal relationships between sleep deprivation (SD) and obesity, previous authors have observed the puzzling contrast between the negative energy balance in rats induced by TSD, despite the positive correlation between short sleep and obesity in human populations (96, 97). On the one hand, as mentioned above, short sleep is considered a risk factor for obesity. This is based partly on evidence from observational studies, such as from (68, 98, 99). The latter form part of the basis of the oft-cited recommendation on healthy sleep duration: obesity has the lowest prevalence at somewhere between 7 and 8 h per night. Longer sleep is also more correlated with higher weight, but this is reasoned to be due to a common cause, where longer sleep is due to conditions that cause fatigue or other disability leading to lower energy expenditure. On the other hand, the association with short sleep is thought to be a result of glucose intolerance and IR. Short sleep in the acute-term reliably results in higher blood glucose responses to meals (100, 101). Since loss of blood sugar control is an early sign of diabetes which is closely related to obesity, it would stand to reason that repeated exposure to this glucose intolerance adds up to the observed long-term association. Moreover, short sleep increases appetite (99).

However, animal studies on total sleep deprivation (TSD) tell a mostly opposite story. It takes rats about 2–3 weeks to die from TSD (102). Before death, TSD reliably results in reduction in core temperature, elevated energy expenditure, weight loss despite hyperphagia, increased catecholamines, and reduced thyroid hormones (103–105). The elevation in energy expenditure is caused by mitochondrial uncoupling (103) to such a degree that before death, rats are expending more than twice baseline rates (106). In mice, ketone bodies are reportedly elevated in the brain (107) indicating inadequate glucose supply, along with increased AMPK (108) In many respects rodents respond to TSD as if experiencing starvation or adaptation to cold, even though food intake is increased and TSD did not reduce RQ in rat models, possibly simply because of their excessive carbohydrate intake (103) (see Table 1).

These pathways are not confirmed in humans, partly because we cannot expose them to TSD until death. TSD does result in a reduction in core body temperature (76). In studies on sleep *restriction* (SR) as mentioned above, hyperphagia is seen, but energy expenditure doesn't seem to rise enough to match. Energy expenditure does in fact rise, an observation that has been used to

TABLE 1 Energy signals in various states.

| | GB-F | GB-LG | KD-F | GB-TSD | GB-SR |
|---|---|---|---|---|---|
| KBs | – | – | + | + | – |
| orexin | – | + | + | + | + |
| AMPK | – | + | + | + | ? |
| mtROS | + | – | + | + | ? |
| UCPs | – | – | + | + | ? |

GB-F, glucose-base, fed; GB-LG, glucose-based, low glucose; KD-F, ketogenic diet, fed; GB-TST, glucose-based, total sleep deprivation (in rodents); GB-SR, glucose-based, sleep restricted (humans). "+" indicates elevated relative to a glucose-based metabolism in the post-absorptive phase. – and ? indicates mixed or incomplete research.

support the hypothesis that energy conservation is a function of sleep (63). But this observation is accompanied by the cautionary warning: "The finding that sleep deprivation increases energy expenditure should not be interpreted that sleep deprivation is a safe or effective strategy for weight loss as other studies have shown that chronic sleep deprivation is associated with impaired cognition and weight gain." (63).

## 6 The role of mitochondrial uncoupling and uncoupling proteins

Mitochondrial uncoupling refers to the process where the transfer of protons across the mitochondrial inner membrane during oxidative phosphorylation is disconnected from ATP synthesis, resulting in the generation of heat instead of storing energy as ATP. However, mitochondrial uncoupling is a subject of multiple controversies. First of all, other than UCP1, it is questionable whether the so-called uncoupling proteins result in uncoupling at all (109, 110). Second, the function of uncoupling when it does occur is disputed. One prominent theory is that mitochondrial uncoupling serves to protect against ROS (see below).

ROS are a normal byproduct of oxidative phosphorylation (111). Although unchecked it can lead to oxidative damage, as a byproduct of a process it is a marker, and hence it signals energy generation. In the hypothalamus, ROS signal satiety (112–115). It's also possible that they signal "satiety" in adipose tissue[1]. ROS have been implicated in IR, the inhibition of glucose uptake via GLUT4 (116–118). While this is normally conceived of as detrimental, because of the connection between IR and diabetes, glucose intolerance at the adipocyte means less adipose expansion. It is a natural cellular signal of "we don't need more energy."

At the same time, the hypothesis that ROS promote sleep (119) has been supported by experiments showing that SD causes oxidation (120–122), that antioxidants can reduce negative consequences of SD (122, 123) and further, that death by TSD can be prevented via antioxidant intake in drosophilia (124). In one model, this is explained by proposing that one function of sleep is to clear ROS (125). Hence they propose that sleep is regulated by ROS levels. A ROS theory of sleep function is thus consistent with Nicolaidis' prediction: ROS promote sleep and satiety, and ROS are an energy balance signal. If uncoupling is indeed a response to protect against ROS [but see (109)], then the extreme rise in energy expenditure in TSD would also support the ROS clearance function of sleep.

Returning to the criticism that most uncoupling proteins do not uncouple, it is notable that what they do have in common is an upregulation of processes related to lipid metabolism. UCP1 was the first uncoupling protein to be discovered, but is now considered further derived from other UCPs (126). It is associated with mitochondrial uncoupling in brown adipose tissue, which is more prevalent in non-human animals than in humans. UCP2 has a glucose sparing role, reducing the entry of pyruvate into the Krebs cycle and reducing insulin secretion (127). UCP3 enhances fat metabolism (128).

Given that SD promotes uncoupling proteins (129) and KDs promote uncoupling proteins (130–132), and likewise SD and KDs promote glucose intolerance that may be benign in the context of low glucose intake (see Section 2.2), the totality of the evidence suggests that SD is concordant with a fat-based metabolism (Table 1). Hence it is possible that the differences observed between rodent and human responses to SD are attributable to either (a) species differences in uncoupling protein activation, such that humans have hyperphagia without compensatory energy expenditure, (b) an incomplete response to SR, such that ROS first induce IR and only under longer periods of restriction activate uncoupling, or (c) a physiological mismatch between short sleep and glucose intake, such that glucose intake is not concordant with long wake times. The former discordance bears some resemblance to mismatches observed when circadian rhythms are disrupted–eating during times usually reserved for sleep also results in IR. In other words, SD under a glucose-based metabolism creates a metabolic mixed state.

## 7 Discussion

If, as posited by the energostatic model, "energy" is the parameter of regulation for satiety (or anything else), it still must be mediated by a signal or set of signals. Many signals that characterize a fat-based metabolism–ketone bodies, orexin, adenosine, AMPK–are at risk of conflation with signals of energy deficiency. That is, they can be present with or without satiation. Because KDs can result in weight loss, weight stability, or weight gain, we need to look at other signals to determine true energy status.

Mitochondrial ROS (mtROS) are a candidate exception, because they are signals of satiety in a glucose-based metabolism even though they are also signals of a high energy state in a fat-based metabolism; in the absence of glucose, FAO leads to ROS (as all energy generation does), but also becomes part of a cascade leading to uncoupling which in turn lowers ROS, allowing even more FAO (113). In other words, FAO in the absence of glucose initiates a hysteresis mechanism that helps to bootstrap the fat-based metabolism via increasing ROS tolerance through uncoupling and the resulting increased energy expenditure (Figure 2). Insofar as ROS reduction is an important function of sleep, it could help to functionally explain the previously observed overlap in sleep and satiety signaling. It could also potentially

1 I attribute this idea to Peter Dobromylskyj.

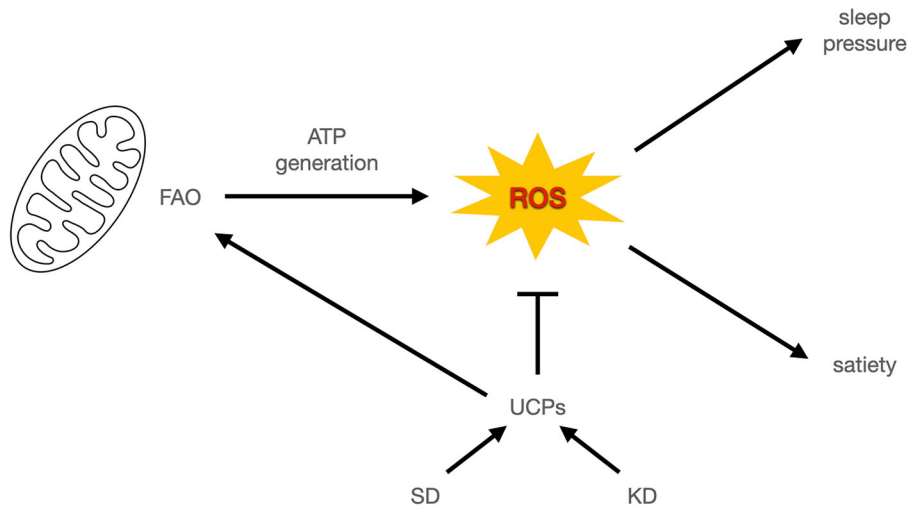


FIGURE 2
ROS signal energy status in sleep and satiety. In this model, mitochondrial ROS from energy generation signals sleep pressure and satiation. Uncoupling proteins enable more energy expenditure by reducing ROS and decreasing satiation. If this is accompanied by increased energy expenditure it leads to weight loss or weight maintenance at higher caloric intake. Otherwise it leads to weight gain.

explain why TSD in rodents increases hunger that cannot keep up with energy expenditure, if the uncoupling response to excess ROS burden increases without bound (Figure 1E). It also helps distinguish how a fat-based metabolism can improve sleep quality under fed conditions, even though starvation, which also has a ketogenic metabolic profile, compromises sleep. For a summary comparison of various states discussed and energy signals, see Table 1. A potential area of further investigation is the role of thermoregulation, given the connection of heat generation to uncoupling and the interactions between temperature and sleep quality.

Taken together, these observations support the conceptual framework of energy availability as the target of homeostasis that sleep and satiety regulate. That is, the signals that promote transitions between sleeping and waking on the one hand, and between eating and not eating on the other, are direct consequences of energy availability and use. This framework can then help to explain why KDs have such broad therapeutic value, through the common effect of energy availability in the brain and periphery. In the brain, many neurological and psychiatric disorders have been described as problems of energy access (133). Moreover, sleep problems are frequently comorbidities (134). Insofar as sleep quality reflects adequate energy, the beneficial effects of KDs on sleep may be seen as confirmation of their ability to restore brain energy. At the same time, adequate sleep allows further restorative processes that may directly contribute to therapeutic effects (78). In the periphery, *ad libitum* KDs treat obesity, not by sending signals of reduced energy availability that serve to induce catabolism of fat stores as in caloric restriction regimes, but by sending signals of *increased* energy availability (and hence satiety) when body fat is used. Use of fat for energy during a glucose-based metabolism would be a mixed state, and less likely to send clear satiety signals, with the exception of ROS. Surprisingly, high fat KDs can in some cases treat anorexia (135). While the mechanism for this is unclear, it may be a combination of brain energy effects and restored satiety signaling in response to fat intake.

## Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

## Author contributions

LO'H: Conceptualization, Writing – original draft, Writing – review & editing.

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## Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Therapeutic ketogenic diet as treatment for anorexia nervosa

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Anorexia nervosa (AN) is a severe psychiatric disorder. However, we lack neurobiological models and interventions to explain and treat the core characteristics of food restriction, feeling fat, and body size overestimation. Research has made progress in understanding brain function involved in the pathophysiology of AN, but translating those results into biological therapies has been challenging. Studies have suggested that metabolic factors could contribute to developing and maintaining AN pathophysiology. Here, we describe a neurobiological model for why using a therapeutic ketogenic diet could address key alterations in brain function in AN and prevent the desire for weight loss and associated eating disorder-specific symptoms. This translational model is based on animal studies and human data and integrates behavioral traits, brain neural energy metabolism, and neurotransmitter function. Pilot data indicate that the intervention can dramatically reduce eating and body-related fears, although larger studies across illness stages still need to be conducted.

KEYWORDS

**anorexia nervosa, metabolism, ketogenic, brain, behavior, treatment**

## Introduction

Anorexia nervosa (AN) is a severe psychiatric illness characterized by food avoidance, severe emaciation, and a perception of being overweight despite a very low body weight (1). AN is a chronic disorder with frequent relapse, high disease burden, and treatment cost (2–6). Treatment effectiveness, however, is limited (7, 8). AN has a mortality rate twelve times higher than the death rate from all causes of death for females 15–24 years old (5, 6, 9). AN shows a complex interplay between neurobiological, psychological, and environmental factors, and little is known about the pathophysiology or biomarkers that characterize AN when underweight or weight recovered (10, 11). Notably, in individuals with AN after weight recovery (wrAN), fears of weight gain, body dissatisfaction, and body image distortion are often elevated similarly or even higher compared to the underweight state, can persist for many years, and pose a risk for renewed self-starvation and relapse (4–6, 12–15).

Brain research before and after weight restoration has indicated alterations in circuits that compute reward valence or motivational salience of stimuli (stimuli that propel an individual's behavior toward or away from a particular stimulus), which, together with a conditioned fear of weight gain, may contribute to the vicious cycle of self-starvation (2, 16, 17). The neural basis of what drives self-starvation remains poorly understood (18). A better mechanistic understanding of what triggers and perpetuates core behaviors such as food restriction neurobiologically in AN and wrAN, besides an environmentally driven ideal of thinness, would help develop more effective treatments (11). However, important aspects of the AN pathophysiology are still largely not yet identified, and there is a lack of biological treatments available for AN when underweight, or relapse prevention after weight restoration, despite decades of brain research. In this

hypothesis and theory article, we propose a neurobiological model based on animal studies and human pilot data and integrates behavioral traits, brain neural energy metabolism, and neurotransmitter function, supporting a therapeutic ketogenic diet in AN.

## Neurobiology of AN

Brain research from various groups over the past decades has provided empirical data to better understand symptoms and behaviors in AN. Studies have found changes in the neurotransmitter systems for serotonin and dopamine in AN (8), altered brain structure, and more recently, tasks that engaged specific brain circuits that separated AN from healthy control groups (19–22). Those latter studies found evidence that AN is associated with altered brain function for processes involving the reward circuitry, cognition, emotion-regulating pathways, and regions that process executive function (21, 23, 24). Studies from our group, for instance, suggested that food avoidance and weight loss in AN alter circuits that process motivational salience (what stimuli to approach or avoid) and reward valence (whether expectations are violated) and involve cortical and subcortical regions that affect appetitive drive (16, 19, 25–33).

The primary brain regions that compute motivational salience and reward valence include the ventral striatum, insula, and orbitofrontal cortex (34). Another region, the amygdala, acts as an "early integrating" brain region for the salience of stimuli. It responds to expectation and triggers the dopamine response and associated behaviors in the nucleus accumbens and ventral striatum (35–37). Importantly, the frontal cortex processes whether an individual feels safe or whether a situation is associated with threat and fear, which activates those dopaminergic circuits to drive either approach or dread and avoidance (38, 39). Those mechanisms apply to AN, where fear of weight gain causes food and eating to become conditioned fear-inducing stimuli, leading to negative ruminations and ambiance (40, 41). The amygdala, in turn, responds to those fear and anxiety-inducing stimuli, modulates the dopaminergic motivational salience response, and triggers food avoidance (36, 42–44).

Individuals with AN overestimate their body size even when they are thin or underweight. Environmental factors, including thin-body messages from the media, may trigger those thoughts and condition a fear response (45–47). A "multisensory impairment of body perception" was proposed in some studies (48–50), but others suggested that affective factors drive body size overestimation in AN instead (50–53). Interestingly, some studies raised the possibility of a frontal cortical cognitive dysfunction in AN (54), and especially in restricting type AN, a psychotic-delusional component to the overvalued ideas of thinness could drive body size overestimation (55, 56). Those overvalued ideas may be driven by diminished sensory processing, which has also been associated with altered dopamine reward prediction error response (57). Brain dopamine activity is tied to glucose utilization, linking brain energy metabolism to a likely central aspect of AN neurobiology (57–59).

## Anxious traits and stress may affect brain metabolism in AN

Negative affect and deficits in regulating emotions, together with elevated anxious traits, are considered important for the etiology of AN (60–62). Unpleasant feelings such as anxiety, sadness, fear, or anger contribute to the negative affect experience and may drive AN behaviors (63). Worry, for instance, was related to fasting and fear of gaining weight or becoming fat in a sample of individuals with AN or wrAN (64). Stress and resulting negative affect may thus drive negative body image and body size overestimation (65, 66), consistent with ecological momentary assessment research showing that negative affect is involved in maintaining restrictive eating across AN subtypes (67–69). In wrAN, negative affect assessed over 2 weeks was related to a self-perception of inefficiency (70). Fear predicted increased dietary restraint, whereas dietary restraint predicted increased guilt and hostility (71). The importance of negative affect has been recognized already in youth with AN, and negative affect may contribute to developing AN (41, 72). Furthermore, difficulties with negative affect and emotion regulation persist long into recovery and may pose significant long-term risk factors for relapse (73).

It has long been known that stress affects glucose metabolism, altering blood sugar levels (74). Recent research has refined those studies. For instance, animal studies found that 40% of mice had a stress-susceptible phenotype associated with elevated blood glucose but reduced brain glucose metabolism, suggesting a specific mechanism in susceptible individuals (75). It was subsequently hypothesized that stress-related disorders could be associated with altered glucose metabolism (76). Research in humans indicated, for instance, altered brain glucose metabolism after acute stress using the Trier Social Stress Test (77), or in individuals with a chronic stress condition, posttraumatic stress disorder, showing lower brain glucose metabolism after administration of the stress hormone hydrocortisone (78). A recent study in cancer patients showed that negative affect was negatively correlated with glucose metabolism across cortical and subcortical brain regions, indicating global effects (79).

Those studies may have direct implications for the pathophysiology of AN or wrAN as self-perceived stress and sensitivity to negative affect may create a condition of chronic stress affecting brain glucose metabolism. This hypothesis is supported by studies that showed elevated baseline levels of the stress hormone cortisol in AN, altered cortisol response to a stressor compared to controls, and altered stress axis response that persisted in wrAN (80). That research directly associated stress and "psychological burden" with the biological stress response in AN, including stress axis function.

It has previously been hypothesized that the pathophysiology of AN may include metabolic abnormalities, or AN may be a "metabolic disorder of psychological origin" (81), which has only recently again received attention (82, 83). We propose, based on the above-described literature, that elevated anxious traits and distress over negative affect in individuals prone to AN interfere with brain glucose utilization and, thus, normal brain metabolism and function (84, 85).

## AN as a metabolic disorder

Several studies have found metabolic abnormalities in AN (81, 82) and associated elevated oxidative stress and inflammatory markers (86, 87). Recent genetic studies suggested that AN is associated with metabolic traits as a possible risk factor for developing the condition (88). A model that integrated biological and environmental factors hypothesized that anxiety and stress are critical factors in AN that drive altered glucose distribution between brain and body and induce changes in the lateral hypothalamus-pituitary–adrenal axis (89). That model is consistent with behavioral studies that indicated elevated

intolerance of uncertainty and anxiety in AN, triggering the body's biological stress response (90, 91). Stress leads to an increased allocation of glucose to the brain; however, while stress is associated with higher glucose *needs*, it is also associated with decreased glucose brain *utilization*, particularly in frontal cortical, thalamic, hippocampal, and temporal regions (85, 92, 93). In some individuals, this increased glucose requirement may deplete body energy resources; in others, reduced glucose utilization in the context of stress may lead to overeating (89, 90, 94). This model has been hypothesized to be relevant for psychiatric disorders, and computational models support the underlying premise (95, 96).

Research on the metabolic underpinnings of AN is still largely lacking. An animal study that evaluated glucose metabolism in nine female rats modeled AN brain response and randomized the animals to food restriction or regular food access (97). That study suggested *increased* glucose metabolism in the cerebellum but *decreased* metabolism in the hippocampus and striatum after food restriction. A few genetic studies suggested altered energy, including glucose homeostasis in AN (83, 98–101), and AN has been associated with altered glucose metabolism related to changes in insulin sensitivity (99). Others found mitochondrial dysfunction in AN related to oxidative stress and altered metabolic signaling (102), or metabolic dysfunction in the gut microbiome in AN that was opposite to that found in high-weight individuals (83). Those data, together with genetic markers, supported the possibility of critical metabolic targets that need to be identified for successful treatment development for AN (83). Only a few human brain imaging studies have investigated glucose metabolism in AN compared to healthy controls, and the samples were generally small and results inconsistent. One earlier study found glucose *hypometabolism* in AN ($n = 10$) that tended to normalize with weight gain (103), while another found glucose *hypermetabolism* in a small sample ($n = 5$) in cortical and subcortical regions (104). Another study in underweight AN ($n = 14$) found *lower* regional glucose metabolism in the anterior and posterior cingulate, dorsolateral prefrontal cortex, left middle temporal, and right superior temporal gyrus (105). After hormone replacement in six individuals with AN, regional glucose metabolism normalized in the anterior and posterior cingulate, premotor, parietal cortex, and caudate nucleus. A study that investigated brain glucose metabolism in AN before and after nucleus accumbens brain stimulation found *increased* regional glucose metabolism in AN ($n = 6$) versus healthy controls ($n = 12$) in the bilateral superior, medial and inferior frontal cortex, bilateral amygdala and hippocampus, left insula and bilateral putamen (106). The authors further reported that frontal cortical and hippocampal hypermetabolism *decreased* with nucleus accumbens stimulation.

Overall, the human neuroimaging results are mixed. The studies, in part, are decades old, and potential confounds such as nutritional status or comorbidity were not considered. Glucose metabolism has been linked to the neurotransmitters dopamine and serotonin, and altered neurotransmitter function found in AN as described above further supports the hypothesis of altered energy homeostasis, including glucose metabolism in AN (107, 108).

We propose that in individuals who have a predisposition for AN, there is reduced utilization of glucose in the brain despite high needs due to high anxious traits and sensitivity to stress and negative affect, which interfere with brain glucose metabolism (Figure 1) (91, 109–114).

While there is evidence that the vicious cycle of weight loss followed by more food restriction is, at least in part, due to the interactions between conditioned fear of weight gain and altered dopamine circuit function, which may drive dread and avoidance (16), we propose that there are fundamental metabolic abnormalities in individuals who develop AN that drive the development of the illness, hinder recovery from AN and trigger relapse in wrAN. Individuals with AN often report that food restriction reduces anxiety and improves mood (115). This may be due to cognitive and emotional factors where weight loss is seen as a success toward a certain body shape or in part due to elevated cortisol release, although the results are mixed (116–119). Here, we postulate that individuals with AN may have a *metabolic reason* why it is so desirable for them to pursue the starvation state. Individuals who develop AN tend to score high on state and trait anxiety and have perfectionistic traits that drive fear of failure and anxiety (28, 42, 120–124).

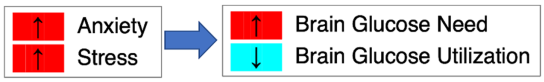


FIGURE 1
Anxiety, stress and brain glucose metabolism. We hypothesize that in AN, high anxiety and stress lead to elevated brain glucose need but reduced glucose utilization.

We hypothesize that high state and trait anxiety levels create ongoing interference with brain glucose utilization in AN as a risk factor before, during, or after weight loss. If a person with that disposition loses weight and enters a ketosis state, the brain will use ketones as an alternative energy source that may be less affected by anxiety. Thus, the individual learns that starvation paradoxically provides a better subjective feeling of having sufficient energy, and food restriction becomes self-reinforcing. However, this state also depletes the body's resources and eventually leads to death. We propose that providing a person with that disposition with ketone bodies while ensuring normal weight will remove the desire to self-starve and support weight maintenance.

## The therapeutic ketogenic diet provides an alternative energy source to reduce anxiety and normalize inflammation

TKD is beneficial in neurological conditions such as seizure disorders, and there is emerging evidence that it might also be an effective intervention to treat psychiatric conditions (125–127).

TKD mimics some aspects of fasting (128). During fasting, the body faces an energy deficit in its cellular fuel supply as glucose and insulin levels decrease. The metabolism of white fat increases, and the resulting fatty acids are used to supplement the energy needs of most organs. The brain is unique, however, because fatty acids cannot easily cross the protective blood–brain barrier (129), and thus, the brain is highly sensitive to drops in glucose. For decades, it was thought the brain could only utilize glucose (130). This presented an enigma because human glucose stores are limited and can be sustained for only a few days. Yet, there have been many documented instances where individuals are capable of fasting (as long as they drink water) for several weeks before succumbing. This paradox was explained in an experiment

performed on three obese patients who were starved for 6 weeks in a metabolic ward, and their internal carotid arteries and jugular veins were cannulated at the start and end of the experiment (131). The study demonstrated that beta-hydroxybutyrate and acetoacetate replaced glucose as the predominant fuel for brain metabolism.

The underlying principle of TKD is that most energy is supplied via fat in the diet, which is then broken down into fatty acids for energy consumption (132). However, sufficient calories are in the food to maintain normal weight. During fasting or TKD, fat metabolism increases, and fatty acids are transported to the liver. Fatty acids are composed of long chains of carbons. In the liver, fatty acids are ordinarily converted into acetyl-CoA, which enters the tricarboxylic acid (TCA) cycle. When fatty acid levels are elevated and exceed the metabolic capacity of the TCA cycle, acetyl-CoA is shunted to ketogenesis. Two acetyl-CoAs can combine through a thiolase enzyme to produce acetoacetyl-CoA, a precursor for acetoacetate synthesis (ACA) and β-hydroxybutyrate (BHB). Acetone, the other major ketone body, is produced primarily from spontaneous decarboxylation of ACA and can be eliminated as a volatile substrate through the lungs and kidneys. In the blood, ACA and BHB are transported from the vascular lumen to the brain interstitial space and both glia and neurons by monocarboxylic acid transporters (MCTs). MCT-1 is the principal carrier localized to the vascular endothelium. Within neurons, both ACA and BHB are transported directly into mitochondria and then converted to acetyl-CoA through several enzymatic steps. BHB is converted to ACA through D-β-hydroxybutyrate dehydrogenase, and ACA undergoes subsequent conversion to acetoacetyl-CoA through a succinyl-CoA transferase enzyme. Finally, acetoacetyl-CoA-thiolase converts acetoacetyl-CoA to two acetyl-CoA moieties, which then enter the TCA cycle (132).

TKD or exogenous ketones have been associated with marked changes in brain glucose metabolism. Specifically, elevated blood ketone levels resulted in lower brain glucose uptake in humans, which was studied using the radiotracer [$^{18}$F]fluorodeoxyglucose ([$^{18}$F]FDG) and positron emission tomography (PET). In one study, infusion of BHB ketone bodies reduced brain glucose uptake and enhanced blood flow, supporting the notion of TKD's neuroprotective effects (133). A study that briefly applied a ketogenic diet found regionally specific effects of blood ketosis on lowering brain glucose uptake (134), including the precuneus, a brain region necessary for visuospatial function, episodic memory retrieval, and self-referential processing, affecting one's perceptual image or mental concept of oneself (135), which could have implications for AN in the pathophysiology of body image distortion (136, 137). The ketogenic diet in that study was maintained only for 48 h, and results may differ after prolonged ketosis as in this study (134). A study testing the effects of ketogenic diet over 4 days led to global decreases in glucose metabolism across widespread cortical and subcortical regions, with the strongest decrease in the middle frontal gyrus (Brodmann area 8, 46) followed by the frontal pole (Brodmann area 10) and cuneus (Brodmann area 17) (138). Three weeks of a ketogenic diet in an animal model also led to widespread cortical reductions in glucose metabolism (139). Thus, short and longer-term ketogenic diets led to extensive regional glucose metabolism reductions, with longer duration associated with more extensive glucose metabolism decreases. The above-referenced study by Courchesne-Loyer et al. (138) suggests that the middle frontal cortex is most affected. However, there were large reductions across all frontal, temporal, parietal, occipital, cingulate, and subcortical regions tested. Those data indicate large global decreases without specific circuits delineated, although some areas were more affected than others (138).

The metabolic shift with TKD is associated with a variety of central nervous system and general effects on the body. Aside from the ketone bodies enhancing cell energy metabolism by replenishing the metabolic pathway, TKD has been associated with reducing oxidative stress and inflammatory processes and regulating neurotransmitter systems (140–142), which are all processes implicated in the pathophysiology of AN (21, 23, 86, 87). Furthermore, replacing glucose with ketone bodies via TKD to supply the brain with energy enhances γ-aminobutyric acid (GABA) in the brain via enhanced glutamate production converted to glutamine and GABA (143). GABA is a primary inhibitory neurotransmitter that reduces anxiety (144, 145). In the animal model, enhancing systemic ketone body levels reduced stress and anxiety (146, 147). In AN, altered GABA function has been reported in an animal model for AN, and enhancing GABA via ketosis might effectively reduce AN-specific and non-specific anxiety (148, 149). Other studies have found elevated inflammatory markers in AN, and elevating blood ketone levels has been shown to reduce inflammation (150).

## Metabolism as neurobiological target in AN

It has been hypothesized that brain metabolic alterations, perhaps relating to cell mitochondria, have a critical role in psychiatric disorders (151, 152). Psychiatric disorders have been associated with inborn errors of metabolism, supporting the link between altered metabolism and psychiatric pathophysiology (153). Research has also increasingly recognized other abnormalities associated with psychiatric conditions, such as elevated inflammatory markers and markers for oxidative stress (154–156). It has been hypothesized that AN's pathophysiology includes metabolic abnormalities (82), or that AN may be a "metabolic disorder of psychological origin" (81). Thus, there is growing evidence that nutrition and mental health are linked, and diet may be particularly appealing as a therapeutic intervention (157).

TKD has received increasing attention since it was found effective in pediatric epilepsy (158). Others have suggested that TKD could improve autism-related behaviors, symptoms associated with Alzheimer's disease, or disorders related to mood or psychotic symptoms (159–161). These findings have led to the suggestion that TKD could be an effective metabolism-directed intervention for psychiatric conditions (162, 163).

## A neurobiological model for TKD as a possible treatment intervention for AN

The TKD may be an effective treatment intervention for AN to normalize energy homeostasis and remove the need to self-starve for nutritional ketosis. Figure 2 provides a conceptual model of dysfunctional brain glucose metabolism and the therapeutic effects of TKD (85, 93, 132, 147, 164). (1) At baseline and under typical conditions, glucose is used by the brain mitochondria to generate energy and support brain function and associated behaviors. (2) In individuals with AN, high levels of anxiety and perfectionism lead to stress, which reduces glucose utilization despite high energy needs. (3) Body dissatisfaction and drive for thinness in susceptible individuals

drive starvation. Transient imbalances between nutritional intake and energy requirements lead to the generation of ketones and the use of beta-hydroxybutyrate (BHB), acetone, and acetoacetate (ACA) as alternative energy compounds that enter the brain mitochondrial Krebs cycle and are better utilized than glucose and independent from the effects of stress. (4) Ketosis leads to elevated production of neuronal GABA via glutamine and glutamate, which may help with emotion regulation and reduce anxiety. (5) Ketosis leads to improved brain energy supply and elevated GABA production, which stabilizes neuronal function and causes positive feedback to promote further starvation-mediated ketosis. (6) A ketogenic diet that is energy-rich to accomplish weight maintenance in wrAN or weight gain in AN eliminates the need for ketosis via starvation, thus replacing "starvation ketosis" with "nutritional ketosis" (85, 93, 132, 147, 164).

## Supporting preliminary studies

A single case study suggested that TKD, followed by ketamine infusion, could help that patient recover (165). That individual remains recovered to this date (Dr. Scolnick, personal communications). That study laid the foundation for an IRB-approved protocol in five wrAN who were still highly affected by the illness (166). In that study, we conducted an open-label trial to test whether the case report response could be replicated. Those five wrAN adults with persistent eating disorder thoughts and behaviors adopted the TKD to maintain weight. In addition, participants received six ketamine infusions after 4 to 8 weeks of stable ketosis and were followed over six months. All participants completed the study protocol without significant adverse effects. The participants consumed the TKD for at least 8 weeks (4 to 8 weeks TKD alone, then with added ketamine for 4 weeks); two individuals continued TKD after the formal study intervention for a total of 4 months on TKD and two individuals for 6 months of TKD, suggesting good tolerability. The group showed significant improvements (repeated measures ANOVA) on the Clinical Impairment Assessment ($p = 0.008$), Eating Disorder Examination Questionnaire (EDEQ) Global score ($p = 0.006$), EDEQ-Eating Concerns ($p = 0.005$), EDEQ-Shape Concerns ($p = 0.016$), EDEQ-Weight Concerns ($p = 0.032$), Eating Disorders Recovery Questionnaire (EDRQ) Acceptance of Self and Body (0.027) and EDRQ-Social and Emotional Connection ($p = 0.001$). Weight remained stable during the trial. Figure 3 shows a change in composite scores and BMI over time. The baseline was at "0"; time point one indicates 4 weeks of TKD for all participants, timepoint 2 indicates 8 weeks of TKD for two subjects, and 4 weeks of TKD plus ketamine in 3 subjects; time points three and later are post study intervention assessments. EDEQ global score, Restraint, Eating Concern, Weight Concern, Acceptance of Self and Body, and Clinical Impairment showed steep improvements before adding ketamine, suggesting that TKD alone was highly effective.

Of note, in the case report and the case series (165, 166), ketamine infusions were added once the subjects had been on the TKD for at least 4 weeks. The choice was clinically driven and based on a small positive report of decreased obsessions/compulsions in a pilot study of twelve patients with AN (167). Ketamine is an N-methyl D-aspartate (NMDA) glutamate antagonist that has been in use since the 1960s as an anesthetic (168). Over the past two decades, ketamine has been in use as a rapid antidepressant agent (169). There have been accelerating efforts to discern the mechanism of action and focus on the effects of ketamine on energy metabolism, mitochondrial function, and glutamate/GABA function (170, 171). All these areas overlap with the effects of TKD, which corresponded to our clinical observation that the two modalities (TKD and ketamine) led to extended improvement. This warrants further study.

Four of the 5 study participants have remained recovered (low symptom scores, normal weight) for at least 12 months since the end

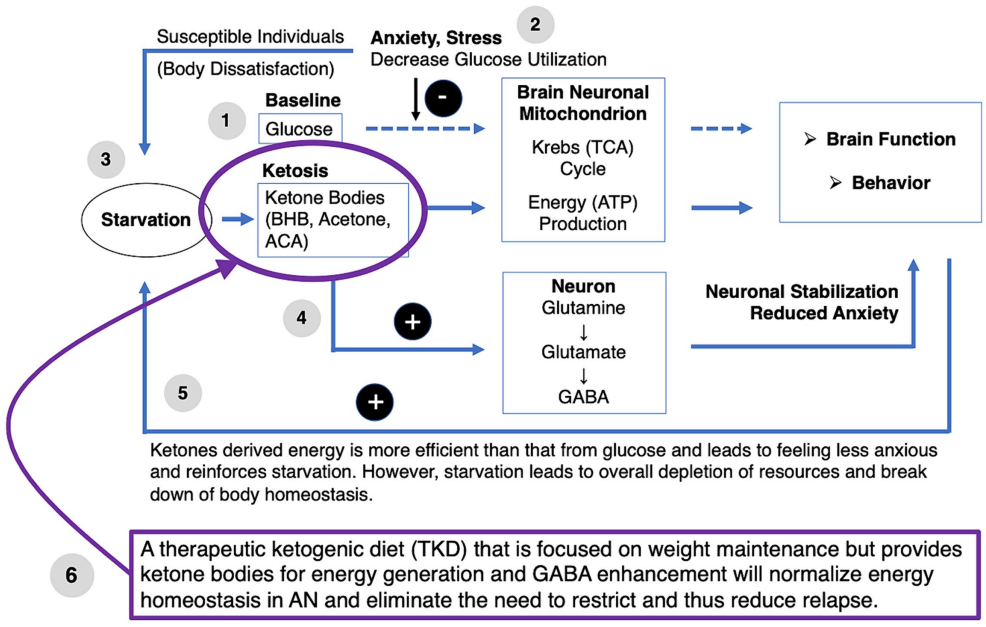


FIGURE 2
Therapeutic ketogenic diet in anorexie nervosa conceptual model. ACA, acetoacetate; BHB, beta-hydroxybutyrate; TCA, tricarboxylic acid cycle.

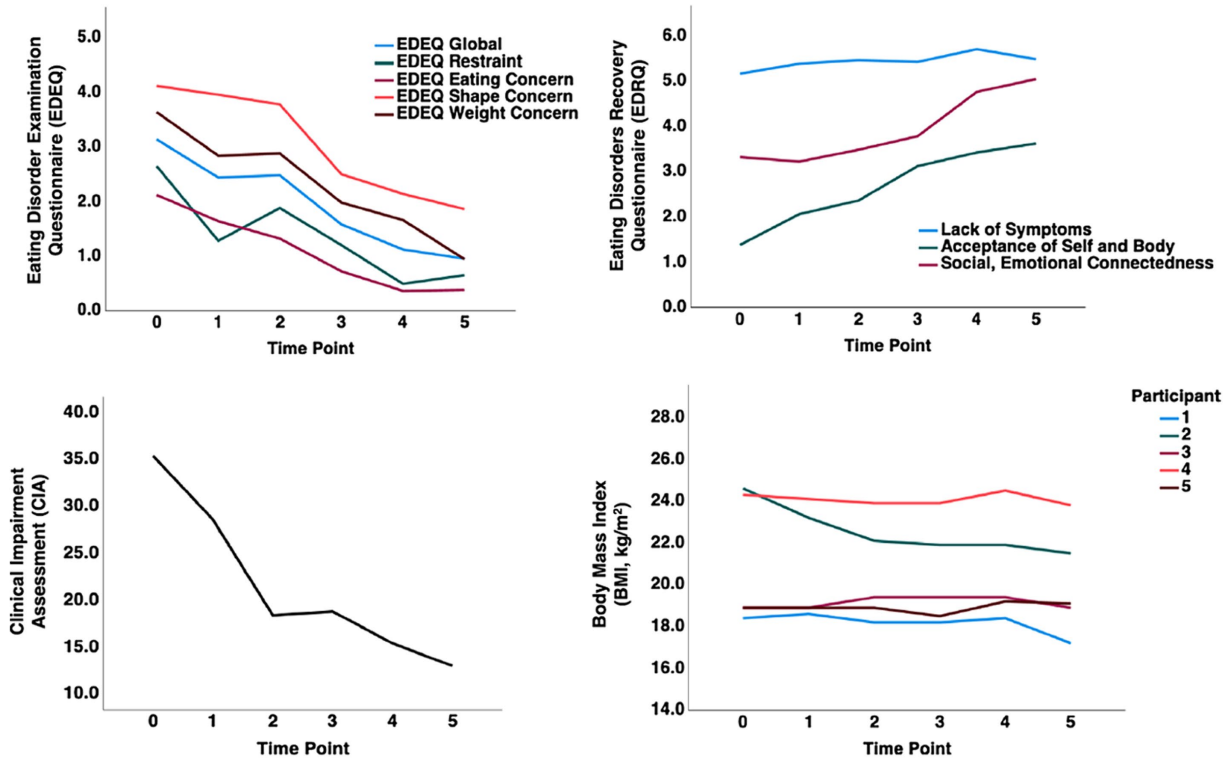


FIGURE 3
A pilot study showing therapeutic ketogenic diet and ketamine infusion effects in the treatment of chronic persistent eating disorder psychopathology in anorexia nervosa [Calabrese et al. (166), with permission]. Graphical representation of composite values for behavioral measures and body mass index (BMI) over time. Timepoint (TP) 0: Baseline, TP 1: 4 weeks TKD all subjects; TP 2: 8 weeks TKD (subjects 3, 4) or 4 weeks TKD + 4 weeks ketamine (subjects 1,2,5); TP 3: 1-month post-intervention; TP 4: 3 months post-intervention; TP 5: 6 months post-intervention.

of the study; one participant who stopped TKD after 8 weeks relapsed 4 months after treatment (unpublished data). The small study suggested that this novel treatment is safe and effective for wrAN adults with chronic AN-related psychopathology. The results from this open trial supported the idea that specific neurobiological underpinnings for AN can be modified with TKD.

## Discussion

AN remains a severe psychiatric disorder without approved biological intervention. The above neurobiological model, with evidence from basic science and human genetic and preliminary clinical data, supports the possibility that brain metabolism may be a key target for intervention to treat this disorder and provide a treatment that targets the disorder's pathophysiology mechanistically. The pilot data to date are from weight recovered individuals. We are currently conducting a follow-up study in a larger group of individuals in the wrAN group to test for reduction of thoughts, feelings, and behaviors that are specific to AN. Future studies will need to investigate individuals underweight with AN when we have further indications that this treatment is safe and effective. An important aspect to also consider is that while we can change neurobiology and provide effective treatment, individuals with AN have often learned to live with the disorder. Once those thoughts, feelings, and behaviors are diminishing, the individual has to re-organize their life, which can be anxiety-provoking in itself. In summary, there is much reason to believe that a TKD could support treatment outcomes in AN, and further study is needed to understand the underlying mechanisms *in vivo* and in relation to specific illness behaviors.

## Author contributions

GF: Conceptualization, Writing – original draft, Writing – review & editing, Funding acquisition, Supervision. BS: Writing – original draft, Writing – review & editing, Conceptualization.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Case report: Ketogenic diet alleviated anxiety and depression associated with insulin-dependent diabetes management

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Differentiating between an irrational versus a rational fear of hypoglycemia has treatment implications and presents significant challenge for clinicians facing patients with type 1 diabetes, illustrated in this case. A 39-year-old woman with autoimmune-positive insulin-dependent diabetes sought help to alleviate severe diabetes distress, and symptoms of depression and anxiety, associated with unpredictable drastic blood glucose drops. After exhausting conventional methods, she adopted a ketogenic diet (KD). Her glucose values decreased from around 20 mmol/L to 12 mmol/L (360 mg/dL to 216 mg/dL) in the first days. Then, by combining a KD with an insulin pump, her time in optimal glucose range increased from 8 to 51% after 2 months, reducing her HbA1c with 25 mmol/mol (2.2%). This reduced biological and psychological stress, immediately improving her mental health and renewing her hope for the future. The main concerns regarding KD in patients with comorbid type 1 diabetes is the assumed increased risk of ketoacidosis, theoretical depletion of glycogen stores, and a potential adverse effect of saturated fat on cardiovascular risk factors. These concerns are evaluated against existing empirical evidence, suggesting instead that a KD may protect against acidosis, hypoglycemia, and cardiovascular risk. The present case, together with available data, indicate that patients with type 1 diabetes experiencing high levels of biological and psychological stress should be informed of the expected benefits and possible risks associated with a KD, to ensure their right to take informed decisions regarding their diabetes management.

KEYWORDS

**ketogenic diet, type 1 diabetes mellitus, diabetes distress, anxiety, depression, glycogen depletion, ketoacidosis, eating disorders**

## 1 Introduction

Although the hallmark of type 1 diabetes is the autoimmune destruction of insulin producing $\beta$-cells, necessitating exogenous insulin, living with diabetes comes with a high psychological burden. This "diabetes distress" can include feelings of being overwhelmed, powerless and hopeless, along with fears of acute and long-term consequences. It includes the stress and frustration of daily management and conflicts with family and health care providers (1, 2). This can develop into a vicious cycle of increasing distress leading to emotional numbing and deteriorated glycemic control, which then in turn increases the psychological burden (3). Approximately 40–60% of individuals with type 1 diabetes experience moderate to high levels of this distress (4). This group is especially at risk for "diabetes burnout"; a state characterized by feeling exhausted, seen in combination with reduced self-care and diabetes management (2). These symptoms may be intense enough to fulfill diagnostic criteria for anxiety and

depression. Individuals with type 1 diabetes are believed to have at least double the risk of various mental disorders and even suicide (5–7).

The situation is further complicated as about 50% of people with type 1 diabetes develop insulin resistance (8), worsening prognosis. To further complicate the picture; insulin resistance in the blood–brain barrier can occur without whole body insulin resistance, making it harder to detect, but with potential harm to the brain (9, 10). Alarmingly, there is an estimated loss of 100 days of life for each year a person's HbA1c exceeds 58 mmol/mol (7.5%) (11).

Insulin resistance, and high levels of insulin and glucose are associated with mitochondrial dysfunction, neuroinflammation, neurotransmitter imbalances, glucose hypometabolism, and lower volume in parts of the brain (5, 9, 12, 13), all of which are also associated with mental disorders (10, 14–16).

Numerous factors complicate the estimation of appropriate insulin dosage. Two key factors are the variability in the effect of insulin administered subcutaneously (17), and miscalculations of the carbohydrate content in food, which may lead to a mismatch with the estimated insulin dosage (18). For example, assuming a combined error of 25%, the absolute value of the error will be lower with lower insulin doses. For instance, a 25% error at a "true" carbohydrate intake of 80 g will result in a miscalculation of 20 g in either direction. In contrast, a "true" carbohydrate intake of 10 g will result in a miscalculation of just 2.5 g in either direction. An insulin pump might compensate for the 2.5 g miscalculation, while a miscalculation of 20 g will significantly interfere with daily life.

Studies of various designs show that a low-carbohydrate diet (under about 100 g/day) lowers HbA1c, even approaching the prediabetic values of <48 mmol/mol (<6.5%), reduces glucose variability, and time spent in hypoglycemia without reducing quality of life (19–23). The ketogenic diet (about 20- 50 g/day of carbohydrates) appears even more beneficial, with HbA1c levels approaching non-diabetic values <42 mmol/mol (<6.0%) and normalize weigh (24–32). In addition, nutritional ketosis protects against the potentially detrimental effects of insulin resistance, high levels of insulin, and high/variable levels of glucose, thereby probably preventing and even treating symptoms of psychiatric disease and neurodegeneration (33). See overviews of the proposed mechanisms elsewhere, for example (34–38).

A key contributor to reduced mental health is the unpredictable nature of type 1 diabetes. A typical experience is that glucose levels tend to drop significantly during even light physical activity and exercise. This is likely due to heightened insulin mediated activation of the signaling pathway controlling GLUT4 glucose transporter activity (39).This effect may be amplified by (i) absence of the glucose sparing effect of nutritional ketosis (40, 41), and (ii) the slightly higher insulin levels by subcutaneous injected insulin compared to the release of endogenous insulin by the pancreas into the portal vein (17). Insulin levels can therefore often become high enough to cause uncomfortable drops during normal daily activities like house cleaning or short walks. This might increase diabetes distress and induce a fear of the very real threat associated with hypoglycemia. However, most cases of hypoglycemia can be easily corrected, often resulting in different threat assessments between healthcare personnel and their patients. Therefore, distinguishing between an anxiety and a rational fear of hypoglycemia has treatment implications, but may be challenging in clinical practice.

This case-report illustrates how introducing a KD mitigated intense diabetes distress and even symptoms of severe anxiety and depression.

## 2 Case description

### 2.1 Patient information and evaluation

A 39-year-old woman with a history of trauma and autoimmune-positive insulin-dependent diabetes for about 2 years was referred to an experienced licensed clinical psychologist familiar with diabetes treatment. Past severe and unpredictable hypoglycemia had frightened the patient, and as a single mother of two, she was particularly concerned about dangerous hypoglycemia. Despite numerous interventions from several diabetes teams, including psychological and dietary approaches, unpredictable glucose levels remained a threat. The expected results did not materialize when she intervened as instructed, leading to increased frustration and fear. Consequently, she felt safe only at high glucose levels (15–20 mmol/L; 270–360 mg/dL). She felt blamed for her fear and failure to control her diabetes. Increasingly desperate, she began to accept the prospect of rapidly deteriorating health and death within a few years, even making plans for her children's care after her death. She reluctantly agreed to start an insulin pump but was terrified of having more insulin and being dependent on a machine.

An emergency session was arranged on a Tuesday as she was scheduled to commence pump treatment on the following Friday.

Based on the patient's descriptions in the clinical assessment interview, the psychologist concluded that the patient's psychological pain was severe, with high levels of diabetes distress, approaching panic. This distress fulfilled the diagnostic criteria for F 40.2 and F 32; specific phobia and depression. Her anxiety symptoms included intense fear of hypoglycemia and insulin, causing her to omit and avoid necessary insulin doses. She felt trapped and a loss of control, becoming agitated and autonomically hyperactivated. Her depression was marked of by a sense of surrender to the prospect of dying due to her diabetes, alongside a loss of energy, interest and joy. She experienced negative thoughts about the future, feelings of guilt, unworthiness, and cognitive difficulties such as problems with concentration, attention and memory. These symptoms had persisted for at least 1 year, had rendered her unable to work and limited her social life. In combination with the fatigue caused by the hyperglycemia, she could barely manage to take care of herself and her children. These symptoms are closely related to her life with diabetes, and most likely exacerbated by hyperglycemia and the unpredictable and uncontrollable glucose drops.

By accepting the patient's narrative, the logical course of action appeared to be to minimize any unnecessary insulin requirement due to "normal" carbohydrate consumption and harness the advantages of a ketogenic diet (KD). The current KD was defined as a diet allowing her body to produce ketones.

## 2.2 Intervention

Due to the patient's severe pain and time constraints, the psychologist promptly provided information on how a KD could mitigate sudden glucose drops, thus addressing psychological distress and biological stress. The psychoeducation included possible benefits and risks of utilizing a KD for mental health with comorbid diabetes, and practical tips on how to implement it, allowing for individualization of the diet. Generally, important aspects of a KD to consider for insulin-dependent diabetes includes:

1 Ensure sufficient insulin: Use a continuous glucose monitor (CGM) with "high alarm" at 10–12 mmol/L (180–215 mg/dL). Consider adding insulin if glucose values exceed 10 mmol/L (180 mg/dL). Expect decreased insulin need of up to 50%. Bolus for 5-10 g carbohydrates when eating a keto meal, to cover protein and notify the pump of the meal. Always have an extra insulin pen handy, in case of pump malfunctions.
2 Prevent and rescue hypoglycemia: The CGM should alert when glucose falls below 4 mmol/L (72 mg/dL). Consider consuming 2-5 g glucose if the alarm sounds, preferably in tablet form. This prevents overeating and subsequent hyperglycemia.
3 Enter nutritional ketosis: Base food intake decisions on three guidelines: (i) Prioritize protein: include meat, fish, egg in all/most meals. (ii) Reduce carbohydrates: avoid sugar, starch, rice, potatoes, bread, and pasta. Aim for 25-50 g carbohydrate per day. Foods with less than 5% carbohydrate per 100 g are typically acceptable. (iii) Add fat to satiety and taste: feel free to include saturated fat, but limit highly processed vegetable oils.
4 Monitor ketones: Aim for blood ketones between 0.5-3 mmol/L (42). Initially measure a few times a week, then two times or less a month may suffice. If ketone levels are 3 mmol/L or higher, consume about 10-30 g of carbohydrates and administer matched insulin. Test ketone levels if you get sick, unusually thirsty, headache, nausea, stomachache, or the like.
5 Regarding other medication: Notify relevant healthcare personnel of the change in diet. Do not combine with SGLT-2 inhibitor. Regularly assess the need to adjust blood pressure medication and psychopharmaceuticals.

# 3 Results

The patient embraced the KD after her first session on the Tuesday, choosing food based on the third guideline above. By the following Thursday, she reported a steady decline in her glucose from about 20 mmol/L to 12 mmol/L (360 to 216 mg/dL). She reported feeling safe for the first time in years and a renewed hope for the future, even her children noticed a positive change in her during these first few days on the new diet. This signified a relief in her depressive state and a reduced threat assessment, including her autonomic overactivation, allowing her to start the hybrid closed-loop insulin pump the following Friday. Thus, this had mitigated her avoidance to insulin, relieved her state of panic and severe depression.

The following months, the combination of her reduced insulin need and the insulin pump, her glucose levels significantly stabilized, with increased time in range [glucose values between 4 and 10 mmol/L (72–180 mg/dL)] from 3 to 51%, reducing her HbA1c from 83 to 58 mmol/mol (9.7 to 7.5%) (See Table 1).

From 2 days after the emergency session and onwards, the clinician observed the patient's amazement and joy of her reduced glucose variability, her relief of being believed in her motivation and efforts to manage her diabetes, and a clinically significant reduction in fear and depression.

# 4 Discussion

Although fulfilling formal criteria for depression and anxiety, the patient's mental state and behavior was interpreted as logical

TABLE 1 Information from continuous glucose monitor.

| Time spent in: | T1<br>16th September to 29th September 2023 | T2<br>20th November to 4th December 2023 |
|---|---|---|
| Hypoglycemia %<br>3–3.8 mmol/L (54–64.4 mg/dL) | 0 | 0 |
| Aim %<br>3.9–10 mmol/L (70.2–180 mg/dL) | 3 | 51 |
| Hyperglycemia %<br>10.1–13.9 mmol/L (181.8–250.2 mg/dL) | 19 | 49 |
| Hyperglycemia %<br>>13,9 mmol/L (>250.2 mg/dL) | 78 | 0 |
| Mean glucose mmol/L (mg/dL) | 16.7 (300.6) | 9.9 (178.2) |
| Standard deviation | No info | 1.2 |
| Coefficient of variation % | 22.1 | 12.5 |
| HbA1c mmol/mol (%) | 83 (9.7) | 58 (7.5) |

T1 is the14 days before starting the ketogenic diet, the insulin pump and a HbA1c test. T2 is the 14 days before the second HbA1c test, about 2 months after T1.

reactions to a dangerous situation, not as irrational fear or poor coping. By addressing the diet, the psychological and biological stress on the brain could be reduced.

Despite the promising effects on diabetes management and mental health outlined in the introduction, both regulatory bodies and the low-carbohydrate community have urged caution when considering nutritional ketosis for people with diabetes. There are three main concerns delaying the implementation of the KD in clinical practice, all of which can be mitigated by evidence. Addressing these concerns is crucial to ensure that patients receive the information they need to make informed dietary choices. Had the current patient received this information earlier, she may not have developed her anxiety and depression, which lead to her avoidance of pump treatment.

## 4.1 Diabetic ketoacidosis

Diabetic Ketoacidosis (DKA) is a potentially lethal condition marked by hyperglycemia [serum glucose >13.9 mmol/L (>250 mg/dL)], increased anion cap metabolic acidosis (anion gap >10–12, serum bicarbonate <18 mEq/L and/or pH <7.3), and ketosis (> 2 mmol/L) (43). Usually, DKA is seen in combination with insulin deficiency and/or increased amounts of counter-regulatory hormones like catecholamines, glucagon, cortisol, and growth hormone (44). The acidosis has been attributed to the increased level of ketones (43). However, the ketones acetoacetate and beta-hydroxybutyrate are not produced as acids but as conjugate bases, and acetone is neither an acid nor a base (45). The acidosis can therefore not be directly caused by the presence of ketone bodies. The acidosis is more likely a related consequence linked to the Krebs cycle's maximum oxidation rate of Acetyl-CoA. Further lipolysis after the maximum oxidation is reached, will result in the release of a substantial number of protons per triglyceride molecule. And when these are not consumed by complex 1 in the electron transport chain, acidification may occur (45).

In contrast to DKA, in nutritional ketosis the blood pH remains withing normal limits and, glucose values are normal, but ketones are about 0.5–3 mmol/L (40, 46). Surprisingly, keto-adaptation has been observed to enhance the oxidation rate in ultra-athletes (47, 48). This could mean that the acidotic process associated with ketone production may be deferred through a KD, and possibly further postponed by including exercise (41, 46, 49).

Information is scarce on the incidence, prevalence, and risk factors of acidosis in type 1 diabetes patients in nutritional ketosis. One study reported a 1% incidence (24), compared to an estimated annual 5–8% incidence in the broader type 1 diabetes population (not on KD) (44). This information is relevant for this case, as it means that the patient is actually safer from a DKA on a KD.

In our opinion, a more pressing concern for type 1 diabetes patients is an increased risk of DKA during acute infections or pump malfunctions. However, if a pump with fast acting insulin malfunctions, the body's insulin reserve depletes within hours. It is unclear how much ketones, induced by nutritional ketosis, will impact DKA development, as it is not the ketones themselves that are acidic. More research is needed. In addition, near normal glucose levels decreases tolerance for glucose fluctuations, thereby rapidly alerting the individual if insulin is needed due to hyperglycemia. And importantly, the improved predictability by combining KD with an insulin pump significantly reduces the mental burden related to diabetes, which was exactly what the current patient needed to reduce her anxiety and depression.

Euglycemic DKA involves acidosis with normal glucose levels and accounts for about 2.6–7% of known DKA cases (43). The main contributor appears to be the off-label use of SGLT-2 inhibitors. Other risk factors could include low-fat zero-carb diets, combined with prolonged fasting and intense exercise (50). Thus, the main contributor is not a KD, which is a high-fat low-carb diet that encourages the individual to eat when hungry and match insulin to maintain normal glucose levels. Keto-adapted people with type 1 diabetes often experience increased energy, satiety, and can thrive during intensive multi-day exercise, even when fasted (31, 32). As the current patient was not on SGLT-2 inhibitors but adhered to the KD aiming to better match her insulin injections to her need, the risk of euglycemic DKA was low.

Regardless of their diet and treatment, all individuals with type 1 diabetes must be vigilant about the risk of DKA.

## 4.2 Hypoglycemia and empty glycogen stores?

Intensive insulin treatment, leading to lower HbA1c levels, has been associated with a threefold increase in hypoglycemia frequency (51). Transitioning to a KD significantly reduces insulin needs, potentially causing a slight increase in hypoglycemic episodes, indicating that further insulin reductions are necessary. As the current patient suffered from severe hyperglycemia, the clinician calculated that the reduced insulin need due to KD would resolve the hyperglycemia without triggering anxiety, avoidance of insulin, nor lead to hypoglycemia. The insulin levels the patient managed to inject would be sufficient.

A primary concern other clinicians has is the belief that a KD depletes glycogen stores before ketone production occurs, potentially rendering glucagon injections ineffective during severe hypoglycemia. A small study (n = 10) found that glucagon injection resulted in a higher glucose rise after a high-carb week compared to a low-carb week. However, the rise was sufficient to rescue hypoglycemia in both groups (52), thereby rendering this finding irrelevant.

Three counterpoints to the glycogen storage total "depletion" notion include: (i) Similar levels of resting muscle glycogen stores and glycogen depletion after 180 min running were observed in keto-adapted endurance athletes and athletes consuming "high-carbohydrate" diet (49), potentially due to increased gluconeogenesis rates and a glucose-sparing effect of ketones (41, 46). (ii) During physical activity, muscles primarily use fat for fuel, and increased gluconeogenesis rates contribute to stabilize blood glucose (41). (iii) If hypoglycemia occurs, the brain uses ketones for fuel, mitigating the impact of reduced glucose availability in keto-adapted individuals (32, 53).

By informing the current patient of the benefits of becoming keto-adapted, including the additional fuel for the brain, the patient was able to accept the prospect of more insulin on board delivered by the upcoming pump treatment.

### 4.3 Cardiovascular disease (CVD)

CVD is the leading cause of death in type 1 diabetes patients (54). The main concern is that a KD, often relatively high in saturated fat, can increase low-density lipoprotein cholesterol (LDL-C) and therefore presumably the risk of CVD. However, there are five counter arguments: (i) Individuals with lower levels of LDL-C can become just as atherosclerotic as people with high LDL-C, if not more (55–57). (ii) A recent study found LDL-C not to be a significant risk factor in type 1 diabetes patients (58), suggesting that interventions should not be based solely on theory, but tested in the relevant populations. (iii) The understanding of CVD is evolving, now attributing more atherosclerotic properties to insulin resistance, inflammation and a subgroup of LDL particles, e.g., small dense LDLs (59, 60). (iv) A KD has been found to redistribute the fractions of small dense and big fluffy LDL, to lower circulating triacylglycerols, and to reduce other more important risk factors associated with high glucose levels and insulin resistance (59, 61). (v) The heart might benefit from running on ketones (62). Furthermore, patients with a normal BMI might be more likely to develop a lean-mass hyper-responder phenotype (LMHR) of very high LDL in combination with high HDL and low triacylglycerols (61), related to the carbohydrate restriction rather than the high saturated fat intake (63). This phenotype may not promote CVD risk in the same way as normal dyslipidemia, and there is therefore consensus that CVD risk assessment needs to be individualized according to metabolic state and other factors (64).The CVD risk was a not a current concern for this patient. In her state, her immediate priority was finding relief to take care of her children. Her main goal was to overcome her fear of insulin and resolve the toxic hyperglycemia. However, her HDL, triacylglycerol, and LDL levels did not indicate signs of LMHR, but her values will be closely monitored.

### 4.4 Strength and weaknesses

This report illustrates how a KD can be used in a normal clinical setting. A weakness is a lack of assessment scales for diabetes distress, anxiety, and depression pre and post the KD intervention, and a relatively short follow-up time.

## 5 Take-away lessons

Insulin avoidance due to anxiety and depression may be relieved through a KD. This observation supports the emerging view that a KD is a viable option for some individuals with type 1 diabetes. Despite concerns about KD for individuals with type 1 diabetes, there exist counterarguments and contradictory evidence, suggesting that the perceived risks might not be as significant as initially thought. On the contrary, being keto-adapted might protect against DKA, hypoglycemia, and CVD, in addition to improve mental health both through biological and psychological mechanisms.

Patients struggling to live with diabetes should be provided with comprehensive information about potential benefits and risks of adopting a KD, to ensure their right to make informed treatment decisions, including dietary interventions.

## 6 Patient perspective

Pre KD: In the summer of 2023, I was severely ill, overwhelmingly fatigued and could no longer function properly. Often, I was haunted by the thought that I may not have much time left and filled with despair at the thought of not being there for my children. I began to plan for their care and well-being if I were to die soon. Consequently, I realized that my only option was to try an insulin pump, a prospect that filled me with dread. I got an emergency phone appointment with a new psychologist. During the call, I was so affected by hyperglycemia that I struggled to think clearly and concentrate. I shared my challenges with managing diabetes and my fear about starting the insulin pump. I immediately felt understood and got quickly reassured by the psychologist's guidance on initiating insulin pump therapy and transitioning to a KD.

On a KD: In a remarkably short period, I noticed significant improvements. With each passing day, I felt I was regaining my vitality. Thanks to the guidance and support of my psychologist, I have been immersing myself in learning about diabetes and KD, gaining new knowledge every day. The patient has continued the KD for 1 year and is closely followed up by her diabetes team.

## Data availability statement

The original contributions presented in this paper are based on the patient's medical records, which are not publicly available due to privacy restrictions. Inquiries can be directed to the corresponding author.

## Ethics statement

Ethical approval was not required for this paper as the information presented was not collected through scientific methods for research purposes, but rather as part of routine clinical practice. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

EW: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization. IL: Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization. SD: Writing

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Exploring diet-induced ketosis with exogenous ketone supplementation as a potential intervention in post-traumatic stress disorder: a feasibility study

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**Background:** Post-Traumatic Stress Disorder (PTSD) is a severe and pervasive mental disorder, and patients experience numerous distressing symptoms and impairments that significantly impact their lives. In addition to being a mental disorder, PTSD is strongly associated with a wide range of metabolic abnormalities that affect the entire body. Existing treatment options of psychotherapy and medications are often ineffective. Exploring other potential treatments is necessitated. The ketogenic diet has shown potential as a metabolic therapy in certain neurological and mental disorders and is a promising intervention in the treatment of PTSD.

**Aim:** This study aimed to examine if a 4-week ketogenic diet intervention supplemented with exogenous ketones (KD-KS) was feasible in adult patients with PTSD, to what extent it was possible to recruit patients, attain and maintain ketosis (plasma concentration of $\beta$-hydroxybutyrate (BHB) $\geq$ 0.5 mmol/L), the occurrence of serious adverse reactions and adverse reactions to KD-KS, and acceptance of treatment. Our exploratory aims were changes in PTSD symptoms and health-related quality of life (QoL) from baseline to 4 weeks.

**Methods:** Patients 18$\leq$65years old, diagnosed with PTSD, and receiving outpatient treatment for PTSD at Southern Oslo District Psychiatric Centre (DPC), Oslo University Hospital, Oslo, Norway, were included. The intervention consisted of a ketogenic diet supplemented with $\beta$-hydroxybutyrate salt to obtain ketosis. PTSD symptoms were measured with the PTSD Checklist for DSM-5 (PCL-5) and QoL was measured with the RAND 36-Item Health Survey 1.0.

**Results:** During a 21-week inclusion period, three of four eligible patients (75% [95% CI: 30 to 95%]) were included. Two patients (67% [95% CI: 21 to 94%]) completed the 4-week intervention and one patient (33% [95% CI: 6 to 79%]) completed 2 weeks of intervention before discontinuing. Ketosis was achieved on day 1 in one patient, and on day 2 in two patients, and was maintained in 87% of the intervention. There were no serious adverse reactions. Adverse reactions were reported in a total of 70% of intervention days, the most frequent being headache followed by fatigue. The participant-perceived degree of adverse reactions was low to moderate. The treatment was accepted by patients on all intervention days. PCL-5 decreased by 20 points (70 to 50) in patient 1 and by 10 points (50 to 40) in patient 2, from baseline to 4 weeks, which is a reliable

and clinically meaningful improvement. QoL improved in six of eight RAND-36 subscales in patient 1 and three of eight in patient 2. Patient 3 did not complete assessments after week 2.

**Conclusion:** To the best of our knowledge, this feasibility study is the first study examining a ketogenic diet intervention in patients with PTSD. Three of four predefined feasibility criteria were achieved. Ketosis was attained fast and maintained, patients were compliant and there were clinically meaningful improvements in PTSD symptoms and QoL. Despite the small sample size, the knowledge obtained in this study is important for the planning of future studies with ketogenic diet interventions in this patient group. It is a first step for potential dietary and metabolic therapies in PTSD. Further feasibility and pilot studies with larger sample sizes are needed to determine feasibility and safety before planning future randomised controlled trials investigating an effect.

**Clinical trial registration:** https://ClinicalTrials.gov, identifier NCT05415982.

KEYWORDS

**post-traumatic stress disorder (PTSD), ketogenic diet (KD), ketosis, ketogenic metabolic therapy (KMT), β-hydroxybutyrate (BHB), exogenous ketones, ketone salts (KS)**

## Introduction

Post-Traumatic Stress Disorder (PTSD) is associated with long-lasting changes and dysfunction in many of the body's biological systems, predisposing both somatic and mental disorders, causing disability, and limiting the quality of life (1–5). Most individuals with trauma disorders have several comorbidities such as anxiety, psychotic, depressive, psychosomatic, eating, and conduct disorders, changes in personality, cognitive difficulties and sexual dysfunction. The stress sustained from PTSD may lead to somatic diseases (cutaneous, digestive, cardiovascular, endocrine and auto-immune) (6). This calls for and necessitates a holistic approach to the treatment of affected trauma patients. PTSD is characterized by a severe and prolonged reaction, often chronic, to a distressing event of an exceptionally threatening or catastrophic nature. Repeated exposure to traumatic events increases the risk of developing PTSD (6, 7). Complex PTSD is a relatively new diagnosis that was included in the International Classification of Diseases, 11th Revision (ICD-11) in June 2018 (8, 9). It is a subtype of PTSD that includes additional symptoms related to prolonged trauma exposure, such as chronic and pervasive disturbances in emotion regulation, identity, and relationships (10). A cross-sectional study on PTSD in Norway showed a lifetime prevalence of 4.3% for women and 1.4% for men, with the average duration of the disorder being nine and 17 years, respectively (11). It is estimated that approximately 1–2% of the population has PTSD at any given time in Norway, which is roughly consistent with European levels (12, 13). Studies suggest that PTSD is underdiagnosed because trauma is often not inquired about, leading to misdiagnosis and mistreatment (14, 15). Studies of individuals at high risk of developing PTSD, i.e., populations with high exposure to trauma, show higher rates (16). In the Norwegian Armed Forces' Afghanistan Report 2020, it is reported that 2.9% of Norwegian Afghanistan veterans who have been exposed to one or more traumatic events have PTSD (17), and 31% of female rape victims were diagnosed with PTSD shortly after the assaults during the war in Croatia and Bosnia-Herzegovina (1991–1995) (18). Similar figures are seen today in Norway, as Norwegian Health Informatics states that just over 30% of rape victims develop PTSD (7). Up to 50% may develop PTSD if the event is not processed, e.g., with trauma therapy (19). A Swedish study showed that 79% of refugees in Sweden who had been subjected to highly traumatic events such as war, torture, and captivity had PTSD (20).

Several neurobiological systems are altered in patients with PTSD (1, 21). Changes have been described in the neuroendocrine system, in the autonomic nervous system with increased sympathetic activation, metabolic changes, increase in inflammation, and imbalance in neurotransmitters (1, 21, 22). Hyperarousal is a cardinal symptom of PTSD. This happens through an increase in brain activity in the limbic and neuroendocrine systems, which leads to increased vigilance and alertness. This heightened activation is also thought to maintain the disorder (1, 2).

PTSD is associated with a wide range of mental, social, and physical disorders (1, 4, 6). PTSD patients are more likely to have hyperglycaemia, hypertriglyceridaemia, high levels of low-density lipoprotein (LDL) and low levels of high-density lipoprotein (HDL) cholesterol, and high blood pressure (3, 23). All are components of metabolic syndrome and factors associated with increased risk of type 2 diabetes and cardiovascular disease, indicating that metabolism outside the brain is also affected (24, 25). Epidemiological data suggest that PTSD increases the risk of developing metabolic syndrome, cardiovascular disease, and premature death (4, 5, 26). In addition to being a mental disorder, PTSD can be seen as a metabolic disorder that affects the entire body (4, 5, 26). The changes result from chronic elevated stress, altered lifestyle, and medications. Targeted therapy aimed at some of the many underlying biological systems that are altered, such as disrupted Hypothalamus-Pituitary–Adrenal axis (HPA axis), high and sustained activation of the sympathetic nervous

system, and inflammation, can potentially help with symptomatic improvement for the individuals affected (27, 28).

Existing treatments consist of various forms of psychotherapy and exposure therapy, largely aimed at fear extinction and memory reconsolidation (29, 30). In some cases, medications such as anxiolytics and antidepressants are given, which may often be more targeted towards sequelae or comorbidities that often occur concurrently with PTSD. Several individuals with PTSD struggle to benefit effectively from treatment due to strong avoidance symptoms and the inability to complete overwhelming exposure. Patients may become hyperaroused during treatment and end up outside the window of tolerance where they can process traumas and consolidate fragmented memories. Around 30% drop out of treatment due to the strain they experience from hyperarousal (29). Many patients are treatment-resistant to the established treatment options available today and may go years without getting better (30). The lack of effective treatment options, especially for the most severely affected trauma patients, necessitates exploring other potential treatments. One possible approach could be a ketogenic diet (KD). The use of lifestyle interventions in the treatment of chronic diseases is attractive due to their availability, possibly fewer side effects, and the potential for reduced medical costs (31, 32).

Physiological ketosis is a metabolic state achieved through fasting, starvation, prolonged intensive exercise, or by following a KD (33–35). A KD is a high-fat, moderate protein, very low carbohydrate diet that induces metabolic changes resembling those seen in a fasting state (33, 35). By restricting carbohydrates, fat oxidation increases in several tissues, and fatty acids are metabolized into ketone bodies (KB) in the liver, which are used as alternative cerebral energy substrates to glucose. KB, such as $\beta$-hydroxybutyrate (BHB) and acetoacetate (AcAc), can supply up to 60–70% of the basal cerebral energy requirements (35–38). BHB is also a signalling metabolite that affects epigenetic gene regulation and cellular function and has important neuroprotective effects (39–42). The definition of physiological ketosis is an increased serum concentration of KB $\geq$ 0.5 mmol/L (35, 43, 44).

Exogenous ketosis can be achieved by consuming exogenous ketone supplements in the form of ketone salts or esters, and ketone salts can also be infused intravenously. Ketone salts consist of BHB bound to minerals like sodium, potassium, or calcium, whereas in ketone esters, BHB and/or AcAc is ester bonded to an alcohol (45). Exogenous ketones can generate rapid, mild to moderate therapeutic ketosis (approximately 1–7 mmol/L) (46–52) and can be combined with a KD to elevate ketone levels and to maintain ketosis if there is a lack of compliance with the KD. For patients not able to, or not wishing to adhere to a KD, exogenous ketones can be added to a standard diet or a less strict moderate to low-carb diet, to induce and maintain exogenous ketosis. To sustain ketosis, exogenous ketones must be administrated several times a day, depending on the dosage and type of exogenous ketone supplement. Ketone esters are prone to elevate blood BHB (b-BHB) more and faster than ketone salts. Ketone salts, and sometimes ketone esters, are often racemic mixtures of the two optical isoforms of BHB, D-BHB and L-BHB, and the metabolism and function of L-BHB are poorly understood (47). D-BHB is the predominant circulating KB and is better oxidized than L-BHB, which only accounts for 2–3% of endogenous BHB production in the fasted state (53, 54). This has led to L-BHB being thought of as not important, which might not be the case (54–56). L-BHB is metabolized more slowly, suggesting that a racemic mixture sustains ketosis for longer (57, 58). Commercial ketone meters and standard laboratory analysis only detect D-BHB, and most do not test for AcAc (53).

KD is an established and effective treatment for refractory epilepsy used since the 1920s, and fasting has been known to reduce seizures for centuries (33, 59–61). To exhibit the anticonvulsant effect seen in epilepsy, KD must suppress excitation in neurons, regardless of underlying mechanisms, and a bidirectional relation between epilepsy and mood disorders is hypothesised (62–64). There are few studies on KD in mental disorders, but some have shown promise in major depressive disorder, bipolar disorder, schizoaffective disorder, schizophrenia, autism spectrum disorder, anorexia nervosa and substance/alcohol use disorder (65–83), and more studies are on their way (84, 85). There is also a therapeutic potential of exogenous ketone supplements in mental disorders (51, 86, 87). It is conceivable that KD raises the threshold for neuronal excitation and contributes to synaptic stability in PTSD, as seen in other conditions (88, 89). Currently the authors are not aware of any previous studies on KD as an intervention for PTSD, yet the hyperexcitability hypothesis may be equally relevant in this condition (90). KD may thus reduce symptom expression in PTSD patients.

The mechanisms of action of KD are not fully understood. Some assumed important components include a decrease in neuroinflammation, reactive oxygen species (ROS) and redox stress, improved energy metabolism/mitochondrial function, membrane properties, direct stimulation of transcription factors and epigenetic changes, ion channels, and maintenance of membrane potential (39, 70, 91). From previous studies, KD seems to be effective in treating dyslipidaemia and reducing systemic inflammation (35, 92–95). This speaks to KD as a promising candidate in the treatment of PTSD, which shares several of the same metabolic abnormalities (1). KD has shown potential as metabolic therapy for a range of metabolic, neurological, and mental disorders, and the mechanisms are now investigated in, e.g., brain injury, migraine, mental illness, Alzheimer's disease, cancer, and diabetes (38, 70, 88, 96–104). Metabolism is a key feature of neurological health and stability, and its role in the treatment of mental disorders has started to receive much attention in the young research field of Metabolic Psychiatry (65, 77, 85, 105–107).

Despite the growing body of evidence supporting the beneficial effects of the KD on the brain, its application in the context of PTSD remains largely unexplored. Based on results from studies in other mental disorders, it was hypothesised that a KD supplemented with BHB salt (KD-KS) may alleviate symptom expression in PTSD patients and no previous studies have been published testing this hypothesis. Therefore, we designed a study to investigate if this intervention is feasible in adult PTSD patients, during a 4-week intervention. The primary aims were to examine to what extent it was possible to recruit patients, attain and maintain ketosis, the occurrence of serious adverse reactions (SARs) and adverse reactions (ARs) to the KD-KS, and acceptance of the intervention. Our exploratory aims were changes in PTSD symptoms and health-related quality of life from baseline to 4 weeks.

## Materials and methods

This single-site, non-randomised, open-label, single group feasibility study was conducted over 6 months on outpatients with PTSD, receiving treatment at Southern Oslo District Psychiatric Centre (DPC), Oslo University Hospital, Oslo, Norway. This study is

reported following the Consolidated Standards of Reporting Trials (*CONSORT*) statement (Supplementary Table S3) (108). Ethics approval was granted by the Regional Committees for Medical and Health Research Ethics South East Norway (REK) (455897) and the study was registered at https://clinicaltrials.gov (Identifier: NCT05415982) on 23 March 2022. The study was conducted following the principles of the Declaration of Helsinki (109).

## Participants

Patients 18 ≤ 65 years old, diagnosed with PTSD, speaking a Scandinavian language, and receiving outpatient treatment for PTSD at DPC, were included. Exclusion criteria were if KD was contraindicated (110) (Supplementary Table S1), body mass index (BMI) < 18, dysregulated diabetes mellitus, treatment with medication for elevated plasma triglycerides, and pancreas-, kidney-, or liver disorders. Following the study entry, baseline measurements were taken including psychological tests, blood samples, and weight measurements (Supplementary Table S2). Energy requirements were estimated from the Harris-Benedict equation corrected for stress and activity factor (111). Ketogenic ready meals (Natural Ketosis, Edinburgh, United Kingdom), ready-to-drink/semi-solid ketogenic formulas (K.Flo®/K.Yo®, Vitaflo International Ltd., Liverpool, United Kingdom), low-carb food products that facilitated the intervention, an exogenous ketone supplement (Ketostart®, Audacious Nutrition LLC, Tampa, Florida, United States), as well as a blood ketone/glucose meter and test strips (Keto-Mojo Europe B.V., Amsterdam, Netherlands) were provided. Participants were trained to perform blood ketone/glucose measurements by finger-prick testing and received instructions on how to register their nutrition intake. They were given a self-assessment form to register serious adverse events (SAEs), adverse events (AEs), SARs, ARs, acceptance of intervention and nutrition intake. Nutrition and fluids were registered daily by the participants and calculated by the investigator using a Danish internet-based software "Vitakost" for nutritional contents (112). The investigator saw the participants weekly at DPC for an interview, in conjunction with blood sampling, and maintained regular contact, at least several times a week, to monitor their progress and the intervention.

## Nutritional intervention

The ketogenic food products provided were intended as full nutrition during the intervention, to ensure a macronutrient composition leading to ketosis. Participants were encouraged to predominantly consume the products but also had the option to prepare their own ketogenic meals with guidance from the investigator. Six different ketogenic ready meals (Natural Ketosis, Edinburgh, United Kingdom) were provided for lunch and dinner, and due to import regulations between the United Kingdom and Norway, all meals were vegan. Participants were encouraged to add additional animal or plant protein to the meals if wanted. As breakfast and meal replacement K.Flo® and K.Yo® (Vitaflo International Ltd., Liverpool, United Kingdom) were used. K.Flo® is a ready-to-drink nutritionally complete, 4:1 ratio, ketogenic formulation in vanilla flavour, consisting of 14.7 g fat, 1.6 g carbohydrate, and 3.4 g protein per 100 mL. K.Yo® is a nutritionally complete, 3:1 ratio, semi-solid ketogenic formulation in vanilla or chocolate flavour, consisting of 30 g fat, 1.5–2.0 g carbohydrate, and 8 g protein per 100 g. To increase levels of b-BHB and to keep participants in ketosis even if not 100% compliant with the intervention, the exogenous ketone supplement Ketostart® (Audacious Nutrition LLC, Tampa, Florida, United States), was used. Ketostart® is a BHB salt (racemic mixture containing D-BHB and L-BHB) in powder form with tropical flavour, consisting of 10 g BHB per serving (17 g). One serving Ketostart® was mixed with water and consumed throughout the day. Patients were encouraged to consume sufficient salt and electrolytes during the intervention to meet increased demand on a KD.

## Feasibility outcomes

The primary objective of this trial was to assess feasibility. The intervention was considered to be feasible if all of the criteria in Table 1 were attained. Limits to determine feasibility were estimated from the results of previous trials (113–117).

### Maintaining ketosis

To assess the level of ketosis and fluctuations in blood glucose (BG), b-BHB and BG were monitored three times daily by the participants: morning, mid-day, and in the evening. It was encouraged that the participants take the measurements before meals and around the same time each day. b-BHB and BG were sampled by a finger-pricker and GKI-Bluetooth Blood Glucose & Ketone Meter® (Keto-Mojo Europe B.V., Amsterdam, Netherlands), a device that measures both b-BHB (D-BHB) and BG with two different test strips. The meter uploaded the data via Bluetooth to MyMojoHealth app on the participants' mobile phones and the investigator followed the data in real-time via the MyMojoHealth webpage for practitioners. This way

TABLE 1 Feasibility outcomes.

| Outcomes | Measures | Limit to be feasible |
|---|---|---|
| Recruitment of patients | Percent of included patients to eligible patients | ≥60% of eligible patients included (114, 115) |
| Maintaining ketosis[a] | Percent of days in ketosis[a] since ketosis[a] was attained | ≥75% of days in ketosis[a] since ketosis[a] was attained (113) |
| Occurrence of serious adverse reactions and adverse reactions to the ketogenic diet supplemented with BHB salt | Percent of intervention days with serious adverse reactions and adverse reactions | ≤5% of intervention days with serious adverse reactions in 100% of patients<br>≤30% of intervention days with adverse reactions in ≥75% of patients (116, 117) |
| Acceptance of treatment | Yes/No, percent of intervention days | ≥75% of patients accepting the treatment in ≥75% of intervention days (113) |

[a]Ketosis was defined as a mean value of the three daily blood $\beta$-hydroxybutyrate measurements ≥ 0.5 mmol/L.

the investigator could intervene if measurements were missed or if the data showed incompliance to the KD-KS. A day in ketosis was defined as a mean value of the three daily b-BHB measurements ≥0.5 mmol/L.

### Occurrence of serious adverse reactions and adverse reactions to the ketogenic diet supplemented with $\beta$-hydroxybutyrate salt

Serious adverse events (SAEs), adverse events (AEs), serious adverse reactions (SARs), adverse reactions (ARs), and suspected unexpected serious adverse reactions (SUSARs) were monitored during the trial and reported according to ICH E6 Good Clinical Practice guidelines (118). SAEs were defined as an adverse event that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity or requires intervention to prevent permanent impairment or damage, whether considered related to the trial intervention or not. AEs were defined as any untoward medical occurrence in a patient that does not necessarily have a causal relationship with the intervention. SARs and ARs were defined as any harmful and undesirable reaction with a direct causal relationship to the intervention, serious or not considered serious (118). SAEs, AEs, SARs, ARs, and participant-perceived degree of ARs (5-point Likert scale (0-4), 0: no adverse reaction, 4: strong adverse reaction) were documented daily by the participants on the self-assessment form and assessed by the investigator.

#### Biochemical analysis for safety

Venous plasma samples were analysed weekly (triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, sodium, potassium, magnesium, phosphate, C-reactive protein (CRP), metanephrine, normetanephrine) or every 2 weeks (alanine aminotransferase (ALAT), alkaline phosphate (ALP), bilirubin, creatinine) to assess safety. Haemoglobin A1c (HbA1c) was analysed at inclusion and completion/exclusion. All blood samples were taken postprandial and not in a fasted state, as the participants had their first meal before blood samples were taken at DPC.

### Acceptance of treatment

Acceptance of treatment was documented daily by the participants on the self-assessment form and was defined as the patients being compliant with the dietary intervention and performing the daily measurements and registrations (yes/no, daily). The participants also filled out two separate 5-point Likert scales (0–4), one for the dietary intervention and one for daily measurements/registrations (0: not demanding, 1: slightly demanding, 2: moderately demanding, 3: quite demanding, 4: very demanding).

## Exploratory outcomes

### Assessment of severity of PTSD symptoms and measure of health-related quality of life

Changes in PTSD symptoms from baseline to 4 weeks were assessed using the PTSD Checklist for DSM-5 (PCL-5) (119). PCL-5 is a 5-point scale with 20 questions. Each question is answered based on the frequency of experiencing a particular symptom, ranging from 0 (not at all) to 4 (very often). The minimum value is 0 and the maximum value is 80, the lower the score the better.

Health-related quality of life was assessed using the RAND 36-Item Health Survey 1.0 (RAND-36) (120) at baseline and after 4 weeks. The score provided represents a percentage of the total possible score, ranging from 0 to 100%. Higher scores are better, and 0 is worse. RAND-36 consists of 36 questions covering eight subscales, each scored from 0 to 100%: physical function, role limitations due to physical health, role limitations due to emotional problems, pain, general health perception, energy and fatigue, social function, and mental health.

### Weight

Patients weighed themselves at home on a digital bathroom scale at baseline and weekly for 4 weeks. The weighing was in a standardised manner on the same scale in the morning, wearing light clothing, before consuming food and drinks, and after using the toilet. The patients sent pictures of the weight on the scale to the investigator.

## Statistical analysis

We aimed in this study to include 10 patients. As this is the first feasibility study with a KD intervention in patients with PTSD, we followed the recommendations of Steven A. Julious, as a formal power calculation was not feasible (121). No formal statistical comparison was carried out due to the low sample size.

# Results

## Feasibility outcomes

### Recruitment of patients

Four patients were found eligible during a 21-week inclusion period, and referred by the treating physician to the investigator, for further information about the study. It was possible to include three of four (75% [95% CI: 30 to 95%]) eligible patients. One patient found the intervention too demanding and declined to participate. Two patients (67% [95% CI: 21 to 94%]) completed the 4-week intervention. One patient (33% [95% CI: 6 to 79%]) completed 2 weeks of the intervention before discontinuing (Figure 1). The reason stated was that the intervention was too demanding, and the patient did not like the food. The patient felt unwell (did not specify how) and exhausted from the measurements/registrations and cooking. At baseline PCL-5 was 59 ± 10 (mean ± SD) and current comorbidities were chronic pain syndrome (fibromyalgia) ($n$ = 3), chronic fatigue ($n$ = 2), chronic headache ($n$ = 2), bipolar disorder ($n$ = 1), prediabetes ($n$ = 1) and metabolic syndrome ($n$ = 1). The baseline characteristics of the patients are summarised in Table 2.

### Maintaining ketosis

All patients attained at least one b-BHB measurement ≥0.5 mmol/L on the first day of intervention. The mean value of the three daily b-BHB measurements (a day in ketosis) were ≥ 0.5 mmol/L on day 2 in patients 1 and 2, and on day 1 in patient 3. Ketosis was maintained in 87% of the intervention. In 96% (27 of 28 days) in patient 1, 71% (20 of 28 days) in patient 2, and in 100% (14 of 14 days) in patient 3. Diagrams of all daily b-BHB and BG measurements throughout the intervention per patient, are found in Figure 2. Out of the planned three daily b-BHB and BG measurements, only 2% (2 of 126) of total measurements were missed (one b-BHB and one BG

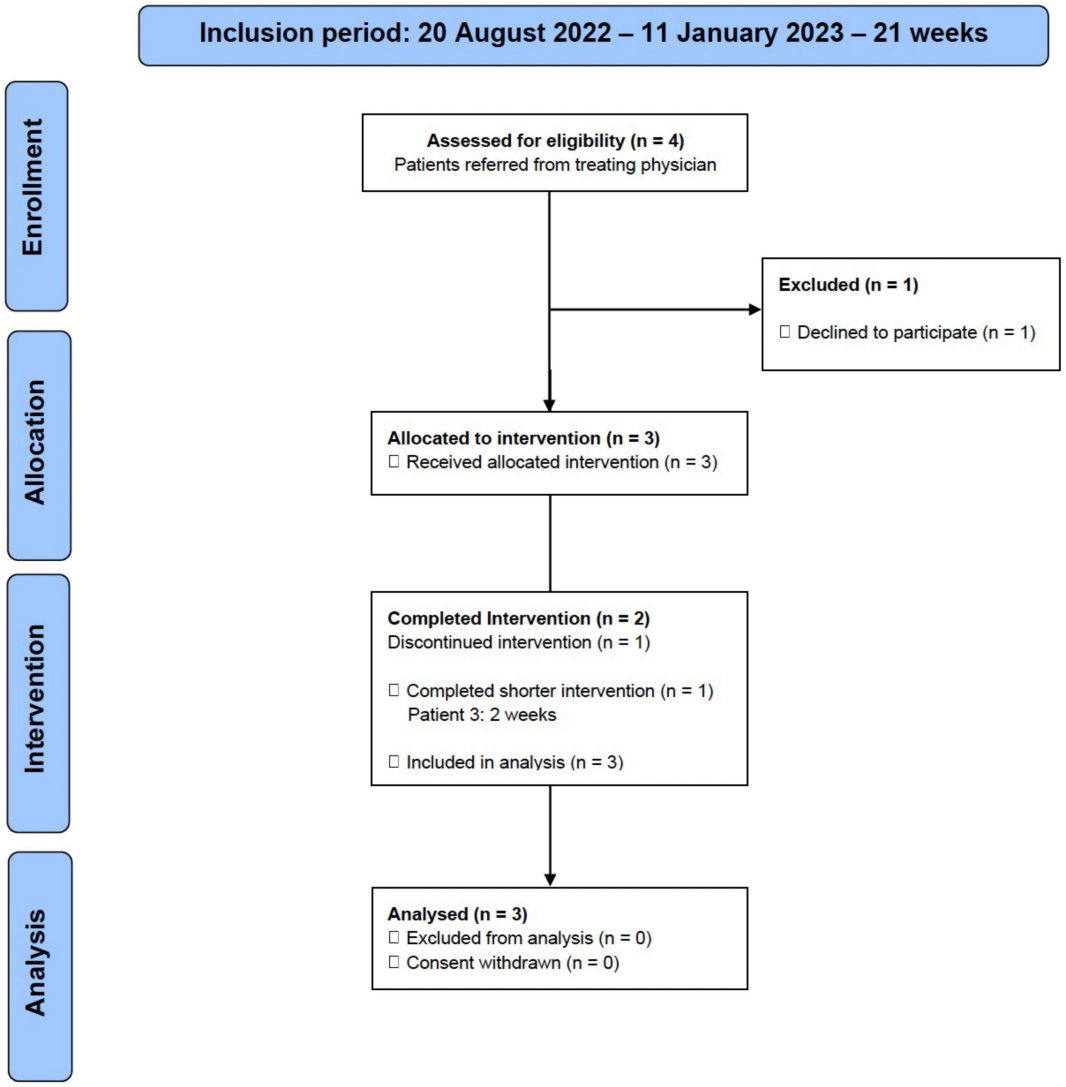


FIGURE 1
Flow diagram describing the inclusion and exclusion of patients in the study.

measurement by patient 2). The ratio of BG to b-BHB, Glucose Ketose Index (GKI) calculated from the three daily b-BHB and BG measurements are seen in Figure 3.

## Occurrence of serious adverse reactions and adverse reactions to the ketogenic diet supplemented with $\beta$-hydroxybutyrate salt

There were no SAEs or AEs, and no observed SARs or SUSARs. All patients experienced ARs and in total there were 70% of intervention days with ARs, many of which occurred on the same days. The most frequent adverse reaction was headache followed by fatigue (Table 3). The participant-perceived degree of ARs was low in most ARs, the strongest perceived ARs were headache and fatigue (Table 3). The ARs did not affect the acceptance of treatment.

### Biochemical analysis for safety

There were no significant changes in sodium, potassium, magnesium, creatinine, phosphate, and bilirubin from baseline and measurements were within reference values during the intervention. Plasma triglycerides were elevated in patient 2 at baseline (4.6 mmol/L), normalised within the reference value of <2.0 mmol/L after 2 weeks, and was 1.6 mmol/L at the end of week 4 (Figure 4). In the same patient, total cholesterol decreased from 8.0 mmol/L at baseline to 5.5 mmol/L after 4 weeks and LDL decreased from 5.7 to 4.0 mmol/L. In patient 1 total cholesterol decreased from 5.2 to 4.5 mmol/L and LDL from 3.4 to 2.5 mmol/L, while HDL increased slightly from 0.9 to 1.0 mmol/L. In patient 3 total cholesterol decreased from 5.2 to 4.6 mmol/L after 1 week, but LDL increased from 3.0 to 3.8 mmol/L (Figure 5). Due to patient 3 dropping out of the study after 2 weeks, only blood measurements after week 1 were taken, as the patient did not come in for measurements at the end of week 2. Plasma levels of metanephrine and normetanephrine were within reference values in all three patients (Figure 6). CRP was normal in patient 1, elevated in patients 2 (7 mg/L) and 3 (8 mg/L), and increased from baseline to week 1 (13 mg/L) in patient 3 and decreased from baseline to week 4 (4 mg/L) in patient 2 (Figure 7). ALAT was elevated in patient 2 at baseline (62 U/L) and almost doubled (115 U/L) at week 2 but normalised at week 4 (41 U/L). ALP was within reference values

TABLE 2 Patients' baseline characteristics.

| Variable | Intervention group ($n$ = 3) |
|---|---|
| Age (years) | 49 ± 4 |
| Gender (Male/Female) | (0/3) |
| Weight | 80.03 ± 15.08 |
| Body mass index (BMI) | 28.93 ± 5.49 |
| **Diagnosis** | |
| Post-Traumatic Stress Disorder (PTSD) | 3 |
| **PTSD symptoms** | |
| PTSD Checklist for DSM-5 (PCL-5) (0–80 points) | 59 ± 10 |
| **Health-Related Quality of Life (RAND-36) (0–100% score)** | |
| Role limitations due to physical health | 20 ± 18.03 |
| Role limitations due to emotional problems | 0 ± 0 |
| Energy | 6.67 ± 5.77 |
| Mental health | 34.67 ± 26.63 |
| Social functioning | 16.67 ± 7.22 |
| Pain | 15 ± 12.99 |
| General health | 15 ± 13.23 |
| Physical function | 62.5 ± 3.54 |
| **Biochemistry** | |
| HbA1c (%) | 33.33 ± 4.51 |
| Alanine aminotransferase (ALAT) (U/L) | 32.33 ± 25.15 |
| Alkaline Phosphatase (U/L) | 79 ± 25.06 |
| Bilirubin (μmol/L) | 6.33 ± 2.08 |
| Triglycerides (mmol/L) | 2.33 ± 1.99 |
| Total cholesterol (mmol/L) | 6.13 ± 1.62 |
| Low-density lipoprotein (LDL) (mmol/L) | 4.03 ± 1.49 |
| High-density lipoprotein (HDL) (mmol/L) | 1.47 ± 0.49 |
| C-Reactive Protein (CRP) (mg/L) | 5.20 ± 4.03 |
| Metanephrine (nmol/L) | 0.18 ± 0.06 |
| Normetanephrine (nmol/L) | 0.43 ± 0.04 |
| **Current comorbidity** | |
| Prediabetes | 1 |
| Metabolic syndrome | 1 |
| Fatigue | 2 |
| Pain syndrome (fibromyalgia) | 3 |
| Headache | 2 |
| Bipolar disorder type 2 | 1 |

Data is presented as number of patients or mean ± SD.

in both patients 1 and 2, and decreased from 105 to 79 U/L in patient 2 (Figure 8).

### Acceptance of treatment

All patients were compliant with the intervention and the treatment was therefore accepted in 100% of intervention days by all patients, even though patient 3 dropped out of the study after 2 weeks. The dietary intervention and daily measurements/registrations were found not demanding by patient 1, and slightly demanding by patient 2. Patient 3 found the dietary intervention moderately demanding in 64% of days (nine of 14), quite to very demanding in the remainder of days (36%, five of 14), and the daily measurements/registrations quite to very demanding in 21% of days (three of 14). Patients 1 and 2 completed the nutrition intake registration on 100% of the days and patient 3 on 93% of the days (13 of 14). The mean daily nutrition intake during the intervention for all patients can be seen in Table 4.

## Exploratory outcomes

Only patients 1 and 2 completed the PCL-5 and RAND-36 after the intervention, due to patient 3 dropping out of the study, and the investigator could not get the patient to complete the last assessments. In patient 1 the PTSD symptoms measured with PLC-5 went from a score of 70 to 50 and in patient 2 from a score of 50 to 40 in 4 weeks (Figure 9). Both patients reported an improved overall quality of life during conversations with the investigator. In patient 1 six of eight of the RAND-36 subscales improved (Figure 10). Role limitations due to emotional problems, energy and fatigue, and general health perception increased from 0 to 33%, 40 and 15%, respectively. The patient described significantly less pain due to fibromyalgia and on the RAND-36 subscale pain, there was an improvement of 13%. Social function increased by 25% and mental health by 16%. Physical function did not change and role limitations due to physical health decreased by 24%. Three of eight of the RAND-36 subscales improved in patient 2: social function by 26%, pain by 10%, and general health perception by 10% (Figure 10). Role limitations due to physical health, role limitations due to emotional problems, and energy and fatigue did not change, physical function decreased by 10% and mental health by 3%.

### Weight

All patients lost weight during the intervention. Patient 1, who had a BMI in the healthy weight range at baseline (22.6), lost 0.2 kg, while patients 2 and 3, who were obese at baseline (BMI 32.0 and 32.2), lost 5.1 kg in 4 weeks and 3.5 kg in 2 weeks, respectively. Changes in weight and BMI from baseline until the end of the intervention are seen in Table 5.

# Discussion

## Feasibility outcomes

### Recruitment of patients

Being the first study investigating KD-KS in PTSD patients, the results can only be compared with PTSD studies examining other interventions. For the recruitment feasibility criteria to be fulfilled, we set a goal of ≥60% eligible patients to be included, based on previous PTSD pilot studies (114, 115) using a lower limit of the 95% confidence interval of ≥60% included eligible patients. The study by Oehen et al., looking at MDMA-assisted psychotherapy in chronic PTSD, included 74% [95% CI: 51 to 88%] of eligible patients (115), while the study by Hall et al., examining community-based exercise in older veterans with PTSD, included 20% [95% CI: 16 to 26%] of eligible patients (114). In our study three of four eligible patients were

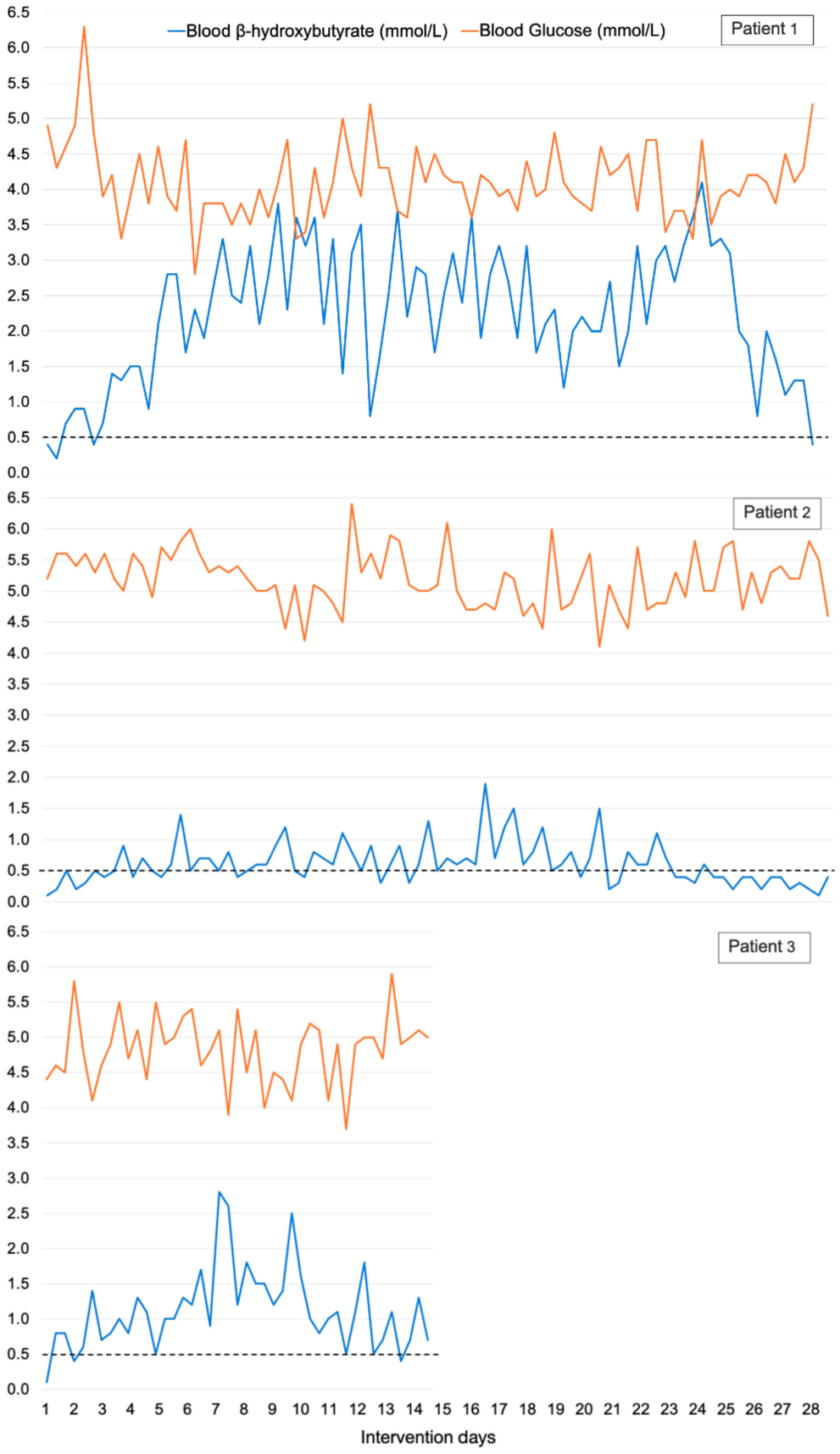


FIGURE 2
Blood $\beta$-hydroxybutyrate and blood glucose levels (mmol/L) in all patients. The three daily measurements are included and not daily mean values. Two of 126 (2%) of total measurements were missed, one blood $\beta$-hydroxybutyrate and one blood glucose measurement by patient 2.

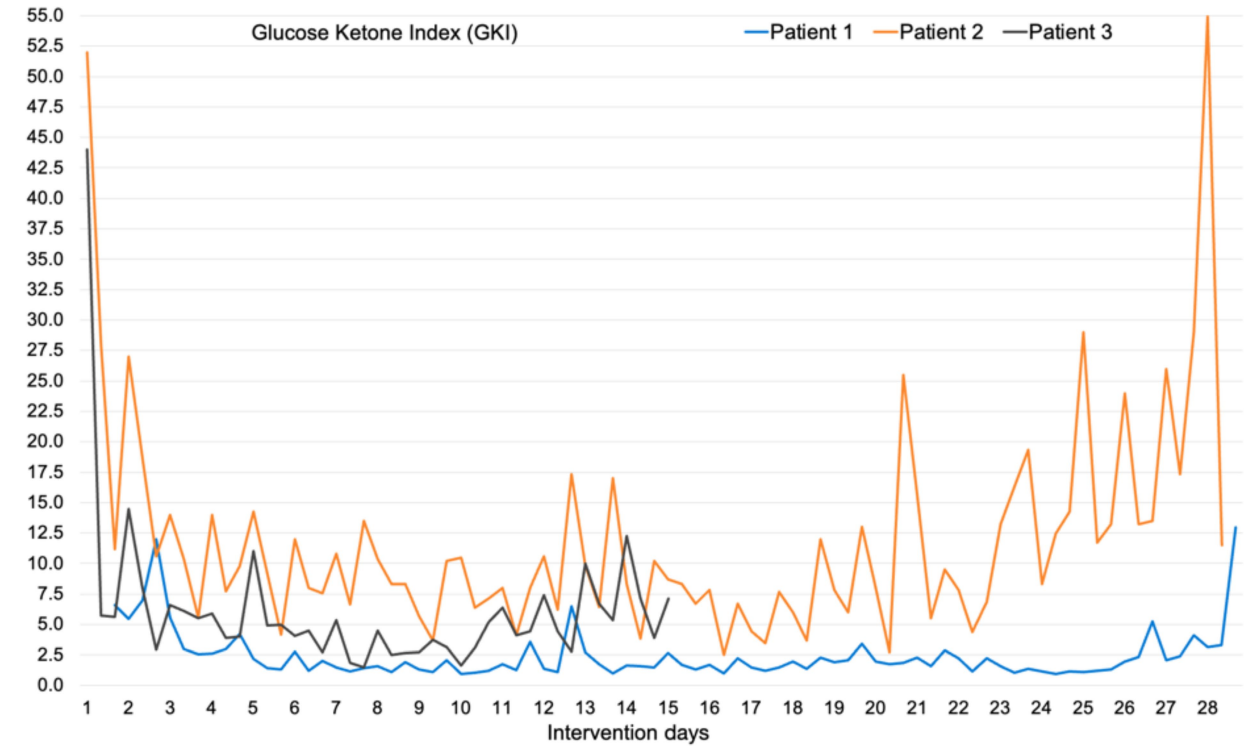


FIGURE 3
Glucose Ketose Index (GKI), the ratio of blood glucose to blood $\beta$-hydroxybutyrate, in all three patients. Calculated from all three daily measurements.

TABLE 3 Number and percent of days with adverse reactions in all patients and participant-perceived degree of adverse reactions measured with a daily self-assessed 5-point Likert scale (0: no adverse reaction, 4: strong adverse reaction).

| Patient | Intervention days | Diarrhoea | Constipation | Nausea | Stomachache | Headache | Dizziness | Fatigue |
|---|---|---|---|---|---|---|---|---|
| 1 | 28 | 1 (4%) | 5 (18%) | 14 (50%) | 6 (21%) | 8 (29%) | 12 (43%) | 5 (18%) |
| 2 | 28 | 3 (11%) | 18 (64%) | 2 (7%) | 3 (11%) | 27 (96%) | 0 (0%) | 26 (93%) |
| 3 | 14 | 1 (4%) | 4 (29%) | 4 (29%) | 14 (100%) | 14 (100%) | 8 (57%) | 14 (100%) |
| Participant-perceived degree of adverse reactions (0: no adverse reaction, 4: strong adverse reaction) | | | | | | | | |
| 1 | 28 | 0.11 ± 0.58 (0) | 0.44 ± 1.09 (0) | 1.5 ± 1.73 (0.5) | 0.35 ± 0.75 (0) | 0.59 ± 0.97 (0) | 1.3 ± 1.73 (0) | 0.22 ± 0.51 (0) |
| 2 | 28 | 0.14 ± 0.45 (0) | 0.96 ± 0.84 (1) | 0.07 ± 0.26 (0) | 0.11 ± 0.31 (0) | 1.75 ± 0.84 (2) | 0 ± 0 (0) | 1.89 ± 0.64 (2) |
| 3 | 14 | 0.08 ± 0.28 (0) | 0.38 ± 0.65 (0) | 0.58 ± 0.9 (0) | 1.77 ± 0.6 (2) | 2.15 ± 0.8 (2) | 1.08 ± 1.04 (1) | 2.69 ± 0.63 (3) |

Data is presented as number of days (percent of days) and mean ± SD (median).

included (75% [95% CI: 30 to 95%]). We therefore surpassed our goal of including ≥60% eligible patients by 15% but did not reach the aim of including 10 patients in total.

In this study, the treating physician performed pre-screening of their patients and referred eligible patients to the investigator for a full screening visit. This recruitment strategy was approved by REK and was intended to inform the patients about the study and inquire about interest, without patients feeling pressured to participate. The ethics approval stated that the investigator could not contact patients directly before a referral was made. We therefore depended on clinicians pre-screening patients for the study. Southern Oslo DPC at Oslo University Hospital receives patients from three Southern districts in Oslo, Norway. It was estimated before the study that a large proportion of the patients would be eligible, yet only four patients were referred by their treating physician to the investigator. The aim was to continue including patients until 10 patients completed the full 4-week intervention, but due to lack of referrals, this was not achievable within the timeframe of the study. It is unlikely that insufficient recruitment for the study is due to a small patient population to recruit from. We speculate that the main reason for the lack of referrals is that patients did not become aware of the ongoing study and were not asked if they were interested. Even though the investigator reminded clinicians about the study, held presentations and handed out material about the study, busyness likely made them forget to pre-screen their patients, and it is also possible that some found it inappropriate to inform patients about the study during treatment sessions. A large number of clinicians in this

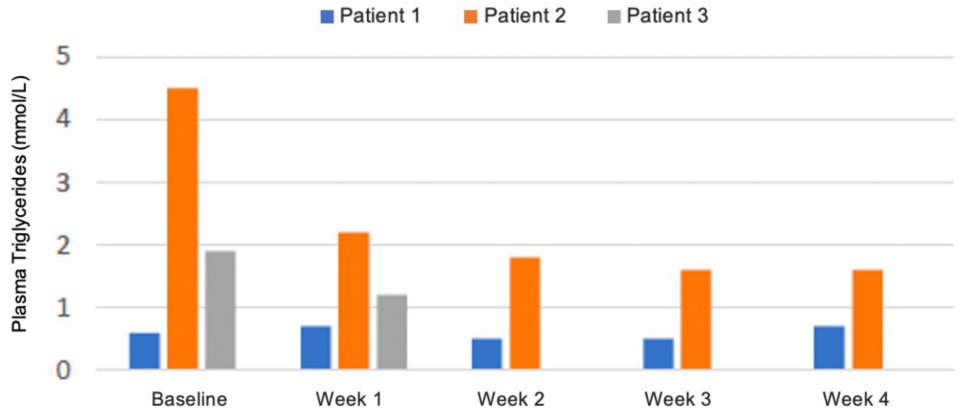


FIGURE 4
Plasma levels of triglycerides in mmol/L from baseline to week 4. Patient 3 dropped out of the study before blood measurements were taken after 2 weeks. Blood samples were taken postprandial and not in a fasted state. *Reference values for adults: triglycerides <2.0 mmol/L.*

clinic are psychologists, and they may be less knowledgeable and perhaps more sceptical about unproven biological treatments. The investigator was not a full-time employee at DCP and was only present at the clinic when seeing patients and attending meetings, conferences and presentations, which could have contributed to the study being easier to forget by the clinicians, than if a full-time colleague was running the study. There could also be other reasons that the clinicians did not want their patients to participate. Patients could also not wish to participate due to diet preferences, the extent of the diet intervention, and measurements/registrations that should fit into everyday life, often with other family members, concurrent with debilitating PTSD. The clinical experience at DPC is that many PTSD patients use food for comfort and emotional regulation. The hospital also has many patients with refugee backgrounds, some who have experienced torture, or other patients who have experienced events that make repeated finger-pricker blood tests a reason not to participate. Five PTSD patients not in treatment at DPC contacted the investigator with interest in participating in the study. Unfortunately, these patients could not be enrolled in the study due to the ethics-approved protocol where only outpatients in treatment at DPC could be included. The study team did also receive requests from PTSD patients and clinicians both in Europe and in the USA, asking for participation in the study. It is therefore our impression that there is a large interest and possible need for this intervention in the PTSD population. A limitation of this study is that clinicians did not register data from the pre-screening and therefore the actual number of eligible PTSD patients at DPC during the inclusion period is not known.

All participants in this study were women, who have a 2 to 3 times greater chance of developing PTSD than men after traumatic events, with an approximate 2:1 ratio of women to men with diagnosed PTSD (122, 123). Women also seem to seek treatment more often than men (124). An overrepresentation of women in the study was expected. The mean age was 49.3 ± 4.0 years and the mean PCL-5 score for severity of PTSD symptoms was 59 ± 10. In a randomised controlled trial (RCT) with female veterans with PTSD ($n = 104$), who experienced sexual trauma during service, the mean age was 48.4 ± 11.1 years. The study included two different treatment groups with baseline mean PCL-5 scores: 50.8 ± 11.7 ($n = 56$) and 50.4 ± 12.1 ($n = 46$) (125). Taking into account the small sample size, the population in this study is similar in age and severity of PTSD symptoms to larger populations with female PTSD patients.

## Maintaining ketosis

Patients 1 and 2 attained ketosis on day 2, and patient 3 on day 1. At least one b-BHB measurement was ≥0.5 mmol/L in all patients on the first day of the intervention, on the first (morning), second (mid-day), or third (evening) measurement of the day. For maintaining ketosis criteria, we set a goal of ≥75% of days in ketosis since ketosis was attained, based on a study by McDonald et al. in epilepsy patients (113). Ketosis was maintained in 87% of the intervention, meaning that this goal was achieved and surpassed by 12%.

Patient 3 maintained ketosis in 100% of days and patient 1 had one day not yet in ketosis on intervention day 1 (mean daily b-BHB 0.43 mmol/L). Patient 2 maintained ketosis in 71% of days (20 of 28 days) despite being 100% compliant with KD-KS, according to daily nutrition registration and conversations several times a week with the investigator. This patient had the highest BG and lowest b-BHB levels (mean b-BHB 0.6 mmol/L, highest b-BHB 1.1 mmol/L) (Figure 2) out of the three patients. Especially in the last week of intervention, b-BHB levels started to drop while BG levels stayed the same, and this seemed to be caused by adding Sukrin® Fibre Bread (low-carb bread, per 100 g: 163 kcal, 8.4 g fat, 2.5 g carbohydrates, 21 g fibre, 8.7 g protein) to the diet. Baseline triglycerides, total cholesterol, and LDL were elevated in this patient, baseline BMI was 32 and the patient had prediabetes, metabolic syndrome, and hypothyroidism, which explains the elevated blood lipids at baseline. b-BHB levels were lower in this patient after a long overnight fast or on days with reported lower food intake, and on days with higher fat intake b-BHB levels were higher. The investigator encouraged the patient to consume more of the provided food products with a high-fat content, but unfortunately, the patient did not find them palatable. Patient 1 achieved the highest b-BHB levels (mean daily b-BHB 2.2 mmol/L) and had the lowest BG throughout the study (Figure 2). This patient was normal weight (baseline BMI 22.6), baseline triglycerides were within the reference range and baseline total cholesterol and LDL were slightly above reference values. This patient had the highest fat intake (Table 4) and primarily consumed the food products provided in the study. b-BHB levels increased in this patient on days with low food intake. In patient 3 mean daily b-BHB was 1.1 mmol/L with the highest measurement of

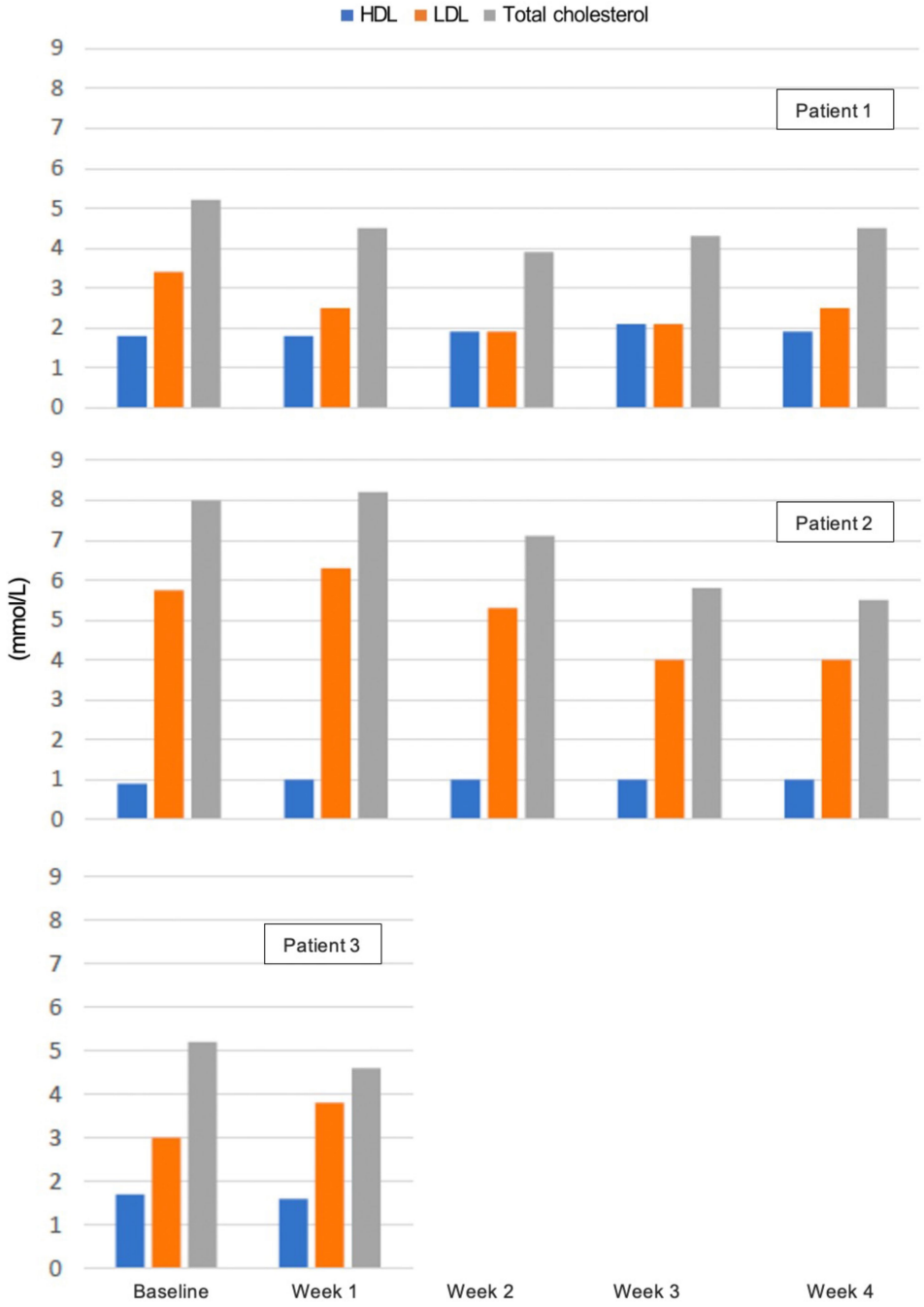


FIGURE 5
Plasma levels of total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) in mmol/L from baseline to week 4. Patient 3 dropped out of the study before blood measurements were taken after 2 weeks. Blood samples were taken postprandial and not in a fasted state. *Reference values for adults: total cholesterol <5.0 mmol/L, HDL > 1.2 mmol/L (women) / >1.0 mmol/L (men), LDL < 2.6 mmol/L.*

2.1 mmol/L. During week 1 mean daily b-BHB was on average approximately 1.0 mmol/L and after increasing fat intake b-BHB levels increased to >2 mmol/L but decreased again to approximately 1.0 mmol/L when the patient could not sustain the higher fat intake. This patient had a baseline BMI of 32.2, normal triglycerides, and total cholesterol and LDL just above the reference range.

In this study, patients were encouraged to predominantly consume the ketogenic ready meals and food products provided, but also had the option to prepare their own ketogenic meals and snacks with guidance from the investigator. Patient 1 primarily consumed the food products provided in the study, while the other patients consumed few of the provided food products and primarily prepared their own ketogenic meals. All patients consumed their exogenous ketone supplement Ketostart® throughout the day. Despite the freedom to choose preferred food items and compose their own meals, ketosis was maintained in 87% of the intervention, which is a strength of this study. With many PTSD patients using food for comfort and emotional regulation, it was a success that ketosis could be maintained

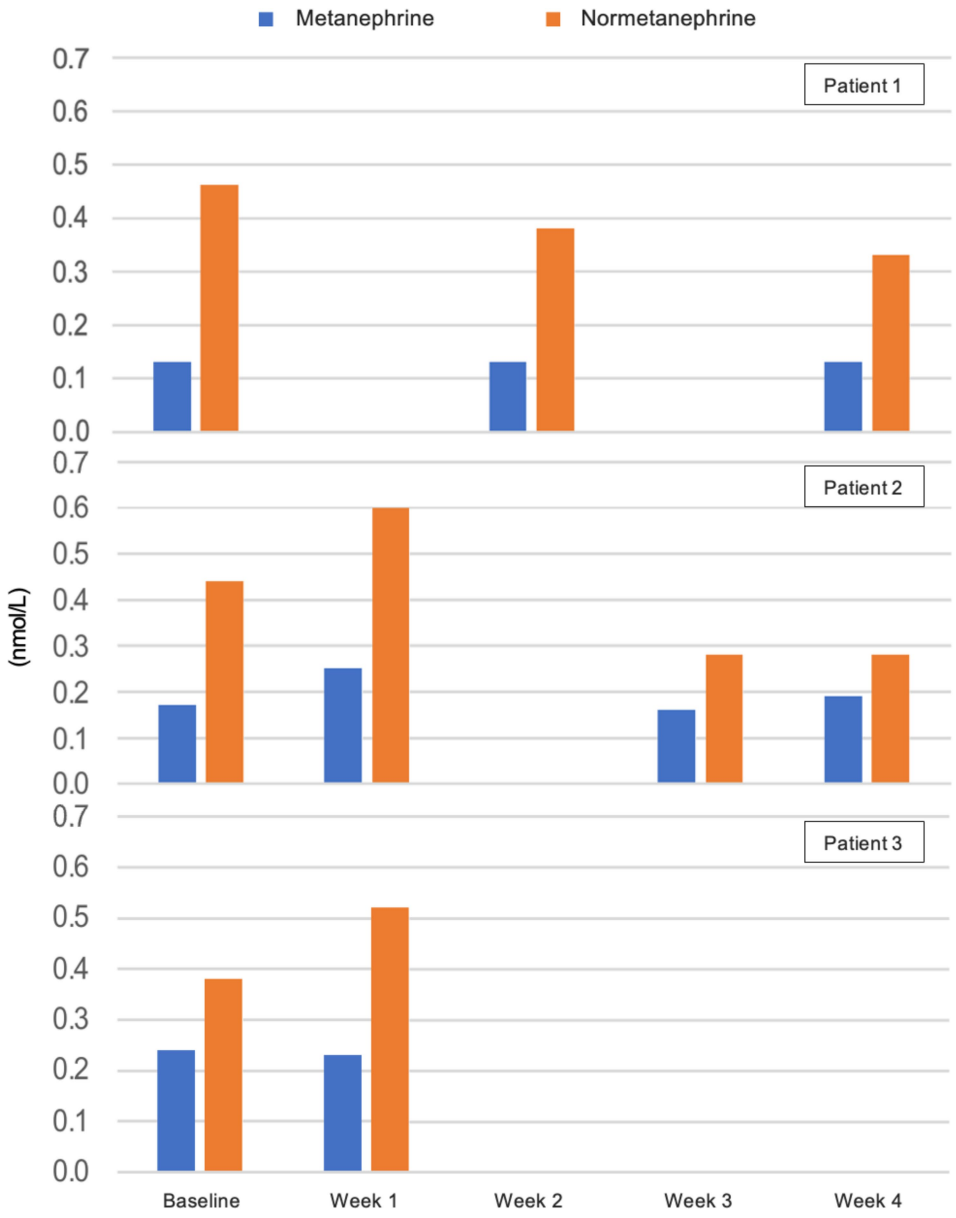


FIGURE 6
Plasma levels of metanephrine and normetanephrine in nmol/L from baseline to week 4. Results lacking at weeks 1 and 3 in patient 1 and in week 2 in patient 2 are due to haemolysis of blood samples. Patient 3 dropped out of the study before blood measurements were taken after 2 weeks. *Reference values for adults: metanephrine <0.34 nmol/L, normetanephrine <0.76 nmol/L.*

to this extent during a 4-week intervention in two patients, and 2 weeks in one patient.

Another strength is that b-BHB and BG were measured three times daily with GKI-Bluetooth Blood Glucose & Ketone Meter® (Keto-Mojo Europe B.V., Amsterdam, Netherlands), and only 2% of measurements were missed. b-BHB and BG measurements were uploaded to an app on the patient's phone, which synchronised with MyMojoHealth's online platform for practitioners. The investigator and study team could follow the measurements in real-time, which allowed reaching out to patients if measurements were missed, or measurements showed a lack of compliance. Furthermore, GKI-Bluetooth Blood Glucose & Ketone Meter® meets the accuracy criteria in ISO 15197: 2013 standard (126, 127) and is commonly used in other trials (65, 128–131). ISO 15197: 2013 does not specify the accuracy of b-BHB measurements. It should be noted that the accuracy of BG measurements may be affected by biochemical changes that often occur in ill patients and by the medication they receive. Little is known about the influence of these factors on b-BHB measurements (132).

## Occurrence of serious adverse reactions and adverse reactions to the ketogenic diet supplemented with $\beta$-hydroxybutyrate salt

For the occurrence of SARs and ARs to the KD-KS we set a goal of ≤5% of intervention days with SARs in 100% of patients and ≤30% of intervention days with ARs in ≥75% of patients, based on the

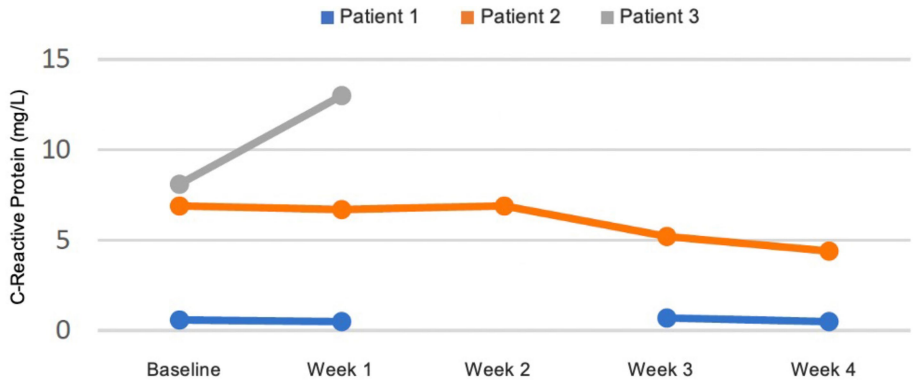


FIGURE 7
Plasma levels of C-reactive protein (CRP) in mg/L from baseline to week 4. Results lacking at week 2 in patient 2 are due to haemolysis of blood samples. Patient 3 dropped out of the study before blood measurements were taken after 2 weeks.

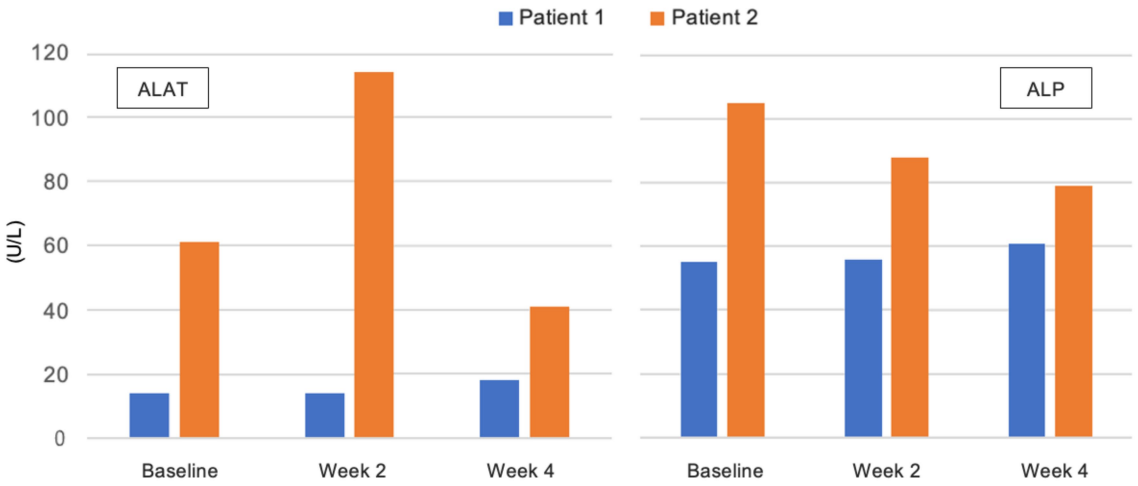


FIGURE 8
Plasma levels of alanine aminotransferase (ALAT) and alkaline phosphate (ALP) in U/L from baseline to week 4. Patient 3 dropped out of the study before blood measurements were taken after 2 weeks. *Reference values for adults: ALAT 10-45 U/L, ALP 35-105 U/L.*

TABLE 4 **Mean daily nutrition intake for all patients during the intervention.**

| Patient | Energy (kcal) | Fat (g) | Carbohydrate (g) | Sugars (g) | Dietary Fibre (g) | Protein (g) | Fat E% | Carbohydrate E% | Protein E% |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1,937 | 152.5 | 26.5 | 14.8 | 27.7 | 94.6 | 69.2 | 8.4 | 20.1 |
| 2 | 1,628 | 126.0 | 13.2 | 8.6 | 21.3 | 99.2 | 67.2 | 6.1 | 25.3 |
| 3 | 1,582 | 117.3 | 15.6 | 10.2 | 12.6 | 91.0 | 65.9 | 5.7 | 24.0 |
| **Mean** | **1,716** | **131.9** | **18.4** | **11.2** | **20.5** | **94.9** | **67.4** | **6.7** | **23.1** |

E%: energy percent.

results from two Cochrane reviews by Martin-McGill et al. in epilepsy patients (116, 117). There were no SARs and a total of 70% of intervention days with ARs, and therefore the occurrence of ARs to the KD-KS were not within the predefined goals.

Headache followed by fatigue were the most frequent and the strongest perceived ARs by the patients. When entering the study two patients suffered from fatigue, all three patients from fibromyalgia, two from headache, and one from bipolar disorder type 2. Headache, particularly migraine, and fatigue are frequent comorbid symptoms of PTSD, fibromyalgia, and bipolar disorder 2 (133–135). In patient 1 there was a 40% improvement of the RAND-36 subscale: energy and fatigue, and in patient 2 there was no change. Pain improved by 13% in patient 1 and by 10% in patient 2. Headache and fatigue are transient symptoms, often referred to as "keto flu", that can occur when adapting to a KD and are most likely due to the sudden decrease in carbohydrates and sugars, and the initial increased urinary excretion of electrolytes, especially sodium, and potassium (136, 137). It is not possible to distinguish between headache and fatigue due to

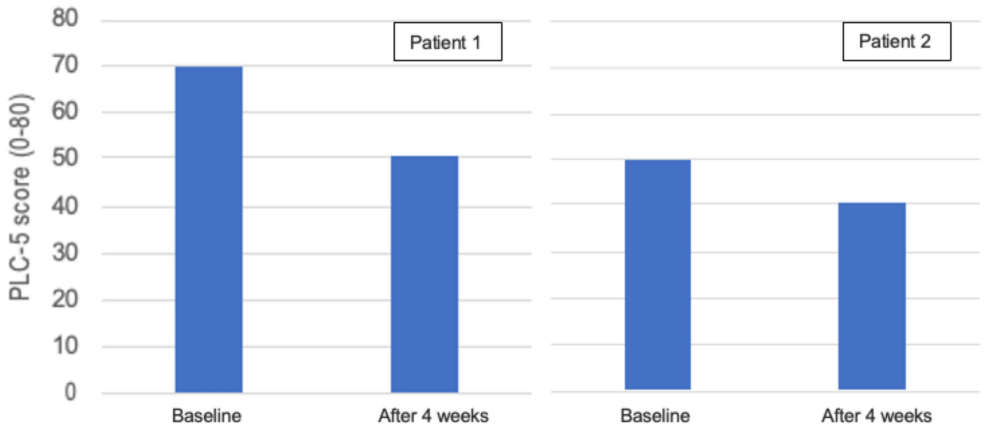


FIGURE 9
PTSD Checklist for DSM-5 (PCL-5) in patients 1 and 2 at baseline and after 4 weeks. PCL-5 is a 5-point scale with 20 questions (119). Each question is answered based on the frequency of experiencing a particular symptom, ranging from 0 (not at all) to 4 (very often). The minimum value is 0 and the maximum value is 80, the lower the score the better.

TABLE 5 Weight and body mass index (BMI) changes from baseline until the end of the intervention in all patients.

| Patient | Weight Baseline (kg) | BMI Baseline | Weight Week 1 (kg) | Weight Week 2 (kg) | Weight Week 3 (kg) | Weight Week 4 (kg) | BMI Week 4 | Weight Difference (kg) | BMI Difference |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 63.1 | 22.6 | 63.1 | 62.9 | 63.6 | 62.9 | 22.6 | −0.2 | 0 |
| 2 | 85.0 | 32.0 | 81.6 | 80.6 | 79.9 | 79.9 | 30.1 | −5.1 | −1.9 |
| 3 | 92.0 | 32.2 | 88.6 | 88.5 | – | – | – | −3.5 | −0.8 |

PTSD and comorbidities, and ARs caused by the intervention. A significant improvement from baseline in energy and fatigue in patient 1, no change in patient 2, and improvement in pain in both patients, suggests that the frequent occurrence of headache and fatigue during the intervention are mainly due to pre-existing conditions. Percent of intervention days with other ARs were constipation 39%, stomachache 33%, nausea 29%, dizziness 29%, and diarrhoea at 7%, and the participant-perceived degree of these ARs was low, with the exception of stomachache in patient 3 which was perceived as moderate. This is consistent with the results of two Cochrane reviews by Martin-McGill and al., examining the KD for drug-resistant epilepsy, where the most commonly reported ARs to the KD were gastrointestinal symptoms (116, 117).

There was a beneficial effect on plasma triglycerides, total cholesterol, and LDL, especially in patient 2, where significantly elevated levels normalised. LDL increased from 3.0 to 3.8 mmol/L in patient 3, but due to the patient dropping out of the study after 2 weeks, there was only one measurement 1 week after baseline, and it is unknown if this value would decrease again, if the patient had completed the 4-week intervention. The KD can result in an often-temporary increase in LDL, but long-term effects are often an increase in HDL and a decrease in LDL (138, 139). An exception is a subgroup of lean individuals called "Lean Mass Hyper-Responders", that responds to carbohydrate restriction with a larger increase in LDL (140). It should be considered that all blood samples were taken postprandial and not in a fasted state, which affects the levels of circulating blood lipids. It would have been optimal to measure fasting levels of blood lipids to eliminate the effect of the previous high-fat meal, but measurements were taken in connection with appointments at DPC at any time of day, and it was not feasible to ask the patients to fast until later in the day.

CRP at baseline in patients 2 (7 mg/L) and 3 (8 mg/L) was indicative of low-grade inflammation seen in obese patients with metabolic syndrome (141). CRP was ≤1 mg/L in patient 1 with a healthy BMI. There was an increase in CRP in patient 3 from baseline (8 mg/L) to week 1 (13 mg/L) which could indicate an incipient infection. In patient 2 CRP decreased from 7 to 4 mg/L in 4 weeks, which may be due to the anti-inflammatory effects of the KD-KS (22, 94, 95). For unknown reasons, ALAT increased in patient 2 from 62 to 115 U/L after 2 weeks and decreased to 41 U/L, within reference range, after 4 weeks. In the same patient and period, ALP decreased from 105 to 79 U/L.

## Acceptance of treatment

For the acceptance of treatment criteria, we set a goal of ≥75% of patients accepting the treatment in ≥75% of intervention days (113). All patients accepted the treatment in 100% of days, even though patient 3 only completed a 2-week intervention, hence this goal was met. With this small sample size of three patients, the dropout rate was 33%. Due to the lack of diet intervention studies in this population, more research is needed to establish the dropout rates in larger powered studies. A high dropout rate was expected despite close monitoring. PTSD is considered the most severe and pervasive trauma disorder, and patients experience numerous distressing symptoms and limitations that significantly impact their lives (6, 10, 142). A strength of the study is that 2 of 3 (67%) patients found the dietary intervention

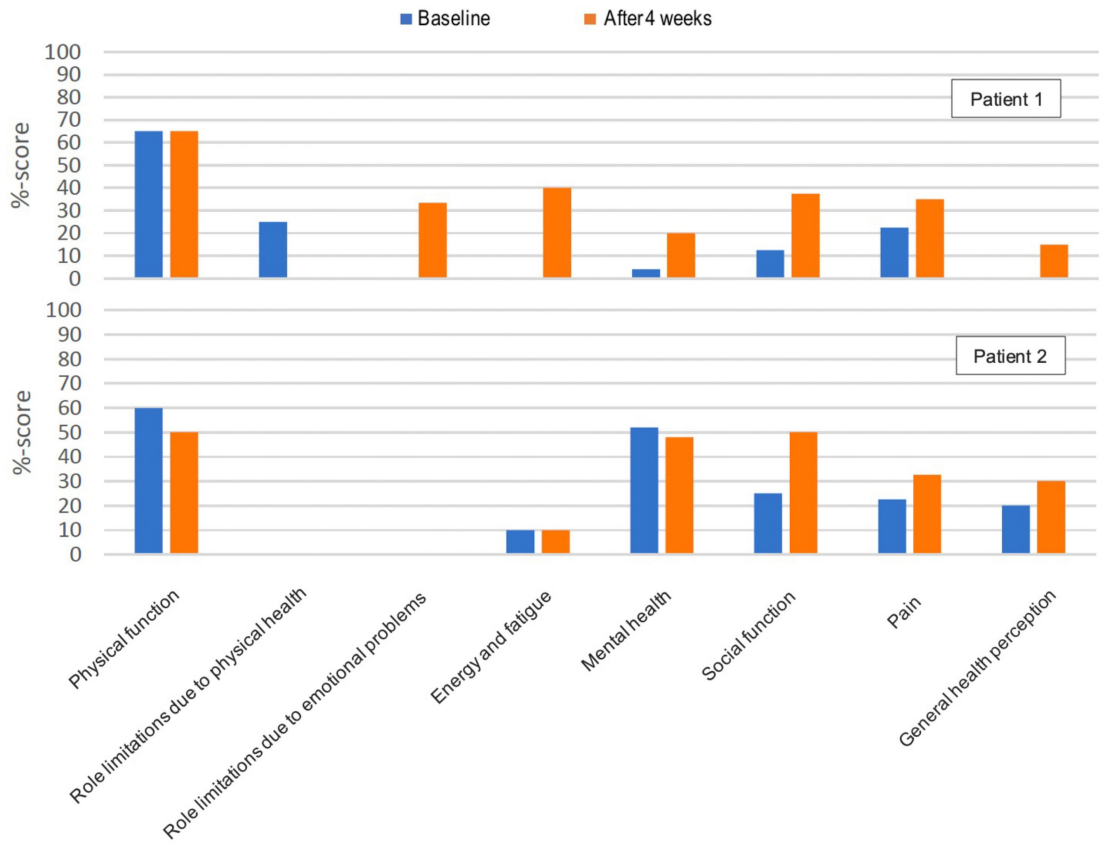


FIGURE 10
Health-related quality of life (RAND-36) (120) in patients 1 and 2 at baseline and after 4 weeks. The score represents a percentage of the total possible score, ranging from 0 to 100%. Higher scores are better, and 0 is worse.

and daily measurements/registrations not demanding to slightly demanding, even though baseline severity of PTSD symptoms (PCL-score) were 70 and 50, respectively. The patient who dropped out of the study found the dietary intervention moderately demanding in 64% of days, quite to very demanding in 36% of days, and the daily measurements/registrations quite to very demanding in 21% of days. The reason given by this patient for withdrawing from the study, was because all the procedures, planning, and cooking became too demanding. The patient did not like any of the food products provided, adding to the burden of planning meals, cooking, measuring food/fluid, and registering daily nutrition intake. Before entering the study, the patient struggled with fatigue, and some days could be particularly challenging, making ready meals and products preferable. After the first intervention week, the patient stated that she found it exhausting but wanted to continue in case the first week was the toughest. She felt increasingly fatigued in week 2 and ultimately chose to withdraw after day 14.

Due to import rules between the United Kingdom and Norway and no other known provider of ketogenic ready meals shipping to Norway from elsewhere, the variety of ready meals offered in this study was limited to six meals that were all vegan. Two were soups, two contained jackfruit and two contained mushrooms. The ready-to-drink ketogenic formulation K.Flo® (vanilla flavour) and semi-solid ketogenic formulation K.Yo® (vanilla/chocolate flavour), were intended for breakfast, snack/dessert, and/or meal replacement. It was intended to provide the patients with complete nutrition to ease the intervention and help with compliance. To prevent dropouts in future studies in this population, a larger variety of ketogenic ready meals must be provided to suit different preferences and ease the burden of food shopping and cooking. In this study, all nutrition and fluids were registered daily. When all meals are provided this is less of a burden for the patients, but when patients prepare ketogenic meals themselves, daily nutrition registration can become too strenuous. For future studies, choosing the most important data to collect and lessening registrations by the patient could potentially lead to more patients completing the intervention.

Continuous glucose monitors have now been on the commercial market for some time and continuous ketone monitors and consumer biowearables that can measure glucose, ketones and other substrates like lactate and ethanol are on their way to market. Especially in the subpopulation of PTSD patients who have experienced bodily harm and torture, finger-pricking to obtain daily ketone and glucose measurements can be triggering and not feasible. To ease the burden of measurements and to be able to include patients who do not want to perform finger-prick blood measurements, a continuous dual ketone/glucose monitor would be optimal for future trials. This will also provide the researchers with more data and may ease compliance in real-time when both patients and investigators can follow the daily glucose and ketone fluctuations. For patients not willing or able to follow a KD intervention, using exogenous ketone supplementation with other more moderate diet protocols or the patients' habitual diet, is also something that should be examined in future trials.

## Exploratory outcomes

The PTSD symptoms measured with PLC-5 decreased by 20 points (70 to 50) in patient 1 and by 10 points (50 to 40) in patient 2. A change of 5–10 points is considered a reliable change (more than random variation) and a change of minus 10–20 points indicates a clinically meaningful change (143). Patient 1 was concurrently in psychological therapy, so any potential isolated treatment effect of the KD-KS intervention cannot be estimated. The patient reported various influences on PTSD symptoms that were perceived positively. She described improved sleep with significantly fewer nightmares, increased energy (Figure 10), and a better ability to concentrate in conversations without "spacing out." Her nightmares returned on days when b-BHB levels were lower (approximately 1.0 mmol/L), due to the introduction of Sukrin® Fibre Bread into the diet. She also experienced more pain on those days, but she thought that stomach discomfort from the high fibre content in the bread made her more sensitive to other bodily pains. Patient 2's psychologist was on sick leave throughout the study, so it can be argued that there may be a more direct connection between ketosis and the reduction in PTSD symptom severity. The patient consistently had lower levels of b-BHB than patient 1 throughout the study. Patient 2 described that her nightmares were less intense than they used to be. She expressed a sense of increased clarity and energy in her mind, and, overall, she felt better. Hypothetically, diet-induced ketosis could be a complementary therapy that potentially can enhance the benefits of psychological therapy by helping the patient stay within the window of tolerance, neither hyperaroused nor hypoaroused, where they are receptive to psychological therapy and able to process trauma (88, 89, 98–100), but this hypothesis needs to be tested in future studies measuring an effect. Reasons for patient 1 experiencing a greater improvement in PTSD symptoms may include a higher initial score, making the change easier to detect. This patient was concurrently undergoing psychological therapy and consistently achieved higher b-BHB levels throughout the study. There is no established knowledge about the optimal level of ketosis for the best therapeutic effect in various neurological and mental disorders, but some studies show a dose–response relationship (65) and there might be an individual threshold to surpass. There is a direct relationship between the concentration of ketones in the blood and the proportion of ketones oxidized to ATP (144). Higher levels of ketones supply the brain with more energy, as an alternative fuel source to glucose, and in addition to being an energetic metabolite, BHB is also a signalling metabolite that affects epigenetic gene regulation and cellular function and has important neuroprotective effects (39, 40).

One can speculate that quality of life measured with RAND-36 also may be correlated with increasing levels of b-BHB. This correlation may be indirect, as the reduction of PTSD symptoms naturally influences it. However, it may also be direct by increasing energy and reducing pain and inflammation (94, 95, 145, 146). During conversations with the investigator, both patients reported improved overall quality of life. At baseline, patient 1 had very low scores on seven of eight of the RAND-36 subscales, where three subscales: role limitations due to emotional problems, energy and fatigue, and general health perception, was 0% which represents the poorest possible function. These three subscales increased to 33, 40, and 15%, respectively and one can argue that an increase in quality of life from 0 to 30% may be more noticeable and valuable for the patient, than a change from 30 to 60%. During this relatively short intervention period of 4 weeks, the six subscales related mostly to mental factors: mental health (+16%), role limitations due to emotional problems (+33%), social function (+25%), general health perception (+15%), energy and fatigue (+40%), and pain (+13%), improved in patient 1, while the two subscales related to physical factors: physical function (+0%) and role limitations due to physical health (-24%), stayed constant or decreased. This suggests that the potential beneficial effects of ketosis that occur rather fast, are predominantly mental, while beneficial effects on physical factors, especially role limitations due to physical health, are not seen during this 4 weeks intervention. This is consistent with trials in weight loss, and in neurological and mental disorders, where ketosis is shown to be beneficial on mental factors (66, 83, 147–149), while studies also show that physical factors can decrease in the initial weeks of "keto-adaptation" and beneficial effects on physical factors, e.g., physical function and performance, happen first after 3–4 weeks and can continue to improve up to 6 months and potentially longer (44, 145, 150–153).

In patient 2 several of the baseline scores were higher than in patient 1, indicating better functions in the subscales: mental health (+44%), social function (+12%), general health perception (+20%), and energy and fatigue (+10%) in this patient, but the baseline score for role limitations due to physical health was lower (-24%). Three of eight subscales improved during the intervention: social function (+26%), pain (+10%), and general health perception (+10%), while role limitations due to physical health and role limitations due to emotional problems remained on a score of 0%, energy and fatigue remained on a score of 10%, physical function decreased by 10% and mental health by 3%. During the last assessment in the study, the patient mentioned that the last week of intervention had been a bit mentally challenging, and motivation had been lower without knowing exactly why. She suggested that it may have influenced the responses to the psychological measurements at the end of the study. This is most noticeable on the subscale: energy and fatigue, where she noted feeling more energised throughout the intervention.

Even though the baseline score for social function was 12% higher in patient 2, the increase in this subscale was 26 and 25% in patient 2 and patient 1, respectively. There was also a similar improvement in both patients in general health perception by 20 and 15%, and in pain by 13 and 10% in patient 2 and patient 1, respectively. Energy and fatigue did not improve in patient 2 while it improved by 40% in patient 1. The difference in the baseline score by +10% in patient 2 could have made a slight difference and patient 2 stated being more energised for the first 3 weeks of intervention. Role limitations due to physical health did not change from 0% in patient 2, while it decreased from 24 to 0% in patient 1. Physical function did not change in patient 1 but decreased by 10% in patient 2. Role limitations due to emotional problems remained at 0% in patient 2 and increased by 33% in patient 2. In patient 2 mental health decreased by 3% while improving by 16% in patient 1. This all shows some similarities in the improvement on the RAND-36 in both patients, but also differences that could depend on various factors such as different baseline function on RAND-36, therapy versus no therapy, differences in metabolic health and

comorbidities, and the severity of PTSD symptoms at baseline, which was higher in patient 1 who also had a two times reduction in PTSD symptoms compared to patient 2, and also in differences in level of ketosis.

Like patient 1, patient 2 experienced an increase in symptoms in the days following the introduction of Sukrin® Fibre Bread as a variation to seed crackers (Norwegian crispbread). On the days when the bread was consumed, the patient fell out of ketosis. Throughout the study, patient 2 had lower levels of b-BHB than patient 1, but there may have been a beneficial effect even at low to moderate b-BHB levels (0.5–1.0 mmol/L). When entering the study, patient 2 suffered from chronic joint pain in the fingers and daily intense headaches. After the first week on KD-KS, joint pain and swelling significantly decreased, and the intensity of headaches was reduced, with some days being completely symptom-free. The KD is investigated as an intervention in migraine and studies are showing promising results (101, 102). The known anti-inflammatory properties of the KD can be why this patient experienced less joint pain and swelling during the intervention (94, 95).

## Conclusion

To the best of our knowledge, this feasibility study is the first clinical human trial examining a KD supplemented with exogenous ketones as a treatment intervention in patients with PTSD. Over 4 weeks, we observed that KD-KS led to clinically meaningful improvements in PTSD symptoms and health-related quality of life. In total, three of four predefined feasibility criteria were achieved, but the aim of including 10 patients was not reached. There is a large uncertainty to whether there were eligible patients not referred to the study. Ketosis was achieved within one to two days and maintained during the intervention, there were no SARs, the occurrence of ARs was high and not within the predefined goals, but the participant-perceived degree of ARs was low. A large proportion of registered ARs were likely due to pre-existent comorbidities and symptoms of PTSD. Despite this, the treatment was accepted by all patients in 100% of intervention days even though one patient dropped out of the study after 2 weeks due to exhaustion and fatigue.

### Recommendations for future research

Even though the sample size is small, the knowledge obtained in this study is important for the planning of future studies with KD and exogenous ketone interventions in this patient group. Further feasibility and pilot studies should be performed with larger sample sizes to determine feasibility and safety before planning future RCTs. Due to the complexity of the patient group with many comorbidities and confounders affecting the results, future RCTs must be carefully planned, and the sample sizes must be powered to examine a possible effect of ketosis on PTSD. To assure higher recruitment for future trials, it is preferable that the investigator works full-time at the study site during the study, and possibly more presentations and conferences can be held to educate and remind the clinicians about an ongoing study. Also, choosing a site with a larger research department and with clinicians more experienced in biological interventions would be a benefit. Designing a multicenter study, performing a study on inpatients, or including patients that are not currently in inpatient/outpatient care are other ways to increase recruitment. Finding other ways to pre-screen patients through a research nurse/assistant or through a survey/internet platform, where all patients at the clinic are systematically pre-screened for eligibility would be optimal. To ease the burden of the intervention on patients and help with compliance, it is recommended to provide the patients with complete nutrition and carefully choose which data to collect, to minimise registrations by the patient. Using continuous glucose and ketone monitors in future trials will collect more data while making it easier for the patients and preferably this data is available in real-time through an app or online platform, for both the patient and investigator, to be able to intervene fast and adjust the diet according to the results of measurements. Using continuous monitors may also make it feasible for patients not wanting to perform finger-prick blood measurements, e.g., PTSD patients who experienced bodily harm and torture, to participate. Using more simple interventions like exogenous ketone- or medium-chain triglycerides (MCT) supplementation with less restrictive diet protocols, is also something that should be examined in future trials. Exogenous supplemental lactate is of interest in brain injury research as it can boost cerebral energy metabolism and potentially reduce neurodegenerative processes (38, 154, 155) and could potentially be investigated in PTSD. To be able to compare the results of future studies, it is important to standardise ketogenic nutrition protocols both in animal and human studies.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

## Ethics statement

The studies involving humans were approved by Regional Committees for Medical and Health Research Ethics South East Norway. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

ME: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. TF-J: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Validation, Visualization, Writing – review & editing. ES: Conceptualization, Resources, Supervision, Writing – review & editing. ST: Conceptualization, Resources, Supervision, Writing – review & editing. JA: Conceptualization, Methodology, Supervision, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1406366/full#supplementary-material

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# Ketogenic diet, adenosine, and dopamine in addiction and psychiatry

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Adhering to the ketogenic diet can reduce or stop seizures, even when other treatments fail, via mechanism(s) distinct from other available therapies. These results have led to interest in the diet for treating conditions such as Alzheimer's disease, depression and schizophrenia. Evidence points to the neuromodulator adenosine as a key mechanism underlying therapeutic benefits of a ketogenic diet. Adenosine represents a unique and direct link among cell energy, neuronal activity, and gene expression, and adenosine receptors form functional heteromers with dopamine receptors. The importance of the dopaminergic system is established in addiction, as are the challenges of modulating the dopamine system directly. A mediator that could antagonize dopamine's effects would be useful, and adenosine is such a mediator due to its function and location. Studies report that the ketogenic diet improves cognition, sociability, and perseverative behaviors, and might improve depression. Many of the translational opportunities based on the ketogenic diet/adenosine link have come to the fore, including addiction, autism spectrum disorder, painful conditions, and a range of hyperdopaminergic disorders.

KEYWORDS

**ketogenic diet, adenosine, dopamine, psychiatric disorder, addiction, mental health, metabolic psychiatry**

## Introduction

Metabolic therapy with the ketogenic diet (KD) has been used successfully to treat epilepsy in adults and children for over 100 years (1). Adhering to this high-fat, low-carbohydrate protocol can reduce or even stop seizures – even when all other treatments fail, and some pediatric patients are able to discontinue the KD and remain seizure-free (2–6). This effect is also found with laboratory animals (7), indicating a disease-modifying, antiepileptogenic effect found only weakly in some but not present at all in most anticonvulsant medications (8, 9). These observations indicate that this metabolic therapy works via mechanism(s) distinct from other available therapies—and demonstrate clinically that a KD may permanently restore normal brain function.

The proven, long-term efficacy in epilepsy has led to interest in the KD's mechanisms for preventing and treating multiple conditions (such as diabetes), but particularly in other neurological conditions such as Parkinson's disease, Alzheimer's disease, and multiple sclerosis (10), as well as conditions where seizures are often comorbid. Several types of behavioral evidence predict benefits of a KD in reducing common comorbidities other than seizures such as depression (11, 12) and anxiety (11, 13). Most studies report that the KD improves cognition (13–19), improves sociability and repetitive behaviors (20–23), and reduces nociception (24–26): all behavioral endpoints with relevance to dopamine-related behaviors (see below), including perseverative behaviors and potentially chronic pain – thought to share multiple mechanisms and comorbidities with addiction (27). Importantly, KD-related behavioral improvement in children with epilepsy is not solely due to seizure reduction (13, 28–32), thus indicating therapeutic benefits that are uncorrelated with the primary anticonvulsant/antiepileptogenic effects.

Diverse lines of evidence point to the neuromodulator adenosine as a key mechanism underlying short and long-term therapeutic benefits of metabolic therapy with a KD. Adenosine is present throughout the extracellular space, and its levels increase with increased neural activity (33, 34) and a variety of physiological conditions (35). We put forth this hypothesis and its translational predictions in 2008 (36). Since then, we developed metabolic models and provided *in vitro* and *in vivo* evidence that KD feeding elevates brain adenosine (7, 36–39). More evidence has since accumulated (40–42), and many of the translational opportunities based on the KD/adenosine hypothesis have come to the fore, including pain, autism spectrum disorder, neuroprotection, and a range of hyperdopaminergic disorders (35, 36). Adenosine represents a unique and direct link among cell energy, neuronal activity, and gene expression and a direct functional relationship with dopamine. Here, we review several molecular/physiological actions of the KD by which the KD might influence addiction and psychiatric disorders, then delve into specific disorders with respect to KD treatment.

## Adenosine/dopamine interactions

The behavioral importance of the dopaminergic system is well-established – as are the challenges and limitations (side effects, limited therapeutic windows) of modulating the dopamine system directly. Dopamine release is clearly related to the reinforcing effect of drugs of abuse, such as cocaine, which blocks re-uptake of dopamine and so increases extracellular levels of this neurotransmitter. The discussion below is largely focused on cocaine. Chronic use of this drug in people leads to a number of behavioral sequelae, including highly-motivated use even in the face of adverse consequences. Laboratory rodents chronically self-administering cocaine show similar behaviors (43), including no diminution of self-administration even in the face of a signal of impending footshock (43, 44). Remarkably, cocaine cravings increase over 60 days of withdrawal in rodents (45), in accordance with reports in human addiction. PET studies in cocaine-addicted patients show reduced D2 dopamine receptor levels in the basal ganglia and reduced metabolism in the cingulate gyrus and orbitofrontal cerebral cortex (46). Brain effects of cocaine progress with extended self-administration, with extension of metabolic changes from the limbic basal ganglia to the entire basal ganglia in Rhesus monkeys (47), and progressively elevated levels of brain-derived neurotrophic factor in the limbic basal ganglia and amygdala; this protein causes long-lasting amplification of cocaine seeking (48).

A mediator that could interfere with the effects of dopamine (without blocking it completely) would be extremely useful, and adenosine is such a mediator due to its function and its location. Manipulating the adenosine system is common – caffeine, a non-selective antagonist for adenosine $A_1$ receptors ($A_1R$) and adenosine $A_2$ receptors ($A_2R$), is the most widely used psychoactive drug worldwide – and other adenosine antagonists are under consideration for neurodegenerative and psychiatric disorders (49, 50). Notably, subpopulations of richly dopamine-innervated basal ganglia neurons express either a combination of $A_1R$ and D1 dopamine receptors ($D_1R$) or $A_{2A}R$ and D2 dopamine receptors ($D_2R$) (51, 52), and these colocalized receptors form functional heteromers with antagonistic effects on 2nd messenger systems (53–58).

These oppositional relationships also appear at the behavioral level in rodents, in work often involving cocaine. For example, $A_{2a}R$ agonists decreased, whereas $A_{2a}R$ antagonists increased, acute cocaine-induced locomotion, in apparent opposition to the $D_2R$ (57). Selectively knocking out $A_{2a}R$ expression in striatal neurons enhances the locomotor response to cocaine or phencyclidine (58). Chronic caffeine in adolescence increases the locomotion to a challenge dose of cocaine or a $D_2R$ agonist in adulthood (59). Outside the brain, $A_1R$ and $D_1R$ oppositely influence spinal motor circuit output (60). Caffeine reduced the locomotor sensitization response to cocaine in a binge protocol (61). Given during a sensitization regimen, $A_{2a}R$ agonists decreased, whereas $A_{2a}R$ antagonists increased, the sensitized response to a later cocaine challenge (57). Alternatively, $A_1R$ or $A_{2a}R$ agonists given during the cocaine challenge but not during sensitization reduced the expression of cocaine sensitization, in a paradigm in which the adenosinergic drugs were directly infused into the basal ganglia (62).

In the conditioned place preference test, adolescent chronic caffeine enhanced the rewarding effect of cocaine in adulthood (59). An $A_{2a}R$ agonist reduced the reinforcing and motivational aspects of cocaine self-administration (63). $A_1R$ agonists inhibited cocaine- or $D_1R$ agonist-induced reinstatement of extinguished cocaine self-administration (64). Caffeine potentiated the seizure-inducing properties and lethality of cocaine and D-amphetamine (65). Also relevant to drug abuse, adenosine and dopamine (mostly the $A_{2a}R$ and $D_2R$) differentially control motivation (66). Overall, there is an abundance of evidence that adenosine and dopamine receptors are in opposition in their influence on several types of behavior and cognition.

Some evidence suggests the KD alters dopamine directly. The dopamine metabolite homovanillic acid was reduced during KD feeding in pediatric epileptic patients in a study that used CSF as a proxy for tissue dopaminergic activity, though this effect did not differ with presence or absence of anticonvulsant response (67). In rats, tissue homovanillic acid (combined with another dopamine metabolite, dihydroxyphenylacetic acid) was elevated by the KD in cerebral cortex but not basal ganglia or midbrain (68). These differences could be explained by a number of factors, such as species differences, differences in subject maturity, differences in KD strength/composition, or the effective whole-brain sampling of CSF collection. A KD-based mechanism to moderate adenosine and/or dopamine systems would have obvious relevance to neurological conditions, including drug abuse (69, 70).

## Cerebrocortical hypometabolism versus energy replenishment

Hypotheses and clinical and basic research on the link between brain energy and mental health has been a rapidly developing field with case reports, reviews, protocols, and cutting-edge conferences helping to foster a robust and thriving community with real collaboration between patients and professionals (71–76). Compensating for the energy impairment due to ongoing hypometabolism may be a useful treatment for many diverse neurological conditions (77–80). Energy homeostasis – particularly changes in ATP and adenosine – is known to be relevant but poorly understood in neuroprotection, psychiatric disorders and addiction

(81, 82). KDs supply a substrate (ketone bodies) for the citric acid cycle that elevates ATP and promotes mitochondrial function, including in impaired states (83–97).

Brain hypometabolism has been reported with alcohol and online gaming addiction (98), with stimulant abuse (99, 100), in Alzheimer's disease and mild cognitive impairment (101, 102), and indeed even with normal aging (103). As a dynamic and energy-demanding organ, and as a survival mechanism, it makes sense that metabolism is reflected in neurological function and behavior and that mitigating metabolic dysfunction is a potent therapeutic strategy.

## Reduced hyperglycemia and/or inflammation

KDs produce a moderately low but very stable blood glucose (104–107), explaining why it is an effective treatment for diabetes (106, 108, 109). This stabilization of blood glucose may blunt the impact of well-known physiological effects of stress and/or dopamine-induced hyperglycemia (110), and therefore may help stabilize a range of mental states that are influenced by metabolic variability, particularly those that are triggered by or associated with hyperglycemia. Hyperglycemia causes inflammation (111, 112) and is associated with psychiatric re-hospitalization. Inflammation is a biomarker for and perhaps a cause of depression (113), and much evidence shows that KDs reduce inflammation in patients (114–117) and in pre-clinical models (118–121). Importantly, some animal studies found reduced inflammatory markers specifically in brain (122–125). KD feeding seems to limit neuroinflammation via several mechanisms (126).

# Disorders

## Addiction

Based on the relationships among adenosine, dopamine, and the KD, we recently investigated the possible moderating effects of KD treatment on the effects of repeated cocaine treatments (127). Five-week old male and female rats were placed on a KD or remained on normal rodent chow for 3 weeks. A well-established cocaine-sensitizing regimen was then applied: animals received once-daily injections of either saline or cocaine for seven consecutive days, followed by seven drug-free days, and then finally a challenge injection of cocaine. Assessments occurred in an automated system for measuring ambulatory (e.g., walking) and stereotyped (e.g., rearing) locomotor responses. KD feeding continued through the sensitization protocol. All animals receiving the daily cocaine injections showed the expected enhancement of the rearing response, but animals on the KD had a significantly mitigated enhancement. Unexpectedly, ambulatory activity did not sensitize at all in KD-fed animals. These effects of KD on locomotor activity were found in both sexes, and were only observed following injections of cocaine (not saline). A similar pattern was found with the challenge injection: KD treatment moderated the stereotypic response to the challenge. Interestingly, here sex was a factor, with this effect occurring in males only. Thus, KD feeding reduces both the responses to acute cocaine (day one of the sensitizing regimen; challenge day for saline-treated animals) and repeated cocaine. Considered together, these data were the first to show that KD treatment can modify behavioral responses to a monoaminergic stimulant, and suggest that KDs are a potential novel therapy for the treatment of addiction to these drugs. Based on prior studies, we posit that the effects of the KD in this paradigm could be mediated by an effect of adenosine on dopaminergic systems, likely in the basal ganglia.

More recently, the effects of KD treatment were tested in a conditioned place preference protocol, wherein animals learn to prefer a section of the experimental apparatus paired with, in this case, cocaine injections (128). KD feeding did not appear to modulate the acquisition of the cocaine-related place preference. However, when cocaine was withheld (i.e. extinction), mice on the KD more quickly lost the place preference. In addition, a cocaine priming injection after extinction reinstated the place preference only for the standard diet mice; mice that were on KD did not experience reinstatement. The authors hypothesized that the KD effects were via an adenosine/dopamine interaction, and suggested that KD treatment might be especially useful in preventing relapse.

Regarding the commonly abused drug ethanol, in rat models of dependence KD-fed animals made fewer lever presses to receive alcohol during acute withdrawal (129) and had reduced withdrawal symptoms (130, 131). In mice, both KD and a ketone monoester (which is metabolized to ketone bodies) reduced withdrawal symptoms even when treatment was started during withdrawal (132). Clinically, benzodiazepines are given to reduce withdrawal symptoms during detoxification: notably, patients eating a KD during treatment required significantly fewer or lower doses of benzodiazepines (129). Alcohol-related stimuli induced fewer or lower doses of "wanting" and more dorsal anterior cingulate gyrus activation in patients on a KD; neuroinflammatory markers were also reduced (129). An alcohol-dependent metabolism has switched from depending on glucose to depending on acetate; ketone bodies might normalize metabolism by replacing acetate (133). It had been hypothesized that alcohol addiction might relate to adenosine dysfunction in the basal ganglia (134) and a recent study provides direct evidence (135).

Adenosine is clearly involved in the effects of opiates. During a dependence-inducing regimen of morphine and during withdrawal, brainstem adenosine was reduced two-fold (136). During withdrawal, symptoms were reduced with an $A_1R$ agonist or an $A_{2a}R$ antagonist (136) or genetic inactivation of $A_{2a}R$ (137). Consistent with these results, KD feeding reduced symptoms of withdrawal from opiates in mice (138, 139). In addition, KD feeding reduced opiate self-administration (139) and hyperalgesia due to chronic opiate treatment (140). These results suggest a KD, through adenosine, might have some utility in opiate abuse. Conversely, a KD elevated locomotor responses and analgesia to oxycodone. This latter effect, however, could be partially explained by the antinociception due to the KD itself (25, 120).

Food cravings, binge eating being an extreme form, are often considered to be a naturalistic analog of drug abuse. Excessive glucose and insulin spikes are thought to modify the brain leading to addiction-like binge eating; KD feeding will temper such spikes (141). Two pilot studies of KD treatment to patients with food addiction/binge eating disorder underwent KD treatment, leading to significant reductions (142) or complete alleviation (143) of the disorder's symptoms.

## Psychiatric disorders

A recent study found that KD treatment in 28 patients with severe refractory mental illness significantly improved psychotic symptoms and depression; virtually every patient improved on multiple scales (144). Twelve of the patients achieved clinical remission on the Clinical Global Impressions Scale. A majority of patients reduced number or dose of psychotropic medications (in a number of cases, diabetes-related medications were reduced or discontinued) (144). After discharge, 18 patients chose to remain or partially remain on the diet to maintain the psychiatric benefits. Subsequent studies have also found broad KD effectiveness in mental illness such as bipolar disorder and schizophrenia (145–151). Much evidence shows that KDs reduce inflammation in patients (114–117, 152) and in pre-clinical models (118–121). Reductions in inflammation might be particularly germane to depression (113).

An involvement of adenosine (specifically, an alteration in normal adenosine/dopamine antagonism) has long been postulated for schizophrenia (153–155), and adenosine modulators have been tried with some success in patients (156). More recent papers have highlighted abnormalities in adenosine receptor expression specifically in frontal cerebral cortex but not other adenosine receptor expressing regions (157, 158). In parallel, hypometabolism, limited to the frontal cerebral cortex, was indicated in schizophrenia by meta-analysis (159). Therefore, the KD might have beneficial effects via multiple mechanisms. One group found positive effects in an animal model of schizophrenia-like behavior (160–162). A very early attempt to use the KD in schizophrenic patients showed promise but was poorly controlled (163). More recently, beneficial results have been reported, but these are either case reports (164, 165) or have a low number of subjects (five schizophrenic or schizoaffective patients) (151). Larger studies are warranted, although in a study with a substantial sample size the KD reduced schizotypy traits in the general population (166).

Relating to hyperglycemia, diabetes is associated with a higher incidence of several mood and psychiatric disorders (167, 168). A meta-analysis found a significant association between depression and both type I and type II diabetes (169). In diabetic individuals, hyperglycemia is associated with depression (170) and feelings of anger and sadness (171), which may be worse in type I diabetes (170). Such effects are not limited to diabetic patients: hyperglycemia is related to higher readmittance to psychiatric hospitalization (172), and high insulin levels in youth raise the odds of psychosis in young adulthood (173). On more acute timescales, there is some evidence for high glycemic variability relating to low quality of life and negative mood in diabetic patients (174–176), although other studies have not found support for this association (177, 178). Notably, high dietary sugar intake is associated with depression and anxiety in non-diabetic individuals (179–181). These associations do not determine causation but, intriguingly, there are suggestions that depression in the elderly might predispose the development of type II diabetes (182, 183). KDs minimize dietary sugar intake, and provided a stable, mild hypoglycemia which should counteract these deleterious effects on mood. A recent review outlined the heightened risk of dementia in type II diabetes, and the use of KDs as a preventative treatment (184).

Cerebral hypometabolism/hypoperfusion is known to factor into cognitive problems in Alzheimer's disease, dementia, and mild cognitive impairment; ketogenic strategies can overcome this problem by delivering high energy fuels (ketone bodies) directly to neural tissue (82). A recent report showed that KD or ketone body treatment restores long-term potentiation in a mouse model of Alzheimer's disease (185). A number of clinical studies have applied the KD (or the modified Atkins diet, also very low carbohydrate) to these disorders (186). Although cognitive tests differ between study groups, the KD is generally found to benefit general cognition, learning and memory, quality of life, general functioning, and mood (187–191). In one study, serum ketones were found to positively correlate with benefits in long term memory (17). Other studies have more directly induced ketosis in these patients with supplements, typically medium-chain triglycerides or ketone esters (which are easily metabolized into ketone bodies), rather than changing diet wholesale. Again, these treatments improved various aspects of cognition (77, 192). A number of studies correlated improved cognition with elevated circulating ketone bodies (193–195) or elevated ketone body uptake in brain (assessed with PET) (196, 197).

There is strong evidence of a metabolic underpinning of ASD, in addition to the genetic and environmental components. For example, this disorder has been found to involve hypoperfusion of specific brain regions (198–200) and to be associated with hyperglycemia, mitochondrial dysfunction, and adenosine dysfunction (201–204). Thus, the KD has multiple mechanisms by which it might be beneficial. KD feeding improved sociability and repetitive behaviors in various animal models of this disorder (26–28, 91, 205, 206). In addition, promising results have been found in autism spectrum disorder patients with KD therapy (207–213).

Addiction and the psychiatric disorders just discussed all have significant co-morbidities; interestingly, KD treatment appears to be helpful with many of these co-morbidities. Diabetes is a co-morbidity in depression, schizophrenia, and Alzheimer's disease; KD feeding is a greatly beneficial treatment for diabetes (214). Obesity is a co-morbidity in schizophrenia and Alzheimer's disease; KD feeding is an effective treatment for obesity (215). Attention deficit/hyperactivity disorder is a co-morbidity in addiction and autism spectrum disorder; KD feeding improves attention during treatment of epileptic patients (31, 216–218). Hyperactivity was improved during treatment in epilepsy and autism spectrum disorder (210, 219), but has not been established as a treatment in a non-epileptic clinical ADHD population. Depression is a co-morbidity in addiction and Alzheimer's disease; KD feeding is effectively antidepressant in non-epileptic populations (11, 117, 144). For rarer co-morbidities such as personality disorder, KD effects remain unknown.

The KD can have some effects on lipids which can be seen as possible negative side effects. However, mild hyperlipidemia was associated with better anticonvulsant effects (219). Even though low-density lipoprotein-C was higher in KD-fed patients, there was no increased coronary plaque burden compared to matched controls (220), and low-density lipoprotein-C levels are generally poorly predictive of cardiovascular disease risk (221, 222).

Taken together, the relationship between metabolic health and a broad range of neurological conditions is emerging, including mental health. The relationship among adenosine, dopamine, and ketogenic metabolic therapy is primary because of the ability to link cell energy, neuronal signaling, and gene expression for both short and long-term effects in key brain areas. The opportunity for metabolic approaches to address multiple comorbidities at once is gaining acceptance. As noted herein there is a wide range of mechanisms and impacts, and reversing and preventing metabolic dysfunction has enormous potential for all ages. However, the opportunity to restore a lifetime of

brain health for young people – who may be suffering from mental illness, drug addiction, or both – should be an enormous motivation for continued attention to this field.

## Author contributions

DR: Conceptualization, Writing – original draft, Writing – review & editing. LM: Investigation, Writing – review & editing. SM: Writing – review & editing, Conceptualization, Supervision, Writing – original draft.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Publisher's note



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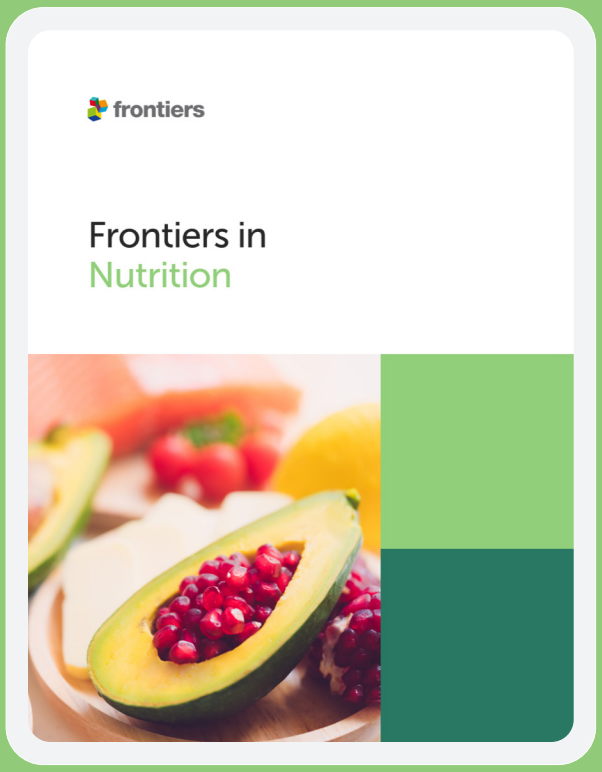


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