



# Ketogenic diet as a metabolic treatment for mental illness

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## Purpose of review

Ketogenic diets, which have been used to treat drug-refractory paediatric epilepsy for over 100 years, are becoming increasingly popular for the treatment of other neurological conditions, including mental illnesses. We aim to explain how ketogenic diets can improve mental illness biopathology and review the recent clinical literature.

## Recent findings

Psychiatric conditions, such as schizophrenia, depression, bipolar disorder and binge eating disorder, are neurometabolic diseases that share several common mechanistic biopathologies. These include glucose hypometabolism, neurotransmitter imbalances, oxidative stress and inflammation. There is strong evidence that ketogenic diets can address these four fundamental diseases, and now complementary clinical evidence that ketogenic diets can improve the patients' symptoms.

## Summary

It is important that researchers and clinicians are made aware of the trajectory of the evidence for the implementation of ketogenic diets in mental illnesses, as such a metabolic intervention provides not only a novel form of symptomatic treatment, but one that may be able to directly address the underlying disease mechanisms and, in so doing, also treat burdensome comorbidities (see Video, Supplementary Digital Content 1, <http://links.lww.com/COE/A16>, which summarizes the contents of this review).

## Keywords

inflammation, ketogenic diet, mental illness, oxidative stress

## INTRODUCTION

Psychiatric conditions are a leading cause of disability and premature mortality, with the most recent reliable epidemiological report estimating that mental illness results in 7.3–10.2 years of life lost [1<sup>■</sup>]. Importantly, the premature mortality exhibited by those with mental illness is mostly the result of comorbid diseases, rather than of suicide or other unnatural causes [1<sup>■</sup>]. For example, the presence of a behavioural, mood or personality disorder, or schizophrenia, is each associated with a two to four-fold increase in mortality due to diabetes. Similar trends hold true for the association between mental illnesses and death from heart, respiratory, infectious disease and cancer [1<sup>■</sup>]. Although some of this association is secondary to poor health behaviours and medication side effects, the relationship between mental illness and the burden of other chronic illnesses persists in healthy-weight and drug-naïve patients [2]. This is consistent with the notion that mental illnesses are not as biopathologically distinct from other chronic diseases as most people assume. Rather, it seems more likely that a set of shared

metabolic diseases, including glucose hypometabolism, neurotransmitter imbalances, oxidative stress and inflammation, commonly underlie schizophrenia, bipolar disorder (BPD) and major depressive disorder (MDD), and their associated comorbidities. These four foundational metabolic diseases warrant a metabolic approach to therapy. One promising approach is the ketogenic diet, a high-fat, low-carbohydrate diet that induces the body and brain to use fat and ketone bodies, rather than glucose, as primary fuels. This switch from glucose to fat and

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## KEY POINTS

- The ketogenic diet is a high-fat, low carbohydrate diet that has been effectively used for the management of paediatric epilepsy for almost 100 years.
- Many neurological diseases, including epilepsy and mental illnesses, share the four underlying diseases of glucose hypometabolism, neurotransmitter imbalances, oxidative stress and inflammation.
- Mechanistically, the ketogenic diet can circumvent dysfunctional glucose metabolism, restore neurotransmitter balance and reduce oxidative stress and inflammation.
- Emerging preclinical and clinical evidence suggests the ketogenic diet may have a therapeutic effect in the management of schizophrenia, bipolar disorder, autism spectrum disorder, binge eating disorder, major depressive disorder, attention deficit hyperactivity disorder and anxiety.

ketones as fuel induces favourable metabolic adaptations with respect to the four foundational metabolic diseases mentioned above. Correspondingly, ketogenic diets have been effectively utilized to treat a range of neurological metabolic diseases and, more recently, mental illnesses. In this review, we will first discuss the major mechanisms by which ketogenic diets treat metabolic diseases. Second, we will provide key examples of how ketogenic diets have been implemented in mental illness comorbidities. Third, we will discuss the most recent preclinical and clinical evidence for the implementation of ketogenic diets in mental illness. Finally, we will comment on the main perceived clinical limitation of high-fat ketogenic diets, namely cardiovascular risk, and suggest directions for future research.

## KETOGENIC DIETS CIRCUMVENT GLUCOSE HYPOMETABOLISM, RESTORE GABA/GLUTAMATE BALANCE AND DECREASE OXIDATIVE STRESS AND INFLAMMATION

### Glucose hypometabolism

Many neurological diseases are characterized by cerebral glucose hypometabolism and insulin resistance, including Alzheimer's disease, Parkinson's disease and epilepsy. Although there is emerging evidence for the utility of ketogenic diets in these first two neurodegenerative disorders [3<sup>■</sup>,4<sup>■</sup>], to say nothing of the compelling evidence in diabetes [5<sup>■</sup>], ketogenic diets have been used as an effective treatment for drug-refractory epilepsy for almost

100 years. The most recent Cochrane review and meta-analysis demonstrated symptom improvement in most epileptic patients, with as many as 55% in one study experiencing complete seizure freedom [6,7]. Cerebral glucose hypometabolism is a feature shared by mental illnesses, including schizophrenia, BPD and MDD [8<sup>■</sup>]. Recent postmortem analyses of schizophrenia brains by Sullivan *et al.* [9] report 19–22% decreases in the expression of the glucose transporters, GLUT1 and GLUT3, and in glycolytic genes. Interestingly, these brains also exhibited a 22% increase in the  $\beta$ -hydroxybutyrate ( $\beta$ H $\equiv$ ) importer (MCT1), suggesting that the brain may be attempting to compensate for glucose hypometabolism by upregulating its capacity to import ketone bodies. Thus, the schizophrenia brain may be metabolically primed to respond to ketogenic diet therapy. We will discuss the emerging clinical evidence [10<sup>■</sup>,11] later.

### GABA/glutamate imbalance

GABA/glutamate imbalance and glutamate excitotoxicity are also predominant features of neurological diseases, from epilepsy [12] to AD [3<sup>■</sup>], which can be corrected by ketogenic diets [3<sup>■</sup>,13<sup>■</sup>,14]. Kraeuter *et al.* [15<sup>■</sup>] recently used pharmacological manipulation of GABA/glutamate balance to generate a mouse model of schizophrenia. They found that direct administration of exogenous  $\beta$ H $\equiv$  for 3 months effectively normalized schizophrenia symptoms in these mice. Unfortunately, this study did not directly assess GABA/glutamate balance or glutamate excitotoxicity, both of which contribute to clinical schizophrenia [16]. However, Olson *et al.* previously demonstrated that a ketogenic diet reduced seizures in a mouse model of epilepsy and that this was associated with an increase in GABA/glutamate and decrease in excitotoxicity. Interestingly, in this latter study, the neurological benefits were mediated by changes to the gut microbiome [14]. As Kraeuter *et al.* [15<sup>■</sup>] observed neurological benefits in their mice with exogenous  $\beta$ H $\equiv$  treatment, which is unlikely to lead to the same microbiome shift as a high-fat, low-carbohydrate ketogenic diet, there is ample room for future investigations on the mechanisms by which ketogenic diets and ketones impact neurotransmitter balance.

### Oxidative stress

It is generally accepted that oxidative stress contributes to most, if not all, chronic diseases, including schizophrenia, BPD and MDD [8<sup>■</sup>]. The myriad of mechanisms by which ketogenic diets can correct oxidative stress in neurological disease are too numerous to cover in-depth in this concise review

and have been reviewed elsewhere [4<sup>8</sup>]. However, it is worth emphasizing that ketogenic diets act to diminish oxidative stress through both metabolic and signalling mechanisms. For example, as compared with glucose catabolism,  $\beta$ H $\equiv$  catabolism produces fewer reactive oxygen species while simultaneously bolstering NADPH and antioxidant defenses [4<sup>8</sup>]. With regards to signalling,  $\beta$ H $\equiv$  binds to the G protein coupled receptor, HCAR2 [4<sup>8</sup>,13<sup>13</sup>], inhibits nonsirtuin histone deacetylases (HDACs) [4<sup>8</sup>,13<sup>13</sup>] and directly modified histones [17]. Through these mechanisms,  $\beta$ H $\equiv$  can inhibit pro-oxidant factors, such as inducible nitric oxide synthase (iNOS) and NADPH oxidase (NOX-2), while enhancing antioxidant factors, such as catalase and superoxide dismutase (SOD) radical scavengers, uncoupling proteins and the FOXO, Nrf2 and sirtuin pathways [4<sup>8</sup>,13<sup>13</sup>].

## Inflammation

Oxidative stress and inflammation are mutually reinforcing diseases [13<sup>13</sup>,18]. Recent postmortem and in-vivo human evidence confirms the tight association between brain inflammation and mental illness. A recent meta-analysis of 69 studies that examined cytokine levels in the MDD patients' postmortem brain tissue and cerebral spinal fluid, or assessed brain inflammation via PET scan for the in-vivo inflammatory marker, translocator protein (TSPO), found significant increases in these parameters in MDD as compared with control brains [19<sup>19</sup>]. The same appears to be true in other mental illnesses. An independent quantitative review likewise found increased TSPO in the brains of living schizophrenia patients [20<sup>20</sup>].

Microglia are immune cells involved in brain inflammation. For an excellent review of the role of pro-inflammatory microglia in mental illness and their relationship to ketogenic diets, please read Morris *et al.* [13<sup>13</sup>]. Briefly, pro-inflammatory microglia play a prominent role in schizophrenia, BPD and MDD, at least in part by activating NOX-2 and the NLRP3 inflammasome, causing mitochondrial dysfunction, and contributing to GABA/glutamate imbalance. Ketogenic diets can switch microglia from their pro-inflammatory to their anti-inflammatory, neuroprotective state by inhibiting NOX-2 and NLRP3, activating PPAR $\alpha$  and  $\gamma$ , and inducing NAD<sup>+</sup>-C-terminal binding protein-mediated suppression of pro-inflammatory microglial genes [13<sup>13</sup>].

## KETOGENIC DIETS AS THERAPY FOR COMORBIDITIES OF MENTAL ILLNESS

As mentioned above, ketogenic diets are historically best known as an effective treatment for drug-

refractory epilepsy [6,7], but more recent clinical data reveal that their utility spans a much wider range of chronic illnesses that share the diseases just discussed. In line with its presumed benefit on insulin resistance, a nonrandomized, but controlled study performed by the Virta health group has demonstrated that a ketogenic diet is a well tolerated and effective strategy for treating type II diabetes, reversing the condition in 54% of individuals, as compared with 5% in those receiving standard care [5<sup>5</sup>].

Alzheimer's disease, which includes brain insulin resistance and has recently been referred to as type III diabetes, is another area of research interest for ketogenic therapy. Indeed, neurodegenerative diseases in general are typified by the fundamental metabolic diseases that are the focus of this review: cerebral glucose hypometabolism, neurotransmitter imbalances and glutamate excitotoxicity, oxidative stress and inflammation [4<sup>8</sup>,18]. Clinical evidence suggests ketosis can help improve these diseases and ameliorate symptoms in patients [3<sup>3</sup>,21]. In one randomized crossover trial conducted in mild-to-moderate Alzheimer's disease patients, 12 weeks of medium chain triglyceride (MCT) supplementation improved cognitive scores on a diverse panel of assessments. Interestingly, these effects of chronic ketosis were not replicated in the acute setting, following a single dose of MCTs, suggesting that the longer-term metabolic adaptations induced by ketosis, such as diminished oxidative stress and inflammation, possibly contribute more to the cognitive benefits than the simple switching from a glucose to ketone fuel source [22]. Importantly, there is a strong association between Alzheimer's disease and psychosis, with 50–80% of Alzheimer's disease patients presenting with psychiatric symptoms commonly seen in diseases such as schizophrenia, BPD and MDD [23,24].

A growing body of evidence suggests that ketogenic diets are not only useful in diabetes [5<sup>5</sup>] and Alzheimer's disease [25<sup>25</sup>,26,27,28<sup>28</sup>,29], but also in other neurological diseases, including Parkinson's disease [30,31], Huntington's disease [32] and multiple sclerosis [33,34<sup>34</sup>]. As mental illnesses share common underlying metabolic diseases with these diseases, it is not surprising that emerging clinical evidence is suggesting that ketosis and ketogenic diets may play a role in treating mental illnesses [34<sup>34</sup>].

## KETOGENIC DIETS FOR MENTAL ILLNESS, PRECLINICAL AND CLINICAL EVIDENCE

Preclinical and clinical evidence for the efficacy of ketogenic interventions in a wide range of mental illnesses is increasing. In rodent models of attention-deficient hyperactivity disorder (ADHD), ketogenic

diets reduced hyperactivity [35,36]. In animal models [37,38], case studies [39,40], and two clinical trials [41,42] of autism spectrum disorder (ASD), ketogenic diets improved social communication as well as other symptoms of ASD, including several patients who exhibited large (>12 point) improvements on the Child Autism Rating Scale and one who, on this scale, transitioned from 'severe autism' to 'nonautistic' [39,41]. The relationship between ketogenic diets and ASD is of particular interest, as both are strongly associated with changes in the gut microbiome, which some studies suggest mediate the therapeutic effects of ketogenic diets [14,43]. Ketogenic diets are also well known to have anxiolytic effects and are thought to help improve MDD [44–46]. Further preclinical and early clinical evidence for the efficacy of ketogenic diets in BPD [47], schizophrenia [10<sup>■</sup>,11,48] and binge eating disorder (BED) [49<sup>■</sup>] also exist. As a comprehensive review of the preclinical and clinical evidence for the therapeutic role of ketosis in mental illness is beyond the scope of this succinct review, and has recently been provided by Krauter *et al.* [34<sup>■</sup>], we will now instead turn to two recent case series from our research groups that afford illustrative examples of the ketogenic diet's clinical potential.

Palmer recently reported on two schizophrenia patients who adopted ketogenic diets to treat metabolic comorbidities and who incidentally experienced dramatic improvements in symptoms [10<sup>■</sup>]. Patient A was an 82-year-old woman with a 53-year history of schizophrenia who suffered from paranoia, auditory hallucinations and multiple suicide attempts. In 2008, she commenced a ketogenic diet for weight loss. Within 2 weeks, her symptoms were markedly improved. She eventually stopped all her psychiatric medications, including antipsychotics. She remains on the ketogenic diet, symptom-free, for over 12 years now. Patient B was a 39-year-old woman who suffered from depression, suicide attempts and schizophrenia for over 20 years. Over the course of a decade, she tried 14 different medications, none of which significantly ameliorated her symptoms. She then began a ketogenic diet for gastrointestinal distress and, within 1 month, noted a dramatic reduction of psychotic symptoms. She has been off antipsychotic medications for over 4 years and remains symptom-free. She has recently completed graduate school and works full-time [10<sup>■</sup>].

Carmen, Carmen *et al.* [49<sup>■</sup>] published a compelling case series ( $n = 3$ ) on successful treatment of severe binge eating, food addiction symptoms and comorbid obesity with a ketogenic diet, characterized by uncontrolled consumption of large quantities of food without compensatory purging, amongst a host of other debilitating symptoms

[50]. It is worth noting that BED, which impacts 1.9% of the global population and 2.6% of Americans, doubles the risk of obesity [51]. The presence of BED also increases the risk of developing other metabolic diseases, including diabetes and cardiovascular disease (CVD) [51]. BED can have a feedforward impact on poor health. This case series quantified symptoms using the validated Binge Eating and Yale Food Addiction Scales. All three patients with obesity experienced remarkable improvements in binge eating, with scores decreasing from the upper limits of the scales to two points or fewer on all scales. Furthermore, these patients reported improvements in symptoms of depression, and significant weight loss between 10 and 25% of initial body mass. All patients were adherent to their diets, achieving nutritional ketosis in the range of 0.5–5.0 mmol/l, and were instructed to lower carbohydrate intake to between 20 and 30 g/day [49<sup>■</sup>].

### KETOGENIC DIETS AND PERCEIVED CARDIOVASCULAR RISK

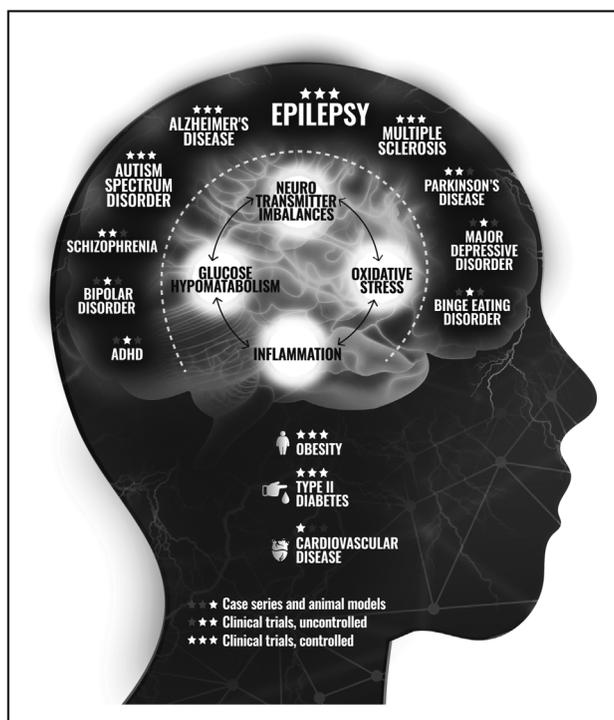
Cardiovascular disease is among the most common comorbidities of mental illness. MDD and BPD confer a 30% and five-fold increased rate of CVD, respectively, and 65% of deaths in schizophrenia are due to CVD [52]. This is not surprising, given that oxidative stress and inflammation contribute to CVD; people with mental illness have higher rates of lifestyle risk factors, such as smoking, lack of exercise and poor diet; and antipsychotic medications have high rates of metabolic side effects [52,53].

Given that ketogenic diets are high-fat diets, they can induce changes in serum lipids. Increases in total and LDL cholesterol have been reported when ketogenic diets are used to treat neurological disease and diabetes [5<sup>■</sup>,7]. Although there is heterogeneity among patients' lipid responses to ketogenic diets, even the possibility of an increase in LDL cholesterol calls into question the safety of using ketogenic diets in people with mental illnesses. However, this issue is more nuanced for two reasons. First, one must consider the impact of antipsychotic medications on obesity and CVD risk. Whereas antipsychotics are obesogenic and can contribute to hyperlipidaemia, ketogenic diets can promote weight loss and sometimes improve hyperlipidaemia [54]. Second, and perhaps more importantly, elevated LDL cholesterol is only one of many risk factors for CVD [55<sup>■</sup>]. Blood pressure, HDL cholesterol, LDL oxidation [25<sup>■</sup>,55<sup>■</sup>] and glycaemic control are also important risk factors that often improve with ketogenic diets. One study of people with type II diabetes on the ketogenic diet for 2 years found an overall lower risk of CVD as measured by the

American College of Cardiology 10-year ASCVD Risk Estimator, despite an increase in LDL [5<sup>■</sup>].

## CONCLUSION

Mental illnesses involve numerous metabolic disturbances in the brain and are comorbid with many other metabolic disorders, such as obesity, diabetes and CVD. Historically, the ketogenic diet is an evidence-based treatment for epilepsy that has been shown to have profound effects on brain metabolism and neurotransmitter function. More recently, the ketogenic diet has been shown to be an effective treatment for obesity and type II diabetes, and evidence is emerging for its use in manifold neurological disorders (Fig. 1). These observations underlie the increased interest in the ketogenic diet



**FIGURE 1.** The state of the evidence supporting the implementation of ketogenic diets in six mental illnesses and seven neurological and peripheral diseases is shown. A three-star ranking system is used to indicate the current quality of best evidence, in which one star indicates case series and animal models, two stars indicate uncontrolled clinical trials and three stars indicate controlled clinical trials. A single reference of particular interest corresponding to each disease is as follows: Schizophrenia [10<sup>■</sup>] Major Depressive Disorder [46], Binge Eating Disorder [49<sup>■</sup>], Bipolar Disorder [47], Autism Spectrum Disorder [42], Attention-Deficit Hyperactivity Disorder [35], Epilepsy [6], Alzheimer's Disease [22], Parkinson's Disease [30], Multiple Sclerosis [33], Obesity [5<sup>■</sup>], Type II Diabetes [5<sup>■</sup>], Cardiovascular Disease [55<sup>■</sup>].

as a novel treatment for mental illness. Future research needs to include randomized, controlled trials of the ketogenic diet as a treatment for mental illnesses. In addition, its safety profile warrants further exploration, including its effects on the risk for CVD.

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## Conflicts of interest

There are no conflicts of interest.

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- of outstanding interest

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