Ketogenic diet as a metabolic treatment for mental illness

Nicholas G. Norwitz[a], *Shebani Sethi Dalal*[b], *and Christopher M. Palmer*[c]

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▪]. 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▪]. 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▪]. 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-naive 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 ketones as fuel induces

[a]Department of Physiology, Anatomy and Genetics, Oxford University, Oxford, UK, [b]Metabolic Psychiatry Clinic, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California and [c]Department of Postgraduate and Continuing Education, McLean Hospital, Harvard Medical School, Belmont, Massachusetts, USA

Correspondence to Christopher M. Palmer, Department of Postgraduate and Continuing Education, McLean Hospital, Harvard Medical School, Belmont, MA 02478, USA. Tel: +1 617 855 2180; e-mail: cpalmer@partners.org

Curr Opin Endocrinol Diabetes Obes 2020, 27:000–000
DOI:10.1097/MED.0000000000000564

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.

favourable metabolic adaptions 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▪,4▪], to say nothing of the compelling evidence in diabetes [5▪], 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 compete seizure freedom [6,7]. Cerebral glucose hypometabolism is a feature shared by mental illnesses, including schizophrenia, BPD and MDD [8▪]. 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 β−hydroxybutyrate (βH≡) 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▪,11] later.

GABA/glutamate imbalance

GABA/glutamate imbalance and glutamate excitotoxicity are also predominant features of neurological diseases, from epilepsy [12] to AD [3▪], which can be corrected by ketogenic diets [3▪,13▪,14]. Kraeuter *et al.* [15▪▪] recently used pharmacological manipulation of GABA/glutamate balance to generate a mouse model of schizophrenia. They found that direct administration of exogenous βH≡ 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▪▪] observed neurological benefits in their mice with exogenous βH≡ 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▪]. 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▪,8▪]. 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, βH≡ catabolism produces fewer reactive oxygen species while simultaneously bolstering NADPH and antioxidant defenses [4▪]. With regards to signalling, βH≡ binds to the G protein coupled receptor, HCAR2 [4▪,8▪,13▪], inhibits nonsirtuin histone deacetylases (HDACs) [4▪,8▪,13▪] and directly modified histones [17]. Through these mechanisms, βH≡ 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▪,8▪,13▪].

Inflammation

Oxidative stress and inflammation are mutually reinforcing diseases [13▪,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▪]. 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▪].

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▪]. 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 PPARα and γ, and inducing NAD^+-C-terminal binding protein-mediated suppression of pro-inflammatory microglial genes [13▪].

KETOGENIC DIETS AS THERAPY FOR COMORBIDITIES OF MENTAL ILLESSS

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▪].

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▪,18]. Clinical evidence suggests ketosis can help improve these diseases and ameliorate symptoms in patients [3▪,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▪] and Alzheimer's disease [25▪,26,27,28▪,29], but also in other neurological diseases, including Parkinson's disease [30,31], Huntington's disease [32] and multiple sclerosis [33,34▪▪]. 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▪▪].

KETOGENIC DIETS FOR MENTAL ILLNESS, PRECLINICAL AND CLINCAL 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▪,11,48] and binge eating disorder (BED) [49▪] 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 Kraeuter *et al.* [34▪▪], 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▪]. 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▪].

Carmen, Carmen *et al.* [49▪] 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▪].

KETOGENIC DIETS AND PERCEIVED CARDIOVASULAR 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▪,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▪]. Blood pressure, HDL cholesterol, LDL oxidation [25▪,55▪] 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▪].

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 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.

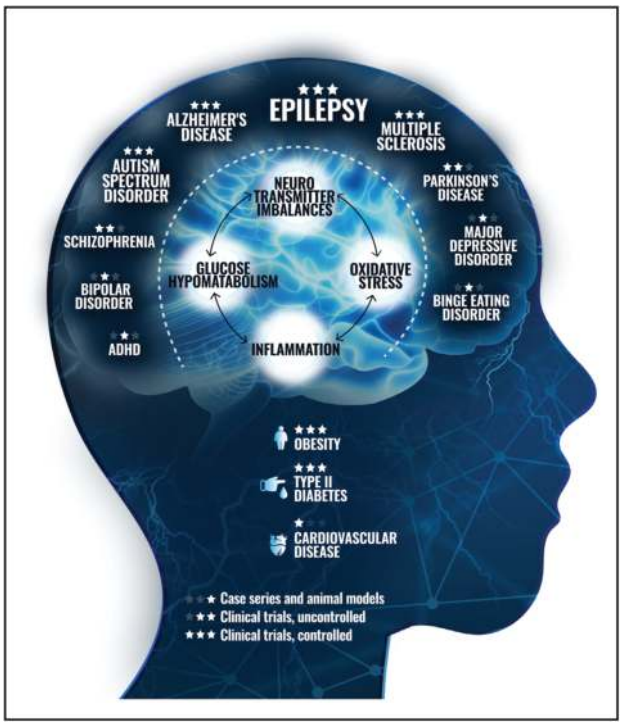

FIGURE 1. The state of the evidence supporting the implementation of ketogenic diets in six mental illnesses and seven neurological and peripheral diseases is shown. A three-star ranking system is used to indicate the current quality of best evidence, in which one star indicates case series and animal 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▪] Major Depressive Disorder [46], Binge Eating Disorder [49▪], 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▪], Type II Diabetes [5▪], Cardiovascular Disease [55▪].

Acknowledgements

All authors would like to thank Eleanor Stanton for her expert support on the figure and video abstract. CP and SSD would like to acknowledge the strength and perseverance of the patients from the case studies who have successfully implemented the ketogenic diet in order to treat their psychiatric symptoms and other comorbidities. NN would like to acknowledge the Keasbey Memorial Foundation for funding his research at Oxford.

Financial support and sponsorship

None.

Conflicts of interest

None.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Plana-Ripoll O, Pedersen CB, Agerbo E, *et al.* A comprehensive analysis of ▪ mortality-related health metrics associated with mental disorders: a nationwide, register-based cohort study. Lancet 2019; 394:1827–1835.

This population-based study is the most recent and comprehensive analysis of mental illness associated mortality. It also highlights the important contribution of metabolic comorbidities to the mortality burden of mental illness.

2. Sun L, Getz M, Daboul S, *et al.* Independence of diabetes and obesity in adults with serious mental illness: findings from a large urban public hospital. J Psychiatr Res 2018; 99:159–166.
3. Rusek M, Pluta R, Ulamek-Koziol M, Czuczwar SJ. Ketogenic diet in ▪ Alzheimer's disease. Int J Mol Sci 2019; 20:3892. doi:10.3390/ijms20163892.

This article gives an excellent overview of the mechanism and evidence for ketogenic interventions in Alzheimer's diease, with an emphasis on the four metabolic diseases highlighted in this review.

4. Norwitz NG, Hu MT, Clarke K. The mechanisms by which the ketone body D- ▪ beta-hydroxybutyrate may improve the multiple cellular pathologies of Parkinson's disease. Front Nutr 2019; 6:63.

This article describes how the ketone body, β-hydroxybutryate, functions both a metabolic fuel and signalling molecule in the brain, and how, through this dual nature, β-hydroxybutryate can address the diseases underlying neurological diseases.

5. Athinarayanan SJ, Adams RN, Hallberg SJ, *et al.* Long-term effects of a novel ▪ continuous remote care intervention including nutritional ketosis for the management of type 2 diabetes: a 2-year nonrandomized clinical trial. Front Endocrinol (Lausanne) 2019; 10:348.

This controlled 2-year human study convincingly demonstrates that a ketogenic diet is an effective intervention for reversing type II diabetes mellitus.

6. Martin K, Jackson CF, Levy RG, Cooper PN. Ketogenic diet and other dietary treatments for epilepsy. Cochrane Database Syst Rev 2016; 2:CD001903.
7. Liu H, Yang Y, Wang Y, *et al.* Ketogenic diet for treatment of intractable epilepsy in adults: a meta-analysis of observational studies. Epilepsia Open 2018; 3:9–17.
8. Morris G, Puri BK, Carvalho A, *et al.* Induced ketosis as a treatment for ▪ neuroprogressive disorders: food for thought? Int J Neuropsychopharmacol 2020; 23:366–384.

This article describes the signalling mechanisms by which ketosis could help to treat certain mental illnesses, with detailed discussions of certain cell signaling pathways.

9. Sullivan CR, Mielnik CA, Funk A, *et al.* Measurement of lactate levels in postmortem brain, iPSCs, and animal models of schizophrenia. Sci Rep 2019; 9:5087https://doi.org/10.1038/s41598-019-41572-9.
10. ■ Palmer CM, Gilbert-Jaramillo J, Westman EC. The ketogenic diet and remission of psychotic symptoms in schizophrenia: two case studies. Schizophr Res 2019; 208:439–440.

This case series provides compelling evidence that ketogenic diets can remarkably improve, and induce remission of schizophrenia.

11. Sarnyai Z, Kraeuter AK, Palmer CM. Ketogenic diet for schizophrenia: clinical implication. Curr Opin Psychiatry 2019; 32:394–401.
12. Bough KJ, Rho JM. Anticonvulsant mechanisms of the ketogenic diet. Epilepsia 2007; 48:43–58.
13. ■ Morris G, Puri BK, Maes M, *et al.* The role of microglia in neuroprogressive disorders: mechanisms and possible neurotherapeutic effects of induced ketosis. Prog Neuropsychopharmacol Biol Psychiatry 2020; 99:109858.

This article describes the important role of pro-inflammatory microglia in mental illness and details the mechanisms by which ketosis can switch microglia to an anti-inflammatory, neuroprotective state.

14. Olson CA, Vuong HE, Yano JM, *et al.* The gut microbiota mediates the anti-seizure effects of the ketogenic diet. Cell 2018; 174:1728–1741.e13.
15. ■■ Kraeuter AK, Mashavave T, Suvarna A, *et al.* Effects of beta-hydroxybutyrate administration on MK-801-induced schizophrenia-like behaviour in mice. Psychopharmacology (Berl) 2020; 237:1397–1405.

This study convicingly demonstrates that the ketone body, β-hydroxybutryate, can amleiorate behavioural symptoms in a GABA/glutamate imbalance mouse model of szchiophrenia.

16. Coyle JT, Basu A, Benneyworth M, *et al.* Glutamatergic synaptic dysregulation in schizophrenia: therapeutic implications. Handb Exp Pharmacol 2012; 267–295.
17. Xie Z, Zhang D, Chung D, *et al.* Metabolic regulation of gene expression by histone lysine beta-hydroxybutyrylation. Mol Cell 2016; 62:194–206.
18. Norwitz NG, Mota AS, Norwitz SG, Clarke K. Multi-loop model of Alzheimer disease: an integrated perspective on the Wnt/GSK3beta, alpha-Synuclein, and type 3 diabetes hypotheses. Front Aging Neurosci 2019; 11:184.
19. ■ Enache D, Pariante CM, Mondelli V. Markers of central inflammation in major depressive disorder: a systematic review and meta-analysis of studies examining cerebrospinal fluid, positron emission tomography and postmortem brain tissue. Brain Behav Immun 2019; 81:24–40.

This meta-analysis of in-vivo and postmortem human studies strongly supports the notion that MDD is a diseae of brain inflammation.

20. ■ Marques TR, Ashok AH, Pillinger T, *et al.* Neuroinflammation in schizophrenia: meta-analysis of in vivo microglial imaging studies. Psychol Med 2019; 49:2186–2196.

This meta-analysis of in-vivo human studies strongly supports the notion that schizophrenia is a diseae of brain inflammation.

21. Broom GM, Shaw IC, Rucklidge JJ. The ketogenic diet as a potential treatment and prevention strategy for Alzheimer's disease. Nutrition 2019; 60:118–121.
22. Ota M, Matsuo J, Ishida I, *et al.* Effects of a medium-chain triglyceride-based ketogenic formula on cognitive function in patients with mild-to-moderate Alzheimer's disease. Neurosci Lett 2019; 690:232–236.
23. Murray PS, Kumar S, Demichele-Sweet MA, Sweet RA. Psychosis in Alzheimer's disease. Biol Psychiatry 2014; 75:542–552.
24. Gottesman RT, Stern Y. Behavioral and psychiatric symptoms of dementia and rate of decline in Alzheimer's disease. Front Pharmacol 2019; 10:1062.
25. ■ Krishnan M, Hwang JS, Kim M, *et al.* beta-hydroxybutyrate impedes the progression of Alzheimer's disease and atherosclerosis in ApoE-deficient mice. Nutrients 2020; 12:471.

This study provides evidence that the ketone body, β-hydroxybutryate, can decrease brain inflammation, amyloid deposition, LDL oxidation and athletogenesis in ApoE-deficient mice, suggesting that ketones can directly protect against Alzhimer's and cardiovasular disease.

26. Newport MT, VanItallie TB, Kashiwaya Y, *et al.* A new way to produce hyperketonemia: use of ketone ester in a case of Alzheimer's disease. Alzheimers Dement 2015; 11:99–103.
27. Neth BJ, Mintz A, Whitlow C, *et al.* Modified ketogenic diet is associated with improved cerebrospinal fluid biomarker profile, cerebral perfusion, and cerebral ketone body uptake in older adults at risk for Alzheimer's disease: a pilot study. Neurobiol Aging 2020; 86:54–63.
28. ■ Mujica-Parodi LR, Amgalan A, Sultan SF, *et al.* Diet modulates brain network stability, a biomarker for brain aging, in young adults. Proc Natl Acad Sci U S A 2020; 117:6170–6177.

This controlled human study provides exceptional evidence that dietary choice, specifically a ketogenic diet versus a western diet, influences the way in which different brain regions intercommunicate. This study also establishes a new marker of brain ageing, 'network stability', and establishes that ketogenic diets increase network stability, thus possibly slowing brain aging and otherwise diminsihing cerebral dysfunction.

29. Fortier M, Castellano CA, Croteau E, *et al.* A ketogenic drink improves brain energy and some measures of cognition in mild cognitive impairment. Alzheimers Dement 2019; 15:625–634.
30. Vanitallie TB, Nonas C, Di Rocco A, *et al.* Treatment of Parkinson disease with diet-induced hyperketonemia: a feasibility study. Neurology 2005; 64:728–730.
31. Phillips MCL, Murtagh DKJ, Gilbertson LJ, *et al.* Low-fat versus ketogenic diet in Parkinson's disease: a pilot randomized controlled trial. Mov Disord 2018; 33:1306–1314.
32. Lim S, Chesser AS, Grima JC, *et al.* D-beta-hydroxybutyrate is protective in mouse models of Huntington's disease. PLoS One 2011; 6:e24620.
33. Choi IY, Piccio L, Childress P, *et al.* A diet mimicking fasting promotes regeneration and reduces autoimmunity and multiple sclerosis symptoms. Cell Rep 2016; 15:2136–2146.
34. ■■ Kraeuter AK, Phillips R, Sarnyai Z. Ketogenic therapy in neurodegenerative and psychiatric disorders: from mice to men. Prog Neuropsychopharmacol Biol Psychiatry 2020; 101:109913.

This is the most recent comprehensive review of the preclincal and clincal literature for the implementation of ketogenic diets and exogenous ketosis in neurodegenerative and psychitric disorders.

35. Murphy P, Burnham WM. The ketogenic diet causes a reversible decrease in activity level in Long-Evans rats. Exp Neurol 2006; 201:84–89.
36. Murphy P, Likhodii SS, Hatamian M, McIntyre Burnham W. Effect of the ketogenic diet on the activity level of Wistar rats. Pediatr Res 2005; 57:353–357.
37. Castro K, Baronio D, Perry IS, *et al.* The effect of ketogenic diet in an animal model of autism induced by prenatal exposure to valproic acid. Nutr Neurosci 2017; 20:343–350.
38. Ruskin DN, Svedova J, Cote JL, *et al.* Ketogenic diet improves core symptoms of autism in BTBR mice. PLoS One 2013; 8:e65021.
39. Herbert MR, Buckley JA. Autism and dietary therapy: case report and review of the literature. J Child Neurol 2013; 28:975–982.
40. Zarnowska I, Chrapko B, Gwizda G, *et al.* Therapeutic use of carbohydrate-restricted diets in an autistic child; a case report of clinical and 18FDG PET findings. Metab Brain Dis 2018; 33:1187–1192.
41. Evangeliou A, Vlachonikolis I, Mihailidou H, *et al.* Application of a ketogenic diet in children with autistic behavior: pilot study. J Child Neurol 2003; 18:113–118.
42. Lee RWY, Corley MJ, Pang A, *et al.* A modified ketogenic gluten-free diet with MCT improves behavior in children with autism spectrum disorder. Physiol Behav 2018; 188:205–211.
43. Newell C, Bomhof MR, Reimer RA, *et al.* Ketogenic diet modifies the gut microbiota in a murine model of autism spectrum disorder. Mol Autism 2016; 7:37.
44. Ari C, Kovacs Z, Juhasz G, *et al.* Exogenous ketone supplements reduce anxiety-related behavior in Sprague-Dawley and wistar albino glaxo/rijswijk rats. Front Mol Neurosci 2016; 9:137.
45. Kovacs Z, D'Agostino DP, Ari C. Anxiolytic effect of exogenous ketone supplementation is abolished by adenosine A1 receptor inhibition in wistar albino glaxo/rijswijk rats. Front Behav Neurosci 2018; 12:29.
46. Murphy P, Likhodii S, Nylen K, Burnham WM. The antidepressant properties of the ketogenic diet. Biol Psychiatry 2004; 56:981–983.
47. Phelps JR, Siemers SV, El-Mallakh RS. The ketogenic diet for type II bipolar disorder. Neurocase 2013; 19:423–426.
48. Palmer CM. Ketogenic diet in the treatment of schizoaffective disorder: two case studies. Schizophr Res 2017; 189:208–209.
49. ■ Carmen M, Safer DL, Saslow LR, *et al.* Treating binge eating and food addiction symptoms with low-carbohydrate ketogenic diets: a case series. J Eat Disord 2020; 8:2.

This case series provides compelling data that ketogenic diets can remarkably improve and treat food addiction behaviour and binge eating.

50. Burrows T, Skinner J, McKenna R, *et al.* Food addiction, binge eating disorder, and obesity: is there a relationship? Behav Sci (Basel) 2017; 7:54. doi:10.3390/bs7030054.
51. Kessler RC, Berglund PA, Chiu WT, *et al.* The prevalence and correlates of binge eating disorder in the World Health Organization World Mental Health Surveys. Biol Psychiatry 2013; 73:904–914.
52. Morris G, Puri BK, Walker AJ, *et al.* Shared pathways for neuroprogression and somatoprogression in neuropsychiatric disorders. Neurosci Biobehav Rev 2019; 107:862–882.
53. Teasdale SB, Ward PB, Samaras K, *et al.* Dietary intake of people with severe mental illness: systematic review and meta-analysis. Br J Psychiatry 2019; 214:251–259.
54. Yancy WS Jr, Olsen MK, Guyton JR, *et al.* A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. Ann Intern Med 2004; 140:769–777.
55. ■ Norwitz NG, Loh V. A standard lipid panel is insufficient for the care of a patient on a high-fat, low-carbohydrate ketogenic diet. Front Med 2020; 7:97.

This case study provides an unprecedented in-depth analysis of the impact of a ketogenic diet on a weight-stable individual's serum lipid profile and invites deeper consideration of the impact of ketogenic diets on cardiovascular risk.