Journal of Inflammation Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

The Ketogenic Diet: An Anti-Inflammatory Treatment for Schizophrenia?

Alexis A Hung[1], James R Krycer[1], Zoltan Sarnyai[2], Christopher M Palmer[3], Severine Navarro[1]

[1]Infection and Inflammation Department, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia; [2]Margaret Roderick Centre for Mental Health Research, James Cook University, Townsville, QLD, Australia; [3]Metabolic and Mental Health Program, McLean Hospital, Department of Psychiatry, Harvard Medical School, Boston, MA, USA

Correspondence: Severine Navarro, Email severine.navarro@qimrb.edu.au

---

Abstract: Schizophrenia, a complex psychiatric disorder, is increasingly understood to involve immune dysregulation intertwined with metabolic and mitochondrial dysfunction. Neuroinflammation, driven by microglial activation, aberrant cytokine signalling, and skewed T cell polarization, intersects with impaired cellular bioenergetics and oxidative stress. Metabolic and mitochondrial alterations, consistently observed in patients, may constitute both cause and consequence of immune imbalance, sustaining a pathological loop that links bioenergetic failure to neuroinflammation. The ketogenic diet (KD), a high-fat, very low-carbohydrate intervention has recently gained attention as a potential therapy for schizophrenia. Emerging clinical reports describe improvements in symptom burden, weight regulation, and sustained remission. However, this evidence remains preliminary and is limited to pilot studies and case series. Preclinical studies provide mechanistic evidence, demonstrating that KD and its primary ketone body, β-hydroxybutyrate, attenuate core pathological features including inflammation, synaptic pruning, mitochondrial dysfunction, T cell imbalances and epigenetic alterations. Mechanistically, KD reshapes immune balance by favoring regulatory T cell induction over T helper 17 cell polarization and dampening pro-inflammatory signalling. Further to this, it improves mitochondrial biogenesis, increases ATP yield and reduces reactive oxygens species through increased efficiency of ATP hydrolysis. Epigenetic regulation by multiple pathways provides an additional layer of transcriptional control that may sustain therapeutic benefits. By framing KD within the context of inflammation research, this review synthesises findings from clinical, preclinical and mechanistic studies to highlight its potential to address fundamental disease mechanisms.

Keywords: schizophrenia, ketogenic diet, β-hydroxybutyrate, inflammation, metabolism, mitochondria, epigenetics

---

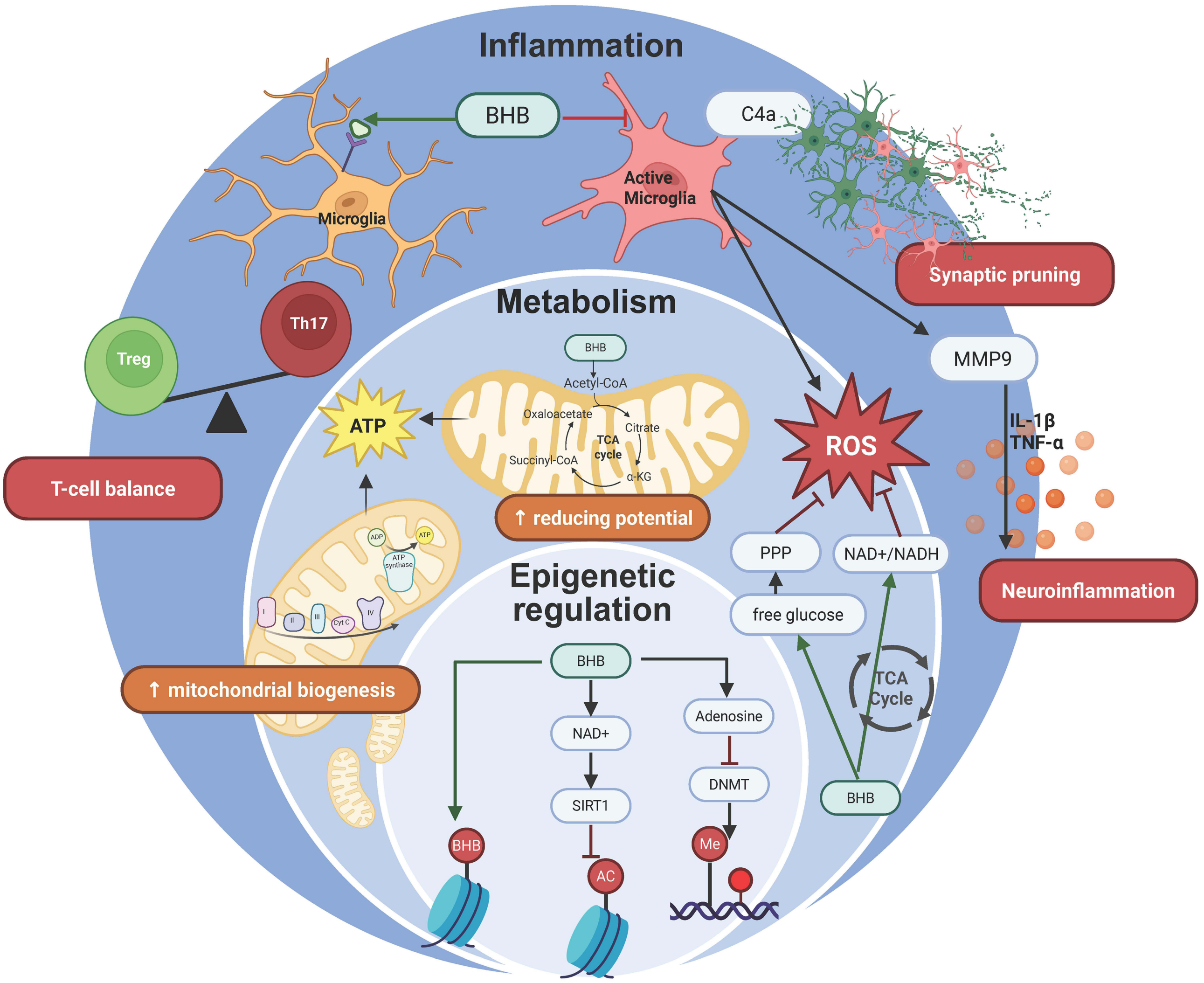
Introduction

Schizophrenia is a psychiatric disorder with a lifetime prevalence estimate of 0.6% of and contributes substantially to morbidity, mortality and social disability.[1] Current therapeutic options primarily target dopaminergic signaling, yet residual symptoms, cognitive impairment, and poor functional outcomes remain untreated.[2] An estimated one fifth to a half of patients suffer from treatment resistant schizophrenia (TRS), defined as a failure of two or more antipsychotic medications.[3] Less than one in seven people affected meet the criteria for recovery.[4] These challenges underscore the need for novel therapeutics approaches.

Beyond dopamine dysregulation, schizophrenia features systemic and central immune activation that correlates with symptom severity and function decline.[5] Metabolic and mitochondrial alterations, consistently observed in schizophrenia, exist as both a cause and consequence of immune dysregulation, sustaining a pathogenic cycle that links bioenergetic failure to neuroinflammation. The ketogenic diet (KD) has garnered clinical interest due to its extensive immunometabolic modulation capabilities, demonstrating therapeutic potential preclinical and clinical schizophrenia cohorts.[6] Its therapeutic efficacy likely stems from integrated modifications involving immune regulation, metabolic reprogramming, and epigenetic alterations. The KD shifts systemic and cerebral energy metabolism from glucose toward ketone body utilisation. This metabolic transition enhances mitochondrial efficiency, increases ATP production, and reduces oxidative

Received: 17 September 2025
Accepted: 24 November 2025
Published: 1 December 2025

Graphical Abstract



stress. Beyond energy metabolism, KD exerts anti-inflammatory and neuroprotective effects through inhibition of microglial activation and suppression of pro-inflammatory cytokines such as IL-6 and IL-17A. Given that schizophrenia is increasingly recognised as a disorder of neuroinflammation, oxidative stress, and metabolic dysregulation, these mechanisms provide a strong theoretical basis for the potential therapeutic benefits of KD. Through coordinated modulation of immunometabolic and redox pathways, KD may help restore neuronal homeostasis and functional connectivity disrupted in schizophrenia.

Here we will outline how this biological starvation-driven metabolic response can be harnessed to attenuate pathological inflammation and address critical metabolic dysregulation in SZ.

Clinical and Preclinical Evidence

Ketogenic metabolic therapy (KMT; ketogenic diet) is an evidence-based therapy for the management of seizure disorders. Its efficacy was first described over 100 years ago in epilepsy and has been supported by numerous studies, clinical trials and Cochrane systematic reviews and meta-analyses.[7–10] More recently, KMT has made inroads in the management of psychiatric disorders, such as schizophrenia and other psychotic conditions. This section summarizes the emerging evidence from clinical studies and reviews mechanistic insights from preclinical research over the past decade.

The recent interest in this treatment modality for schizophrenia has its roots in earlier work. The first publication suggesting the potential efficacy of KMT in schizophrenia was published 60 years ago, in 1965, in an open-label pilot study of 10 females who responded well to two weeks of KMT as determined by significantly decreased symptomology by two independent clinicians, although no controls were included and dietary adherence was unclear (Table 1).[11] Kraft and Westman later reported a case of a 70-year-old woman with chronic schizophrenia in whom KMT, which in this case involved restriction of dietary carbohydrate intake to fewer than 20 grams per day, produced resolution of longstanding hallucinations and delusions after eight days on the diet, with no recurrence over 12 months.[12] More recently, Palmer and collaborators demonstrated the notable efficacy of KMT in a series of case studies. In one instance, a male and a female patient with schizoaffective disorder showed an approximately 50% reduction in psychotic symptom scores, as measured by positive symptoms score in the gold-standard Positive and Negative Syndrome Scale (PANSS), which returned when they stopped the diet but improved again upon resumption of KMT.[13] Two opposite-sex twins with chronic schizophrenia experienced reduced PANSS scores from baselines over a 6-week period on 3:1 ratio KMT with less than 15 grams of daily carbohydrate intake, although adherence and thus time in ketosis were limited.[14] In a small case series of two individuals (one being the same person described by Kraft and Westman,[12] now 80 years old, both showed a remarkable and sustained full remission for 5 and 12 years on KMT without antipsychotics.[15] Very recently, in a retrospective case series of two females with schizoaffective disorder, 2:1 ratio KMT produced full remission of psychotic symptoms as described by treatment teams, and mood symptoms as assessed by The Generalized Anxiety Disorder-7 (GAD-7), Depression Anxiety Stress Scales (DASS-42), and PTSD Checklist for DSM-5. Additionally, substantial functional recovery, and reduced need for medications were reported.[16] Across these reports, patients on KMT have shown consistent weight loss and overall improvements in quality of life. A retrospective analysis of 10 patients with schizoaffective disorder treated with KMT found, similar to Palmer's case studies, nearly a 50% reduction in psychiatric symptoms measured by PANSS.[17] In addition, an open-label pilot trial of five individuals with chronic schizophrenia showed a 32% reduction in psychosis rating scale scores, along with improvements in clinical global impression, life satisfaction, and sleep quality.[18] Taken together, these early clinical data indicate clear promise for KMT in reducing symptoms while improving metabolic health and overall daily functioning in schizophrenia.

Table 1 Clinical Trials of Ketogenic Metabolic Therapy (KMT) for Schizophrenia

Study Type	Year	Number of Participants	KMT Duration	Key Psychiatric Finding	Reference
Pilot study	1965	N=10	2 weeks	Decreased symptomology reported by two independent clinicians	[11]
Case study	2009	N=1	12 months	Resolution of hallucinations and delusions	[12]
Case series	2017	N=2	1 year and 4 months respectively	50% reduced in positive symptom score measured by PANSS	[13]
Case series	2018	N=2	6 weeks	Reduced PANSS score	[14]
Case series	2019	N=2	5 years and 12 years respectively	Full remission	[15]
Case series	2025	N=2	6 weeks and 6 months respectively	Full remission	[16]
Retrospective study	2022	N=10	Varied from 14–250 days	50% reduced in positive symptom score measured by PANSS	[17]
Pilot study	2024	N=5	4 months	32% reduction in psychosis rating Brief Psychiatric Rating Scale scores	[18]

The emerging clinical evidence, although encouraging, is limited to small pilot studies or individual case reports, with insufficient monitoring of dietary adherence. Additionally, these studies provide little insight into the potential mechanisms that may underlie the efficacy of KMT in schizophrenia. Preclinical studies using mouse models of schizophrenia over the last ten years may help guide our mechanistic understanding. In a series of studies, Kraeuter et al showed that a three-week KD normalized the entire schizophrenia-related behavioral sequelae in a mouse model based on the hypoglutamatergic theory of schizophrenia, using the NMDA glutamate receptor antagonist dizocilpine (MK-801).[19,20] These behaviors included locomotor hyperactivity, stereotyped behavior, social deficits, impaired working memory, and deficits in sensorimotor gating (prepulse inhibition of startle). Importantly, they demonstrated that the improvement in the prepulse inhibition (PPI) deficit was independent of the weight-loss-inducing effects of KMT,[20] a crucial consideration since weight loss is a universal metabolic consequence of successful adherence to the diet, reflected in a ketotic metabolic state.

Based on the initial clinical studies, questions have been raised regarding the potential interaction between antipsychotics and KMT. It was shown that chronic KMT was as efficacious in normalizing the PPI deficits in the glutamate hypofunction model of schizophrenia as chronic administration of olanzapine, a clinically used antipsychotic. The combination of KMT and olanzapine did not produce an additive effect, but neither interfered with each other in a deleterious way.[21] This finding supports the safe and effective combination of the dietary metabolic approach and a pharmacological treatment modality.

In examining how KMT exert its beneficial effects, one of the first questions is the potential mediating role of the main circulating ketone body, beta-hydroxybutyrate (BHB), which is produced by the liver during KMT. Chronic BHB injections (for three weeks, to mimic the duration of effective KMT) normalized hyperlocomotion, social withdrawal, and PPI deficits in the glutamate hypofunction model of schizophrenia.[22] Supporting the generalizability of the KMT's efficacy across mechanistically distinct preclinical models, studies in DBA mice, which carry a genetically-driven auditory gating impairment similar to what may exist in people with psychosis, showed improved auditory gating on KMT, an effect also seen in individuals with schizophrenia treated with antipsychotics.[23] Furthermore, plasma ketone levels were found to correlate with improvements in auditory gating.[23] Although more research is needed using a broader range of etiologically relevant preclinical models, such as the maternal immune activation model, current preclinical data strongly support the initial clinical findings and provides a foundation for better mechanistic understanding.

Changes in Inflammation

Mounting clinical and translational evidence indicates that schizophrenia is characterized by concomitant neuroinflammatory processes within the central nervous system (CNS) and systemic immune activation in the periphery. Microglia are the resident immune cells of the central nervous system, responsible for maintaining neural homeostasis through surveillance, phagocytosis, and cytokine signaling. Microglia play a pivotal role in the CNS as key regulators of immune surveillance, by switching between steady and activated states they critically maintaining inflammatory balance necessary for neural homeostasis and proper brain function. Pro-inflammatory microglia have been implicated as central mediators of neuropathology in schizophrenia.[24] Genetic risk factors and environmental stressors, such as prenatal infection, can prime microglia towards an activated phenotype. Activated microglia release cytokines including IL-6, IL-1β, and TNF-α, and upregulate inflammasome components such as NLRP3, initiating a self-sustaining inflammatory cascade.[25] One central pathway involves matrix metalloproteinase-9 (MMP-9) and the receptor for advanced glycation end-products (RAGE): MMP-9 disrupts the blood–brain barrier and generates RAGE ligands that activate nuclear factor κB (NF-κB) signaling, amplifying cytokine transcription and maintaining chronic neuroinflammation.[26] Activated microglia also upregulate complement and phagocytic markers, including C4a, a hallmark of schizophrenia pathology.[27] In humans, increased brain gene expression of the complement component C4a has been associated with greater schizophrenia risk. Overexpression of C4a in adult, but not juvenile, mice led to excessive pruning, measured by reduced cortical synaptic density, through increased microglia-mediated pruning and altered behavior, parallelling schizophrenia pathophysiology.[27] These processes collectively drive excessive synaptic pruning, particularly of glutamatergic synapses, contributing to cortical thinning and cognitive deficits observed in patients.

Emerging evidence suggests that BHB engages hydroxycarboxylic acid receptor 2 (HCAR2) receptors on microglia to suppress NLRP3 inflammasome activation, attenuate pro-inflammatory gene expression, and promote an immunoregulatory phenotype.[28,29] Importantly, KD has been shown to decrease NF-κB expression and inhibit MMP-9 in preclinical studies.[30,31] This shift mitigates microglia-mediated synaptic pruning and downstream cytokine production. Preclinical studies in Alzheimer's disease models demonstrate that ketogenic interventions reduce microglial activation and restore synaptic density, supporting the neuroprotective potential of metabolic therapy.[32] Translating these findings to schizophrenia, the ketogenic diet may represent a promising strategy to modulate microglial reactivity, preserve synaptic integrity, and counteract neuroinflammatory cascades.

Beyond cytokine signaling, activated microglia exacerbate neuronal injury through excessive reactive oxygen species (ROS) generation, predominantly via NADPH oxidase-2 (NOX-2).[33] Elevated ROS disrupts mitochondrial respiration, oxidizes membrane lipids, and contributes to cortical thinning and cognitive deficits through synaptic damage.[34] This oxidative stress not only results from but also perpetuates microglial activation, establishing a feed-forward loop between inflammation and redox imbalance.[35–37]

Ketogenic metabolism interrupts this cycle by enhancing mitochondrial efficiency and providing ketone bodies as oxidative fuels that generate fewer free radicals than glucose.[38] BHB directly scavenges ROS and upregulates antioxidant defense pathways, while improved mitochondrial redox balance reduces NOX-2 activation.[39] Collectively, these processes limit oxidative injury and support neuronal survival in an environment otherwise dominated by microglia-mediated oxidative stress.

Among the immune mediators implicated in schizophrenia, interleukin-17 (IL-17) has emerged as a key contributor to neuroinflammatory processes.[40] Produced predominantly by T helper 17 (Th17) cells, IL-17A has been linked to cortical deficits in a developmental mouse model.[41] Specifically, preclinical evidence indicates that IL-17A impairs the migration and maturation of cortical inhibitory interneurons, particularly parvalbumin-positive (PV) gamma-aminobutyric acid (GABA)ergic inhibitory interneurons, which are essential for coordinated cortical activity and cognitive functions.[42] The high metabolic demand of these neurons makes them especially vulnerable to ROS-mediated injury, in addition to the depletion of their protective perineuronal nets (PNNs) observed in both schizophrenia patients and preclinical models.[43–46] Animal models have additionally linked dysfunction of PV interneurons as contributing to heightened oxidative stress and striatal dopamine dysregulation previously observed in patients.[37,47] Additional inflammatory consequences arise from sustained excitatory signaling which increases extracellular glutamate, contributing to excitotoxicity and subsequent microglial activation.

The KD supports inhibitory signaling by promoting glutamate-to-GABA conversion and facilitating GABAergic neuron function, as ketone bodies provide an efficient energy source for these metabolically demanding cells.[48] This is particularly relevant given substantial evidence of glucose hypofunction and energy deficits in the brains of individuals with schizophrenia. By improving metabolic support for this susceptible population of inhibitory neurons, the KD may help rebalance excitatory-inhibitory balance, thereby reducing ROS production and downstream neuroinflammation.

Importantly, the metabolic state induced by the KD also influences adaptive immunity, shifting T cell subsets away from an inflammatory phenotype. Pathogenic Th17 cells are highly dependent on glycolysis and de novo fatty acid synthesis (FAS) to fuel their pro-inflammatory differentiation and function.[49] The key enzyme in de novo FAS, acetyl-CoA carboxylase 1 (ACC1), catalyzes the conversion of acetyl-CoA into malonyl-CoA, and elevated ACC1 expression enhances Th17 cell polarization by promoting retinoic acid-related orphan receptor gamma t (RORγt) binding to the IL-17 gene locus.[50] In contrast, regulatory T cells (Tregs) rely on mitochondrial oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO) to support their anti-inflammatory programs.[51] The ketogenic metabolic state suppresses ACC1 activity and favors FAO, thereby promoting Treg stability and function while inhibiting Th17 polarization.[52] BHB-mediated downregulation of mechanistic target of rapamycin (mTOR), and hypoxia-inducible factor 1 alpha (HIF-1α) signaling pathways further reinforce this shift.[53] This immunometabolic reprogramming fosters a systemic anti-inflammatory environment, potentially mitigating the neuroinflammatory cascades associated with schizophrenia.

Changes in Systemic Metabolic Health

Insulin resistance represents a key metabolic disturbance that limits glucose availability to the brain and contributes to neural dysfunction. Metabolic disturbances, particularly insulin resistance and impaired glucose tolerance, are frequently observed in patients with schizophrenia, independent of antipsychotic medication effects.[54] Studies indicate heightened prevalence and severity of insulin resistance in both medicated and antipsychotic-naïve individuals.[55] Such systemic metabolic abnormalities not only complicate clinical management but also exacerbate neuronal dysfunction by impairing glucose utilization, thereby influencing cognitive and functional outcomes.[56] Genome-wide association studies (GWAS) have identified schizophrenia-associated genetic loci, including *TCFL2, FTO* and *SLC2A2*, which are established risk genes for type 2 diabetes.[57] Given the intrinsically intertwined functions of the metabolic and immune systems, including immune cell-fate determination, cytokine-insulin crosstalk, and metabolite signaling, insulin resistance may represent both a cause and consequence of the low-grade chronic inflammation observed in schizophrenia.[58,59] Indeed, oxidative stress has been identified as point of convergence of these dynamic systems, propagating feedforward mechanisms irrespective of the primary affected system or trigger.[37] The ketogenic diet, by reducing systemic insulin levels and enhancing insulin sensitivity through improved glycemic control and reduced carbohydrate dependency, has the potential to mitigate these metabolic disturbances.[60] Indeed, a pilot trial including 23 participants with bipolar or schizophrenia reported a 17% decrease in insulin resistance as scored by the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) following a 4-month KD intervention period.[18] In the absence of dietary glucose, ketone bodies become the primary fuel source for both the brain and peripheral tissues, lowering glucose-induced insulin secretion thereby alleviating insulin resistance. KD-induced improvements in insulin sensitivity may significantly contribute to reducing the metabolic dysfunction commonly associated with schizophrenia, indirectly supporting neuronal health and cognitive function, as reported in clinical studies on patients with psychiatric conditions, as well as in preclinical studies on mouse skeletal muscle.[18,61,62] Supporting this mechanistic pathway, metformin, classically prescribed for the treatment of type 2 diabetes, has recently shown promise in improving both inflammatory and cognitive profiles in patients with schizophrenia.[63]

Changes in Cellular Metabolism

Longstanding and emerging research underscores metabolic dysfunction as a significant contributor to the pathogenesis of schizophrenia. Although the metabolic complications associated with atypical antipsychotics are well documented, evidence indicates that metabolic abnormalities precede pharmacological intervention.[54,64] Notably, studies reveal an elevated incidence of diabetes among antipsychotic-naïve patients with schizophrenia compared to the general population, which, paired with evidence of genetic overlap, suggests inherent metabolic dysregulation associated with disease onset.[57,65]

Neuroimaging and postmortem studies further support this, consistently demonstrating disrupted energy metabolism and mitochondrial dysfunction in schizophrenia brains.[66,67] Efficient cellular energy metabolism sustains neuronal signaling, antioxidant defenses, and overall brain homeostasis. Although the adult human brain only constitutes about 2% of total body weight, it consumes nearly 20% of resting metabolic energy. This energy, primarily supplied as glucose, supports essential processes such as neurotransmitter synthesis, synapse development, and neuronal plasticity. While glycolysis and OXPHOS are the principal pathways for ATP production, their balance and efficiency appear compromised in schizophrenia.[68] Evidence includes elevated cerebral lactate levels, diminished activity of mitochondrial enzymes, particularly within respiratory chain complexes I and IV.[67,69] Reduced mitochondrial biogenesis, indicated by decreased mitochondrial DNA content, coupled with unchanged energetic demand, results in an increased workload for the remaining organelles and a net rise in cellular ROS.[70,71] One mechanism by which this may occur is via reduced cortical peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α)-dependent transcripts, as reductions PGC-1α expression is accompanied by increased ROS production.[72] Disrupted mitophagy, resulting in inefficient clearance of damaged mitochondria, may further exacerbate oxidative stress, thereby contributing centrally to neuroinflammation and neurotransmitter dysregulation.[68,73]

The KD addresses mitochondrial impairment through multiple integrated mechanisms. Chronic ketosis has been shown to increase neuronal ATP availability, likely through enhanced mitochondrial biogenesis, elevated mitochondrial protein expression, and improved energy utilization efficiency from ketone oxidation.[74] Indeed, rats with selectively induced mitochondrial dysfunction in forebrain neurons exhibited upregulation of PGC-1α, NAD-dependent protein deacetylase sirtuin-3 (SIRT3) and uncoupling protein 2 (UCP2) following ketogenic diet treatment, leading to improved mitochondrial mass and bioenergetics.[75] Ketone bodies can also be advantageous from a bioenergetics perspective. Like fatty acids, ketone bodies have a higher energy yield per mol compared to glucose, yet can bypass limitations in fatty acid transport, including across the blood-brain barrier and into neuronal mitochondria for oxidation.[76] Ketone bodies normally spare glucose under times of nutrient scarcity (fasting) or high energy demand (long-distance exercise), but under nutritionally replete conditions, this enables glucose to fuel ancillary pathways such as the production of NAPDH (eg via the pentose phosphate pathway) for antioxidant (glutathione) generation.[77,78] Additionally, ketone utilization elevates the NAD+/NADH ratio, promoting more efficient mitochondrial OXPHOS. Coupled with upregulation of the antioxidant system, this reduces steady-state mitochondrial ROS output, thereby alleviating oxidative stress.[79]

Converging evidence implicates oxidative stress as both an upstream catalyst and perpetual amplifier of neuroinflammation, with the redox-immune axis creating a vicious cycle that drives neuronal injury.[37] The KD disrupts this cycle by enhancing bioenergetic efficiency and mitigating oxidative damage, thereby demonstrating considerable therapeutic potential for managing metabolic dysregulation in schizophrenia.

Epigenetic Modifications

Epigenetic regulation controls gene expression through reversible molecular modifications, allowing environmental and metabolic cues to influence neural function without altering DNA sequence. These mechanisms are increasingly recognised as contributors to the pathophysiology of schizophrenia, mediating the complex interplay between genetic susceptibility and environmental exposures.[80] EWAS have been instrumental in identifying novel epigenetic markers associated with treatment response, as well as methylation profiles that confer genetic risk.[81] These changes have been linked to dysregulation of key neurotransmitter systems, particularly dopaminergic and glutamatergic signaling, and have been correlated with clinical symptoms.[82,83] Additional epigenetic alterations have been observed in genes related to oligodendrocytes and myelin sheaths, highlighting potential mechanisms underlying white matter abnormalities in schizophrenia.[84] Enhanced DNA methyltransferase (DNMT) activity and increased histone deacetylation via HDACs are characteristic epigenetic disruptions reported in schizophrenia, reinforcing chromatin condensation and gene silencing.[85] Furthermore, aberrant expression of specific microRNAs (miRNAs) has been identified, which may regulate oxidative stress, inflammation, and neurotransmitter biosynthesis.[86] These miRNA changes have been associated with illness course, symptom severity, and variability in treatment response, although the causal pathways remain under active investigation.

The KD has been shown to exert regulatory effects on the epigenome and is linked to changes in both energy metabolism and neuroprotection.[87] Importantly, diet significantly influences epigenetic regulation, both through the direct production of metabolites (benzoyllysine, phytochemicals) and indirect, gut microbiome-derived metabolites (short-chain fatty acids), particularly butyrate.[88] BHB also participates in histone modifications, including lysine β-hydroxybutyrylation (Kbhbh), a post-translational modification that alters chromatin structure and transcriptional activity.[89,90] In parallel, ketosis-induced increases in intracellular NAD+ enhance the activity of sirtuins, a class of NAD+-dependent histone deacetylases, further modulating chromatin accessibility and gene expression profiles.[91] The KD may also indirectly reduce pathological DNA hypermethylation through increased neuronal adenosine availability, thereby constraining DNA methyltransferase (DNMT)-mediated gene silencing.[92] Although the downstream functional consequences of these transcriptional changes remain to be fully elucidated, it is plausible that alterations in the epigenetic landscape contribute to the therapeutic efficacy of the KD via modulation of key pathophysiological processes, including neuroinflammation and oxidative stress.

Conclusion

Clinical and preclinical evidence converge to support the ketogenic diet (KD) as a promising therapeutic approach for schizophrenia. Pilot clinical and case studies demonstrate symptomatic and cognitive improvements, while preclinical models show that KD can be as efficacious as antipsychotic treatment in normalising behavioural and neurobiological

https://doi.org/10.2147/JIR.S540859

abnormalities. At the immunological level, KD reduces microglial activation, dampens Th17-associated cytokine signalling, and restores T-cell balance. These immune effects are linked to the metabolic state of immune cells, connecting inflammation to the broader metabolic adaptations induced by KD. Consistent with this, KD enhances insulin sensitivity and reduces oxidative stress, indicating improved systemic regulation. At the cellular level, KD promotes mitochondrial biogenesis and efficiency while limiting reactive oxygen species, thereby supporting neuronal energy metabolism and redox stability. In parallel, KD-derived β-hydroxybutyrate mediates direct and indirect epigenetic modifications that may further modulate neuroinflammatory gene expression. Despite these promising mechanisms, current clinical evidence remains limited by small cohorts, short intervention periods, and adherence challenges. KD may not be an appropriate intervention for individuals with absolute contraindications such as pancreatitis, liver failure, or inherited disorders of fat metabolism.[93] Large-scale, rigorously controlled clinical studies are essential to confirm efficacy, safety, and define the therapeutic scope for KD as an adjunct or alternative therapy in schizophrenia.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this study.

Acknowledgments

Graphical abstract created in BioRender. Navarro, S. (2025) https://BioRender.com/nuzjpsn.

Author Contributions

Conceptualisation - AAH, ZS, JRK, CMP and SN; Writing original draft - AAH, ZS and SN; Writing review and editing - AH, JRK, ZS, CMP; Supervision - SN and ZS. All authors have agreed on the journal to which the article will be submitted; reviewed and agreed on the final version for publication; agree to take responsibility and be accountable for the contents of the article.

Funding

The authors did not receive funding for this work.

Disclosure

The authors have no competing interests.

References

1. Peritogiannis V, Ninou A, Samakouri M. Mortality in schizophrenia-spectrum disorders: recent advances in understanding and management. *Healthcare*. 2022;10(12):2366. doi:10.3390/healthcare10122366
2. Lähteenvuo M, Tiihonen J. Antipsychotic polypharmacy for the management of schizophrenia: evidence and recommendations. *Drugs*. 2021;81 (11):1273–1284. doi:10.1007/s40265-021-01556-4
3. Potkin SG, Kane JM, Correll CU, et al. The neurobiology of treatment-resistant schizophrenia: paths to antipsychotic resistance and a roadmap for future research. *NPJ Schizophr*. 2020;6(1):1. doi:10.1038/s41537-019-0090-z
4. Vita A, Barlati S. Recovery from schizophrenia: is it possible? *Curr Opin Psychiatry*. 2018;31(3):246–255. doi:10.1097/yco.0000000000000407
5. Goldsmith DR, Massa N, Miller BJ, Miller AH, Duncan E. The interaction of lipids and inflammatory markers predict negative symptom severity in patients with schizophrenia. *NPJ Schizophrenia*. 2021;7(1):50. doi:10.1038/s41537-021-00179-8
6. Pietrzak D, Kasperek K, Rękawek P, Piątkowska-Chmiel I. The therapeutic role of ketogenic diet in neurological disorders. *Nutrients*. 2022;14 (9):1952. doi:10.3390/nu14091952
7. Mustafa MS, Shafique MA, Aheed B, et al. The impact of ketogenic diet on drug-resistant epilepsy in children: a comprehensive review and meta-analysis. *Ir J Med Sci*. 2024;193(3):1495–1503. doi:10.1007/s11845-024-03622-8
8. Díez-Arroyo C, García-García M, Soto-Méndez MJ, et al. Effect of the ketogenic diet as a treatment for refractory epilepsy in children and adolescents: a systematic review of reviews. *Nutr Rev*. 2024;82(4):487–502. doi:10.1093/nutrit/nuad071
9. Ruan Y, Chen L, She D, Chung Y, Ge L, Han L. Ketogenic diet for epilepsy: an overview of systematic review and meta-analysis. *Eur J Clin Nutr*. 2022;76(9):1234–1244. doi:10.1038/s41430-021-01060-8
10. Martin-McGill KJ, Bresnahan R, Levy RG, Cooper PN. Ketogenic diets for drug-resistant epilepsy. *Cochrane Database Syst Rev*. 2020;6(6): Cd001903. doi:10.1002/14651858.CD001903.pub5
11. Pacheco A, Easterling WS, Pryer MW. A pilot study of the ketogenic diet in schizophrenia. *Am J Psychiatry*. 1965;121:1110–1111. doi:10.1176/ajp.121.11.1110
12. Kraft BD, Westman EC. Schizophrenia, gluten, and low-carbohydrate, ketogenic diets: a case report and review of the literature. *Nutr Metab*. 2009;6:10. doi:10.1186/1743-7075-6-10

13. Palmer CM. Ketogenic diet in the treatment of schizoaffective disorder: two case studies. *Schizophr Res*. 2017;189:208–209. doi:10.1016/j.schres.2017.01.053
14. Gilbert-Jaramillo J, Vargas-Pico D, Espinosa-Mendoza T, et al. The effects of the ketogenic diet on psychiatric symptomatology, weight and metabolic dysfunction in schizophrenia patients. *Clin Nutr Metab*. 2018;1(1):1–5.
15. 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. doi:10.1016/j.schres.2019.03.019
16. Laurent N, Bellamy EL, Tague KA, Hristova D, Houston A. Ketogenic metabolic therapy for schizoaffective disorder: a retrospective case series of psychotic symptom remission and mood recovery. *Front Nutr*. 2025;12:1506304. doi:10.3389/fnut.2025.1506304
17. Danan A, Westman EC, Saslow LR, Ede G. The ketogenic diet for refractory mental illness: a retrospective analysis of 31 inpatients. *Front Psychiatry*. 2022;13:951376. doi:10.3389/fpsyt.2022.951376
18. Sethi S, Wakeham D, Ketter T, et al. Ketogenic diet intervention on metabolic and psychiatric health in bipolar and schizophrenia: a pilot trial. *Psychiatry Res*. 2024;335:115866. doi:10.1016/j.psychres.2024.115866
19. Kraeuter AK, Loxton H, Lima BC, Rudd D, Sarnyai Z. Ketogenic diet reverses behavioral abnormalities in an acute NMDA receptor hypofunction model of schizophrenia. *Schizophr Res*. 2015;169(1–3):491–493. doi:10.1016/j.schres.2015.10.041
20. Kraeuter A-K, van den Buuse M, Sarnyai Z. Ketogenic diet prevents impaired prepulse inhibition of startle in an acute NMDA receptor hypofunction model of schizophrenia. *Schizophr Res*. 2019;206:244–250. doi:10.1016/j.schres.2018.11.011
21. Kraeuter AK, Archambault N, van den Buuse M, Sarnyai Z. Ketogenic diet and olanzapine treatment alone and in combination reduce a pharmacologically-induced prepulse inhibition deficit in female mice. *Schizophr Res*. 2019;212:221–224. doi:10.1016/j.schres.2019.08.002
22. Kraeuter AK, Mashavave T, Suvarna A, van den Buuse M, Sarnyai Z. Effects of beta-hydroxybutyrate administration on MK-801-induced schizophrenia-like behaviour in mice. *Psychopharmacology*. 2020;237(5):1397–1405. doi:10.1007/s00213-020-05467-2
23. Tregellas JR, Smucny J, Legget KT, Stevens KE. Effects of a ketogenic diet on auditory gating in DBA/2 mice: a proof-of-concept study. *Schizophr Res*. 2015;169(1–3):351–354. doi:10.1016/j.schres.2015.09.022
24. Hartmann SM, Heider J, Wüst R, Fallgatter AJ, Volkmer H. Microglia-neuron interactions in schizophrenia. *Front Cell Neurosci*. 2024;18:1345349. doi:10.3389/fncel.2024.1345349
25. Howes OD, Onwordi EC. The synaptic hypothesis of schizophrenia version III: a master mechanism. *Mol Psychiatry*. 2023;28(5):1843–1856.
26. Dwir D, Giangreco B, Xin L, et al. MMP9/RAGE pathway overactivation mediates redox dysregulation and neuroinflammation, leading to inhibitory/excitatory imbalance: a reverse translation study in schizophrenia patients. *Mol Psychiatry*. 2020;25(11):2889–2904.
27. Yilmaz M, Yalcin E, Presumey J, et al. Overexpression of schizophrenia susceptibility factor human complement C4A promotes excessive synaptic loss and behavioral changes in mice. *Nat Neurosci*. 2021;24(2):214–224. doi:10.1038/s41593-020-00763-8
28. Yamanashi T, Iwata M, Kamiya N, et al. Beta-hydroxybutyrate, an endogenic NLRP3 inflammasome inhibitor, attenuates stress-induced behavioral and inflammatory responses. *Sci Rep*. 2017;7(1):7677. doi:10.1038/s41598-017-08055-1
29. Jayashankar SS, Tajul Arifin K, Nasaruddin ML. β-hydroxybutyrate regulates activated microglia to alleviate neurodegenerative processes in neurological diseases: a scoping review. *Nutrients*. 2023;15(3):524.
30. Sastriques-Dunlop S, Elizondo-Benedetto S, Arif B, et al. Ketosis prevents abdominal aortic aneurysm rupture through C–C chemokine receptor type 2 downregulation and enhanced extracellular matrix balance. *Sci Rep*. 2024;14(1):1438. doi:10.1038/s41598-024-51996-7
31. Zhang N, Liu C, Jin L, et al. Ketogenic diet elicits antitumor properties through inducing oxidative stress, inhibiting MMP-9 expression, and rebalancing M1/M2 tumor-associated macrophage phenotype in a mouse model of colon cancer. *J Agric Food Chem*. 2020;68(40):11182–11196. doi:10.1021/acs.jafc.0c04041
32. Xu Y, Jiang C, Wu J, et al. Ketogenic diet ameliorates cognitive impairment and neuroinflammation in a mouse model of Alzheimer's disease. *CNS Neurosci Ther*. 2022;28(4):580–592. doi:10.1111/cns.13779
33. Smith AN, Shaughness M, Collier S, Hopkins D, Byrnes KR. Therapeutic targeting of microglia mediated oxidative stress after neurotrauma. *Front Med*. 2022;9:1034692. doi:10.3389/fmed.2022.1034692
34. Houldsworth A. Role of oxidative stress in neurodegenerative disorders: a review of reactive oxygen species and prevention by antioxidants. *Brain Comm*. 2024;6(1):fcad356. doi:10.1093/braincomms/fcad356
35. Garner KM, Amin R, Johnson RW, Scarlett EJ, Burton MD. Microglia priming by interleukin-6 signaling is enhanced in aged mice. *J Neuroimmunol*. 2018;324:90–99. doi:10.1016/j.jneuroim.2018.09.002
36. Woodburn SC, Bollinger JL, Wohleb ES. The semantics of microglia activation: neuroinflammation, homeostasis, and stress. *J Neuroinflammation*. 2021;18(1):258. doi:10.1186/s12974-021-02309-6
37. Cuenod M, Steullet P, Cabungcal J-H, et al. Caught in vicious circles: a perspective on dynamic feed-forward loops driving oxidative stress in schizophrenia. *Mol Psychiatry*. 2022;27(4):1886–1897. doi:10.1038/s41380-021-01374-w
38. Shahpasand S, Khatami SH, Ehtiati S, et al. Therapeutic potential of the ketogenic diet: a metabolic switch with implications for neurological disorders, the gut-brain axis, and cardiovascular diseases. *J Nutr Biochem*. 2024;132:109693. doi:10.1016/j.jnutbio.2024.109693
39. Rana AK, Bhatt B, Kumar M. β-hydroxybutyrate improves the redox status, cytokine production and phagocytic potency of glucose-deprived HMC3 human microglia-like cells. *J Neuroimmune Pharmacol*. 2024;19(1):35. doi:10.1007/s11481-024-10139-5
40. Chenniappan R, Nandeesha H, Kattimani S, Nanjaiah ND. Interleukin-17 and Interleukin-10 association with disease progression in schizophrenia. *Ann Neurosci*. 2020;27(1):24–28. doi:10.1177/0972753120929565
41. Choi GB, Yim YS, Wong H, et al. The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring. *Science*. 2016;351(6276):933–939. doi:10.1126/science.aad0314
42. Canetta S, Bolkan S, Padilla-Coreano N, et al. Maternal immune activation leads to selective functional deficits in offspring parvalbumin interneurons. *Mol Psychiatry*. 2016;21(7):956–968. doi:10.1038/mp.2015.222
43. Cabungcal J-H, Steullet P, Kraftsik R, Cuenod M, Do KQ. A developmental redox dysregulation leads to spatio-temporal deficit of parvalbumin neuron circuitry in a schizophrenia mouse model. *Schizophr Res*. 2019;213:96–106. doi:10.1016/j.schres.2019.02.017
44. Kann O, Papageorgiou IE, Draguhn A. Highly energized inhibitory interneurons are a central element for information processing in cortical networks. *J Cereb Blood Flow Metab*. 2014;34(8):1270–1282. doi:10.1038/jcbfm.2014.104
45. Wen TH, Binder DK, Ethell IM, Razak KA. The perineuronal 'Safety' net? Perineuronal net abnormalities in neurological disorders. *Front Mol Neurosci*. 2018;11:270. doi:10.3389/fnmol.2018.00270

46. Enwright JF, Sanapala S, Foglio A, Berry R, Fish KN, Lewis DA. Reduced labeling of parvalbumin neurons and perineuronal nets in the dorsolateral prefrontal cortex of subjects with schizophrenia. *Neuropsychopharmacology*. 2016;41(9):2206–2214. doi:10.1038/npp.2016.24
47. Nunes C, Laranjinha J. Nitric oxide and dopamine metabolism converge via mitochondrial dysfunction in the mechanisms of neurodegeneration in Parkinson's disease. *Arch Biochem Biophys*. 2021;704:108877. doi:10.1016/j.abb.2021.108877
48. hertz L, Rothman DL. Glucose, lactate, β-hydroxybutyrate, acetate, GABA, and succinate as substrates for synthesis of glutamate and GABA in the Glutamine-Glutamate/GABA cycle. *Adv Neurobiol*. 2016;13:9–42. doi:10.1007/978-3-319-45096-4_2
49. Karmaus PWF, Chen X, Lim SA, et al. Metabolic heterogeneity underlies reciprocal fates of TH17 cell stemness and plasticity. *Nature*. 2019;565 (7737):101–105. doi:10.1038/s41586-018-0806-7
50. Zhang S, Gang X, Yang S, et al. The alterations in and the role of the Th17/Treg balance in metabolic diseases. *Front Immunol*. 2021;12:678355. doi:10.3389/fimmu.2021.678355
51. Shi Y, Zhang H, Miao C. Metabolic reprogram and T cell differentiation in inflammation: current evidence and future perspectives. *Cell Death Discov*. 2025;11(1):123. doi:10.1038/s41420-025-02403-1
52. Endo Y, Onodera A, Obata-Ninomiya K, et al. ACC1 determines memory potential of individual CD4(+) T cells by regulating de novo fatty acid biosynthesis. *Nat Metab*. 2019;1(2):261–275. doi:10.1038/s42255-018-0025-4
53. Okawa T, Nagai M, Hase K. Dietary intervention impacts immune cell functions and dynamics by inducing metabolic rewiring. *Front Immunol*. 2020;11:623989. doi:10.3389/fimmu.2020.623989
54. Pillinger T, Beck K, Gobjila C, Donocik JG, Jauhar S, Howes OD. Impaired glucose homeostasis in first-episode schizophrenia: a systematic review and meta-analysis. *JAMA Psychiatry*. 2017;74(3):261–269. doi:10.1001/jamapsychiatry.2016.3803
55. Zhuo C, Zhang Q, Wang L, et al. Insulin resistance/diabetes and schizophrenia: potential shared genetic factors and implications for better management of patients with schizophrenia. *CNS Drugs*. 2024;38(1):33–44. doi:10.1007/s40263-023-01057-w
56. Salvi V, Tripodi B, Cerveri G, et al. Insulin-resistance as a modifiable pathway to cognitive dysfunction in schizophrenia: a systematic review. *Schizophr Res*. 2024;274:78–89. doi:10.1016/j.schres.2024.09.008
57. Ding H, Xie M, Wang J, et al. Shared genetics of psychiatric disorders and type 2 diabetes:a large-scale genome-wide cross-trait analysis. *J Psychiatr Res*. 2023;159:185–195. doi:10.1016/j.jpsychires.2023.01.037
58. Rehman K, Akash MSH. Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked? *J Biomed Sci*. 2016;23(1):87. doi:10.1186/s12929-016-0303-y
59. Momtazmanesh S, Zare-Shahabadi A, Rezaei N. Cytokine alterations in schizophrenia: an updated review. *Front Psychiatry*. 2019;10:892. doi:10.3389/fpsyt.2019.00892
60. Paoli A, Bianco A, Moro T, Mota JF, Coelho-Ravagnani CF. The effects of ketogenic diet on insulin sensitivity and weight loss, which came first: the chicken or the egg? *Nutrients*. 2023;15(14):3120. doi:10.3390/nu15143120
61. Ma Q, Jiang L, You Y, et al. Ketogenic diet ameliorates high-fat diet-induced insulin resistance in mouse skeletal muscle by alleviating endoplasmic reticulum stress. *Biochem Biophys Res Commun*. 2024;702:149559. doi:10.1016/j.bbrc.2024.149559
62. Sethi S, Ford JM. The role of ketogenic metabolic therapy on the brain in serious mental illness: a review. *J Psychiatr Brain Sci*. 2022;7(5): e220009. doi:10.20900/jpbs.20220009
63. Shao T, Huang J, Zhao Y, et al. Metformin improves cognitive impairment in patients with schizophrenia: associated with enhanced functional connectivity of dorsolateral prefrontal cortex. *Transl Psychiatry*. 2023;13(1):315. doi:10.1038/s41398-023-02616-x
64. Pillinger T, McCutcheon RA, Vano L, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2020;7(1):64–77. doi:10.1016/S2215-0366(19)30416-X
65. Holt RIG. Association between antipsychotic medication use and diabetes. *Curr Diab Rep*. 2019;19(10):96. doi:10.1007/s11892-019-1220-8
66. Townsend L, Pillinger T, Selvaggi P, Veronese M, Turkheimer F, Howes O. Brain glucose metabolism in schizophrenia: a systematic review and meta-analysis of (18)FDG-PET studies in schizophrenia. *Psychol Med*. 2023;53(11):4880–4897. doi:10.1017/s003329172200174x
67. Pruett BS, Meador-Woodruff JH. Evidence for altered energy metabolism, increased lactate, and decreased pH in schizophrenia brain: a focused review and meta-analysis of human postmortem and magnetic resonance spectroscopy studies. *Schizophr Res*. 2020;223:29–42. doi:10.1016/j.schres.2020.09.003
68. Sarnyai Z, Ben-Shachar D. Schizophrenia, a disease of impaired dynamic metabolic flexibility: a new mechanistic framework. *Psychiatry Res*. 2024;342:116220. doi:10.1016/j.psychres.2024.116220
69. Morén C, Olivares-Berjaga D, Martínez-Pinteño A, et al. Mitochondrial oxidative phosphorylation system dysfunction in schizophrenia. *Int J Mol Sci*. 2025;26(9):4415.
70. Holper L, Ben-Shachar D, Mann JJ. Multivariate meta-analyses of mitochondrial complex I and IV in major depressive disorder, bipolar disorder, schizophrenia, Alzheimer disease, and Parkinson disease. *Neuropsychopharmacology*. 2019;44(5):837–849. doi:10.1038/s41386-018-0090-0
71. Cieślik M, Zawadzka A, Czapski GA, Wilkaniec A, Adamczyk A. Developmental stage-dependent changes in mitochondrial function in the brain of offspring following prenatal maternal immune activation. *Int J Mol Sci*. 2023;24(8):7243. doi:10.3390/ijms24087243
72. McMeekin LJ, Fox SN, Boas SM, Cowell RM. Dysregulation of PGC-1α-dependent transcriptional programs in neurological and developmental disorders: therapeutic challenges and opportunities. *Cells*. 2021;10(2):352. doi:10.3390/cells10020352
73. Yang W, Lian K, Ye J, Cheng Y, Xu X. Analyses of single-cell and bulk RNA sequencing combined with machine learning reveal the expression patterns of disrupted mitophagy in schizophrenia. *Front Psychiatry*. 2024;15:1429437. doi:10.3389/fpsyt.2024.1429437
74. Zweers H, van Wegberg AMJ, Janssen MCH, Wortmann SB. Ketogenic diet for mitochondrial disease: a systematic review on efficacy and safety. *Orphanet J Rare Dis*. 2021;16(1):295. doi:10.1186/s13023-021-01927-w
75. Hasan-Olive MM, Lauritzen KH, Ali M, Rasmussen LJ, Storm-Mathisen J, Bergersen LH. A ketogenic diet improves mitochondrial biogenesis and bioenergetics via the PGC1α-SIRT3-UCP2 axis. *Neurochem Res*. 2019;44(1):22–37. doi:10.1007/s11064-018-2588-6
76. Sato K, Kashiwaya Y, Keon C, et al. Insulin, ketone bodies, and mitochondrial energy transduction. *FASEB J*. 1995;9(8):651–658.
77. Zilberter Y, Zilberter T. Glucose-sparing action of ketones boosts functions exclusive to glucose in the brain. *eNeuro*. 2020;7(6):1. doi:10.1523/eneuro.0303-20.2020
78. Cherkas A, Holota S, Mdzinarashvili T, Gabbianelli R, Zarkovic N. Glucose as a major antioxidant: when, what for and why it fails? *Antioxidants*. 2020;9(2):140.

79. Rojas-Morales P, Pedraza-Chaverri J, Tapia E. Ketone bodies, stress response, and redox homeostasis. *Redox Biol*. 2020;29:101395. doi:10.1016/j.redox.2019.101395
80. Yang H, Sun W, Li J, Zhang X. Epigenetics factors in schizophrenia: future directions for etiologic and therapeutic study approaches. *Ann Gen Psychiatry*. 2025;24(1):21. doi:10.1186/s12991-025-00557-x
81. Kiltschewskij DJ, Reay WR, Geaghan MP, et al. Alteration of DNA methylation and epigenetic scores associated with features of schizophrenia and common variant genetic risk. *Biol Psychiatry*. 2024;95(7):647–661. doi:10.1016/j.biopsych.2023.07.010
82. Liu J, Chen J, Ehrlich S, et al. Methylation patterns in whole blood correlate with symptoms in schizophrenia patients. *Schizophr Bull*. 2014;40(4):769–776. doi:10.1093/schbul/sbt080
83. Pries L-K, Gülöksüz S, Kenis G. DNA Methylation in Schizophrenia. In: Delgado-Morales R, editor. *Neuroepigenomics in Aging and Disease*. Springer International Publishing; 2017:211–236.
84. Li M, Xiao L, Chen X. Histone acetylation and methylation underlie oligodendroglial and myelin susceptibility in schizophrenia. *Front Cell Neurosci*. 2022;16:823708. doi:10.3389/fncel.2022.823708
85. Wawrzczak-Bargieła A, Bilecki W, Maćkowiak M. Epigenetic targets in schizophrenia development and therapy. *Brain Sci*. 2023;13(3):426.
86. Zhang HC, Du Y, Chen L, Yuan ZQ, Cheng Y. MicroRNA schizophrenia: etiology, biomarkers and therapeutic targets. *Neurosci Biobehav Rev*. 2023;146:105064. doi:10.1016/j.neubiorev.2023.105064
87. Ren Q, Fu J, Duan X, et al. The effects of ketogenic diet on brain gene expressions in type 2 diabetes background. *Neuroscience*. 2024;549:101–109. doi:10.1016/j.neuroscience.2024.04.008
88. Zhang Y, Kutateladze TG. Diet and the epigenome. *Nat Commun*. 2018;9(1):3375. doi:10.1038/s41467-018-05778-1
89. Chriett S, Dąbek A, Wojtala M, Vidal H, Balcerczyk A, Pirola L. Prominent action of butyrate over β-hydroxybutyrate as histone deacetylase inhibitor, transcriptional modulator and anti-inflammatory molecule. *Sci Rep*. 2019;9(1):742. doi:10.1038/s41598-018-36941-9
90. Zhou T, Cheng X, He Y, et al. Function and mechanism of histone β-hydroxybutyrylation in health and disease. *Front Immunol*. 2022;13:981285. doi:10.3389/fimmu.2022.981285
91. Tozzi R, Campolo F, Baldini E, et al. Ketogenic diet increases serum and white adipose tissue SIRT1 expression in mice. *Int J Mol Sci*. 2022;23(24):15860. doi:10.3390/ijms232415860
92. Chen F, He X, Luan G, Li T. Role of DNA methylation and adenosine in ketogenic diet for pharmacoresistant epilepsy: focus on epileptogenesis and associated comorbidities. *Front Neurol*. 2019;10:119. doi:10.3389/fneur.2019.00119
93. Watanabe M, Tuccinardi D, Ernesti I, et al. Scientific evidence underlying contraindications to the ketogenic diet: an update. *Obes Rev*. 2020;21(10):e13053. doi:10.1111/obr.13053