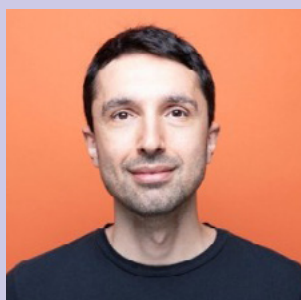


Food for Thought: How Nutrition Shapes Mental Health



Dr. Timur Liwinski

Clinic for Adults, University
Psychiatric Clinics Basel,
University of Basel

Author — Dr. Timur Liwinski

The connection between nutrition and mental health is gaining recognition, with evidence showing that traditional diets rich in whole, minimally processed foods and emerging approaches like ketogenic metabolic therapy (KMT) may offer protective and therapeutic benefits for mood disorders, anxiety, and depression. By balancing nutrients that support brain function, reducing inflammation, and improving gut health, these dietary strategies hold promise for advancing mental well-being.

In the realm of psychiatry, we find ourselves at a crucial juncture. The predominant paradigm, heavily reliant on pharmacotherapy, has yielded but modest advancements in tackling the pervasive challenges of mental health worldwide [1]. Acknowledging the intricate web of factors that shape mental health, a growing body of persuasive evidence underscores the pivotal role of nutrition in the emergence and course of mental disorders. Begdache et al. underscored the intricate interplay between mental well-being and healthy lifestyle practices – a self-reinforcing loop where poor habits erode mental health, which in turn weakens the resolve to adopt healthier choices [2]. Beyond diet as a whole, deficiencies or imbalances in key micronutrients can subtly yet profoundly shape mood and mental health [3]. This recognition beckons a fundamental shift: psychiatry must regard diet with the same gravity that cardiology, endocrinology, and gastroenterology have long afforded it [4]. This realization compels us to widen the lens of psychiatric practice, acknowledging nutrition not as a peripheral concern but as a fundamental pillar of mental health – one that demands thoughtful integration alongside traditional interventions [5]. Emerging evidence points to poor nutrition as a silent accomplice in the onset and course of mental disorders –

undermining both treatment and recovery [6]. The International Society for Nutritional Psychiatry Research calls for embedding nutritional medicine into mainstream psychiatry – urging research, education, policy, and advocacy to drive this essential shift [7]. Yet, this integration faces hurdles, as both mental health and nutrition are intricate, multifaceted domains – resisting simple solutions [8]. The research community is increasingly focused on food as a variable influencing mood and mental health [9]. Given the brain's reliance on nutrition for its structure and energy metabolism, diet should logically be central to mental health. Yet, despite this, there is a notable lack of research, particularly of high quality, on the role of diet in mental health. The field of nutritional psychiatry has long been overlooked, with many studies in this area suffering from poor design [10]. Mental health disorders are multifaceted and typically lack a singular cause or treatment that ensures lasting relief. This review advocates for integrating nutritional strategies into comprehensive psychiatric treatment, alongside established interventions like psychopharmacology (when necessary), psychotherapies, occupational therapy, social work interventions, exercise, etc.

Microbiome-Gut-Brain-Axis

The microbiome-gut-brain axis (MGBA) represents the dynamic, bidirectional dialogue between the gut – including its vast microbial ecosystem – and the brain, intertwining emotional and cognitive processes with intestinal function. Trillions of symbiotic bacteria reside in the gut, exerting a profound influence on brain regulation and behavior [11]. The exact mechanisms of gut-brain interplay remain under exploration, yet key players include the vagus nerve, endocrine and immune pathways, and the gut's role in metabolizing neurotransmitters and bioactive compounds (reviewed in [12]). The human colon harbors a dense and diverse microbial community, reaching $\sim 10^{11}$ microorganisms per gram of content, predominantly anaerobic bacteria. Beyond bacteria, this ecosystem includes archaea, yeasts, and other eukaryotes, forming a complex network within the gut. Collectively, the gut microbiome, comprising ~ 100 trillion microorganisms, carries a genetic repertoire nearly 150 times larger than the human genome. [13]. The gut microbiota harbors enzymes and metabolic pathways absent in the host, enabling the breakdown of complex molecules like dietary fibers and other indigestible compounds. Within the colon, microbes synthesize and release vital vitamins, including K, biotin, pantothenic acid, and select B vitamins. Diet and nutritional supplements, such as probiotics and prebiotics, can modulate the gut microbiome, influencing its composition and function [14,15]. Evidence suggests that consistent use of probiotic supplements can alleviate depressive symptoms [16,17]. Additionally, consuming fermented foods appears to have a positive impact on mood [18]. The term psychobiotics has been coined to describe prebiotics, probiotics, and postbiotics (metabolites produced by the microbiome) that, when consumed, promote mental health through their interactions with the gut's commensal bacteria [19]. A recent review outlined five mechanisms through which the microbiota may impact brain health: 1) modulation of the hypothalamic-pituitary-adrenal axis, 2) alteration of inflammation and gut permeability, 3) vagus nerve stimulation

affecting gut function, 4) production of neurotransmitters and hormonal changes, and 5) modification of myelination and gene expression in the pre-frontal cortex [20].

The Simultaneous Rise of Metabolic and Mental Health Disorders

Over one-third of the global population is estimated to be overweight or obese, with a body mass index (BMI) of 25–29.9 defining overweight and 30 or higher marking obesity. This rising prevalence, steadily increasing over recent decades, highlights the pressing need to address obesity as a significant public health challenge [21]. Mental health disorders, affecting roughly 25% of the population, carry a significant global burden. Obesity, in turn, is increasingly recognized as a key factor that intensifies the risk and severity of these conditions [22]. Indeed, two out of five individuals with overweight or obesity are diagnosed with a psychiatric disorder, most commonly mood disorders, anxiety disorders, psychotic spectrum disorders (PSD), or eating disorders [23]. The temporal relationship between obesity and psychiatric disorders, including major depressive disorder (MDD), anxiety disorders, and PSD, remains debated. This complexity is further heightened by the many proposed biological, psychosocial, and economic connections between these conditions. Beyond the reciprocal psychosocial impacts of obesity on mental well-being and the influence of impaired mental health on lifestyle, biological mechanisms like inflammation and cellular stress, as well as the iatrogenic effects of psychopharmacological treatments – often accompanied by adverse metabolic outcomes – demand close scrutiny [24–27]. What is often termed the Standard American or Western Diet is rapidly spreading worldwide. This diet is characterized by high levels of refined carbohydrates, especially sugar, a high glycemic load, ultra-processed foods, and a significant proportion of unhealthy fats from refined seed oils rather than natural, unprocessed fats [28]. The Western diet is increasingly linked to a range of health risks, including obesity, metabolic dysfunction, mental health disorders, and disruption of the gut microbiota [29].

The Good, the Bad, and the Ugly
Ultra-processed foods are industrially produced items made from compounds extracted, derived, or synthesized from food or food substrates [30]. These products generally contain five or more ingredients, including artificial additives like preservatives, colorants, texturizing agents, and flavor enhancers – substances seldom found in home-cooked meals. Ultra-processed foods are often inexpensive, convenient, shelf-stable, easy to consume, and highly palatable [31]. In early 2021, a systematic review and meta-analysis revealed that ultra-processed foods accounted for 17% to 56% of total daily energy intake, with an average of 37%, across 28 countries [32]. Emerging evidence increasingly connects higher

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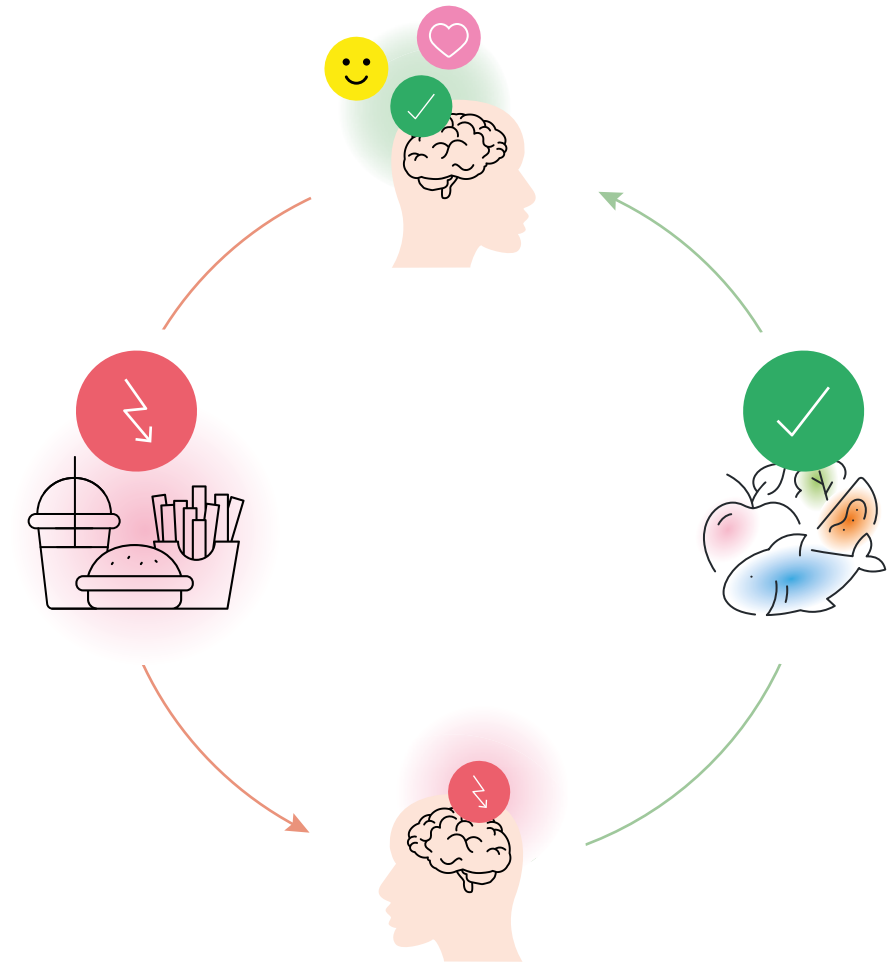
consumption of ultra-processed foods with greater risks of cardiovascular disease-related mortality, type 2 diabetes, and adverse mental health outcomes [33]. Pesticides are widely used in agriculture, gardening, households, and veterinary practices globally, with this trend expected to continue [34]. In the general population, pesticide exposure primarily occurs through consuming food and drinking water contaminated with pesticide residues [35]. Several studies suggest a strong association between pesticide use and negative mental health outcomes, including anxiety, depression, and suicidal behavior

[36–41]. Consumption of conventionally grown fruits and vegetables leads to higher pesticide exposure, potentially carrying long-term health risks. Emerging evidence indicates that certain pesticides may disrupt the gut microbiota, influencing the gut-brain axis [42,43]. A similar concern pertains to microplastics in human food chains [44]. However, the impacts of microplastics on mental health remain largely unknown at present. Modern diets are typically high in refined seed oils. Growing evidence suggests that highly processed oils are pro-inflammatory, increasing oxidative stress in the body. This contributes to damage across multiple organ systems and disrupts metabolism [45]. In contrast, virgin oils have been shown to exert beneficial effects on the gut microbiota, which in turn influence both the nervous system and overall health, while also helping to regulate inflammatory and metabolic changes [46].

Healthful Diets – Current Evidence

Many authors regard mental health disorders as “diseases of modernity” [47]. This perspective highlights the notion that a departure from traditional lifestyles is driving the increasing prevalence of mental health disorders [9,48]. This theory aligns with the evolutionary mismatch hypothesis, which posits that the rising incidence of mental disorders, such as depression, stems from a stark contrast between the environments humans have evolved to thrive in and the modern environment [49]. Food is a key factor shaping modern environments, distinctly differing from pre-modern conditions [50]. Evidence suggests that traditional diets are more favorable to health [51]. Several population studies have established a link between adherence to traditional dietary practices and a reduced risk of anxiety and depression [52–57]. For historical reasons, much of nutritional research has disproportionately focused on the so-called Mediterranean diet. However, this may also apply to traditional diets as a whole, both within and outside the Western world [58]. A substantial body of evidence indicates that the Mediterranean diet offers protection against depressive symptoms and major depression [59,60]. This finding is supported by both population surveys and

randomized controlled trials [61–67]. The health benefits of the Mediterranean diet may be attributed to its high content of antioxidants, fibers, monounsaturated and omega-3 fatty acids, phytosterols, and probiotic microorganisms [68,69]. The Mediterranean diet is also rich in lacto-fermented foods, such as pickles and dairy products like yogurt and cheese, which are fermented by lactic acid bacteria [70]. The traditional Japanese diet is abundant in fermented foods, including probiotic-rich items like black rice vinegar, soy sauce, miso, natto, and tempeh. These foods are made using time-honored methods that rely on a mix of microorganisms such as lactic acid bacteria, acetic acid bacteria, sake yeast, koji molds, and natto bacteria [71]. Adherence to traditional Japanese dietary customs has been linked to lower rates of depressive symptoms [72,73].



Graphical summary: Risky eating behaviors, often linked to a Western diet, are characterized by refined carbohydrates, sugars, high glycemic load, ultra-processed foods, and pro-inflammatory ingredients – while lacking essential nutrients. These factors contribute to mental health disorders. In contrast, traditional diets like the Mediterranean or Japanese diets, rich in whole foods and nutrients, support brain and mental health. Well-formulated ketogenic diets, high in healthy fats and essential nutrients, foster recovery from mental illness through ketosis.

Source: Baumgartner, Imfeld & Persson et al., J Periodontol (2009)

Metabolic Psychiatry and Ketogenic Metabolic Therapy

The ketogenic diet significantly reduces carbohydrate intake, typically allowing only 20–50 grams of net carbs per day, which makes up about 5% of daily caloric intake. In contrast, fat intake is increased to 75–80% of calories. By limiting carbohydrates and promoting

lipolysis, the diet stimulates the production of ketone bodies, which can be measured through reliable, self-administered tests. This makes the ketogenic diet unique in offering a clear biomarker to assess both physiological target achievement and adherence [74]. These ketone bodies provide an alternative fuel source for the brain, reducing its dependence on glucose [75]. Furthermore, ketone bodies have a range of

therapeutic effects, including improving metabolic function (such as lipid profile and insulin stability), inhibiting the mTOR signaling pathway, enhancing mitochondrial function and energy production, reducing oxidative stress and inflammation, and rebalancing the inhibitory-excitatory balance in the brain [76–79]. Therefore, we suggest reserving the term “ketogenic diet” for an interesting but still inadequately scientifically validated approach to illness prevention and wellness in healthy individuals. In contrast, its therapeutic use in serious disorders, based on pathophysiological reasoning, should be referred to as “ketogenic metabolic therapy” (KMT). Ketosis has a long history in human biology, with mild ketosis commonly observed in both mothers and infants during the third trimester of pregnancy and at birth [80]. Prolonged fasting and ketosis were the norm during human evolution, particularly in the Paleolithic era, when social structures were centered around small groups of hunter-gatherers [81,82]. The use of ketogenic diets for therapeutic purposes in modern medicine dates back to the 1920s [83]. A century ago, the ketogenic diet was a standard treatment for diabetes, extending the lives of children with type 1 diabetes and managing type 2 diabetes in adults. However, the discovery of insulin in the 1920s allowed people with diabetes to control hyperglycemia, even on high-carbohydrate diets [81]. Today, the ketogenic diet is an established, effective non-pharmacologic treatment for drug-resistant epilepsy in both children and adults, earning its place in modern epilepsy treatment guidelines [84]. Randomized controlled trials have shown that short-term ketogenic interventions consistently reduce body weight and visceral adipose tissue, improve metabolic health markers (including increased HDL cholesterol, lowered triglycerides, HbA1c, and diastolic blood pressure), all while preserving muscle mass [79]. However, research on the ketogenic diet’s efficacy in psychiatric illness is still in its early stages. In a study of 28 treatment-resistant patients with MDD, bipolar disorder, and schizophrenia, KMT led to a significant reduction in psychiatric symptoms for

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all patients. Clinical remission was achieved by 43%, and 64% were discharged with reduced psychiatric medication. Metabolic health improved, and nearly all patients, except one, experienced significant weight loss [85]. In a 4-month single-arm pilot trial involving 23 patients with bipolar disorder and schizophrenia, KMT reversed metabolic syndrome. Patients with schizophrenia showed an average improvement of 32% on the Brief Psychiatric Rating Scale. Additionally, 69% of participants with bipolar disorder had a greater than one-point improvement on the Clinical Global Impression score. Overall,

Abstract

The growing prevalence of both metabolic and mental health disorders has led to increasing interest in the relationship between nutrition and mental well-being. Evidence suggests that traditional diets, which prioritize minimally processed whole foods and avoid highly industrially processed oils and refined sugars, may play a crucial role in preventing and treating mental health conditions. These diets promote a balance of nutrients that support brain function and reduce inflammation, offering a potential protective effect against mood disorders, anxiety, and depression. Ketogenic metabolic therapy (KMT), which has demonstrated significant success in treating drug-resistant epilepsy, is gaining attention for its potential in psychiatric applications. Preliminary studies suggest that KMT may offer therapeutic benefits in mental health conditions such as depression, bipolar disorder, and schizophrenia. The diet works by altering metabolism to promote ketone body production, which provides an alternative energy source for the brain and may have neuroprotective effects. Additionally, KMT has been shown to improve metabolic health, reduce oxidative stress, and stabilize insulin levels, providing dual benefits for both brain and body health. Moreover, the gut microbiome plays an essential role in regulating brain function and behavior, with emerging evidence highlighting its impact on psychiatric disorders. While initial studies indicate that well-formulated ketogenic diets may modulate the gut microbiome in beneficial ways, further high-resolution human trials are necessary to fully understand these effects, particularly in the context of mental health. Thus, both traditional diets and the emerging KMT offer promising approaches to preventing and treating mental health disorders.

the trial suggests dual metabolic and psychiatric benefits from KMT [86]. In another pilot trial lasting 6 to 8 weeks, KMT in bipolar disorder, involving 27 participants, demonstrated the feasibility and safety of this approach in a psychiatric population [87]. Before the recent surge of trials on KMT in mental illness, a series of studies in the pediatric domain showed its potential to alleviate core symptoms and improve key features of autism spectrum disorder [88–91]. Despite limitations such as small sample sizes and the lack of control groups, existing studies have shown the feasibility, tolerability, and significant improvements in psychiatric symptoms associated with ketogenic metabolic therapy in various severe, chronic, and refractory mental disorders. Preliminary evidence indicates that ketogenic nutrition may alter the gut microbiome. Well-designed human trials suggest potential neuroprotective modulation through ketogenic diets. In a randomized crossover trial involving subjects with mild cognitive impairment, a Mediterranean-style ketogenic diet increased the beneficial genus *Akkermansia muciniphila*, reduced fecal lactate and acetate, and raised propionate and butyrate compared to the American Heart Association diet [92]. Preliminary animal research suggests that this bacterium may have antidepressant effects [93]. In a weight-loss trial, a very low-calorie ketogenic diet (VLCKD) increased gut microbiota diversity compared to a standard low-calorie diet (LCD) [94]. In an RCT with obese individuals, calorie restriction (CR), intermittent fasting (IF), and ketogenic diet significantly increased microbiota diversity compared to a habitual ad libitum diet. Only the ketogenic diet group showed an increase in the beneficial *Faecalibacterium prausnitzii* [95]. Secondary analysis of this trial suggested that lipopolysaccharide (LPS)-induced inflammatory processes may mediate the favorable impact of gut microbiota modulation on mitochondrial function. Changes with ketogenic nutrition depend on the specific formulation and control condition. In a recent RCT comparing therapeutic carbohydrate restriction (<8% of daily calories) with a moderate-sugar and

a low-sugar diet adhering to public health guidelines, no differences were observed between groups after 12 weeks in taxonomic composition, circulating short-chain fatty acids, or lipopolysaccharide-binding protein (a proxy for intestinal barrier integrity) [96]. Further high-resolution studies on microbiota changes in controlled human trials are essential to fully understand the impact of ketogenic regimes on the human gut microbiota, especially within the psychiatric context, where such research remains scarce.

Conclusions
Nutritional neurometabolic factors are increasingly recognized in psychiatry. The concurrent rise in metabolic and mental health disorders has sparked exploration into their shared mechanisms. Traditional diets, focused on whole, minimally processed foods, show strong potential for preventing and treating mental illness. Complementarily, ketogenic metabolic therapy offers a promising treatment for certain psychiatric patients (Figure 1).

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