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EXPERT REVIEW

Diet and depression: exploring the biological mechanisms of action

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Abstract

The field of nutritional psychiatry has generated observational and efficacy data supporting a role for healthy dietary patterns in depression onset and symptom management. To guide future clinical trials and targeted dietary therapies, this review provides an overview of what is currently known regarding underlying mechanisms of action by which diet may influence mental and brain health. The mechanisms of action associating diet with health outcomes are complex, multifaceted, interacting, and not restricted to any one biological pathway. Numerous pathways were identified through which diet could plausibly affect mental health. These include modulation of pathways involved in inflammation, oxidative stress, epigenetics, mitochondrial dysfunction, the gut microbiota, tryptophan–kynurenine metabolism, the HPA axis, neurogenesis and BDNF, epigenetics, and obesity. However, the nascent nature of the nutritional psychiatry field to date means that the existing literature identified in this review is largely comprised of preclinical animal studies. To fully identify and elucidate complex mechanisms of action, intervention studies that assess markers related to these pathways within clinically diagnosed human populations are needed.

Introduction

The field of Nutritional Psychiatry has generated observational and efficacy data supporting a role for healthy dietary patterns in depression risk and symptom management [1–4]. Dietary patterns including the Mediterranean diet and an 'anti-inflammatory' diet are associated with a reduced risk of depression in both cross-sectional and prospective studies [3]. There are also observational data showing similar associations for anxiety [5] and bipolar disorder [6]. Associations between diet quality and mental health outcomes appear to be present across the lifespan including in children and adolescents, [7] and are also seen in intergenerational studies investigating the role of maternal diet on childhood mental health [8].

Intervention studies also support the use of adjunctive dietary interventions in improving clinical depression and depressive symptoms. A meta-analysis of 16 studies in primarily non-clinical populations concluded that dietary interventions can effect a small reduction in depressive symptoms [4]. However, larger effects from dietary interventions may be observed in samples with higher baselines levels of depression, as three recent randomised controlled trials (RCTs) in adults with current depression have observed consistently moderate-to-large improvements in symptoms from Mediterranean diet-based interventions compared to control conditions. First, The SMILES trial [2] and The Healthy Eating for Life with a Mediterranean Diet (HELFIMED) trial [9] reported significant reductions in depressive symptoms following adjunctive Mediterranean diet interventions in adults with depression compared to control conditions. Similar findings were subsequently found in an independent trial conducted in young adults with current depression [10]. Furthermore, dietary interventions have also been applied within broader collaborative care programmes for adults with comorbid obesity which similarly produce significant reductions in depressive symptoms [11]. Data are less clear for the role of dietary change in the primary prevention of clinical depression. For instance, while the large PREDIMED trial suggested that a

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Mediterranean diet supplemented with tree nuts may prevent incident depression in patients with type 2 diabetes, the recent MoodFood trial observed no preventive benefit of a behavioural activation intervention focused on dietary improvement [12, 13]. However, the minimal dietary change in the intervention group from the MoodFood trial highlights some of the challenges of conducting dietary interventions in populations with mental health conditions.

While the emerging efficacy data supporting adjunctive dietary interventions for mental health are promising, many questions remain unanswered, including what works for whom and under which circumstances. Such questions, and the optimal design of studies required to answer them, ideally require an understanding of the key biological mechanisms underpinning the relationship. With a focus on key pathways in the pathology of depression that have been identified in prior reviews [14–18], here we provide an overview of what is currently known regarding underlying mechanisms of action by which diet may affect mental and brain health (Fig. 1). While most human research to date has focused on the role of diet in depression, this review will also draw on the evidence of mechanistic pathways from conditions that share pathophysiologic characteristics and risk pathways with depression, including anxiety, bipolar disorder and schizophrenia.

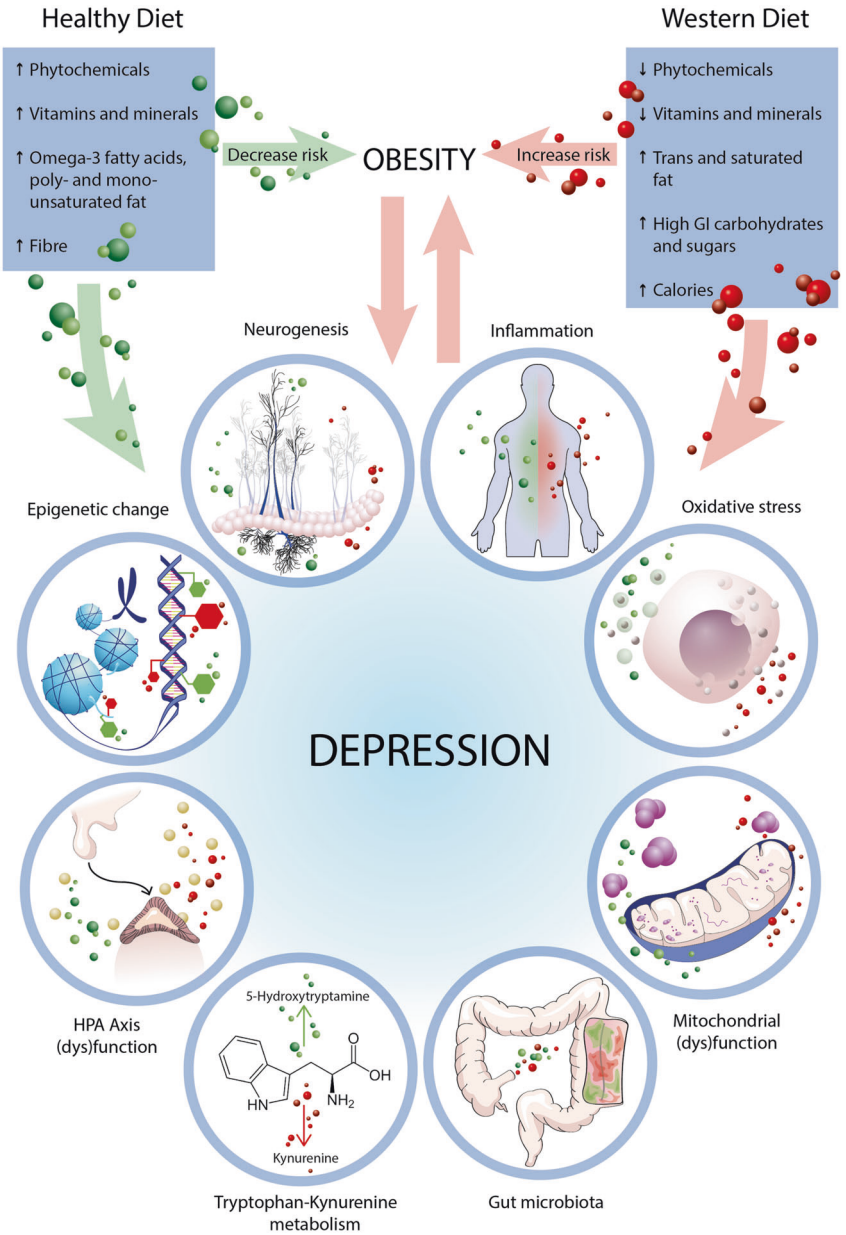

Fig. 1 Overview of the role of diet quality on implicated mechanisms of depression. This figure details the identified pathways implicated in depression that may be amenable to dietary manipulation. The black arrows represent increased or decreased consumption related to the opposing dietary patterns. Green arrows represent a posited beneficial modulation of the included pathways while red represent potentially detrimental modulation.

Inflammation

Around 25% of patients with neuropsychiatric conditions, including mood disorders and schizophrenia, exhibit increased levels of inflammation [19, 20]. Such hyperactivation of the immune system is induced by diverse factors. It is commonly induced by stress, where different types of stressors, such as psychosocial stress or early life adversities as well as physiological and lifestyle sources (e.g. physical inactivity and smoking), are capable of eliciting increases in inflammatory activity in a manner that may promote depressive symptoms [14, 21]. Upon exposure to stressors, a typical inflammatory response consists of three major components: (i) inflammatory inducers (e.g. pathogen- or damage-associated molecular patterns); (ii) sensors detecting the inducers (e.g. receptors expressed by immune cells); and (iii) inflammatory mediators induced by the sensors, including cytokines, chemokines and prostaglandins [19]. Once activated, these inflammatory molecules can influence physiological domains relevant to mood disorders, such as neurotransmitter metabolism, neuroendocrine function, and functional brain activity [21]. Moreover, administration of cytokines for medical purposes (e.g. interferon alpha infusions) can cause changes in emotions and behaviour, such as low mood, fatigue, anxiety, sleep disturbances, anhedonia, and cognitive dysfunction, all of which closely resemble symptoms of depression [22–24]. Furthermore, a recent meta-analysis concluded that anti-inflammatory agents, such as cytokines inhibitors, non-steroidal anti-inflammatory drugs, and antibiotics including minocycline, may be efficacious adjunctive treatments for depressive disorders [25].

Healthy dietary patterns (and individual dietary components) have demonstrated anti-inflammatory properties that may be relevant to mental health disorders. Both longitudinal observational studies and clinical trials in populations with chronic metabolic disease show that adoption of healthy dietary patterns, such as the Mediterranean diet, reduces systemic inflammation [26–28]. Observational studies have also recently confirmed that individuals with severe mental illness have substantially higher levels of 'dietary inflammation' than the general population, i.e. greater intakes of pro-inflammatory foods (such as refined carbohydrates and trans fats) and lower intakes of anti-inflammatory nutrients (primarily derived from whole foods and plants) [29]. Furthermore, recent meta-analyses of longitudinal studies provide compelling evidence that individuals with a more inflammatory dietary pattern have greater risk of developing depression over time [3]. Thus, modifying the pro-inflammatory diets typically associated with mental illness towards a more Mediterranean or otherwise anti-inflammatory dietary pattern could present a novel strategy for counteracting the inflammatory status associated with the onset and severity of mental disorders.

There are many nutritional components of a healthy dietary pattern. Some are of particular interest due to their ability to reduce inflammation. Among them, phytochemicals such as polyphenols, present in blueberries, cocoa and curcumin, amongst others, have strong anti-inflammatory properties that might be beneficial for a variety of neuropsychiatric disorders [30]. Omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid, polyunsaturated fatty acids that are found in high concentrations in marine food products such as salmon, have anti-inflammatory properties and can improve clinical outcomes [31], and delay onset of cytokine-induced depression [32]. Baseline inflammation also appears to be a predictive marker of clinical response to omega-3 fatty acid treatment in people with depression [33]. Furthermore, research in animal models suggest that omega-3 fatty acids can mitigate inflammation-induced reductions in neurogenesis to a similar magnitude as antidepressants [34].

Oxidative stress

Oxidative stress, the imbalance of oxidative and antioxidant processes, can result in cellular injury to lipids, proteins, and DNA. Persistent oxidative stress has been implicated as a potential mechanistic pathway in depression and other mental health disorders [35]. A meta-analysis of 115 studies reported that people with depression had elevated oxidative stress markers, such as malondialdehyde and 8-F_2-isoprostanes, as well as lower antioxidant markers, such as total antioxidant capacity, when compared to healthy controls [36]. Furthermore, oxidative stress markers were reported to decrease after antidepressant treatment, supporting a causal relationship [36]. Post-mortem studies also show elevated oxidative stress markers in the brains of people with depression, bipolar disorder, and schizophrenia compared to healthy controls [37, 38]. In addition to the direct effect of oxidative stress on cellular injury, increased production of reactive oxygen and nitrogen species can lead to mitochondrial dysfunction, inflammation, and altered tryptophan metabolism, which are all implicated in mental health disorders [35].

Diet can both exacerbate and ameliorate oxidative stress by either depriving or increasing the supply of dietary compounds with antioxidant properties. Animal studies suggest that high-fat Western-style diets can increase markers of oxidative stress such as protein oxidation and lipid peroxidation within the brain as well as peripherally [39, 40]. Due to the high oxidative stress load reported in people with mental disorders [35], increasing dietary quality may be a viable intervention for replenishing depleted antioxidant defences. A nutrient-dense diet is rich in a range

of compounds with both direct and indirect antioxidant properties that are associated with reduced oxidative stress markers such as F2-isoprostanes and plasma oxidised low-density lipoprotein [41–43]. Vitamins such as ascorbic acid (vitamin C) and alpha tocopherol (vitamin E) have direct free radical scavenging properties [44]. Nutrients such as selenium, zinc and cysteine are cofactors for antioxidant systems such as glutathione peroxidase and superoxide dismutase. There is also preliminary evidence to indicate that supplementation with antioxidant compounds such as n-acetyl cysteine may improve depressive symptoms [45]. Preclinical studies suggest that polyphenols may also reduce oxidative stress, via upregulation of antioxidant defence systems including induction of nuclear factor erythroid-related factor (Nrf)-2 and modulation of the inflammatory pathways nuclear factor kappa B (NFkB) and mitogen-activated protein kinase (MAPK) [46].

The gut microbiota

A rapidly growing body of literature has implicated the gut microbiota in regulating physiological processes, including cognitive function, neuropsychiatric disorders, and behaviour, via the microbiota–gut–brain axis [47]. As the gut microbiome is one of the first bodily systems to interact with consumed food, many other implicated mechanisms in depression pathophysiology (e.g. inflammation [48], neurogenesis [49], tryptophan metabolism [50]; see Fig. 2) may, at least in part, be modulated by the gut microbiome. Further support for this comes from animal models that suggest a direct link between diet, microbiota and mechanisms implicated in depression [51, 52]. The gut microbiota thus presents a potentially critical mediating pathway in the connection between diet and brain health [53]. Data from animal models support this; diet-driven alterations in gut microbiota can contribute to behavioural changes that mimic symptoms of common mental disorders such as anxiety and depression. A high-fat, Western-style diet, for example, resulted in an increased Firmicutes/Bacteroidetes ratio as well as reduced exploratory behaviour, increased anxiety-like behaviour, and decreased memory in rodent models [54, 55]. Other preclinical studies demonstrated that high calorie diets increased the abundance of *Clostridiales*, *Ruminococcaceae*, and *Bacteroidales*, and resulted in poorer cognitive flexibility, as well as impaired social and object recognition [56, 57]. Prebiotic supplementation (fructo- and galactooligosaccharide) reversed chronic stress-induced alterations in the gut microbiota, by preventing the reduction of beneficial microbes such as *Bifidobacterium* or *Lactobacillus* and normalised chronic stress-induced pro-inflammatory cytokines and depressive like behaviours in mice [58]. Although the exact mechanisms are still being elucidated, multiple direct and indirect pathways have been proposed by which the gut microbiota

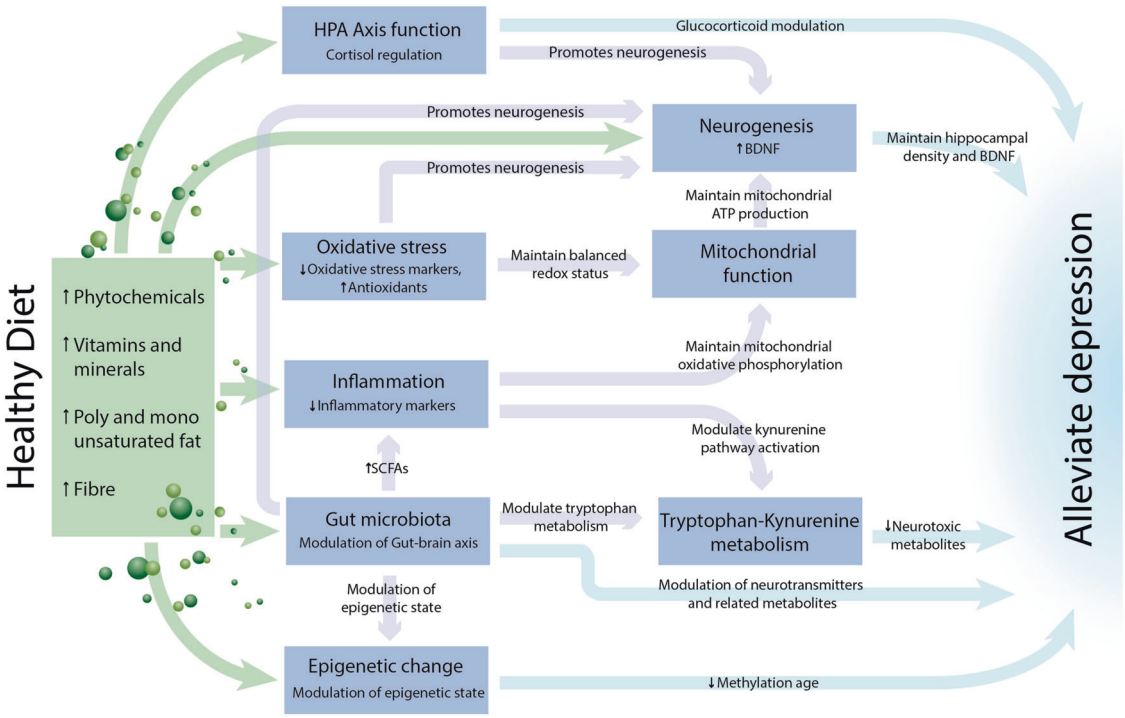

Fig. 2 Proposed interplay between dietary quality and implicated mechanisms in alleviating depression. This figure represents the likely interconnected and overlapping nature of the implicated pathways in this review. The black arrows represent increased consumption of individual components of a healthy dietary pattern.

can modulate brain function and behaviour, including microbial metabolites (e.g. short-chain fatty acids from bacterial fermentation of fibre), neuronal pathways (e.g. vagus nerve), neuroactive pathways (neurotransmitters such as serotonin, and neuroactive metabolites), the hypothalamus–pituitary–adrenal (HPA) axis, immune and endocrine pathways [59] as well as direct neuroactive metabolic potential of the microbiota [60].

Both short-term nutrient intake and long-term dietary patterns are recognised as influential factors in shaping gut microbiota diversity, composition, and metabolic function [61, 62]. Interestingly, animal studies have reported that transferring the microbiota from animals exposed to a high-fat diet can result in behavioural changes such as exploratory and cognitive behaviour in the absence of the diet [63]. To date, there are few human data with only one uncontrolled dietary intervention study to have demonstrated that a diet high in inulin-rich vegetables increased Bifidobacterium and led to improvements in satiety and levels of intrapersonal competence (but no difference in mood or perceived stress) [64]. Similarly, a recent study demonstrated that bacterial taxa enriched by a 1-year Mediterranean dietary intervention in elderly participants were associated with improved cognitive function and reduction of the inflammatory markers C-reactive protein and interleukin-17 [65]. The effect of individual nutrients (e.g. fibre, polyunsaturated fatty acids and polyphenols) on brain health may also be mediated by their direct effects on the microbiota [66, 67]. For example, short-chain fatty acids that are produced by fermenting dietary fibre by the gut microbiota have been shown to have important immunomodulatory functions. This relationship may also be bi-directional, with the gut microbiota implicated in enabling the bioavailability of these compounds [68].

Manipulating the gut microbiota via dietary supplements (probiotics and prebiotics) and dietary strategies (e.g. fermented foods such as kimchi, yoghurt and sauerkraut) as a means of modulating the microbiota–gut–brain axis has thus garnered much attention [69]. The introduction of living microorganisms—a *Lactobacillus* spp. alone or in combination with *Bifidobacterium spp*.—may improve both depression and anxiety, yet evidence for an impact of pro- and prebiotics on mental health is limited and highly variable [70]. The limited evidence-base is particularly relevant for prebiotic interventions as demonstrated by a recent meta-analysis that reported no significant difference in depression or anxiety symptoms following prebiotic supplementation compared to control [70]. However, this was in a limited sample ($n = 4$–5 trials) of largely non-clinical participants, and in general, biological interventions are likely to show efficacy in clinical rather than non-clinical participants. Fermented foods, containing functional microorganisms, prebiotics, and biogenics, are another food group with the potential to manipulate the gut–brain communication [71]. Although strong clinical evidence is lacking to date, some studies have shown promise in improving mood outcomes following fermented foods consumption [71]. Because of the viability and variable colonising ability of probiotics, which may account for the inconsistent efficacy between species/strains and combinations thereof [72, 73], dietary patterns that include a diverse range of plant food sources may be preferential for promoting the consumption of various prebiotic substrates and probiotic strains.

Microbiota may also mediate the connection between diet and brain health through food hypersensitivity. Self-reported food allergy is more common in those with depression than in healthy controls (13% vs. 9%) [74], although these rates are much higher estimates compared with prevalence data that use appropriate diagnostic criteria [75]. In the case of true food allergy, IgE sensitisation of mast cells in the gastrointestinal mucosa become triggered by the dietary allergen, resulting in a cascade of inflammatory mediators that can impair intestinal permeability [76]. Increased intestinal permeability has been associated with enhanced translocation of gram-negative *Enterobacteria* and immune activation [77] which may contribute to systemic inflammation, including neuroinflammation, [74] a characterising feature in depression [14]. Further large-scale studies of individuals with true food allergy are needed to clarify its contribution to the development of depression. Research into non-IgE mediated food hypersensitivity (i.e. food intolerance), such as to gluten [78], and casein [79], may also reveal insights into how diet-induced changes to the gut microenvironment may affect mood.

The hypothalamic–pituitary–adrenal (HPA) axis

The HPA axis, comprising the brain (hypothalamus), pituitary and adrenal glands, regulates glucocorticoid production and has been implicated in the pathophysiology of neuropsychiatric disorders. More than 60% of people with depression exhibit excessive cortisol production or other disturbances to the HPA system such as altered response to dexamethasone suppression testing and adrenocorticotropic hormone levels [80]. Normalisation of some measures of altered HPA-axis activity is observed after clinical recovery, suggesting a role in disease pathophysiology [80]. Furthermore, early childhood trauma can result in permanently dysregulated HPA axis, resulting in increased risk of mental health disorders across the lifespan [80]. For example, animals exposed to maternal deprivation have altered HPA response to stress in adulthood and memory impairment [80].

Clinical intervention trials with nutrients such as vitamin C reported a reduction in cortisol reactivity to acute

physiological stress in healthy adults [81]. Omega-3 fatty acid intervention studies also demonstrated improved cortisol levels in healthy adults as well as people with depression [82, 83]. Similarly, intervention studies using polyphenol-rich foods such as pomegranate juice and dark chocolate have reported a reduction in cortisol levels in healthy individuals [84, 85]. For example, a recent 4-week trial in healthy participants found that total daily cortisol, morning cortisol, and the cortisol/cortisone ratio were significantly reduced in participants that received high-flavonoid dark chocolate [84]. Although the mechanisms by which these dietary factors influence cortisol and other HPA-axis related measures is unclear, this influence may be mediated via modulation of the pro-inflammatory response to hypothalamic activation following psychological stressors [86]. In contrast, a small ($N = 12$) 3-day feeding study found that a high-glycaemic index diet was associated with a small increase in cortisol secretion [87]. Due to the emerging role of the gut–brain axis in mental health, probiotics have also been explored as potential interventions targeting the HPA axis. In animal studies, probiotics ameliorated enhanced basal HPA-axis activity induced by maternal separation stress in rats and mitigated elevations in serum corticosterone levels induced via the water avoidance stress test, a non-invasive method to induce psychological stress [88]. Preliminary clinical intervention studies in healthy adults corroborate these results. For example, in a double-blind, randomised, controlled trial, a multi-strain probiotic intervention improved 24 h urinary-free cortisol and self-reported stress outcomes compared to placebo in healthy individuals [89]. However, in a similar probiotic clinical trial in 60 people with depression, there was no significant difference in blood cortisol levels between groups [90].

Adult hippocampal neurogenesis and brain-derived neurotrophic factor (BDNF)

The hippocampus is a critical component of the limbic system and has a central role in learning, memory formation and mood [91]. In rodents, functional studies have shown that the level of neurogenesis in the adult hippocampus is directly linked to cognition and mood [92]. For example, in mice, increased neurogenesis in the hippocampus is associated with improved learning and memory abilities, whereas a decrease is often associated with behaviours modelling certain aspects of depression [93]. BDNF is a neurotrophin that is highly expressed in the hippocampus and is involved in critical cellular functions such as synaptic plasticity and cell metabolism underlying normal behaviour and its neuropsychiatric aberrations. Indeed, BDNF is the prototypical molecule epitomised to explicate the action of diet, exercise, and antidepressant therapeutics on depressive- and anxiety-like behaviours. Lowered levels of serum BDNF has been described in patients with major depression [94], and the protective action of BDNF against the pathogenesis of depressive disorders has received some experimental support [95, 96].

There is compelling evidence that BDNF and adult hippocampal neurogenesis regulation can be modulated through diet [97]. Animal models have demonstrated that Western-style diets high in fat and sucrose can impair neurogenesis and lower BDNF levels within the hippocampus and adversely impact cognitive performance [98]. In contrast, a considerable body of research in animal models suggest a beneficial effect of dietary components such as omega-3 fatty acids, probiotics, and vitamins [99, 100]. Individual polyphenol compounds such as resveratrol, blueberries, green tea, curcumin, and cacao have also been shown to reverse adverse changes and preserve the integrity of adult hippocampal neurogenesis under conditions of psychopathology, ageing and disease [101]. Furthermore, animal models suggest that other dietary parameters including calorie intake, meal frequency, and meal texture may modulate hippocampal neurogenesis [102].

Observational studies provide further evidence with reported direct associations between healthy dietary patterns and larger hippocampal volume, independent of a wide range of explanatory factors (e.g. age, gender, education) [103–105]. In a subgroup analysis of participants that had depression at baseline in the PREDIMED study, participants that were randomised to a Mediterranean diet supplemented with nuts had a higher level of plasma BDNF at the 3 year timepoint compared to the control intervention [106]. However, the relationship between systemic and central levels of BDNF is not straightforward and circulating levels may be influenced by sample processing methods and storage conditions as well as other peripheral sources of BDNF (e.g. blood platelets) [107, 108]. Additional dietary paradigms, such as caloric restriction via a consistent reduction of total daily food intake or intermittent fasting (e.g. every-other-day feeding), may also influence BDNF expression [109]. In contrast, recent human intervention studies suggest that Western-style diets can impair hippocampal-dependent learning and memory [110, 111]. Finally, neurogenesis can be modulated via other pathways included in this review such as via the gut microbiota and inflammatory pathways, suggesting that additional dietary factors may indirectly influence neurogenesis via modulation of these secondary pathways.

Tryptophan–kynurenine metabolism

Tryptophan, an essential amino acid that must be supplied in the diet, is an important building block for a number of

key neuroactive molecules [112]. The focus on tryptophan availability and metabolism in psychiatry has largely centred on its conversion into serotonin, the therapeutic target for the vast majority of antidepressants and first line anxiolytics [113]. However, the dominant physiological pathway for tryptophan is along the kynurenine pathway, which leads to the production of the neurotoxic quinolinic acid and the neuroprotective kynurenic acid [114]. There is increasing recognition of the importance of peripheral mechanisms leading to increased kynurenine production and that the metabolites produced along this pathway are vital neurobiological mediators in a range of neurological and psychiatric disorders, including but not limited to depression [115] and schizophrenia [116]. Moreover, the initiation of this metabolic cascade can arise due to either stress [117] or following activation of the immune system and inflammatory pathways [118]. This makes the availability of tryptophan for metabolism along this pathway an important consideration in the management of mental health.

Tryptophan is found in a wide variety of foods including chicken, tuna, oats, peanuts, bananas, milk, cheese, and chocolate [119]. Although the majority of tryptophan derived from ingested protein is absorbed in the small intestine, significant amounts may also reach the colon, where the gut microbiota plays a key role in its fate and activity [120, 121]. In the context of using dietary interventions for mental health prevention and treatment, understanding tryptophan availability and metabolism may be important. For example, increased protein intake can lead to increased tryptophan availability, variations in carbohydrate intake can impact on free tryptophan levels, and non-esterified fatty acids can physiologically displace tryptophan from albumin [122, 123]. Fluctuations in the availability of other amino acids that compete with tryptophan for transport across the blood brain barrier can also affect the central nervous system metabolic pool [122]. Direct tryptophan supplementation has been trialled as an intervention in people with depression as a way to improve serotonergic signalling [112]. These studies have provided mixed results and where there is activated metabolism of tryptophan along the kynurenine pathway (e.g. as a consequence of stress or immune activation), this may result in an increased production of the neurotoxic quinolinic acid.

In addition to the role of dietary tryptophan on kynurenine metabolism, there is an emerging body of research that has investigated the role of dietary interventions in modulating kynurenine metabolism via other means including the modulation of indoleamine 2,3 dioxygenase (IDO) activity [124, 125]. In vitro and animal models have reported individual dietary components such as curcumin [126] and green tea [127] as well as dietary regimens including a ketogenic diet [128] and fasting [129] to modulate kynurenine pathway activity. Preliminary intervention studies also suggest that dietary regimens such as caloric restriction [130] and individual dietary components including probiotic interventions, resveratrol, and black tea may modulate kynurenine metabolism [90, 131, 132]. For example, in a recent trial of 60 participants with depression, a probiotic intervention significantly decreased kynurenine levels and increased 3-hydroxykynurenine levels compared to placebo [90].

Mitochondrial dysfunction

Depression, like other primary psychiatric disorders including bipolar disorder and schizophrenia, is associated with mitochondrial dysfunction [133]. Indeed, many core symptoms of depression such as fatigue and cognitive complaints are concordant with both central and peripheral mitochondrial dysfunction and decreased biogenesis [134]. Disrupted oxidative phosphorylation and impaired mitochondrial ATP production may lead to dysfunctional neuronal plasticity and reduced neurogenesis, both of which are core elements of the neurobiology of depression [133]. A novel piece of evidence supporting a mitochondrial element in the pathophysiology of depression comes from a recent study showing that mitochondrial transplantation in mice restored ATP production in the hippocampus and reversed a lipopolysaccharide-induced model of depression [135].

Considerable preclinical evidence suggests that poor diet may contribute to mitochondrial dysfunction [136]. A high-fat diet is associated with abnormal mitochondrial biogenesis, which is also associated with increased free radical production, inflammation and insulin resistance [137–139]. A hypercaloric high-carbohydrate diet drives similar pathways [140], as well as a high salt diet [141]; these are core constituents of a poor quality Western-style diet. It is also possible that there is trans-generational inheritance of mitochondrial dysfunction induced by poor diet [142]. In humans, there are discrepant data on the potential beneficial impact of caloric restriction on mitochondrial function. Some human studies have shown increased markers of mitochondrial biogenesis with caloric restriction [136]. Another study showed increased levels of citrate synthase, a marker of mitochondrial content, [143] and other animal research suggests enhanced mitochondrial uncoupling protein activity [144]. To date, there are no studies of caloric restriction in depression that have measured mitochondrial dysfunction. One dietary model that has been proposed to reverse mitochondrial dysfunction, especially the shift from aerobic to glycolytic energy generation in depression, is the ketogenic diet, although clinical trials assessing this hypothesis in humans are still awaited [145]. A ketogenic diet increases both the activity and levels of mitochondrial uncoupling proteins [146]. The extent to which alteration in

mitochondrial biogenesis mediates the beneficial effects of a healthy Mediterranean type diet in depression is yet to be determined. Some food derivatives also have a putative role in increasing mitochondrial biogenesis, with quercetin, N-acetylcysteine and resveratrol each having some supportive evidence [147, 148].

Epigenetics, early life and maternal/paternal diet exposure

Epigenetics describes the molecular mechanisms that control gene activity and enable development to occur, in the absence of changes to the underlying DNA sequence [149]. For example, epigenetic processes can influence DNA methylation age, which has been associated with depression in adults [150] as well as a number of other neurodevelopmental outcomes and comorbidities including cognitive function [151], alcohol dependence [152], bipolar disorder [153], and reduced hippocampal volume [154], but not schizophrenia [155]. Very few studies have evaluated the effect of nutritional interventions on methylation age, but those that have, found evidence for its deceleration [156–158]. Epigenetic state is influenced by genetic sequence, internal and external environments, and stochastic processes that occur during development. Environmental influence during the sensitive periods of prenatal development, gamete formation, and adolescence has been linked with risk for chronic diseases that share common pathways with depression, including cardiometabolic and neurodevelopmental disorders [159]. This phenomenon is referred to as the 'developmental origins of health and disease' (DOHaD) [160, 161].

Nutrition has been the most studied environmental influence on epigenetics in the DOHaD context [162, 163]. Studies examining the effects of the Dutch famine demonstrated the involvement of epigenetic dysregulation in adult disease risk owing to nutritional adversity during early development [164]. Few observational human studies have assessed the role of epigenetic change in mediating the effect of early life nutrition on neurodevelopmental outcomes, and most are cross-sectional in nature. A recent review concluded that some evidence exists that certain early life nutritional exposures such as breastfeeding and maternal obesity can influence epigenetic state, which in turn may mediate child and adolescent psychopathology such as internalising and externalising behaviours [165]. One example is the Barbados Nutrition Study, which found adults hospitalised in infancy due to protein and energy undernutrition exhibited DNA methylation changes in neuropsychiatric risk genes [166]. In vitro cell culture experiments and rodent studies have shown that restriction or surfeit of macronutrients have reproducible effects on multiple epigenetic mechanisms on many different genes including those involved in metabolism and behaviour [167, 168]. Metabolic perturbations are becoming known as a driving force for genomic and epigenomic alterations by which the effects of diet are saved in the genes [169]. Components of nutrient-rich dietary patterns including vitamins such as folate, biotin, B6 and B12; polyphenols such as curcumin, resveratrol and genistein [170]; and omega-3 fatty acids [171] have all been shown to influence epigenetic state through multiple mechanisms. In addition, butyrate, typically considered a beneficial microbial metabolite that is produced during fermentation of dietary fibre, can also influence epigenetic state of host cells [172].

Obesity as cause and consequence of mood disorders

The multifactorial relationship between diet, mood disorders and obesity is bi-directional and complex [173]. Meta-analytic data show that both men and women with obesity have a 55% increased risk of developing depression, while individuals with depression have a 58% increased risk of developing obesity [174]. A recent review reported several interconnected pathways that may be involved in the relationship between diet, mood disorders, and obesity [175]. One such pathway includes the HPA axis, with its dysregulation, hyperactivation, and excessive synthesis and secretion of glucocorticoids being implicated in both mood disorders and obesity. [175] In addition, reduced levels of various neurotransmitters involved in regulating neurological reward circuitry, mood, and dietary intake are reported following exposure to a high-fat diet, including serotonin and dopamine [175]. In an attempt to mitigate stress-related anxiety—and due to phenomena known as emotional eating and comfort food—chronic stress and HPA-axis hyperactivation may lead to the overconsumption of Western-style food and subsequent obesity [176].

Higher levels of inflammation and related cytokines have been reported in both mood disorders and obesity, suggesting another common link between their underlying aetiology [177, 178]. A mediating role of obesity in the association between depression and inflammatory markers (i.e. interleukin-6 and C-reactive protein) was reported in a cross-sectional study, with the inferred causal nature of relations leading from depression to increased adiposity to elevated inflammatory markers [179]. This inflammatory effect of obesity may, in turn, drive the observed relationships between weight gain and higher rates of relapse [180] and impeded recovery [181] in individuals treated for a mental illness. Promisingly, caloric restriction and weight loss diets may be a reliable method for reducing inflammatory status [182, 183] and depressive symptoms in overweight individuals [184]. At the same time, findings from the SMILES clinical trial showed that a 12-week Mediterranean dietary intervention was efficacious for

lowering symptoms of clinical depression in the absence of weight change [2]. Similarly, prospective observational studies have repeatedly reported evidence of associations between diet quality and common mental disorders that are independent of measures of body weight (e.g. [185]).

Conclusion

Growing evidence supports the potential use of dietary interventions as an adjunctive treatment for mental disorders. This review has identified numerous pathways through which diet could plausibly affect mental health. These include modulation of pathways involved in inflammation, oxidative stress, mitochondrial dysfunction, the gut microbiota, tryptophan–kynurenine metabolism, the HPA axis, neurogenesis and BDNF, epigenetics, and obesity (Fig. 2). We do, however, acknowledge that there are numerous other potential mechanisms implicated in depression pathophysiology that were not captured in this paper but that may be modulated by dietary intervention (e.g. effect of diet on leptin, adiponectin, mitochondrial biogenesis and insulin/blood sugar balance) [18]. Furthermore, while the interplay between diet, obesity, and depression was discussed, diet may also affect depression via other chronic diseases not included in this review that are commonly comorbid with depression including diabetes, metabolic syndrome, and cardiovascular disease [186, 187].

Mechanisms of action associating diet with health outcomes are complex, multifaceted, interacting, and not restricted to any one biological pathway. Dietary interventions can include nutrient interventions (e.g. zinc, omega-3 fatty acids), food interventions (e.g. green tea, olive oil), and whole diet interventions (e.g. Mediterranean diet). The wide range and diversity of bioactive compounds found within various dietary interventions, as well as the pleiotropic properties of these compounds, makes their effects and the study of these effects inherently complex. Further complicating this is the lack of research that has investigated the comparative efficacy of the wide array of potentially therapeutic dietary interventions (e.g. Mediterranean diet vs. ketogenic diet vs. caloric restriction), which greatly differ in macro- and micro-nutrient composition.

The nascent nature of the Nutritional Psychiatry field to date means that the existing literature identified in this review is largely comprised of preclinical animal studies. To fully identify and elucidate complex mechanisms of action, intervention studies that assess markers related to these pathways within clinically diagnosed human populations are needed. Further research is also needed to identify individual demographic (e.g. age, BMI, comorbid medical conditions), behavioural (e.g. motivation to change), and biological (e.g. oxidative stress, inflammation) factors that might influence the appropriateness of dietary interventions as well as dietary treatment response. In particular, due to the disparity in the prevalence of depression between men and women, there is a need to explore sex differences in treatment response. While animal models exploring sex differences are lacking, a recent meta-analysis suggests that dietary interventions may benefit women more than men [4]. A further meta-analysis reported that obesity decreased the risk of depression in men while the risk was increased in women [188]. There are likely a number of bio-behavioural mechanisms responsible for this potential gender-specific effect that require further investigation. First, women may have a greater ability to alter their fat or glucose metabolism in response to a dietary intervention [189]. Second, men have been shown to be more pleasure oriented in their food choices—potentially owing to differences in dopamine receptors—making adherence to healthier diets more difficult [190]. Third, men are more likely to prefer foods associated with masculinity (e.g. red meat) above fruits and vegetables that are considered more ‘feminine’ [191, 192]. Further investigation of factors that may influence treatment response is also required in order to guide novel interventions and clinical guidelines for mental health patients. The expansion of the field of Nutritional Psychiatry research, affording an understanding of what works for whom under which circumstances, has the potential to result in new and targeted strategies for those affected by mental illness.

Compliance with ethical standards

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