

UCLA

UCLA Previously Published Works

Title

Diet and depression: exploring the biological mechanisms of action

Permalink

<https://escholarship.org/uc/item/2bd8s6q3>

Journal

Molecular Psychiatry, 26(1)

ISSN

1359-4184

Authors

Marx, Wolfgang
Lane, Melissa
Hockey, Meghan
et al.

Publication Date

2021

DOI

10.1038/s41380-020-00925-x

Peer reviewed



Diet and depression: exploring the biological mechanisms of action

Wolfgang Marx¹ · Melissa Lane¹ · Meghan Hockey¹ · Hajara Aslam¹ · Michael Berk^{1,2,3} · Ken Walder⁴ ·
Alessandra Borsini⁵ · Joseph Firth^{6,7} · Carmine M. Pariante⁵ · Kirsten Berding⁸ · John F. Cryan^{8,9} ·
Gerard Clarke^{8,10,11} · Jeffrey M. Craig¹² · Kuan-Pin Su^{13,14,15} · David Mischoulon^{16,17} · Fernando Gomez-Pinilla¹⁸ ·
Jane A. Foster¹⁹ · Patrice D. Cani²⁰ · Sandrine Thuret²¹ · Heidi M. Staudacher¹ · Almudena Sánchez-Villegas^{22,23} ·
Husnain Arshad²⁴ · Tasnime Akbaraly^{24,25} · Adrienne O'Neil¹ · Toby Segasby²¹ · Felice N. Jacka^{1,26,27,28}

Received: 1 June 2020 / Revised: 1 October 2020 / Accepted: 9 October 2020
© Springer Nature Limited 2020

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 inter-generational 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

✉ Wolfgang Marx
wolf.marx@deakin.edu.au

Extended author information available on the last page of the article

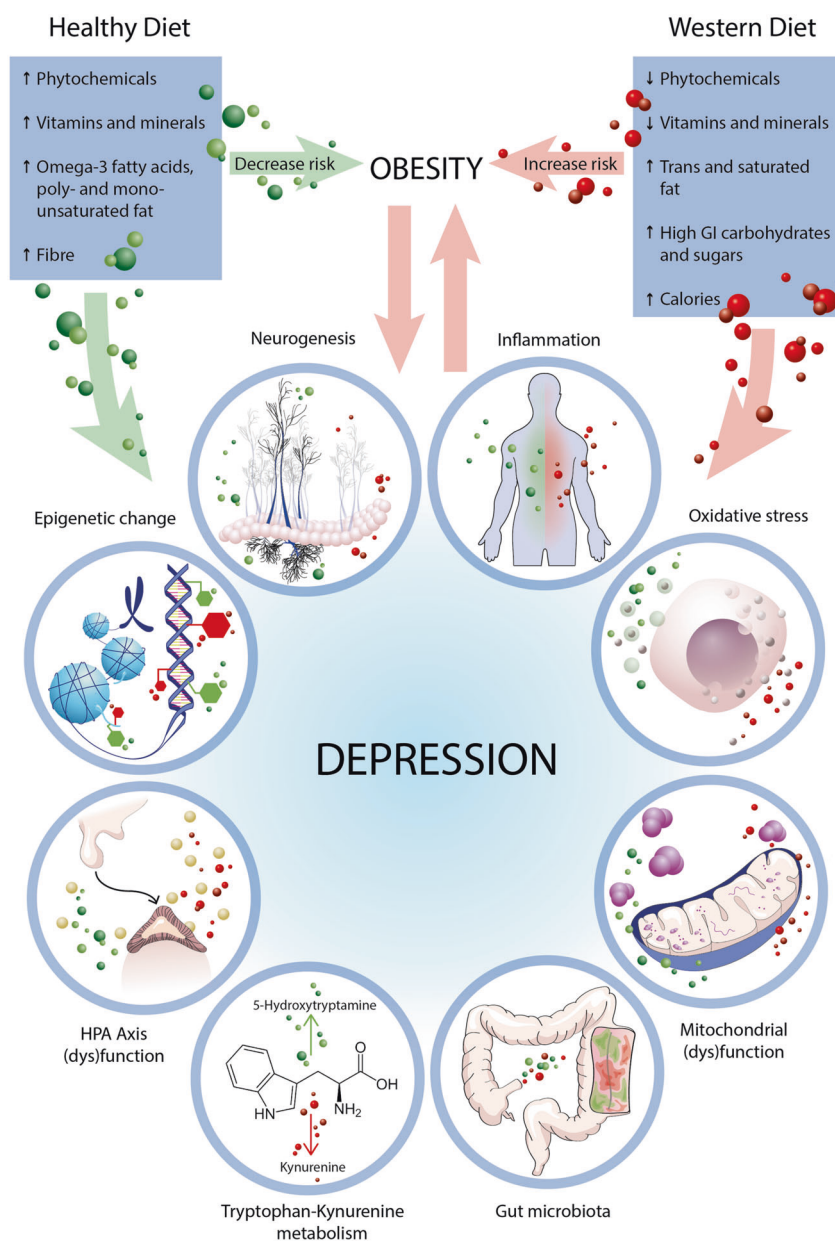
Mediterranean diet supplemented with tree nuts may prevent incident depression in patients with type 2 diabetes, the recent MoodFood trial observed no preventive benefit of a behavioural activation intervention focused on dietary improvement [12, 13]. However, the minimal dietary change in the intervention 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-F₂-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

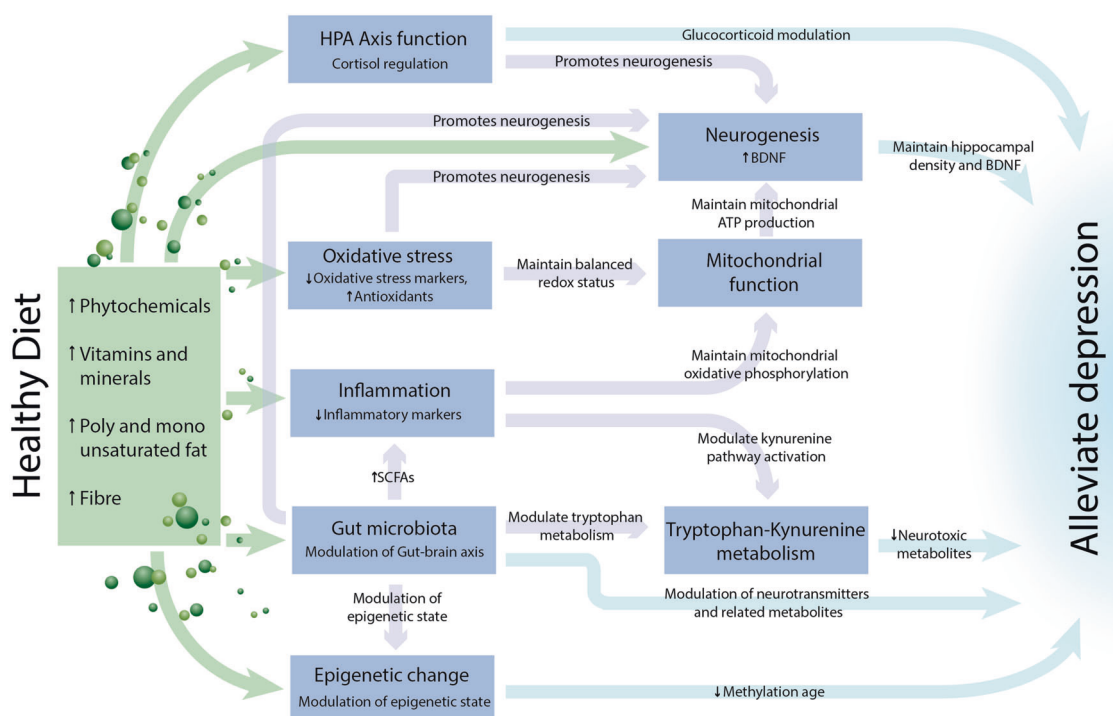


Fig. 2 Proposed interplay between dietary quality and implicated mechanisms in alleviating depression. This figure represents the likely interconnected and overlapping nature of the implicated

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 bidirectional, 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 ($n = 4\text{--}5$ 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

Conflict of interest WM is currently funded by an Alfred Deakin Postdoctoral Research Fellowship and a Multiple Sclerosis Research Australia early-career fellowship. WM has previously received funding from the Cancer Council Queensland and university grants/fellowships from La Trobe University, Deakin University, University of Queensland, and Bond University. WM has received industry funding and has attended events funded by Cobram Estate Pty Ltd. WM has received travel funding from Nutrition Society of Australia. WM has received consultancy funding from Nutrition Research Australia. WM has received speakers honoraria from The Cancer Council Queensland and the Princess Alexandra Research Foundation. ML is funded by a Deakin University Ph.D. Scholarship and has received research support from Be Fit Foods. MH is supported by an Australian Rotary Health Ph.D. Scholarship and has received research support from The A2 Milk Company. HA is supported by a Deakin University Postgraduate Industry Research Scholarship. MB is supported by a NHMRC Senior Principal Research Fellowship (1059660 and 1156072) and has received Grant/Research Support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, Medical Benefits Fund, National Health and Medical Research Council, Medical Research Futures Fund, Beyond Blue, Rotary Health, A2 milk company, Meat and Livestock Board, Woolworths, Avant and the Harry Windsor Foundation, has been a speaker for Astra Zeneca, Lundbeck, Merck, Pfizer, and served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Lundbeck Merck, Pfizer and Servier. KW has previously received funding from Australian Research Council, National Health and Medical Research Council, and ChemGenex Pharmaceuticals. AB and CMP have received research funding from Johnson & Johnson for research on depression and inflammation which included

cellular work (2012–2018); moreover, CMP is funded by a Wellcome Trust strategy award to the Neuroimmunology of Mood Disorders and Alzheimer's Disease (NIMA) Consortium (104025), which is also funded by Janssen, GlaxoSmithKline, Lundbeck and Pfizer. The work presented in this paper is unrelated to this funding. AB and CMP are funded by the UK Medical Research Council (grants MR/L014815/1, MR/J002739/1 and MR/N029488/1), the European Commission Horizon 2020 (grant SC1-BHC-01-2019) and the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. CMP is a NIHR Senior Investigator (2017–2025). KB is funded by an Irish Research Council postdoctoral fellowship. JFC is supported by Science Foundation Ireland in the form of a Research Centre grant (SFI/12/RC/2273-P2), Joint Programming Initiative JPI-HDHL-NutriCog project 'AMBROSIAC' (15/JPHDHL/3270); Joint Programming Initiative HEALTHMARK: Metabolic HEALTH through nutrition, microbiota and tryptophan bioMARKers, 16/ERAHDHL/3362. (EU Horizon 2020 funding—DISCOVERIE (Development, diagnosis and prevention of gender-related Somatic and mental COMorbiditiEs in iRrtable bowel syndrome in Europe), Swiss National Foundation Sinergia grant GUT-BRAIN; Irish Research Council; European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 797592 and 754535.; Irish Research Council Postgraduate Scholarship GOIPG/2019/3198; GOIPG/2018/2560. Health Research Board (HRB) Grant number ILP-POR-2017-013; Institute for Scientific Information on Coffee, and the Saks Kavanaugh Foundation. JFC received research support from Mead Johnson, Cremo, 4D Pharma, Pharmavite, and Nutricia. He has been a consultant for Alkermes and Nestle and has spoken at meetings sponsored by Mead Johnson, Abbott Nutrition, Roche, Ordesa and Neuraxpharm. GC is a principal investigator in APC Microbiome Ireland, a research centre funded by Science Foundation Ireland (SFI) (grant no. 12/RC/2273-P2). His research is currently supported by the Irish Health Research Board (HRB) (Grant number ILP-POR-2017-013). He has spoken at meetings sponsored by food (Probi) and pharmaceutical companies (Janssen) and is also in receipt of research funding from Pharmavite. JF is supported by a University of Manchester Presidential Fellowship (P123958) and a UK Research and Innovation Future Leaders Fellowship (MR/T021780/1) and has received support from a NICM-Blackmores Institute Fellowship. JMC is currently funded by the Australian Research Council (DP190103081); the National Health and Medical Research Council (APP114333; APP1079102); the Waterloo Foundation; DNA Genotek; and Trajan Scientific and Medical. KPS has received the following research grants related to this work: MOST 106-2314-B-039-027-MY3, 108-2320-B-039-048, 108-2813-C-039-133-B and 108-2314-B-039-016 from the Ministry of Science and Technology, Taiwan; NHRI-EX108-10528NI from the National Health Research Institutes, Taiwan; MYRG2018-00242-ICMS from University of Macau, China; CMRC-CMA-3 from Higher Education Sprout Project by the Ministry of Education (MOE), Taiwan; CMU108-SR-106 from the China Medical University, Taichung, Taiwan; and CRS-108-048, DMR-108-216 and DMR-109-102 from the China Medical University Hospital, Taichung, Taiwan. KPS has been a speaker and/or consultant for Johnson & Johnson, Astra Zeneca, Lundbeck, Eli Lilly, Merck, Pfizer, Servier, Otsuka, Excelsior Biopharma, Chen Hua Biotech, Nutrarex Biotech, and Hoan Pharmaceuticals—all unrelated to this work. DM has received research support from Nordic Naturals and heckel medizintechnik GmbH. He has provided unpaid consulting for Pharmavite LLC and Gnosis USA, Inc. He has received honoraria for speaking from the Massachusetts General Hospital Psychiatry Academy, Blackmores, Harvard Blog, and PeerPoint Medical Education Institute, LLC. He has received royalties from Lippincott Williams and Wilkins for published book "Natural medications for Psychiatric Disorders: considering the Alternatives. He also works with the MGH Clinical Trials Network and Institute (CTNI), which has received research funding from multiple pharmaceutical companies and NIMH. FGP is currently funded by

research awards from the NINDS of National Institute of Health. He serves as a consultant and member of the Scientific Advisory Board of Nutrient Foods, LLC. JF received research funding from the National Sciences and Engineering Research Council of Canada (NSERC) and the Ontario Brain Institute, which is an independent non-profit corporation, funded partially by the Ontario Government. Jane Foster has received consultancy fees from Novozymes A/S and Rothmans, Benson & Hedges Inc. PDC is a senior research associate at FRS-FNRS (Fonds de la Recherche Scientifique), Belgium. He is supported by the Fonds Baillet Latour (Grant for Medical Research 2015), the Fonds de la Recherche Scientifique (FNRS, FRFS-WELBIO: WELBIO-CR-2019C-02R) and ERC Starting Grant 2013 (336452-ENIGMO). PDC is co-founder of A-Mansia biotech SA and inventors on patent applications about the therapeutic use of Akkermansia muciniphila and its components. ST: Diet and mental health research in the Thuret lab is funded by grants awarded by the Medical Research Council UK (MR/N030087/1 and MR/S00484X/1, the European Union's H2020 Joint Programming Initiative 'A Healthy Diet for a Healthy Life' and the Network of Centres of Excellence in Neurodegeneration (COEN). HS has previously received non-financial and financial support from CD investments VSL pharmaceuticals and is currently funded by an Alfred Deakin Postdoctoral Research Fellowship. HA declares no funding declarations. TA is supported by the Centre of Excellence for Neurodegenerative disorders (COEN—Hospital Centre of Montpellier). AON is supported by a Future Leader Fellowship (#101160) from the Heart Foundation Australia and Wilson Foundation. She has received research funding from the National Health & Medical Research Council, Australian Research Council, University of Melbourne, Deakin University, Sanofi, Meat and Livestock Australia and Woolworths Limited and Honoraria from Novartis. The Food & Mood Centre has received funding from the Fernwood Foundation, the A2 Milk Company and Be Fit Foods. HS has previously received non-financial and financial support from CD investments VSL pharmaceuticals and is currently funded by an Alfred Deakin Postdoctoral Research Fellowship. TS has no funding declarations. FNJ has received Grant/Research support from the Brain and Behaviour Research Institute, the National Health and Medical Research Council (NHMRC), Australian Rotary Health, the Geelong Medical Research Foundation, the Ian Potter Foundation, Eli Lilly, Meat and Livestock Australia, Woolworths Limited, Fernwood Foundation, Wilson Foundation, The A2 Milk Company, Be Fit Foods, and The University of Melbourne and has received speakers honoraria from Sanofi-Synthelabo, Janssen Cilag, Servier, Pfizer, Health Ed, Network Nutrition, Angelini Farmaceutica, Eli Lilly and Metagenics. Felice Jacka has written two books for commercial publication and has a personal belief that good diet quality is important for mental and brain health.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Marx W, Moseley G, Berk M, Jacka F. Nutritional psychiatry: the present state of the evidence. *Proc Nutr Soc.* 2017;76:427–36.
2. Jacka FN, O'Neil A, Opie R, Itsiopoulos C, Cotton S, Mohebbi M, et al. A randomised controlled trial of dietary improvement for adults with major depression (the 'SMILES' trial). *BMC Med.* 2017;15:23.
3. Lassale C, Batty GD, Baghdadli A, Jacka F, Sanchez-Villegas A, Kivimaki M, et al. Healthy dietary indices and risk of depressive outcomes: a systematic review and meta-analysis of observational studies. *Mol Psychiatry.* 2019;24:965–86.
4. Firth J, Marx W, Dash S, Carney R, Teasdale SB, Solmi M, Stubbs B, Schuch FB, Carvalho AF, Jacka F, Sarris J. The effects

- of dietary improvement on symptoms of depression and anxiety: a meta-analysis of randomized controlled trials. *Psychosomatic medicine*. 2019;81:265.
5. Jacka FN, Pasco JA, Mykletun A, Williams LJ, Hodge AM, O'Reilly SL, et al. Association of western and traditional diets with depression and anxiety in women. *Am J Psychiatry*. 2010;167:305–11.
 6. Jacka FN, Pasco JA, Mykletun A, Williams LJ, Nicholson GC, Kotowicz MA, et al. Diet quality in bipolar disorder in a population-based sample of women. *J Affect Disord*. 2011;129:332–7.
 7. Khalid S, Williams CM, Reynolds SA. Is there an association between diet and depression in children and adolescents? A systematic review. *Br J Nutr*. 2016;116:2097–108.
 8. Borge TC, Aase H, Brantsæter AL, Biele G. The importance of maternal diet quality during pregnancy on cognitive and behavioural outcomes in children: a systematic review and meta-analysis. *BMJ Open*. 2017;7:e016777.
 9. Parletta N, Zarnowiecki D, Cho J, Wilson A, Bogomolova S, Villani A, Itsiopoulos C, Niyonsenga T, Blunden S, Meyer B, Segal L. A Mediterranean-style dietary intervention supplemented with fish oil improves diet quality and mental health in people with depression: A randomized controlled trial (HEL-FIMED). *Nutritional neuroscience*. 2019;22:474–87.
 10. Francis HM, Stevenson RJ, Chambers JR, Gupta D, Newey B, Lim CK. A brief diet intervention can reduce symptoms of depression in young adults—A randomised controlled trial. *PLoS one*. 2019;14:e0222768.
 11. Ma J, Rosas LG, Lv N, Xiao L, Snowden MB, Venditti EM, et al. Effect of integrated behavioral weight loss treatment and problem-solving therapy on body mass index and depressive symptoms among patients with obesity and depression: the RAINBOW randomized clinical trial. *Jama*. 2019;321:869–79.
 12. Bot M, Brouwer IA, Roca M, Kohls E, Penninx B, Watkins E, et al. Effect of multinutrient supplementation and food-related behavioral activation therapy on prevention of major depressive disorder among overweight or obese adults with subsyndromal depressive symptoms: the MoodFOOD randomized clinical trial. *Jama*. 2019;321:858–68.
 13. Sanchez-Villegas A, Martinez-Gonzalez M, Estruch R, Salas-Salvado J, Corella D, Covas M, et al. Mediterranean dietary pattern and depression: the PREDIMED randomized trial. *BMC Med*. 2013;11:208.
 14. Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, et al. So depression is an inflammatory disease, but where does the inflammation come from? *BMC Med*. 2013;11:200.
 15. Cryan JF, O'Riordan KJ, Cowan CS, Sandhu KV, Bastiaansen TF, Boehme M, et al. The microbiota-gut-brain axis. *Physiol Rev*. 2019;99:1877–2013.
 16. Maes M, Galecki P, Chang YS, Berk M. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro) degenerative processes in that illness. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35:676–92.
 17. Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. *Trends Neurosci*. 2008;31:464–8.
 18. Carvalho AF, Solmi M, Sanches M, Machado MO, Stubbs B, Ajnakina O, et al. Evidence-based umbrella review of 162 peripheral biomarkers for major mental disorders. *Transl Psychiatry*. 2020;10:1–13.
 19. Bauer ME, Teixeira AL. Inflammation in psychiatric disorders: what comes first? *Ann N Y Acad Sci*. 2019;1437:57–67.
 20. Osimo EF, Cardinal RN, Jones PB, Khandaker GM. Prevalence and correlates of low-grade systemic inflammation in adult psychiatric inpatients: An electronic health record-based study. *Psychoneuroendocrinology*. 2018;91:226–34.
 21. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol*. 2016;16:22–34.
 22. Capuron L, Miller AH. Cytokines and psychopathology: lessons from interferon-alpha. *Biol Psychiatry*. 2004;56:819–24.
 23. Pollak Y, Yirmiya R. Cytokine-induced changes in mood and behaviour: implications for 'depression due to a general medical condition', immunotherapy and antidepressive treatment. *Int J Neuropsychopharmacol*. 2002;5:389–99.
 24. Heggul N, Pariante CM, Baraldi S, Borsini A, Bufalino C, Russell A, et al. Depression and anxiety in patients receiving interferon-alpha: the role of illness perceptions. *J Health Psychol*. 2018;23:1405–14.
 25. Köhler-Forsberg O, Lydholm CN, Hjorthøj C, Nordentoft M, Mors O, Benros ME. Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: meta-analysis of clinical trials. *Acta Psychiatr Scand*. 2019;139:404–19.
 26. Kastorini C-M, Milionis HJ, Esposito K, Giugliano D, Goudevenos JA, Panagiotakos DB. The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. *J Am Coll Cardiol*. 2011;57:1299–313.
 27. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, et al. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *Jama*. 2004;292:1440–6.
 28. Giugliano D, Ceriello A, Esposito K. The effects of diet on inflammation: emphasis on the metabolic syndrome. *J Am Coll Cardiol*. 2006;48:677–85.
 29. Firth J, Stubbs B, Teasdale SB, Ward PB, Veronese N, Shivappa N, et al. Diet as a hot topic in psychiatry: a population-scale study of nutritional intake and inflammatory potential in severe mental illness. *World Psychiatry*. 2018;17:365–7.
 30. Yahfoufi N, Alsadi N, Jambi M, Matar C. The immunomodulatory and anti-inflammatory role of polyphenols. *Nutrients*. 2018;10:11.
 31. Liao Y, Xie B, Zhang H, He Q, Guo L, Subramaniapillai M, et al. Efficacy of omega-3 PUFAs in depression: a meta-analysis. *Transl Psychiatry*. 2019;9:190.
 32. Su KP, Lai HC, Yang HT, Su WP, Peng CY, Chang JP, et al. Omega-3 fatty acids in the prevention of interferon-alpha-induced depression: results from a randomized, controlled trial. *Biol Psychiatry*. 2014;76:559–66.
 33. Rapaport MH, Nierenberg AA, Schettler PJ, Kinkead B, Cardoso A, Walker R, et al. Inflammation as a predictive biomarker for response to omega-3 fatty acids in major depressive disorder: a proof of concept study. *Mol Psychiatry*. 2016;21:71–9.
 34. Borsini A, Alboni S, Horowitz MA, Tojo LM, Cannazza G, Su KP, et al. Rescue of IL-1beta-induced reduction of human neurogenesis by omega-3 fatty acids and antidepressants. *Brain Behav Immun*. 2017;65:230–8.
 35. Moylan S, Berk M, Dean OM, Samuni Y, Williams LJ, O'Neil A, et al. Oxidative & nitrosative stress in depression: why so much stress? *Neurosci Biobehav Rev*. 2014;45:46–62.
 36. Liu T, Zhong S, Liao X, Chen J, He T, Lai S, et al. A meta-analysis of oxidative stress markers in depression. *PLOS ONE*. 2015;10:e0138904.
 37. Che Y, Wang J-F, Shao L, Young LT. Oxidative damage to RNA but not DNA in the hippocampus of patients with major mental illness. *J Psychiatry Neurosci*. 2010;35:296.
 38. Gao S-F, Qi X-R, Zhao J, Balesar R, Bao A-M, Swaab DF. Decreased NOS1 expression in the anterior cingulate cortex in depression. *Cereb Cortex*. 2013;23:2956–64.

39. Morrison CD, Pistell PJ, Ingram DK, Johnson WD, Liu Y, Fernandez-Kim SO, et al. High fat diet increases hippocampal oxidative stress and cognitive impairment in aged mice: implications for decreased Nrf2 signaling. *J Neurochem*. 2010;114:1581–9.
40. Studzinski CM, Li F, Bruce-Keller AJ, Fernandez-Kim SO, Zhang L, Weidner AM, et al. Effects of short-term Western diet on cerebral oxidative stress and diabetes related factors in APP \times PS1 knock-in mice. *J Neurochem*. 2009;108:860–6.
41. Cocate PG, Natali AJ, de Oliveira A, Longo GZ, Rita de Cássia GA, Maria, et al. Fruit and vegetable intake and related nutrients are associated with oxidative stress markers in middle-aged men. *Nutrition*. 2014;30:660–5.
42. Dai J, Jones DP, Goldberg J, Ziegler TR, Bostick RM, Wilson PW, et al. Association between adherence to the Mediterranean diet and oxidative stress. *Am J Clin Nutr*. 2008;88:1364–70.
43. Meyer KA, Sijtsma FP, Nettleton JA, Steffen LM, Van Horn L, Shikany JM, et al. Dietary patterns are associated with plasma F2-isoprostanes in an observational cohort study of adults. *Free Radic Biol Med*. 2013;57:201–9.
44. Traber MG, Stevens JF. Vitamins C and E: beneficial effects from a mechanistic perspective. *Free Radic Biol Med*. 2011;51:1000–13.
45. Fernandes BS, Dean OM, Dodd S, Malhi GS, Berk M. N-acetylcysteine in depressive symptoms and functionality: a systematic review and meta-analysis. *The Journal of clinical psychiatry*. 2016;77:457–66.
46. Zhang H, Tsao R. Dietary polyphenols, oxidative stress and antioxidant and anti-inflammatory effects. *Curr Opin Food Sci*. 2016;8:33–42.
47. Cryan JF, O’Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, et al. The microbiota-gut-brain axis. *Physiol Rev*. 2019;99:1877–2013.
48. Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. *Science*. 2012;336:1268–73.
49. Ogbonnaya ES, Clarke G, Shanahan F, Dinan TG, Cryan JF, O’Leary OF. Adult hippocampal neurogenesis is regulated by the microbiome. *Biol Psychiatry*. 2015;78:e7–9.
50. Gheorghe CE, Martin JA, Manriquez FV, Dinan TG, Cryan JF, Clarke G. Focus on the essentials: tryptophan metabolism and the microbiome-gut-brain axis. *Curr Opin Pharmacol*. 2019;48:137–45.
51. van de Wouw M, Walsh AM, Crispie F, van Leuven L, Lyte JM, Boehme M, et al. Distinct actions of the fermented beverage kefir on host behaviour, immunity and microbiome gut-brain modules in the mouse. *Microbiome*. 2020;8:1–20.
52. Shi H, Wang Q, Zheng M, Hao S, Lum JS, Chen X, et al. Supplement of microbiota-accessible carbohydrates prevents neuroinflammation and cognitive decline by improving the gut microbiota-brain axis in diet-induced obese mice. *J Neuroinflammation*. 2020;17:1–21.
53. Dinan TG, Stanton C, Long-Smith C, Kennedy P, Cryan JF, Cowan CSM, et al. Feeding melancholic microbes: MyNewGut recommendations on diet and mood. *Clin Nutr*. 2019;38:1995–2001.
54. Ohland CL, Kish L, Bell H, Thiesen A, Hotte N, Pankiv E, et al. Effects of *Lactobacillus helveticus* on murine behavior are dependent on diet and genotype and correlate with alterations in the gut microbiome. *Psychoneuroendocrinology*. 2013;38:1738–47.
55. Pyndt Jorgensen B, Winther G, Kihl P, Nielsen DS, Wegener G, Hansen AK, et al. Dietary magnesium deficiency affects gut microbiota and anxiety-like behaviour in C57BL/6N mice. *Acta Neuropsychiatr*. 2015;27:307–11.
56. Magnusson KR, Hauck L, Jeffrey BM, Elias V, Humphrey A, Nath R, et al. Relationships between diet-related changes in the gut microbiome and cognitive flexibility. *Neuroscience*. 2015;300:128–40.
57. Reichelt AC, Loughman A, Bernard A, Raipuria M, Abbott KN, Dachtler J, Van TT, Moore RJ. An intermittent hypercaloric diet alters gut microbiota, prefrontal cortical gene expression and social behaviours in rats. *Nutritional neuroscience*. 2020;23:613–27.
58. Burokas A, Arboleya S, Moloney RD, Peterson VL, Murphy K, Clarke G, et al. Targeting the microbiota-gut-brain axis: prebiotics have anxiolytic and antidepressant-like effects and reverse the impact of chronic stress in mice. *Biol Psychiatry*. 2017;82:472–87.
59. Cryan JF, O’Riordan KJ, Sandhu K, Peterson V, Dinan TG. The gut microbiome in neurological disorders. *Lancet Neurol*. 2020;19:179–94.
60. Valles-Colomer M, Falony G, Darzi Y, Tigchelaar EF, Wang J, Tito RY, et al. The neuroactive potential of the human gut microbiota in quality of life and depression. *Nat Microbiol*. 2019;4:623–32.
61. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*. 2014;505:559–63.
62. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, et al. Linking long-term dietary patterns with gut microbial enterotypes. *Science*. 2011;334:105–8.
63. Bruce-Keller AJ, Salbaum JM, Luo M, Blanchard Et, Taylor CM, Welsh DA, et al. Obese-type gut microbiota induce neurobehavioral changes in the absence of obesity. *Biol Psychiatry*. 2015;77:607–15.
64. Hiel S, Bindels LB, Pachikian BD, Kalala G, Broers V, Zamariola G, et al. Effects of a diet based on inulin-rich vegetables on gut health and nutritional behavior in healthy humans. *Am J Clin Nutr*. 2019;109:1683–95.
65. Ghosh TS, Rampelli S, Jeffery IB, Santoro A, Neto M, Capri M, Giampieri E, Jennings A, Candela M, Turroni S, Zoetendal EG. Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: the NU-AGE 1-year dietary intervention across five European countries. *Gut*. 2020;69:1218–1228.
66. Robertson RC, Seira Oriach C, Murphy K, Moloney GM, Cryan JF, Dinan TG, et al. Omega-3 polyunsaturated fatty acids critically regulate behaviour and gut microbiota development in adolescence and adulthood. *Brain Behav Immun*. 2017;59:21–37.
67. Pasinetti GM, Singh R, Westfall S, Herman F, Faith J, Ho L. The role of the gut microbiota in the metabolism of polyphenols as characterized by gnotobiotic mice. *J Alzheimers Dis*. 2018;63:409–21.
68. Ozdal T, Sela DA, Xiao J, Boyacioglu D, Chen F, Capanoglu E. The reciprocal interactions between polyphenols and gut microbiota and effects on bioaccessibility. *Nutrients*. 2016;8:78.
69. Long-Smith C, O’Riordan KJ, Clarke G, Stanton C, Dinan TG, Cryan JF. Microbiota-gut-brain axis: new therapeutic opportunities. Annual review of pharmacology and toxicology. 2020;60 (Jan):477–502.
70. Liu RT, Walsh RF, Sheehan AE. Prebiotics and probiotics for depression and anxiety: a systematic review and meta-analysis of controlled clinical trials. *Neuroscience & Biobehavioral Reviews*. 2019;102(Jul):13–23.
71. Aslam H, Green J, Jacka FN, Collier F, Berk M, Pasco J, Dawson SL. Fermented foods, the gut and mental health: a mechanistic overview with implications for depression and anxiety. *Nutritional neuroscience*. 2020;23(Sep):659–71.

72. Bambury A, Sandhu K, Cryan JF, Dinan TG. Finding the needle in the haystack: systematic identification of psychobiotics. *Br J Pharmacol*. 2018;175:4430–8.
73. Suez J, Zmora N, Segal E, Elinav E. The pros, cons, and many unknowns of probiotics. *Nat Med*. 2019;25:716–29.
74. Hidese S, Nogawa S, Saito K, Kunugi H. Food allergy is associated with depression and psychological distress: a web-based study in 11,876 Japanese. *J Affect Disord*. 2019;245:213–8.
75. Portsmouth Uo. Literature searches and reviews related to the prevalence of food allergy in Europe. EFSA Support Publ. 2013;10:506E.
76. Jarvinen KM, Konstantinou GN, Pilapil M, Arrieta MC, Noone S, Sampson HA, et al. Intestinal permeability in children with food allergy on specific elimination diets. *Pediatr Allergy Immunol*. 2013;24:589–95.
77. Maes M, Kubera M, Leunis JC. The gut-brain barrier in major depression: intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. *Neuro Endocrinol Lett*. 2008;29:117–24.
78. Lerner BA, Green PH, Lebowitz B. Going against the grains: gluten-free diets in patients without celiac disease—worthwhile or not? *Dig Dis Sci*. 2019;64:1740–7.
79. Haq MRU, Kapila R, Sharma R, Saliganti V, Kapila S. Comparative evaluation of cow β -casein variants (A1/A2) consumption on Th 2-mediated inflammatory response in mouse gut. *Eur J Nutr*. 2014;53:1039–49.
80. Naughton M, Dinan TG, Scott LV. Corticotropin-releasing hormone and the hypothalamic–pituitary–adrenal axis in psychiatric disease. *Handb Clin Neurol*. 2014;124:69–91.
81. Brody S, Preut R, Schommer K, Schürmeyer TH. A randomized controlled trial of high dose ascorbic acid for reduction of blood pressure, cortisol, and subjective responses to psychological stress. *Psychopharmacology*. 2002;159:319–24.
82. Barbadoro P, Annino I, Ponzio E, Romanelli RM, D’Errico MM, Prospero E, et al. Fish oil supplementation reduces cortisol basal levels and perceived stress: a randomized, placebo-controlled trial in abstinent alcoholics. *Mol Nutr Food Res*. 2013;57:1110–4.
83. Delarue J, Matzinger O, Binnert C, Schreiner P, Chioloro R, Tappy L. Fish oil prevents the adrenal activation elicited by mental stress in healthy men. *Diabetes Metab*. 2003;29:289–95.
84. Tsang C, Hodgson L, Bussu A, Farhat G, Al-Dujaili E. Effect of polyphenol-rich dark chocolate on salivary cortisol and mood in adults. *Antioxidants*. 2019;8:149.
85. Tsang C, Smail NF, Almoosawi S, Davidson I, Al-Dujaili EA. Intake of polyphenol-rich pomegranate pure juice influences urinary glucocorticoids, blood pressure and homeostasis model assessment of insulin resistance in human volunteers. *J Nutr Sci*. 2012;1:e9.
86. Dhabhar FS. Stress-induced enhancement of cell-mediated immunity. *Ann N Y Acad Sci*. 1998;840:359–72.
87. Al-Dujaili EA, Ashmore S, Tsang C. A short study exploring the effect of the glycaemic index of the diet on energy intake and salivary steroid hormones. *Nutrients*. 2019;11:260.
88. Gareau MG, Jury J, MacQueen G, Sherman PM, Perdue MH. Probiotic treatment of rat pups normalises corticosterone release and ameliorates colonic dysfunction induced by maternal separation. *Gut*. 2007;56:1522–8.
89. Messaoudi M, Lalonde R, Violle N, Javelot H, Desor D, Nejdi A, et al. Assessment of psychotropic-like properties of a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) in rats and human subjects. *Br J Nutr*. 2011;105:755–64.
90. Rudzki L, Ostrowska L, Pawlak D, Malus A, Pawlak K, Waszkiewicz N, et al. Probiotic *Lactobacillus plantarum* 299v decreases kynurenine concentration and improves cognitive functions in patients with major depression: a double-blind, randomized, placebo controlled study. *Psychoneuroendocrinology*. 2019;100:213–22.
91. Fanselow MS, Dong HW. Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron*. 2010;65:7–19.
92. Anacker C, Hen R. Adult hippocampal neurogenesis and cognitive flexibility—linking memory and mood. *Nature Reviews Neuroscience*. 2017;18(Jun):335–46.
93. Toda T, Parylak SL, Linker SB, Gage FH. The role of adult hippocampal neurogenesis in brain health and disease. *Mol Psychiatry*. 2019;24:67–87.
94. Karege F, Perret G, Bondolfi G, Schwald M, Bertschy G, Aubry JM. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychiatry Res*. 2002;109:143–8.
95. Filus JF, Rybakowski J. [Neurotrophic factors and their role in the pathogenesis of affective disorders]. *Psychiatr Pol*. 2005;39:883–97.
96. Caviedes A, Lafourcade C, Soto C, Wyneken U. BDNF/NF-kappaB signaling in the neurobiology of depression. *Curr Pharm Des*. 2017;23:3154–63.
97. Zainuddin MS, Thuret S. Nutrition, adult hippocampal neurogenesis and mental health. *Br Med Bull*. 2012;103:89–114.
98. Kanoski SE, Davidson TL. Western diet consumption and cognitive impairment: links to hippocampal dysfunction and obesity. *Physiol Behav*. 2011;103:59–68.
99. Savignac HM, Corona G, Mills H, Chen L, Spencer JP, Tzortzis G, et al. Prebiotic feeding elevates central brain derived neurotrophic factor, N-methyl-D-aspartate receptor subunits and D-serine. *Neurochemistry Int*. 2013;63:756–64.
100. Balanza-Martinez V, Fries GR, Colpo GD, Silveira PP, Portella AK, Tabares-Seisdedos R, et al. Therapeutic use of omega-3 fatty acids in bipolar disorder. *Expert Rev Neurother*. 2011;11:1029–47.
101. Dias GP, Cavegn N, Nix A, do Nascimento Bevilacqua MC, Stangl D, Zainuddin MS, et al. The role of dietary polyphenols on adult hippocampal neurogenesis: molecular mechanisms and behavioural effects on depression and anxiety. *Oxid Med Cell Longev*. 2012;2012:541971.
102. Zainuddin MSA, Thuret S. Nutrition, adult hippocampal neurogenesis and mental health. *Br Med Bull*. 2012;103:89–114.
103. Jacka FN, Cherbuin N, Anstey KJ, Sachdev P, Butterworth P. Western diet is associated with a smaller hippocampus: a longitudinal investigation. *BMC medicine*. 2015;13:1–8.
104. Akbaraly T, Sexton C, Zsoldos E, Mahmood A, Filippini N, Kerleau C, et al. Association of long-term diet quality with hippocampal volume: longitudinal cohort study. *Am J Med*. 2018;131:1372–81.e4.
105. Croll PH, Voortman T, Ikram MA, Franco OH, Schoufour JD, Bos D, et al. Better diet quality relates to larger brain tissue volumes: the Rotterdam study. *Neurology*. 2018;90:e2166–73.
106. Sánchez-Villegas A, Galbete C, Martínez-González MÁ, Martínez JA, Razquin C, Salas-Salvadó J, et al. The effect of the Mediterranean diet on plasma brain-derived neurotrophic factor (BDNF) levels: the PREDIMED-NAVARRA randomized trial. *Nutr Neurosci*. 2011;14:195–201.
107. Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ. Transport of brain-derived neurotrophic factor across the blood–brain barrier. *Neuropharmacology*. 1998;37:1553–61.
108. Gejl AK, Enevold C, Bugge A, Andersen MS, Nielsen CH, Andersen LB. Associations between serum and plasma brain-derived neurotrophic factor and influence of storage time and centrifugation strategy. *Sci Rep*. 2019;9:1–9.
109. Mattson MP, Duan W, Guo Z. Meal size and frequency affect neuronal plasticity and vulnerability to disease: cellular and molecular mechanisms. *J Neurochem*. 2003;84:417–31.

110. Stevenson RJ, Francis HM, Attuquayefio T, Gupta D, Yeomans MR, Oaten MJ, et al. Hippocampal-dependent appetitive control is impaired by experimental exposure to a Western-style diet. *R Soc Open Sci.* 2020;7:191338.
111. Attuquayefio T, Stevenson RJ, Oaten MJ, Francis HM. A four-day Western-style dietary intervention causes reductions in hippocampal-dependent learning and memory and interoceptive sensitivity. *PLoS ONE.* 2017;12:e0172645.
112. Fernstrom JD. A perspective on the safety of supplemental tryptophan based on its metabolic fates. *J Nutr.* 2016;146:2601S–8S.
113. Russo S, Kema IP, Bosker F, Haavik J, Korf J. Tryptophan as an evolutionarily conserved signal to brain serotonin: molecular evidence and psychiatric implications. *World J Biol Psychiatry.* 2009;10:258–68.
114. Cervenka I, Agudelo LZ, Ruas JL. Kynurenines: tryptophan's metabolites in exercise, inflammation, and mental health. *Science.* 2017;357:6349.
115. Pu J, Liu Y, Zhang H, Tian L, Gui S, Yu Y, Chen X, Chen Y, Yang L, Ran Y, Zhong X. An integrated meta-analysis of peripheral blood metabolites and biological functions in major depressive disorder. *Molecular Psychiatry.* 2020:1–2.
116. Lovelace MD, Varney B, Sundaram G, Lennon MJ, Lim CK, Jacobs K, et al. Recent evidence for an expanded role of the kynurenine pathway of tryptophan metabolism in neurological diseases. *Neuropharmacology.* 2017;112:373–88.
117. O'Farrell K, Harkin A. Stress-related regulation of the kynurenine pathway: Relevance to neuropsychiatric and degenerative disorders. *Neuropharmacology.* 2017;112:307–23.
118. Strasser B, Becker K, Fuchs D, Gostner JM. Kynurenine pathway metabolism and immune activation: Peripheral measurements in psychiatric and co-morbid conditions. *Neuropharmacology.* 2017;112:286–96.
119. Agus A, Planchais J, Sokol H. Gut microbiota regulation of tryptophan metabolism in health and disease. *Cell Host Microbe.* 2018;23:716–24.
120. Roager HM, Licht TR. Microbial tryptophan catabolites in health and disease. *Nat Commun.* 2018;9:3294.
121. Lukic I, Getselter D, Koren O, Elliott E. Role of tryptophan in microbiota-induced depressive-like behavior: evidence from tryptophan depletion study. *Front Behav Neurosci.* 2019;13:123.
122. Badawy AA. Tryptophan availability for kynurenine pathway metabolism across the life span: Control mechanisms and focus on aging, exercise, diet and nutritional supplements. *Neuropharmacology.* 2017;112:248–63.
123. Fernstrom JD. Effects and side effects associated with the non-nutritional use of tryptophan by humans. *J Nutr.* 2012;142:2236S–44S.
124. Wirleitner B, Schroecksnadel K, Winkler C, Schennach H, Fuchs D. Resveratrol suppresses interferon- γ -induced biochemical pathways in human peripheral blood mononuclear cells in vitro. *Immunol Lett.* 2005;100:159–63.
125. Dolpady J, Sorini C, Di Pietro C, Cosorich I, Ferrarese R, Saita D, et al. Oral probiotic VSL# 3 prevents autoimmune diabetes by modulating microbiota and promoting indoleamine 2, 3-dioxygenase-enriched tolerogenic intestinal environment. *J Diabetes Res.* 2016;2016:7569431.
126. Jeong YI, Kim SW, Jung ID, Lee JS, Chang JH, Lee CM, et al. Curcumin suppresses the induction of indoleamine 2, 3-dioxygenase by blocking the Janus-activated kinase-protein kinase C δ -STAT1 signaling pathway in interferon- γ -stimulated murine dendritic cells. *J Biol Chem.* 2009;284:3700–8.
127. Min SY, Yan M, Kim SB, Ravikumar S, Kwon SR, Vanarsa K, et al. Green tea epigallocatechin-3-gallate suppresses autoimmune arthritis through indoleamine-2, 3-dioxygenase expressing dendritic cells and the nuclear factor, erythroid 2-like 2 antioxidant pathway. *J Inflamm.* 2015;12:1–15.
128. Heischmann S, Gano LB, Quinn K, Liang LP, Klepacki J, Christians U, et al. Regulation of kynurenine metabolism by a ketogenic diet. *J Lipid Res.* 2018;59:958–66.
129. Lemieux GA, Cunningham KA, Lin L, Mayer F, Werb Z, Ashrafi K. Kynurenic acid is a nutritional cue that enables behavioral plasticity. *Cell.* 2015;160:119–31.
130. Strasser B, Berger K, Fuchs D. Effects of a caloric restriction weight loss diet on tryptophan metabolism and inflammatory biomarkers in overweight adults. *Eur J Nutr.* 2015;54:101–7.
131. Gostner JM, Becker K, Croft KD, Woodman RJ, Puddey IB, Fuchs D, et al. Regular consumption of black tea increases circulating kynurenine concentrations: a randomized controlled trial. *BBA Clin.* 2015;3:31–5.
132. Gualdoni GA, Fuchs D, Zlabinger GJ, Gostner JM. Resveratrol intake enhances indoleamine-2, 3-dioxygenase activity in humans. *Pharmacol Rep.* 2016;68:1065–8.
133. Rezin GT, Amboni G, Zugno AI, Quevedo J, Streck EL. Mitochondrial dysfunction and psychiatric disorders. *Neurochem Res.* 2009;34:1021.
134. Filler K, Lyon D, Bennett J, McCain N, Elswick R, Lukkahatai N, et al. Association of mitochondrial dysfunction and fatigue: a review of the literature. *BBA Clin.* 2014;1:12–23.
135. Wang Y, Ni J, Gao C, Xie L, Zhai L, Cui G, et al. Mitochondrial transplantation attenuates lipopolysaccharide-induced depression-like behaviors. *Prog Neuro-Psychopharmacol Biol Psychiatry.* 2019;93:240–9.
136. Sergi D, Naumovski NN, Heilbronn LHK, Abeywardena M, O'Callaghan N, Lionetti L, et al. Mitochondrial (dys) function and insulin resistance: from pathophysiological molecular mechanisms to the impact of diet. *Front Physiol.* 2019;10:532.
137. Kuipers EN, Held NM, in het Panhuis W, Modder M, Ruppert PM, Kersten S, et al. A single day of high-fat diet feeding induces lipid accumulation and insulin resistance in brown adipose tissue in mice. *Am J Physiol Endocrinol Metab.* 2019;317:E820–30.
138. Marín-Royo G, Rodríguez C, Le Pape A, Jurado-López R, Luaces M, Antequera A, et al. The role of mitochondrial oxidative stress in the metabolic alterations in diet-induced obesity in rats. *FASEB J.* 2019;33:12060–72.
139. Yang X-X, Wang X, Shi T-T, Dong J-C, Li F-J, Zeng L-X, et al. Mitochondrial dysfunction in high-fat diet-induced nonalcoholic fatty liver disease: the alleviating effect and its mechanism of Polygonatum kingianum. *Biomed Pharmacother.* 2019;117:109083.
140. Sihali-Beloui O, Aroune D, Benazouz F, Hadji A, El-Aoufi S, Marco S. A hypercaloric diet induces hepatic oxidative stress, infiltration of lymphocytes, and mitochondrial reshuffle in Psammomys obesus, a murine model of insulin resistance. *C R Biol.* 2019;342:209–19.
141. Woodman AG, Mah R, Keddie DL, Noble RM, Holody CD, Panahi S, et al. Perinatal iron deficiency and a high salt diet cause long-term kidney mitochondrial dysfunction and oxidative stress. *Cardiovasc Res.* 2020;116:183–92.
142. Ferey JL, Boudoures AL, Reid M, Drury A, Scheaffer S, Modi Z, et al. A maternal high-fat, high-sucrose diet induces transgenerational cardiac mitochondrial dysfunction independently of maternal mitochondrial inheritance. *Am J Physiol Heart Circ Physiol.* 2019;316:H1202–10.
143. Menshikova EV, Ritov VB, Dube JJ, Amati F, Stefanovic-Racic M, Toledo FG, et al. Calorie restriction-induced weight loss and exercise have differential effects on skeletal muscle mitochondria despite similar effects on insulin sensitivity. *J Gerontol Ser A.* 2018;73:81–7.

144. Hancock CR, Han D-H, Higashida K, Kim SH, Holloszy JO. Does calorie restriction induce mitochondrial biogenesis? A reevaluation. *FASEB J*. 2011;25:785–91.
145. Brietzke E, Mansur RB, Subramaniapillai M, Balanzá-Martínez V, Vinberg M, González-Pinto A, et al. Ketogenic diet as a metabolic therapy for mood disorders: evidence and developments. *Neurosci Biobehav Rev*. 2018;94:11–6.
146. Sullivan PG, Rippey NA, Dorenbos K, Concepcion RC, Agarwal AK, Rho JM. The ketogenic diet increases mitochondrial uncoupling protein levels and activity. *Ann Neurol*. 2004;55:576–80.
147. Cocco T, Sgobbo P, Clemente M, Lopriore B, Grattagliano I, Di Paola M, et al. Tissue-specific changes of mitochondrial functions in aged rats: effect of a long-term dietary treatment with N-acetylcysteine. *Free Radic Biol Med*. 2005;38:796–805.
148. Timmers S, Konings E, Bilet L, Houtkooper RH, van de Weijer T, Goossens GH, et al. Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. *Cell Metab*. 2011;14:612–22.
149. Cavalli G, Heard E. Advances in epigenetics link genetics to the environment and disease. *Nature*. 2019;571:489–99.
150. Li M, D'Arcy C, Li X, Zhang T, Joob R, Meng X. What do DNA methylation studies tell us about depression? A systematic review. *Transl psychiatry*. 2019;9:1–14.
151. Bressler J, Marioni RE, Walker RM, Xia R, Gottesman RF, Windham BG, Grove ML, Guan W, Pankow JS, Evans KL, Mcintosh AM. Epigenetic age acceleration and cognitive function in African American adults in midlife: the atherosclerosis risk in communities study. *The Journals of Gerontology: Series A*. 2020;75(Feb):473–80.
152. Rosen AD, Robertson KD, Hlady RA, Muench C, Lee J, Philibert R, et al. DNA methylation age is accelerated in alcohol dependence. *Transl Psychiatry*. 2018;8:182.
153. Fries GR, Bauer IE, Scaini G, Valvassori SS, Walss-Bass C, Soares JC, Quevedo J. Accelerated hippocampal biological aging in bipolar disorder. *Bipolar disorders*. 2020;22(Aug):498–507.
154. Davis EG, Humphreys KL, McEwen LM, Sacchet MD, Camacho MC, MacIsaac JL, et al. Accelerated DNA methylation age in adolescent girls: associations with elevated diurnal cortisol and reduced hippocampal volume. *Transl Psychiatry*. 2017;7:e1223.
155. Voisey J, Lawford BR, Morris CP, Wockner LF, Noble EP, Young RM, et al. Epigenetic analysis confirms no accelerated brain aging in schizophrenia. *NPJ Schizophr*. 2017;3:26.
156. Chen L, Dong Y, Bhagatwala J, Raed A, Huang Y, Zhu H. Effects of vitamin D3 supplementation on epigenetic aging in overweight and obese African Americans with suboptimal vitamin D status: a randomized clinical trial. *J Gerontol A Biol Sci Med Sci*. 2019;74:91–8.
157. Stubbs TM, Bonder MJ, Stark AK, Krueger F, Team BIAC, von Meyenn F, et al. Multi-tissue DNA methylation age predictor in mouse. *Genome Biol*. 2017;18:68.
158. Sae-Lee C, Corsi S, Barrow TM, Kuhnle GGC, Bollati V, Mathers JC, et al. Dietary intervention modifies DNA methylation age assessed by the epigenetic clock. *Mol Nutr Food Res*. 2018;62:e1800092.
159. O'Neil A, Itsiopoulos C, Skouteris H, Opie RS, McPhie S, Hill B, et al. Preventing mental health problems in offspring by targeting dietary intake of pregnant women. *BMC Med*. 2014;12:208.
160. Mill J, Heijmans BT. From promises to practical strategies in epigenetic epidemiology. *Nat Rev Genet*. 2013;14:585–94.
161. Bianco-Miotto T, Craig JM, Gasser YP, van Dijk SJ, Ozanne SE. Epigenetics and DOHaD: from basics to birth and beyond. *J Dev Orig Health Dis*. 2017;8:513–9.
162. Choi SW, Friso S. Epigenetics: a new bridge between nutrition and health. *Adv Nutr*. 2010;1:8–16.
163. Remely M, Stefanska B, Lovrecic L, Magnet U, Haslberger AG. Nutriepigenomics: the role of nutrition in epigenetic control of human diseases. *Curr Opin Clin Nutr Metab Care*. 2015;18:328–33.
164. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci USA*. 2008;105:17046–9.
165. Barker ED, Walton E, Cecil CAM. Annual research review: DNA methylation as a mediator in the association between risk exposure and child and adolescent psychopathology. *J Child Psychol Psychiatry*. 2018;59:303–22.
166. Peter CJ, Fischer LK, Kundakovic M, Garg P, Jakovcevski M, Dincer A, et al. DNA methylation signatures of early childhood malnutrition associated with impairments in attention and cognition. *Biol Psychiatry*. 2016;80:765–74.
167. McGowan PO, Meaney MJ, Szyf M. Diet and the epigenetic (re) programming of phenotypic differences in behavior. *Brain Res*. 2008;1237:12–24.
168. Burdge GC, Lillycrop KA. Nutrition, epigenetics, and developmental plasticity: implications for understanding human disease. *Annu Rev Nutr*. 2010;30:315–39.
169. Gomez-Pinilla F, Yang X. System biology approach intersecting diet and cell metabolism with pathogenesis of brain disorders. *Prog Neurobiol*. 2018;169:76–90.
170. Remely M, Lovrecic L, de la Garza AL, Migliore L, Peterlin B, Milagro FI, et al. Therapeutic perspectives of epigenetically active nutrients. *Br J Pharmacol*. 2015;172:2756–68.
171. Gonzalez-Becerra K, Ramos-Lopez O, Barron-Cabrera E, Riezu-Boj JI, Milagro FI, Martinez-Lopez E, et al. Fatty acids, epigenetic mechanisms and chronic diseases: a systematic review. *Lipids Health Dis*. 2019;18:178.
172. Qin Y, Wade PA. Crosstalk between the microbiome and epigenome: messages from bugs. *J Biochem*. 2018;163:105–12.
173. Agustí A, García-Pardo MP, López-Almela I, Campillo I, Maes M, Román-Pérez M, et al. Interplay between the gut-brain axis, obesity and cognitive function. *Front Neurosci*. 2018;12:155.
174. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry*. 2010;67:220–9.
175. Mansur RB, Brietzke E, McIntyre RS. Is there a “metabolic-mood syndrome”? A review of the relationship between obesity and mood disorders. *Neurosci Biobehav Rev*. 2015;52:89–104.
176. Dallman MF, Pecoraro N, Akana SF, La Fleur SE, Gomez F, Houshyar H, et al. Chronic stress and obesity: a new view of “comfort food”. *Proc Natl Acad Sci USA*. 2003;100:11696–701.
177. Bornstein SR, Schuppenies A, Wong ML, Licinio J. Approaching the shared biology of obesity and depression: the stress axis as the locus of gene–environment interactions. *Mol Psychiatry*. 2006;11:892–902.
178. Schachter J, Martel J, Lin CS, Chang CJ, Wu TR, Lu CC, et al. Effects of obesity on depression: a role for inflammation and the gut microbiota. *Brain Behav Immun*. 2018;69:1–8.
179. Miller GE, Freedland KE, Carney RM, Stetler CA, Banks WA. Pathways linking depression, adiposity, and inflammatory markers in healthy young adults. *Brain Behav Immun*. 2003;17:276–85.
180. Manu P, Khan S, Radhakrishnan R, Russ MJ, Kane JM, Correll CU. Body mass index identified as an independent predictor of psychiatric readmission. *J Clin Psychiatry*. 2014;75:e573–7.
181. Bellavia A, Centorrino F, Jackson JW, Fitzmaurice G, Valeri L. The role of weight gain in explaining the effects of antipsychotic drugs on positive and negative symptoms: an analysis of the CATIE schizophrenia trial. *Schizophr Res*. 2019;206:96–102.

182. Fontana L, Meyer TE, Klein S, Holloszy JO. Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. *Proc Natl Acad Sci USA*. 2004;101:6659–63.
183. Rizza W, Veronese N, Fontana L. What are the roles of calorie restriction and diet quality in promoting healthy longevity? *Ageing Res Rev*. 2014;13:38–45.
184. Jebeile H, Gow ML, Baur LA, Garnett SP, Paxton SJ, Lister NB. Association of pediatric obesity treatment, including a dietary component, with change in depression and anxiety: a systematic review and meta-analysis. *JAMA Pediatr*. 2019;173:e192841.
185. Jacka FN, Mykletun A, Berk M, Bjelland I, Tell GS. The association between habitual diet quality and the common mental disorders in community-dwelling adults: the Hordaland Health study. *Psychosom Med*. 2011;73:483–90.
186. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. *Diabetes Care*. 2008;31:2383–90.
187. Huffman JC, Celano CM, Beach SR, Motiwala SR, Januzzi JL. Depression and cardiac disease: epidemiology, mechanisms, and diagnosis. *Cardiovasc Psychiatry Neurol*. 2013;2013:695925.
188. Jung SJ, Woo HT, Cho S, et al. Association between body size, weight change and depression: systematic review and meta-analysis. *Br J Psychiatry*. 2017;211:14–21.
189. Power ML, Schulkin J. Sex differences in fat storage, fat metabolism, and the health risks from obesity: possible evolutionary origins. *Br J Nutr*. 2008;99:931–40.
190. Kiefer I, Rathmanner T, Kunze M. Eating and dieting differences in men and women. *J Men's Health Gen*. 2005;2:194–201.
191. Buening-Fesel M, Rueckert-John J. Why do men eat how they eat?: considerations from a nutritional-and gender-sociological perspective. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*. 2016;59:950–6.
192. Wardle J, Haase AM, Steptoe A, Nillapun M, Jonwutiwes K, Bellisle F. Gender differences in food choice: the contribution of health beliefs and dieting. *Ann Behav Med*. 2004;27:107–16.

Affiliations

Wolfgang Marx¹ · Melissa Lane¹ · Meghan Hockey¹ · Hajara Aslam¹ · Michael Berk^{1,2,3} · Ken Walder⁴ · Alessandra Borsini⁵ · Joseph Firth^{6,7} · Carmine M. Pariante⁵ · Kirsten Berding⁸ · John F. Cryan^{8,9} · Gerard Clarke^{8,10,11} · Jeffrey M. Craig¹² · Kuan-Pin Su^{13,14,15} · David Mischoulon^{16,17} · Fernando Gomez-Pinilla¹⁸ · Jane A. Foster¹⁹ · Patrice D. Cani²⁰ · Sandrine Thuret²¹ · Heidi M. Staudacher¹ · Almudena Sánchez-Villegas^{22,23} · Husnain Arshad²⁴ · Tasnime Akbaraly^{24,25} · Adrienne O'Neil¹ · Toby Segasby²¹ · Felice N. Jacka^{1,26,27,28}

¹ Deakin University, IMPACT (the Institute for Mental and Physical Health and Clinical Translation), Food & Mood Centre, Geelong, VIC, Australia

² Orygen, The National Centre of Excellence in Youth Mental Health, Centre for Youth Mental Health, Florey Institute for Neuroscience and Mental Health, Melbourne, VIC, Australia

³ Department of Psychiatry, The University of Melbourne, Melbourne, VIC, Australia

⁴ Deakin University, IMPACT (the Institute for Mental and Physical Health and Clinical Translation), Metabolic Research Unit, Geelong, VIC, Australia

⁵ Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

⁶ Division of Psychology and Mental Health, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

⁷ NICM Health Research Institute, Western Sydney University, Westmead, NSW, Australia

⁸ APC Microbiome Ireland, University College Cork, Cork, Ireland

⁹ Department of Anatomy and Neuroscience, University College Cork, Cork, Ireland

¹⁰ Department of Psychiatry and Neurobehavioural Science, University College Cork, Cork, Ireland

¹¹ INFANT Research Centre, University College Cork, Cork, Ireland

¹² Deakin University, IMPACT (the Institute for Mental and Physical Health and Clinical Translation), Geelong, VIC, Australia

¹³ Departments of Psychiatry and Mind-Body Interface Laboratory (MBI-Lab), China Medical University Hospital, Taichung, Taiwan

¹⁴ An-Nan Hospital, China Medical University, Tainan, Taiwan

¹⁵ College of Medicine, China Medical University, Taichung, Taiwan

¹⁶ Department of Psychiatry, Depression Clinical and Research Program, Massachusetts General Hospital, Boston, MA, USA

¹⁷ Harvard Medical School, Boston, MA, USA

¹⁸ Departments of Neurosurgery and Integrative Biology and Physiology, University of California Los Angeles, Los Angeles, CA, USA

¹⁹ Department of Psychiatry & Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada

²⁰ UCLouvain, Université catholique de Louvain, WELBIO—Walloon Excellence in Life Sciences and BIOTEchnology, Louvain Drug Research Institute, Metabolism and Nutrition Research Group, Brussels, Belgium

²¹ Basic and Clinical Neuroscience Department, Institute of Psychiatry Psychology and Neuroscience, King's College London, London, UK

²² Nutrition Research Group, Research Institute of Biomedical and Health Sciences, University of Las Palmas de Gran Canaria, Gran Canaria, Spain

- ²³ Biomedical Research Center Network on Obesity and Nutrition (CIBERObn) Physiopathology of Obesity and Nutrition, Institute of Health Carlos III, Madrid, Spain
- ²⁴ Université Paris-Saclay, UVSQ, Inserm, CESP, “DevPsy”, 94807 Villejuif, France
- ²⁵ Department of Epidemiology and Public Health, University College London, London, UK
- ²⁶ Centre for Adolescent Health, Murdoch Children’s Research Institute, Melbourne, VIC, Australia
- ²⁷ Black Dog Institute, Randwick, NSW, Australia
- ²⁸ James Cook University, Townsville, QLD, Australia