The gut microbiome and diet in psychiatry: focus on depression

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Purpose of review
With depressive disorders the leading source of disability globally, the identification of new targets for prevention and management is imperative. A rapidly emerging field of research suggests that the microbiome–gut–brain axis is of substantial relevance to mood and behaviour. Similarly, unhealthy diet has recently emerged as a significant correlate of and risk factor for depression. This review provides evidence for the gut microbiota as a key factor mediating the link between diet and depressive illness.

Recent findings
The development of new technologies is affording a better understanding of how diet influences gut microbiota composition and activity and how this may, in turn, influence depressive illness. New interventions are also suggesting the possible utility of pre and probiotic formulations and fermented food in influencing mental health.

Summary
Although in its early stages, the emerging field of research focused on the human microbiome suggests an important role for the gut microbiota in influencing brain development, behaviour and mood in humans. The recognition that the gut microbiota interacts bidirectionally with other environmental risk factors, such as diet and stress, suggests promise in the development of interventions targeting the gut microbiota for the prevention and treatment of common mental health disorders.

Keywords
depression, diet, inflammation, microbiota, psychiatry

INTRODUCTION
The naturally occurring ‘commensal’ bacteria that exist symbiotically with our bodies are estimated to number 100 trillion in the human gut alone [1]. The gut microbiome – the community of bacteria and their genetic material living in the gut – is often referred to as a virtual organ [2,3]. Much of the early microbiota research was subject to the limitations of culturing technology, restricting our understanding of bacterial composition and functioning. More recently, the development and use of new metagenomic and molecular technologies has afforded detailed insights into the important role of microbiota in human health and disease [4,5,6]. These new insights have, in turn, pointed to the pathophysiological role of the gut microbiota in diverse disorders from atopy to depression. The recognition that the gut microbiota interacts with other environmental risk factors, such as stress and diet, suggests promise in the development of interventions targeting the gut microbiota for the prevention and treatment of disease. In this review, we address the evidence linking the gut microbiome to the recently established associations between dietary intake in humans and the prevalence of or risk for depressive illness [25,7,8] and highlight new possibilities and implications for the prevention and treatment of depressive disorders arising from this evidence.

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The gut microbiome is essential in immune development and function and is thus a key determinant of human health.

New evidence suggests that gut microbiota also influences mood and behaviour.

Unhealthy diet is a correlate and risk factor for depression and dietary improvement prevents depression.

Modification of the gut microbiome by dietary and related strategies may have significant utility in preventing and treating depression.

The gut microbiota is considered essential for the development of the immune system as well as the regulation of gastrointestinal motility and maintenance of gut barrier function. The diverse functional repertoire of the gut microbiota has been classified in terms of both a metabolic organ and an endocrine organ in addition to its key role in immune system development. The understanding of the gut microbiota as a primary driver of host development and physiology now extends to key features of brain and behaviour. The microbial composition of an individual begins to establish itself at birth and can vary depending on infant delivery method and feeding. The gut microbiome stabilizes in the first few years of life but continues to be influenced by age, genetics, geography, medication use, and, most relevant to this review, diet.

The influence of the gut microbiome extends across multiple physiological domains. For example, bacterial colonization of the intestine is considered essential for the development of the immune system as well as the regulation of gastrointestinal motility and maintenance of gut barrier function. The diverse functional repertoire of the gut microbiota has been classified in terms of both a metabolic organ and an endocrine organ in addition to its key role in immune system development. The understanding of the gut microbiota as a primary driver of host development and physiology now extends to key features of brain and behaviour. The microbial composition of an individual begins to establish itself at birth and can vary depending on infant delivery method and feeding. The gut microbiome stabilizes in the first few years of life but continues to be influenced by age, genetics, geography, medication use, and, most relevant to this review, diet.

**Diet and Mental Health**

There have been a rapidly increasing number of observational studies documenting cross-sectional and prospective associations between habitual diet quality and the prevalence of risk for depression. These associations have been consistently observed in adults, adolescents and children across a multitude of different countries and cultures. A recent systematic review and meta-analysis, including results from 13 observational studies, concluded that a healthy diet is significantly associated with a reduced odds for depression (odds ratio (OR) 0.84; 95% confidence interval (95% CI) 0.76–0.92; \( P < 0.001 \)) [25]. Similarly, a meta-analysis of 22 studies investigating the protective effects of adherence to a Mediterranean-style diet on brain diseases demonstrated that higher adherence was associated with a reduced risk for depression (relative risk 0.68, 95% CI 0.54–0.86), as well as cognitive decline [7]. Moreover, increased consumption of unhealthy, sugar and fat-rich foods is related to an increased risk of psychological symptomatology in children and adolescents [8]. Of particular note are results from two new, large, cohort studies suggesting an independent role for early life nutritional exposures in influencing the mental health of offspring [26,27]. These observational studies are supported by two recent trials that indicate the efficacy of dietary improvement as a strategy for the prevention of depression [28,29]. Although this field is still evolving, treatment trials are currently underway [30]. The focus is now turning to the explication of biological pathways that may mediate this well-established association, foremost being the gut microbiota.

**Microbiota and Mental Health**

Bested et al. [31] provide an intriguing overview of the long history of investigation into the ‘gut–brain’ axis, including the first suggestions in the 1800s that systemic disease, including mental health disorders, could be rooted in intestinal ‘self-infective’ processes and that increasing rates of melancholia may be a by-product of urban and western civilization, possibly mediated by dietary habits and toxins arising from the gastrointestinal tract.

The evidence that the gut microbiota influences brain and behaviour is now rapidly expanding and is a view that has started to gain traction in the literature. This is largely due to compelling preclinical evidence that the gut microbiota can influence behaviours of relevance to anxiety and depression. It has been demonstrated that manipulation of the gut microbiota with specific probiotics or with antibiotics can influence depression-like behaviours. The microbiota likely recruits the gut–brain axis to exert effects at the level of the central nervous system (CNS). This is a reciprocal relationship, with the CNS moderating, for example, gut motility and secretion. Both humoral and neural mechanisms are plausible, with the role of the vagus nerve in particular receiving much attention.

Independent studies have now confirmed that an anxious phenotype can be transferred via the gut microbiota. Moreover, it appears that both prenatal and early-life stress, both risk factors for psychopathology, engender potentially deleterious gut microbiota alterations that can manifest during critical neurodevelopmental periods and that may
persist into adulthood. For example, Bailey et al. [46] monitored gut bacteria colonization in infant monkeys whose mothers were either undisturbed or stressed during pregnancy, finding marked changes in microflora concentrations in the offspring of stressed mothers. Certainly, the animal data suggest that early colonization of gut microbiota influences the programming of the stress response system in offspring [47]. Moreover, preclinical studies have shown that both early life stress and surgically induced depression produce alterations in the gut microbiota [48*,49]. Adverse early life exposures are related to the stress response and the risk for mental disorders in offspring [50]; thus, the understanding that prenatal and early life stress modulates the microbial composition of the gut in infants suggests implications for the vulnerability to mental disorders in children. It is worth noting that the adult gut microbiome appears to be resilient and begins recovery immediately after disruption [51], although the impact of very early life or repeated antibiotic use on the microbiome can be pervasive and long-lasting [52].

Given the ability of the gut microbiota to influence serotonin and its precursor, tryptophan [53], regulate the stress response [54,55] and modulate cognition [56,57] and behaviour [58*,59], the potential importance of the gut microbiota to psychiatry in general and to depression specifically is apparent. Microbiome alterations are evident in irritable bowel syndrome (IBS), a functional gastrointestinal disorder with significant psychiatric comorbidity [60]. However, only one preliminary study has specifically examined microbiome alterations in depression and, although some correlations were established, the overall species richness and diversity was not different to healthy controls [61]. More detailed studies are now warranted to interrogate this intriguing proposition. Recent indications that certain probiotic formulations can both produce beneficial psychological effects in healthy populations [62] and modulate brain activity in an imaging study [63**] underline the importance of such a venture.

**LEAKY GUT**

Beyond metabolism, microbial balance influences the protective epithelial gut barrier. The integrity of the mucosal gut barrier is maintained by tight junctions that control the flow of molecules between the gastrointestinal tract and bloodstream [64]. Compromised integrity of the epithelial barrier has been termed ‘leaky gut’ and this condition has been associated with a wide range of intestinal and systemic diseases, including allergies, autoimmune disorders, asthma, IBD and, speculatively, to mental health [65,66], although it is important to note that most data are correlational at this stage [67].

One consequence of intestinal permeability, or leaky gut, is the increase in circulating bacteria-derived lipopolysaccharide (LPS), which triggers both an immunological and inflammatory response characterized by increased systemic pro-inflammatory cytokines [68]. Inflammation is suggested as a causative factor in depression [69] and it is notable that elevated serum levels of IgM and IgA against Gram-negative enterobacteria-derived LPS are elevated in chronic depression [70]. Moreover, bacterial translocation across the gut wall induces an auto-immune response to serotonin that is associated with fatigue and illness behaviour [71]. A novel animal model of depression has been developed on the basis of this model whereby chronic LPS administration induces the behavioural phenotype of depression and is reversed by antidepressants [72]. Relevant to this review, intestinal permeability is promoted by high-fat diets [73].

**MICROBIOTA AND DIET**

The gut microbiota is central in metabolism, breaking down dietary components of foods to fuel energy generation [74]. Metabolism of dietary components supports energy production, signalling and homeostatic functions. A previous study [75] postulated that modern modifications to diet and subsequent changes to the gut microbiota are responsible for the increasing rate of inflammatory disease such as cardiovascular disease, rheumatoid arthritis and depression. The Mediterranean diet, a gold standard healthy eating model, can have a beneficial effect on the host microbiota, and in turn, on host health and wellness [76].

Carbohydrate consumption, particularly of dietary fibre, is an important determinant of microbial composition and results in short chain fatty acid (SCFA) production, promoting a shift towards different types of ‘beneficial’ bacteria and inhibiting the proliferation of ‘bad’ bacteria [77]. Dietary fibre provides substrates for bacterial fermentation that results in the SCFAs acetate, propionate and butyrate; these are mediators of the colonic inflammatory response [78]. A recent trial placed 10 healthy volunteers on either a ‘plant-based’ or ‘animal-based’ diet, showing rapid (5-day) change in the function profile of the gut [79**]. Poor quality or ‘western’ diets, particularly low in nondigestible fibre, lessen microbial diversity and support fewer antipathogenic bacteria [20]. A recent review suggests that microbiota may even affect eating behaviour by eliciting cravings for

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Dash et al. The gut microbiome and diet in psychiatry

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foods that fuel bacterial fitness, but not necessarily host health, and that increased microbial diversity may limit bacterial control over dietary choices [80].

Microbial exposure and long-term, habitual diets are shown to be one of the strongest influences on gut microbial composition, determining an individual ‘enterotype’ [81]. Data from studies examining the effect of dietary modification on microbial composition are beginning to emerge, with evidence that the consumption of complex carbohydrates, plant-based foods/fruits and vegetables [81,82] and fermented food [83] influence microbial composition, synthesis of anti-inflammatory SCFAs and host health. Conversely, high-fat diets trigger microbial dysbiosis, intestinal permeability and inflammation [73], with behavioural disruptions that are independent of obesity [44**].

In a landmark study, De Filippo et al. [20] saw significant differences in gut microbial composition between African children consuming a ‘traditional’ diet compared with European children eating a ‘Western’-style diet. In this study, African children on a plant-based diet had greater microbial diversity and had anti-inflammatory bacteria that were functionally absent in the European children consuming a Western-style diet. In support of this finding, Wu et al. [81] found that diets higher in fat and lower in fibre were associated with more Bacteroidetes and Actinobacteria in healthy volunteers. Conversely, a healthy diet, high in fibre and low in fat, was characterized by the phyla Firmicutes and Proteobacteria. These bacterial ratios are important in determining pro and anti-inflammatory balance in the gut. The authors then conducted a controlled feeding study with 10 of the healthy individuals, who followed either a high-fat/low-fibre or a low-fat/high-fibre diet for 10 days. Phenotypal microbiota composition was noted to change quite quickly; however, microbial enterotype remained constant over the 10 days [81]. This suggests that longer-term dietary change may be required to make lasting, significant changes to gut health. Concordantly, reviewers Power et al. [84] reported that levels of dominant phyla of bacteria in the gut are diet-depandent and may be specifically related to the type of nondigestible carbohydrate consumed. However, relationships between diet and bacteria might be dependent on individual factors and people may have different responses to dietary change. More data are needed to understand the complex ways in which dietary patterns influence gut microbiota composition and activity, with the ultimate objective aimed at achieving precise changes in the gut microbiota composition that can lead to improved mental health [85].

**OPPORTUNITIES FOR PREVENTION AND TREATMENT**

The gut may be a feasible focus for prevention and treatment interventions. As before, the gut microbiota appears to have a reciprocal and regulatory relationship with the stress response system [47,49,86]. However, the disruptive impact of stress on the gut has been prevented and even partially reversed by probiotic administration in animal studies [87]. Dietary manipulation, including the consumption of prebiotics (fermented dietary ingredients including fructans and oligosaccharides) and fermented foods, result in specific changes in the activity of the gastrointestinal microbiota and may provide a feasible means of intervention to address depression and other disorders [83]. In considering the role of diet in gut health, it should be acknowledged that a healthy diet will often coexist with other health behaviours, such as exercise [88*], that also promote microbial health.

**CONCLUSION, DISCUSSION, FUTURE DIRECTION**

With depression currently one of the leading causes of global disease burden [89], the imperative to develop effective prevention and treatment strategies is clear. The gut microbiome has been implicated as an important health determinant relevant to both physical and mental health. The emerging literature from this nascent field suggests that the recently established association between diet quality and depressive disorders [90] is likely to be, at least partly, mediated by the gut microbiota. Depressive symptoms prompt the increased consumption of high-fat, sugary foods [91], although the long-term impact of these dietary habits is noxious [92]. Microbial changes perpetuated by poor diet may drive and exacerbate depressive symptoms. On the contrary, dietary improvement has been shown to prevent depression [29,93]. As a readily accessible and effective tool for modifying microbial composition, diet may provide a more acceptable alternative to drug therapy with unpleasant side effects, particularly in patients with milder symptoms of depression. This provides an important target for the prevention and treatment of common mental disorders [24].

It is important to bear in mind that the field is in its early stages and has not yet been able to comprehensively identify and describe the composition of a ‘healthy’ gut, nor the full functional capacity of most bacterial phyla. Importantly, microbial composition seems to be individualized; overall, microbiome function can vary greatly between persons, yet different microbiome compositions between individuals can also have the same range of functions. Advances in analytical technology will
continue to shed light on this rapidly developing field of investigation. Although early probiotic and dietary research provides support for diet as a possible target for microbial modification and in turn, the alleviation of mental health symptoms, there is a clear need for more high quality research, including randomized controlled trials, to investigate the effectiveness and feasibility of mental health improvement as a function of microbial modulation. Although pre and probiotics (whose presence is transient and dependant on continued consumption) offer tantalising promise for efficacy in psychiatry, holistic dietary changes may be necessary to promote long-term improvements in health.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as: ● of special interest ■ of outstanding interest


A comprehensive and accessible recent review detailing the methodological advances in the assessment of the gut microbiota.


An important overview of the favourable effects of the Mediterranean diet on the occurrence of stroke, cognitive impairment and depression.


An outstanding overview of the critical importance of the gut microbiota in human physiology.


A field-defining review that provides the framework for future studies charting the impact of the gut microbiota at the level of the CNS.


An important review exploring the relationship mode of delivery and development of the immune system.


An important paper which demonstrates that metabolic side effects of antipsychotic medication can be mediated by the gut microbiota.


A notable demonstration that early nutritional exposures influence behavioural and emotional outcomes in the offspring.


An important study using germ-free rats that further confirms the importance of the gut microbiota in brain and behaviour.


Together with refs [34,37], this study links the gut microbiota to alterations in neurotransmitters and neurotrophic factors in the brain as well as alterations in anxiety-like behaviour.
Mood and anxiety disorders


An interesting study which shows that doxycholine in addition to monoamine, both of which are from the same class of antibiotic, can potentially modulate depressive-like behaviours.


45. Taken together with ref [43], these studies independently verify that relevant behaviours can be transferred via gut microbiota transplants.


An interesting preclinical study highlighting the potential links between the gut microbiota and depression.


This study demonstrates that exercise might have an effect on the gut microbiota.


