

# The role of the gut microbiome in mental health

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**Target audience:** For healthcare professionals interested in learning about the role of the microbiome in mental health.

**Publication date:** May 2021

**Review date:** May 2022

## **Learning objectives:**

**By the end of this article, you should understand:**

1. The role of the gut-brain axis in mental health
2. How gut microbiome dysbiosis may play a role in mental health conditions
3. The evidence base for interventions to manage mental health conditions by targeting the gut microbiome

## Introduction

There is a high prevalence of mental health conditions in the UK. One in six adults have a common mental health condition, with 40% being personally affected during their lifetime (1).

The most common mental health conditions are depression and anxiety (1); half of people diagnosed with these conditions do not respond to existing treatments (2).

Many patients with mental health conditions present with gut dysbiosis and altered communication between the gut and brain. However, at present, there is no clear guidance on the best interventions to improve mental health, by optimising gut health.

This article will explore the research into the relationship between depression, anxiety, stress and the gut microbiome.

## The gut-brain axis

The gut-brain axis (GBA) can be defined as 'a bi-directional system of communication between the brain and the gastrointestinal tract, linking emotional and cognitive centres of the brain with peripheral control and function of the gut' (3). GBA dysfunction is now being implicated as a factor in the pathology of many conditions including mental health conditions.

The gut microbiota (GM) (a collection of microorganisms, predominantly bacteria, which reside in our gastrointestinal tract) (4) are now seen as an essential mediator of the GBA. The GBA involves many different pathways of direct and indirect communication involving neural, hormonal and immune messengers, many of which are mediated by or involve the GM (see table 1).

**Table 1: Routes of communication between the gut and brain**

Communication route	Detail/example
Nervous system	<ul style="list-style-type: none"><li>The vagus nerve directly connects the gut and brain and acts as their primary communication method.</li><li>Messages are bi-directional and involve the central, peripheral and enteric nervous systems.</li><li>The GM can produce factors which stimulate neural pathways, they are involved in the production of neurotransmitters such as gamma-aminobutyric acid (GABA) (2).</li></ul>
Endocrine system	<ul style="list-style-type: none"><li>Various hormones pass messages from the gut and brain, including centrally produced stress hormones such as cortisol, to coordinate responses to external stimulators. This involves the hypothalamic–pituitary–adrenal (HPA) axis.</li><li>The GM modulates the production of certain hormones and produces serotonin, which can impact brain function including mood. This is thought to be a major route as to how GBA dysfunction impacts mental health (3,6).</li></ul>
Immune system	<ul style="list-style-type: none"><li>Immune factors are another route of GBA communication. Gut associated lymphoid tissue (GALT) makes up 70% of immune cells.</li><li>The GM can impact these processes by altering gut wall integrity and inflammatory messengers (cytokines) (2).</li><li>The GM produces short chain fatty acids (SCFA), which have anti-inflammatory effects and support barrier immunity.</li><li>Lower SCFA levels have been associated with depressive symptoms (7).</li></ul>

# Role of the GBA in mental health

## Dysbiosis in mental health conditions

Dysbiosis describes a change to the composition of the gut microbes, associated with altered function or disease, relative to those found in healthy individuals (5,8). Dysbiosis can be defined as (9):

- An increase in potentially harmful microbes
- Loss of microbial diversity
- Loss of beneficial microbes

GM alterations have been found in people with depression versus healthy controls, however study findings are inconsistent and many fail to account for key confounding factors (such as diet or medications) (2).

Diversity is seen as a marker of a healthy GM10. In a 2020 systematic review, half of the studies found reduced GM diversity in people with depression, although the remaining studies found no significant difference (2). Some differences were found in the abundance of specific bacteria including lower levels of anti-inflammatory SCFA-producing species (such as *Faecalibacterium*) (2). Dysbiosis may impact the GBA by various proposed mechanisms outlined in table 2.

**Table 2: Proposed mechanisms of GBA dysfunction in mental health conditions**

Factor	Detail
Development of the nervous system	<ul style="list-style-type: none"><li>• Studies in mice show that the GM plays an important role in early life development of the brain. Mice raised 'germ free', with no GM, have impaired nervous system development, function and altered response to stress (11).</li></ul>
Behaviour and response to stress	<ul style="list-style-type: none"><li>• Further studies in mice show that alterations in microbial balance can lead to poorer response to stress and alterations in their behaviour to exhibit anxiety/depressive-like behaviours (5). In animal models, these behaviours can be normalised upon the provision of probiotics (12). In a murine preclinical study, a multi-strain probiotic improved symptoms of anxiety and depression, with the <i>Lactobacillus</i> species thought to be most responsible for the effect via alteration of GBA communication (13).</li></ul>
Altered tryptophan and serotonin metabolism	<ul style="list-style-type: none"><li>• GM dysbiosis may lead to altered levels of serotonin and other tryptophan metabolites which impact brain function and mood (3,6).</li></ul>
Inflammation and impaired barrier function	<ul style="list-style-type: none"><li>• Can lead to translocation of bacteria and their metabolites into the bloodstream which may impact brain function (2). The administration of bacterial cell wall material, lipopolysaccharide, induces sickness related depressive symptoms in mice and humans (14).</li></ul>

More research in this area is needed, as much of the existing research relies on preclinical, animal studies. Therefore, results cannot be directly transferred to humans. However, epidemiological evidence in humans supports the theory of gut involvement in mental health conditions.

There is a high concurrence of gastrointestinal and mental health disease, with 80% of people with Irritable bowel syndrome (IBS) also having a mental health condition (15). Some successful IBS treatments target the GBA including cognitive behavioural therapy and tricyclic antidepressants (16).

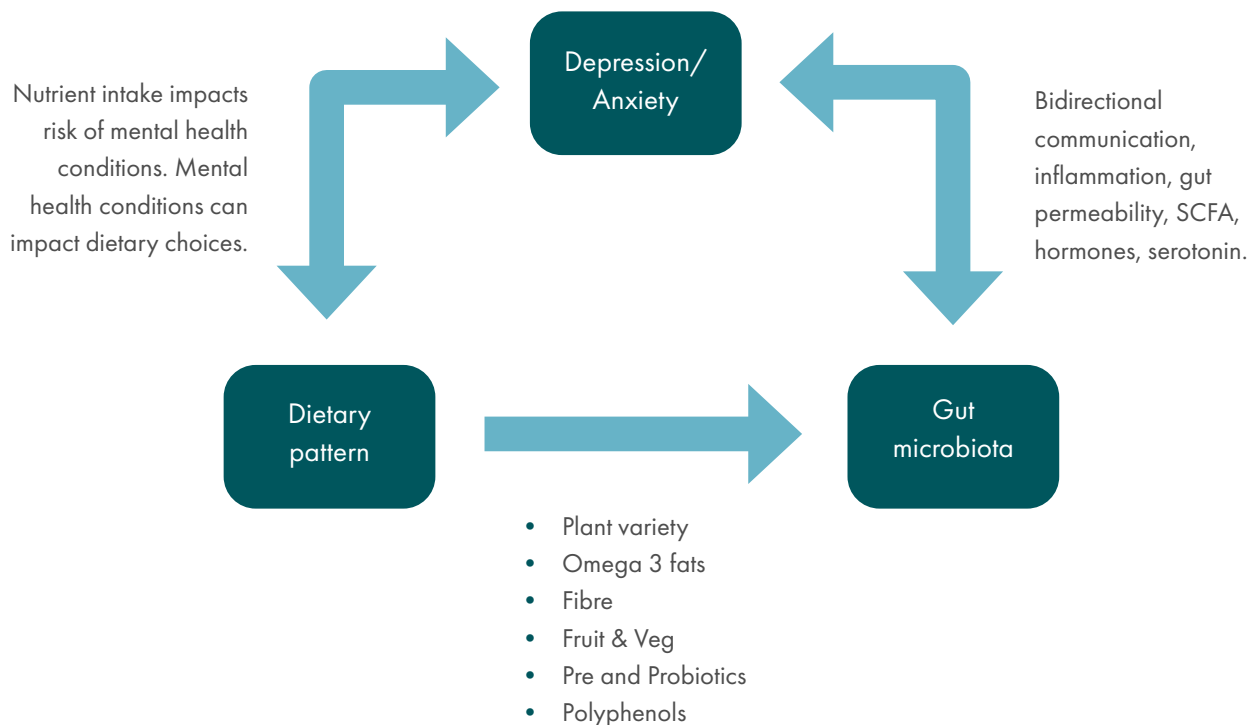
# Current research into GM-targeted therapies in mental health

## Dietary patterns

A poor-quality diet is associated with increased risk of depression and other mental health conditions, however the direction of causation is not clear (17). Animal studies show that a high calorie, 'western' style diet typically high in saturated fat can induce depressive-like symptoms. This can be transferred to other mice via faecal microbiota transplant (FMT), indicating a role of gut microbes (18).

There is a complex relationship between diet, mental health and GM, outlined in Figure 1, adapted from Bear et al. 2020 (19). Human intervention studies in this area are few in number. Overall, 'healthy' dietary interventions show efficacy in protecting from depression (20). We will explore some specific dietary patterns showing the most benefit in the section below.

**Figure 1: Complex relationship between diet, mental health and the GM**



## Mediterranean-style diet

The Mediterranean dietary pattern and its link with improvements in mental health (and potentially neurological disorders such as Parkinson's disease (21)) is beginning to emerge. The strongest evidence of which is for the prevention and management of depression and depressive symptoms (17).

A landmark randomised controlled trial (RCT) supporting this is the 'Supporting the Modification of lifestyle in Lowered Emotional States' (SMILES) study (22). This trial recruited 67 participants, with a poor diet quality (low self-reported intake of dietary fibre, lean proteins and fruit and vegetables, and a high intake of sweets, processed meats and salty snacks), and who fulfilled the diagnostic criteria for a major depressive episode. Dietetic counselling was to follow a Mediterranean-style diet, rich in whole grains, vegetables, fruit, legumes, low fat dairy, nuts, fish and olive oil with low intakes of refined cereals, fast food, processed meats and sugary drinks.

After the 12-week intervention, the dietary group (n=33) had significantly improved symptoms versus the control group (n=34) who received social support only. Remission (in accordance with the MADRS score) was achieved in 32.3% of the dietary group versus 8% of the controls. Improvements were related to adherence to the diet (22).

Some limitations of this study are that it was not possible to blind participants to the intervention as well as the short intervention period to see impact of changed dietary patterns. Regardless, these findings have been supported by other intervention trials, (23,24) and many epidemiological studies (17,25).

A large limitation of the evidence in this area is that none of the studies measured GM outcomes, so we cannot conclude why the Mediterranean diet resulted in improvements and whether this was due to the GM. However, the Mediterranean diet contains a variety of fruit and vegetables, pulses and wholegrains, which contain beneficial components such as different dietary fibres including prebiotics and phytochemicals (e.g. polyphenols). As a dietary pattern, it has been shown to have specific, beneficial effects on the GM (26).

In conclusion, encouraging patients with mental health conditions to follow a Mediterranean-style diet alongside dietetic support may be a useful adjunct when delivered as part of a multidisciplinary approach. However, further research is required to determine whether this dietary approach is superior to other dietary patterns associated with health (e.g., Japanese, Nordic diets etc.).

## Plant-based diets

A plant-based diet consists of mainly plant-based foods; however, this dietary pattern is not the same as vegetarian or vegan diets as it doesn't exclude animal products or fish. Research in this area is mixed, potentially due to the lack of consensus and standardisation of what a plant-based diet encompasses and the risks of poorly planned plant-based diets on mental health (e.g. micronutrient deficiencies such as vitamin B12 which is commonly found in animal products (17)). A 2020 systematic review found broad spectrum vitamin and mineral supplementation alleviated symptoms of depression and anxiety, with a B vitamin complex (including B1, B2, B3, B5, B6 and B12, at doses at or above the RDA) appearing particularly important (27).

Another recent systematic review concluded that there is not sufficient evidence to support use of a plant-based diet in the management of mental health conditions (28).

The Mediterranean diet focuses on plants but does not exclude animal products or fish. It appears that this shift is more beneficial for mental health than complete avoidance of animal products, potentially due to the lesser risk of developing micronutrient deficiencies which can be more common with poorly planned vegetarian or vegan diets, and/or higher bioavailability of animal products or fish (e.g. haem vs. non-haem iron, EPA/DHA vs. ALA). In addition, a variety of plant foods ( $\geq 30$  different types per week versus 10 per week) has been found beneficial for our GM composition (10).

## Individual foods and nutrients

The literature shows benefits of many of the individual components of these dietary patterns mentioned above for both mental and GM health. Research has highlighted benefits of a high fibre intake (29), high fruit and vegetable intake (30) and increased polyphenol intake (31,32). Many plant-based foods contain a mix of different fibres which feed different bacterial groups, so consuming a diverse and varied diet is key. However, more research is needed to unravel the evidence for individual components of diet, overall dietary patterns and individual nutrients.

## Supplements

### Psychobiotics

Psychobiotics are a newer class of probiotic supplements which influence mood and/or behaviour via the GBA (33). Preclinical trials have found beneficial effects of psychobiotics on depression and/or anxiety-like behaviours in animal models. Most research has focused on strains of *Lactobacillus* and *Bifidobacterium* (33,34).

The evidence in humans, however, is weaker. A limited number of clinical trials have observed benefits of single strain, milk-based and multi-strain probiotic formulations on anxiety, stress and depressive behaviours (33,35). Again, the strongest evidence exists for depression (34). Interestingly, a four-week human intervention trial (in healthy women without mental health conditions) found that daily consumption of a fermented milk drink containing probiotics affected activity of brain regions that control central processing of emotion and sensation (36).

While safe to trial, psychobiotics may have limited, or no effect on mental health conditions, and therefore should not replace standard treatment (34).

## Omega-3 fatty acids

A meta-analysis of 10 RCTs found overall benefit of adding omega-3 supplements to antidepressant treatment in patients with major depressive disorder (37).

The evidence is so compelling that omega-3 supplements are included in US (38), Australian (39) and international (40) clinical guidelines as an adjunct therapy, or as an alternative treatment where other medications are unsuitable (for example, in children or pregnant women).

The mechanisms by which they help are not fully understood, however may include positive GM changes, and subsequent anti-inflammatory SCFA production (41).

## Prebiotic fibre

Prebiotics are types of non-digestible carbohydrates (fibre) which selectively promote the growth of beneficial bacteria (usually *Lactobacilli* and *Bifidobacteria*) in the gut (42). They can be found naturally in plant foods and can also be taken as a dietary supplement.

A 2020 review concluded that prebiotic fibre supplements reduce neuroinflammation, and therefore may reduce mental health symptoms (42), however clinical trial evidence in this area is scarce. Furthermore, a 2019 meta-analysis found prebiotic supplementation had no beneficial effect on depression or anxiety versus placebo (43).

While safe to trial, more human clinical evidence is needed before prebiotic fibre supplements can be recommended as a treatment option for mental health conditions.

## Faecal Microbiota Transplant

FMT (or stool transplantation) involves the transfer of faecal microorganisms from a healthy donor to a recipient in order to alter gut microbiome composition in order to treat disease (44).

Interestingly, studies in animals show that depressive symptoms can be transferred from humans to rats and mice by FMT (45–47). This highlights the need for strict control and appropriate screening etc..

There is a lack of research into FMT in humans with depression, although some positive case studies appear in the literature (44). Additionally, a recent systematic review (which included 8 clinical studies in humans) found that FMT from healthy humans to humans with depression resulted in significant short-term improvements in depressive symptoms (48). However, at this stage, while FMT appears a promising future treatment for depression, high-quality RCTs are required to confirm this (49,50).

## Conclusion

Dietary patterns that promote a healthy GM can help reduce risk and manage symptoms of depression, although the exact mechanisms of actions are unknown, and more evidence is needed to conclude whether or not changes in GM are responsible for these improvements.

Modulation of the GBA via food and certain nutritional supplements provide promising avenues to modify symptoms of depression, but further research is needed before clear recommendations can be made.

In the future, the GBA is likely to be a key target for treatment of mental health conditions as part of a holistic approach to management.

Patients with mental health conditions should be supported to adopt achievable and realistic healthy dietary interventions, such as following the Mediterranean diet and considering omega-3 supplementation, where possible, in addition to standard treatment within a multidisciplinary team approach.

## Continuing Professional Development (CPD) questions

**1) The gut microbiota (GM) are involved in which pathways of the gut-brain axis:**

- a. Neural
- b. Endocrine
- c. Immunological
- d. All of the above.

**2) What proportion of people with IBS also have a mental health condition?**

- a. 40%
- b. 60%
- c. 80%

**3) Which dietary pattern has the best evidence for patients with depression?**

- a. Plant-based eating
- b. Mediterranean diet
- c. Vegan diet

**4) Which of the following dietary aspects support a healthy gut microbiome?**

- a. Fibre
- b. Omega-3 fatty acids
- c. Polyphenols
- d. A variety of plant foods
- e. All of the above

**5) Which of the following supplements have the best evidence base as an adjunct therapy for the management of depression?**

- a. Psychobiotics
- b. Prebiotic fibre supplements
- c. Omega-3 supplements

**6) Which of the following statements is false? Faecal microbiota transplant is:**

- a. The transfer of intestinal microflora from a healthy person to one with disease, in order to treat disease.
- b. Most commonly used to treat gastrointestinal disease.
- c. Is currently recommended as a treatment for mental health conditions.

[Answers the on the last page](#)



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## Answers

1. d
2. c
3. b
4. e
5. c
6. c