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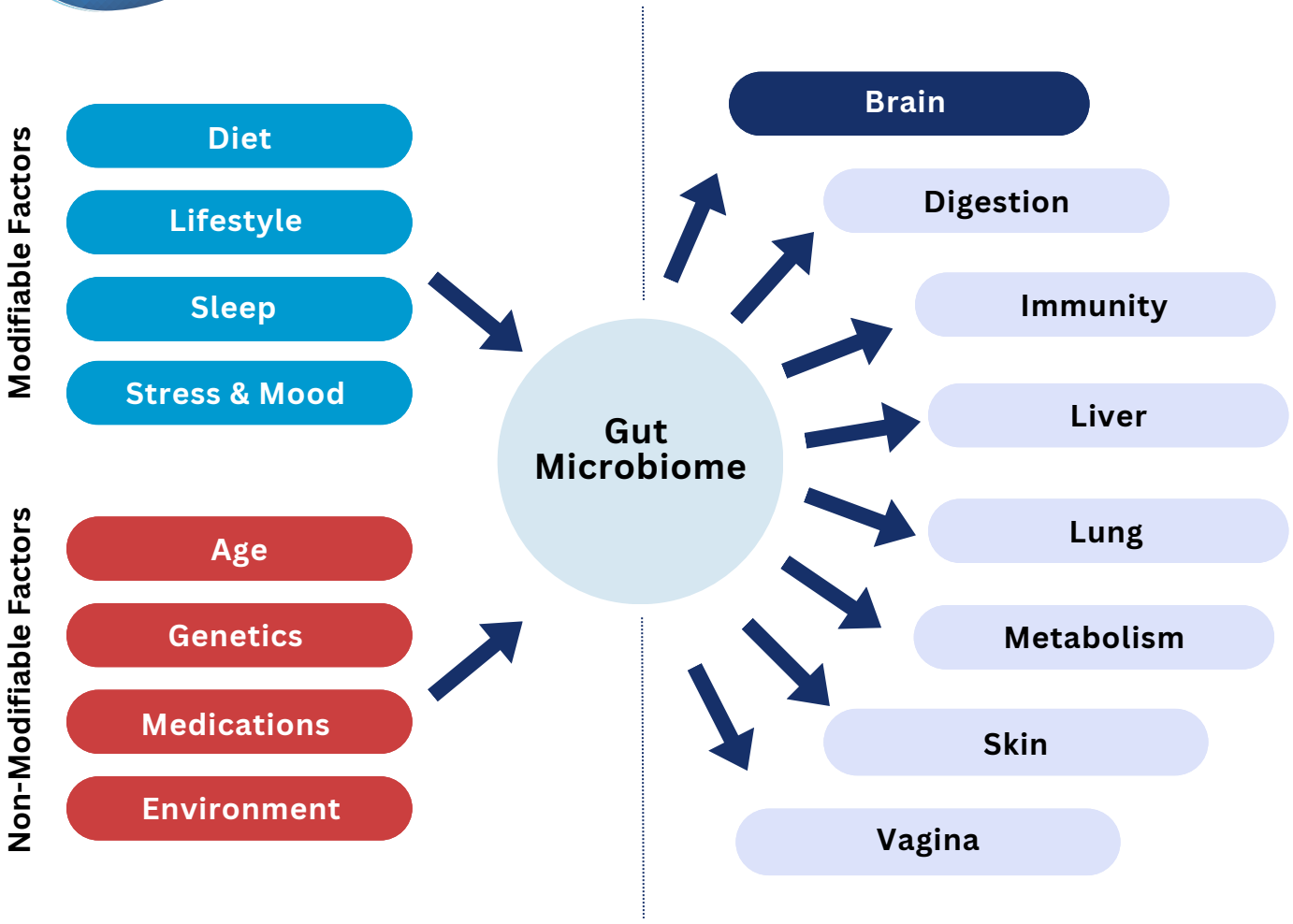
GUT-BRAIN AXIS
HCP RESOURCE

The gut microbiome could be considered as "the conductor of health", orchestrating with organs and systems in the human body, via different axes, to maintain homeostasis and optimal health.

The diagram below outlines some of the main axes whereby the gut communicates with other organs and systems in the body.



Gut Microbiome: The collection of microbes living in the digestive tract, their collective genetic material present and the metabolites that they produce.

This resource explains the relationship between the gut microbiota and brain, known as the gut-brain axis. An overview of the gut microbiota and brain is provided before diving into the gut-brain axis, outlining the pathways of communication and how to support the gut-brain axis, with a particular focus on dietary approaches.

Yakult Science - making the science of the gut microbiota easy to digest

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CONTENTS

KEY POINTS

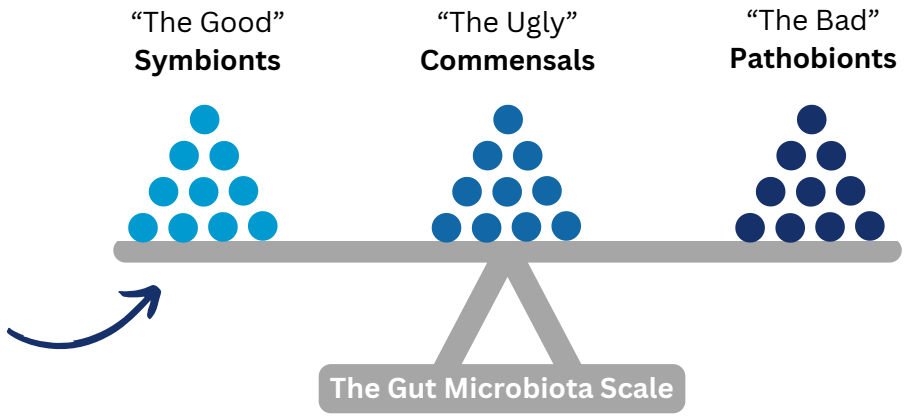
- A **bidirectional relationship** exists between the gut microbiome and the brain, known as the **gut-brain axis**.
- Communication between the gut microbiome and the brain is complicated and involves many different pathways including **endocrine, immune, metabolic** and **neurological**.
- Observational research shows a link between **gut dysbiosis** and certain neurological conditions such as **autism, psychiatric stress disorders, Alzheimer's disease** and **Parkinson's disease**.
- A **Mediterranean style diet** which is abundant in **fibre** from fruits, vegetables and wholegrains, and low in ultra-processed foods, is associated with the lowest risk of **depression** and **cognitive decline**.
- **Psychobiotics** (live microorganisms which offer mental health benefits) may have a role in the management of mental disorders, especially depression, when prescribed as an adjunct to traditional treatment (i.e., medications).
- Treatment options for disorders of the gut-brain axis (e.g., **irritable bowel syndrome**) are shifting focus not only to include dietary strategies to improve gut health, but also interventions which **target mental wellbeing** (e.g., breathwork, meditation, yoga).

THE GUT MICROBIOTA

What is the gut microbiota?

The gut microbiota is the **collection of microbes** (e.g., bacteria, archaea, fungi and viruses) living throughout the **gastrointestinal tract**. Everyone has a **unique** gut microbiota.

There is no core "healthy" microbiota that is common to all individuals. Instead, a gut microbiota is considered to be optimal when balanced (a state called **symbiosis**) and **diverse**.



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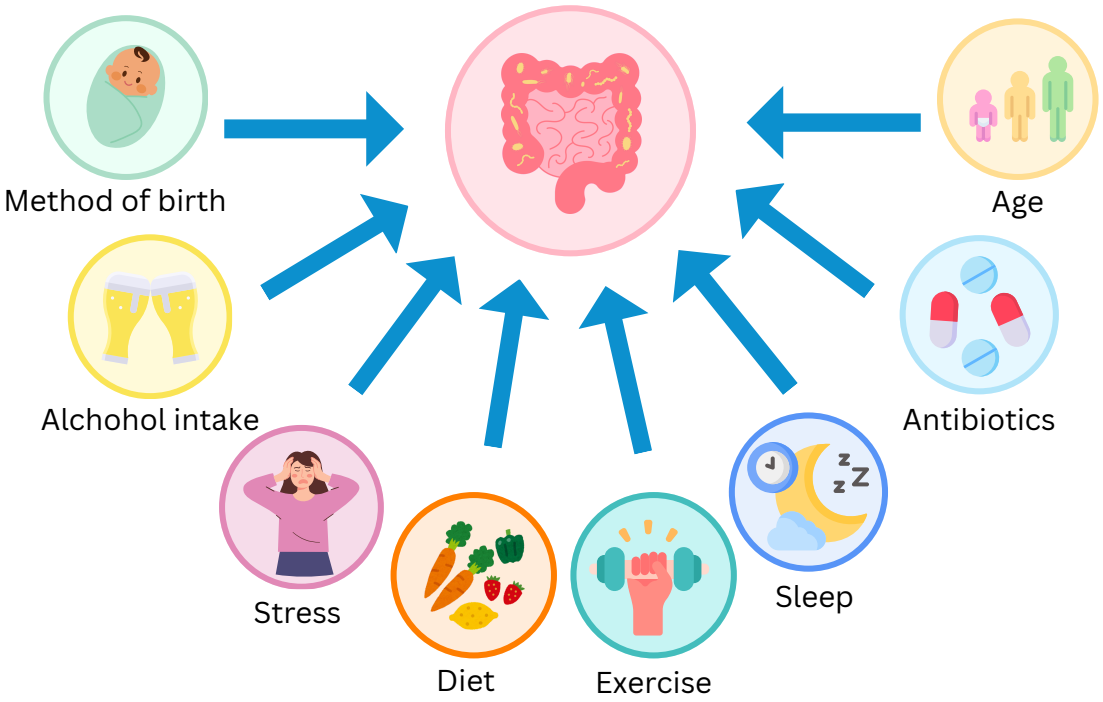
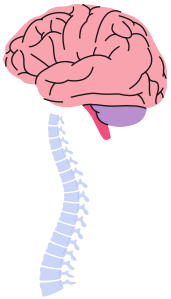
FACTORS AFFECTING GUT MICROBIOTA DIVERSITY

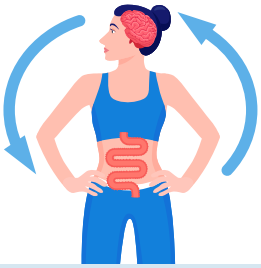


THE BRAIN

The human brain is the most complex organ in the body. It controls thought, memory, emotion, touch, motor skills, vision, breathing, temperature, hunger and every process that regulates the human body. In the adult human brain, which weighs on average 1.5kg, around 86 billion neurons form 100 trillion connections with each other.[1] Together, the brain and spinal cord that extends from it make up the central nervous system (CNS). The CNS influences and is influenced by all other body systems including the cardiovascular, endocrine, gastrointestinal and immune systems.



THE GUT-BRAIN AXIS



The gut-brain axis refers to the **bidirectional communication** between the gut and the brain. This interaction involves the **central and the enteric nervous system**, linking emotional and cognitive centres of the brain with peripheral intestinal functions.[2]

An essential part of the gut-brain axis is the **vagus nerve**. The vagus nerve originates from the medulla of the brainstem and branches in the thorax to the abdomen, **physically connecting** the gut and the brain. Communication between the gut and the brain primarily takes place via the vagus nerve.[3'4]

FACT CHECKER: "The gut is your second brain"

The facts: It is commonly said that the gut is the "second brain" but this is not entirely true. More specifically, the second brain is the enteric nervous system (ENS) - a network of around 500 million neurons embedded along the gastrointestinal (GI) tract – which is a large division of the peripheral nervous system (PNS) that can control gastrointestinal behaviour independently of central nervous system (CNS) input. The ENS connects to the vagus nerve[3] and can communicate with the brain via several neuromodulators and neurotransmitters, as well as microbial metabolites such as short-chain fatty acids (SCFAs).[4]

THE GUT-BRAIN-MICROBIOTA AXIS

Recent advances in research have described the importance of the gut microbiota in influencing the gut-brain connection. To date, the majority of research has been conducted in animal models, while the limited number of human studies have focused on psychiatric conditions.

Communication Pathways

The interaction between the microbiota and gut-brain axis appears to be bidirectional, involving signalling from gut-microbiota to brain and from brain to gut-microbiota through neural, endocrine, immune, metabolic and neurological links.[2,5]

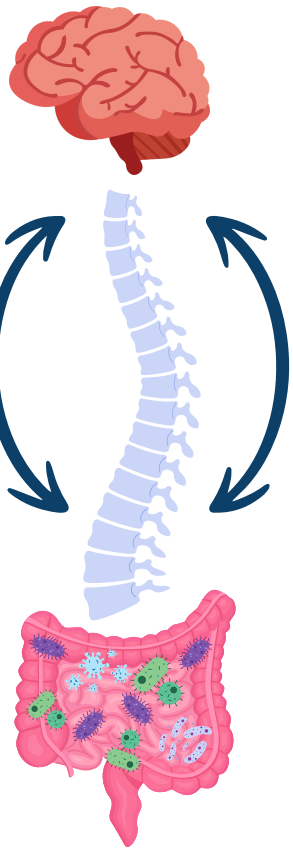
Neural pathways: This includes communication along and between the vagus nerve, the enteric nervous system and the central nervous system.[5]

Neurological compounds: The gut microbiota encourages the production of neurotransmitters responsible for mood regulation, such as tryptophan and serotonin.[5]

Endocrine system: The gut microbiota alters nutrient availability and thus influences the release of biologically active peptides from enteroendocrine cells (e.g., galanin which stimulates cortisol secretion and noradrenaline release), which in turn can affect the gut-brain axis.[5,6]

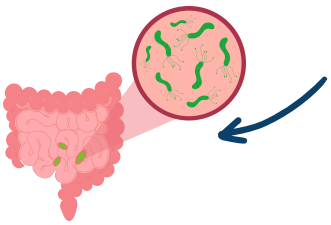
Humoral/metabolic pathway: Microbiota-derived SCFAs are able to cross the blood-brain barrier and have been shown to regulate microglia homoeostasis, which is required for proper brain development and brain tissue homoeostasis.[6,7]

Immune system: Metabolic regulation of inflammation within the GI tract is influenced by the gut microbiome, which can also impact systemic inflammation in the brain.[6]



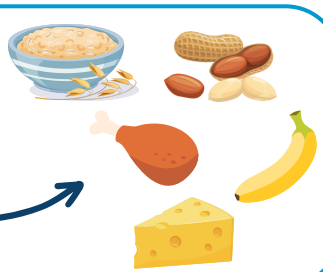
Did you know?

While it is true that approximately **95% of serotonin** (dubbed the "happy hormone") is produced in the gut,[6,8] it is unlikely that it can cross the **blood-brain barrier**.[9] Despite this, it seems that gut-produced **neurotransmitters** such as serotonin may still **indirectly** influence mood via the immune system and vagus nerve; this is an active area of research. However, **tryptophan** (an essential amino acid and the precursor molecule for serotonin) can cross this barrier, therefore indirectly modulating serotonin production and function in the brain.[10]



Gut microbes can metabolise tryptophan directly and shift its accessibility to the kynurenine pathway (an alternative metabolic route for tryptophan).[11]

Tryptophan is also found in foods such as poultry, oats, bananas, dried prunes, milk, tuna fish, cheese, bread, peanuts and chocolate.[10]



Research in a depressed mouse model has shown reduced levels of tryptophan in faeces which correlated with significantly decreased levels of *Lactobacillus*.[12] However, the exact mechanisms by which tryptophan metabolism in the gut can affect the brain remains an active area of research.

THE GUT-BRAIN AXIS THROUGHOUT LIFE

This page describes age-related and compositional changes in the gut microbiota throughout life. It outlines observational research which highlights the co-occurrence of gut disorders with different mental health conditions at key life stages.

Pregnancy

The maternal gut microbiota changes during pregnancy and differs from non-pregnant women. Maternal physical, nutritional and mental health plays a vital role in foetal development, and can contribute to the neurodevelopment of the infant with potentially long-term and multi-generational outcomes.[13]

Birth Delivery Mode

Babies born by vaginal delivery are exposed to diverse maternal microbes[14] and have been shown to have increased bifidobacteria. Evidence is mixed regarding the association between caesarean section birth and lower offspring cognitive functioning,[15,16] however many factors can influence brain development during early life.

Childhood

Excessive antibiotic usage and/or increased hygiene measures are associated with a reduction in gut microbiota diversity during childhood.[18,19]

Milk Source

Greater amounts of *Bifidobacterium* and *Bacteroides*, and lower amounts of *Streptococcus* and *Enterococcus* are seen in breastfed babies compared to those consuming formula milk.[17]

Adolescence/ Adulthood

The gut microbiota composition is determined by modifiable diet and lifestyle factors. Too little exercise, disrupted sleep, heightened stress levels and a lack of plant diversity and fibre in the diet can all negatively impact its composition and consequently the gut-brain axis. See pages 11 and 12 for more information.

Perimenopause/ Menopause

GM becomes less diverse and reflects the male gut microbiota.[20] Changes in sex hormones can cause changes to brain function.[21]

Older Adulthood

GM diversity declines with age,[22] as well as cognitive function (which may be associated, at least in part, to reduced GM composition).

Environment: GM is influenced by those you live with (including pet ownership) and those in the same household will have a more similar microbiota.[23,24] Exposures such as pollution and pathogens will also affect GM.[25–27]

See next page for information on autism, psychiatric stress disorders, Alzheimer's disease and Parkinson's disease.

GM = Gut Microbiota

LINK BETWEEN CONDITIONS AND THE GUT-BRAIN AXIS

AUTISM

Autism, also referred to as autism spectrum disorder (ASD), is a lifelong neurological and developmental disorder that affects how people interact with others, communicate, learn and behave. GI symptoms are common in those with autism.[28,29] Many studies have shown that early gut microbiota colonisation, mode of birth delivery and antibiotic use significantly affect the gut microbiome and the onset of autism.[28]

PSYCHIATRIC STRESS DISORDERS

Individuals suffering from psychiatric stress disorders, such as anxiety and depression, display gut dysbiosis.[30] Typically, the GM is characterised by a higher abundance of proinflammatory species, and lower short-chain fatty acid producing-bacteria.[30] An association exists between certain bacteria (e.g., *Eggerthella*, known to be important in the synthesis of key neurotransmitters in depression) and symptom severity.[31]

ALZHEIMER'S DISEASE (AD)

Emerging research suggests a link between AD and gut dysbiosis.[32] Patients have an increase in bacteria such as *Acinetobacter rectum* and *Bacteroides* which have been implicated in the formation of amyloid plaques in the brain - hallmark signs of AD which can disrupt communication between brain cells.[33]

PARKINSON'S DISEASE (PD)

Dysbiosis and GI symptoms are commonly observed in PD patients, affecting up to 80%, and can manifest prior to diagnosis[34,35] e.g., constipation can occur ~20 years before motor symptom onset.[36] Certain bacteria have been associated with certain PD symptoms[35,37,38] e.g., low counts of *Bifidobacterium* at onset (year 0) were associated with worsening of hallucinations after 2 years.[39]

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DEPRESSION & THE GUT-BRAIN AXIS

A **meta-analysis** of **observational studies** suggested that the **Mediterranean diet** is associated with the **lowest risk** of **depression**.[40] Nutrients abundant in this type of dietary pattern which appear to be important for supporting the gut-brain axis include **fibres**, **polyphenols** and **omega-3 fatty acids**. In contrast, poor diet quality (high intakes of 'fast food', red and processed meat, salty snacks and sweets) has been associated with a higher risk of depression.[41]

STUDY SPOTLIGHT

Transferring the Blues[42]

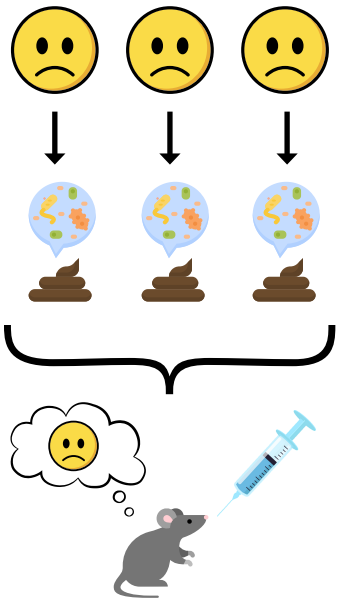
Depression is a common mental health condition, responsible for significant disability worldwide.[43,44] It is associated with an altered gut microbiota composition, richness and diversity. The 'Transferring the Blues' study was an important step forward in understanding the relationship between diet, the gut microbiome and depression.

Methods

This observational study recruited 67 participants to investigate changes in the gut microbiota and how this could influence depression symptoms:

- 34 patients with major depression
- 33 matched healthy controls

In addition, 28 rats received faecal microbiota transplantation (FMT) from 3 of the most severely depressed male patients and 3 matched healthy controls to identify how an altered gut microbiota specifically influences symptoms of depression.



Findings

- Depression was associated with decreased gut microbiota richness and diversity.
- Microbiota-depleted rats that received faecal microbiota transplants from depressed patients showed behavioural and physiological features characteristic of depression.
- Targeting the gut microbiota may be a viable strategy to support the treatment and prevention of depression.

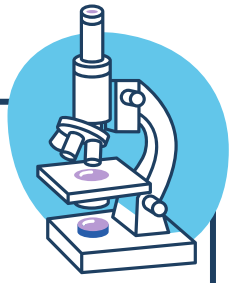
Critical Analysis

✓ Majority of depressed patients were prescribed antidepressant medication which may have altered the gut microbiota composition.

✓ Regardless of the reason for gut microbiota differences, this study provides definitive evidence that depression-associated alterations in the gut microbiome are sufficient to disrupt behavioural and physiological homeostasis.

⚠ As FMT was conducted in mice, results may have limited applicability to humans.

NUTRITIONAL PSYCHIATRY



STUDY SPOTLIGHT

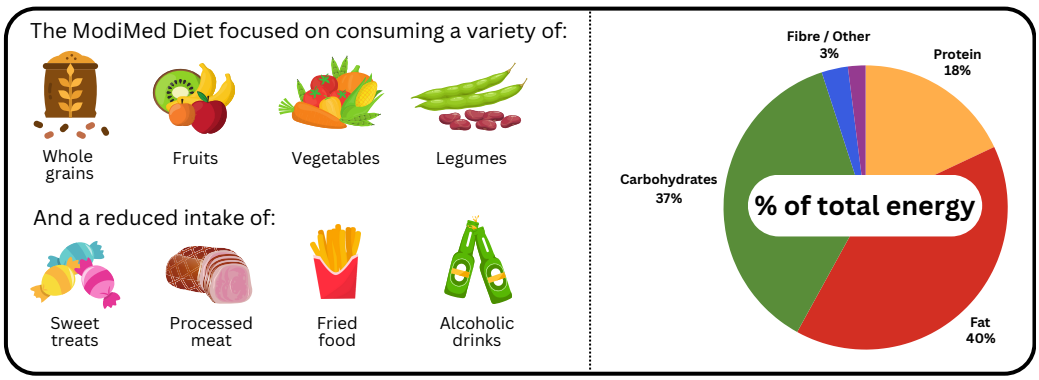
The SMILES Trial[45]

Nutritional psychiatry is a growing discipline that focuses on using food and/or food supplements as alternative, or adjunct, treatments for mental health disorders. The SMILES trial was the first of its kind to study the impact of improving diet on symptoms of depression in those with moderate to severe depression.[45]

Methods

This 12-week single-blind randomised controlled trial (RCT) investigated the efficacy of a dietary improvement programme for the treatment of depression. Sixty-seven participants with moderate to severe depression and poor diet quality were assigned to either:

- Dietary intervention consisting of 7 individual nutritional consulting sessions following a modified Mediterranean diet (n=33)
- Control intervention comprising of a social support protocol of the same visit length and schedule (n=34)



Findings

- The dietary intervention group significantly improved depression symptoms between baseline and 12 weeks compared to social support control group ($p<0.001$).
- Remission was significantly higher in the intervention group ($p=0.028$).
- At 12 weeks, the dietary intervention group had significantly lower anxiety than the social support control group ($p=0.013$).
- There was no significant difference in total mood disturbance scores between the two groups.

Critical Analysis

✓ Considered affordability of dietary intervention; participants' baseline diet cost was similar to their diet during intervention.

✓ High completion rate (94%) in the intervention group suggests acceptability of the dietary intervention to the participants.

⚠ Small sample size.

⚠ Recruitment of patients with a pre-existing 'poor' quality diet may have reduced generalisability of results.

⚠ Mechanisms of action (e.g., gut microbiota composition) were not measured and thus remain unknown.

PSYCHOBIOTICS

"Psychobiotics" is a term used by researchers to describe **live microorganisms that, when administered in adequate amounts, can confer mental health benefits**. In research settings, the term often also encompasses **prebiotics** (a substrate that is selectively utilised by host microorganisms conferring a health benefit), as well as **synbiotics** (a mixture comprising live microorganisms and substrate(s) selectively utilised by host microorganisms that confers a health benefit on the host).[46]

The administration of psychobiotics as a tool to manipulate the gut microbiome is an active area of research to identify their efficacy as an adjunct treatment in mental disorders. Below are some examples of promising human trials in this area.

THE EVIDENCE

Psychobiotics is a nascent area of research, so the evidence base is currently limited. Further studies are required in this area to investigate and explore potential mechanisms of action.

A systematic review and meta-analysis of RCTs (229 individuals randomised) looked at the effect of probiotics on patients with depression either as a supplementary or standalone treatment. There was an overall positive effect of probiotics on depressive symptoms when used as an adjunct therapy. It was concluded that probiotics are effective in reducing depressive symptoms when administered in addition to antidepressants but they do not seem to offer significant benefits when used alone.[47]

An RCT involving 40 healthy individuals found that, compared to the placebo intervention, participants who received a 4-week multispecies probiotic (*Bifidobacterium* and *Lactobacilllus* strains) had significantly reduced cognitive reactivity to sad mood (an established marker of vulnerability to depression). This result was largely accounted for by reduced rumination and aggressive thoughts. Although further research is needed, this study suggests that the intake of probiotics may help reduce negative thoughts associated with sad mood.[48]

An RCT involving 36 elderly (≥60 y) twin pairs (72 individuals), found that prebiotic consumption (comprising of inulin and fructo-oligosaccharides) for 12 weeks significantly improved cognitive function compared to placebo; specifically, those in the prebiotic arm exhibited better performance on memory and learning tests, which are used to detect early signs of Alzheimer's disease. This positive outcome was partially attributed to the increase in *Bifidobacterium*, stimulated by the prebiotic consumption.[49]

STRESS

STUDY SPOTLIGHT

Exam stress & *Lacticaseibacillus paracasei* Shirota (LcS; formerly *Lactobacillus casei* Shirota)[50]

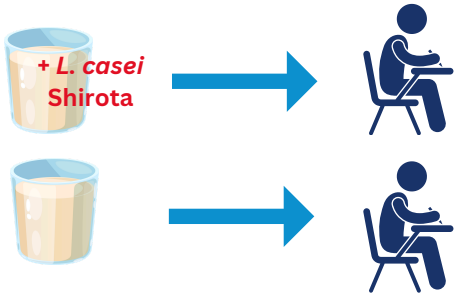
Stress can have a major influence on physical and mental health. Growing evidence suggests that the gut-brain-microbiota axis contributes to the regulation of stress both directly and indirectly.[51] This study investigated the efficacy of a probiotic on stress scores.

Methods

This double-blind, placebo-controlled trial was conducted with healthy medical students (n=47) in Japan undertaking an examination for academic advancement. For 8 weeks, until the day before the examination, participants were assigned to consume daily either:

- 100ml *L. casei* strain Shirota-fermented milk containing more than 1.0×10^{11} CFU* (n=23)
- 100ml placebo milk i.e., nonfermented milk with the same nutritional content, colour, flavour, taste and pH (n=24)

***CFU** = colony forming units i.e., a unit commonly used to indicate of the number of viable bacteria cells present in a sample.



The primary outcomes were **stress-induced abdominal dysfunction** and **feelings of stress** (measured by questionnaires). Researchers also measured **salivary stress markers** (cortisol levels) and **gut microbiota composition**.

Findings

- Consumption of *L. casei* strain Shirota, but not placebo, significantly reduced GI symptoms e.g., abdominal discomfort and pain, and straining during bowel movement.
- Salivary cortisol levels (i.e., stress marker) and and perceived levels of stress before the examination were significantly lower in the *L. casei* strain Shirota group compared baseline.
- Gut microbiota diversity was maintained in the *L. casei* strain Shirota group and was significantly higher than the control group.
- Daily consumption of probiotics, such as *L. casei* strain Shirota, preserves the diversity of the gut microbiota and may alleviate stress-related responses in healthy subjects exposed to stressful situations.

Critical analysis

✓ Compliance rates were high (99%) suggesting that simply adding a probiotic could be considered an 'easy' addition to normal dietary habits during periods of stress.

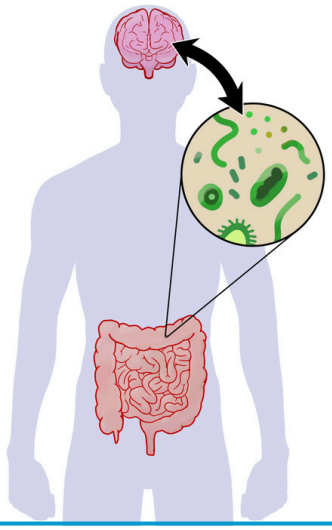
⚠ Small sample size.

⚠ Due to the complex interactions existing between probiotics and the host, the exact mechanisms of action for *L. casei* strain Shirota are still being researched.

IBS SPOTLIGHT

Irritable bowel syndrome (IBS) is a common **GI disorder** affecting approximately **5-20%** of the general population and greater prevalence is seen in females.[52] This condition is now recognised as a **dysregulation** of the **gut-brain axis**.[53] Physical symptoms include **stomach pain** or **cramps**, **bloating**, **diarrhoea** and **constipation**, and patients are shown to have **gut dysbiosis**.[54]

However, those with IBS also have a **threefold increased** likelihood of **anxiety** and **depression**,[55] and their GI symptoms appear to **worsen** during periods of **stress** and/or anxiety. When advising patients with IBS, it is important to consider not only dietary interventions but also **mental health support**.



ADVICE FROM OUR EXPERT

Dr. Alexa Duff

Clinical Psychologist

Founder of The Gut Brain Connection

@thegutbrainconnection

As a clinical psychologist specialising in supporting people with gut conditions, I would explore with patients how their early life events, current mood, and lifestyle factors such as sleep, eating patterns and exercise are impacting on their physical and mental health.

It's important that HCPs start to take an interdisciplinary approach to patient care - working together where best possible, to identify the optimal strategies to support patients presenting with gut issues.

Gut triggers that are unrelated to specific foods by Dr Alexa Duff

- Stress
- Avoiding emotions
- People pleasing
- Restrictive eating
- Constant activity
- Anxiety

SUPPORTING THE GUT-BRAIN AXIS

FOODS IN FOCUS

Emerging evidence highlights the potential for diet to support mood and mental health, via the gut-brain axis. Preliminary research emphasises the need to increase the diversity of the gut microbiome to support communication between the gut and the brain. Below are important foods and nutrients which can increase gut microbial diversity.

FIBRE

Soluble dietary fibres are fermented by the gut microbiota, producing SCFAs. SCFAs play an important role in the gut-metabolism axis. Diets high in fibre are associated with greater microbial richness and diversity.[56] Sources of fibre include fruits, vegetables, wholegrain carbohydrates, beans and lentils, nuts and seeds, herbs and spices.

PLANT DIVERSITY

Restrictive diets can starve the gut microbiota, whereas a diet focused on adding more – more plants, more variety, and more fibre – can increase gut microbial diversity. Research has shown that those who ate more than 30 different plant-based foods per week had a far more diverse gut microbiome compared to those who ate less than 10.[57]

MEDITERRANEAN DIET

The Mediterranean diet is characterised by an abundance of high-fibre plant foods and contains sources of omega-3 fatty acids, vitamin D and polyphenols, all of which have been associated with increased gut microbiota diversity.[58–64] These nutrients are also key for supporting brain health.[65] Following a Mediterranean diet has been shown to help in the prevention and treatment of certain mental conditions, including depression.[40]

FERMENTED FOODS

Fermented foods (e.g., fermented milk drinks, kimchi, sauerkraut, kombucha) can be a source of live dietary microbes and can support gut health. Human studies have shown that fermented foods increase gut microbiota diversity[66–69] and early research has demonstrated they can also improve certain brain functions, such as relational memory.[70]

For practical dietary tips, read our Diet Diversity guide via our Key Resources page

"When encouraging **more fibre** into your patients' diets, remind them to go **low and slow** - gradually increasing the amount to **avoid** uncomfortable **gut symptoms** and make sure they **stay well hydrated**".

DR EMILY PRPA

Science Manager
Yakult UK & Ireland

SUPPORTING THE GUT-BRAIN AXIS

MOVEMENT & MICROBES

Exercise, even in small amounts, offers many health benefits, including the improvement of our mental health. Exercise is a powerful stress reliever, reducing anxiety and improving mood. This is because when we exercise, our body releases 'feel good' neurotransmitters such as dopamine, serotonin and endorphin. A recent review demonstrated that exercise was 1.5x more effective at reducing mental health symptoms than traditional medication or counselling.[71]

Exercise has also shown to increase the diversity and growth of beneficial bacteria in the gut independently of other factors.[72] Therefore, in turn, exercise could help to regulate bowel movements and balance gut bacteria.[73]

Movement doesn't need to be complicated. Recommend simple ways that your patients can incorporate more regular physical activity into their daily routine. These include:

Park the car further away from the shops

Take stairs instead of escalators

Take walking meetings at work if possible

Get up and move during TV breaks

STRESS MANAGEMENT

Managing stress is crucial for maintaining a healthy mind and body. Chronic stress leads to elevated cortisol levels which can lead to anxiety, mood disturbances and low self-esteem, as well as affecting gut health[74] via:

Disrupted gut microbiota balance: Creates an environment conducive to harmful bacteria whilst inhibiting beneficial bacteria. This disruption not only impacts gut health but also negatively affects mood and energy levels over time.[74]

Altered gastrointestinal motility: Dysfunction of the nerves or muscles can cause either delayed or accelerated transit through the stomach, small intestine or colon.

Increased intestinal permeability: A weakened mucosal gut lining allows unwanted material to pass, often referred to as a "leaky gut".

These changes can often lead to digestive issues such as constipation, flatulence or diarrhoea. It can also exacerbate conditions such as IBS, which often worsens during periods of heightened stress.[75]

To help manage stress, incorporate mindfulness techniques such as breathwork, walking in nature, or yoga.

SLEEP HYGIENE

Sleep is essential for managing stress levels and supporting the gut-brain axis.[76] Aim for 7-9 hours of quality sleep each night to support your body's daily recovery and maintain balanced stress hormones. An interrupted night's sleep can disrupt our circadian rhythm and when this happens it can impact the balance of beneficial and harmful bacteria in the gut.[77]

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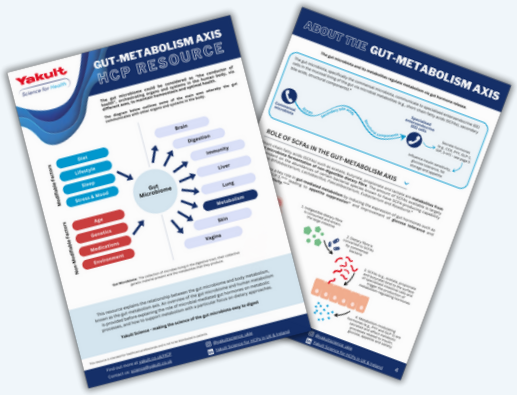

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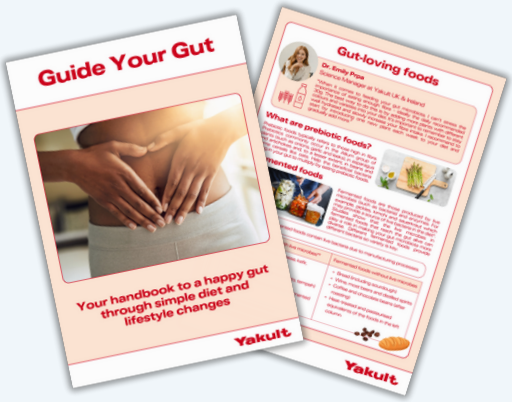

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