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Fibre & fermented foods: differential effects on the microbiota-gut-brain axis

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The ability to manipulate brain function through the communication between the microorganisms in the gastrointestinal tract and the brain along the gut-brain axis has emerged as a potential option to improve cognitive and emotional health. Dietary composition and patterns have demonstrated a robust capacity to modulate the microbiota-gut-brain axis. With their potential to possess pre-, pro-, post-, and synbiotic properties, dietary fibre and fermented foods stand out as potent shapers of the gut microbiota and subsequent signalling to the brain. Despite this potential, few studies have directly examined the mechanisms that might explain the beneficial action of dietary fibre and fermented foods on the microbiota-gut-brain axis, thus limiting insight and treatments for brain dysfunction. Herein, we evaluate the differential effects of dietary fibre and fermented foods from whole food sources on cognitive and emotional functioning. Potential mediating effects of dietary fibre and fermented foods on brain health via the microbiota-gut-brain axis are described. Although more multimodal research that combines psychological assessments and biological sampling to compare each food type is needed, the evidence accumulated to date suggests that dietary fibre, fermented foods, and/or their combination within a psychobiotic diet can be a cost-effective and convenient approach to improve cognitive and emotional functioning across the lifespan.

Keywords: Fibre: Fermented foods: Microbiota-gut-brain axis: Psychobiotics: Cognition: Emotion

Introduction

The interplay between diet and brain health is receiving ever more attention[1–3]. In tandem, over the past two decades, the importance of the bidirectional communication between the gut microbiota (bacteria, viruses, fungi, protozoa, archaea) and the brain has also surfaced, positioning this community of microorganisms as an

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accessible target to alter brain function and behaviour. It is now well-established that diet is a potent manipulator of the gut microbiota, with the capacity to alter both microbial abundance and functionality[4,5], and therefore its potential to improve brain health, is emerging as a plausible therapeutic intervention strategy[6]. While several dietary foods and patterns have been shown to modify the gut microbiota, dietary fibre and fermented foods with their capacity to act as substrates for microbial digestion and to supply live microorganisms as well as the associated enzymatically converted food components, respectively, have been identified as key modulators of the gut microbiota and subsequent signalling to the brain[7–9].

Increasing attention is now given to the concept of a diet-microbiota-gut-brain axis[7] with an appreciation that it is not just what microbes are present in the gut but what they are doing and how they interact with diet to affect host health[10]. Undigested fibre is a major energy source for the gut microbiota and short-chain fatty acids (SCFAs) that are produced upon gut microbial fermentation of fibre influence cognitive and emotional responses of the host[11,12]. Similarly, fermented foods produced through enzymatic conversion of food components by live microorganisms also house a large community of microbes at the time of consumption (e.g. kefir, kimchi)[13] that can increase gut microbiota diversity[14,15]. These new or expanded members of the gut microbiota can subsequently produce neuroactive metabolites (e.g. SCFAs, polyphenolic, tryptophan, bile, gamma-aminobutyric acid (GABA)). Intriguingly, there is a growing appreciation that, behaviourally, both food types have been shown to benefit cognitive and emotional processing[16–20], effects which are suggested to be mediated via the microbiota-gut-brain axis[19,21]. It is therefore worth evaluating the relative efficacy of fibre and fermented foods to alter brain functioning and signalling along the microbiota-gut-brain axis to inform future interventional research and move toward personalised medicine approaches for brain health management. Currently, there are very few studies investigating the biological basis explaining the beneficial actions of fibre and fermented foods[15,20]. While the studies that have been conducted provide tentative evidence of the scope of influence that fibre and fermented foods have on human health, it is clear that observational and interventional studies directly/systematically evaluating each food component on the microbiota-gut-brain axis are, in general, lacking. In this narrative review, we evaluate the differential neuroactive potential of dietary fibre and fermented foods to modulate cognitive and emotional functioning in humans. We further discuss possible pathways through which fibre and fermented foods can act on the brain *via* the microbiota-gut-brain axis. Future directions for the field and the therapeutic potential of fibre and fermented foods to improve brain health are highlighted.

Fibre

The widely-adopted definition from Codex Alimentarius defines fibre, natural and synthetic, as 'carbohydrate polymers with ten or more monomeric units, which are not hydrolysed by the endogenous enzymes'[22]. Although the terms are often used interchangeably, prebiotics only represent the subset of fibres that are 'substrates that are selectively utilised by host microorganisms conferring a health benefit'[23]. While most prebiotics are dietary fibres, not all fibres are prebiotics, nor are all prebiotics fibres. Indeed, certain polyphenols and omega-3 fatty acids also exhibit prebiotic-like effects on the gut microbiota[23,24], although not being classed as dietary fibres. Despite the large body of research examining the impact of fibre supplements on the microbiota-gut-brain axis, whole dietary approaches more closely resemble the variety of foods that humans consume each day, particularly in terms of the fibre delivery matrix. Therefore, only studies that examine fibre from dietary sources, including whole grains, legumes, fruits and vegetables, are included in this review.

Dietary fibre and the gut microbiota

Fructo- and galacto- oligosaccharides, inulin and pectins from plants, animal tissue, or food-borne microbes are important energy sources for the gut microbiota[25]. Fermentation of dietary fibre increases the abundance of *Bifidobacterium* and lactobacilli[26]. It has been proposed that roughly 30 % of the dietary fibre found in grain products is accessible for microbial metabolism, while estimates suggest that 75–90 % of fibres from fruits and vegetables are metabolised by the gut microbiota[27,28]. However, insoluble fibres can increase faecal bulk to reduce gut transit time, which also shapes gut microbiota composition[29].

The gut microbiota is highly responsive to both acute and chronic fibre intake. A dramatic restructuring of the gut microbiota, including a significant alteration of over 25 bacterial genera, was observed after just 24 hours with an intervention of reduced carbohydrate and fibre diet in participants with obesity and metabolic dysfunction-associated steatotic liver disease. Moreover, the carbohydrate reduction expectedly decreased the abundance of fibre-degrading bacteria (*Lactococcus, Eggerrthella* and *Streptococcus*), which resulted in decreased levels of SCFAs[30]. On the other hand, observational data showing a prolonged loss of fibre intake linked to the Western Diet was associated with reduced fibre-fermenting *Prevotella* strains in Asians who emigrated to the United States. Further losses in the functional capacity to degrade complex fibres were observed, alongside reductions in microbial diversity that decreased with each generation[31]. This data is consistent with observational comparisons of individuals from cultures who consistently consume higher quantities of fibre. For example, children from rural Burkina Faso whose staple diet includes larger quantities of cereals, legumes and vegetables displayed a greater abundance of bacteria from *Prevotella* and *Xylanibacter* genera and increased levels of SCFAs than European children[32]. An overall increased microbial diversity has also been detected in observational studies examining regular fibre consumers compared to non-consumers[33,34]. Fibre intake has further been shown to manipulate gut microbiota functionality.

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Fermented foods

Fermented foods are defined as 'foods made through desirable microbial growth and enzymatic conversions of food components'[35]. Fermented foods have been culturally embedded as staple foods in nearly all societies since the beginning of human civilisation. Given this rich history, it is unsurprising that the process of fermentation is often relatively simple and requires few ingredients and minimal preparation/processing to achieve an end-product that (1) naturally prolongs shelf-life, (2) reduces toxicity of raw materials and increases digestibility, and (3) alters the flavour profile[20,36]. As such, fermented foods are an affordable and convenient food option that are already available and frequently consumed in most societies.

The primary microbes involved in fermented foods include yeast, acetic acid bacteria, lactic acid bacteria (such as *Leuconostoc,* members of the former genus *Lactobacillus,* and *Streptococcus), Propionbacterium freudenreichii, Bacillus,* and moulds[36]. There is an assumption that the bacteria in fermented foods are probiotic, but this is not necessarily so. Probiotics are defined as 'live microorganisms, when administered in adequate amounts confer a health benefit on the host'[37]. Fermented foods house a rich repertoire of microorganisms (some of which have the potential to be probiotics), bioactive peptides, phytochemicals and peptides that can influence human health[20]. Predominantly by manipulating the composition and enhancing microbial diversity, fermented foods can also modulate the production of several metabolites with neuroactive potential including SCFAs, polyphenolic, tryptophan and bile metabolites[36,38,39].

Because the ingestion of live microbes may be an important aspect underlying their health effects, for the purpose of this review, we focus on fermented foods with viable microorganisms at the time of consumption (e.g. sauerkraut, kombucha, yogurt). Foods where the microorganisms have been deactivated through heat (tea, coffee, bread, cocoa) or through the addition of vinegar (pickles) are also interesting but outside of the scope of the current narrative. Due to the known direct behavioural properties resulting from acute consumption of alcoholic products (e.g. memory lapse, reduced alertness, changes in affect), alcohol is also not relevant to the current discussion.

Fermented foods and the gut microbiota

Observational reports demonstrate increased microbial diversity with fermented food consumption[40,41]. For example, a higher alpha diversity and enrichment of *Lactobacillus*, *Ruminococcus* and *Eubacterium* was reported within an observational study comparing Koreans who consume large amounts of fermented legumes and high-fibre foods, including vegetables and nuts/seeds, showing potential synergistic effects from fermented food and fibre intake combinations[40]. Differences in beta diversity were also observed in another observational study comparing regular fermented food consumers to occasional consumers, alongside increased abundances of *Faecalibacterium prausnitzii, Prevotella spp, Pseudomonas spp, Clostridiales, Enterobacteriaceae, Lachnospiraceae* and *Bacteroides spp.*[41]. Conversely, interventions with fermented foods largely fail to alter microbial diversity[8,14,42,43]. This discrepancy could be due to a number of factors that include differences in the food matrix of the fermented foods, minimal frequency/quantity of fermented foods consumed, differences in baseline microbial composition and provenance of raw materials, heterogeneity in analysis techniques with 16S rRNA sequencing being unable to capture changes at the strain level, and, importantly, diversity of the fermented foods selected for intervention. Moreover, the duration of the intervention may be insufficient to significantly shift the composition of gut microbiota, potentially masking effects detected in observational studies that reflect regular eating habits.

Cognition

Much of the evidence linking fibre intake to cognitive performance comes from observational data investigating whole dietary patterns such as fruit and vegetable intake, often in older adults. Greater fibre intake was associated with protection against age-related cognitive decline[44–49]. Similar beneficial effects of fibre on cognitive inhibition[50] and reasoning[51] have been observed in children aged 6–9 years. Observational studies linking fibre to cognitive performance in young-middle adulthood is lacking, but the fact that higher intake of fruits and vegetables at 18–30 years was associated with better executive functioning, attention and verbal memory in middle adulthood[52] provides tentative support for a potential relationship.

Evidence from randomised-controlled trials (RCTs) with fibre intervention is mixed, both in terms of study quality and results obtained. A mixed-grain dietary intervention for 9 weeks to high school students improved sustained attention and inhibition alongside increased plasma brain-derived neurotrophic factor (BDNF) levels[53]. In undergraduates, increased fibre intake from various sources improved memory performance and microbial richness[54]. In adults aged 50–70, a berry beverage containing 11 g of fibre and 795 mg of polyphenols improved working memory performance[55]. However, administration of a whole grain rye bread diet supplemented with resistant starch for 3 days to adults aged 52–70 improved mood but failed to improve cognitive performance despite increasing plasma SCFAs[56]. The discrepant RCT data suggests that habitual intake/longer intervention may be needed to capture/facilitate the effects of fibre on cognition, and that elevated BDNF levels may mediate these effects. Supporting evidence can be seen in the fact that 3 ounces of almonds consumed daily for 6 months improved learning, planning, working memory, and visual memory in adults 50–75 years old, but no effects were seen after 3 months[57]. However, this delayed effect could be due to the accumulation of tocopherol, which is also related to cognitive functioning[58,59]. The combination of fibre with other bioactives that are known to be associated with healthier eating patterns, including fatty acids and polyphenols[60–62], and also to influence cognitive function

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is problematic and requires unravelling to parse specific mechanisms of action of fibre *per se*.

The majority of RCTs with fermented food measure age-related cognitive decline in older adults to which fermented foods show a protective effect[63–68], which is also reported in the observational literature[69,70]. The RCTs conducted in older adults largely lack biological sampling with the exception of a small number of studies. In older adults, elevated serum BDNF levels from consumption of fermented soybean for 12 weeks positively correlated with improved attentional and memory performance[63], but camembert consumption for 12 weeks failed to improve memory despite an increase in serum BDNF levels[71], suggesting divergent results from different food substrates. Such heterogenous results, in general, are unsurprising given the broad definition of fibre and fermented foods.

While studies that examine the effects of fermented foods on cognitive processes in younger/middle-aged adults are sparse, the fact that a fermented milk drink altered brain activity in the frontal cortex of healthy women with a mean age of 30[72] suggests potential effects on executive functioning in addition to the observed hippocampal effects. Moreover, in younger adults aged 25–45, 4-week kefir consumption improved performance on hippocampal-dependent relational memory-associated tasks, but memory improvements were not correlated with the increased *Lactobacillus* levels[73], suggesting indirect effects of microbial signalling to the brain that were not measured in that study.

Taken together, fibre intake appears to alter attention, memory, and executive functioning when consumed habitually for longer periods across the lifespan, although more research in younger/middle-aged adults is still warranted. For older adults, in which much of the data is derived, fermented foods exhibit a protective effect against global age-related cognitive decline, both over time and following briefer interventions. Nevertheless, additional effects of fermented foods on executive functioning in younger/middle-aged adults cannot be ruled out given the lack of studies that directly assess these cognitive domains in younger populations. The effects of fermented foods on cognitive processes in children and adolescents also remain largely unknown. Moreover, the lack of functional imaging data to determine a psychophysiological interaction for each food type precludes neurological insights. Increased BDNF could be a mediating signalling pathway, but formal exploration within a statistical mediation model is needed wherein BDNF is entered as a predictor to determine if it partially or fully explains the relationship between fibre/fermented foods on cognition. By determining the mechanism or pathway through which an independent variable influences a dependent variable, mediation models are useful analyses for statistically disentangling causal factors[74]. Moreover, the relationship between peripheral and central BDNF is disputed[75], thus warranting some caution in interpreting effects on the brain. More attention is required to parse the mechanisms from the gut to the brain that are mediating such effects[76].

Emotion

Fibre consumption alone and as part of a healthy dietary pattern has been consistently associated with better mood in clinical and non-clinical populations[77–81], but a systematic review and meta-analysis concluded that the extant RCT data is inconsistent with observational findings[18]. Recently, it was shown that an 8-week diet with a high potential prebiotic content improved anxiety, stress, and sleep in adults compared to a probiotic alone, a combination of the pre- and probiotic (synbiotic), or placebo and diet as usual. The prebiotic diet comprised a minimum of 5 g/d of asparagus, garlic, onion, oats, whole wheat, chickpeas, or watermelon. The probiotic contained *Bifidobacterium bifidum* (Bb-06), *Bifidobacterium animalis* subsp. *lactis* (HNO19), *Bifidobacterium longum* (R0175), *Lactobacillus acidophilus* (La-14), *Lacticaseibacillus helveticus* (R0052), *Lacticaseibacillus casei* (Lc-11), *Lactiplantibacillus plantarum* (Lp-115), *Lacticaseibacillus rhamnosus* (HN001)[82]. The beneficial effects observed in this study may be attributed to the high dosage of prebiotic-specific foods, meriting further attention. On the other hand, very few studies have explored the link between fermented foods and emotion, indicating a gap in understanding their chronic effects on mood. In young adults, higher frequency of fermented food consumption from sources that included live and inactive fermented foods in addition to non-fermented foods (i.e. yogurt, kefir, soy beverages and foods, miso soup, sauerkraut, dark chocolate, juices that contain microalgae, pickles, tempeh, kimchi) over the previous 30 days was linked to reduced social anxiety symptoms[83]. Conversely, Karbownik *et al.* discovered that higher total fermented food consumption from a variety of sources (cheese, yogurt, kefir, soured milk, kvass, unpasteurised beer, fermented and pickled vegetables with brine) over the previous 7 days was associated with increased depressive and anxiety symptoms in healthy medical students, but the inverse was found for medical students who reported an ongoing psychiatric disorder[84]. The difference in the timeframe of the assessment of fermented foods intake and the discrepancy in criteria for fermented foods might explain the inconsistent results.

RCTs with fermented food intervention show inconsistencies in effects, which could be due to differences in participant demographics. For example, fermented dairy products for 2 weeks[73], 8 weeks[68], or 12 weeks[66] failed to improve mood in healthy adults. However, yogurt and the fermented dairy product, quark, improved mood only in participants with poor health status (i.e. immune depressed or chronic disease) and not for healthy participants[85]. Similarly, fermented kefir improved mood in participants with overweight[86] and fermented bonita fish broth improved fatigue and mood disturbances in adults with chronic fatigue[87]. Despite reports of improved mood in healthy women after consuming bonita broth for 2 weeks[88], the results collectively suggest that fermented foods have larger effects on mood for individuals with compromised health status.

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Similar to the cognitive data, prolonged fibre intake is likely to improve mood more than briefer periods of intake. Moreover, research that examines the impact of fibre and fermented foods on emotion in adolescence or middle adulthood is currently lacking. Considering this is a period with greater mood disturbances[89,90], more research is urgently needed in this population. The effects of fermented foods on mood in clinical and non-clinical populations, especially over longer time periods, is still largely unknown[91]. However, it appears that fermented foods may have preferential effects on individuals with comorbid health conditions.

Signalling pathways

Few studies incorporate the assessment of potential biological mechanisms to support behavioural findings, which precludes insight into mediating pathways. Given the demonstrated capacity for fibre and fermented foods to concurrently modulate gut microbiota and the brain, each food likely alters signalling pathways from the gut to the brain. It is now accepted that the gut microbiota communicates with the brain along several pathways including immune, hypothalamic-pituitary-adrenal (HPA) axis, serotonin/tryptophan/kynurenine, vagal, neuroendocrine, and metabolome signalling[92] (see Fig. 1). In the next sections we outline the effects of fibre and fermented foods on each communication pathway, prioritising evidence from humans where possible and available, to determine potential mechanisms of action underlying cognitive and emotional effects.

Immune system

The immune system is one of the most direct signalling pathways along the microbiota-gut-brain axis and has been shown to be fundamental in modifying behaviour across the lifespan[93–95]. The highest concentration of immune cells is located within the gastrointestinal tract, and these cells are in constant communication with the gut microbiota for the identification of potentially harmful pathogens. In mice, short-term exposure to a Western Diet deprived of fibre was sufficient to impair mucosal and systemic immunity, which created a window for opportunistic pathogens to invade intestinal tissue[96]. Re-introduction of dietary fibre re-programmed T cell metabolism and restored mucosal and systemic immunity. In this same study, healthy adults received a high-fibre diet comprised of a variety of food sources for five days before receiving a low-fibre diet for an additional five days. Not only did fibre deprivation reduce the abundance of fibre-fermenting bacteria (*Eubacterium* and bacteria from Lachnospiraceae family), but the main butyrate producer in the human microbiota (*Agathobaculum butyriciproducens* and *Faecalibacterium prausnitzii*) was decreased. These results were mirrored by a significant peripheral reduction of systemic T_H17 cells co-expressing IL-17A and TNF-α and T_H1 cells[96]. However, the anti-inflammatory effects of fibre have been shown to be moderated by baseline conditions of the individual. For example, Wastyk *et al.* found differential effects of fibre on inflammation that was dependent on baseline inflammation levels[15]. Similarly, the efficacy of soluble fibre intake on inflammation markers was reduced in individuals with lower microbiota richness[97].

In a recent RCT that compared administration of fermented yogurt against heat-treated yogurt with inactivated bacteria and two unfermented controls of whole milk and chemically acidified milk for 16 weeks to men with obesity, there were no differences between fermented yogurt and controls on c-reactive protein (CRP), IL-6, and TNF alpha levels[98]. Despite these null effects, it is worth noting the sophisticated design of this study which incorporated several different fermented controls in line with our previous recommendations to enhance the scientific quality of future research[20]. These findings are also accordant with the results of a meta-analysis on the effects of fermented food intervention on inflammation in heterogeneous cohorts, which revealed that there was no dose-dependent association between fermented food consumption and inflammatory cytokine profile (IL-6, TNF-α, CRP)[99]. However, similar to dietary fibre, these effects interact with other factors such as age and food substrate. Differential results were shown when the analysis was split between participants below or above 50 years of age, such that fermented foods enhanced CRP and IL-6 levels in participants under 50 but significantly reduced IL-6 levels in participants over 50. Fermented foods decreased TNF-α levels in both age groups. The authors suggested the moderating effects of age are likely due to increased inflammation associated with aging. Furthermore, subgroup analyses of fermented dairy products demonstrated a reduction in CRP and elevation in IFN-γ, and no effect on other inflammatory markers (IL-10, IL-6 and Il-12)[99]. This may explain the anti-inflammatory effects observed following a varied, but predominantly yogurt, 10-week dietary intervention in healthy adults[15]. Pooling fermented foods for a meta-analysis likely obscures physiological effects of each food individually given their diverse substrate nature, bioactive profile, and microbial consortia that they host.

Hypothalamic-pituitary-adrenal (HPA) axis and stress

The HPA axis and its hormone, cortisol, is activated in response to acute and chronic stress and has been shown to be crucially regulated by the microbiota-gut-brain axis[100–102]. Germ-free rodents, deprived of exposure to microorganisms at birth and reared in sterile environments, display exaggerated HPA axis responsiveness to stressors compared to colonised controls[103–106], and *Bifidobacterium infantis* administration reverses this response in a time-window dependent manner[103]. Additionally, administration of strains of *Lactobacillus* and *Bifidobacterium* has been shown to attenuate anxiety and depressive-like behaviour brought about by early-life stress[107,108], indicating a key signalling pathway from the gut to the brain[92].

In humans, responses to stressors can be evaluated from naturally occurring acute and chronic stressors to provide greater generalisability. Conversely, experimental induction of acute stress in a laboratory setting has the

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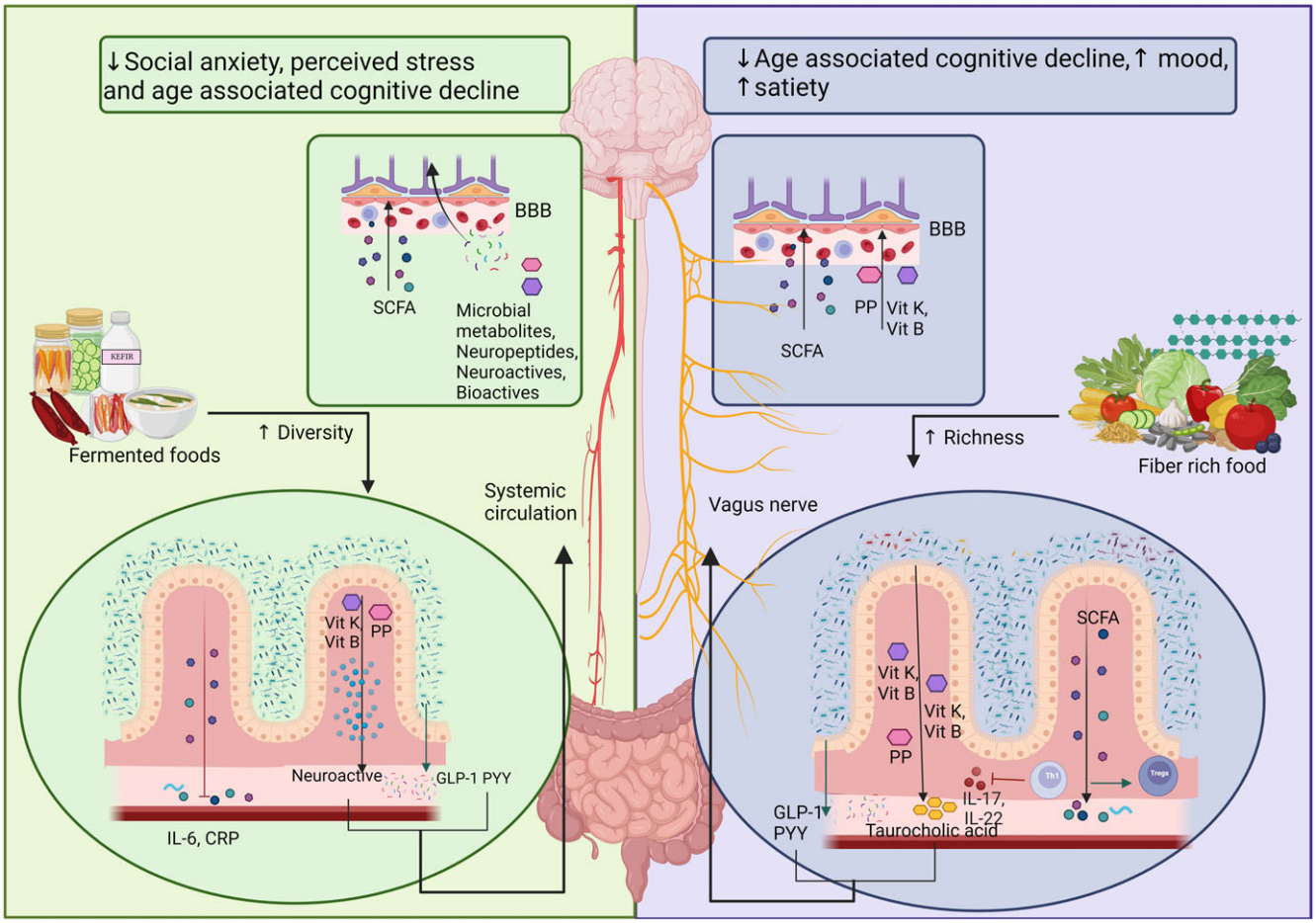

Fig. 1. Fermented foods are rich in microorganisms, bioactive peptides, phytochemicals, and peptides that can modulate brain function through enhancing microbial diversity leading to an enrichment of diverse microbial metabolites. Dietary fibre increases microbial richness, and neuroactive SCFAs are produced as a result of microbial fermentation of dietary fibre. Both fermented foods and fibre support intestinal and BBB integrity to prevent peripheral and central inflammation for optimal cognitive and emotional functioning. BBB: blood-brain barrier. GLP-1: glucagon-like peptide 1. IL: interleukin. PP: polyphenol. PYY: peptide YY. SCFA: short-chain fatty acid. Vit K, B: Vitamin K and B. Created with BioRender.com.

advantage of reducing extraneous factors, but insights into chronic stress cannot be gained[109]. Reductions in salivary cortisol levels from fermented milk with *Lacticaseibacillus casei* strain Shirota[110,111], but not from *Lactobacillus casei* DN-114001 fermented milk[112], have been observed in students undergoing academic exams and in school-aged students consuming a West African fermented milk product containing sugar and millet[113]. Despite this encouraging evidence, more studies are needed that assess the impact of non-dairy fermented foods on acute and chronic stress in heterogeneous populations including older aged adults and patients with clinical stress disorders.

Much of the evidence for a link between dietary fibre and cortisol comes from observational or RCT studies that examine dietary patterns as opposed to fibre alone. For example, acute intake of low-fibre/high-sugar meal to ethnic minority adolescents with obesity was related to elevated cortisol levels compared to a low-sugar/high-fibre meal[114]. Chronic adherence to a healthy diet rich in fibrous foods and polyunsaturated fats decreased cortisol levels in response to an acute laboratory stressor in women with overweight/obesity[115]. Intriguingly, sweet, fatty and snack food consumption frequency was positively linked to cortisol levels in a large sample of children aged 5–10, but fruit and vegetable intake had no effect[116]. Combined, these results suggest that the negative effects of high-fat/sugar foods may have a greater impact on cortisol levels than from fibre alone[117]. While dietary patterns more closely resemble actual eating patterns, specificity in determining the mechanism of action of the efficacious compound is needed to determine if the effects observed are due to fibre or polyunsaturated fat intake.

Vagus nerve

The vagus nerve is the most direct pathway linking the gut to the brain[118]. Interestingly, specific probiotic bacteria, such as *Limosilactobacillus reuteri* and *Lacticaseibacillus rhamnosus,* that are present in some fermented foods have demonstrated dependency on vagal signalling to exert effects on the brain[119–121]. Similarly, SCFAs have been shown to stimulate vagal signalling[122,123], suggesting another pathway through which fibre influences cognition.

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In rodents, a high-fat, high-sugar carbohydrate diet impaired vagus nerve signalling of satiety[124], and administration of potato-derived resistant starch inhibits remodelling of vagal satiety signalling from a high-fat diet[125].

Short-chain fatty acids

Microbial fermentation of undigested dietary fibre stimulates the formation of organic acids (lactic, succinic acid) and SCFAs (acetate, propionate, and butyrate). There are several pathways through which SCFAs influence brain activity, indicating the prominence of this pathway between fibre intake and the brain. First, SCFAs can modulate concentrations of neurotransmitters (e.g. GABA, serotonin, glutamate) and neurotropic factors[126] that are directly involved in cognitive and emotional processes. Through supporting the intestinal and blood-brain barrier (BBB), SCFAs protect against neuroinflammation[11,127]. Finally, a combination of SCFAs (acetate, propionate, and butyrate), but not butyrate alone[128], alters the HPA axis to attenuate stress-induced cortisol increases[129], suggesting synergistic effects of different SCFAs on stress. Fermented foods have also been shown to alter SCFAs. For example, Spanish residents who consumed greater amounts of cheese had higher levels of all SCFAs[130]. However, given that SCFAs are produced as a result of fibre fermentation, fibre is likely to have stronger effect on concentrations than fermented foods.

Other signalling pathways

Enteroendocrine. Enteroendocrine L cells within the intestinal epithelial cells secrete glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) in the postprandial state. Beyond their effects on satiety, gut-derived peptides GLP-1 and PYY have be linked to cognitive and emotional processing[131,132]. Short- and long-term dietary fibre intake concurrently increases self-report feelings of satiety and the release of gut peptides GLP-1 and PYY[133–135]. Moreover, SCFAs can alter the production of GLP-1 and PYY, indicating indirect pathways[136]. GLP-1 can also be stimulated by certain *Lactobacillus* strains present in fermented foods[137], but further research is needed that assesses GLP-1 and PYY release from whole foods in human participants.

Bile acids. Primary bile acids that are formed in the liver from cholesterol breakdown are further transformed into secondary bile acids by gut microbiota[138]. Bile acids can cross the blood-brain barrier to influence brain function. Indeed, altered bile acid profiles have been shown in mild cognitive impairment and Alzheimer's Disease[139,140], but bile acids have also shown neuroprotective effects on the brain in preclinical models[141]. The binding of dietary fibre to conjugated bile acids prior to metabolism by the gut microbiota hints at the connection between dietary intake and microbial metabolites[142]. Indeed, increased secondary bile acid, taurolithocholic acid, was observed following a four-week diet high in whole grains, legumes, fruits, and vegetables in healthy adults[143]. Although the relationship between fermented foods and bile acids is less established, fermented milk kefir increased secondary bile acids that were decreased from high-fat diet in rats[144].

Other metabolites

Polyphenols and polyamines. Fibrous and fermented foods are rich sources of polyphenols, and fermentation of plant and vegetables through lactic acid bacteria enhances the conversion of phenolic compounds to biologically active metabolites leading to an increase the production of phenolic metabolites[145,146]. Moreover, polyamines (spermine, spermidine and putrescine), which are also produced by the gut microbiota and affect the brain[147], are found in plant-derived foods linked to phenolic compounds[148,149]. Gut microbiota utilisation of polyphenols results in phenolic compounds, which has shown associations with cognitive resilience in rats[150]. As such, it is still largely unknown if polyphenols in fibrous and fermented foods are driving their beneficial impact on health.

Neurotransmitters. The gut microbiota indirectly and directly stimulates the production of neurotransmitters to influence central nervous system activity. There is a growing appreciation that tryptophan and its metabolic pathways to serotonin or kynurenine can be key signalling pathways within the microbiota-gut-brain axis[151–153]. Although the gut produces the majority of serotonin[154], it is unable to cross the BBB directly. However, dietary-derived tryptophan is absorbed by the gut and then transported, along with its metabolite kynurenine, to the brain to influence behaviour[155]. A strain of *Bifidobacterium infantis,* a bacterium present in fermented foods, has been shown to elevate plasma tryptophan levels to increase supply to the central nervous system for serotonin production[108]. Evidence for neuromodulatory capacity of dietary fibre and fermented foods in humans is sparse. One study showed that *Lacticaseibacillus casei* fermented milk product consumption for 8 weeks increased faecal serotonin and decreased gastrointestinal distress without altering serum tryptophan or kynurenine levels[111]. High dietary fibre intake positively correlates with indolepropionic acid, a microbial metabolite of tryptophan[156], and administration of whole grain rye lowered plasma serotonin concentrations in healthy adults[157].

Like serotonin, dopamine produced within the gut[158] cannot cross the BBB, but its precursor L-3,4-dihydroxyphenylalanine (L-DOPA) can via large neutral amino acid transporters[159]. Given the known relationship between dopamine and cognitive and emotional processing[160], and the fact that hyper-palatable foods deprived of fibre consumed chronically blunts central dopaminergic activity[161], it is necessary to understand how the gut microbiota and brain communicate through food-induced/microbiota mediated alteration of peripheral and central dopamine.

The primary inhibitory neurotransmitter, GABA, plays a key role in affective and cognitive processing[162,163]. GABA is synthesised by bacterial strains found in fermented

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foods[164,165], and fermented foods that contain high levels of lactobacilli frequently also contain millimolar levels of GABA[166]. Intriguingly, fermentation by *Lactiplantibacillus plantarum* VTT E-133328 of faba bean flour enhanced GABA levels of the faba bean flour[167], indicating additive effects from fermenting high-fibre foods. Notably, the ability of GABA to cross the BBB in appreciable quantities is disputed and further research in warranted to understand the contribution of peripheral *v.* central mechanisms[168].

The cholinergic neurotransmitter, acetylcholine, is found in both the central and peripheral nervous system. Acetylcholine is highly implicated in shaping emotional and cognitive processes[169]. Several bacteria commonly found in fermented foods produce acetylcholine[170], demonstrating the potential for fermented food interventions to modulate peripheral acetylcholine and possibly its signalling to the brain. It was recently shown that a cafeteria diet deficient in dietary fibre impaired hippocampal-dependent memory and hippocampal acetylcholine signalling in rats[171]. It will be interesting to test whether fibrous or fermented foods can rescue deficits in acetylcholinergic signalling induced by the Western Diet.

Vitamins and minerals. The effects of vitamin and mineral deficiencies on cognitive and emotional health are well-defined[172]. Vitamin K and several B vitamins are produced by gut microbiota and host intake of these vitamins increases microbial diversity and richness, alongside an increase in the production of SCFAs[173]. Dietary fibre and substrates used for fermentation are rich in vitamins, and fermentation further increases the abundance of vitamins[174]. Similarly, minerals, such as magnesium and zinc found in both fibrous and fermented foods, have limited bioavailability when obtained from vegetable sources due to the presence of phytates and oxalates[175], which form complexes with minerals and limit their absorption. Fermentation through different microorganisms improves their bioavailability and absorption by breaking down phytate and oxalate complexes with minerals[176,177]. Like polyphenols, more granularity is needed to understand mechanisms of action specific to the vitamin and mineral content present in fibrous and fermented foods.

Future directions

In addition to evaluating the unique effects of fermented foods or fibre on the microbiota-gut-brain axis, we have highlighted several gaps in the literature that are summarised in Fig. 2 and described herein.

A review of the cognitive and emotional literature has emphasised the need for multimodal outcomes that assess behavioural changes on a full battery of cognitive tasks and self-report measures of affect in addition to biological samples within the same study design. To the best of our knowledge, only two studies directly assess the impact of fermented foods on brain functioning, and no studies used imaging techniques to study the neurological effects of fibre in humans. Combined methodology will shed light on the biopsychological mechanisms necessary to inform the development and selection of potential psychobiotic treatments.

We continue to know very little about how genetic backgrounds moderate the effects of each food type on gut-brain signalling. For example, some individuals exhibit differences in the metabolism of fermentation byproducts including biogenic amines such as histamine, which can indirectly affect cognitive and emotional processing through physical side effects and alterations of arousal[178]. Alternatively, fermented foods can also indirectly improve brain activity through enhancing digestibility in individuals with certain food intolerances by, for example, converting lactose into lactic acid. Future studies should investigate how individuals from different populations and genetic backgrounds respond to interventions with fibre or fermented foods. Baseline gut microbiota composition and functionality is also highly individual, and baseline differences in the fermentation and/or colonic absorption of fibre can impact butyrate production[26,179]. Employment of a crossover design, where each participant serves as their own control, is a possible solution to this confound. It is imperative, however, to counterbalance experimental arms in a crossover design and include a washout period to ensure the absence of prolonged effects on the gut microbiota that can spillover into the next experimental arm. The duration of the intervention should also be prolonged, because effects of fibre on cognition were observed at six months, but not three months, which may explain the discrepancies between observational and interventional data[57]. It is likely that longer interventions are needed in healthy populations for which changes may be small in effect size. Longer interventions are also useful to allow for tolerance to a high-fibre and/or fermented food diet that may initially cause gastric distress and therefore affect cognitive/emotional measures. Testing in healthy populations may further necessitate selection of behavioural measures that can capture small changes alongside utilisation of next generation sequencing of the microbiota and metabolome (e.g. shotgun metagenomics) to detect resolution at the strain level alongside functional changes[180]. Moreover, biomarkers are needed to identify food consumption patterns and their potential downstream metabolites that are produced as a consequence of intake and can affect the overall health of the consumer[181]. Throughout the intervention, longitudinal captures of the gut microbiota via repeat faecal sampling can provide valuable information about the time course of effects.

A granular understanding of specific fibre subtypes on health outcomes is needed for personalised/precision approaches. However, the fact that fibrous foods can simultaneously comprise fermentable soluble and insoluble fibre provides a challenge. Collaboration with bioinformaticians to establish an open-source database that catalogues the constituents of each fibre is needed to advance mechanistic insight. More specificity is similarly required for fermented foods. There are several studies that evaluate the effects of singular fermented foods, but heterogeneity in the participants, length of the intervention, and outcomes limits insights gained from aggregating data[21]. In an RCT where participants consumed a variety of fermented foods,

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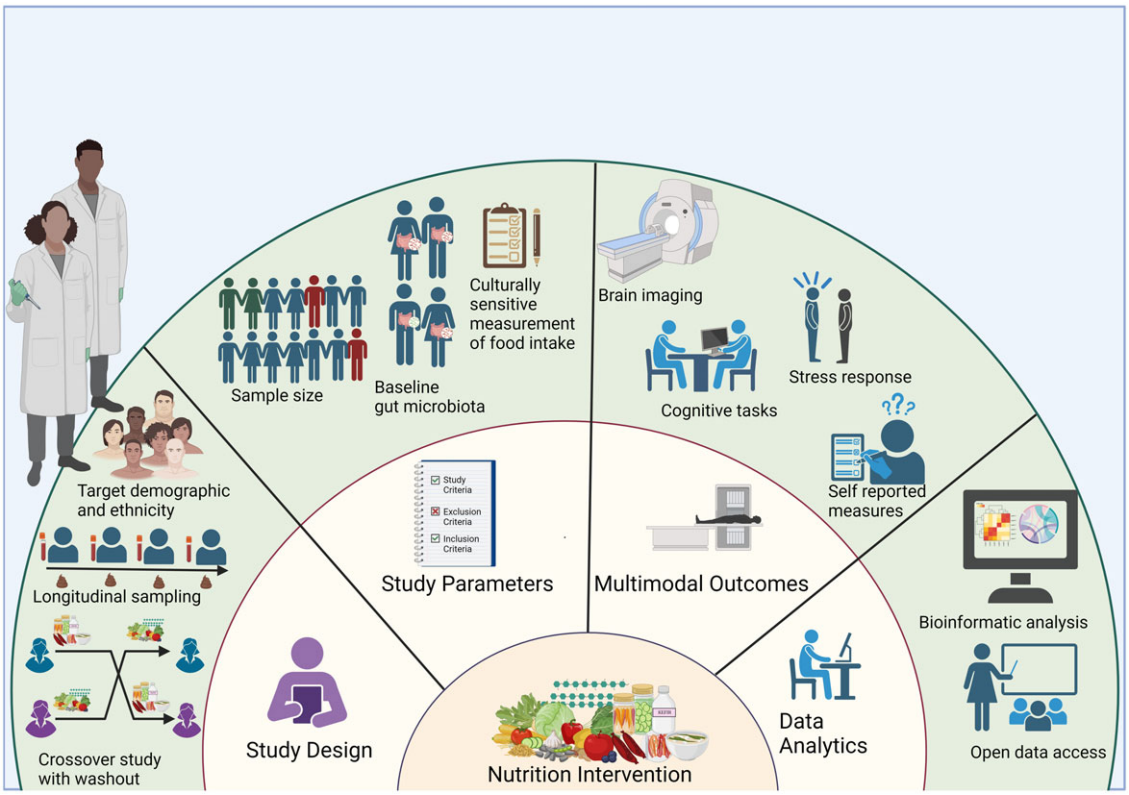

Fig. 2. Potential approaches to address challenges in nutrition studies for the microbiota-gut-brain axis. Created with BioRender.com.

a stronger correlation to alpha diversity from yogurt and vegetable brine drink consumption was observed, but this could be due to the higher consumptions rates of these items relative to the other fermented food types (kefir, cottage cheese, kombucha, and fermented vegetables)[15]. Exploitation of large datasets from individuals who consume a variety of fermented foods is needed to avoid floor effects and to achieve adequate statistical power required to determine which fermented foods are superior in modulating brain activity. It is worth noting that metagenomics revealed that, of those studied, water kefirs, sauerkrauts, and kvasses contained the greatest concentration of potential health-associated gene clusters[182]. Combining *in silico* methods with functional behavioural readouts is a promising approach to identify top-performing fermented foods to improve neurobehaviour. Another limitation in the isolation of specific fermented foods is the lack of validated, culturally sensitive and/or feasible tools to measure fermented food intake[183,184]. Specifically, fermented foods are currently assessed via unvalidated self-report measures of frequency or through self- or dietitian-led food logging or food recall, which is onerous for the participant and/or the researcher.

Towards new psychobiotic therapies

To date, only one study has directly compared the differential effects of fibre and fermented foods in humans within the same experimental design[15]. In this study, healthy adults were randomly allocated to consume a high quantity of a variety of fibrous foods (n=18) or fermented foods (n=18) for 10 weeks with no control group. Distinct effects on the gut microbiome were found such that fibre altered microbial functionality by decreasing the production of branched-chain fatty acids (isobutyric, isovaleric, valeric acid), while fermented foods increased alpha diversity. Fermented foods further reduced inflammatory markers, while fibre inflammatory effects were person-dependent. Unexpectedly, no differences were observed on self-reported perceived stress, wellbeing, fatigue, or cognition[15], but this could be due to a reliance on self-report measures of cognitive performance and the small sample size that obscured effects.

The results from Wastyk *et al.* suggested potential additive effects from combining fermented and fibrous foods on the microbiota-gut-brain axis[15]. When combined with fermented foods, fibre can enhance the colonisation, survival and function of the microbes within fermented foods and from host microbes[185]. Recently, we have shown in our own lab that a combined diet rich in fibre and fermented foods from a variety of food sources for four weeks improved perceived stress in a dose-dependent manner in healthy adults compared to a healthy diet in line with Irish dietary guidelines[8]. However, the combined diet had only subtle effects on gut microbiota composition and local gastrointestinal functional outputs, but this could be due the short duration of the intervention. Similarly, an inulin-enriched fermented yogurt decreased self-report scores of anxiety and depression in menopausal women compared to yogurt alone[186]. Future work should

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investigate whether consuming fermented and fibrous foods within the same meal elicits additive benefits, both acutely and chronically. The collective data provides support for the use of psychobiotics[187], as a combination of pre-, pro-, post-, and/or synbiotics, to treat disorders related to dysfunction in cognitive and/or emotional processes. Psychobiotics have already demonstrated efficacy in attenuating depressive symptoms[188] and improving cognition in healthy populations[189] and populations with cognitive impairments[190], but more research with whole-food interventions in healthy and clinical populations is needed.

Conclusion

Taken together, both fibre and fermented foods exert protective effects on cognitive and emotional processes. Although only one study has investigated the differential mechanisms of fibre and fermented foods on the microbiota-gut-brain axis[15], there is a growing interest in understanding the role of the gut microbiota underlying dietary patterns that have been shown to alter central nervous system processes[191]. Such advancements are essential for development of future therapeutics to treat brain dysfunction.

In considering future therapeutics, the challenge in consuming high-fibre foods is reflected by reports of inadequate consumption of fibre in nearly all Western societies[192,193]. For some, fermented foods could be an alternative solution for individuals who struggle to consume dietary fibre due to issues with taste and/or tolerance, for example. It is worth highlighting the encouraging work currently underway by Jeff Gordon and colleagues. In this pioneering work, Gordon *et al.* aims to treat cognitive dysfunction in children brought upon by malnutrition to the gut microbiota in early life by fibrous food formulations that are culturally appropriate, environmentally sustainable, and affordable to produce[194–196]. This work suggests that the inexpensive and ubiquitous nature of fibre and fermented foods is a viable means of targeting brain health, at least partially via the gut microbiota, to ensure optimal functioning across all stages of life.

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Author contributions

Authors ES and JFC were responsible for the design, and ES drafted the article. Authors ES, RB, AF, PDC, GC and JFC assisted in the interpretation and revision of the content.

Competing interests

Author ES has received honorarium from Janssen Sciences Ireland UC. PC is a co-founder and is the CTO of SeqBiome Ltd. and also serves as the Field Chief Editor for Frontiers in Microbiology. He has also been occasionally paid, or received hospitality, to deliver talks on his research. Research in the Cotter laboratory has been funded by Danone, PepsiCo, Friesland Campina and the PrecisionBiotics Group. GC has received honoraria from Janssen, Probi and Apsen as an invited speaker, is in receipt of research funding from Pharmavite, Reckitt, Tate and Lyle, Nestle and Fonterra, and has received payments as a consultant from Yakult, Zentiva and Heel Pharmaceuticals. JFC has received research funding from 4D Pharma, Cremo, Dupont, Mead Johnson, Nutricia and Pharmavite; has been an invited speaker at meetings organised by Alimentary Health, Alkermes, Ordesa, and Yakult; and has served as a consultant for Alkermes and Nestle.

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