REVIEW

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Diet and the microbiota–gut–brain-axis: a primer for clinical nutrition

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Purpose of review
Diet is an essential modulator of the microbiota–gut–brain communication in health and disease. Consequently, diet-induced microbiome states can impact brain health and behaviour. The integration of microbiome into clinical nutrition perspectives of brain health is sparse. This review will thus focus on emerging evidence of microbiome-targeted dietary approaches with the potential to improve brain disorders.

Recent findings
Research in this field is evolving toward randomized controlled trials using dietary interventions with the potential to modulate pathways of the microbiota–gut–brain-axis. Although most studies included small cohorts, the beneficial effects of Mediterranean-like diets on symptoms of depression or fermented foods on the immune function of healthy individuals shed light on how this research line can grow. With a clinical nutrition lens, we highlight several methodological limitations and knowledge gaps, including the quality of dietary intake information, the design of dietary interventions, and missing behavioural outcomes.

Summary
Findings in diet–microbiome–brain studies can have groundbreaking implications in clinical nutrition practice and research. Modulating brain processes through diet via the gut microbiota raises numerous possibilities. Novel dietary interventions targeting the microbiota–gut–brain-axis can offer various options to prevent and treat health problems such as mental disorders. Furthermore, knowledge in this field will improve current nutritional guidelines for disease prevention.

Keywords
clinical nutrition, diet, mental health, microbiota–gut–brain-axis

INTRODUCTION

The gut microbiota refers to the trillions of microorganisms residing within the gut, with the microbiome referring to the full collection of genes of these gut microbes. It is now established that this community of bacteria is an essential determinant of key set points across multiple aspects of human physiology [1], including critical functions in energy metabolism [2▪▪] and immunity [3▪▪], extending from gastrointestinal health to brain function and behaviour [1,4,5,6▪]. A central question is whether 'feeding the microbiome' modulates brain function and human behaviour [7]. The beneficial effects of diet can be moderated or mediated via processes involving the communication pathways between the gut microbiome and the brain (i.e., the microbiota–gut–brain-axis) [8].

Although clinical evidence is limited, recent systematic reviews and meta-analyses of the available evidence have shed light on microbiota signatures in psychiatric disorders [9,10▪▪,11,12]. These findings led to novel research in microbiome-targeted therapies termed 'psychobiotics', including administration of live organisms (i.e., prebiotics, synbiotics, postbiotics), faecal microbial transplants, and dietary interventions to reshape microbiome composition and function to a protective profile with beneficial effects on brain and behaviour [7,13,14]. Among psychobiotic therapies, the administration of probiotic organisms (mostly *Bifidobacterium* and

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KEY POINTS

- The microbiota–gut–brain-axis comprises several pathways and mechanisms prone to dietary modulation and is of vital interest in clinical nutrition.
- A healthy dietary pattern with varied sources of fibres, phytochemicals and beneficial live bacteria is health-promoting through physiological modulation of the microbiota–gut–brain-axis.
- A western-like diet can lead to altered microbiota composition and low-grade systemic inflammation, as observed in mental illness.
- The use of randomized controlled trials to test microbiome–target dietary approaches with the potential to improve brain disorders is increasing.
- Despite promising findings, methodological limitations in diet–microbiome–brain studies remain to be addressed.

Lactobacillus strains, alone or combined) has been the most tested, for example, in clinical depression [14]. In contrast, dietary therapies, either using specific dietary factors (e.g., dietary fibre supplements) or whole dietary interventions (e.g., Mediterranean diet), are much less studied in terms of their impact on the gut microbiome, at least in part, due to their methodological challenges. Compared with other psychobiotic interventions, the effect of diet is ubiquitous, extending across the entire lifespan with implications for neurodevelopment and neurodegeneration [7,13]. Therefore, modulating the microbiota–gut–brain-axis through diet is a promising approach to preventing and treating mental health disorders. However, dietary gut microbiota–target interventions are in their early stage of research. Although more randomized clinical trials (RCTs) are emerging, it is crucial to address methodological limitations inherent to dietary intervention studies and collect high-quality microbiome, brain, and behavioural data simultaneously. Thus, this opinion review will focus on recent studies that used dietary gut microbiota–target interventions, emphasizing those with behavioural data in the context of mental health. In addition, we will discuss recommendations for establishing more informative and robust dietary assessment protocols and interventions in diet–microbiome studies.

THE MICROBIOTA–GUT–BRAIN-AXIS

There are many pathways through which the gut–microbiota communicates with the brain that are prone to dietary modulation [1,5,7,13,15,16▪]. Although most of this knowledge comes from preclinical studies, there is emerging interest in translating diet–microbiome–brain findings into clinical research [7,12,13,16▪]. The bidirectional communication between the gut microbiome and the brain, known as the microbiota–gut–brain-axis, comprises neuroendocrine-immune pathways [15]. The most studied microbial-derived metabolites are short-chain fatty acids (SCFAs – acetate, propionate, and butyrate), resulting from microbial processing of dietary indigestible fibres [15,17]. SCFAs act on enteroendocrine L cells secreting glucagon-like peptide-1 (GLP-1) and peptide Y.Y. (PYY). These anorexigenic peptides act on hypothalamic centres to control feeding behaviour and energy balance [5,15,18,19]. Additionally, bacteria-derived secondary bile acids and bacterial lipopolysaccharide (LPS) can enhance GLP-1 secretion in L cells. SCFAs also have immune functions, for example, by promoting host intestinal barrier integrity (e.g., stimulation of mucus production and tight junction assembly) [15]. Other actions of SCFAs include regulating the suppression of cytokine production from myeloid cells and differentiating T regulatory and T helper cell differentiation [15].

Gut microbes synthesize key neuroactive molecules such as the γ-aminobutyric acid (GABA), catecholamines (noradrenaline, norepinephrine, dopamine), serotonin (5-HT) and tryptophan metabolites and precursors. However, the relative effects of bacterial-derived catecholamines in host physiology are mainly unknown [5,15,18,19]. Gut bacteria can convert neurotransmitters precursors into active forms, such as the amino acid glutamate to GABA by *Escherichia* spp., while *Lactobacillus* spp. can stimulate the conversion of dietary tryptophan into 5-HT by enterochromaffin cells [15]. These neuroactive molecules can interact with the autonomic nervous system or stimulate vagal sensory neurons in the gut leading to neuronal activation in the *nucleus tractus solitarius* (NTS) [5,15,18,19]. The NTS then conveys information to other brain structures, such as the hypothalamus, nucleus accumbens, and ventral tegmental area, thus controlling homeostatic and reward-related feeding behaviour [5,15,18,19].

The composition of the diet can impact these pathways through several factors [16▪] (Fig. 1). For example, a healthy diet (with varied sources of dietary fibre [20▪,21], phytochemicals [22], or live bacteria [3▪▪,23]) can promote increased microbial diversity and production of SCFA and other bioactive compounds with beneficial physiological effects from gastrointestinal and metabolic health to brain processes [3▪▪,13,16▪,20▪,21,23]. On the contrary, a western-like pattern comprising processed foods lacking the recommended quantity of

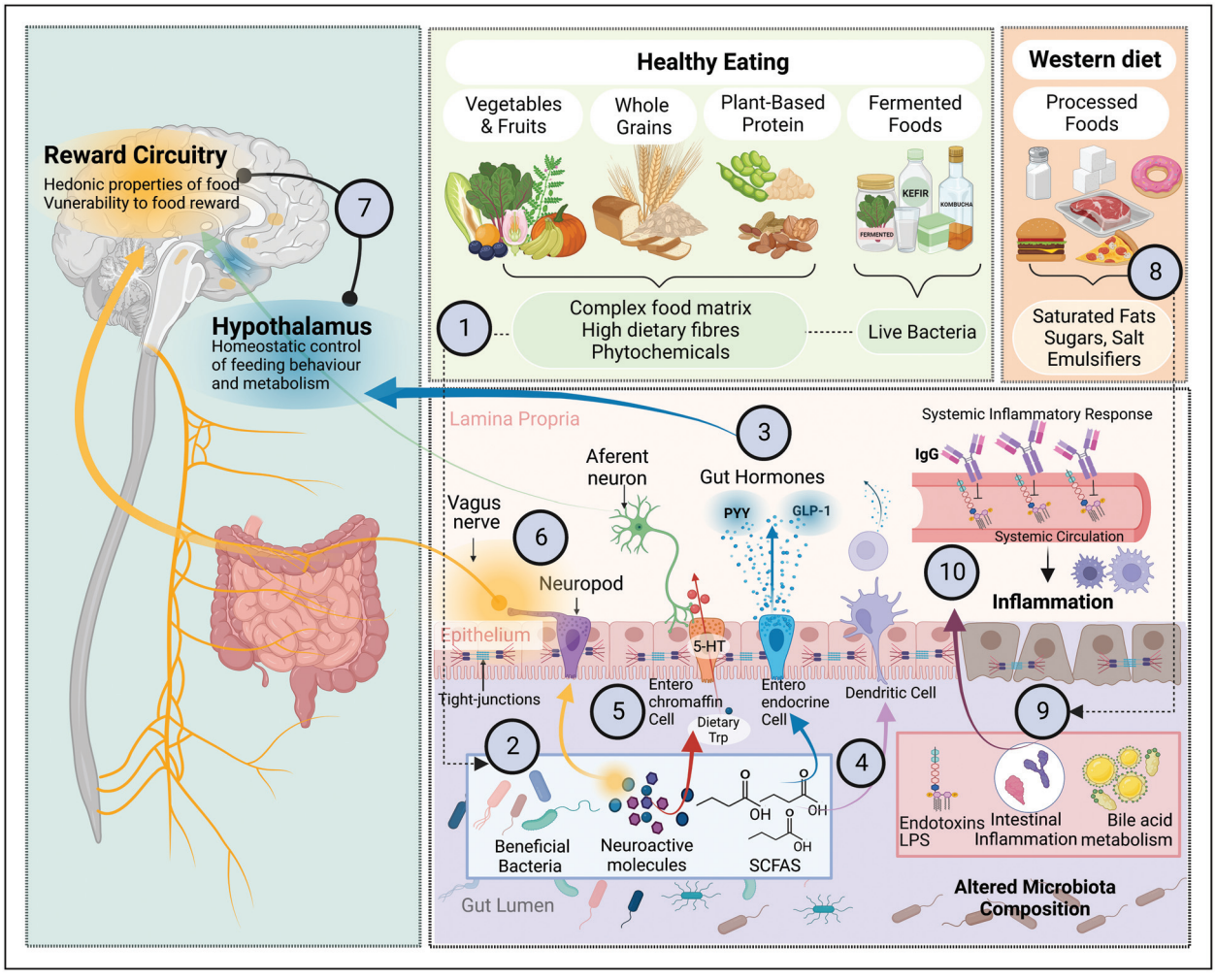

FIGURE 1. Interactions between diet and microbiota-gut-brain-axis mechanisms. A healthy diet comprising foods with complex food matrices, varied sources of dietary fibre, phytochemicals, or live bacteria (green box, 1) results in the growth of beneficial bacteria, production of neuroactive molecules and other health-promoting metabolites such as short-chain fatty acids (SCFA), 2. SCFA can act on enteroendocrine L cells secreting the anorexigenic peptides glucagon-like peptide-1 (GLP-1) and peptide Y.Y. (PYY), acting on hypothalamic centres for homeostatic control of feeding behaviour (3). SCFAs also contribute to the host intestinal barrier integrity and immunity, regulating the suppression of cytokine production from myeloid cells and differentiating T regulatory and T helper cell differentiation (4). In addition, gut bacteria can stimulate the conversion of neurotransmitter precursors into active forms, such as the dietary tryptophan (Trp) into 5-hydroxytryptamine (5-HT) by Enterochromaffin cells (5). Other bacteria can produce active neurotransmitters such as norepinephrine and dopamine that can interact with the enteric nervous system or stimulate vagal sensory neurons (e.g., neuropod) in the gut (6), leading to activation in the brain structures, controlling homeostatic and reward-related feeding behaviour (7). Contrary, a western-like dietary pattern comprising processed foods lacking dietary fibre and with higher content of saturated fat, salt, and food additives (red box, 8) can lead to decreased gut microbiome's diversity, altered bile acids metabolism, lower abundance of mucus-stimulating microorganisms and consequently, compromised gut-barrier integrity, including loosening of tight-junctions (9). In addition, the release of intestinal inflammation markers and translocation of endotoxins from the gut lumen to the bloodstream can induce a low-grade systemic inflammation (10) that has been associated with mental illness and impaired metabolic regulation.

dietary fibre and with higher content of saturated fats, salt and sugars can result in suboptimal gut microbiota composition and a low-grade systemic inflammation associated, for example, with mental illness, gastrointestinal pathology and metabolic disorders [11] and obesity [24,25] (Fig. 1).

EVIDENCE FROM GUT–MICROBIOME TARGETED DIETARY INTERVENTIONS IN MENTAL HEALTH

Recent systematic reviews and meta-analyses have supported the role of the gut microbiome in mental health [9,10▪▪,11]. For example, there is evidence of

a lower relative abundance of SCFA-producing genera and a higher relative abundance of lactic acid-producing bacteria genera across different psychiatric disorders [9,10▪▪]. And, increased circulating levels of the tight-junction protein zonulin, the endotoxin LPS and gut-related systemic inflammatory markers have been shown in patients with severe mental illness and chronic fatigue relative to controls [11]. In addition, recent RCTs have raised attention to the efficacy of dietary interventions in outcomes relevant to mental disorders, such as improvement of depression symptoms [3▪▪,26▪,27–29]. This section will provide a nonextensive discussion of recent findings of diet–microbiome studies, highlighting those with behavioural outcomes whenever possible.

The Mediterranean diet, which has long been recognized as health-promoting [30], was first tested as an adjunct to conventional antidepressant therapy in the 'SMILES' trial [29,31]. This 12-week Mediterranean diet-like intervention showed a significant improvement in depression symptomatology compared with befriending support (control intervention) for patients with major depressive disorder. The beneficial effects of the Mediterranean Diet on mood were corroborated in a cohort of young males with clinical depression in which 12 weeks of dietary intervention resulted in decreased symptoms of depression relative to befriending therapy [26▪]. In adults with depression, a Mediterranean-like diet combined with fish oil (i.e., omega-3) supplementation improved symptoms of depression relative to controls that received social support [32]. However, most studies focused on the impact of diet on behavioural outcomes and did not provide data on the gut microbiome. On another side, in a multicountry cohort of elderly subjects, adherence to a Mediterranean-like intervention for 1 year was associated with enriched microbial taxa and multiple markers of decreased frailty and improved cognitive function [27].

Fermented foods such as yoghurt, kefir and kombucha obtained from microbial growth and enzymatic conversions of food components [33] have been associated with improved gastrointestinal and metabolic health [13,16▪,34]. However, studies reporting brain and behaviour outcomes are few. For example, a prospective RCT in healthy participants showed that a diet high in fermented foods (4–6 portions per day) led to increased microbiome's diversity and reduced pro-inflammatory cytokines such as serum interleukin (IL)-6 [3▪▪]. Another RCT with a double-blind placebo-controlled design showed that daily consumption of a fermented milk beverage improved symptoms of depression and decreased serum IL-6 in patients with depression. However, an improved mood was also observed in the placebo group [35].

Moreover, a randomized crossover trial in healthy volunteers demonstrated that consuming a kefir beverage did not change mood outcomes but resulted in improved memory performance and increased relative abundance of *Lactobacillus* [36]. Finally, in a prospective study of healthy medical students under psychological stress (academic exams), higher fermented foods consumption was associated with the severity of depressive and anxiety symptoms [37], which was not found for food-derived prebiotics. In contrast, higher consumption of fermented foods was associated with lower severity of depressive symptoms in medical students with psychiatric illness, while no association was found for anxiety symptoms [23]. These results suggest that interventions with fermented foods can modulate brain processes through changes in the gut microbiome and gut–brain-axis pathways, which are worthy of further investigation. Nevertheless, larger trials in healthy and clinical populations, such as those including patients with mood and anxiety disorders, are needed to establish a role for fermented foods as dietary interventions to target the microbiota–gut–brain-axis.

Other diet-related approaches to target the microbiota–gut-axis include even less explored avenues such as ketogenic diets and intermittent fasting. For example, there is preclinical evidence that gut microbiota mediates the effects of ketogenic diets in rodent models of epilepsy [38]. Additionally, evidence comes primarily from studies in children where those with epilepsy showed different microbiota relative to healthy controls, with either increased or decreased diversity depending on the disease status and the response to drugs or ketogenic diets [39]. Furthermore, children that benefited from ketogenic diets had increased butyrate levels and decreased relative abundance of specific genera such as *Bifidobacterium*, *Akkermansia*, *Enterococcaceae* and *Actinomyces* [39].

Intermittent fasting has gained attention mainly in weight management and improved metabolic outcomes, although the underlying mechanisms are not yet clarified. The gut microbiome may have a potential role in those outcomes. However, diet–microbiome studies in humans have been limited to Ramadan fasting. For example, 1-month intermittent fasting in Ramadan induced an increased relative abundance of butyric acid-producing *Lachnospiraceae* and improved body mass index and blood glucose relative to nonfasting controls [40]. But, since Ramadan fasting results in decreased energy intake and a profound dietary modification [41], it does not necessarily reflect the more common intermittent fasting approaches. Energy consumption and dietary macronutrient distribution are not necessarily modified in

the latter. Thus, controlled studies using fasting as an intervention are needed, accounting for energy intake, dietary composition, gut microbiota, and behavioural data.

KEY POINTS FOR DESIGNING A DIET–MICROBIOME–BEHAVIOUR STUDY

Human studies aiming to assess diet–microbiome–behaviour effects face several levels of complexity, from intra-individual variability in the microbiome [42] to limitations inherent in diet studies (e.g., difficulty in assessing dietary intake and adherence to diet) [42]. One major challenge is the lack of standardized protocols for dietary assessment or interventions in microbiome studies [43]. This section will provide a nonexhaustive critical review of fundamental aspects for designing diet–microbiome–behaviour studies, including selecting dietary assessment methods and implementing dietary interventions.

ESTABLISHING AN APPROACH FOR DIETARY INTAKE ASSESSMENT

The assessment of dietary intake in free-living settings is a major challenge in nutrition research [44], extending to diet–microbiome studies. In brief, dietary intake can be evaluated using direct methods, comprising direct observation, duplicate diets, and nutritional biomarkers [45,46]. More commonly, indirect (self-report) methods, such as food diaries (weighed or estimated), 24-h dietary recalls and Food Frequency Questionnaires (FQs) [45,46], are used due to their lower cost and burden [45]. However, all subjective techniques rely on the participant's self-report and, thus, on memory, past experiences, and perceptions [46]. Therefore, all self-report methods are prone to systematic bias and misreporting issues [44,46].

Conversely, more objective methods such as nutritional biomarkers, despite being more expensive and complex to measure, are less susceptible to misreporting [44,45]. Examples of nutritional biomarkers in dietary assessment are total energy intake measured by doubly-labelled water and omega-3 and -6 fatty acids evaluated by blood fatty acid concentration or tissue lipid compartment [45]. Other examples are concentrations of minerals and vitamins in urine (e.g., potassium, iodine), serum (e.g., calcium, phosphorus, magnesium, iron, zinc, vitamins D, E and C) and plasma (e.g., selenium, zinc, vitamin K, folate and vitamin B12) [45]. Specific nutritional biomarkers include phytochemicals, carotenoids, caffeine metabolites, flavones, isoflavones and phytosterols [45]. Despite the potential of biomarkers for assessing dietary intake, particularly given the specificity of diet–microbiome studies, they do not replace self-reported data entirely [44]. Thus, ideally, both methods should be combined for optimal results [44].

In the microbiome literature, indirect methods have been primarily used, particularly Food Frequency Questionnaire (FFQ)s. The latter provided insight into the relationship between dietary patterns and gut–microbiome features, such as the microbial genera abundance [47]. FFQs have several strengths: lower participant burden, lower cost than other dietary assessment methods, and relatively quick and automated data analysis. However, the self-report intake in FFQs is memory dependent and limited to items comprised by the food list [46]. Thus, it may not capture specific foods relevant to diet–microbiome studies (e.g., fermented foods) or ethnic differences since they are developed for particular populations [43]. On the other side, food diaries provide reasonable estimates of energy intake and most nutrients, foods, and food groups.

Furthermore, FFQs may lead to higher misreport when compared to other tools such as food diaries. For example, in a 12-month study including over 1000 participants, energy intake was more underestimated by FFQs than automated self-administered 24-h recalls or unweighted 4-day food diaries when compared against its biomarker (i.e., energy intake assessed by doubly labelled water) [48]. Additionally, the validity of the assessment tool can depend on the nutrient being evaluated. For example, the EPIC-Norfolk Study showed that a 7-day food diary performed consistently better than the FFQ for vitamin C (both urinary and plasma measures). At the same time, consistent results were found for polyunsaturated fatty acid intakes [45].

However, food diaries can result in a higher participant burden, data entry requires substantial time, and human resources with expertise in dietetics are necessary [45]. Technology assistance (e.g., smartphone applications) can attenuate these limitations, decreasing researcher burden in data collection and entry and improving standardization across multiple assessments [45]. For example, mobile app-recorded food diaries were successfully applied in a gut–microbiota–targeted dietary intervention study in healthy volunteers [3▪▪]. Furthermore, among other digital-based dietary programs, the app version had higher engagement and lower nonusage attrition in patients with depression [49], reinforcing the utility of digital-based dietary assessment in future diet–microbiome–behaviour studies.

In summary, direct and self-report methods have advantages and disadvantages, and there is not a one-size fit solution for dietary assessment methods. However, according to the study design and research question, researchers can decide which

instruments to include based on available toolkits (see Dao *et al.* [46] for details). Furthermore, in diet–microbiome–behaviour studies, nutritional biomarkers can be an asset to address food composition variability and the effects of food processing and cooking methods [44]. Although this approach needs further validation [44], it has the potential to change current dietary assessment practices. Lastly, using digital-based options is also recommended [44], mainly when the software uses validated databases and calculation methods [44].

DESIGNING MICROBIOME-TARGETED DIETARY INTERVENTIONS

Several aspects must be considered when designing a dietary intervention in a microbiome study. One critical question is the optimal duration of the dietary intervention [43]. Preclinical evidence showed rapid diet-induced changes in the gut–microbiome, consistent with results from different dietary interventions in humans that resulted in microbiome composition changes within days [28,50]. However, there is also evidence of gut–microbiota resilience as shown in long-term dietary interventions for weight loss [51▪]. The initial shift in the microbiota was followed by a return to baseline characteristics even though the participants maintained the prescribed diet and weight loss [51▪]. Accordingly, the length of a dietary intervention required to induce changes at the host level is suggested to be weeks or months, depending on the outcomes of interest and the study design (longer for crossover design) [43]. In addition, other factors such as baseline microbiota composition and extent of change in a dietary intervention (e.g., increasing fibre intake vs. switching to vegetarian from a meat-based diet) will probably play a role. Also, the impact of dietary interventions on the habitual diet and overall feeding behaviour in diet–microbiome studies has not been consistently assessed and reported to the best of our knowledge. For example, increasing dietary fibre intake or introducing novel foods can impact satiety and satiation [21], and thus habitual dietary intake regarding energy content and macronutrient composition. Therefore, diet–microbiome studies would benefit from assessing the participants' baseline diet and feeding behaviour characteristics (e.g., hunger, satiety and fullness) and monitoring the relationship between these parameters throughout the follow-up.

Furthermore, participants must be willing to comply with the changes in diet that can comprise novel foods, unusual textures, cooking methods,

Table 1. Critical points for designing diet–microbiome–brain and behaviour studies

	Assessment of dietary intake types of methods		Dietary Intervention		
Domain	**Subjective**	**Objective**	**Planning**	**Baseline**	**Follow-up**
General advice	Food diaries 24 h dietary recalls FFQs Diet checklists Diet histories Technology-assisted dietary assessment Consult dietary assessment toolkits to guide selecting and implementing the most appropriate dietary assessment protocol Preferred validated methods that allow for data comparability and harmonization of nutritional databases	Direct observation Duplicate diets Nutritional biomarkers	Define a dietary educational plan according to the social and cultural specificities of the target population Integrate national dietary guidelines Choose an appropriate control intervention Define measures of compliance Develop measures to reduce attrition	Characterize baseline diet using a representative time frame Estimate energy requirements and energy expenditure to define the diets' caloric value. Conduct assessment of nutritional status, including anthropometry Individualize diet according to baseline preferences	Conduct structured visits to address difficulties in diet records or diet compliance Monitor anthropometric measures and nutritional biomarkers Assess diet-related side effects Evaluate potential changes in habitual diet, appetite, or lifestyle
Challenges	Find a balance between the burden of the participants and researchers and data accuracy and specificity		Define a sufficiently specific intervention without compromising feasibility	Personalize the intervention without compromising its specificities	Deal with attrition and compliance
Solutions	Use web-based methods such as smartphone apps for dietary intake registering and data processing: The latter can be validated with conservative software and databases Consider combining subjective measures with objective methods such as nutritional biomarkers		Anticipate barriers to diet compliance in the target population Examples: lower acceptance for specific textures and tastes (e.g., high-fibre foods) Motivation to consume novel foods (e.g., fermented foods) Consider providing prepared meals or a laboratory setting if the budget allows	Provide varied and equivalent food alternatives to high-fibre or high fermented foods Use behavioural strategies such as motivational interview to deliver information Use a nonstigmatizing approach	Use behaviour change techniques (e.g., goal setting, problem-solving, feedback and monitoring) Potential need to utilize different methods for delivering the intervention that does not require in-person attendance (e.g., telehealth) Measure and analyse both usage and intensity-of-use measures of web-based interventions

and shopping habits. In this context, knowledge acquired from lifestyle programs (e.g., diabetes prevention) [52], including behavioural change techniques and strategies to promote engagement and attenuate retention, can be translated into diet–microbiome–behaviour studies, particularly relevant when studying individuals with mental disorders [52]. Thus, researchers must design dietary interventions, considering available resources and the specificities of the targeted population, among other relevant factors such as assessment of compliance to diet, as shown in Table 1.

CONCLUSION

Diet–microbiota–gut–brain-axis is an emerging topic with high potential application for clinical nutrition. Controlled diet–microbiome studies in humans are emerging with promising findings for brain health. However, much work is needed to address current limitations in this field. Future diet–microbiome studies will benefit from standardized methods for dietary assessment based on validated approaches but with sufficient specificity for the microbiome field. In terms of intervention studies, it is critical to determine the optimal length of dietary intervention, to test behavioural approaches to promote compliance with diet specificities and to include behavioural outcomes along with microbiome and nutritional data. Lastly, the resources required for deploying technologically assisted methodologies, including mental health populations, should be considered when designing new diet-microbiome studies.

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Conflicts of interest

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