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Authors	Sanz, Yolanda;Cryan, John F.;Deschasaux-Tanguy, Mélanie;Elinav, Eran;Lambrecht, Rebekka;Veiga, Patrick
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University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

The gut microbiome connects nutrition and human health

Yolanda Sanz*[1], John F. Cryan[2], Mélanie Deschasaux-Tanguy[3,4], Eran Elinav[5,6], Rebekka Lambrecht[5] & Patrick Veiga[7,8]

[1]Microbiome Innovation in Nutrition and Health Research Unit, Institute of Agrochemistry and Food Technology, Spanish National Research Council (IATA-CSIC), Valencia, Spain.

[2]APC Microbiome Ireland, University College Cork, Cork, Ireland.

[3]Department of Anatomy and Neuroscience, School of Medicine, University College Cork, Cork, Ireland.

[4] Université Sorbonne Paris Nord and Université Paris Cité, INSERM, INRAE, CNAM, Center for Research in Epidemiology and Statistics (CRESS), Nutritional Epidemiology Research Team (EREN), Bobigny, France.

[5]Dept. of Systems Immunology, Weizmann Institute of Science, Rehovot, Israel.

[6]Microbiome & Cancer Division, German Cancer Research Center (DKFZ), Heidelberg, Germany.

[7]Université Paris-Saclay, INRAE, AgroParisTech, Micalis Institute, Jouy-en-Josas, France.

[8]Université Paris-Saclay, INRAE, MetaGenoPolis, Jouy-en-Josas, France.

*email: yolsanz@iata.csic.es

TOC blurb

In this Review, Sanz and colleagues discuss how diet shapes the gut microbiome, the role of diet-microbiome interactions on the immune, nervous and cardiometabolic systems, and implications for dietary guidelines and precision nutrition.

Abstract

The gut microbiome has an undeniable role in mediating the health effects of the diet, given its ability to co-digest nutrients and influence nutrient signaling to multiple organ systems. As a sub-optimal diet is a major risk factor for and contributor to disease, understanding the multidirectional interactions between the food we eat, the gut microbiome, and the different body organ systems is crucial from a public health perspective. Indeed, this research area is leading to the refinement of nutritional concepts and strategies to optimize health through diet. In this Review, we provide an update on how dietary patterns and food intake shape gut microbiome features, the mode of action of diet-microbe interactions on the immune, nervous and cardiometabolic systems and how this knowledge could explain the heterogeneity of dietary responses, and support food-based dietary guidelines and medical and precision nutrition. Finally, we discuss the knowledge gaps and research efforts needed to progress toward the integration of microbiome science with more precise dietary advice to leverage the role of nutrition in human health.

[H1] Introduction

Diet is a major risk factor for the development of non-communicable diseases (NCDs) and is therefore instrumental in disease prevention. Suboptimal diets accounted for 7.2 million deaths and 178 million disability-adjusted life-years in 2021[1]. It is estimated that healthy diets could, in contrast, prevent 11.1 million global deaths yearly and premature mortality by 19% in 2030[2].

Nutrient-based and food-based recommendations are part of the public health approaches originally intended to avoid nutrient deficiencies and, more recently, to prevent and even mitigate NCDs. Today, however, dietary advice and policies are insufficient to prompt an effective move towards healthier diets with substantial effects on public health [3]. Dietary guidelines still provide common grounds to act on common disease risk factors at the population level[4], but adjustments at the individual level might be necessary as chronic disease determinants and dietary responses vary greatly among individuals[5]. This observation raises the question of whether optimizing nutrition requires a closer examination of population heterogeneity to determine the suitability of foods, diets and dietary patterns for individuals or subgroups, enabling adaptation and improving adherence and effectiveness in disease management.

Our gut microbiome has the potential to modify dietary health effects and act as a mediator of those effects on the human host. The food we eat nourishes not only our body but also the microorganisms inhabiting our gut, influencing their ability to thrive and the microbes-body-brain interactions that affect different domains of our health. The gut microbiome also participates in nutrient metabolism and determines the fate and functions of food components in different organ systems. The idea that the gut microbiome needs to be fueled by our diet and, in turn, modifies the nutritional value of food is a paradigm shift in the way we think about optimal nutrition, which could help inform the scientific basis of dietary advice[6].

Several reviews on the role of diet in shaping the gut microbiome and human health have been published. Some have been restricted to interactions with specific nutrients[7] or diets, without insights into causal relationships[8], or focused only on concrete diseases such as autoimmune[9] or metabolic[10,11] diseases or on personalized nutrition[12].

Unlike others, this Review integrates investigations into the role of nutrition in modulating the gut microbiome at different scales, from dietary patterns to food groups and nutrients, and recaps conceptual methodological frameworks to capture diet-microbiome interactions and the multidirectional effects more precisely. It also addresses the causal role of the gut microbiome and microbially produced metabolites in mediating the effects of the diet in the main organ systems influencing human health (immune, nervous and cardiometabolic systems) from a wide perspective. Finally, the Review summarizes and discusses how gut microbiome data could help optimize dietary advice and medical, precision and personalized nutrition from a public health perspective.

[H1] Dietary determinants of gut microbiome variations

Diet is generally recognized as a key determinant of gut microbiome variations. Yet, to go deeper in our understanding of diet-microbiome interactions, this Review considers multi-level dietary data (dietary patterns, individual foods, and nutrients) and approaches to establish their relationship to different gut microbiome features, encompassing the complexity of both systems.

[H2] Dietary indices and patterns

Diet is the combination of quantities, frequencies and variety of foods and beverages that are habitually consumed by individuals. Focusing on diet, rather than single nutrients, acknowledges the fact that people consume a combination of foods, which might interact with one another. In line with this, the role of diet and not only of specific nutrients in shaping the gut microbiome has become central to understanding the effect of diet-microbe interactions on human health. There are two primary approaches for assessing the habitual diet. First, index-based (or 'a priori') methods were designed to evaluate adherence to specific diets or nutritional recommendations. The most commonly used dietary indexes are related to the Mediterranean diet (Mediterranean Dietary Score (MDS), Alternate Mediterranean Diet score (aMED)), the Healthy Eating Index (HEI), and Dietary Approaches to Stop Hypertension (DASH) [13,14]. Dietary indexes are derived from dietary data using pre-defined consensus criteria, facilitating their implementation and inter-study comparisons. One limitation of dietary indexes is that individuals with similar scores might consume different foods. Conversely, 'a posteriori' methods are data-driven and use multivariate statistical techniques to derive patterns from actual dietary data[13]. A posteriori methods have the potential to better reveal dietary patterns specific to the studied populations; however, their specificity in terms of the exact foods contributing to these patterns and the strength of their contribution hinders inter-study comparisons.

The extent to which habitual diets can explain gut microbiome variations is an active research question and has been explored in large population cohorts, mainly using a priori indexes (HEI, aMED, MDS, Dietary Diversity Score (DDS), Healthy Food Diversity index (HFD), Healthy/Unhealthy Plant-based Dietary Indices (hPDI/uPDI) [15–17]. While results vary across studies, a general trend indicates the diversity and quantity of healthy plant-based foods and fibers in the diet are one of the main contributors to the microbiome variations of alpha-diversity and beta-diversity [16,18]. Inconsistencies between studies might arise from the fact that current a priori indices were not designed to optimally capture factors involved in gut microbiome-diet associations. Applying methods borrowed from microbiome analyses to diet provides additional ways to look at dietary intake. For example, the Dirichlet Multinomial Mixtures model, similar to that used for enterotyping, was used to identify five diet clusters from the dietary data of the American Gut Project [19]. These diet clusters ('Plant-based' or 'Flexitarian' Prudent-like diets, 'Standard' or 'Health-Conscious' Western-like diets and 'Exclusion' diet) could explain up to 1.3% of the beta-diversity variations, whereas the a priori HEI-2010 index explains only 0.42%. The 'Flexitarian' diet (enriched in plant-based foods and dairy, with low amounts of meat) had the best overall diet quality (as measured by the HEI-

2010 score) and was associated with higher gut microbiome alpha-diversity. This study highlighted the need to develop specific dietary indices that better capture dietary factors that influence the gut microbiome. Efforts in this direction include the dietary index for gut microbiome[20] and the dietary protein/fiber ratio[21]. Overall, a combination of a priori and a posteriori approaches can be of value to ensure comparability with other studies and better fit to the studied population and to reflect diet-microbe associations.

Many studies have investigated the dynamics of gut microbiome response to dietary shifts in the short or long term in humans [22–28]. While the results vary across studies, a general observation is that most short-term dietary interventions elicit a response from the gut microbiome, as evidenced by clear changes in diversity indexes, taxa abundance or enterotypes, within the first days or weeks [22,23,28]. Dietary interventions sustained over a longer period (>12 months) reported modest changes and suggested some resilience in overall gut microbiome structure (enterotypes, diversity indexes),[26,27], but still detected changes in the abundance of some taxa, which could be functionally relevant for human health[24,25,29]. The apparent differences in gut microbiome variations between short-term and long-term dietary interventions might seem paradoxical, but they can be explained by the magnitude of the dietary change (usually more drastic in short-term interventions) and the challenges in maintaining adherence to dietary shifts over extended periods. Indeed, dietary acculturation associated with long-term immigration from a non-Western country to the United States led to persistent changes in the gut microbiome observed after several months and across the first and second generations of immigrants, associated with metabolic disease post-immigration[30]. Globally, evidence supports the relevance of considering the short and long-term changes in the diet as a driver of the overall gut microbiome structure and/or specific taxa abundance, with possible health consequences, and the potential of the habitual diet to leverage its role in human health through the modulation of the gut microbiome. In addition to long-term dietary habits, eating timings influence daily gut microbiome oscillations linked to circadian rhythms controlling physiological functions (digestion, immune responses, hormone secretion). Alterations of circadian rhythms are linked to adverse health outcomes, which could also underlie disruption of gut microbiome oscillations [31,32]. Phenomena such as social jetlag, when daily rhythms dictated by social norms and obligations are at odds with the habitual circadian rhythms, eating fasting cycles, and intermittent fasting, are under scrutiny for possible consequences on both the gut microbiome and health [33,34].

[H2] Foods and food groups

Disentangling the complexity of the diet into component foods and nutrients has also been necessary for understanding how the whole diet relates to gut microbiome variations and human health. In the past decade, population-based studies (involving from several hundred to thousands of participants) have emerged from different geographical locations[17,35–48] (**Table 1, Table 2, and Supplementary Table 1**), providing a broad overview of associations between long-term food intakes and gut microbiome characteristics. Although variation in food and nutrient intakes across different regions could lead to differences in diet-microbiome associations, we can identify some commonalities across studies. The most-reproduced associations with the gut microbiome are those for fruit, vegetables, grains and

to some extent dairy products. The consumption of healthier and plant-based food items, especially fruit, was usually associated with a greater diversity. Conversely, a lower diversity was usually observed with the consumption of less healthy foods such as high-sugar drinks and fried products, red and processed meat, or refined grains. Associations with dairy products were less clear, with differences between yogurt (fermented), cheese or milk. All of these foods contributed to inter-individual dissimilarities in gut microbiome composition and were associated with differential abundance of numerous bacterial taxa, including inverse patterns of associations between healthier plant-based and less healthy plant-based or animal-based food items [17,35–48] (**Supplementary Table 1**). Relative abundance of species from *Clostridium*, *Ruminococcus*, *Eubacterium*, *Bifidobacterium*, *Bacteroides* and *Prevotella* were those displaying the highest number of associations with food items and were potentially the best candidates to provide functional flexibility to the host through nutrition. For instance, *Eubacterium eligens* abundance was associated positively with the consumption of fruit, vegetables, nuts and seeds, eggs and red wine, but negatively with the consumption of grain products, dairy, red meat, savory snacks, pizza or fried products, and sugar-sweetened beverages (**Supplementary Table 1**). Globally, these results at the food level partly echoed those observed with overall dietary patterns. Healthier plant-based foods are those contributing to 'Prudent' or 'Healthy' dietary patterns, for which there is consolidated evidence of associations with better human health and increased gut microbiome alpha-diversity [49] . Conversely, red meat and foods high in sugar, fat or salt are those contributing to Western diets or unhealthy dietary patterns and are associated with adverse health outcomes and lower gut microbiome diversity [49]. However, further understanding of the granularity of food-microbe associations is needed regarding differences in food items within food categories and the specificity of their associations at much deeper taxonomic (species/strains) and functional microbiome levels. Furthermore, given the variability of dietary habits across countries and regions, global initiatives for dietary data collection and standardization[50] will be key to facilitating data integration in microbiome studies and, thus, disentangling commonalities and particularities of diet-microbe associations that help identify global and local priorities for further research and translation into nutritional practice.

[H2] Nutrients and other food constituents

The food-level associations with microbial features are partly explained by established interactions between specific food constituents and the gut microbiome.

Dietary fibres, derived from plant-based foods, constitute the primary source of energy for the gut microbiome, which through fermentation produces short-chain fatty acids (SCFAs) that benefit the host (described later). Yet, dietary fibers encompass a large variety of compounds, differing in their structure, length, solubility and fermentability so that differential effects on the gut microbiome are likely [51].

Other carbohydrates might also be poorly digested and become available in the colon. For instance, fructose, when consumed in excess, which is often observed in Western diets, or

high lactose intake in lactase non-persistence, will induce microbial fermentation and by-products that might affect intestinal homeostasis [52,53].

Dietary proteins also greatly influence gut microbiome structure and function, with potential downstream consequences for the host[54]. The unabsorbed fraction (approximately 10%) is fermented into a variety of metabolites, including ammonia or phenol (considered detrimental), as well as indols and hydrogen sulfide (considered beneficial)[51,55,56]. The production of protein by-products depends on the amount of protein reaching the colon but also on the protein source (animal or plant), influencing their digestibility, amino acid profiles, and derived metabolites generated by the gut microbiome[55,57]. The ratio between intakes of proteins and fibres has been suggested to have more influence on the gut microbiome than dietary fibre alone[21], affecting the balance between saccharolytic and proteolytic bacteria[51], showing the need to investigate diet as a whole system - although a mechanistic understanding also requires reductionistic approaches. A benefit of plant protein sources such as legumes has been attributed to the simultaneous intake of proteins and fibers, although plant proteins show lower digestibility and nutritional quality. In turn, animal proteins are generally considered of higher nutritional quality but their food sources are accompanied by choline or carnitine, which can be metabolized by gut bacteria and the host into adverse metabolites[58].

The lipid content of the diet, including fatty acids of various lengths and saturation profiles, is another important driver of gut microbiome composition[59]. Approximately 5% of dietary fatty acids reach the colon, a proportion that increases when the lipid content exceeds the intestinal-absorbing capacities, which is usually observed for typical Western diets[60]. High-fat diets, usually rich in saturated fats and trans fats, have mostly been associated with detrimental effects on the gut microbiome, reducing-alpha diversity and increasing the abundance of bacterial species potentially adverse for human health (*Bilophila wadsworthia, Turicibacter* spp.)[59,61]. Evidence for an effect of omega-6 polyunsaturated fatty acids (PUFAS) on the gut microbiota is very limited [59,60]. On the other hand, monounsaturated and omega-3 PUFAS have shown favourable effects through interactions with specific bacterial taxa (*Lactobacillus* spp., *Holdemanella* spp.; discussed later) or no effects[59,60]. Bile acids, which are involved in lipid digestion, usually reach the colon in small amounts (approximately 5%) but might become more abundant when high-fat diets are consumed, affecting effects of dietary fats on gut microbiome. They have antimicrobial properties and serve as substrates for the production of secondary bile acids by gut bacteria, for which both detrimental and potentially beneficial effects on health are reported, as explained in the next sections[62].

Vitamins and minerals can affect the gut microbiome, either through an influence on the host immune system or directly through ecological competition. Vitamins (A, beta-carotene, B, C, D, E, K) are mostly considered to have beneficial effects on gut microbiome diversity, and certain gut microorganisms are known producers of vitamins B2, B12, K2 or C [63]. Sodium intake seems to have a detrimental effect on the gut microbiome, depleting the presence of commensal bacteria (for example, *Lactobacillus*)[64,65], which could also partly explain the adverse effect of Western diets and highly processed foods. Likewise, heme iron abundant in red meat is suspected to alter the gut microbiome composition through nutrient competition

(for example, fueling enteropathogens)[66], with adverse downstream effects, for example on the gut barrier (discussed later)[67,68].

In addition to nutrients, plant-based foods also exhibit high contents of non-nutritious bioactive compounds such as polyphenols. These are found especially in fruit, vegetables, and whole grains, and also coffee, tea, red wine, and chocolate. Polyphenols (phenolic acids, flavonoids, or lignans) affect gut microbiome structure and function and, in turn, the gut microbiome metabolizes many polyphenols, which could partly mediate their potential health effects (discussed later) [69,70]. Although red wine is a polyphenol-rich food with potential beneficial interactions with the gut microbiome (**Table 1, Table 2**), it also contains alcohol, for which a detrimental effect on the gut ecosystem is documented[71]. Studies have also shown deleterious effects of ultra-processed foods on the gut microbiome [72], as a result of their usually less favorable nutritional profiles (e.g., higher in sugars and saturated fats), their modified food matrix limiting microbiome-accessible residual compounds (fibers), and the presence of food additives such as emulsifiers or sweeteners as well as other substances resulting from processing and food contact materials[72].

Overall, integrating dietary intakes at different levels, from nutrients to foods and diets, to comprehensively capture microbiome variations requires fresh conceptual frameworks. While reductionistic approaches, such as interventional studies documenting the effects of individual nutrients on the gut microbiome, help decipher mechanisms [7,57], more holistic approaches better reflect the reality of substitutions and interactions (synergistic or antagonistic effects, or matrix effects affecting bioavailability and absorption) that occur between nutrients and foods in a diet. It should also be acknowledged that food is multi-dimensional, far beyond its nutritional composition. Consequently, considering additional aspects such as how food was produced and processed and food-related behavior, could bring new insights about the associations between the habitual diet, the gut microbiome, and human health (**Box 1**) [73,74]. Finally, diet-microbiome interactions should also be considered in light of the variability of both dietary habits and the gut microbiome across different human populations. Altogether, rethinking nutritional tools and concepts and the way nutrition is included in gut microbiome studies around the globe will be essential not only for revealing the true extent of diet's influence on the gut microbiome but also for unlocking new avenues for public health measures aimed at protecting microbiome health.

[H1] Gut microbiome contributes to dietary effects on human health

The gut microbiome acts as a conduit of dietary effects on human health in many ways. Such microbial effects could be driven by the diet-modified microbiome community interacting with the host and by metabolites produced by the bacterial digestion of foods. The number of metabolites generated by the gut microbiome and by host-microbiome co-metabolic processes identified has rapidly increased in the past few years, but many more remain to be annotated [74]. The evidence on the microbially mediated dietary health effects through actions on the main host organs and systems (immune, nervous and cardiometabolic systems) is reviewed and discussed in this section.

[H2] Gut integrity and immunity

The interplay between diet and the gut microbiome contributes to the regulation of the intestinal immune system and the integrity of the gut barrier. The presence of commensal microorganisms, coupled with a host mucosal barrier (maintained by tightly adherent intestinal epithelial cells (IECs) and an overlying mucus layer) and an innate and adaptive mucosal immune response, ensures that the abundant microbial and food-related antigens are tolerated, while preserving a capacity to prevent or react to pathogen invasion into the sterile host[75]. Perturbation of any of the components of this tightly integrated mucosal defense can lead to low-grade inflammation, a breach in gut barrier function (also simplistically known as 'leaky gut syndrome'), and a resultant persistent microbiome-dependent activation of immune cells [76]. Dietary regulation of intestinal homeostasis mediated directly or indirectly by the gut microbiome is illustrated in **FIG.1** and explained below.

The intestinal mucus is regulated by several nutrients. In particular, dietary fibers stimulate mucus-producing goblet cells, as shown in rodents, [77] and nourish commensal bacteria (**FIG. 1 part 1**). In fiber-deprived mice with humanized microbiota, microorganisms excessively degraded intestinal mucus as an alternative energy source, fatally increasing pathogen susceptibility [78]. Nonetheless, appropriate commensal glycan degradation is essential for a healthy, diverse microbiome and is associated with an intact gut barrier[79]. Intestinal mucus also contains antimicrobial peptides (AMPs) and secretory IgA antibodies to oppose pathogenic species colonization. AMPs are mainly secreted by Paneth cells or IECs upon luminal stimulation of bacteria-sensing Toll-like receptors (TLRs) and NOD-like receptors (NLRs), or by basolateral activation of IL-22 receptor [80] (**FIG. 1 part 1**). IL-22 is in fact central for intestinal homeostasis and its secretion is critically modulated by several dietary compounds and their bacterially processed metabolites[81] (**FIG. 1 part 4**). Microbiome-generated SCFAs and PUFAs bind to G protein-coupled receptors (GPCRs) on immune cells, promoting IL-22 expression[82], which is further supported by SCFA-mediated histone deacetylase (HDAC) inhibition. Among others, IL-22 expression is mediated by aryl hydrocarbon receptor (AHR)[83] upon activation through dietary phytochemicals[84], microbiome-processed vitamin D [85,86] and tryptophan metabolites[87], or by retinoic acid receptor (RAR) in response to retinoic acid (RA), a vitamin A derivative from bacterial metabolism[88] (**FIG. 1 part 4**). In addition, an interplay of bacterial stimuli and dietary compounds, particularly RA, influences intestinal plasma cells, dendritic cells (DCs) and T cells, leading to secretory IgA production[89] (**FIG. 1 part 1**). Hence, diet affects mucus composition and thickness both directly by providing nutrients such as fibers to microorganisms that prevent excessive mucus degradation and indirectly by fostering a microbiome that converts these nutrients into active, mucus-promoting dietary metabolites while suppressing mucus-degrading species.

The physical barrier is further reinforced by tight junctions between the single IEC lining. Dietary bacterial metabolites such as lactate, SCFAs, tryptophan metabolites and phytochemicals directly influence tight junction protein expression by binding to GPCRs, inhibiting HDACs, or activating AHR in IECs[90–93] (**FIG. 1 part 3**). Additionally, many 'beneficial' dietary products oppose pro-inflammatory and tight junction-loosening signaling that is

triggered by pathogens via TLR/NLR signaling or proinflammatory cytokines[94,95] (**FIG. 1 part 3**). Thus, any diet that triggers intestinal inflammation inevitably also increases gut permeability by targeting tight junctions. Furthermore, diets rich in sugar[96], fat[97], or surfactants[98] directly compromise tight junctions and intestinal integrity (**FIG. 1 part 3**). Hence, unhealthy, poor diets lower mucus quality and quantity and loosen the IEC layer, dramatically lowering intestinal barrier integrity, which is linked to multiple diseases (discussed later).

Dietary compounds also actively shape intestinal immune cells[99] (**FIG. 1 part 5**). Immunological homeostasis in the gut is safeguarded by regulatory T (Treg) cells[100], IL-22-expressing cells (as discussed previously)[81] and the communication between commensals and immune cells. Intriguingly, Treg cell differentiation and maintenance and cytokine profiles critically depend on bacterially processed dietary metabolites such as RA[101], SCFAs[102], PUFAs[103], vitamin D derivatives[104] , and AHR ligands, for example from tryptophan[105,106] (**FIG. 1 part 5**). These dietary factors integrate with local cytokines to influence Treg cells either directly or by modulating IECs and tolerogenic DCs[107]. Some nutrients also exert direct inhibitory effects on pro-inflammatory immune cells[105,108], hence synergizing with Treg cells to maintain immune homeostasis. Furthermore, gut-homing, differentiation and cytokine production of T cells[108,109], neutrophils[110], macrophages[111], DCs[112], innate lymphoid cells (ILCs)[113] and intraepithelial lymphocytes (IELs)[114] is dependent on dietary metabolites (**FIG. 1 part 5**). The importance of the trialogue between microorganisms, diet and intestinal health is exemplified by the fact that a lack of dietary AHR ligands, AHR signaling-dependent cells (for example, ILCs and IELs) or AHR ligand-producing bacteria provokes or worsens intestinal auto-inflammation and human inflammatory bowel disease[83].

Notably, microbiome modulation by diet also greatly affects intestinal inflammation (**FIG. 1 part 2**). Certain gut microorganisms synthesize secondary bile acids that enhance barrier integrity in IECs through IL-18 and mucus production[115] and inhibit pro-inflammatory mononuclear phagocytes[116] by acting on farnesoid X receptor (FXR) or binding to Takeda G protein-coupled receptor 5 (TGR5)[117] (**FIG. 1 part 2**). Furthermore, symbiotic and pathogenic microorganisms are constantly screened by pattern recognition receptors on IECs and immune cells, inducing inflammasome signaling[118] (**FIG. 1 part 2**). In fact, inflammasomes represent another central but versatile modulator of intestinal health[118] as they can promote inflammation or contribute to homeostasis, depending on the type of inflammasome, bacterial stimuli and cell type [119,120]. Dietary substances directly influence inflammasome activity[121], for example, the pro-inflammatory NLRP3 activity is reinforced by saturated fatty acids[122] and suppressed by omega-3 PUFAs[123]. Thus, diet-shaped microbial triggers and dietary modulators of inflammasomes represent another nexus in the intricate network between diet, microbiome and intestinal health.

[H2] Nervous system

Diet has long been known to have direct effects on the nervous system and behavior, and evidence now suggests that some of these effects could be mediated via the gut microbiome and the so-called gut-brain axis. The diet-sensitive mechanisms as to how the microbiome influences the brain in health and disease are slowly being elucidated and involve a variety of pathways including neural mechanisms involving the enteric nervous system and vagus nerve, as well as immune and hormonal pathways and microbial metabolites (**FIG. 2**). In the past decade, the concept of a diet-microbiota-gut-brain axis has emerged to capture the multiplicity of such interactions and how they might affect different stages in the lifespan (infancy versus older age) and contribute to neurodevelopmental, psychiatric and neurodegenerative disorders [124]. In this regard the microbiome is being investigated as a conduit of both the preventative and therapeutic aspects of diet in a host of disorders ranging from depression, anxiety and ADHD to epilepsy, Alzheimer disease and Parkinson disease.

The microbially generated SCFAs can directly affect brain function (**FIG. 2**). Animal studies have shown that SCFAs can be detected in the brain and can attenuate the effects of insults at the blood-brain barrier level[125,126]. In line with this, human studies have shown that various neuropsychiatric disorders are associated with a reduction in bacteria that produce SCFAs[127–129]. Dietary fibers have been reported to have protective effects on the brain and behavior, especially in cognitive performance, which could be partly mediated by the effects of gut microbiome-derived SCFAs. In depression and anxiety, observational data suggest a potential benefit for higher fiber intake, but evidence from human interventional trials does not fully support fiber supplementation for improving depression or anxiety outcomes[130].

Fatty acids, including omega-3 PUFAs, have been suggested to modify the gut microbiome (increasing alpha diversity and/or specific bacterial taxa), and such changes might contribute to their beneficial effects on cognition and mood [131,132]. Gut microbiome modulation could help restore the Western diet-induced gut barrier disruption and inflammation, which can lead to activation of eicosanoids and cytokine production, affecting the brain (**FIG 1 and 2**) [132]. Some bacterial species can also metabolize fatty acids, such as omega-6 PUFAs, influencing their effects[133]. In line with this, it is suspected that the response's variability to omega-3 PUFA interventions for cognitive benefits could be explained by the gut microbiome and background diet variations, but further evidence is needed to confirm this notion[132]. Phospholipoids are also being investigated for their effect on the gut microbiome-brain axis, but the relative contribution of the microbiome to such effects needs further attention [134].

Polyphenols are seen as dietary components that modulate brain and cognitive function (**FIG. 2**). Anthocyanins found in berries have received the most interest for their potential neuroprotective roles[135]. Polyphenol intake has been linked to enhanced cognitive functioning, especially in individuals with a low baseline intake of flavonoid-rich foods. [136]

Regarding fermented foods, which are rich in protein and live bacteria (**FIG. 2**), observational studies in humans show a separation of gut microbiome profiles between consumers and non-consumers, along with lowered anxiety in the former[137], but understanding the causal role requires more studies in humans with appropriate controls[138,139]. Studies in experimental models suggest that both live bacteria and metabolites (acetate, indole-3-lactic acid, etc.)

resulting from fermentation could have a role, for example, in neurogenesis or microglia maturation[139]. Of amino acids, tryptophan metabolism is strongly regulated by gut microorganisms and its degradation through the kynurenine pathway has been negatively correlated to depression and perceived stress in humans[140]. Also, ɣ-aminobutyric acid, an inhibitory neurotransmitter, is produced by gut microorganisms and is suggested to mediate the gut-brain connection in health and disease[141]. The amino acid metabolite p-cresol, which is associated with autism spectrum disorders in humans, has been causally related to social behavioural deficits in mice [142].

[H2] Cardiometabolic system

The gut microbiome synthesizes and co-transforms nutrients into other metabolites and provides structural bioactive components through diet-induced microbiome changes, which exert biological effects on the cardiometabolic system, as illustrated in **FIG. 3** and explained below.

The main functions of microbially produced SCFAs (acetate, propionate and butyrate) and organic acids (lactate and succinate) are summarized in **FIG. 3a**. Butyrate and propionate stimulate enteroendocrine cells (EECs) via GPCR41/43 to induce glucagon-like peptide-1 (GLP-1) and peptide tyrosine-tyrosine (PYY) production, thus regulating insulin secretion and glucose homeostasis and reducing appetite through brain signaling (**FIG 2; FIG. 3a**), as supported by rodent and human studies[143,144]. Lactate administration increases GLP-1, insulin and glucagon, likely via upper intestinal signaling in humans[145]. SCFAs can also induce cholecystokinin (CCK), which facilitates fat digestion and reduces food intake[146] (**FIG 2, FIG 3a**), and together with lactate can inhibit the production of the orexigenic hormone ghrelin[147] , but evidence of causality mainly comes from experimental models. SCFAs are linked to reduced pH and increased intestinal transit, promoting neuronal excitability and serotonin (5-HT) secretion (**FIG 2, FIG 3a)** and influencing nutrient absorption[148]. Butyrate, propionate and succinate can be used as substrates by enterocytes to promote intestinal gluconeogenesis (IGN), thus improving glucose tolerance, as shown in rodents[149]. SCFAs and lactate strengthen the gut barrier and reduce inflammation, partly by inducing Treg cells, as described previously[150,151] (**FIG 1**), which are altered by diet-associated metabolic disorders.

SCFAs, lactate and succinate can also act in peripheral tissues. They can inhibit lipolysis in adipose tissue to limit the release of free fatty acids and their accumulation in other tissues, causing insulin resistance[152–157] and activated thermogenesis[143], based mainly on evidence from rodents[149,155]. In humans, blood concentrations of SCFAs (but not stool concentrations) have been negatively associated with metabolic risk markers (whole-body lipolysis, triacylglycerols and free fatty acids)[158], but evidence varies across studies. The lack of consistency could be partly due to sampling limitations in humans and the fast utilization of those metabolites by host tissues, which make it difficult to establish firm conclusions in human trials. SCFAs and acetate can also act via vagal afferents and access the brain, reducing appetite in rodents[159], although for acetate an opposite effect via vagal signaling was reported as well[160]. Overall, the roles of butyrate and propionate in protecting cardiometabolic health

are the most well-documented in models and humans, while those of acetate are more inconsistent. The roles of lactate and, especially, of succinate in metabolic health are less well-established than those of SCFAs. Both gut microbial production and depletion of succinate have been related to metabolic benefits in obesity models [149,161]. In humans, elevated plasma succinate has been associated with obesity and cardiometabolic complications[162] and is related to reductions in succinate-consuming bacteria[163]. Given these paradoxical findings, it could be speculated that the physiological role of microbially produced metabolites could vary depending on the individual's health status, as occurs with host hormones such as leptin whose signaling is impaired in obesity.

The main microbially produced metabolites from proteins and amino acids linked to cardiometabolic health are shown in **FIG 3b**. Tryptophan is transformed into indole metabolites (indole propionic acid (IPA) and indole-3-acetic acid (IAA)), which can improve steatosis, type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD)[164–166] through their effects in strengthening the gut barrier[167] and reducing inflammation (**FIG 1**). However, indoles can also be transformed into indoxyl sulfate (IS) in the liver, which has been linked to CVD[168]. Other aromatic amino acid (phenylalanine and tyrosine) metabolites such as phenylacetylglutamine (PAGln), p-cresol (p-C), and p-cresyl sulfate (p-CS) are related to CVD in humans[169–171]. Histidine can be microbially converted into imidazole propionate (IP), which is increased in humans with T2DM and has been shown to impair insulin signaling in the liver[172]. In humans, increased serum levels of branched-chain amino acids (BCAAs) and/or enriched gut microbiome potential for BCAA biosynthesis have been associated with insulin resistance[173], T2DM[174], and CVD risk[175]. A potential pathogenic role was attributed to BCAA producers, such as *Prevotella copri*, in causing insulin resistance and glucose intolerance in mice fed this bacterium species, which was related to increased circulating BCAAs [173]. More recently microbial depletion of BCAAs in the intestine has been linked to reduced peripheral serotonin synthesis and improved glucose tolerance in mice[176]. This depletion could compensate for alterations in BCAA catabolism in metabolic tissues, which is impaired in individuals with obesity and insulin resistance and seems to contribute to metabolic dysfunction[177]. However, increased levels of circulating amino acids, including BCAAs (valine, leucine and isoleucine), have also been associated with increased GLP-1 and PYY, improved glucose metabolism, and reduced appetite[178] . The role of dietary protein in inducing satiety and reducing appetite and body-weight control is well-established [179]. This observation is not incompatible with the adverse effects directly attributed per se to BCAAs in organ metabolic dysfunction through alternative mechanisms.

The gut microbiome influences lipid metabolism in multiple ways (**FIG 3c**). Cholesterol can be microbially converted to coprostanol, leading to its secretion in feces and to reduced serum levels in humans[180]. Gut microorganisms also contribute to the synthesis, absorption and catabolism of long-chain fatty acids (LCFAs). Linoleic acid (an omega-6 PUFA) can be microbially converted into 10-hydroxy-cis-12-octadecenoic acid (HYA), which enhances GLP-1 and increases peristalsis, limiting lipid absorption[133]. A strain of *Holdemanella biformis* elevated intestinal luminal levels of omega-3 linolenic acid and oleic acid under a Western diet, increasing serum GLP-1 and PYY[181]. However, *Fusimonas intestini* strains produce trans-

unsaturated LCFAs (elaidate), which has been linked to CVD in humans and to glucose metabolic impairment in obesity models[182]. A pentadecanoic acid (PDA) – produced by *Parabacteroides distasonis* from inulin strengthens the gut barrier, alleviating nonalcoholic steatohepatitis in rodents[183]. Microbially synthesized sphingolipids can also be transferred to the hepatic portal vein, increasing liver ceramides in mouse models, which may worsen insulin resistance. 184 Choline and carnitine, which are mainly present in animal foods and are involved in host lipid metabolism, can be transformed by gut bacteria into trimethylamine (TMA), leading to the production of trimethylamine-N-oxide (TMAO) in the liver, which is linked to cardiometabolic disease [58](**FIG 3c**).

The gut microbiome modifies conjugated primary bile acids secreted by the liver in response to lipid intake in many ways, generating unconjugated primary and secondary bile acids with diverse signaling roles via FXR or TGR5 (**FIG 3d**). Microbially deconjugated primary bile acids and some secondary bile acids such as acylated bile acids (O-acyl-CAS) can act as inhibitors of the FXR receptor, thus activating the synthesis of bile acids from cholesterol and improving circulating lipid levels[185]. Secondary bile acids, such as deoxycholic acid (DCA), lithocholic acid (LCA), and 6α-hydroxylated bile acid (6α-HO-BAs) act as ligands of TGR5 and, thus, can activate GLP-1 production in EECs [186–188] and improve metabolism in other tissues [187,189]. Isoforms of LCA modulate the T cell balance and could reduce Western-diet-induced inflammation in cardiometabolic disorders (**FIG 1, FIG 3d**)[190]. However, DCA elevation has also been related to impaired glucose metabolism[191], revealing our limited understanding of the role of bile acids and the bile acid pool's complexity [185]. For example, the dual acyltransferase activity attributed to bacterial bile salt hydrolase enzymes would diversify the amino acids used in conjugation and, thus, the composition of the bile acid pool [192]. In this line, new microbiome conjugated bile acids (for example, phenylalanocholic acid, tyrosocholic acid, etc.) generated from cholic acid (CA) have been identified, with still unknown functions[74].

Concerning vitamins**,** the gut microbiome can be involved in biotin deficiency linked to T2DM [193] and severe obesity[194]. The gut microbiota has been demonstrated to contribute to host biotin status, as shown in mice with absence or antibiotic-depleted microbiota and diet-induced obese mice fed with fructo-oligosaccharides [194]. Gut microorganisms can also provide nicotinic acid (also known as vitamin B3) and thus alleviate diet-induced insulin resistance via GPR109A-mediated effects on the gut barrier (**FIG 1; FIG 3c**)[195].

Of non-nutritious food compounds, it is mainly polyphenol intake that has been related to cardiometabolic benefits (**FIG 3d**). Microbially produced polyphenol metabolites can protect cardiometabolic health, not only through immune mechanisms (**FIG 1**) but also through actions on energy homeostasis; for example, gallic acid promotes thermogenesis and reduces adiposity and 3-(3'-hydroxyphenyl) propionic acid reduces blood pressure via nitric oxide production[196] (**FIG 3d**). Polyphenol-induced increases in *Akkermansia muciniphila* could also mediate dietary improvements in metabolic health through the effects attributed to this bacterial species on strengthening the gut barrier (**FIG 1**) and inducing GLP-1 production in rodents[197].

Moreover, the gut microbiome composition defined by the diet is also a source of structural microbial components that can regulate immune (**FIG. 1**) and neuroendocrine pathways with effects on cardiometabolic health (**FIG 3d**). For example, bacterial muramyl dipeptide (MDP) and LPS via NOD and TLR4 binding, respectively, are required for GLP-1-mediated glucose metabolic control in rodents[198]. The bacterial peptidoglycan can also induce PYY secretion via activation of TLR2 signaling in experimental models[199]. This would mean that bacteria do not strictly need to be alive and metabolically active in the gut to exert some of their health effects, although viability would contribute to multiplying the stimulus load on host receptors mediating these outcomes.

[H1] Optimizing nutrition and public health through gut microbiome science

[H2] Dietary guidelines

Diet is now recognized as a key lever to improve human health. Consequently, most countries around the globe have adopted food-based dietary guidelines (FBDGs) as part of their public health nutritional strategies, to broadcast general indications of what constitutes a healthy diet for their populations, which represents the first call for action to prevent disease. FBDGs are based on consolidated general scientific evidence and, as a result, are mostly consistent around the globe[200], enabling tackling of common risk factors and facilitating applicability. At the same time, this generalized approach might require adjustments to account for differences in chronic disease determinants and dietary responses within a given population to increase effectiveness.

A prominent aspect of FBDGs is the promotion of plant-based foods such as fruit, vegetables, legumes, nuts, seeds and whole grains, with the intention to promote sufficient intake of dietary fibers, vitamins and minerals, and polyphenols. Conversely, virtually all guidelines recommend limiting the consumption of foods with high content of (added) sugars, saturated fat or salt. Regarding proteins, while some countries first aim to ensure a sufficient intake through protein-rich foods (either animal or plant-based), FBDGs in developed countries, where protein intake usually exceeds requirements, aim at rebalancing sources towards more plant-based proteins and at reducing the consumption of red and processed meat. They also promote the use of vegetable oil and fat (especially those with valuable unsaturated fatty acids) instead of animal saturated fat, as well as the consumption of oily fish to provide omega-3 PUFAs. Breastfeeding is also promoted, with health benefits for infants and their mothers. It is recommended that the consumption of alcohol and sugary drinks is limited. Finally, some guidelines also consider non-nutritional dimensions of food by recommending the reduction of ultra-processed foods (for example, Brazil, France, Zambia, and Sri Lanka) and promoting foods from organic production (for example, France) [200]. Other policies such as nutritional food labelling have been set. For example, in some European countries the Nutri-Score has been implemented to guide consumers towards healthier food choices [201]. This label displays five colours and letters based on the nutrient profile of foods that is relevant for disease prevention. Nutri-Score considers dietary fiber, fruit, vegetable, legumes and protein as favorable items, and saturated fatty acids, salt, energy and sugars, as well as artificial sweeteners in beverages, as unfavorable items [202], which can also benefit the gut

microbiome. In several South American countries, octagonal warnings are displayed for foods with high content in sugars, sodium, calories, or saturated fats[203], which are also detrimental to the gut microbiome. Specific labelling for ultra-processed foods is also under consideration[204]. The relevance of effects on the gut microbiome or effects mediated by the gut microbiome as part of the safety (re)evaluation of regulated products (for example, additives) and substances entering the food chain is being scrutinized by authoritative bodies for its possible implications in future food-related regulations and policies[205,206]. Yet, so far knowledge of the effects of diet-microbe interactions on human health has almost been neglected to inform dietary recommendations, except for some mentions of their potential importance in a few expert reports. For example, the European Food Safety Authority (EFSA) acknowledged the role of the gut microbiome in providing vitamin K and contributing to fiber fermentation and enhanced fecal bulk, and thus to normal bowel habits[207]. Along the same lines, Belgium and South African FBDGs attribute benefits to microbial fermentation of some dietary fibers (pectins, gums, oligosaccharides and resistant starch) on bowel functions, and reducing the pH, ensuring a favorable microbiome balance between potential beneficial and adverse bacteria[208,209]. The Dietary Guideline for Americans 2020-2025 has also underlined that advances in our understanding of the gut microbiome's role in mediating or moderating diet-disease associations could inform dietary guidance in the future[210], an aspect not considered in most guidelines so far. In the meantime, existing FBDGs, although not directly microbiome-oriented, already provide recommendations that are highly relevant for maintaining a 'healthy' gut microbiome on a population basis, as detailed in previous sections of this Review. However, current FBDGs might require refinement in light of emerging microbiome insights. For example, dietary fiber target intake levels are typically >25–30 g/day, depending on the country[207,211], which might be suboptimal as they are based on epidemiological studies in populations with low fiber consumption. Higher intakes (35-50 g/day) that would more closely align with prehistorical fiber intake estimates[211] could be required for achieving higher protection against NCDs, such as cardiometabolic and chronic inflammatory conditions such as cancer, through gut microbiome-mediated effects[144,212]. In addition to quantity, fostering diversity in fiber types and sources, and more generally diversity in foods consumed, would also be an action point to promote microbial diversity upon consolidation of causal links to health. While fiber is a promising and readily accessible target for microbiome-oriented dietary guidelines, other candidates, such as polyphenols[196] and live bacteria [139], which can mediate health benefits through the gut microbiome, also hold potential. Dietary recommendations for choline intakes could also be reconsidered, on the basis of evidence of the gut microbiome-mediated conversion of choline into TMAO[58]. However, these will require further mechanistic research and evidence of causality to establish robust, science-based recommendations. Another challenge of future FBDGs will be to account for the variability in the gut microbiome's ability to process various food components, which is highly individual. This emphasizes the need for stratified approaches based on microbiome composition in addition to general public health recommendations to enhance their efficacy. Knowledge gaps and research needs are summarized in **Box 1**[73,74].

[H2] Preventive and therapeutic nutrition

As the gut microbiome is suggested to be involved in the risk and pathogenesis of most NCDs and to be shaped by diet, microbiome-tailored nutrition has been proposed as a possible adjuvant for preventing or treating NCDs[213], partly by modulating the disease-contributing commensal ecosystems.

Diets that are intended to prevent or mitigate pathological conditions are displayed in **Table 3**[58,64,214–228,228–244]. One such dietary approach consists of excluding dietary components that are causally involved in the disease, as in the case of celiac disease, primary lactose intolerance, and phenylketonuria. Avoidance of the pre-determined disease-causing dietary components mitigates disease ramifications driven by dietary exposure, although secondary consequences of the dietary restriction on microbiome diversity or functions should also be considered, as for example with a low-lactose diet (**Table 3**). More complex and less genetically defined food-influenced diseases such as irritable bowel syndrome (IBS) or some forms of epilepsy might be similarly managed by dietary modifications, for example using low-fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diets or ketogenic diets, respectively [240]. The gut microbiome is known to be affected by these diets, but its role in the patient's response has not been extensively considered so far. Importantly, extended low-carbohydrate diets often lack essential fibers, which can also critically worsen some IBS symptoms[245]. Dietary approaches for mitigating other diseases and the possible nutritional and gut microbiome mediators are depicted in **Table 3**.

So far, microbiome-directed preventive and therapeutic nutrition has been mainly focused on the use of prebiotics and the supply of microorganisms to the ecosystem (known as probiotics). Of prebiotic fibers, inulin-type fructans have been reported to help mitigate obesity[246], T2DM[247], and inflammatory bowel disease (IBD)[248], and reduce CVD risk[249] in some of the clinical trials performed. However, in mouse models, dietary fibers have also been suggested to exacerbate IBD or allergic inflammation[250], or even promote colon tumorigenesis[251]. Omega-3 PUFAs are increasingly considered for preventing neurological and cardiovascular diseases (Table 3; MedDiet, MIND), but comprehensive meta-analyses also emphasize the need for personalized adjustments and more robust clinical studies[252,253]. Breast milk is recommended as the optimal food for infants, particularly as clinical studies link its prebiotic human milk oligosaccharides (HMOs) to reduced risks of fatal gastrointestinal inflammation in infancy and chronic diseases in adulthood[254]. Nowadays, various approaches, such as synthetic HMOs, prebiotic fibers or probiotics, aim to mimic HMO benefits in infant formulas but still fall short of replicating the complexity of natural HMOs, with ongoing research focused on improving these substitutes.

In addition to traditional probiotics, such as the widely used *Lactobacillus* and *Bifidobacterium*, other indigenous bacterial species inhabiting the gut, known as next-generation probiotics and identified through bottom-up, drug development-like approaches, promise disease-specific therapeutic effects. Yet, strong evidence from human studies is still needed to substantiate these claims[255]. In general, clinical trials with probiotics still yield mixed and sometimes controversial results [256,257]. This can be partially attributed to their failure to survive and colonize the intestine (although this is not always required) or to

replicate a more-complex network of functional bacteria that is effective in repairing the disease ecosystem[256,257].

Of dietary components, tryptophan has a promising role for patients with IBD and metabolic syndrome, as its bacterially produced metabolites (known as indols) engage the local AHR-IL-22 axis[258]. In contrast, comprehensive re-analyses of studies on dietary vitamin A or D supplementation in non-deficient individuals failed to confirm the initially encouraging benefits [259,260]. This example highlights the broader issue of numerous trials claiming generalized benefits of nutritional supplements, which often mislead the public and underscore the need for more targeted clinical studies.

Overall, nutritional intervention studies based on diets, food constituents or pre/probiotics still generate contradictory results[256], which is evident from ongoing debates over fiber-rich diets for IBD [245], as similarly occurs with low-fat diets for obesity-related diseases[261]. For example, some patients with IBD might respond very poorly to dietary fibers, which appears to conflict with the fact that diets such as the Crohn's disease exclusion diet (CDED), which include selected fibers, achieve much better compliance, tolerance and longer-lasting benefits compared with fiber-restricted exclusive enteral nutrition (EEN) diet, which is likely due to enhanced microbiome diversity and SCFA production[245] (**Table 3;** EEN). These inconsistent findings stem from enormous patient variability due to highly individual microbiomes, background dietary intake, lifestyles, ethnicities, and clinical manifestations (for example, disease flare or remission in IBD), which represent parameters that are often disregarded in region-restricted or small-sized studies. This vast complexity makes one-size-fits-all approaches ineffective and discouraging (**Box 1**). Thus, rigorous, randomized, placebo-controlled trials with comprehensive participant metadata collection, including habitual diet, will be essential for more accurate and informative findings. Future studies on therapeutic nutrition might also consider microbiome profiling and focusing on smaller, well-defined patient subgroups to enable a clearer understanding of treatment responses and potential side effects. For example, pre-screening of patients with IBD could help predict tolerability to certain fiber types and guide towards targeted prebiotic therapy.

[H2] Precision and personalized nutrition

Precision approaches, also known as stratified nutrition, aim to provide more precise and efficient dietary recommendations by targeting homogeneous subgroups[262]. Compared to fully personalized approaches, they offer an intermediate level of personalization, balancing efficacy with feasibility and aligning with global public health strategies to combat NCDs[1].

Initially focusing on gene-diet and epigenome-diet interactions[263], research in precision nutrition has expanded to include the gut microbiome. Initial studies have focused on identifying specific gut microbiome stratifying factors, such as *Prevotella:Bacteroides* ratio[26,264,265], enterotypes[266], gene richness[49], gut microbiome subtypes, or *Akkermansia muciniphila* levels [267], which could help predict metabolic response to dietary interventions.

Probiotic uses might also benefit from microbiome-informed precision approaches, owing to the capacity of the gut microbiome to distinguish responders from non-responders[90,257,268],

and to, together with dietary factors, influence efficacy [269,270]. Categorization of the gut microbiome into permissive and resistant types shows promise for predicting responders to probiotics whose mechanisms of action rely on persistence or gut microbiome changes, with permissive microbiome types displaying longer persistence[271,272], but relationships with efficacy still need to be established.

Moreover, given the mode of action of fibers, and especially prebiotics, substantial efforts have been made to predict the responses on the basis of the baseline individual's microbiomes[172]. Key features that are currently associated with the responsiveness of the gut microbiome to fibers include the abundance of *Bifidobacterium* spp., alpha-diversity, CAZy genes, and the average number of genes per organism, but these are not necessarily related to health effects. A few studies searching for gut microbiome predictors of host health responses to fibers have been launched, but they are still yielding different and non-comparable results [273,274]. For example, while the response to arabinoxylans was predicted first by microbiome changes and, to a lesser extent, by baseline microbiome composition[273], the responses to inulin were reported to be explained by the initial microbiome composition, pointing to a role for different microbiome signatures in humans [274].

Personalized nutrition, which is understood as that specifically tailored to the individual, has emerged as a game-changer for reducing disease risk and for improving disease therapy[275]. This is a data-driven, evidence-based strategy that relies on the individual's features (microbiome and other omics, clinical, and personal data) and can be translated into improved disease preventive and mitigating dietary strategies based on known mechanistic rationales. For example, the bacterially produced metabolite TMAO is associated with atherosclerosis, and patients with high levels of TMAO-producing bacteria might benefit from receiving a diet low in TMAO precursors such as red meat[276]. Moreover, to tackle the overall disease complexity, machine-learning and artificial intelligence-based computational approaches integrating big data sets are being investigated [277]. A successful example is the prediction of glycaemic responses to certain foods[278,279] in order to personalize diets to individually control glycemia in patients with pre-diabetes and diabetes, with better efficiency than conventional dietary recommendations[280]. Similar approaches have also been shown to help predict postprandial lipaemia and insulinaemia[28]. Those studies show that gut microbiome data explain 6-9.5% of postprandial response variations, sometimes surpassing genetic factors or meal composition[281]. Although the precision and personalized nutrition fields are still evolving and more research is needed to fully unravel the intricacies between diet, microbiome and health, it heralds a future of more effective dietary strategies driven by the profiling of individual features and smart, holistic bioinformatic and machine-learning strategies.

[H1] Conclusions

The gut microbiome has an irrefutable role in catalyzing nutrient conversions and providing signals that regulate the host immune, endocrine and nervous systems in response to diet, with effects on all aspects of human health. Advances in our understanding of these

intertwined actors could be key to addressing today's challenge of optimizing nutrition and leveraging its role in chronic disease prevention and management (**Box 1**).

The overall diet better explains gut microbiome variations and the health consequences, but disentangling the contribution of food and nutrients to those effects is also crucial for acquiring mechanistic knowledge and for messaging on the best food choices. Yet, existing dietary quality indexes do not well-capture microbiome-diet interactions and their health consequences. In this regard, adapting current tools and models to better capture dietary intakes relevant to the gut microbiome, such as fiber and polyphenol diversity and live bacteria ingestion, and considering the non-nutritional dimension of food and eating behavior (for example, eating timings and food processing) is very much needed (**Box 1**).

The gut microbiome contributes to the variability of dietary responses (glycemic or lipemic) and the pool of metabolites generated from the diet, but most metabolic processes, especially those occurring in the upper gut, and microbial metabolites are uncharacterized and their connection to human health and disease is still limited. Long-term epidemiological, interventional and mechanistic data are needed to progress our understanding of the roots of dietary response variations and prove causality (**Box 1**). Efforts are also required to define global standards for studies investigating diet-microbe-host interactions to gain consistency.

Overall, fundamental and applied research in this area could help to reinforce existing diet-health relationships with additional supportive evidence (for example, of the protective roles of fibers and plant foods through microbiota-mediated mechanisms); discover as yet overlooked beneficial or detrimental effects stemming from diet-host-microbe interactions (for example, TMAO producers); and inform more precisely what foods and diets are better suited to a particular individual or population subgroup (for example, which are the best fiber or protein sources or dietary patterns), thus progressing towards microbiome-informed food guidelines and medical, precision, and personalized nutrition.

Yet, little progress has been made in embedding scientific knowledge of microbiome-diet-host interactions into nutritional and clinical practice, as reality still falls short of expectations. While these challenges remain unresolved, existing dietary guidelines already offer an actionable point for promoting beneficial diet-microbe-host interactions in the general population and improving the engagement of individuals in healthier eating habits through responsible communication of the diet-microbe-health interlinks.

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Author contributions

The authors contributed equally to all aspects of the manuscript.

Competing interests

Y.S. is a co-author of probiotic patents and serves as a scientific advisor for Arla Foods. P.V. serves as a scientific consultant and advisor for Arla Foods and New Road Innovations LTD. J.F.C. is the co-author of probiotic patents and has received research funding from IFF, Nutricia and Kerry Foods and has been an invited speaker at meetings organized by Bromotech & Nestle. The other authors declare no competing interests.

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Key points

- Exploring the granularity of the diet and multidimensional aspects of foods together with advanced big data-driven analyses offers opportunities to better capture diet-microbiome-health relationships and explain unsolved response patterns and mechanisms in humans.
- Microbially produced metabolites from dietary sources and microbial cell structural constituents have been demonstrated to regulate immune, endocrine and nervous system functions, supporting their causal role in diverse health domains.
- Current food-based dietary guidelines are not yet microbiome-oriented but generally provide advice for maintaining diet-microbe synergies relevant to human health.
- Further understanding of the contribution of the gut microbiome to the heterogeneity of diet-related responses is vital to optimizing the role of nutrition in public health.
- The gut microbiome contributes to postprandial responses to meals, suggesting the potential to predict the long-term health consequences of our diet more accurately.
- The response to the diet and the links to the gut microbiome vary in health and disease contexts and need to be scrutinized for the development of more-precise nutritional practices.

Figure 1. Dietary orchestration of gut barrier and immunity is linked to the microbiome.

Dietary substances and their microbially produced metabolites (in red) modulate intestinal barrier integrity and immunity through various mechanisms involving the resident microbiome. **1)** Dietary fibers mechanically stimulate mucus-producing goblet cells and prevent mucus digestion by nurturing commensal bacteria. Microbiota sensing via TLR/NLRs triggers plasma cells and Paneth cells to secrete sIgAs and AMPs. Dietary metabolites such as RA and IEC-derived cytokines further facilitate plasma cell development. **2)** Dietary substances shape microbiome composition, thereby indirectly influencing anti-inflammatory and mucus-promoting bile acid levels and triggering TLR/NLR/CLR-mediated inflammasome activation in IECs and immune cells. Inflammasome activity is also directly influenced by dietary metabolites. **3)** Tight junctions are disrupted by TLR signaling, pro-inflammatory cytokines and diet-induced ROS or transcriptional reprogramming as it triggers NF-κB- and ROCK-regulated MLC signaling. Dietary metabolites such as SCFA or AhR ligands counteract these disruptions and enhance TJ protein expression. **4)** IL-22 signaling, primarily from ILC3s and T_H22 cells, is crucial for mucus production and IEC maintenance, and is multifactorially supported by dietary substances. SCFAs and PUFAs activate GPCRs and downstream transcription factors, and SCFAs inhibit HDACs, further promoting transcription. AhR ligands and vitamin metabolites directly activate different IL-22 transcription factors. **5)** Dietary metabolites influence the abundance and function of several intestinal immune cells. Particularly, vitamin A-derived RA and AhR ligands integrate with cytokines to support Tregs and establish an anti-inflammatory milieu. AhR, Aryl hydrocarbon receptor; AMP, Anti-microbial peptide; APRIL, A proliferation-inducing ligand; BAFF, B-cell activating factor; CLR, C-type lectin receptor; DC, Dendritic cell; FXR, Farnesoid X receptor; GPCR, G-protein coupled receptor; HDAC, Histone deacetylase ; HIF1α, Hypoxia-inducible factor 1α; IDO, Indolamin-2,3-Dioxygenase; IEC, Intestinal epithelial cell; IEL, Intraepithelial lymphocytes; IFNγ, Interferon γ; IL-22R, Interleukin-22 receptor; ILC, Innate lymphoid cell; MLC/K, Myosin light chain /kinase; NF-κB, Nuclear factor kappa B; NKT, Natural killer T cell; NLR, NOD-like receptor; NLRP3, Nucleotide-binding oligomerization domain 3; PPARγ, Peroxisome proliferator-activated receptor γ; PUFA, Poly-unsaturated fatty acid; PXR, Pregnane X receptor; RA, Retinoic acid; RAR, Retinoic acid receptor; ROCK, Rho-associated coiled-coil-containing protein kinase; RORγt, RAR-related orphan receptor γ; ROS, Reactive oxygen species; SCFA, Short-chain fatty acid; SFA, Saturated fatty acid; sIgA, Secretory immunoglobulin A; STAT3, Signal transducer and activator of transcription 3; TGFβ, Transforming growth factor β; TGR5, Takeda G protein-coupled receptor 5; T_H1, Type 1 T helper cell; TJs, Tight junctions; TLR, Toll-like receptor; TNF, Tumor necrosis factor; TSLP, Thymic stromal lymphopoietin; VDR, Vitamin D receptor.

Figure 2. Diet and gut microbiome interactions orchestrate nervous system function

As shown in the section containing beneficial bacteria, diets rich in fiber, fermented foods, and polyphenols, and with moderate levels of proteins sustain the growth of mutualistic microorganisms and contribute to the generation of metabolites that favorably regulate the nervous system function. SCFAs induce the secretion of the anorexigenic peptides GLP-1, PYY and CKK by EECs, which act on the hypothalamus centers of food intake control; SCFAs strengthen the gut barrier integrity and induce protective immune responses, avoiding chronic inflammation. Gut bacteria participate in the provision and metabolism of amino acids that are precursors of neurotransmitters such as tryptophan, which can be transformed to 5-HT in ECCs, or tyrosine, which can be converted to catecholamines (e.g. norepinephrine and dopamine), which can interact with the enteric nervous system or stimulate vagal sensory neurons in the gut, leading to activation in the brain structures, controlling mood, behavior and mental health. As shown in the red section, unhealthy diets (i.e. Western diets rich in energy, saturated fat, and simple sugars) alter the composition and function of the gut microbiome, damage gut integrity, and contribute to inflammation in the gut and systemically through the translocation of endotoxins from the gut lumen to the bloodstream and other inflammatory mediators that can induce systemic inflammation associated with behavioral and mental disorders. CKK, cholecystokinin; ECCs, enterochromaffin cells; EECs, enteroendocrine cells; ENS, enteric nervous system; GLP-1, glucagon-like peptide-1; 5-HT, 5-hydroxytryptamine; LPS, lipopolysaccharide; PYY, peptide tyrosine-tyrosine; SCFAs, short-chain fatty acids.

Figure 3. Dietary influence on cardio-metabolism is linked to the gut microbiome

Gut microbiome-produced metabolites from dietary sources or synthesized de novo affect different aspects of cardiometabolic health, depicted in four panels according to their main nutrient source. **a) Dietary fiber** fermentation leads to the generation of SCFAs that, via GPCR signaling, induce anorexigenic (GLP-1, PYY, CKK) and inhibit orexigenic (ghrelin) hormone production by EECs. SCFAs may act on peripheral organs and the brain, regulating energy homeostasis. SCFAs reduce pH and increase 5-HT and intestinal transit, affecting nutrient absorption. SCFAs, lactate and succinate may act as substrates for IGN, improving glucose metabolism; lactate may induce GLP-1 and with succinate regulate metabolic health and inflammation, but their roles are less well established. SCFAs repair the gut barrier and with lactate reduce inflammation caused by hypercaloric diets (Fig. 1)**. b) Dietary amino acids** are metabolized and supplied to the host by gut microorganisms. Indole metabolites from tryptophan (IPA, IAA) protect against gut barrier disruption and inflammation (Fig. 1), but IS generated in the liver, and microbial metabolites generated from other aromatic amino acids (PAGln, p-C, p-CS) and histidine (IP), exert deleterious cardiometabolic effects; BCAA-producing bacteria are associated with metabolic disorders, but BCAAs plus other amino acids could induce satiety. **c) Dietary lipids** such as cholesterol are metabolized by gut bacteria, favoring its excretion; the absorption and synthesis of LCFAs can be catalyzed by gut microbes, increasing or generating other molecules with potentially beneficial (omega-3 PUFAS; HYA; PDA) or detrimental (elaidate, sphingolipids) effects. **d) Bile acid composition** depends on host-microbe co-metabolic processes. Microbially deconjugated primary BAs and 3-O-acyl-

CAS signal via FXR and secondary BAs (DCA, LCA, and 6α-HO-BAs) via TGR5 expressed in gut and peripheral organs, and thus, can improve metabolism, but opposite effects are also reported (e.g. for DCA). Isoforms of LCA can reduce inflammation. Microbial metabolites of **non-nutritious compounds** (polyphenols) protect cardiometabolic health; **Microbial cell structural components** (MDP, LPS) can activate enteroendocrine hormone production (GLP-1, PYY) that regulate glucose metabolism and appetite. Red boxes indicate hormones and blue boxes indicate food constituents or metabolites. AhR, Aryl hydrocarbon receptor; BAs, bile acids; BCAAs, branched chain amino acids; CKK, cholecystokinin; CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; G, Glycine; Cyp7a1, cholesterol 7 alpha-hydroxylase; FG15/9, fibroblast growth factor 15/9; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; GPCRs, G protein-coupled receptors; HDAC, Histone deacetylase; 6α-HO-BAs, 6α-hydroxylated BA; HRs, hormone receptors; HYA, 10-hydroxy-cis-12-octadecenoic acid; IAA, indole-3-acetic acid; IPA, indole propionic acid; IGN, intestinal gluconeogenesis; IP, imidazole propionate; IS, indoxyl sulfate; LCA, lithocholic acid; LCFAs, long-chain fatty acids; LPS, lypopolysaccharide; MDP, muramyl dipeptide; NODs, nucleotide-binding and oligomerization domain-like receptors; 3- O-acyl-CAS, acylated BAs; PAGln, phenylacetylglutamine; p-C, p-cresol; p-CS, p-cresyl sulfate; PDA, pentadecanoic acid; PYY, peptide tyrosine-tyrosine; SCFAs, short-chain fatty acids; T, Taurine; TGR5, Takeda G protein-coupled receptor 5; TLR, Toll-like receptor; Type 1 T helper cell; TJs, Tight junctions.

Table 1. Large-scale population-based studies of the relationships between food intakes and gut microbiome structure

Study name, country and size	Food intake assessment tool	Fecal microbiome sequencing method	Reference
PREDICT 1 study: UK, N=1001 (discovery) and USA, N=97 (validation)	131-item FFQ	Shotgun sequencing	[17]
LifeLines-DEEP cohort: Netherlands, N=1135	Food frequency for 78 items	Shotgun and 16S rRNA gene sequencing	[35]
Flemish Gut Flora Project: Belgium, N=1106 LifeLines-DEEP cohort: Netherlands, N=1135 (replication)	Food questionnaire	16S rRNA gene sequencing	[36]
Adiposity Phenotype Study (Multiethnic Cohort Study): USA, n=1709	Serum carotenoids and tocopherols (biomarkers of fruit and vegetable dietary intake)	16S rRNA gene sequencing	[37]
Arivale non-medical lifestyle intervention program (Arivale Inc., Seattle, WA): USA, n=3409	Short food frequency list (Dietary Targets Monitor)	16S rRNA gene sequencing	[38]
Milieu Intérieur study : France, n=862	Food frequency for 19 items	16S rRNA gene sequencing	[39]
FINRISK/FINDIET 2002 study: Finland, n=1273	48h-dietary recall	Shallow shotgun sequencing	[40]
FINRISK 2002 study: Finland, n=4930	Food propensity questionnaire, 42 items	Shallow shotgun sequencing	[41]
Shanghai Women's Health Study (SWHS) and Shanghai Men's Health Study (SMHS): China, n=1920	Repeated FFQs (81 items)	16S rRNA gene sequencing	[42]
Adiposity Phenotype Study and microbiome Genome-Wide Association Study (Multiethnic Cohort Study): USA, n=5267	180-item FFQ (2003-2008)	16S rRNA gene sequencing (stool collection in 2013-2016)	[43]
Microbioma Español Project: Spain, n=528	Frequency for 43 food items	16S rRNA gene sequencing	[44]
HELIUS study: Netherlands, n=1309	Ethnic-specific 200 item-FFQ	16S rRNA gene sequencing	[45]
TwinsUK registry: UK, n=1457	131-item FFQ → yogurt consumption	16S rRNA gene (n=1457) and shotgun (n=544) sequencing	[46]
Guangzhou Nutrition and Health Study: China, n=1879 Guangdong Gut Microbiome Project: China, n=6626 (replication)	79-item FFQ → fruit and vegetables	16S rRNA gene sequencing	[47]
Estonian Microbiome Project (EstMB): Estonia, n=2509	Dietary preferences (21 items)	Shotgun sequencing	[48]

Table 2. Associations between food groups and gut microbiota alpha- and beta-diversity

Alpha-diversity	**Increased diversity**	-fruit and berries[35,38–41,47,48], vegetables [35,38,48], fruit and vegetable intake biomarkers (carotenoids)[37] -fiber-rich bread [41] -dairy (yogurt[46], buttermilk[35], low-fat cheese [41] -fish [17,38,39,44], poultry[41] -coffee or caffeinated beverages [35,38], tea [35], alcoholic drinks (red wine) [35,38] -chocolate type [36], sweets [48]
	Decreased diversity	-sugary drinks [35,36,38,39,48], beer[35,36] -(white) bread [35,48], potatoes/pasta/rice [38,48] -whole-fat milk/cream [35,40] -meat and processed meat [39,48] -desserts, ice cream, fatty-sweet products [38–40] -fried products [39], ready-cook meals [39], snacks[35], sauces/spreads[35] -legumes and pulses [35], fruit and vegetable intake biomarkers (tocopherol and retinol)[37]
	Explained variance	grains, low-fiber rice and pasta, vegetables, olive oil, other oils, salad dressing, sugar-sweetened beverages or bread fillings [45]
Beta-diversity	**Explained variance**	-fruit and berries [17,35,36,39,40,41,47,48], juices [41], compote and jams [48], vegetables [17,35,40,41,48], fruit and vegetable intake biomarkers (tocopherol, carotenoids) [37], potatoes [44,48], legumes [17,40], soy products [36], nuts and seeds [17,40] -(whole) grains [17,40,48], (fiber-rich) bread [35,36,41,48] -dairy [17,42,44]: cheese [39–41], milk, cream, ice-cream [40] -meat and processed meat [17,36,41,44,48], fish [41,48], poultry [41] -sugary drinks [17,35,36,44,51], alcoholic drinks (beer, red wine) [17,35,36], coffee or tea [17,35,36,48] -sweets or desserts [17,48], chocolate type [36] -snacks [35], ready-cook meals [39], fried products [39], dressings and oils [41]

Table 3: Examples of established medical diets and their potential gut microbiome-mediated effects on diseases

Medical diet	Disease focus	Dietary characteristics	Microbiome-related findings	References
DASH	Hypertension, CVDs, kidney diseases	Rich in - Whole grains - Fruits, vegetables (fibers) - Lean proteins - Low-fat diary Low in - Sodium (salt) - Processed foods - Saturated lipids - Red meat	- High salt induces dysbiosis promoting inflammation linked to hypertension and CVDs - Dysbiosis affects microbiota-derived metabolites, such as tryptophan metabolites, affecting CV health - Bacteria metabolize red meat, dairy, and eggs to TMA; its hepatic metabolite TMAO acts as a vasoconstrictive and promotes atherosclerosis - Microbiota-produced SCFAs act as anti-inflammatory and vasodilatory	58,64,214–216
MedDiet	Diet-induced obesity and related CVDs, T2D and T1D; mental disorders such as depression	Rich in - Complex carbohydrates / whole grains - Olive oil and nuts (MUFAS, PUFAS) - Vegetables, fruits (polyphenols) - Legumes (fibers, plant proteins) - Fish, lean proteins - Balanced ratio of Omega-6/Omega-3 fatty acids Low in - Red meat - Processed foods	- Dysbiosis in patients with obesity, prediabetesT2D or T1D is linked to inflammation and metabolic dysfunction - MedDiet elevates microbiome diversity and increases fiber-metabolizing species - Microbiome partly mediates MedDiet-induced effects (improved glycemic response, reduced plasma cholesterol and triglyceride levels, reduced inflammation) - Microbiota-produced SCFAs induce satiety and help mitigate obesity - MedDiet improves depression symptoms - Depression improvement is believed to be mediated by anti-inflammatory and neuromodulatory effects of bacterial metabolites (from fibers, polyphenols, tryptophan-kynurenine metabolism), but more research is required to clarify mechanistic causalities	217–219

		- Sweets		
MIND	Neurodegenerative diseases (dementia, AD, Parkinson disease); psychiatric disorders such as anxiety	Combination of DASH diet and MedDiet, with higher consumption of berries, green leafy vegetables (phytochemicals) and nuts	- Inverse correlation between MIND diet, microbiota and neurodegenerative disease progression - Phytochemical-rich diets foster protective bacteria and limit growth of potential pathogens - Bacterial components and metabolites can reduce systemic and neuro-inflammation - Bacteria can modulate microglia functioning, affecting degenerative disease progression - Elevated levels of bacteria-derived secondary bile acids characterize early AD and positively correlate with cognitive impairments - Bacterial-derived dietary metabolites can serve as direct neuroactive substances, e.g. serotonin derivatives, affecting anxiety	[220–225]
FODMAP-low diet	IBS	Phases of elimination, reintroduction and maintenance of FODMAPs	- FODMAP fermentation by colonic bacteria can cause gas, diarrhea, cramping, and abdominal pain - High FODMAPs cause dysbiosis in some individuals leading to intestinal barrier dysfunction and visceral hypersensitivity via mast cell activation - Low/no FODMAP diets improve symptoms of patients with IBS - Some microbiota dependent on FODMAPs to produce SCFAs, consequently, prolonged low-FODMAP diet reduces these beneficial bacteria and SCFA production - Long-term low FODMAP diet may contribute to small intestinal bacterial overgrowth - Specific prebiotic fibers may improve IBS symptoms in some individuals and counteract low FODMAP diet-induced dysbiosis, but more research and likely personalized diets are required	[226–229]

Gluten-free diet	Coeliac disease	Life-long exclusion of gluten-containing foods (wheat, barley, rye)	- Patients with celiac disease have dysbiosis - Gluten-free-diet alleviates symptoms, but dysbiosis partly persists, necessitating alternative approaches - Dysbiosis can aggravate celiac disease by increasing inflammatory pathobionts and reducing mutualistic bacteria that provide immunoregulatory factors - Oral and some gut microbiota-derived enzymes can modulate immunogenic gluten peptides - Probiotics might help fight dysbiosis and mitigate symptoms, but more research is required	230–232
Phenylalanine-low diet	Phenylketonuria	Life-long exclusion of high phenylalanine-containing foods (meat, dairy, eggs) Rich in: - Vegetables, legumes (high fiber, often semi-vegan diet) - Carbohydrates - Special Phe-free amino acid formula Low in: - Proteins	- Dysbiosis in children and adults with phenylketonuria, partly diet-independent - Dysbiosis characterized by decreased SCFA production despite high fiber intake - Adjusted pre-/probiotic supplementation and engineered probiotics that express phenylalanine-metabolizing enzymes are suggested to mitigate disease, but more research is required	233–235
Lactose-low diet	Lactose intolerance	Life-long exclusion or reduction of lactose-rich foods (diary)	- Lactose from human milk and habitual diet nurtures specific bacteria (*Lactobacillus* and *Bifidobacterium*), which degrade lactose to produce SCFAs by other commensals - Colonic microorganisms adapt to the level of lactose - Complete lactose withdrawal stops colonic adaptation and lowers lactose-metabolizing species and the threshold for intolerance - Clinical trials with bifidobacteria and yogurt starter cultures (providing beta-galactosidase activity), galactooligosaccharides or small amounts of lactose	236–238

			elevated lactose-metabolizing bacteria, mitigated symptoms, and increased the intolerance threshold	
KD	Drug-resistant epilepsy and ASD; obesity and metabolic disorders	Rich in: - Fat - Proteins Low in: - Carbohydrates (restriction to induce ketosis)	- KD alters microbiome, reducing alpha-diversity, depleting *Bifidobacterium* and SCFAs, and increasing *Akkermansia* and *Parabacteroides* species - KD-induced *Akkermansia* and *Parabacteroides* species are responsible for seizure protection in epilepsy - KD-microbiota generate less gamma-glutamylated amino acids due to reduced peptidase activity, affecting brain GABA/glutamate ratios crucial for seizure prevention - KD-microbiota reduce Th17-mediated inflammation and increases neuromodulatory factors that improve behavioral symptoms in ASD - Very low-calorie KD is effective against obesity by changing microbiome, reducing inflammation and increasing intestinal integrity	239–242
EEN / PEN	IBD, particularly CD	Short-term liquid diet with elemental (amino acid-based), semi-elemental (oligopeptides) or polymeric (whole protein-based) formula EEN is often combined with CDED diet, which allows selective solid foods similar to MedDiet	- CD inflammation is driven by disturbed host-microbiome interaction; patients with CD have dysbiosis and altered metabolome - EEN is effective in mitigating symptoms due to low food antigen exposure and resting bowel (intestinal healing) but adherence to EEN diet is challenging - EEN modifies microbiome and luminal bacterial metabolites (e.g. SCFAs) but the exact mechanism remains elusive - EEN alters CD-associated dysbiosis but reduces microbiota diversity, indicating a non-'healthy' microbiome but a renewed host-microbiome interaction - PEN with CDED includes foods that do not negatively affect microbiome and intestinal integrity; PEN/CDED improves compliance to diet and strengthens long-term effects on the microbiome	243,244

			- EEN/PEN also suggested for ulcerative colitis and juvenile idiopathic arthritis due to anti-inflammatory and microbiome-modulating effects	

*Abbreviations: AD, Alzheimer's disease; ASD, autism spectrum disorder; CD, Crohn's disease; CDED, CD exclusion diet; CVD, cardiovascular disease; DASH, dietary approaches to stop hypertension; Exclusive enteral nutrition, EEN; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; GABA, ɣ-aminobutyric acid; IBD/IBS, inflammatory bowel disease / syndrome; KD, Ketogenic diet; MedDiet, Mediterranean diet; MIND, Mediterranean-DASH Diet Intervention for Neurodegenerative Delay; MUFAS, monounsaturated fatty acids; PEN, partial enteral nutrition; PUFAS, polyunsaturated fatty acids, SCFAs, short-chain fatty acids; T1D, type 1 diabetes; T2D, type-2 diabetes TMA, Trimethylamine; TMAO, trimethylamine-N-oxide

Box 1. Knowledge gaps to advance microbiome-informed optimal nutrition

- Dietary assessment tools and analytical methods need to be adapted to better capture the heterogeneity of food-microbiome interactions, integrating the multiple dimensions of the diet (habitual food and nutrient intake, daily variations and eating times and chronobiology, food quality, and processing).
- Adverse variations in food-microbiome associations over normal fluctuations need to be explored in large-scale longitudinal and interventional studies to progress from associations to causality.
- Investigating the role of the diet-microbe interactions in different gut compartments, showing regional specialization in endocrine, immune and neural functions, will lead to discoveries and better mechanistic understanding, as most studies have been focused on the large intestine. Exploring regions of the upper gut has been ethically and technically challenging as it required the use of invasive sampling methods (e.g. endoscopy), but recent developments of ingestible devices (e.g. capsules) targeting and sampling at specific gut sites would permit us to overcome those limitations [73,74].
- A plethora of microbially produced metabolites and structural bioactive constituents with effects on the immune, nervous and cardiometabolic systems remain to be discovered[74], along with the dietary nutrient gradients, patterns and ecological factors that drive their production.
- Precision (stratified) nutrition strategies based on the categorization of individuals according to their gut microbiome features could improve the efficacy of microbiome-directed interventions (fibers, probiotics, etc.), but robust predictors still need to be identified.
- Personalized nutrition approaches that integrate gut microbiome data with other host parameters seem to be promising in predicting postprandial responses, but whether this can be translated to improvements in chronic disease prevention has yet to be established.
- The role of nutrition in patient care has been practically neglected, although malnutrition, immune dysregulation and gut microbiome alterations underlie most chronic conditions, and dietary components affect health and disease populations in different ways. Understanding how diet-microbe interactions might shift the disease course would help tailor dietary advice and develop medical nutrition.