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Review article

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The interplay between diet and the gut microbiome: implications for health and disease

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Abstract

Diet has a pivotal role in shaping the composition, function and diversity of the gut microbiome, with various diets having a profound impact on the stability, functionality and diversity of the microbial community within our gut. Understanding the profound impact of varied diets on the microbiome is crucial, as it will enable us not only to make well-informed dietary decisions for better metabolic and intestinal health, but also to prevent and slow the onset of specific diet-related diseases that stem from suboptimal diets. In this Review, we explore how geographical location affects the gut microbiome and how different diets shape its composition and function. We examine the mechanisms by which whole dietary regimes, such as the Mediterranean diet, high-fibre diet, plant-based diet, high-protein diet, ketogenic diet and Western diet, influence the gut microbiome. Furthermore, we underscore the need for exhaustive studies to better understand the causal relationship between diet, host and microorganisms for the development of precision nutrition and microbiome-based therapies.

Sections

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Introduction

The human gut microbiome, composed of bacteria, fungi, viruses and protozoa, constitutes an intricate and dynamic ecosystem that has a substantial role in human health and disease[1]. The gut microbiome is intricately involved in multiple aspects of host physiology throughout life, from the development and maturation of immune responses to stress response and behaviour. During early life, factors such as delivery mode, feeding, diet and environment shape the gut microbiome[2]. In adulthood, although the microbiome tends to be relatively stable, external factors, particularly diet, substantially influence its composition and function. This complex interplay among nutrients, the microbiota and the immune system serves as a critical regulatory mechanism for preserving homoeostasis and defending against external pathogens[3]. Studies have shown that both short-term and long-term dietary regimes alter the composition and functionality of the gut microbiota, demonstrating the power of diet in influencing human health[4–6].

Detailing the current knowledge of diet and the microbiome is timely, given the recent progress in metagenomic sequencing and machine learning[7,8]. These advancements have deepened our understanding of the microbiome and human health, facilitating the development of microbiome-targeted therapies and precision nutrition to combat diet-related diseases. The Mediterranean diet, for instance, has been shown to positively influence the gut microbiota and human health, potentially aiding in the prevention and slowing of disease progression[5,9–11]. However, recent studies report that the same diet consumed by two different people can result in differing metabolic health effects[12] and a personalized microbial response[13]. Furthermore, owing to the global rise in the Western diet and ultra-processed food consumption, non-communicable diseases such as cardiovascular disease, obesity and type 2 diabetes have become an epidemic of our time[14]. A healthy microbiome cannot be defined by a single configuration; rather, multiple configurations may be linked to well-being[15]. It is also important to note that certain bacterial phyla, genera or species can be associated with either a healthy or disease state[16]. For example, *Prevotella copri*, although not ubiquitous, is a common human gut microorganism (found in 39.1% of healthy individuals[17]) that has been both positively and negatively linked to host health[18]. Therefore, it is important to emphasize that many species have relatively large pangenomes and, as such, strains within those species can exhibit substantial differences in both genomes and functionalities. This complexity can pose challenges when associating species with host health[19]. Hence, it is imperative to recognize which foods and dietary patterns promote health or exert adverse effects, to transform this knowledge into practical dietary recommendations for health promotion and disease prevention[20].

In this Review, we focus on the influence of different whole diets on the gut microbiome, detailing their known mechanisms. We delve into diet-related chronic diseases associated with the gut microbiome during early life and adulthood, and we highlight specific diets used in clinical practice to mitigate or prevent disease progression. We acknowledge the extensive advancement in metagenomic sequencing and bioinformatic analysis that have greatly increased our understanding of diet and its impact on the microbiome, while discussing persistent gaps and challenges.

Whole diets and their effect on the gut microbiome

Diets can have considerable beneficial or negative influences on the composition and functionality of the gut microbiome. This section delves into instances of documented gut microbial changes and causal relationships in response to different dietary patterns (Fig. 1), including specific dietary components (Figs. 2 and 3).

Mediterranean diet

More than 50 years following the Seven Countries Study[21], the Mediterranean diet has emerged as the 'gold standard' in preventative medicine and health promotion[5,22–25]. The Mediterranean diet emphasizes a high intake of unprocessed, whole-plant foods, olive oil, dairy products, moderate consumption of poultry and fish, and low amounts of red meat. Two intervention studies have associated the Mediterranean diet with specific taxonomic characteristics, including an increased abundance of health-promoting *Faecalibacterium prausnitzii* and *Roseburia* spp., alongside a reduced abundance of *Ruminococcus gnavus*, *Collinsella aerofaciens* and *Ruminococcus torques*[5,23]. These changes in the microbiome as a result of diet were linked to enhanced production of short-chain fatty acids (SCFAs) and reduced production of metabolic by-products (such as, ethanol, para-cresols and carbon dioxide)[5]. A prior study has used metagenomic shotgun sequencing to analyse longitudinal microbiome data from 307 male subjects with long-term dietary information[25]. The results revealed that the Mediterranean diet was associated with 36 functional pathways, mostly resembling a plant-based diet, with enriched microbial functions for SCFA fermentation and dietary fibre degradation. Notably, adherence to the Mediterranean diet showed positive associations with specific functional pathways, such as the D-fructuronate degradation pathway for pectin breakdown and the mannan degradation pathway for hemicellulose degradation. Additionally, the authors have noted that Mediterranean dietary adherence and reduced cardiovascular disease risk were notably more pronounced in individuals with lower levels of *P. copri*[25].

More recently, the DIRECT-PLUS study, which included 294 participants with obesity or dyslipidaemia, has found more substantial compositional changes associated with a green Mediterranean diet compared to a Mediterranean diet[26]. The green Mediterranean diet, which is an enhanced version of the Mediterranean diet that incorporates a higher intake of plant-based foods and reduced red meat, as well as daily polyphenol-rich green tea and Mankai aquatic plant consumption, yielded even greater changes in microbial composition and diversity. This included increased *Prevotella* spp. abundance and branched-chain amino acid (BCAA) degrading enzymes (isoleucine degradation), along with decreased *Bifidobacterium* spp. and BCAA biosynthesis enzymes (valine and isoleucine biosynthesis). These changes were linked with positive alterations in body weight and cardiometabolic indicators[26].

High-fibre diet

Dietary fibre is important for human health as it lowers long-term weight gain, with low fibre intake leading to an increased risk of type 2 diabetes and colon cancer[27]. High-fibre diets alter gut microbial composition, including a substantial increase in beneficial *Lactobacillus* spp. and *Bifidobacterium* spp. abundance[28]. Various dietary fibre fractions impact gut microbial populations differently. For instance, breast-feeding infants show a higher abundance of *Bifidobacterium* species adapted to the utilization of human milk oligosaccharides (HMOs) — highly abundant non-digestible prebiotic sugars in breast milk. After weaning there are noticeable changes in gut microbiota composition, primarily attributable to the altered diet composition. This results in an expansion of Bacteroidetes and Firmicutes, which can metabolize more complex polysaccharides[29]. In individuals with overweight, intervention with arabinoxylan oligosaccharides increased the abundance

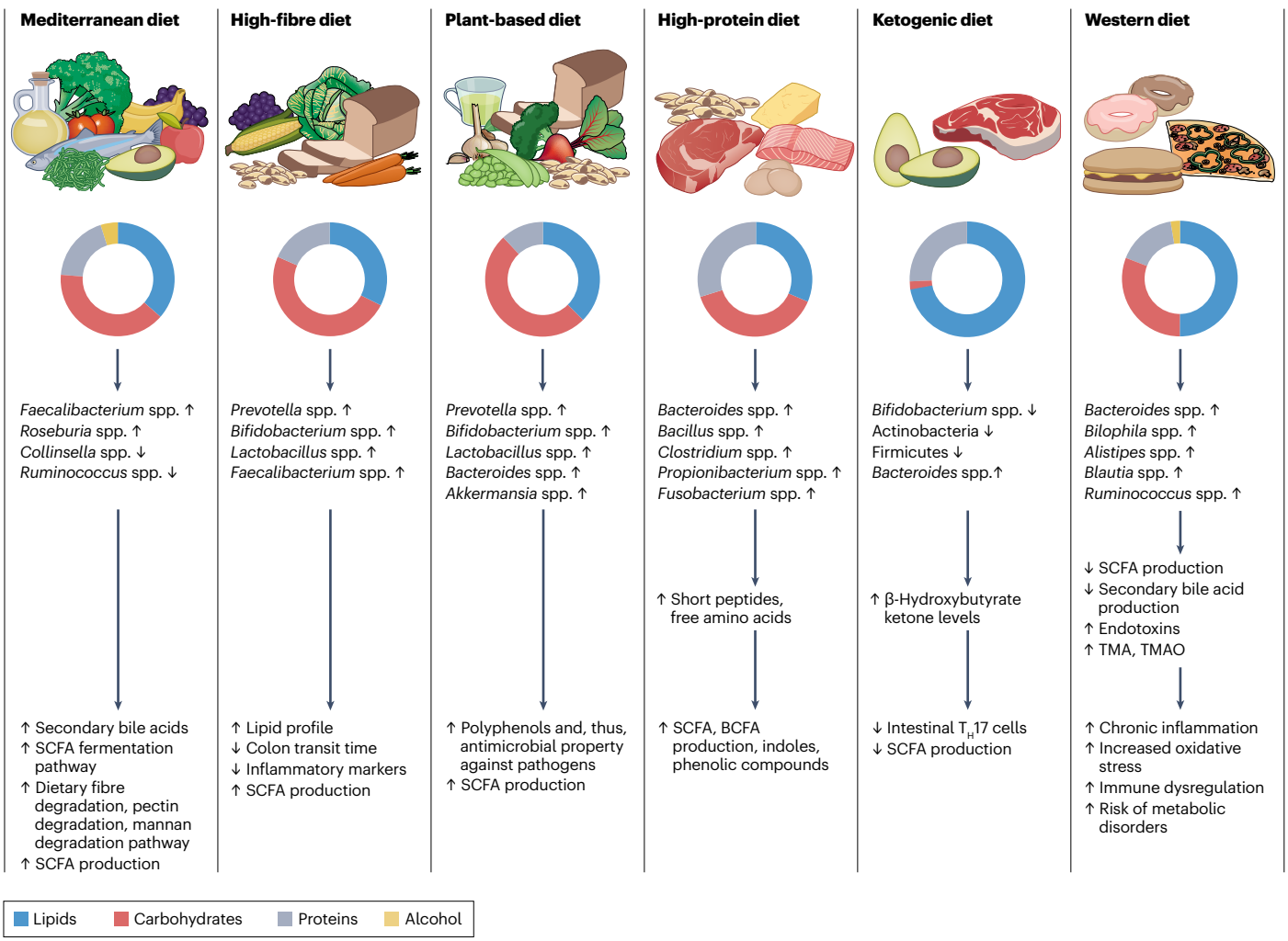
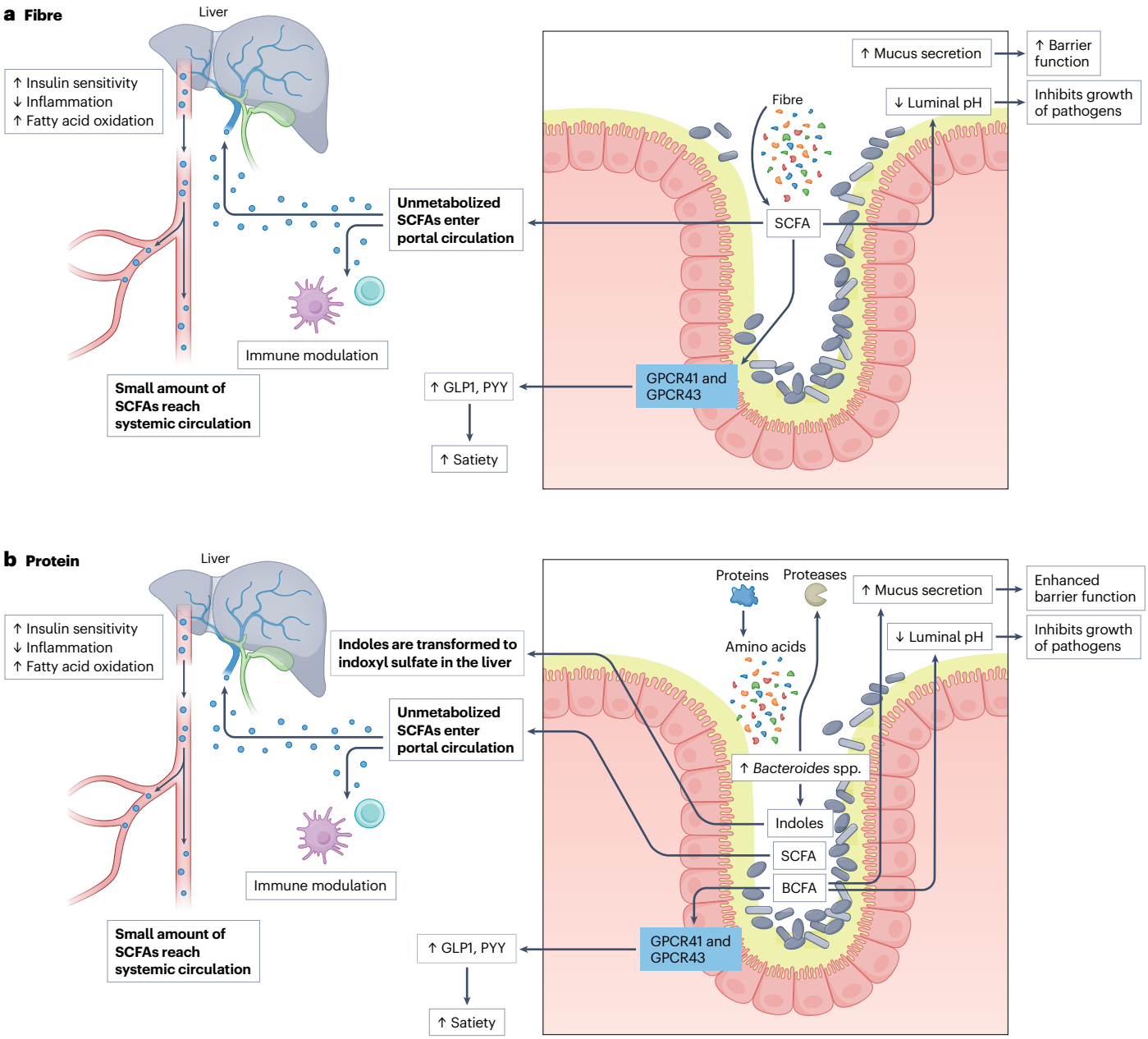


Fig. 1 | Macronutrient composition of whole diets and their effect on the gut microbiota. Each column represents a specific whole diet: Mediterranean diet, high-fibre diet, plant-based diet, high-protein diet, ketogenic diet and Western diet. Pie charts detail the distribution of macronutrients (lipids, carbohydrates and proteins) and alcohol content for each diet. The figure illustrates the alterations of bacterial taxa associated with each diet and the consequent effects on metabolite production. Upward arrows refer to an increase in bacterial taxa or metabolites, whereas downward arrows denote a reduction in bacterial taxa or metabolites. The Mediterranean diet is associated with increased *Faecalibacterium* spp. and is associated with short-chain fatty acids (SCFAs) and production of anti-inflammatory molecules. The high-fibre diet is associated with enriched *Prevotella* and *Faecalibacterium* species, which are associated with enriched SCFA production and also a decrease in colon transit time. Similarly, a plant-based diet is associated with increased abundance of *Prevotella* and *Akkermansia* species, together with an enrichment in polyphenols and SCFA production. A high-protein diet is associated with enriched Bacteroidetes and *Fusobacterium* species, with higher production of branched-chain fatty acids (BCFAs), indoles and short peptides. The ketogenic diet is linked to decreased Firmicutes and Actinobacteria species and shows high ketone levels. A Western diet is associated with increased abundance of *Blautia* spp., *Bacteroides* spp. and *Ruminococcus* spp., which is in turn linked to increased risk of metabolic disorders and chronic inflammation. This comprehensive depiction elucidates how different dietary compositions can modulate the gut microbiota, providing insights into their potential implications for overall health and well-being. T_H17, T helper 17 cells; TMA, trimethylamine; TMAO, trimethylamine *N*-oxide.

of *Prevotella* spp. and *Eubacterium rectale*, which was accompanied by favourable changes in metabolomics profile potentially protecting against metabolic disease[30]. Supplementation with whole grain and wheat bran in 31 volunteers resulted in increased levels of *Bifidobacterium* spp. and *Lactobacillus* spp. The increase was more pronounced in individuals consuming whole grains; both groups experienced a reduction in total cholesterol[31]. Oat-derived high molecular weight β-glucan decreased Firmicutes and increased Bacteroidetes, accompanied by a reduction in cardiovascular disease risk markers[32]. Dietary fibre in the form of type-IV resistant starch induced varying effects on the composition and function of gut microbiota and the production of either butyrate or propionate[33]. Simple carbohydrates are absorbed in the small intestine, whereas complex carbohydrates such as dietary fibres undergo colonic microbial fermentation, resulting in SCFA production[33]. Humans only produce very limited carbohydrate-active enzymes (CAZymes) for carbohydrate degradation (17) and, thus, rely



on the gut microbiota to indirectly metabolize several dietary fibres. A diet low in fibre is associated with a reduced CAZyme reservoir within gut microbiota[34].

SCFAs exhibit several health benefits, including signalling through G protein-coupled receptors (GPCRs) and stimulation of the secretion of satiety hormones (glucagon-like peptide 1 and peptide YY) from enteroendocrine cells. This influences appetite regulation and modulates the function of regulatory T cells, as well as lipid and glucose metabolism, having a pivotal role in regulating host energy metabolism and colonic homoeostasis[35,36]. Butyrate acts as an energy source for colonocytes, mediates anti-inflammatory properties through intestinal cells (macrophages and dendritic cells) and enhances mucus production, which highlights its role in intestinal homoeostasis optimizing nutrient absorption and gut barrier function[37]. The role and interaction of SCFAs with GPCRs and other cells are not limited to the intestine but extend to peripheral tissues, organs and immune cells. Reports in mouse models suggest the potential role of SCFAs and high-fibre diets in reducing the risk of type 1 diabetes, type 2 diabetes, asthma and stress, as well as decreasing fatty acid synthesis and lipolysis, resulting in reduced body weight and enhanced neurocognitive development[38]. SCFA absorption leads to reduced luminal pH, which inhibits the growth of pH-sensitive pathogens belonging to the Clostridia class and the Enterobacteriaceae family and increases nutrient absorption[35] (Fig. 2a).

Insoluble fibres found in whole grains influence gut transit rate and bacterial fermentation. Two randomized controlled crossover trials involving 50 individuals who had overweight or were at risk of developing metabolic syndrome have shown that a whole-grain diet

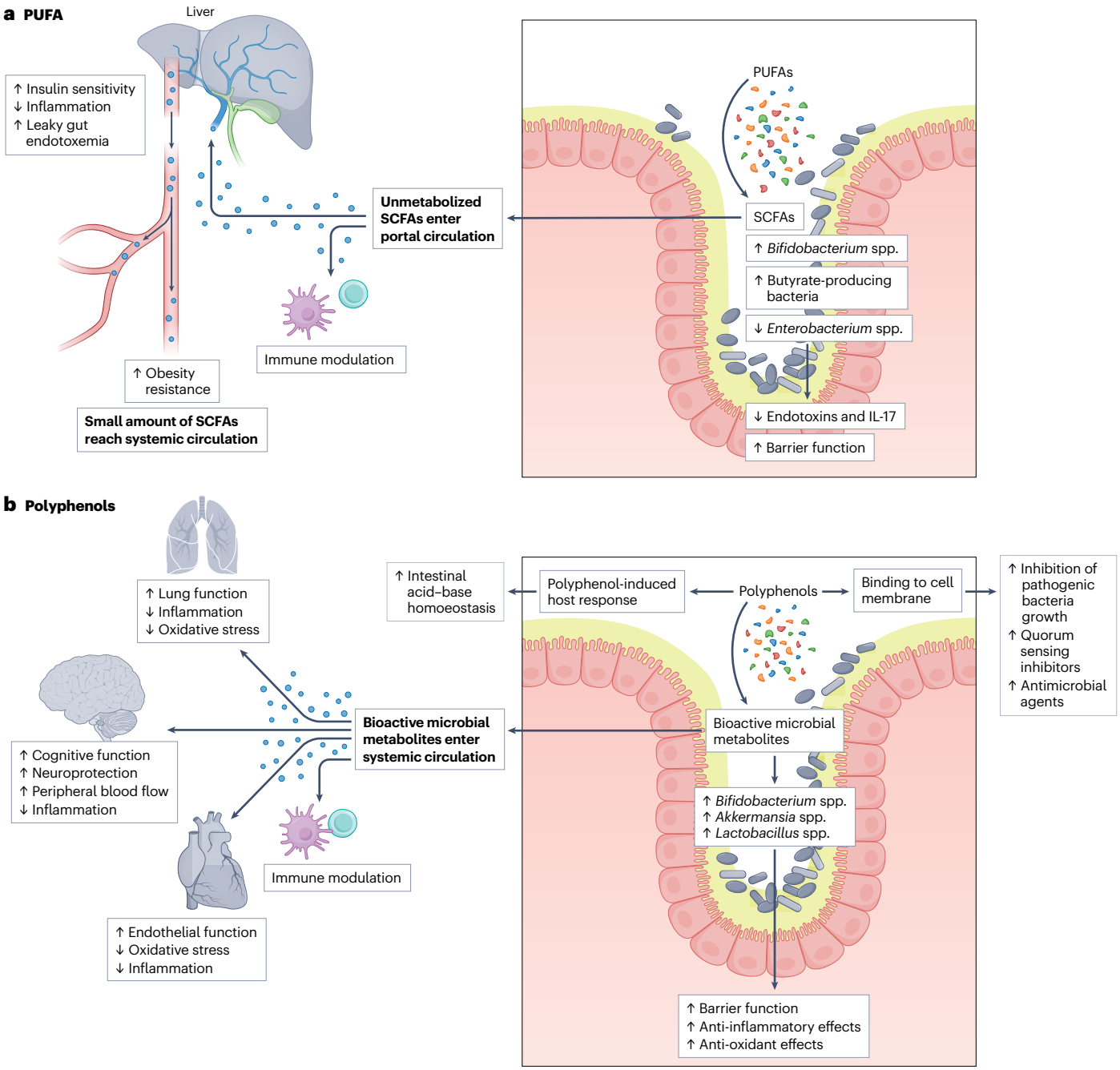
Fig. 2 | Impact of dietary fibre and protein on human health. Breakdown of dietary fibre and protein by the gut microbiota, the resulting metabolites and their impact on host health. **a**, This part of the figure delineates the breakdown of fibre by gut microbiota and its implications for barrier function and immunity, showing the downstream effects of unmetabolized short-chain fatty acids (SCFAs) entering portal circulation and their advantageous effects on host health. Upon reaching the intestine, dietary fibre undergoes fermentation by the gut microbiota, resulting in the production of SCFAs such as acetate, propionate and butyrate. This activates G protein-coupled receptors (GPCRs) 41 and 43, which trigger the secretion of gut hormones, including glucagon-like peptide (GLP) and peptide YY (PYY). GLP1 and PYY have crucial roles in regulating appetite, slowing down gastric emptying and promoting satiety. Additionally, SCFAs enhance gut barrier function by increasing mucus secretion and decreasing luminal pH, thereby protecting the intestinal lining from damage and preventing the entry of harmful pathogens into the bloodstream. Furthermore, SCFAs have anti-inflammatory and immunomodulatory effects, contributing to overall gut health and reducing the risk of gastrointestinal diseases. Thus, the metabolism of dietary fibre by gut microbiota leads to a cascade of beneficial effects on human health, including improved insulin sensitivity and fatty acid oxidation, and reduced inflammation. **b**, This part of the figure shows the metabolism of proteins by the gut microbiota and the subsequent effect of SCFA and indoles on human health. In the gut, dietary protein undergoes metabolism by gut microbiota, which has been associated with an increased abundance of *Bacteroides* species. This results in the production of various metabolites, including SCFAs, branched-chain fatty acids (BCFAs) and indoles. BCFAs can activate GPCR41 and GPCR43, triggering the secretion of gut hormones such as GLP1 and PYY. Additionally, BCFAs can increase mucus secretion and decrease luminal pH, thereby enhancing gut barrier function and protecting the intestinal lining. The effects of SCFAs, BCFAs, gut hormones such as GLP1 and PYY, mucus secretion and luminal pH on human health include improved gastrointestinal function, appetite regulation, reduced inflammation and improved insulin sensitivity and fatty acid oxidation, thereby promoting overall gut health. Upward arrows refer to an increase in bacterial taxa or metabolites, whereas downward arrows denote a reduction in bacterial taxa or metabolites.

increased faecal butyrate and caproate, improved blood lipid profiles, reduced inflammatory markers and improved weight loss compared to a refined grain diet[39]. SCFA producers have shown an inverse relationship with colon transit time[39,40]. This further helps in modulating intestinal microbial composition and diversity, thereby alleviating various enteric conditions such as irritable bowel syndrome, inflammatory bowel disease, colorectal and gastric cancer, and constipation[41,42]. The majority of studies conducted to date have been performed in animal models, which sometimes fail reproducibility in humans. The interplay between microbiota and human health underlines the need for a holistic approach and larger human studies, recognizing the complex relationship between dietary carbohydrates, gut microbiota composition and disease susceptibility.

Plant-based diet

Plant-based diets are enriched in polyphenols, host-digestible and indigestible carbohydrates and exert both prebiotic and postbiotic effects. Vegetarian diets lead to the formation of a distinct bacterial environment, as evidenced by alterations in bacterial functional capabilities (for example, vegetarians exhibit low carnitine degradation but increased nitrogen assimilation)[41]. These diets promote the abundance of Bacteroidetes and *Prevotella* species compared to omnivore diets, albeit with studies yielding contradictory results owing to microbial individuality and inconsistencies in research methodologies[42,43]. Contrasting levels of certain genera or species can be attributed to the microbial stress caused by rapid versus gradual shifts in diets, the presence of healthy versus unhealthy dietary components, and various sources of bioactive compounds[44,45].

Polyphenols, categorized as either flavonoids or non-flavonoids, are plant secondary metabolites found in fruits, vegetables, cereals, wine, tea and coffee[46,47]. Small quantities of polyphenols (5% to 10%) are absorbed in the small intestine, predominantly those featuring monomeric and dimeric structures. Following absorption, aglycones undergo biotransformation within enterocytes and then within hepatocytes. These metabolites are transported via the circulatory system to organs such as the kidneys and liver and are ultimately excreted in urine[46]. The majority of polyphenols (90% to 95%) interact with gut microorganisms in the ileum and colon, wherein they promote the abundance of *Bifidobacterium*, *Akkermansia* and *Lactobacillus* species, thereby providing substantial anti-inflammatory and anti-pathogenic properties, as well as cardiovascular protection[45,48,49]. A recent randomized controlled trial that involved over 20,000 adults has demonstrated that consumption of cocoa extract, rich in polyphenols, reduced death by cardiovascular disease. However, the event of cardiovascular disease was not reduced[50]. Polyphenols can inhibit bacterial growth through several mechanisms, including binding to and altering the functional features of cell membranes[51]. They also[51] exert antimicrobial activities against foodborne pathogens[52] and serve as quorum-sensing inhibitors and antimicrobial agents in a dose-dependent manner[53]. The gut microbiota bidirectionally modulate and metabolize polyphenols, transforming them into more bioactive microbial metabolites and enhancing their absorption compared to their original compounds[46,54,55]. Research has shown that consuming bioactive microbial metabolites can have beneficial effects on human health. For example, urolithin A supplementation improved cellular and mitochondrial health, *S*-equol supplementation improved bone health, skin ageing and cardiovascular health, and 8-prenylnaringenin intake showed endocrine and immunomodulatory effects[55]. Polyphenols can regulate several gut microbial metabolites, including SCFAs, trimethylamine *N*-oxide (TMAO), dopamine, lipopolysaccharides and bile acids, by altering gut microbiota composition and influencing the functionality of various microbial enzymes. This can ultimately evoke a polyphenol-induced host response in various ways, for example, by acting as a regulator of intestinal acid–base homoeostasis[45]. Modulation of the gut microbiota by polyphenols has been demonstrated to support homoeostasis in lung function, central nervous system function and intestinal barrier integrity[45] (Fig. 3b). Moreover, differences in protein and fat types between plant and animal sources result in disparities in gut microbial composition and, hence, metabolomes. For instance, animal-based diets lead to a higher abundance of bile-tolerant bacterial species belonging to *Alistipes* and *Bilophila* genera while decreasing the abundance of Firmicutes, reducing the levels of BCAAs and increasing SCFAs and dimethylsulfone[4,56]. Other plant compounds, such as fibre, terpenes and carotenoids, have also demonstrated health benefits, as reviewed in ref. 57. Inter-individual variations in the production of phenolic-derived metabolites from dietary polyphenols are attributed to the unique composition of the gut microbiome of each individual. Consequently, the use of metabotyping for the analysis of polyphenol metabolites could serve as a valuable approach for gaining deeper insights into the effects of bioactive compounds and offer a comprehensive understanding of the substantial diversity among individuals[55].



High-protein diet

A diet with protein consumption of more than 1.5 g kg^{-1} per day is generally considered to be a high-protein diet. It is typically used for athletes or prescribed for overweight people for weight loss. Dietary proteins are mostly broken down by host proteases, yet up to 12–18 g of dietary proteins can reach the large intestine daily and be metabolized by the microbiome[58]. Different types of complex proteins have different levels of digestibility, as well as various amino acid compositions. A few bacterial species are involved in proteolysis and are enriched in the gut microbiota of consumers of high-protein diets, mainly *Bacteroides*, *Bacillus*, *Clostridium*, *Phocaeicola*, *Propionibacterium*, *Fusobacterium*, *Lacticaseibacillus* and *Streptococcus*. Other bacteria can use amino acids directly and benefit from proteolytic degradation, forming cross-feeding interactions. Proteolytic bacteria use a variety of external peptidases, proteases (including metallo, serine, cysteine, aspartic, threonine, glutamic and asparagine proteases) and endopeptidases to release short peptides and free amino acids[59]. Most amino acids are fermented into SCFAs. Butyrate is derived from lysine and glutamate, acetate is derived from alanine, aspartate and glutamate, whereas propionate is derived from aspartate, alanine and methionine. Additionally, BCAA (for example, isoleucine, valine and leucine) fermentation results in the production of branched-chain fatty acids such as isobutyrate, 2-methyl butyrate and isovalerate[60]. Other fermentation products include potentially

Fig. 3 | Impact of dietary polyunsaturated fatty acids and polyphenols on human health. Breakdown of dietary polyunsaturated fatty acids (PUFAs) and polyphenol components by the gut microbiota, the resulting metabolites and their impact on host health. **a**, When dietary PUFAs reach the intestine, they are metabolized by the gut microbiota. This process increases the abundance of specific bacteria, such as *Bifidobacterium* spp. and butyrate-producing bacteria. Consequently, various metabolites such as short-chain fatty acids (SCFAs), for example butyrate, are produced. Additionally, PUFAs can reduce the abundance of pro-inflammatory *Enterobacterium* spp., thus reducing inflammation and improving gut barrier function. This can result in the reduced production of endotoxins and interleukin 17 (IL-17), leading to reduced inflammation and improved effects on human health. Unmetabolized SCFAs resulting from PUFA metabolism enter systemic circulation, wherein they exhibit immunoregulatory effects. They can enhance resistance to obesity by improving insulin sensitivity, reducing inflammation and improving leaky gut endotoxemia. **b**, Polyphenols are metabolized by gut bacteria and are, therefore, broken down into bioactive microbial metabolites. Polyphenols have been shown to increase the abundance of beneficial bacteria such as *Bifidobacterium*, *Akkermansia* and *Lactobacillus* species in the gut lumen. These bacteria have a crucial role in maintaining gut barrier function, regulating the immune system, promoting gut homoeostasis and inhibiting the growth of pathogenic bacteria. Additionally, polyphenols exhibit substantial anti-inflammatory and antioxidant effects within the gut. The by-products of polyphenol metabolism, phenolic-deprived metabolites, are absorbed in systemic circulation wherein they exert substantial immunoregulatory effects. For example, these metabolites have been shown to improve lung, brain and heart function by reducing inflammation and oxidative stress and by improving endothelial function, thereby increasing peripheral blood flow. Upward arrows refer to an increase in bacterial taxa or metabolites, whereas downward arrows denote a reduction in bacterial taxa or metabolites.

inflammatory compounds such as indoles and phenolic compounds derived from aromatic amino acids (for example, tryptophan), as well as ammonia, amines, organic acids and gases (that is, hydrogen sulfide produced from sulfur-containing amino acids cysteine and methionine, and carbon dioxide) (Fig. 2b). It is worth noting that some of these end-products are potentially involved in disease. Indoles and indole-related compounds can reach the liver to be transformed into indoxyl sulfate, a toxic metabolite that is deleterious for the kidneys and that is involved in endothelial dysfunction[61]. Additionally, hydrogen sulfide is potentially mutagenic and may have a role in inflammation, increasing the risk of colon cancer[62].

Ketogenic diet

The ketogenic diet is a very low-carbohydrate, moderate-protein and high-fat dietary pattern replicating the metabolic responses seen during fasting, which elevates circulating ketone bodies (molecules derived from fatty acids serving as an alternative energy source when glucose availability is limited)[63]. The traditional long-chain triglyceride ketogenic diet follows a 4:1 ratio of fat (in grams) to the sum of protein and carbohydrates. Variations include the medium-chain triglyceride ketogenic diet, the modified Atkins diet and the low glycaemic index treatment, each with slightly altered macronutrient ratios. The ketogenic diet has long been used as a dietary therapy for the treatment of epilepsy, with emerging research showing the benefits of this diet in treating various disorders such as Alzheimer disease, obesity and cancer[64]. A typical high-fat diet consistently elevates the abundance of Firmicutes and reduces Bacteroidetes[63,65]; however, a ketogenic diet has a different effect. In a study involving 17 adults with overweight, a 4-week ketogenic diet has shown substantial reductions in Actinobacteria and Firmicutes phyla within the human gut. Specifically, 19 species of beneficial *Bifidobacterium* were decreased, whereas there was an increase in the abundance of Bacteroidetes species. These alterations were partially induced through the host production of ketone bodies[63]. Similarly, a 3-month study involving 12 children with severe epilepsy who followed a ketogenic diet has revealed a substantial reduction in health-promoting and fibre-consuming *Bifidobacterium* spp., *E. rectale* and *Dialister* spp. Conversely, children showed an increased abundance of *Bacteroides* spp. and *Escherichia* spp., with the latter partly owing to elevated *Escherichia coli*[66]. Additionally, preclinical research also indicates a substantial modification in gut microbiome composition in response to a ketogenic diet, most notably marked by increased levels of *Akkermansia* species[67–69] (particularly *Akkermansia muciniphila*)[67,69], as well as *Lactobacillus*[69], *Roseburia*[68] and *Parabacteroides*[67] species, and substantial reductions in *Turicibacter*, *Desulfovibrio*[69], *Escherichia* and *Shigella*[68] species.

A study analysing the mechanism underlying changes in gut microbiome composition in response to a ketogenic diet has reported a substantial inverse correlation between *Bifidobacterium* spp. and the ketone body β-hydroxybutyrate (βHB) in both human and mouse subjects[63]. This research has established a causal link between the gut microbiota and immune responses associated with ketogenic diet consumption, revealing that transplanting faecal microbiota from ketogenic diet-fed human donors into germ-free mice led to variations in intestinal T helper 17 (T_H17) cell accumulation[63]. In alignment with earlier research demonstrating the robust induction of intestinal T_H17 cells by *Bifidobacterium* spp.[70], this modulation, characterized by lower pro-inflammatory T_H17 cells in both the gut and adipose tissues, highlights the impact of a ketogenic diet on gut microbiota composition and its subsequent impact on host immune responses[63]. However, owing to the subsequent decrease in beneficial gut microbiota and the promotion of pro-inflammatory and pathogenic gut bacteria, further investigation is needed to understand the long-term effects of the ketogenic diet on host health.

Western diet

The Western diet is characterized by a high calorie content and is enriched in animal protein, saturated fats, simple sugars and ultra-processed foods, with inadequate amounts of fibre, fruits and vegetables. The Western diet is associated with a marked reduction in gut microbiome diversity compared to other diets, with a shift towards an enterosignature dominated by *Bacteroides* species[71]. Other enriched species belong to *Ruminococcus*, *Faecalibacterium*, *Bifidobacterium*, *Alistipes*, *Blautia* and *Bilophila* genera[72–76]. Because of the lower fibre input and the different microbial composition, the associated microbiome produces less SCFA. Specific compounds from red meat, such as choline and carnitine, can also be transformed by the gut microbiome into trimethylamine, which is then converted in the liver to TMAO that is associated with chronic diseases. Processed food contains a variety of additives, preservatives and emulsifiers capable of interacting directly or indirectly with the gut microbiome[77]. Non-nutritive artificial sweeteners such as saccharin, sucralose and aspartame, present in low-calorie or diet food and drink items, have potential long-term effects on microbiome diversity and composition but these effects are unclear[78]. Other additives, such as carrageenan (a thickening or gelling agent

derived from red seaweed that is present in many processed foods such as dairy products), are known to favour gut inflammation and disrupt the mucus layer, causing changes in the gut microbiome. Artificial food colourings, such as Allura Red AC present in candies and bakery products, confer colour and modify sulfur homoeostasis through interactions with gut bacteria[79]. Some preservatives, such as sodium nitrate present in processed meat can also modulate gut microbiome composition, whereas emulsifiers, such as carboxymethylcellulose (a thickening agent present in sauces) and polysorbate-80 (an emulsifier and stabilizer present in sauces and baked goods) directly impact gut microbiome composition and functionality[80]. The Western diet is overall linked to the surge of chronic inflammation[72,73,81] leading to diet-related diseases, including obesity and many other non-communicable diseases[14].

Global diets associated with the microbiome

Global regions have unique dietary patterns that impact the gut microbiome and host health. However, distinguishing its impacts from host-specific attributes to global or local environmental influences poses a challenge, as other factors such as ethnicity also notably influence gut microbiota composition[74,82]. A recent study has characterized 5,230 gut metagenomes, reporting that members of the *Bacteroides* and *Prevotella* genera and the Firmicutes phylum are the dominant enterosignatures of Western populations, whereas non-Western populations have predominantly *Prevotella* spp. and Firmicutes enterosignatures, with minimal *Bacteroides* spp., highlighting that ultra-processed foods and dietary habits, along with other factors such as hygiene, antibiotic usage and physical activity levels may contribute to these disparities[71]. Many studies consistently reveal greater bacterial diversity and microbial richness in traditionally non-Western populations. These differences distinguish them from urban-industrialized individuals with diets characterized by low fibre and high saturated fats, as reported in various large-scale studies[75,76,83–87].

To investigate global disparities in gut microbiome composition and functionality and the subsequent impact of diet, studies have compared the gut microbiomes of Hadza hunter–gatherer communities[72,83,88], Papua New Guineans[73], Nomads[89] and African populations (both children[90] and adults[86]) to those of individuals from the USA. Other studies have compared the gut microbiome of children from Italy to those of children in Burkina Faso[75,76]. Industrialized countries typically adhere to a Western-style diet, whereas non-industrialized populations prioritize diverse, whole plant-based foods, maintaining a rich gut microbiota. Although urban and hunter-gatherer microbiomes exhibited the greatest contrast, agricultural, rural and agropastoral microbiomes represented intermediary states of microbiome composition between the two extremes[72,91]. Ultra-deep metagenomic sequencing revealed that gut microbiomes from Hadza individuals comprised 730 bacterial species, surpassing the 436, 317 and 277 species found in Nepali agrarian, Nepali forager and Californian populations, respectively[88]. Gut microbiomes of the Hadza people exhibited characteristics that align with a heavily plant-based diet; however, they were also enriched with xylan-degrading *Prevotella* and *Treponema* species, along with unclassified Bacteroidetes and *Clostridiales* species, which are scarce or absent in industrialized microbiomes. These groups are recognized for their fibrinolytic capabilities and, thus, highlight how the Hadza community exhibits distinct glycan-degrading abilities that enable them to manage resistant organic materials introduced into their diet[72].

Similarly, 15 children living in Burkina Faso had a unique abundance of *Prevotella* and *Xylanibacter* species that were absent in European children, revealing that the coevolution of gut microbiota with the polysaccharide-rich diet of individuals in Burkina Faso enables them to optimize energy extraction from fibres. The loss of gut microbial diversity is concomitant with a Western diet, as demonstrated in the METS-Microbiome study, which used amplicon sequencing and metabolomics on 1,904 individuals from African and US cohorts. The *Prevotella* enterotype had a higher prevalence in Africans, with 81% and 62% observed in individuals from Ghana and South Africa, respectively. The *Bacteroides* enterotype was more prevalent in the US (75%) and Jamaican cohorts (68%)[86]. Studies have also identified consequential functional alterations associated with these changes in gut microbiome composition. For example, an analysis of ancient stool samples has found that Westernization had a role in diminishing the prevalence of *P. copri*[17,18]. A meta-analysis of over 6,500 metagenomes has found that *P. copri* prevalence is 95.4% among individuals living a non-Western lifestyle and 29.6% among individuals with a Western lifestyle[92]. Strain-level differences have been associated with habitual diet, with subsequent functional potential of these strains differing between Western and non-Western populations[18]. High-fibre diets were associated with *P. copri* strains that had enhanced carbohydrate catabolism potential, whereas omnivorous diets exhibited higher levels of *P. copri* strains with an upregulation of the *leuB* gene that is associated with BCAA biosynthesis[18], a risk factor for glucose intolerance and type 2 diabetes[93].

Population-based studies have additionally demonstrated variations in the gut microbiomes of individuals within the same country. Regional diets in populous countries such as India, characterized by diverse lifestyles and dietary habits, have varying impacts on the gut microbiome. In North-Central India, wherein plant-based diets are prevalent, a higher abundance of *Prevotella* spp. is found, whereas Southern India, known for its omnivorous diet, shows an increased abundance of *Bacteroides*, *Faecalibacterium* and *Ruminococcus* species[94]. A microbiome analysis conducted on Mongoloid and proto-Australoid tribes — known for high consumption of fermented foods, rice, vegetables, fish, meat and whole grains — consistently exhibited elevated levels of *Prevotella* spp. and decreased *Bacteroides* spp. across all tribes. Large variations across lifestyle gradients were apparent among different tribes, with a high prevalence of *Faecalibacterium, Eubacterium* and *Blautia* species in the Assam and Telangana tribes, and *Bacteroides*, *Bifidobacterium* and *Lactobacillus* species in the Sikkim tribe[95]. Similarly, another study has shown that four traditional Himalayan populations (the Thary, the Raute, the Raji and the Chepang) exhibited distinct gut microbiomes compared to American (US) individuals. The gut microbiomes of the communities that adopted farming showed greater similarity to those of Americans. The Himalayan populations showed a higher abundance of Proteobacteria, whereas levels of Actinobacteria, Firmicutes and Verrucomicrobia were higher in the Americans, intermediate in farmers populations (Tharu, Raji and Raute) and lowest in the forager population (Chepang)[87].

Travel and migration have also been shown to have profound impacts on gut microbiome composition and functionality. One example can be seen in the gut microbiomes of Irish Travellers, an ethnic minority group native to Ireland, that revealed remarkable similarities with non-industrialized populations, persisting two decades after the end of nomadism in Ireland. Shared abundant species between Irish Travellers and non-industrialized communities include *Coprococcus catus*, *C. aerofaciens*, *Streptococcus salivarius* and *Coprococcus comes*,

despite the adoption of a Western style diet[96]. Although non-dietary factors may also contribute to these findings, this study expands our understanding of how modernization impacts the gut microbiome[96]. Moreover, immigration to the USA and the adoption of the Western diet have been shown to contribute to the increased development of metabolic disease among immigrant populations. A study conducted on 514 stool samples collected from first-generation and second-generation immigrants from the Hmong and Karen communities (two minority ethnic groups from China and Myanmar, respectively), along with 36 samples from European Americans born in the USA, has revealed substantial changes in gut microbiome traits as a result of both short-term and long-term immigration to the USA. Reduced gut microbial diversity and a shift from *Prevotella* to *Bacteroides* species dominance led to the loss of key strains, resulting in diminished fibre degradation capability, including the loss of glycoside hydrolases (GH17, GH64 and GH87) for glycosaminoglycans and the loss of GH5 and GH26 glycoside hydrolases indicating reduced cellulose, β-mannan and probably xyloglucan degradation potential[34].

The impact of diet on microbiome-mediated diseases

The intricate interplay between diet and disease underscores the pivotal role of nutritional choices in influencing health outcomes. The following section discusses how dietary patterns may contribute to microbiome-mediated disease progression.

The role of early-life and maternal diet in adult health outcomes

Breast milk is a source of a plethora of bioactive compounds including HMOs, immunoglobulin G (IgGs), immune cells and microRNA (miRNA), some of which can influence the gut microbiota of an infant. Breastfeeding, as opposed to formula, leads to higher levels of inflammation markers such as faecal calprotectin and β-defensin 2, reflecting immune maturation with a decrease in pro-inflammatory serum cytokines[97]. HMO utilization by *Bifidobacterium* species (*Bifidobacterium breve*, *Bifidobacterium bifidum*, *Bifidobacterium longum* subsp. *longum* (referred to as *B. longum*), *B. longum* subsp. *infantis* (referred to as *B. infantis*) and *Bifidobacterium pseudocatenulatum*) and by *Bacteroides* spp. leads to their dominance in the gut of breastfed infants[98]. Furthermore, this can alter the relationship between microorganisms and metabolites in the host, as evidenced by the correlation between reduced inosine levels and increasing *B. longum* abundance, which suggests a potential role in the immunological and neurological development of infants[97]. HMOs function as prebiotics, protecting infants from infections, promoting brain development and mucus barrier, reducing intestinal permeability and exerting immunomodulatory effects[99]. Lactoferrin and lysozyme exert antimicrobial properties that mediate protection against infections.

SCFAs formed in the gut by HMO utilization are used as an energy source by the host. Formula-fed, not exclusively breastfed, infants harbour higher *Streptococcus*, *Enterococcus*, *Veillonella* and *Clostridioides* species and exhibit differences in functional capability with more carbohydrate metabolism pathways, demonstrating the importance of diet on the gut microbiome[100,101]. Shorter breastfeeding duration is associated with a highly diverse and adult-like microbial composition in early life[101]. HMOs in breast milk modulate the infant gut microbiota and provide several health benefits such as long-term protection from allergy, atopic dermatitis and obesity, as well as enhanced intestinal barrier function[102–104]. Similarly, the introduction of weaning foods leads to changes in the gut microbiota that promote carbohydrate utilization, vitamin synthesis and xenobiotic degradation resulting in increased levels of microorganisms belonging to Firmicutes and Bacteroidetes. The association between infant gut microbial composition and maternal seafood consumption, as well as high-fibre and high-fat diets during pregnancy, has been documented[105]. A recent study has reported that maternal dietary intervention involving fat and sugar intake altered the functionality of the infant gut microbiome[106], whereas another study has reported no association[107]. Recent studies have shown that mice subjected to a low-fibre diet during pregnancy experienced delayed plasmacytoid dendritic cells and perturbation of regulatory T cell expansion in their offspring, leading to enhanced severity of respiratory infections[108]. Similarly, mice on a no-fibre diet exhibited lower proportions of *A. muciniphila*, innate lymphoid cells and T_H17 cells in pups, whereas mice lacking *A. muciniphila* that were fed with fibre showed reduced innate and adaptive RORγt-positive immune cell subsets[109]. Another study in sows and mice has shown that a maternal diet rich in fermented foods affected neonatal gut microbiota development and reduced colonic inflammation via phosphorylation of p38 mitogen-activated protein kinase and c-Jun N-terminal kinase activation of caspase 3 (ref. 110). The extent to which maternal diet affects infant health in the long term warrants further investigation.

Diet, the microbiome, and metabolic disorders

The gut microbiota has a key role in regulating host metabolism, with certain changes in microbial composition and reduced diversity linked to a rise in several metabolic disorders (Fig. 4a). Using germ-free rodent models, researchers have established a link between the gut microbiota and obesity. Colonization of germ-free mice with the gut microbiota from obese mice resulted in a substantial increase in body weight and insulin resistance[111,112], whereas obesity development was absent when germ-free mice were fed a Western diet[113], highlighting the role of gut microbiota in obesity. However, several other studies agreeing with the role of microbiota in energy homoeostasis have failed to show its definitive role in obesity development and point towards the need for more studies to explore this complex relationship[114–116]. The gut microbiota is dominated by Firmicutes and Bacteroidetes, and their increased ratio has been linked to obesity, accompanied by an overall reduced microbial diversity[111,117]; however, results regarding this link are not consistent across studies[115,118,119]. A recent meta-analysis has reviewed ten studies examining the link between the gut microbiome and obesity and reported that all, except one, were underpowered to detect substantial changes in microbial diversity[120]. This emphasizes the importance of large cohort studies to validate the hypothesized causal relationship between microbiome alterations and obesity[120,121].

Type 2 diabetes, cardiovascular disease and hypertension are linked to obesity, and the role of the microbiome in these metabolic conditions has been investigated. Individuals with type 2 diabetes and obesity generally present a reduction in butyrate producers and an increase in acetate and pro-inflammatory species, which are linked to elevated insulin resistance. A research study conducted in mice with obesity supports the role of the gut microbiota in type 2 diabetes. *Bifidobacterium*, *Bacteroides*, *Faecalibacterium* and *Akkermansia* species are negatively associated with type 2 diabetes, with *Bifidobacterium* spp. increasing the levels of glucagon-like peptide-2 (GLP2) and, thus, improving intestinal permeability and reducing metabolic endotoxemia[122]. Metformin, a common type 2 diabetes medication, interacts with the gut microbiota, potentially mediating its antidiabetic effects via the modulation of glucose homoeostasis and the production of

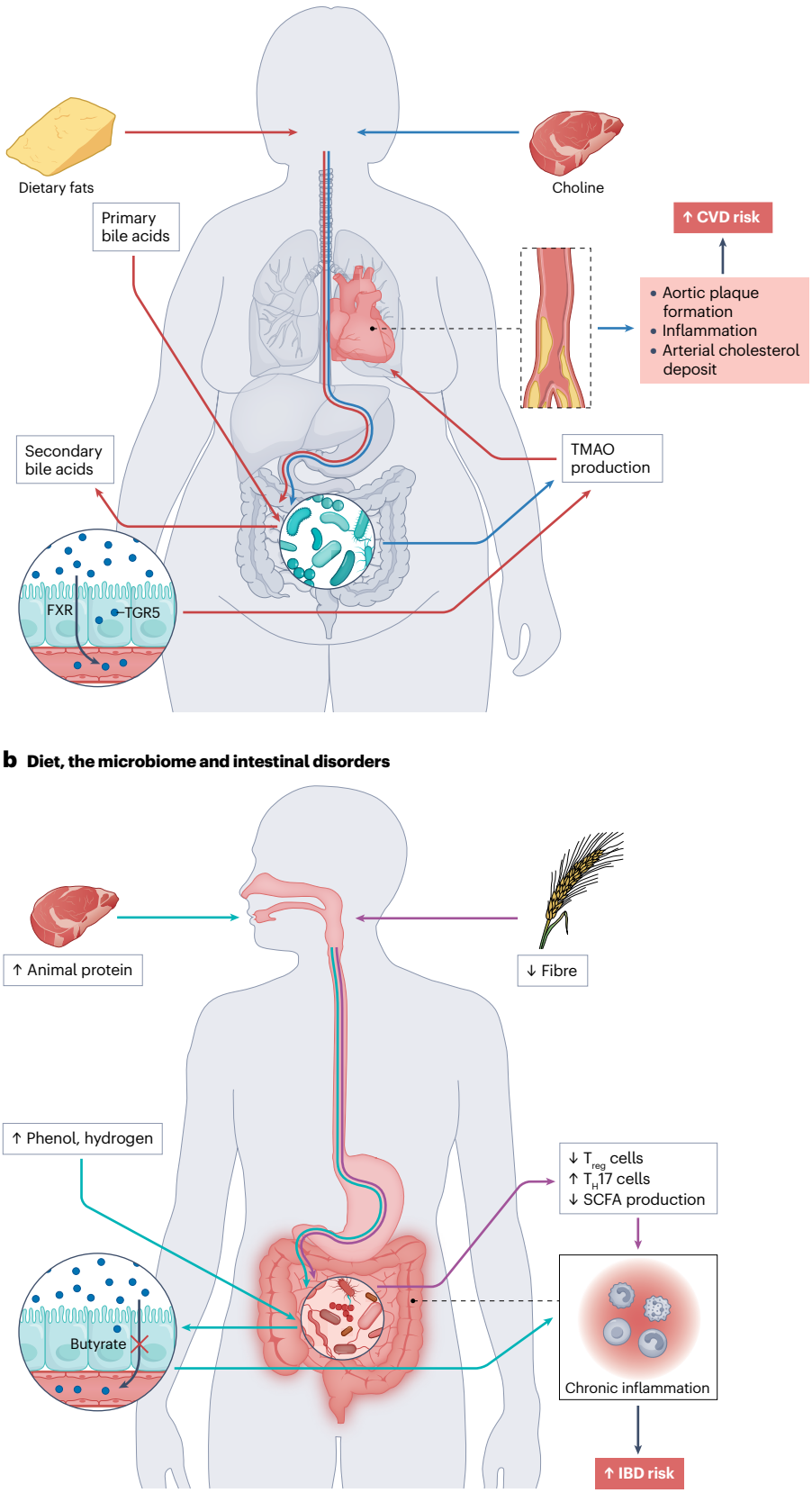


Fig. 4 | Diet, the gut microbiome, and metabolic and intestinal disorders. Diet can impact the gut microbiota, therefore influencing the development of both metabolic and intestinal disorders. **a**, Increased consumption of red meat containing choline can lead to an increase of trimethylamine. Subsequently, trimethylamine is converted into trimethylamine *N*-oxide (TMAO) by hepatic flavin monooxygenases in the gut. TMAO has been implicated in the development of cardiovascular disease (CVD) by promoting atherosclerosis and increasing the risk of adverse cardiovascular events, including aortic plaque formation, inflammation and arterial cholesterol deposition. Additionally, increased dietary fats can affect the activation of bile acid receptors such as farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5), which have important roles in lipid and glucose metabolism. The dysregulation of these pathways can contribute to the development of CVD. Red arrows indicate the mechanism of action whereby dietary fats can have downstream effects on host health, ultimately leading to CVD risk. Additionally, blue arrows indicate how choline (found mostly in animal products) can cause CVD risk. **b**, Increased animal protein (green arrows) and low-fibre (purple arrows) diets can have downstream effects on physiological functioning and host health. Increased consumption of red meat can lead to elevated choline levels, resulting in higher production of hydrogen and phenol in the small intestine due to haem malabsorption. This, in turn, can reduce butyrate production in the gastrointestinal tract (indicated by the 'X' mark), leading to increased inflammation. Similarly, decreased fibre intake in the diet can negatively impact intestinal health by increasing T helper 17 cells (T_H17) production while reducing T regulatory cells (T_{reg}) and short-chain fatty acid (SCFA) production. This imbalance ultimately leads to heightened chronic inflammation within the gastrointestinal tract. Prolonged chronic inflammation in the intestine can substantially increase the risk of developing inflammatory bowel disease (IBD).

SCFA[123]. Although changes in the human gut microbiota are associated with metabolic disorders, attempts to transfer this microbiota to mice to replicate diabetes conditions have been unsuccessful, suggesting they are not specific to type 2 diabetes[124,125]. Individuals with cardiometabolic disease present an altered gut microbiota characterized by increased Enterobacteriaceae spp. and reduced *Bacteroides* spp. and anti-inflammatory *F. prausnitzii*[124]. These changes in the gut microbiota are associated with a more inflammatory and less fermentative gut environment. TMAO, a metabolite produced from dietary compounds by gut bacteria, is linked to arteriosclerosis, platelet aggregation and thrombosis. Studies in mice and humans have shown that dietary factors impact TMAO levels, with antibiotics lowering TMAO in some cases and omnivorous diets increasing it. Elevated TMAO levels are associated with higher mortality in patients with heart failure[125]. However, the results are inconsistent, as some studies suggest potential benefits of certain dietary components such as L-carnitine and foods rich in TMAO to prevent atherosclerosis, raising questions about the complex interplay between diet, the microbiome and host genetics in arteriosclerosis development[124,125]. Small changes in energy homoeostasis owing to microbiome alterations can have long-term effects, having roles in metabolic diseases, as both causal and contributing factors. Additionally, they can act as a target for ameliorating these conditions using microbiome-targeted therapeutics.

Diet, the microbiome and intestinal disorders

Diet has a pivotal role in the pathophysiology of intestinal disorders, particularly inflammatory bowel disease, irritable bowel syndrome and colon cancer (Fig. 4b). Hypersensitivity, food intolerance, shifts in microbiota composition, mild mucosal inflammation and increased intestinal permeability may contribute to the manifestation of irritable bowel syndrome[126]. Studies have noted a substantial difference in microbial profiles from patients with irritable bowel syndrome compared to controls[127–129]. Earlier studies have generated inconsistent findings in relation to the gut microbiota composition of patients with irritable bowel syndrome; however, in alignment with recent studies[129], it was observed that human microbiomes resembling pathogenic irritable bowel syndrome exhibited reduced abundance of Bacteroidetes species, as well as increased abundance of Firmicutes species and genes related to amino acid and carbohydrate metabolism[127]. Diet can also alter gut microbiota composition in inflammatory bowel disease, encompassing Crohn's disease and ulcerative colitis, impacting the metabolism of substances such as SCFAs and fibre, which in turn can contribute to the onset of the disease. Food components such as animal protein, dairy, carbohydrates and polyunsaturated fatty acids (Fig. 3a) have been linked to the risk of developing inflammatory bowel disease[130]. One proposed mechanism connecting inflammatory bowel disease to animal proteins involves amino acid and haem malabsorption in the small intestine, resulting in the production of harmful by-products such as phenol and hydrogen. This contributes to the pathogenesis of inflammatory bowel disease by inhibiting butyrate production and reducing disulfide bridges in the intestinal barrier[131]. Diets rich in fat are also strongly associated with the development of inflammatory bowel disease. In experimental models, a high-fat diet can disrupt binding protein functionality among enterocytes, thereby altering the composition of the mucous layer and the intestinal microbiota[132] (Box 1).

Persistent and inadequately controlled inflammatory bowel disease, along with chronic gastrointestinal inflammation owing to poor dietary patterns such as the Western diet, are major external factors influencing colitis-associated colorectal cancer risk. These factors affect immune response, intestinal tissue balance and the gut microbiome[133]. Diet can also have a role in sporadic colorectal cancer pathogenesis. A study has found an association between a low-fibre, high-fat diet and *Fusobacterium nucleatum*[134].

Box 1 | The effect of diet on the intestinal mycobiome, virome and resistome

The human gut is home to fungal and viral populations, known as the mycobiome and the virome, respectively. Although these communities make up only 0.1% to 1% of total microorganisms present in the gut[1], they are both influenced by diet. In the infant gut mycobiome, *Saccharomyces cerevisiae* is the dominant species, but after weaning, it is replaced by *Cystofilobasidium* spp., *Ascomycota* spp. and *Monographella* spp.[159]. The gut fungal compositions of people living in urban areas comprise *S. cerevisiae* and fewer SCFA-producing bacteria, whereas rural residents exhibit a diversity of understudied fungal species. *Candida* species are associated with carbohydrate-rich diets while negatively associated with protein-rich diets (reviewed in ref. 160).

Differences in the gut virome composition between breastfed and formula-fed infants are caused by variations in the gut microbiota and intricate virus–bacteria interactions as a result of vertical transfer of viruses through breast milk, which does not occur in formula feeding[161].

A diet rich in fat was associated with a decreased abundance of viruses belonging to the Siphoviridae family and an increased abundance of bacteriophages from the Microviridae family[162]. A gluten-free diet was associated with an opposite change, with the Siphoviridae dominating over the Microviridae family. Like the bacterial microbiome, a shift in viral composition was observed in individuals with obesity and type 1 and type 2 diabetes[163]. A faecal viral transplant in mice fed with a high-fat diet reduced the risk of obesity, though the exact mechanism is not known (reviewed in ref. 163).

The gut resistome — the collection of all genes or genetic material conferring antimicrobial resistance — varies with the bacterial microbiome and virome. Some studies have reported that genera belonging to the class Gammaproteobacteria have rich antibiotic resistance gene (ARG) reservoirs[164]. A recent study has shown a higher ARG load in formula-fed infants compared with breastfed infants and such a difference was associated with bacterial composition[165]. Although individuals adopting a vegan and pescatarian diet exhibited different microbial compositions in their gut, they did not exhibit substantial differences in their resistome profiles, suggesting that the resistome is primarily shaped by antimicrobial exposure instead of diet, with potential exceptions for foods containing specific preservatives[166]. However, a different study has found that high-fibre consumers in the USA had a lower abundance of ARG[167]. Detailed dietary intervention studies are needed to understand whether diet can reduce the ARG burden.

Fusobacterium species have been associated with colorectal cancer through mechanisms including activation of E-cadherin–β-catenin signalling, epigenetic changes and alteration of the tumour microenvironment, thus contributing to malignant transformation[135]. Similarly, oncogenic bacteria, such as enterotoxigenic *Bacteroides fragilis*, have been hypothesized to trigger the onset of colorectal cancer by directly engaging with colonic epithelial cells and altering local microbiota composition[136].

Diets specific to disease states

The Mediterranean diet has been effective in mitigating and managing multiple conditions including cardiovascular disease[25,26,137,138], type 2 diabetes[139], inflammatory bowel disease[140], irritable bowel syndrome[141], cognitive decline[5] and depression[10] (Box 2). Additionally, alterations to this diet, such as the MIND, have been successful in lowering the risk of Alzheimer disease and slowing cognitive decline[142]. Similarly, the DASH (Dietary Approaches to Stop Hypertension) diet has demonstrated efficacy in treating hypertension[81]. A specific carbohydrate diet is used in clinical practice to treat the symptoms of inflammatory bowel disease. The specific carbohydrate diet has demonstrated its efficacy in paediatric[143] and adult cohorts[144] and has been associated with improved clinical parameters and inflammatory markers[143]. However, it is essential to keep nutritional control with this diet to avoid nutrient deficiency and weight loss[130].

For the treatment of irritable bowel syndrome, a low-fermentable oligosaccharides, disaccharides, monosaccharides and polyols (low-FODMAP) diet is routinely used, with 50% to 80% of patients having a positive clinical response[145]. Although the mechanism of action is incompletely understood, a 4-week study in 41 patients following a low-FODMAP diet exhibited a compositional and functional shift from a pathogenic-like irritable bowel syndrome gut microbiome towards a health-associated gut microbiome[127]. Similarly, studies have shown that adhering to a low-FODMAP diet exhibited a substantial reduction in *Bifidobacterium adolescentis*[128,146], which disrupts gut barrier function and alters tight junction integrity, thus supporting the hypothesis that positive effects of a low-FODMAP diet are mediated by the gut microbiota[128].

Gluten-free diets are currently the only treatment for coeliac disease, with studies establishing the effectiveness of this diet in alleviating gastrointestinal symptoms[147]. Adopting this dietary regimen has been linked to alterations in microbial composition and microbial pathways in the intestine[148,149]. A recent study has analysed small RNA and metagenomic sequencing data from individuals with coeliac disease, comparing those who strictly adhered to a gluten-free diet with those who did not. The findings have shown that adopting a gluten-free diet altered both miRNA and microbial profiles. The study has also revealed miRNA–bacterial relationships and specific molecular patterns in subjects with coeliac diseases, suggesting potential biomarkers to monitor adherence to a gluten-free diet and assess gut inflammatory status[149].

Low-protein diets are recommended for the management of chronic kidney disease, which aims to decelerate the progression to end-stage kidney disease and delay the need for renal replacement therapy[150]. A systematic review has concluded that very low-protein diets may effectively reduce the occurrence of stage 4 or 5 kidney disease. However, adopting a low-protein diet alone did not impact the development of end-stage kidney disease[150]. Furthermore, results from a systematic review and meta-analysis of five articles found that a diet low in protein increased the abundance of *Bacteroidaceae*, *Lactobacillaceae* and *Streptococcus anginosus*, while reducing the abundance of *Roseburia faecis* and *Bacteroides eggerthii*. However, without global compositional shifts in microbial diversity and richness, these alterations, predominantly at the species and family levels, seem inadequate to impact metabolic or clinical outcomes[151].

The glycaemic index diet, used for the management of type 2 diabetes, is of interest owing to its effect on the gut microbiome and its potential role in influencing disease development and severity. This diet involves the consumption of carbohydrates characterized by a low glycaemic index, (for example, legumes, oats and wheat) promoting a gradual and sustained rise in blood sugar levels. Although research on the effect of this diet on the gut microbiota is limited, mice studies have shown that it is associated with an increased abundance of *Lactobacillus* spp., *Prevotella* spp. and members of the fibre-degrading S24-7 bacterial family as a result of barley intake[152], or increases in *Bifidobacterium* spp. and *Lactobacillus-Enterococcus* spp. as a result of wholegrain oat intake[153].

Box 2 | Food for thought

Psychiatric disorders have been associated with alterations in the brain–gut microbiota axis and dietary patterns, fuelling the growing interest in dietary interventions aimed at mitigating and preventing the advancement of mental health conditions. Numerous studies have shown that following a Mediterranean diet has been associated with increased mental health and reduced risk of depression[10,155,156,168,169], whereas adherence to a Western diet has been reported to increase metabolic endotoxemia (a condition in which there are elevated levels of endotoxins such as the lipopolysaccharide in the bloodstream) and reduce microbial diversity, with multiple downstream effects linked to depression[170]. Many hypotheses have been brought forward to explain the underlying mechanisms associated with diet and psychiatric disorders. In Alzheimer disease, reduced flow-mediated vasodilation and diet-related endothelial dysfunction may be the underlying causes of disease onset[171,172]. Studies have shown that high-quality diets, such as the Mediterranean and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diets, may reduce cognitive decline[5,9]. Interestingly, a psychobiotic diet — rich in fermented foods and postbiotics — showed promising results in reducing perceived stress. The study has observed substantial changes in faecal lipids and urinary metabolites of tryptophan[173]. Additionally, small-scale studies have shown that a gluten-free, casein-free diet improved some of the symptoms of autism spectrum disorder, such as hyperactivity, communication and behavioural disorders[174,175].

Diet has a substantial role in influencing the communication between the gut microbiome and the brain through various pathways, including the modulation of neurotransmitters and tryptophan metabolism[176]. Dietary factors can impact the inflammatory signalling between the gut and the brain, with specific microorganisms and metabolites either promoting or inhibiting immune activation, potentially contributing to neuroinflammatory processes in various psychiatric disorders. Further research, particularly through human intervention trials, is needed to establish a causal relationship between diet, the gut microbiota and psychiatric diseases[162].

Precision nutrition targeting the gut microbiome

Precision nutrition is an emerging field that aims to tailor dietary recommendations to the unique characteristics of an individual, including their microbiome in health and disease. By analysing microbiome composition and function, it is possible to identify insufficient or missing dietary components based on specific microbial signatures, as well as select the right probiotics or prebiotics for optimal gut health. Utilizing diet as a form of precision nutrition can be useful in the prevention, treatment and alleviation of disease. However, the effectiveness of dietary interventions in treating these diseases depends substantially on the individual host and their unique gut microbiome composition. Additionally, precision medicine must consider precision nutrition owing to its influence on microbiota composition, particularly in the context of immunotherapies for cancer wherein the gut microbiota can impact drug efficacy. It is imperative to conduct large-scale randomized controlled trials that span such diverse factors as geography, sex, ethnicity and age to gain a deeper understanding of the intricate and individualized impact of diet on various health outcomes.

Conclusions and outlook

To elucidate the intricate relationship between the microbiome, the host and nutrition, the integration of multi-omics techniques, including metagenomics, metatranscriptomics, metaproteomics, metabolomics, culturomics and isotope techniques to name a few, becomes crucial. To ensure consistency and reproducibility among differing datasets and populations, it is necessary to validate the results through cross-platform comparisons and assessment of clinical outcomes. Next-generation sequencing gives insight into the bacterial species, strains, genes, pathways and metabolites underpinning the diet–microbiome interplay, with the future striving towards predominantly long-read metagenomic sequencing to substantially enhance metagenomic assemblies. This approach will improve structural variation detection, enable a comprehensive study of time-specific gut microbiome functionality, and deepen our understanding of diet–microbiome–disease interactions in humans[154]. Many challenges remain to decipher the causal relationships between diet, the host and its microbiome. Different databases are built for this purpose, including FoodDB and USDA Food composition databases, along with databases combining food, human and bacterial metabolic capacities such as Virtual Metabolic Human and AGORA2 (ref. 7). These databases feed mathematical models, especially genome-scale metabolic models, offering insight into the metabolic potential and interactions of the gut microbiome[7]. The combination of artificial intelligence (that is, machine and deep learning) with mathematical models[8] enhances predictive performances.

Microbiome research has advanced greatly but gaps and challenges remain. Faecal microbiome analysis is a proxy for understanding the true composition and complexity of the microbiota residing along the human gastrointestinal tract. This was demonstrated through the use of an ingestible device and multi-omics analysis, whereby 240 intestinal samples from 15 healthy individuals revealed notable distinctions in the composition of bacteria, phages, host proteins and metabolites between the intestines and stool[155]. Further research incorporating this technique to investigate how diet and disease impact the intestinal microbiota, metabolome, virome and proteome is required. Complex individual diets in clinical studies hinder our comprehension of the effects of specific dietary components on the gut microbiota. This is further complicated by a lack of quantification of bacterial plumes. For example, the extent to which psychological factors such as stress responses affect the microbiome in healthy individuals remains a question. Confounding factors persistently complicate our understanding of diet–microbiome interactions. To overcome these challenges, it is essential to understand the unique microbiome of an individual and their historical exposure to environmental factors that could impact microbiome composition and functionality. Variations in food composition across global regions owing to different production parameters and the impact of additives such as pesticides and antibiotics must be considered when comparing global intervention studies.

More in-depth microbiome intervention trials involving large cohorts that manipulate the microbiome through diet are essential to validate causal relationships between dietary modifications, microbiome modulation and health outcomes. Additionally, comprehensive, standardized, long-term (spanning decades) studies are crucial for capturing dietary impacts on the human microbiome accurately, including continuous and real-time tracking of diverse cohorts across various life stages on a global scale, akin to the Human Genome Project[156]. Integration of dietary metadata, which encompasses factors such as nutritional intake and meal timing, could be achieved through mobile applications or wearable devices. With less than 15% of the world living in Europe or North America and over 70% of published human microbiome data coming from these regions[157], low-income countries are being overwhelmingly under represented and their associated diseases such as malnutrition receiving much less focus[158]. Gathering global microbiome data to understand unique microbial associations in different regions and develop targeted therapeutics specific to the needs of each area is vital and requires large-scale collaboration between multiple research centres worldwide. It is evident from this Review that recent research highlights diet as a confounding factor in the interpretation of causal relationships between gut microorganisms and disease in clinical studies, emphasizing the need for comprehensive dietary metadata to generalize clinical findings for the advancement of microbiome-targeted therapies.

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