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Gut Microbiome, Disease, and Diet: Leveraging Big Data for Precise Nutrition

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ABSTRACT: Gut microbiota has profound effects on host health and disease. It is now well acknowledged that diet is a key determinant in shaping gut microbiota. Meanwhile, gut microbiota is an important mediator of the effects of dietary metabolism on the body. Understanding the specific effects and underlying mechanisms of nutrients in diet-microbe-host interactions would support innovation of new intervention strategies to improve health through gut microbiome regulation and nutrient intervention. Advances in multi-omics and artificial intelligence (AI) enable precise gut microbiota modulation and precise nutrition through big data and modeling algorithms. In this context, this review introduces the microenvironment of gut microbiota and its potential mechanisms in diseases. Then, we detail current knowledge regarding how diet modulates gut microbiota and its metabolic activity. Furthermore, we explore how diet can be used as a therapeutic and preventive tool based on big data and AI algorithms. However, causal inference among diet, the gut microbiota, and disease remains limited, and more importantly, the lack of high-quality datasets and standardized analytical frameworks further constrains the clinical translation of precision nutrition strategies. Future research should focus on integrating diverse data with AI-driven modeling to uncover causal diet-microbiome-health relationships, while also building more comprehensive datasets and conducting large-scale, standardized clinical validation. These developments will support the implementation of precision dietary interventions and their translation into real-world applications for personalized disease prevention and health management.

Keywords: Peptidomicgut microbiota, precise nutrition, personalized diet, multi-omics, machine learning

1. Introduction

The human gut harbors a vast array of microbes, such as bacteria, fungi, archaea, viruses, and other microorganisms. Among these, bacteria occupy the highest proportion and represent the most well-studied group^[1,2], with the vast majority being obligate anaerobes. The abundance of microbiota varies across different regions of the gastrointestinal tract, and the highest proportion is found in the colon. The acidity of the gut environment gradually decreases, and oxygen content diminishes along the tract. Meanwhile, the abundance and diversity of these commensal microbiota increase.

The gut microbiota's structure and function are increasingly considered important factors influencing human wellness. These intestinal organisms participate in a wide range of physiologic activities, such as nutrient absorption, vitamin production, immune system functioning, detoxification, inflammation, satiety signaling, neurotransmitters, and protection against pathogen invasion. Research over the last decades has revealed that there are tight cross-species interactions between the gut microbiota and the digestive, immune, and nervous

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systems of the host^[6–9]. The microbiome could affect our metabolism^[10], immunity^[11], mood^[12], and even cognition^[13]. Until now, the gut microbiome has been linked to hundreds of phenotypes and diseases, which are recorded in different repositories^[14,15]. Besides, the gut microbiota is reckoned as a pivotal factor in *Clostridioides difficile* infections (CDI)^[16], obesity^[17], and diabetes^[18,19], as its dysbiosis promotes the onset, development, and progression of these diseases. Hence, it comes naturally to take advantage of gut microbiota status to predict and diagnose diseases, as well as prevent and treat diseases by modulating gut microbiota^[20], though the causal relationships and underlying mechanisms are not yet fully understood^[21–24].

The gut microbiota is shaped by various internal and external factors of the host, including mode of delivery, host genetics, medication, diet, physical exercise, and age, and it exhibits plasticity (i.e., ability to change in response to stimuli)^[25,26]. All of these constitute the macroenvironment that gut microbiota needs to go through, compared to the microenvironment of the intestinal lumen. As a result, gut microbiota also presents distinctive features of inter-individual and intra-individual variations^[27,28]. Comparative models have analyzed the human gut microbiota across different subsistence gradients^[29–31] and provided knowledge for understanding how host genetics, diet, and lifestyle intersect to influence the human microbiome^[32]. Several studies reported that phylogenetic conservation, likely linked to host physiology, outweighs diet in shaping gut microbiota^[33], while others argue that diet is a primary driver of the gut microbiome of humans^[17,34,35]. Diet, diseases, and gut microbiota exhibit a strongly interconnected triangular relationship. Manipulating external influences to regulate microbial ecological balance has been proven to be an effective disease intervention measure^[36], of which regulating diet is an important and promising method^[37], considering its effectiveness, gentleness, non-invasiveness, cost-effectiveness, widespread acceptance, and ease of implementation.

However, one-size-fits-all guidelines to nutrition recommendations seem improper due to personalized dietary responses^[38] and individualized gut microbiota responses^[39], which means that the same dietary configuration has different effects on an individual's gut microbiome and health. This variability limits the broader application of diet interventions and gut microbiota modulation for improving human health. On one hand, as the microbial analysis techniques advance, the accumulation of microbiota-disease data from large cohorts in public databases is accelerating^[40]. On the other hand, wearable devices have made the collection of dietary information and other personalized data more convenient and accurate^[41]. In addition, AI algorithms, particularly in machine learning, have been developed and extensively applied in nutrition and biomedicine research. Therefore, big data-driven precision nutrition, grounded in the complex interplay of gut microbiota, diet, and disease, may break through this barrier. The massive data that comes from the gut microbiota, diet, and disease can be conducive to a deeper understanding of their relationship and serve as the foundation of predictive models for precise gut microbiota regulation and precise nutrition recommendations, which could further advance the prevention, diagnosis, and treatment of diseases.

In this review, we emphasize the role of the gut microenvironment in microbial ecology, metabolism, and host interactions. By integrating this spatial and physicochemical context with dietary modulation and disease

mechanisms, we provide a mechanistic and biologically grounded interpretation of diet–microbiota–disease relationships. Furthermore, we connect these mechanistic insights to advances in big data and AI, highlighting that data integration and predictive modeling can enable precision nutrition and personalized dietary interventions. This will encourage nutritionists, medical researchers, and microbiome researchers to initiate large-scale studies and meta-analyses, then further develop robust predictive models to generate more valuable insights and applications. These studies will contribute to developing precise gut microbiota modulation and personalized nutritional recommendations to improve human health.

2. Gut microbiota and gastrointestinal microenvironment

The human digestive system involves the hollow gastrointestinal tract and other solid organs (Figure 1A), which is highly compartmentalized, with each individual segment performing separate physiological functions. These organs collaborate to break down food into simple nutrients for better absorption. The nutrient availability, pH, and oxygen gradients, bile acids (BAs), mucus, immune factors, and gastrointestinal peristalsis together constitute a variety of highly distinct microenvironments along the twisting gut (Figure 1B).

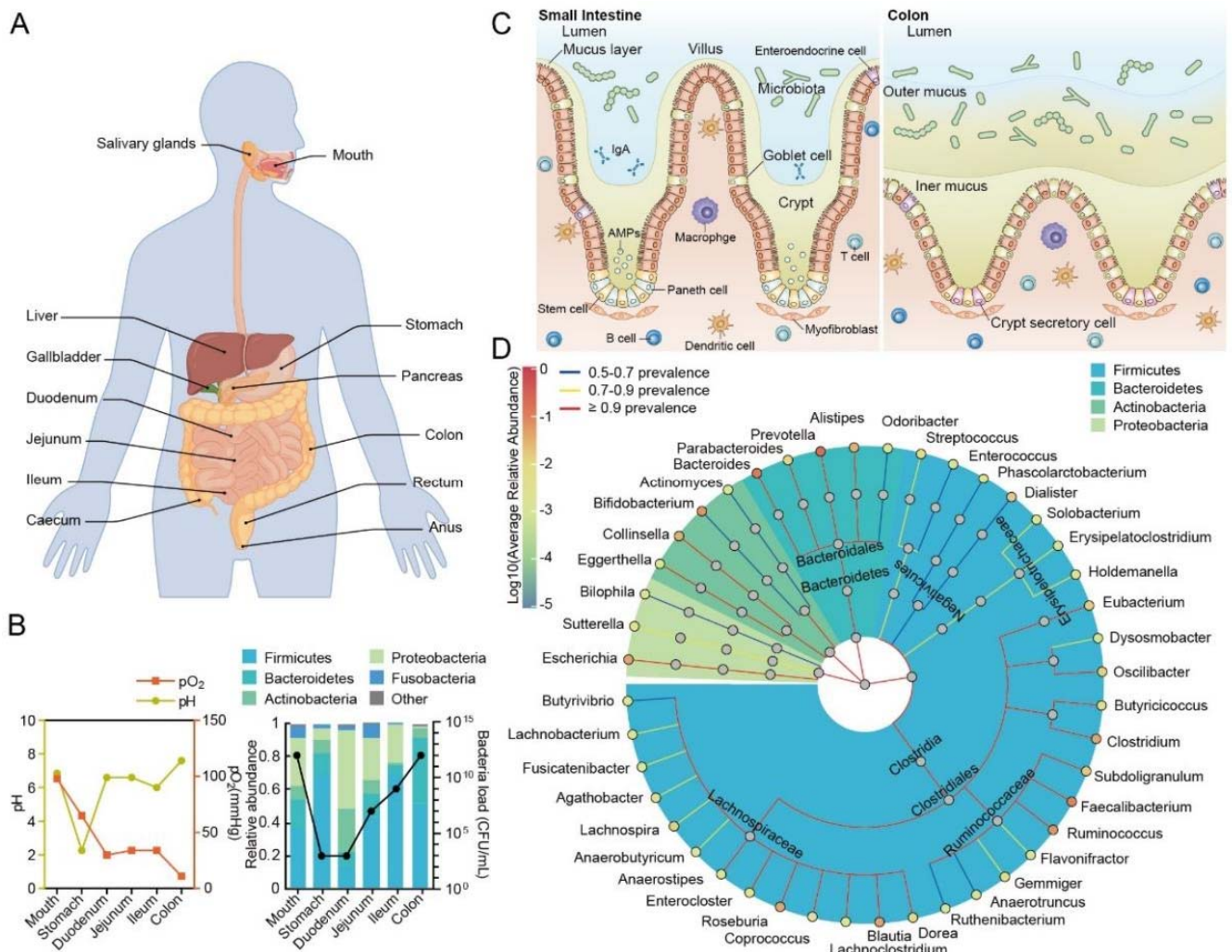


Figure 1. Digestive system and microbial niches in the gut. (A) Structure of the digestive system; (B) Microenvironment of different regions and bacteria composition[155–157]; (C) The small intestine and colon; (D) Universal healthy human gut microbiota[143].

2.1 pH gradient

Gastrointestinal tract pH, as a fundamental and important characteristic, reflects the physiological processes, including immune response, gut motility, nutrient digestion, and absorption^[42]. As chyme passes through different intestinal regions, its physical and chemical properties change due to digestion and absorption. This also impacts proton and other ion concentrations. The pH values of the gastrointestinal tract vary slightly among studies, but the overall pH gradient remains consistent^[43–45]. Generally, the proximal small intestine is more acidic (pH 1–2), with the pH gradually increasing to around 6 in the ileum, after which the pH level slowly increases again to the rectum (Figure 1B). This is referred to as a longitudinal pH gradient in the lumen, which has not only contributed to the development of drug delivery systems targeting specific intestinal locations^[46,47] but also facilitated the design of intestinal bacteria sampling devices for different regions^[48,49]. Another pH gradient, known as the transversal pH gradient or mucosal pH gradient, emerges along the epithelial crypt axis. This is evidenced by the maintenance of near-neutral intracellular and mucosal pH, despite dramatic pH changes in the intestinal lumen. The intracellular pH homeostasis relies on activation and rapid shuttling of various ion transporters, such as H^+ and HCO_3^- cotransporters, to the apical microvilli and basolateral domains^[50]. Furthermore, the mucus layer traps H^+ and HCO_3^- , retarding their diffusion^[51]. The acidic microclimate is not only associated with the absorption of electrolytes and short-chain acids (SCFAs) but also potentially regulates intestinal epithelial proliferation and differentiation^[52].

There is a bidirectional interaction between gut microbiota and intestinal pH. The luminal pH can modulate the composition and activity of the gut microbiota, as different microbial taxa vary in their sensitivity to pH changes. Generally, the majority of opportunistic pathogens exhibit optimal growth within a circumneutral pH, while their proliferation is significantly restricted under acidic conditions. For example, *Bacteroides spp.* exhibit broad pH tolerance, whereas *Veillonella* and *Streptococcus* show growth inhibition at acidic pH. The colonic pH has an effect on saccharolytic fermentation, proteolytic fermentation, and bacterial BA metabolism. Notably, butyrate-producing genera *Faecalibacterium* and *Roseburia* present enhanced proliferation and butyrate biosynthesis under weakly acidic conditions compared to neutral environments^[44]. Early studies indicated that pH affects the taxonomic profile and population density of enteric bacteria, and gut pH alteration may impact the gut microbiota community structure and SCFAs production^[53,54]. The change in colonic pH directly influences microbiota competition for nutrients. Recently, experiments *in vitro* have found that pH is the strongest driver of microbial composition, function, and metabolic interactions among pH-sensitive fermentative species^[55]. Another *in vitro* simulation experiment reveals that the elevation of environmental pH levels significantly increased luminal microbiota richness and decreased mucosal microbiota evenness, and total SCFAs levels also increased, which is mainly attributable to the increase in acetic and 2-methylbutanoic acids^[56]. In the upper gastrointestinal tract, luminal pH is largely determined by host-derived secretions such as gastric acid, bile, and bicarbonate. By contrast, pH regulation in the colon is strongly shaped by microbial metabolic activity. The gut microbiota generate a range of acidic and basic metabolites that modulate the intestinal environment. For instance, SCFAs and BCFAs, along with lactate,

formate, and succinate, dissociate into organic anions that acidify the colonic lumen. In contrast, ammonia produced during protein fermentation is alkaline and contributes to an increase in colonic pH.

The impact of the gut microbiota on intestinal pH largely depends on individual microbial composition and diet. Notably, diet can modulate the community structure and activity of gut microbiota. This effect is partly due to the selective utilization of colonic substrates by specific microbes and may also result from pH changes induced by substrate fermentation^[57]. The types and quantities of dietary components available in the gut modify gut microbial composition and fermentation processes, leading to the production of acidic or alkaline metabolites, which in turn influence pH. The acidification of the intestinal environment inhibits the colonization of acid-sensitive microorganisms, further influencing the microbial composition. Breastfed infants have lower faecal pH than formula-fed infants, probably due to the presence of human milk oligosaccharides (HMO) in breast milk, which promote HMO-degrading *Bifidobacterium* species metabolizing HMOs into lactate, formate, and acetate. By contrast, formula-fed infants, unexposed to HMOs, tend to display higher faecal pH and lower abundance of bifidobacteria^[58]. Similarly, high-fibre diets reduce faecal pH due to elevated colonic SCFA production, whereas refined-grain diets increase faecal pH^[59]. Conversely, proteolytic fermentation generates nitrogenous products such as indoles and ammonia, which can increase colonic pH and exert a stronger alkalizing effect than the acidifying influence of BCFAs. Additionally, dietary pH can also alter the gut's acidity and microbial ecosystems^[60].

Abnormal pH levels in the gut can influence microbial composition and metabolism and are associated with various conditions. In patients with inflammatory bowel disease (IBD), colonic pH becomes notably more acidic compared to the healthy colon^[47]. Additionally, fecal pH decreases with disease severity in patients with ulcerative colitis (UC)^[61]. Some diseases, such as atrophic gastritis and chronic pancreatitis, can directly alter gastrointestinal pH, primarily by influencing host secretions, which in turn can affect microbial composition and metabolism^[58]. High gastric pH, along with impaired clearance, leads to small intestinal bacterial overgrowth (SIBO). Low colonic pH could inhibit pathogens, but excessive acidity from lactate accumulation is harmful, while elevated pH is linked to conditions such as pseudomembranous colitis. A mildly acidic pH enhances beneficial metabolites such as SCFAs, whereas a more alkaline pH increases detrimental metabolites, including protein fermentation products and secondary BAs, potentially influencing the risk of several diseases, including colorectal cancer (CRC) and chronic kidney disease^[58].

2.2 *O₂ gradient*

The oxygen concentration in the intestinal tract plays an important role in both physiological and pathological contexts. It provides an appropriate environment for the metabolic needs of intestinal microbes^[62]. Similar to pH gradients, there are oxygen gradients within the human intestinal tract along two axes. The partial pressure of oxygen (pO_2) decreases along the gastrointestinal tract and is generally lowest in the colon, which forms the longitudinal oxygen gradient. The oxygen supplied by the subepithelial mucosa is mainly employed by intestinal epithelial cells, and the rest gradually diffuses from the intestinal tissue into the lumen, which forms the vertical oxygen gradient. The estimated pO_2 levels in the small intestine are about 59 mm Hg

in the intestinal wall, approximately 22 mm Hg at the villus tip, and <10 mm Hg in the lumen^[63]. As for pO₂ in the colon, the estimate is 42mm–71 mm Hg across the muscle wall, around 42 mm Hg in the vascularized submucosa, 5–10 mm Hg near the crypt-lumen interface, and 11 and 3 mm Hg in the ascending and sigmoid colon lumens, respectively (Figure 1B)^[64].

The oxygen concentration is related to the enterocyte energy metabolism types, luminal biochemical reactions, and activities of microbiota that actively consume oxygen^[65]. The gut microbiota is thought to participate in establishing and maintaining the anaerobic microenvironment by consuming oxygen. The newborn intestines exhibit relatively higher oxygen levels compared to adult intestines and are inhabited by aerobes and facultative anaerobes, including Enterobacteriaceae, *Enterococcus spp.*, and *Streptococcus spp.* Due to the consumption of oxygen, the bacterial community gradually transforms into strict anaerobic bacteria in early life^[65]. Although luminal oxygen in the caecum and colon is the lowest, surprisingly, a large fraction of gut microbiota possesses the ability for aerobic respiration or survival under microaerobic conditions, including previously considered strict anaerobes^[66]. This observation suggests the adaptability of commensal bacteria to fluctuations in the intestinal environment. The gut of germ-free mice is also highly anaerobic, indicating that mechanisms other than microbial respiration contribute to oxygen consumption, such as oxidation of lipids and other organic substrates^[65]. Therefore, oxygen homeostasis in healthy intestines is maintained through the dynamic metabolic activity of gut microbiota and fluctuations in cellular oxygen tension. The oxygen distribution in the intestinal lumen, in turn, influences the gut microbiota community. Oxygen consumption by aerobic bacteria around the epithelium and the increase of tissue oxygenation promote the growth of aerotolerant microbes at the epithelia-lumen interface^[67]. Intermittent hypoxia exposures could cause hypoxia/re-oxygenation patterns in the gut epithelium and further induce a change in the gut microbiota^[68]. Similarly, acute high-altitude hypoxia can lead to intestinal damage and changes in gut microbiota; oxygen enrichment treatment has positive effects on gut structure and microbiota in animals experiencing acute hypobaric hypoxia^[69]. Elevating tissue oxygenation through hyperbaric oxygen exposure changed the gut microbiome composition in mice^[70].

The changes in luminal O₂ concentration in gastrointestinal disease and the consequent impact on hosts are not yet fully understood. But numerous intestinal diseases are believed to be associated with high oxidative stress, which can lead to gut dysbiosis^[67]. Notably, one of the characteristic features of dysbiosis is an excessive abundance of oxygen-consuming bacteria. The heightened microbial oxygen consumption may contribute to localized gut tissue hypoxia, which can trigger and exacerbate inflammation by activating hypoxia-inducible pathways and promoting immune cell infiltration. It has been hypothesized that excessive oxygen in the gut can disturb the normal microbiota and further cause inflammation and infiltration by pathogens^[71]. If the host fails to control luminal oxygen concentrations, then the gut microbiota will shift from obligate to facultative anaerobes in response to oxidative stress, thereby increasing susceptibility to pathogen invasion^[72,73]. DSS-induced colitis reduces oxygenation in the intestinal tissue and increases the flux of oxygen from the tissue into the lumen. The elevated oxygen flux further promotes the proliferation of

polysaccharide-degrading bacteria enriched in glycoside hydrolases, which are known to reside on the mucosal surface of the gut. Through this mechanism, the persistent disruption of the intestinal mucus barrier may contribute to the perpetuation of gut inflammation^[74]. Moreover, inflammatory processes can elevate tissue oxygen consumption, further exacerbating local hypoxia. Neutrophil infiltration during inflammation may also deplete oxygen, intensifying hypoxic conditions in colitic tissue. The oxidative damage induced by inflammatory infiltrates has been implicated in the initiation and progression of multiple chronic illnesses, including IBD, diabetes, and intestinal malignancies.

Although the intestinal lumen is deprived of oxygen, maintaining overall oxygen homeostasis is critical for preserving mucosal integrity and normal immune function. Currently, studies on the effects of diet on the intestinal oxygen environment remain limited. It is reported that the flow of food through the gut affects both the concentration and amount of O₂ in gut luminal contents^[75]. Elemental iron can serve as an antioxidant and reverse the oxygen-induced dysbiosis. However, the efficacy of the oxygen scavenging effect varies among individuals, likely due to differences in microbial consortia responsiveness^[76]. In addition, microscopic redox balance is also crucial for host-microbiota interaction. Dietary components may promote the overproduction of reactive species with oxidative potential in the gastrointestinal tract, representing another pathway that may contribute to pathological conditions. Conversely, dietary antioxidants may help alleviate mucosal oxidative stress, reducing mucosal inflammation with modified gut microbiota^[77].

2.3 Mucus layer

In the gastrointestinal tract, the epithelium surface is covered with mucus, which contributes to the absorption of nutrients and keeps bacteria away from the epithelium. The mucus is secreted by goblet cells, and the proportion of goblet cells compared to enterocytes rises from 4% in the duodenum to 16% in the distal colon^[78]. Thus, in comparison with the mucus in the colon, the mucus in the small intestine is thinner (single layer, ~20 µm in rats), patchy, and penetrable (Figure 1C)^[79]. Due to the abundant antimicrobial peptides and proteins, particularly secreted from the Paneth cells, most gut microbiota are kept at a distance from the epithelium by the mucus layer^[80,81], except at the tips of the villi (mucus layer is thinner here) or for segmented filamentous bacteria (SFB)^[82]. In contrast, the colon has relatively thicker (two layers, ~116 µm in rats), well-defined and continuous mucus layers, and the thickness of colonic mucus is gradually increasing along the colon (Figure 1C)^[79]. The mucus is composed of water (up to 95%), ions, lipids, and mucins (a core set of about 30 proteins)^[83,84]. These glycoproteins, especially with *O*-glycans, assemble into a gel-like polymer network that expands > 100 fold in volume by binding water, and this gives the mucus viscous properties^[85]. The primary gel-forming mucin in the gastrointestinal tract is mucin 2 (Muc2), forming the mucus skeleton^[86], which is compressed and stored in secretory granules of the goblet cell. The firmly adherent inner layer in colon mucus is constantly replenished by the Muc2 and keeps attached to the epithelial surface, which separates microbiota from the epithelium. The thickness of the inner layer is approximately 22 µm, as recently observed in murine colonic mucus using both fluorescence *in situ* hybridization^[87] and three-dimensional imaging^[88]. The renewal rates of mucus vary across different segments, but mucus is generally refreshed

within the range of hours^[89], forming a sharp border between them. Mucus is estimated to expand at a rate of about 100 $\mu\text{m}/\text{h}$ in mice and 240 $\mu\text{m}/\text{h}$ in humans^[90,91]. This might be another way that mucus blocks bacteria out. The outer layer of colon mucus is converted from the inner mucus layer, where Muc2 is cleaved by proteases and becomes soluble. This transition is also observed in germ-free mice, which means this process depends on the host. Human digestive enzymes are only able to cleave specific glycosidic linkages and those in a few disaccharides. Besides, these mucins form a highly tight and stable framework where the specific cleavage sites are unable to be reached by pancreatic proteases. Given these properties, the host digestion seems to have a limited impact on intestinal mucus. The bacteria can also contribute to it due to their proteases and glycosidases^[92]. However, some gut microbiota are specialized in breaking down the mucin glycans as energy sources and feeding not only themselves but also their host, such as *Akkermansia muciniphila* and *Bacteroides thetaiotaomicron*^[93]. There are likely many other members of the gut community with the capacity to degrade mucins^[94]. Therefore, the loose outer layer has a less well-defined outer border.

The various densities of mucus in the gastrointestinal tract not only act as a physical barrier and lubrication against the luminal material but also provide a habitat and energy sources for microbiota. Gut microbiome structure varies laterally from the lumen to the mucosa, which has been confirmed in both animal and human studies^[95,96]. Besides, the mucus-associated intestinal microbial community also differed and was not reflected in fecal microbiota in both animal and human studies, although luminal microbiota will inevitably be mixed with the species that have proliferated in the mucus layer^[96–98]. The gut microbiota nearest to the mucosa exhibits significantly greater species richness^[87]. The deep bacterial communities closely adhere to the mucosa and are relatively stable, known as fixed or membrane microbial communities, most of which belong to the native or resident microbial communities. This means that it is more resistant to dysbiosis after antibiotic treatment, compared to the shallow (superficial) layer that mostly belongs to the foreign or passing microbial community^[87]. Notably, the mucus-associated biofilms could be manipulated through dietary changes targeting Clostridia^[87]. In the ileum, microbiota is not unevenly distributed across the villi and is primarily found in large clusters of food particles and mucus adhering to the epithelium. At higher resolution, microbiota are contained by mucus in a layer near the top of the villi^[88]. In the cecum, all crypts produce mucus, and the mucus is evenly distributed across crypts. The gut microbiota colonize in partial crypts, and the colonization is not homogeneous. In the proximal colon, microbiota blend with chyme, taking up the lumen evenly. Highly dense bacterial communities reside at the interface between the inner and outer mucus layer^[87], and blended with mucus and granules, forming a discontinuous layer with an average thickness of 125 μm ^[88].

The bidirectional interaction between intestinal epithelial cells (IECs) and intestinal bacteria is achieved through various mechanisms. IECs can regulate the intestinal bacteria through secreting type 2 immune mediators, mucins, antimicrobial peptides (AMPs), and hormones^[99]. For example, IL33 is generated by IECs in response to injury and inflammatory stimulation and does not directly inhibit bacterial growth. However, it promotes IECs expression of REG3 γ , an antimicrobial peptide, and controls the intestinal bacteria of the host^[100]. Inversely, intestinal bacteria can also impact IECs through adhesion, signal transduction, and

metabolites. It was reported that the composition of IECs can be influenced by microbiota through the regulation of intestinal stem cell differentiation in an immune-dependent manner^[101]. In addition, microbiota regulates IECs expression of AMPs and intestinal homeostasis; microbiota metabolites SCFAs promoted IECs RegIII γ and β -defensins in a GPR43-dependent manner^[102].

The mucus layer defends against microorganisms by forming a physical barrier and its continuous renewal. Thus, pathogens need to penetrate the intestinal mucus layer to induce gastrointestinal symptoms. In addition, disruption of the mucus layer is an important determinant of IBD and CRC. In IBD, excessive activation of the intestinal immune system and damaged intestinal mucosa are prominent features, whereas in CRC, increased mucus secretion and alterations in its chemical composition are hallmarks of disease progression. It is noteworthy that intestinal mucosal injury may be caused by dysregulation of the gut microbiota. Changes in the abundance of bacteria involved in mucin synthesis and degradation can compromise mucus integrity^[103]. The alterations in the composition of gut microbiota may degrade the mucus layer involving glycoside hydrolases, internalins, and flagella^[103]. For example, *Ruminococcus gnavus*, which is enriched in UC patients' gut, is mucolytic and produces an inflammatory response, potentially explaining the increased permeability detected in UC. The impaired mucus layer can lead to microbial translocation and interaction with intestinal tissue, thereby triggering inflammation and affecting gastrointestinal oxygen levels^[74].

Dietary emulsifiers have become particularly concerning due to their disruptive effects on the mucus layer. Carboxymethylcellulose (CMC) and polysorbate 80 (Tween), respectively, reduce mucus pore size and mucus layer permeability or increase the speed of migration of *E. coli* in mucus^[104]. Additionally, both emulsifiers reduced the quantity and thickness of mucus in rat intestinal tissue, diminishing the integrity of the barrier, increasing microbial invasion, and potentially contributing to a proinflammatory milieu. In patients with UC in remission, administration of the emulsifier, carrageenan, led to relapse of UC compared with those who received a placebo^[105]. The Western diet is potentially damaging to the mucus layer. One of the key features of the Western diet is the lack of dietary fiber, which may lead to microbiota using mucus glycoproteins as nutrients, thereby degrading barrier integrity^[106]. Conversely, prebiotic supplementation, such as inulin, pectin, and guar gum, can increase colonic mucus^[107,108]. Gut microbiota-derived SCFAs from fiber fermentation, particularly butyrate, directly stimulate the production of mucus by activating the macrophage/WNT/ERK signaling pathway^[109].

2.4 Microbiota distribution

Maternal and environmental microbiota seed the offspring's gut microbiota at birth. Throughout the entire life, the microbiota undergoes continuous and dynamic changes. During the first month after birth, the intestinal microbiota shows very low diversity. At about age three, the diversity and density of the intestinal microbiota increase and stabilize to adult-like^[110,111], and gradually achieve the adult status by the age of 7–12 years^[112]. Gut microbiota population investigation shows each individual possesses a unique microbial profile^[113,114]. In generally, there are 200 to more than 1,000 species of microbiota inhabiting an individual

intestinal tract^[115–118]. It is estimated that at least 1,800 genera and 15,000–36,000 species are in the collection of human gut microbiota^[119–121], and new species are continually uncovered^[121–125]. The gut microbiota structure keeps relatively stable across populations at the phylum level, and mainly belongs to four phyla, including Bacillota (formerly Firmicutes), Bacteroidota (formerly Bacteroidetes), Pseudomonadota (formerly Proteobacteria), and Actinobacteria, which make up about 90% of the total community in a normal healthy human^[126]. Meanwhile, Firmicutes and Bacteroidetes are two predominant phyla that represent more than half of the gut bacteria. Some studies proposed Firmicutes/Bacteroidetes (F/B) ratio (now known as Bacillota/Bacteroidota ratio) as a microbial biomarker, and it has been associated with obesity and other pathological conditions, but contradictions over the alteration of this ratio in obesity also emerged. It should be noted that the F/B ratio as a proxy for the microbiota oversimplifies the community, because the microbial metabolism and interactions need to be considered. There is broad variation in the composition of the human gut microbiome, but within a limited selection of microbial taxa drawn mostly from the Bacillota phylum. In parallel, gut microbiomes exhibit a wide range of alpha diversity among individuals, with a median Shannon diversity of 2.33 and values reaching up to 5.07. Microbiome composition and diversity also vary markedly across global regions. Each region occupies a unique niche within the ordination space defined via multidimensional scaling and clusters in ways that are detectable by multiple machine learning classification approaches^[126]. Notably, geographic information may capture composite effects of diet, habitat, and ethnicity. Early estimations of gut microbiota number were 10^{14} , ~10-fold more bacteria in the body than human cells^[127,128]. But a more recent study indicates a bacterial-to-human cell ratio of approximately 1.3:1 in the human body^[129]. Now, metagenomic studies and the database of the human microbiota have indicated that there are 3.3 million non-redundant gut microbial genes^[115,130], about 150 times more than human genes^[131–134].

The gut bacterial distribution also varies in gastrointestinal regions within an individual due to the microenvironmental gradients as mentioned above, and presents a trend of increasing microbial abundance and diversity from the stomach to the distal colon^[135]. The stomach harbors only low numbers of commensal microbiota (about 10^2 CFU/mL). Most bacteria with low acid tolerance are eliminated because the acidic environment and swift peristaltic movements hinder persistent colonization. But a few acid-resistant bacteria (such as *Helicobacter pylori*) can still survive and colonize in a subset of the human population. Similar to the stomach, the duodenum and the jejunum host a relatively small number of bacteria, ranging from 10^3 to 10^4 CFU/mL. Acidic pH and bile, as well as their high fluidity in the proximal to mid-small gut, restrict microbiota proliferation^[136–138]. The species diversity is also low and mainly contains aerobic or facultative anaerobic bacteria, such as *Candida albicans*, *Lactobacillus*, and *Streptococcus*. Microbial cell population densities increase along the jejunum, ileum, and colon. The ileum, as a transition region, has bacterial density and species diversity that lie between the proximal small intestine and the colon, with a bacterial count of 10^7 – 10^8 CFU/mL. It has more species than the proximal small intestine, also mainly aerobic or facultative anaerobic bacteria, such as *Bacteroides*, *Clostridium*, *Enterobacterium*, and *Lactobacillus*. Although microbiota is

distributed throughout the gastrointestinal tract, the colon has the highest bacterial density (up to 10^{12} CFU/mL), and has the most genera present, and the majority of which are strict anaerobes. The colon is typically populated by genera such as *Bacteroides*, *Streptococcus*, *Enterococcus*, *Ruminococcus*, and *Prevotella*. In healthy adults, the fecal wet weight is about 100–200 g/day, of which 25–50 g is solid matter. The bacterial component accounts for 30–40% of the wet fecal mass and around 44% for dry weight. Bacterial counts range from 10^{10} – 10^{11} /gram of dry feces^[139–141], mainly include *Bacteroides*, *Faecalibacterium*, *Blautia*, *Roseburia*, *Bifidobacterium*, *Ruminococcus*, *Lachnospiraceae*, *Anaerostipes*, and *Coprococcus*. The microbial communities require continuous growth to sustain their characteristic high cell density, as a large proportion of the bacterial biomass in the colon is expelled daily through feces, and minimal microbial biomass is introduced from ileal inflow to replenish colonic populations. Therefore, it should be emphasized that the structure of the intestinal microbiota is a direct result of bacterial growth^[142]. Although there are apparent lifestyle differences among individuals and significant inter- and intra-individual as well as temporal and spatial variations in gut microbiota at the species or genus level, the core analysis revealed a conserved and high-prevalence set of bacterial taxa in the healthy human gut microbiota worldwide (Figure 1D)^[143].

Most studies on the gut microbiota utilize stool samples due to their easy collection and they can be sampled repeatedly. But the composition of fecal microbiota predominantly captures the microbial profile of the colonic ecosystem. Accumulating evidence indicates that the fecal microbiota does not represent the overall structure and function of the gut microbiota, and shows different responses to the same treatment compared to other regions^[135,144–152]. As described before, different regions of the gastrointestinal tract have distinct physiological features that are important for particular microbiota species, which result in regional diversity of the gastrointestinal microbiome. Therefore, it is urgent to develop novel methods that achieve precise sampling while being non-invasive, non-contaminating, and minimizing their impact on intestinal physiology. A recent study developed a capsule device that collects luminal contents from the different intestinal regions, and subsequent analyses revealed distinct bacterial communities and metabolic profiles between the intestines and stool^[48]. Gut microbial dysbiosis is often considered to be one of the underlying features of disease pathogenesis; however, it seems difficult to identify a more specific and common pattern. The strength of the association between gut microbiota and certain diseases may be related to the location where gut microbiota reside. For example, a study involving a large cohort of pediatric Crohn's disease (CD) patients revealed that evaluating the mucus-associated microbiota is more efficient in early diagnosis of diseases compared to the ileum, rectum, and fecal samples^[153]. All of the above address the importance of specifying gut biogeography. We should not only focus on the microbial composition in the gut, but also the location of those microbes and with which host cells and other microorganisms they interact. However, this does not mean the analysis of fecal microbiome should be discarded, as long as it has a robust association with diseases^[154].

In summary, the physicochemical microenvironment of the gastrointestinal tract not only determines the colonization and spatial distribution of microbial communities but also affects their metabolic functions and

interactions with the host. In addition, the interactions among diet, gut microbiota, and the intestinal microenvironment influence various physiological and pathological processes. Alterations in factors such as pH, oxygen levels, and mucus composition can disturb microbial balance, and vice versa, thereby collectively contributing to disease susceptibility. Dietary components are major modulators of these environmental conditions and individual microbial composition, thereby linking diet, gut microbiota, and disease through shared ecological mechanisms. Therefore, exploring the relationship between the gut microbiota and diseases, as well as how diet modulates the gut microbiota, will lay the foundation for developing microbiome-based precision nutrition strategies designed to prevent and treat chronic diseases.

3. Gut microbiota and diseases

The diversity of gut microbiota is crucial to the physiology of the host and the development of diseases. Because of the characteristics of chronic diseases and gut microbiota, research into the associations and mechanisms of chronic diseases related to the gut microbiota is generally more extensive and profound than research into acute diseases. The gut microbiota and host maintain a symbiotic relationship and constant interaction. Chronic diseases are usually linked to long-term consistent lifestyles, and their onset often involves multiple factors, where gut microbiota dysbiosis contributes directly or indirectly through various pathways, such as triggering intestinal inflammation, reducing the integrity of the gut barrier, and releasing harmful microbial metabolites. The low-grade inflammation induced by gut microbiota typically does not present overt clinical symptoms immediately. Besides, the structure of gut microbiota is resilient, and short-term or minor changes in the microbiota do not cause acute illness.

The gut microbiome can elevate disease susceptibility. The gut microbiota impacts the epidemiology and pathogenesis of various diseases, spanning from gut inflammation to cancers. So far, more than 100 diseases and phenotypes have been linked to gut microbiota. These studies mainly focus on uncovering associations between activities of gut microbiota and host outcomes and discerning underlying mechanisms, and the research pattern is gradually shifting from animal models towards large cohort studies. Additionally, these topics have gained significant attention in disease prevention, diagnosis, treatment, and prognosis based on the gut microbiota^[158]. These diseases and phenotypes span the entire life cycle, from infancy to old age, targeting multiple organs in the human body and involving multiple systems. Here, six disease tags related to gut microbiota are summarized (Figure 2A, 2B), and potential mechanisms are discussed.

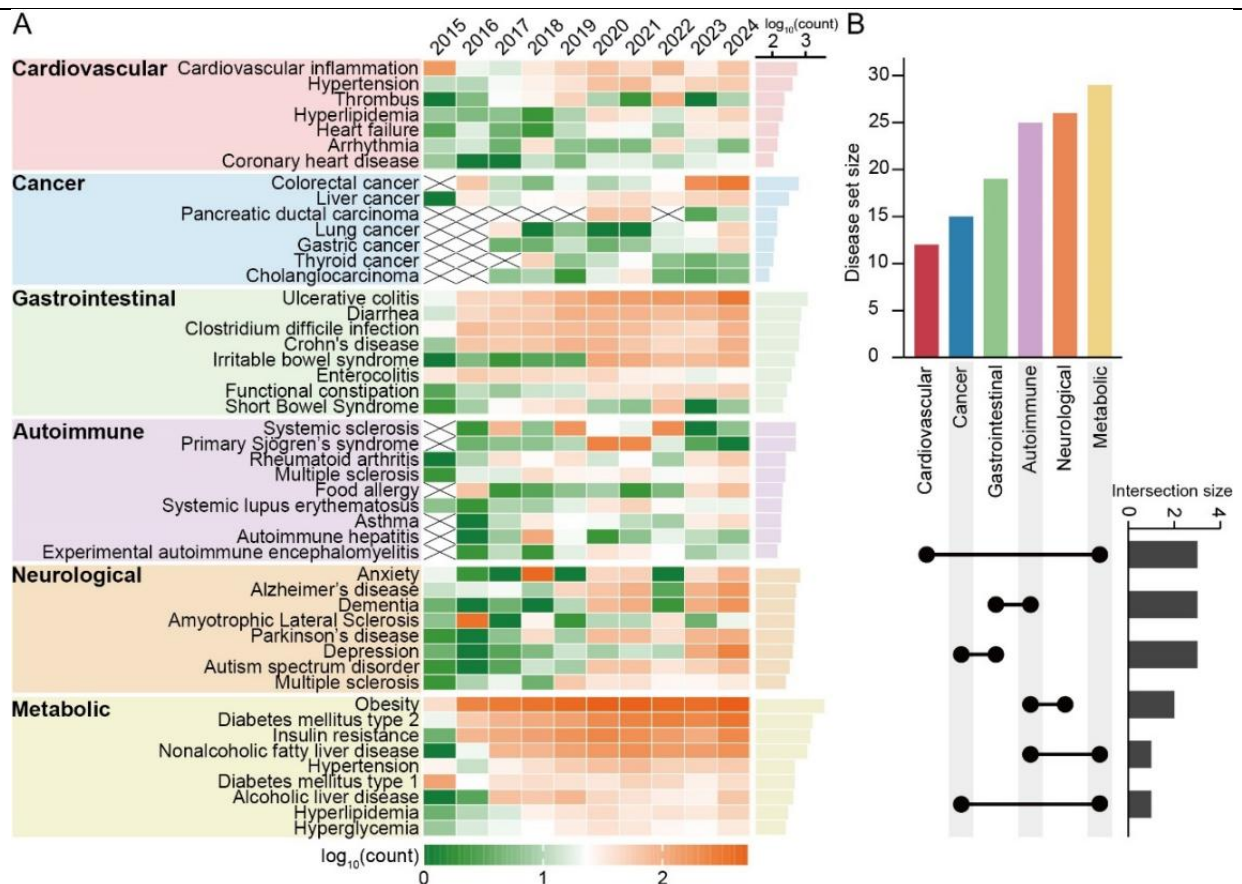


Figure 2. Statistics and research trends of gut microbiome-related diseases (2015-2024). (A) Number of papers on gut microbiome-related diseases published between 2015 and 2024; the bars on the right indicate the total number. Data were retrieved from PubMed using Advanced Search with the following query: (disease name [MeSH Terms]) AND (gut microbiota [MeSH Terms]); (B) Statistics and classification of gut microbiome-related diseases. The intersection size represents the number of diseases shared across different disease categories.

3.1 Neurological diseases

The alterations in microbial composition have been connected with neurological developmental disorders, such as autism spectrum disorder (ASD)^[159], affective disorders like depression^[160], and neurodegenerative diseases like Parkinson's disease (PD)^[161]. The interplay between the gut and the brain has been noted in medical history for centuries^[162]. The intricate nature of neurological disorders, which involve alterations in behavior, diet, and immune function, makes it difficult to determine whether changes in the microbiota drive disease pathogenesis or result from disease progression. Currently, multiple potential mechanisms have been proposed for how gut bacteria act on the nervous system. These mechanisms are involved in the pathogenesis of neurodegenerative and other neurological diseases and could act simultaneously.

There is a bidirectional communication system between the intestinal microbiota and the host brain that uses biochemical, hormonal, and neural signals, often referred to as the gut-brain axis, which has gained significant attention in recent decades^[163]. It includes the autonomic nervous system, enteric nervous system, central nervous system (CNS), hypothalamic-pituitary-adrenal (HPA) axis, and peripheral immune systems. The brain can regulate intestinal function and homeostasis, including motility, secretion, blood flow, nociception, and immune function during neurological stressors^[164], and can also directly impact the structure and function of the intestinal bacteria^[165]. In turn, the gut microbiota can also modulate brain function and

neural development by producing neurotransmitters and their precursors, and by secreting or upregulating essential proteins and metabolites involved in the release of neuropeptides and intestinal hormones. The HPA axis serves as a critical neuroendocrine system, managing physiological responses to stress and regulating digestion and emotion. An early study suggested that gut bacteria could influence the postnatal development of the HPA stress response in mice^[166]. Recent research indicates that early alterations in intestinal microbiota affect the future risk of mental illness through the HPA axis, and suggests that the endocrine pathway may be a potential mediator of the infant microbiota gut-brain axis^[167]. The Microbiome-Gut-Brain axis is an important pathway through which stress dysregulates HPA-axis activity and thus exerts deleterious effects on the adolescent brain. Probiotic agents, which alter the gut microbiota composition by introducing bacterial strains with beneficial physiological effects, normalize aberrant HPA-axis activity and reduce depressive symptoms in both animal studies and adult clinical trials^[168].

The gut microbiota participates in signal transduction via metabolites, including neurotransmitters or neurotransmitter precursors, SCFAs, secondary BAs, and gut hormones. Neurotransmitters, including glutamate, γ -aminobutyric acid (GABA), dopamine, norepinephrine, serotonin (5-hydroxytryptamine, 5-HT), and histamine, do not penetrate the blood-brain barrier, but the intestinal microbiota can yield various neurotransmitter precursors or modulate the catabolism of neurotransmitters, because they possess genes that code for enzymes responsible for transforming substrates into neurotransmitters or precursors^[169,170]. Several gut microbiota have been observed to synthesize a range of mammalian neurotransmitters. For instance, both *Bacteroides vulgatus* and *Campylobacter jejuni* can affect glutamate metabolism in the gut, which has an impact on cognitive function in patients with Alzheimer's disease (AD)^[171–173]. Specific strains of *Lactobacilli* and *Bifidobacteria* can produce GABA^[174], while *Enterococcus faecalis* and *Enterococcus faecium* can produce or metabolize dopamine^[175]. Moreover, most of these precursors consist of diet-derived amino acids, including tyrosine and tryptophan, and the gut microbiota plays an important role in food digestion and absorption. It has been reported that a diet rich in tryptophan can have a positive influence on emotion and cognition^[176,177], and the gut microbiota mediates the metabolism of tryptophan, thereby regulating serotonin signaling under certain situations^[178]. Besides, administering the *Lactobacillus rhamnosus* JB-1 to mice has been demonstrated to reduce anxiety and depression, but these effects were eliminated in mice that underwent vagotomy^[179]. Therefore, the intestinal microbiota could affect neural development, cognition, and behavior by influencing the secretion of neurotransmitters, and can participate in the onset and progression of mental illnesses. Administration of a high-sugar and fat diet induced dysbacteriosis, damaged the intestinal tract, changed the neurotransmitter metabolism in the intestine and brain, and then caused changes in brain function and circularRNAs profiles^[180].

Certain microbiota and their byproducts have been found to directly influence the development of neuropathology. For instance, disordered amyloid proteins produced by *Escherichia coli* in the gut can interact with host amyloids, promoting aggregation that spreads from the gut to the brain and initiating or exacerbating pathology-linked phenotypes observed in neurodegenerative diseases^[181]. Likewise, isoamylamine, a

metabolite produced by *Ruminococcaceae*, has been demonstrated to activate microglia, inducing inflammation and exacerbating age-related cognitive decline in older animals^[182]. Broadly, bile transformations, which are redundantly or differentially performed by many bacterial groups, can influence neurobiology, potentially exacerbating anxiety^[183].

The gut microbiota stimulates the immune system and induces inflammatory responses in the gastrointestinal tract, further influencing the immune responses in the periphery and the CNS^[184]. For example, SFB^[185], *Staphylococcus aureus*^[186], and *Prevotella heparinolytica*^[187] promote the generation of Th17 cells. Microbial imbalance in the gut coincides with breakdown of intestinal barrier integrity and immune dysregulation. Antibiotic-induced disruptions to the gut microbiota trigger systemic immune responses, particularly favoring a pro-inflammatory profile^[188]. Similarly, the CNS becomes more vulnerable to exaggerated inflammatory reactions when the gut microbiota is disrupted by antibiotics during early life. The immune responses are activated by microbes with associated molecular patterns (MAMPs). The MAMPs, including bacterial lipopolysaccharides (LPS), lipoproteins, flagellin, CpG DNA, and other metabolites, are recognized by toll-like receptors (TLRs) to activate the various immune cells, which subsequently produce inflammatory cytokines such as TNF- α , IL-1 α , and IL-1 β ^[189,190]. Cytokines may have key mediating effects in causing neurological disorders. Inflammation in the CNS can result in significant brain damage after cytokines enter the brain^[191]. An exaggerated inflammatory response increases circulating cytokines and recruits leukocytes, which can infiltrate tissues or release cytokines that trigger the brain's innate immune system. Growing evidence reveals that neurological diseases, such as PD, AD, multiple sclerosis (MS), and ASD, are all related to significant neuroinflammation^[192–194]. Altered gut bacteria showed an association with plasma concentrations of IFN γ and TNF α , and the elevated plasma cytokine responses were confirmed in an additional independent cohort^[195]. It has also been confirmed that multiple peripheral cytokines can be reduced through the regulation of gut bacteria in AD animal models^[196]. A recent study also shows that the levels of serum LPS and IL-1 β increase in chronic ethanol-exposed mice, and intestinal microbiota contribute to both hippocampal NLRP3-mediated neuroinflammation and depressive-like behavior^[197].

Microbial metabolites have both pro-inflammatory and anti-inflammatory effects in neuroinflammation. LPS treatment can induce cognitive dysfunction and neuroinflammation in the mouse model^[198]. Peptidoglycans, the primary cell wall components of gram-positive bacteria, are known to enhance dendritic cell maturation via TLR2 activation. This process boosts pro-inflammatory cytokine secretion and facilitates effector T cell generation during experimental autoimmune encephalomyelitis (EAE) progression^[199]. Polysaccharide A (PSA), a capsular polysaccharide from *Bacteroidetes fragilis*, is known to strongly activate immune cells, inducing clonal proliferation of CD4⁺ T cells and stimulating IL-10 production in T and B cells^[200,201]. Oral administration of PSA can protect against CNS demyelinating disease^[202]. In addition, SCFAs reduce neuroinflammation by blocking the cytokine storm and viral pathogenesis^[203]. *Roseburia hominis* alleviates neuroinflammation by increasing SCFAs and further inhibiting histone deacetylases^[204]. A recent study demonstrated that sodium oligomannate, a mixture of acidic linear oligosaccharides, reduces

metabolite-driven peripheral infiltration of immune cells into the brain, inhibits neuroinflammation, and reverses cognitive impairment by reconditioning the gut microbiota in an amyloidosis animal model. This study further supports the emerging idea that gut microbiome modulation using prebiotics can be a novel strategy to slow AD progression^[205].

Although neuroinflammation is a currently plausible hypothesis for mechanistic explanations in this domain, shaping host neural circuits may also be involved in the interaction. The microbiota regulates the maturation and function of glial cells, which maintain neuronal health through cellular debris clearance and pathogen defense. Microbial depletion through either germ-free rearing or antibiotic treatment could induce microglial immaturity and impaired antiviral responsiveness in mice; meanwhile, SCFAs are also involved in this interaction^[188,206]. *Clostridium butyricum* is a notable probiotic that can ferment carbohydrates into butyric acid. Treatment with *Clostridium butyricum* has been shown to attenuate microglia-mediated neuroinflammation via the metabolite butyrate^[207]. Furthermore, the transcriptional profiles of microglia were preferentially impacted, and this could be effectively restored by microbial colonization^[208]. Cross-species analysis showed that transcriptomic alterations in these microglial subpopulations were mainly linked to AD and major depressive disorder, results further reinforced by behavioral tests in animals^[208]. Dietary tryptophan metabolites from the gut microbiota influence microglial activation and TGF α and VEGF-B secretion. These metabolites modulate astrocyte gene expression and CNS inflammation via the aryl hydrocarbon receptor mechanism^[209].

3.2 Cardiovascular diseases

Cardiovascular diseases are a chronic inflammatory state of the blood vessels. Atherosclerosis, the primary driver of cardiovascular diseases, is driven by complex interactions among the vasculature, immune system, and lipid metabolism. The intestinal microbiota directly and indirectly influences the risk factors of atherosclerosis.

Atherosclerosis is characterized as an inflammatory condition, with growing evidence suggesting it may involve autoimmune processes. Infections contribute to the progression of atherosclerosis through two main mechanisms: 1) direct infection of the blood vessel wall makes it more prone to plaque formation, 2) indirect effects from infections at distant sites, where systemic immune responses promote the release of pro-inflammatory mediators that influence plaque growth. Over 50 species of bacterial DNA have been identified in human atherosclerotic plaques. The Proteobacteria phylum, especially the *Chryseomonas* and *Helicobacter* genera, is most prevalent in atherosclerotic plaques^[210]. Damaged gut barrier function causes the translocation of microbiota and their products into host circulation, and further leads to a pro-inflammatory state. Patients with heart failure frequently exhibit bowel wall edema and compromised barrier function^[211].

A broad range of cardiac diseases, such as coronary heart disease and atherosclerotic heart disease, are associated with increased levels of pro-inflammatory cytokines, including IFN- γ , IL-1 β , IL-6, and TNF- α ^[212]. These cytokines play a significant role in the formation of atherosclerotic plaque. Microbiota promote atherosclerosis by producing inflammatory cytokines and stimulating acute-phase reactants, exacerbating

chronic inflammation within atheromatous plaques. Mastrangelo et al. have identified a gut microbiota-derived metabolite, imidazole propionate (ImP), that appears in the blood during the early stages of atherosclerosis and is a driver agent. ImP led to the formation of arterial plaques by activating the imidazoline receptor type 1 (IIR), which increases systemic inflammation and promotes atherosclerosis development^[213]. When the gut barrier is damaged, LPS and other bacterial wall components can translocate into the bloodstream and are primarily recognized by TLRs^[214]. Study shows that blood endotoxin levels rise substantially with heart failure decompensation^[215], and the elevated endotoxin levels in the hepatic vein indicate the LPS migration from the gut lumen into systemic circulation^[216]. Major adverse cardiac events in atrial fibrillation patients can be predicted by elevated circulating LPS levels, which suggests that endotoxin translocation affects cardiovascular disease complications^[217,218]. Recognition of microbial ligands by TLRs triggers signaling cascades that promote pro-inflammatory cytokine production, establishing systemic inflammation. Several studies indicate that heart failure patients experience impaired intestinal integrity, with increased pro-inflammatory cytokine levels in the blood linked to symptom severity^[219,220].

Trimethylamine N-oxide (TMAO) — an intestinal microbiota metabolite formed from the digestion of choline-, lecithin-, and L-carnitine-containing foods, predominantly animal products, with a few plant-derived elements^[221]. The gut microbiota, encoding choline trimethylamine-lyase (cutC) and carnitine oxygenase (cntA), metabolizes these dietary components into trimethylamine (TMA), which is subsequently oxidized into TMAO in the liver by flavin-monooxygenase-3 (FMO3) before re-entering systemic circulation^[222,223]. Distinct bacterial strains participating in TMA formation have been identified, such as *Anaerococcus hydrogenalis*, *Clostridium hathewayi*, and *Edwardsiella tarda*^[224]. High levels of TMAO in the arteries are linked to an increased risk of cardiovascular diseases and mortality, and boost cholesterol accumulation from circulation, driving the progression of atherosclerosis^[225]. It suppresses reverse cholesterol transport, thereby decreasing cholesterol clearance from peripheral macrophages^[226], and additionally impairs the atheroprotective functions of high-density lipoprotein^[227,228]. TMAO also enhances platelet hyperreactivity by promoting Ca^{2+} release from intracellular stores, thereby increasing thrombotic risk^[229]. Besides, TMAO has been shown to activate pro-inflammatory proteins in vascular cells, including interleukin-6, cyclooxygenase-2, intercellular adhesion molecule-1, and E-cadherin, via the NF- κ B signaling pathway^[230]. FMO3 plays a key role in TMAO synthesis and is controlled by the farnesoid X receptor (FXR), whose expression is enhanced by BAs^[231]. Gut microbiota convert BAs into secondary BAs, which function as signaling molecules and are associated with lipid and glucose metabolism and atherosclerosis prevention^[232,233]. Intermittent fasting significantly impacts the gut microbiota, cecal and plasma metabolome, and prevents the development of hypertension in the spontaneously hypertensive stroke-prone rat^[234]. This indicates the beneficial effects of intermittent fasting on blood pressure are attributable to the modulation of the gut microbiota through BA metabolism. SFCAs are known for their potent anti-inflammatory and antioxidative effects^[235,236], butyrate has been demonstrated to prevent atherosclerosis by enhancing ABCA1-mediated cholesterol efflux in peripheral macrophages^[237]. Phenylacetylglutamine (PAGln) represents a newly recognized microbial

metabolite that promotes cardiovascular diseases and signals via adrenergic receptors, such as $\alpha 2A$, $\alpha 2B$, and $\beta 2$ -adrenergic receptors. Research reveals that the bacterial *porA* gene mediates phenylalanine metabolism to phenylacetic acid, ultimately generating PAGln and phenylacetyl glycine - metabolites that enhance platelet activity and thrombotic risk^[238].

3.3 Metabolic diseases

The intestinal microbiota and their metabolic byproducts significantly influence the development of metabolic diseases, such as obesity, type 2 diabetes mellitus (T2DM), and nonalcoholic fatty liver disease (NAFLD). Notably, significant microbiota changes were detected at study entry in individuals who subsequently developed fatty liver disease or diabetes during the 5-year follow-up, even though these diseases were not present initially^[239]. The increased intestinal mucosal permeability, inflammatory response, and microbial metabolites contribute to the development of metabolic diseases.

Chronic inflammatory responses derived from gut microbiota play an important role in metabolic diseases. The LPS enters the blood and causes an inflammatory cascade, resulting in a low-grade inflammatory state. It was reported that *Enterobacter*, a pathogen that produces LPS and was isolated from obese patients, was found to cause obesity and insulin resistance in germ-free mice^[240]. The LPS from *Escherichia coli* triggers dysglycemia and adipose inflammation, delays glucose absorption in the intestine, and enhances insulin and GLP-1 secretion, whereas LPS from other bacteria at the same doses does not^[241]. This highlights that not only LPS load but also LPS characteristics, such as lipid A acylation, should be considered in metabolic endotoxemia. Probiotic therapy has been shown to reduce serum LPS levels, inhibit inflammatory factors, enhance insulin sensitivity, and slow disease progression in the metabolic syndrome mouse models^[242–244]. It was reported that *Lactobacillus rhamnosus* LRA05 ameliorated insulin resistance in T2DM mice by reshaping gut microbiota and alleviating metabolic LPS-related inflammation, in addition to regulating the glucagon-mediated signaling pathway^[245]. Moreover, *Lacticaseibacillus rhamnosus* CCFM1060 mitigates alcoholic liver disease by modulating the gut microbiota and intestinal barrier and by regulating the Nrf2/HO-1 and NF- κ B pathways^[246]. Although chronic inflammation is known to disrupt signaling pathways and induce insulin resistance^[247,248], the precise mechanisms and direct relationship are yet to be fully understood. The increased carbohydrate metabolism in the gut microbiota can lead to insulin resistance, and excessive monosaccharides can promote lipid accumulation and activate immune cells, resulting in an enhanced response of pro-inflammatory cytokines in the host^[249]. Inflammation in non-alcoholic fatty liver disease (NAFLD) is influenced by both intrahepatic and extrahepatic factors. Particularly, the gut microbiota has attracted widespread attention in recent years, as NAFLD, Non-alcoholic steatohepatitis, and metabolic syndrome present a notable connection with intestinal microbial disruption^[250]. Several compounds of the Mediterranean diet, such as whole grains and monounsaturated fatty acids (MUFAs), have been attributed to NAFLD improvement through butyrate production, which has been found to decrease insulin resistance and have anti-inflammatory effects in animal models^[251]. In addition, recent research has linked changes in the gut virome and mycobiome to NAFLD^[252].

BAs regulate glucose metabolism via the FXR/GLP-1 pathway. Gut microbiota influences BA cycling by modulating FXR and further impacts glucose and lipid metabolism. Peripheral BAs activate Takeda G protein-coupled receptor 5 (TGR5) in intestinal L-cells to stimulate the release of GLP-1, thus resulting in better glucose tolerance and decreased obesity^[253]. BAs have also been shown to improve diet-related obesity through TGR5 signal transduction in the hypothalamus, including the regulation of food intake and energy expenditure^[254]. The *in vivo* studies indicated that BAs and TGR5 activation blocked NLRP3 inflammasome-dependent inflammation, such as LPS-induced systemic inflammation, alum-induced peritoneal inflammation, and T2DM-related inflammation^[255,256]. BAs are generated in the liver from cholesterol and subsequently metabolized in the gut by intestinal bacteria^[257]. Therefore, gut microbiota imbalance could impair BA signaling and contribute to the development and progression of metabolic diseases.

Gut microbial metabolites and components act as appetite-related signaling molecules to affect host satiety and energy intake by regulating gut hormones (GLP-1, PYY, etc.), and neural signal secretion from the gastrointestinal tract through different pathways^[258]. SCFAs trigger the release of anorectic hormones like GLP-1 and PYY from intestinal L-cells via the G protein-coupled free fatty acid receptors FFAR2 (GPR43) and FFAR3 (GPR41)^[259,260]. The nuclear receptor FXR also responds to inulin-derived SCFAs; FXR activation decreases L-cell GLP-1 secretion by reducing FFAR2 expression and signaling^[261]. It has been reported that gut bacteria, represented by *Desulfovibrio*, can inhibit GLP-1 production by producing hydrogen sulfide and promote the occurrence of metabolic diseases such as obesity^[262]. Gut bacteria such as *Klebsiella pneumoniae* regulate host glucose and lipid metabolism by producing a novel secondary BA, acylcholic acid, targeting the gut liver signaling axis. It is also proven that *Klebsiella parvus* and acylcholic acid have potential applications in the treatment of chronic metabolic diseases such as T2DM^[263].

Gut microbiota-derived metabolites can also modulate appetite by influencing the central nervous system. Colonic acetate has been demonstrated to pass through the blood-brain barrier to the hypothalamus, where it boosts glutamate-glutamine and GABA glial circulation, raises lactate levels, and inhibits appetite^[264]. Besides, oral administration of butyrate suppressed NPY-expressing appetite-stimulating neurons in the hypothalamus, lowered activity in the solitary tract nucleus and dorsal vagus nerve complex in the brainstem, and indirectly affected the host's appetite and feeding behavior^[265]. A 9-amino-acid peptide called D3 mitigates diet-induced obesity through reducing appetite and modulating the gut microbiota^[266].

3.4 Gastrointestinal diseases

There is a strong correlation between intestinal microbiota and the risk of gastrointestinal diseases, such as CDI and irritable bowel syndrome (IBS). The pathogenesis of CDI has been recognized as being linked to the use of antimicrobials, and long-term antibiotic use is the leading cause of CDI development^[267]. Antimicrobials significantly alter the intestinal microbial structure, which highlights the relationship between gut perturbation and the development of CDI^[268]. Other risk factors implicated in its pathogenesis, including obesity and proton-pump inhibitors (PPIs), are also associated with intestinal microbiota disorder^[269]. The intestinal microbiota of healthy individuals provides resistance against the colonization of *Clostridioides*

difficile through nutrient competition, secretion of growth-inhibiting bacteriocins, and spore germination-suppressing metabolites^[270–273]. However, the disruption of the normal gastrointestinal microbiota favors the acquisition of the organism from an exogenous source and enables *Clostridioides difficile* colonization and consecutive toxin production^[268,274,275]. Besides, CDI may also be associated with alterations in the gut microenvironment. A higher fecal pH has been observed in patients with pseudomembranous colitis resulting from the overgrowth of *Clostridioides difficile*^[276]. In contrast, a lower pH has been shown to inhibit *Clostridioides difficile* spore germination and growth both *in vitro* and *in vivo*^[277,278]. Notably, PPIs use is linked to an increased risk of CDI, probably due to the effect of PPIs in raising gastrointestinal pH, which might facilitate *Clostridioides difficile* colonization in the gut^[279]. Hazleton et al. found that the Western diet had a pro- *Clostridioides difficile* BAs composition that was driven in part by the gut microbiome^[280]. Recurrent CDI is difficult to cure. Although antibiotics remain the standard and mainstay treatment of choice for CDI^[281,282], the effectiveness of treatment is declining with the rising prevalence of antibiotic resistance of *Clostridioides difficile*, especially due to the overuse of antibiotics during the pandemic^[283]. Restoring gut microbiome diversity through effective treatment methods is vital to avoid CDI recurrence. As a new therapy, fecal microbiota transplantation (FMT) has recently emerged as a validated approach to rapidly and effectively reshape a patient's gut microbial ecosystem. In 2013, a Dutch research group carried out a randomized controlled trial against rCDI and demonstrated that FMT had superior efficacy and cost-effectiveness compared to antibiotics^[20,284–286].

Evidence indicates that the gut microbiota also plays an important role in IBS^[287]. Current evidence suggests that gut dysbiosis triggers immune activation and causes low-grade inflammation, which increases the risk of developing IBS^[288]. Decreased gut microbiota diversity, along with the presence of *Clostridiales*, *Prevotella*, and methanogenic species, has been identified as an IBS-specific microbial signature linked to symptom severity^[289,290]. FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) can exacerbate irritable bowel syndrome (IBS) symptoms through colonic gas production resulting from bacterial fermentation and altered intestinal motility. In contrast, low-FODMAP diets have been shown to effectively reduce IBS symptoms. This effect may result from alterations in gut microbiota and the metabolites they produce^[291]. Small intestinal bacterial overgrowth (SIBO) is characterized by a duodenal bacterial load of $> 10^5$ CFU per millilitre. High gastric pH, along with impaired clearance, leads to SIBO. SIBO could lead to a spectrum of clinical manifestations, from mild and nonspecific gastrointestinal symptoms to severe malabsorption, by affecting gastrointestinal motility, visceral sensitivity, immune activation, carbohydrate digestion, BA metabolism, and intestinal permeability^[292]. Furthermore, these abnormalities are also involved in the pathogenesis of IBS. Therefore, a potential link between SIBO and IBS has been suggested.

3.5 Autoimmune diseases

Autoimmune diseases are characterized by aberrant immune responses against self-antigens that result in chronic inflammation. The genetic and environmental factors act on the immunological system and are implicated in the development of autoimmune diseases. The intestinal microbiota is involved in the maturation

and activation of the mucosal and systemic immune^[293]. Changes in gut microbiota structure and their association with disordered immune responses have been widely investigated in numerous diseases. Hence, it has also been hypothesized that the rising incidence of autoimmune diseases may be connected to significant disruptions in the gut microbiota. Recent studies have shown that patients with autoimmune diseases, including MS, rheumatoid arthritis, and systemic lupus erythematosus (SLE), have distinct gut microbiota structure compared to healthy individuals^[294]. Extensive evidence indicates that the gut microbiota plays a role in both triggering and exacerbating disease progression in autoimmune conditions. The potential mechanisms include intestinal mucosa permeability, bacterial translocation, bacterial metabolites, molecular mimicry, bystander activation, and epitope spreading.

Patients with autoimmune diseases typically exhibit impaired gut barrier function, leading to a disruption in mucosal immune tolerance^[295]. In addition, abnormal immune responses targeting the gut microbiota could increase disease severity. A leaky gut is common in SLE patients. *Lactobacillus* has been revealed to have beneficial impacts on the disease, as oral administration of *Lactobacillus spp.* to the lupus-prone MRL/lpr mouse model alleviated symptoms and enhanced intestinal barrier integrity^[296]. After disease onset, MRL/lpr mice receiving mixed antibiotics presented improved lupus-like symptoms, with a rise in *Lactobacillus spp.* and a reduction in *Lachnospiraceae*^[297]. Likewise, vancomycin treatment replicated these results and decreased intestinal permeability and the plasma level of LPS^[297]. IBD patients consistently exhibit gut microbiota dysbiosis accompanied by elevated microbial translocation markers (LPS and bacterial DNA), indicating that compromised intestinal barrier function contributes to disease pathogenesis. Intestinal permeability could also act as a type 1 diabetes (T1D) trigger by facilitating bacterial components leakage, initiating mucosal T cells responses, which subsequently migrate to the pancreatic draining lymph nodes and islets. Before the onset of clinical disease in EAE-induced B6 mice, elevated gut permeability was observed, along with decreased expression of antimicrobial peptides and tight junction proteins, which are essential for the mucus layer and intestinal epithelial layer. These detrimental effects were alleviated after probiotic administration of *E. coli* Nissle 1917, which supports the concept that gut microbes can directly influence intestinal permeability and disease progression^[298].

Increased intestinal permeability favors mucosal inflammation and results in the translocation of intraluminal components. Bacterial translocation has been reported in animal models and patients with SLE^[299,300]. The translocation of microbial molecules due to gut leakage increased vulnerability to stress-induced apoptosis, particularly in lupus^[301]. For example, LPS interacts with TLR4, and its activation has been found to exacerbate lupus. Indeed, translocated LPS and (1→3)-β-D-glucan could lead to a severe inflammatory response^[301]. It was reported that dietary timing significantly modulates RA inflammatory fluctuations via gut microbiota. Specifically, *Parabacteroides distasonis* uses β-glucosidase to release glycitein from the diet in response to daily nutritional cues, influencing RA inflammatory rhythms dependent on the sirtuin 5-nuclear factor-κB axis^[302]. Besides, fiber consumption prevented the development of hypertension by rebalancing the dysfunctional gut-immune system-vascular wall axis in SLE^[303].

Molecular mimicry refers to the shared structural features between components of the intestinal microbiota and self-antigens, which may contribute to autoimmune diseases. For example, some peptides originated from microbiota consortium, including *Bacteroides fragilis*, *Prevotella copri*, *Candida albicans*, and *Streptococcus sanguis*, can imitate collagen and synovial/ribosomal peptides, and stimulate cross-reactive immune responses and result in the emergence of autoimmune conditions^[304]. Intestinal microbes containing epitopes similar to host proteins, like the RNA-binding protein Ro60, can stimulate T and B cells in SLE^[305]. The sustained colonization of bacteria expressing cross-reactive epitopes in the host increases the risk of autoimmune diseases, especially when the intestinal barrier is impaired. Early studies suggested that some strains of *Klebsiella pneumoniae* can imitate HLA-B27; thus, exhibiting shared structural characteristics with these strains could result in autoimmunity, inflammation, and tissue damage in ankylosing spondylitis^[306,307]. Emerging studies have identified a growing number of microbial peptides that share structural similarities with host self-antigens, resulting in autoimmune responses. For example, a peptide from *Roseburia intestinalis* have been found to cross-react with DRB1*04:01-restricted T cells targeting β 2GPI epitopes, which trigger pro-inflammatory Th1 cell responses^[308]; a sequence from *Parabacteroides distasonis* mimics insulin epitope, and accelerate diabetes onset in a mouse model of T1D^[309]; gut microbial antigens are found to cross-react with autoantigenic targets in MS, such as myelin basic protein^[310] and guanosine diphosphate-L-fucose synthase protein^[311]; a strain of *Lactobacillus reuteri* produces peptides that potentially mimic myelin oligodendrocyte glycoprotein, and mice co-colonized with the bacterial strain exhibited significantly exacerbated EAE symptoms compared to germ-free controls or monocolonized animals mice^[312]. In addition, specific microbial species could transfer host self-proteins with their enzymes into neoepitopes that are modified versions of host antigens. These neoepitopes could trigger cross-reactive immune responses that potentially initiate or exacerbate autoimmunity. For instance, some bacterial enzymes can convert arginine residues to citrulline and produce citrullinated self-antigens, which are associated with rheumatoid arthritis^[313].

Bystander activation is a process where immune cells, such as CD8⁺ T, CD4⁺ T, or B cells, are activated in an antigen-independent manner. This can happen when a microbial infection stimulates TLRs and other pattern recognition receptors on antigen-presenting cells. Bystander activation is beneficial for clearing pathogens. However, it can also trigger auto-reactive T and B cells in people who are susceptible to autoimmune diseases. In T1D, autoreactive T cells that target the islet beta cells are abnormally activated. A recent study suggests that the islet-specific CD8⁺ T cells obtain effector function through bystander activation influenced by the gut microbiota^[314].

3.6 Cancers

Although the exact pathogenesis of most cancers is not yet clear, mainly related to genetic susceptibility and environmental factors, growing studies have shown the multifaceted role of the gut microbiota in cancer development and the therapeutic response, including CRC, adenocarcinoma, and pancreatic cancer. Integrated multi-omics profiling reveals dynamic, stage-dependent gut microbiome configurations across CRC patients^[315]. Indeed, early research has observed the possibility of intestinal bacteria inducing cancer^[316].

Although only one species of bacteria (*Helicobacter pylori*) and seven species of viruses are designated as being directly carcinogenic to humans by the International Agency for Research on Cancer, several other gut microorganisms have also been associated with cancers. For instance, *Salmonella enterica* serovar *Typhi* with gall bladder cancer[317,318]; *Fusobacterium nucleatum* and enterotoxigenic *Bacteroides fragilis* with CRC^[319]. Cancer is essentially a genetic disease. Therefore, these gut microorganisms could trigger genetic mutations directly via genotoxins or indirectly by promoting error-prone cellular processes in cancer initiation. Cancer cells need to escape from surveillance and elimination from the immune system, while bacteria could protect cancer cells from immunosurveillance. The gut microbes are also considered to drive tumorigenesis through multiple pathways, including DNA damage, DNA repair pathway disruption, abnormal signaling pathways, and Immunosuppressive modulation.

The strains isolated from patients with IBD, including *Clostridium perfringens*, *Clostridium ramosum*, and *Morganella morganii*, displayed oncogenic DNA-damaging effects associated with malignant transformation from IBD to colon cancer^[320]. Moreover, a novel group of genotoxic molecules, known as indolimines, was identified, capable of enhancing intestinal permeability and worsening colon tumor development in gnotobiotic mice^[320]. Likewise, colibactin, a genotoxin produced by pks+ *E. coli*, was demonstrated to cause DNA damage in colonic epithelial cells and cause the same mutational signature in both human intestinal organoids and independent cohorts, which suggests colibactin-producing pks+ bacteria directly induce the characteristic mutational signature through their genotoxic activity^[321,322]. Interestingly, colibactin has also been identified in the family Enterobacteriaceae^[323], suggesting potential oncogenic properties of these microbial strains. Other genotoxin-producing bacteria, including *Helicobacter pylori*, *Bacteroides fragilis*, *Salmonella enterica*, as well as genotoxins, such as cell-lethal bulking toxin and *Bacteroides fragilis* toxin (BFT), can lead to genetic mutations at different levels in colorectal and other cancers^[322,324].

Except for genotoxins, DNA damage can also result indirectly from promoting error-prone cellular processes triggered by microbiota or their metabolites. Microbiota-induced oxidative stress represents a key mechanism of genotoxicity in the gastrointestinal tract. Free radicals, such as reactive oxygen species (ROS), are important DNA-damaging agents. Pathogens, including *Helicobacter pylori*, *Bacteroides fragilis*, and *Chlamydia trachomatis*, can trigger the generation of excessive amounts of hydrogen peroxide and ROS in infected cells. *Helicobacter pylori* activates spermine oxidase (SMO) in the host by expressing cytotoxin-associated gene A (CagA)^[325] and produces large amounts of hydrogen peroxide and ROS. Similarly, *Bacteroides fragilis* toxin can also increase SMO levels and lead to ROS production, and inhibition of SMO could significantly reduce colon tumorigenesis induced by *Bacteroides fragilis* in animal experiments^[326]. *Enterococcus faecalis* can produce extracellular superoxide and derived oxygen^[327], which increases chromosomal instability in the host cell. Meanwhile, antibiotic treatment or intestinal sterility may decrease ROS production^[328]. Further, intestinal microbiota influence redox regulation through their metabolites, including fatty acids, LPS, tryptophan metabolites, TMAO, and polyphenolic derivatives^[329].

Helicobacter pylori can lead to DNA double-strand breaks (DSBs) after attaching to host cells^[330]. *Helicobacter pylori* and *Shigella flexneri* can induce host cell p53 degradation and increase the frequency of DNA mutations^[331]. The development of CRC is strongly associated with hypermethylation. CRC-enriched *Hungatella hathewayi* and *Fusobacterium nucleatum* showed significant correlations with the promoter hypermethylation of tumor suppressor genes. It has been shown that *Hungatella hathewayi* and *Fusobacterium nucleatum* can increase DNA methyltransferase *in vitro* and *in vivo*^[332].

DNA adducts can trigger DNA damage response events because they hinder replication and transcription of DNA. It was observed that the amount of DNA adduct was associated with gut microbiota, which supported the link between gut microbiota and cancers^[333]. But the detailed molecular mechanisms mediated by gut microbiota require further investigation.

Gut microbiota can also hinder the repair of damaged DNA. Enteropathogenic *Escherichia coli* depletes DNA mismatch-repair proteins via EspF secretion, and further drives a substantial increase in infection-induced cell point mutations^[334]. *Helicobacter pylori* and *Chlamydia trachomatis* inhibit proper DNA damage response and repair mechanisms^[335,336]. Additionally, *Helicobacter pylori* suppresses error-free homologous recombination and simultaneously activates error-prone non-homologous end-joining^[330].

Microbes can adversely modulate tumor-related signaling pathways, such as the Wnt pathway associated with various cancers. Fusobacterium adhesin A (FadA) is a virulence factor produced by *Fusobacterium nucleatum*, which can impact E-cadherin/ β -catenin signaling, resulting in the aberrant activation of the Wnt pathway^[337]. Likewise, a virulence factor known as BFT can also trigger Wnt signaling through the cleavage of E-cadherin^[338]. *Helicobacter pylori*-derived CagA binds to SHP-2 and activates it to promote the ERK signaling cascade and trigger the abnormal proliferation of host T-cells^[339]. *Porphyromonas gingivalis* can invade cells and promote the proliferation of CRC cells by activating the MAPK/ERK signaling pathway with gingipains^[340]. *Salmonella Typhi* can also activate the MAPK pathway and AKT pathway, which may accelerate the transformation of cells with silent p53 and overactive MYC^[341]. Bacterial metabolites, such as BFT, gingipains, LPS, and butyrate, can be recognized by TLR4, then activating the NF- κ B and NFAT signaling pathways to promote abnormal proliferation of cancer cells^[342].

Microbes modulate the tumor-immune microenvironment and help cancer cells escape from surveillance and elimination by the immune system. *Helicobacter pylori* can stimulate PD-L1 surface presentation on gastric epithelial cells, promoting immune evasion and neoplastic progression in gastric epithelium^[343]. *Fusobacterium nucleatum* mediates immune evasion through Fap2-TIGIT interaction, suppressing NK cell cytotoxicity against tumor cells^[344]. *Fusobacterium nucleatum* can also specifically recruit tumor-infiltrating myeloid-derived suppressor cells (MDSCs), which potentially accelerates colorectal carcinogenesis by generating a pro-inflammatory microenvironment^[345]. On the contrary, *Clostridium butyricum* can remodel the tumor-immune microenvironment through the secD/GRP78/IL-6 pathway, thereby improving anti-PD-1 efficacy in CRC^[346]. Likewise, by increasing PMN-MDSCs, the gut microbiota modulates hepatocytes to establish an immunosuppressive environment, which drives liver cancer development^[347]. Dietary cholesterol

induced gut bacterial metabolites alteration, including increased taurocholic acid and decreased 3-indolepropionic acid, which drives NAFLD-associated hepatocellular carcinoma formation^[348]. Gut microbiota metabolites, such as indole compounds and tryptophan produced by *Lactobacillus*, also suppress anticancer immunity^[349].

4. Diet alters gut microbiota

Chronic diseases are associated with multiple gut microbiota features, and the gut microbiota contributes to the initiation and progression of these diseases through diverse mechanisms, as discussed in the previous section. There is an intricate interplay among diet, host, and intestinal microbiota via various components and pathways. Food provides nutrients and energy for both the human body and intestinal microbiota. Through the collaborative action of the digestive system and gut microbes, a range of nutrients and metabolites are generated, and some of these metabolic products serve as signaling molecules to regulate metabolism and the immune system in return. The types and intake quantity of nutrients in the diet can become significant factors influencing the structure, diversity, and species richness of the gut microbiota over time. More importantly, diet-induced microbial alterations can serve as upstream determinants of disease-related microbial dysfunction. Therefore, this section highlights how dietary components and patterns reshape gut microbiota and subsequently drive or alleviate relative chronic disease risk and progression.

4.1 Water

Water is consumed in the largest amount among food items and has been widely associated with human health. Notably, the gut microbes have the potential to mediate this association. The majority of water absorption (about 90%) occurs in the proximal small intestine, and around 5% of water is absorbed by the large intestine. Despite its essential role in health, drinking water is a forgotten nutrient and neglected as a part of the diet in most gut microbiota research cohorts.

Daily water intake alters gut homeostasis. Chronic underhydration affects human health and is associated with diseases, particularly metabolic disorders such as obesity, insulin resistance, and diabetes in adults. Water restriction disrupts gut homeostasis, which is accompanied by a bloom of gut microbes and decreased numbers of immune cells, especially Th17 cells, within the colon. These microbial and immunological changes in the gut are associated with an impaired ability to eliminate the enteric pathogen *Citrobacter rodentium*^[350]. The water source significantly shapes the gut microbiota, with impacts similar to those of alcohol or diet type^[351]. It has been revealed in both *in vitro* and *in vivo* studies that microbiota structure and diversity are remarkably different among culturing and drinking water types^[351–354]. Under anaerobic culture conditions, commercial bottled mineral water and tap water showed advantages in microbiota diversity^[352]. Clinically important taxa, such as *Acinetobacter* and *Staphylococcus*, increased in the feces of mice exposed to tap water^[353]. Well water consumption was associated with increased gut microbial α -diversity and altered taxonomic composition, featuring elevated *Dorea* abundance but reduced *Bacteroides*, *Odoribacter*, and *Streptococcus*^[351]. Except for distilled water, drinking river water, tap water, and commercial bottled water

distinctly impacts the gut microbiome structure and also induces alterations in the antibiotic resistance profile^[354]. Although these studies compared the impacts of multiple water sources on gut microbiota, a detailed description and comparison of the properties of water sources is lacking.

Further analysis indicates that solutes in water play key roles, such as microorganisms, ions, and the byproducts of specific treatment (e.g., hydrogenation, chlorination, and disinfection). Microbes from tap water can potentially be horizontally transmitted and subsequently colonize the human gut^[355]. Tap water changed gut microbiome diversity, whereas autoclaved tap water did not^[353]. Moreover, a lack of interaction with water and food-derived live microorganisms will lead to a more uniform microbial community. Bicarbonate-rich mineral water consumption compared with tap water consumption increased the fecal composition of lean-inducible bacteria after intake^[356]. Long-term drinking of alkaline mineral water showed a significant shift in the microbiota population^[357]. Bowyer et al. assessed the associations of water composition with the gut microbiome from mono-zygotic twins. The result showed that there are significant associations between the average daily dose (ADD) of sodium with microbiota diversity, chloride, sodium, and sulphate ADD with dissimilarity between samples is observed, and all components and ADD-adjusted solutes are associated with abundances of individual microbial taxa^[358]. Hydrogen-rich water (HRW) intake primarily causes an increase in the abundance of *Lactobacillus*, *Ruminococcus*, *Clostridium_XI*, and a decrease in *Bacteroides*^[359]. Besides, HRW-driven protection of gut barrier integrity and the rise of butyrate-producing bacteria were considered relevant^[360]. A randomized controlled study shows that HRW improved metabolic health by reducing fasting glucose and visceral adipose tissue, which enhanced insulin sensitivity and lipid metabolism. Further metabolomic analyses suggest that the gut microbiota may play a potential mediating role in these processes^[361]. Drinking water chlorination has no influence on the overall richness or diversity of taxa, but it is associated with increased abundance of several microbiota genera. Although several clinically relevant antibiotic resistance genes were relatively more abundant in the gut microbiome of treatment children, drinking water chlorination did not substantially impact child gut microbiome development^[362]. Drinking water content varies significantly depending on the region or the treatment method applied. Besides, the quality of drinking water for laboratory animals has not yet been subject to the same requirements. These would bring in confounding factors.

Colonic microbiota composition appears independent of water activity parameters^[363], while another important water property—pH, can shape the gut microbiota structure and function. Gut microbiota grow best at their own optimum growth pH. Duncan et al examined 33 representative bacterial isolates from human feces for their ability to grow in the anaerobic batch culture at different pH values. Eight *Bacteroides* species and *Escherichia coli* grew poorly at pH 5.5, whereas 19 Gram-positive anaerobes growth rates at pH 5.5 were at least 50% of those at pH 6.7^[364]. A pH-driven shift of human gut microbiota in a continuous flow fermentation chamber was observed, which was also confirmed by Wang et al.^[365]. The richness and Shannon index were not affected by the pH, but the abundance of *Bacteroidetes* and *Verrucomicrobia* increased with an increasing cultivation pH, and the cell count, acetate, propionate, and total amount of SCFAs also increased. Consistent

with previous results, the bacterial community shift was observed, and *Bacteroides ovatus* showed a good adaptability within the pH range from 6.0 to 8.0. Besides, the butyrate producing *Faecalibacterium* and *Coprococcus*, *Akkermansia muciniphila* present different sensitive to pH^[366]. The metabolic products of gut microbiota vary depending on pH. Gas production significantly increased below pH 6.5, and methane production occurred exclusively under alkaline conditions (pH > 7), correlating with a concurrent proliferation of *Methanobrevibacter smithii*^[366]. The SCFAs production is also affected by pH. The total SCFAs levels were significantly higher with raising pH, and vice versa^[56]. Two similar mouse experiments revealed a dramatical alteration in the structure and diversity of gut microbiota when the acidity of drinking water was altered for nonobese diabetic mice (NOD)^[367,368], but the taxonomic signatures are exact opposite. NOD-N mice (pH 7) also presented significantly decreased amounts of *Lactobacillus spp.* and *Clostridium coccoides* compared to acidified water (pH 3). On the contrary, NOD-N animals also exhibited an increase in *Bacteroides spp.*, *Actinobacteria*, and *Proteobacteria*. Mice receiving acidified water (pH 3) exhibited a substantial decrease in the diversity of their microbes, characterized by a reduction in *Bacteroides spp.* and an increase in the proportion of *Lactobacillus spp.*. pH of drinking water affects the composition of gut microflora, leading to an altered autoimmune response and Type 1 Diabetes incidence in NOD mice^[367]. The pH in the above studies was all controlled with NaOH and HCl solution. Hitherto, there is no evidence to suggest that pure water intake can alter gut microbiota, though it may have an effect on gut pH and osmotic pressure. *In vivo*, the pH and water in the intestine are regulated by the host, i.e., the neutralization and water absorption of the gastrointestinal tract. On the other hand, pH largely depend on the concentrations of SCFAs being produced by the fermentation of dietary fiber^[369]. Therefore, it is assumed that the intestinal tissues may not be affected directly by the pH of drinking water, and the regulation of the gut bacteria through the pH of drinking water may require more extreme conditions and long-term effects. This also highlights the importance of drinking water for experimental animals in the study of gut microbiota.

4.2 Carbohydrates

Carbohydrates are primarily classified based on the composition of sugar monomers, the type of linkage, and molecular size. Based on molecular structure and composition, carbohydrates are systematically categorized as mono-, di-, oligo-, or polysaccharides. Complex carbohydrates can further be divided into starch and dietary fiber. The former is composed of long chains of glucose molecules linked together, and is the primary human-digestible polysaccharide, while the latter consists of non-digestible oligo- and polysaccharides. Resistant starch is non-digestible and is consequently classified as dietary fiber. According to the digestibility and structural complexity of carbohydrates, the general classification of dietary carbohydrates is summarized in Table 1.

Table 1. General classification of dietary carbohydrates.

Digestibility	Structural complexity	Dietary carbohydrates
Digestible Carbohydrates (DCs)	Simple carbohydrates	Glucose, fructose ¹ , galactose, sucrose, lactose ¹ , maltose
	Non-resistant starch	Starch
Non-Digestible	Non-Digestible Oligosaccharides	Fructo-oligosaccharides (FOS), galacto-

Carbohydrates (NDCs)	(NDOs)	oligosaccharides, (GOS) mannans-oligosaccharides (MOS), isomalto-oligosaccharides (IMO, isomaltose, pantose, isomaltotriose), raffinose, stachyose, verbasco, inulin, polydextrose
	Resistant Starch (RS)	RS1 (physically inaccessible), RS2 (resistant granules), RS3 (retrograded or crystallized), RS4 (chemically modified), RS5 (amylose-lipid complexes)
	Non-Starch Polysaccharides (NSPs)	Celluloses, hemicelluloses, xylans, mannans, lignins, chitins, gums, pectins, beta-glucans, psyllium

¹ Fructose and lactose may, in part, escape digestion and absorption in the small intestine.

The metabolic pathways and locations of carbohydrates vary due to their physicochemical properties and microbial enzymatic profiles. Except for lactose and fructose at high doses, simple carbohydrates and starch can be directly hydrolyzed by digestive enzymes and absorbed in the small intestine and rapidly released as glucose into the bloodstream. In contrast, NDCs, also referred to as microbiota-accessible carbohydrates, cannot be degraded in the small intestine but are fermented in the large intestine by microbiota, and consequently metabolized into SCFAs, lactate, and gases such as CO₂, H₂, and methane (Figure 3). This is because the human genome encodes only 17 carbohydrate-degrading enzymes targeting only a few different linkages^[370]. On the contrary, intestinal microbes have the corresponding enzymatic tools to degrade dozens of polysaccharides^[371,372]. As they are enriched for genes encoding saccharolytic enzymes, galactosidases, hexosaminidases, proteases, and enzymes in the glycolysis and pentose phosphate pathways^[373]. The properties of polysaccharides affect the fermentation process in the colon; soluble fibers are more prone to microbial degradation than insoluble fibers due to their higher swelling capacity. Generally, the sequence of carbohydrate utilization by gut microbiota is sugar residues $\approx$ NDOs > Starch residues > Soluble NSPs > RS $\approx$ Insoluble NSPs^[374]. Notably, large amounts of fermentable carbohydrates can lead to rapid lactic acid production and a significant pH decrease.

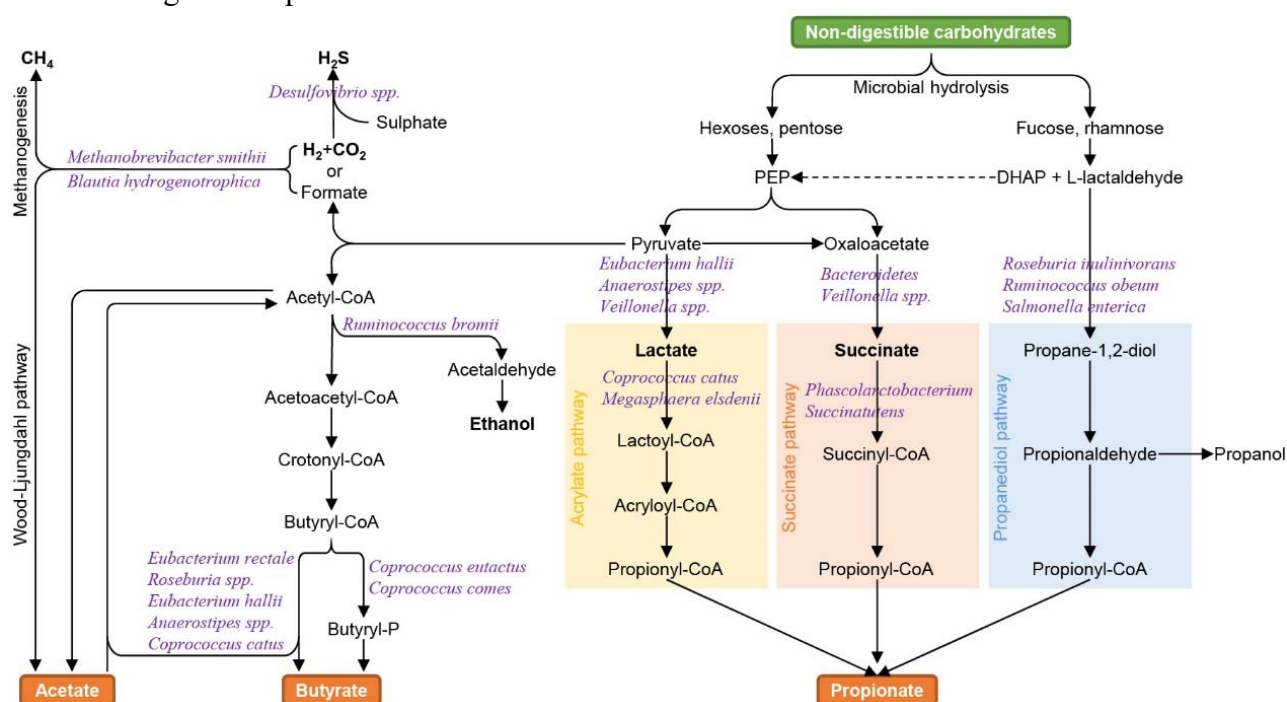


Figure 3. Pathways for the synthesis of SCFAs^[375].

Early studies showed that the microbiota in the human small intestine is primarily influenced by the rapid absorption and metabolism of simple carbohydrates^[376]. Simple carbohydrates, such as sucrose, induce rapid microbial community shifts and metabolic dysregulation in animal models^[377]. A recent study shows that the administration of glucose and fructose to mice resulted in a marked reduction in Bacteroidetes abundance and a concurrent rise in Proteobacteria. These mice also exhibited elevated gut permeability, along with intestinal and liver inflammation^[378]. Since simple carbohydrates are mostly absorbed in the small intestine, only a small quantity reaches the colon. Thus, simple carbohydrates are more likely to indirectly affect the gut microbiota.

NDOs are known to selectively promote the growth and activity of gut microbiota, particularly *Lactobacilli* and *Bifidobacteria*, and the industrial applications for NDOs have rapidly increased. The glycosidic bonds and monosaccharide composition of NDOs affect the selective utilization and in the metabolites produced by gut bacteria. Fermentation of xanthan gum oligosaccharides and gellan gum oligosaccharides specifically enhanced butyrate production and the abundance of butyrate-producing microbiota, compared with inulin, FOS, Astragalus polysaccharides, Astragalus oligosaccharides, oats β -glucans, oats β -glucan oligosaccharides, curdlan oligosaccharides, and pullulan oligosaccharides. This phenomenon might be explained by their similar β (1 $\rightarrow$ 4) glycosidic linkages and branched configurations^[379]. Inulin supplemented daily for 2 weeks decreased brain activation in reward-related brain regions for high-calorie food stimuli, effects that correlated with increased levels of SCFA-producing bacteria, in adults with overweight^[380]. This indicates that fibre could modulate the gut microbiota to improve reward hypersensitivity, thereby regulating energy balance. Inulin can also alter the colitis patients' characteristic microbial community, and further ameliorate experimental colitis by inhibiting the TLR4/MyD88/NF- κ B signaling pathway—improving the inflammatory response and enhancing the intestinal barrier^[381]. Xanthan gum-based fluid thickener decreases postprandial blood glucose associated with an increase of Glp1 and Glp1r expression in the ileum and alteration of gut microbiome^[382]. Besides, xanthan gum can change antibiotic efficacy against the murine gut microbiota and attenuate *Clostridioides difficile* colonization^[383]. *Bifidobacteria* exhibit a preference for shorter-chain fructans, partly due to their sucrose transporter, which can also import GF2 and GF3 molecules for metabolic use^[384]. This also happened in *Lactobacilli* due to their weak ability to transport polysaccharides^[385]. In *Lacticaseibacillus paracasei*, the FOS transport system has a high affinity for chains with a lower degree of polymerization (DP) than for longer ones; thus, DP3 and DP4 are absorbed more rapidly than DP5^[386]. A similar scenario has been noted in *Lactiplantibacillus plantarum*^[387]. The effects of GOS on different *Lactobacillus plantarum* strains are not entirely the same, due to their genetic characterization^[388].

Generally, increasing the content of RS in the diet changes the gut microbiota composition, and also increases the content of SCFAs (especially butyrate) in the intestine and feces. A randomized placebo-controlled crossover design trial has confirmed that RS can facilitate weight loss at least partially through *Bifidobacterium adolescentis* and that the gut microbiota is essential for the action of RS^[389]. Another study shows that gut microbiome alteration mediates the effect of RS on alleviating NAFLD, and the reduction of

IHTC is achieved effectively and independently of weight loss^[390]. However, different types of RS have different impacts on gut bacteria. Study shows that RS2 significantly increased the abundance of *Ruminococcus bromii* and *Eubacterium rectale* compared to RS4^[391]. Furthermore, even the same type of RS with subtle structural differences also generates distinct impacts. It was found that RS3, containing more DP36–100 chains and a smaller molecular size, can increase the portion of specific microbiota^[392]. Therefore, from a health perspective, the current definition system of RS types may be incompatible with their health impacts. It has been proposed that RS should be reframed according to microbiota and health impacts. Their structures should be integrated with the gut microbiota genome to achieve predictable and targeted modulation in gut microbiota and further health outcomes^[393,394].

The potential mechanism of the above phenomena is related to gut bacteria and RS structure. Different colonic bacteria have distinct abilities to utilize RS. For example, four bacteria all present the ability to break down and utilize RS, namely *Bacteroides thetaiotaomicron*, *Ruminococcus bromii*, *Eubacterium rectale*, and *Bifidobacterium adolescentis*, but *Ruminococcus bromii* demonstrated a significantly higher RS degradation ability than the other three bacterial species^[395]. Given that host factors influence the structural integrity of starch reaching the colon, these *in vitro* findings may not accurately represent *Ruminococcus bromii*'s actual substrate preferences in the colonic environment. Further, the utilization rate of RS depends on the type, quantity, and activity of metabolic enzymes secreted by intestinal bacteria. *Ruminococcus bromii* possesses multi-enzyme complexes anchored to its cell surface. While other gut microbiota typically have only single surface enzymes with limited starch degradation capacity. There is a single amylase on the surface of *Eubacterium rectale* for starch degradation. But the enzyme's carbohydrate-binding domains cannot recognize RS, which constrains the spectrum of nutrients available for this microorganism's proliferation. The different strategies used for complex carbohydrate utilization by gut microbiota are further reflected in the types and abundance of CAZyme genes. Compared to Firmicutes, which encode an average of 39.6 GH (glycoside hydrolases) and PL (polysaccharide lyase) genes per genome, Bacteroidetes encode 137.1 GH and PL genes^[396], making Bacteroidetes capable of degrading multiple polysaccharides a highly coordinated process, while Firmicutes target a few selected carbohydrates^[397]. Although belonging to the same family, the total number of CAZymes is vastly different. It has been reported that CAZymes are 410 in the genome of *Bacteroides muris*, while 73 CAZymes were identified within the genome of *Adlercreutzia aquisgranensis*^[398]. Bioinformatics analyses of 92 *Ruminococcus gnavus* genomes show that the total number of CAZymes varies between *Ruminococcus. gnavus* strains (ranging from 60 to 116 GH families)^[399]. Therefore, we should not only focus on taxonomy but also on enzymes and their gene expression, even at the strain level, when exploring how RS modulates gut bacteria^[400,401]. However, the investigation of the human gut microbiota genome and its CAZymes data is still limited. The RS structure is inherently correlated with its digestive characteristics^[402], which also results in intestinal microbiota responding differently to structurally distinct RS. The types of chemical bonds and groups, and spatial configurations in polysaccharides, reduced the accessibility of enzymes for binding and cleavage. Due to spatial repulsion, it is difficult for enzymes to cleave

glycosidic bonds deeply embedded in complex three-dimensional molecular networks of polysaccharides. RS digestibility is also affected by several extrinsic factors, which further complicate the RS bioavailability. Therefore, starch digestion profiles should be evaluated along a kinetic gradient (slower to faster) instead of being characterized by a binary trait (resistant or nonresistant).

The physiological impacts of NSPs and RS are similar. A recent study shows that industrialized populations exhibit lower levels of gut microbes capable of breaking down cellulose. While such microbes were highly prevalent in ancient humans, hunter-gatherers, and rural populations, this suggests that these gut microbial strains are declining in industrialized populations, likely due to shifts in dietary habits and modern lifestyles^[403]. Rural children consuming agricultural diets high in NSPs possessed a higher abundance of beneficial bacteria and genetic diversity in their intestinal microbiota compared to Western children consuming processed foods high in refined carbohydrates^[404]. NSPs can improve UC by protecting the intestinal mucosal barrier, regulating the immune response of the intestinal mucosa, and remodeling the intestinal flora and metabolites^[405]. A low-cellulose diet can modulate gut microbiota and lipid metabolism to prevent gut inflammation. This led to an increased population of *Oscillibacter* while simultaneously reducing the prevalence of *Akkermansia* species. In addition, cellulose intake predominantly influenced metabolic pathways related to linoleic acid, nicotinate, and nicotinamide^[406]. By simultaneously improving gut barrier function, modifying microbiota composition, and shifting metabolic pathways, hemicellulose represents a potential therapeutic approach for T2DM^[407]. The metabolites promote beneficial microbes like *Bifidobacterium* and *Lactobacillus*, while inhibiting pro-inflammatory bacteria like *Salmonella*. Xylan intervention can partially restore gut dysbiosis caused by dietary fiber deprivation^[408]. Sustained low-fiber intake results in diminished diversity and reduced quantities of fiber-fermenting microbiota, with significant depletion observed among Bacteroidetes species. Even after high-fiber diet restoration, complete microbial recovery was not achieved over generations^[409]. These findings indicate that adequate dietary fiber consumption plays a crucial role in preserving gut microbial diversity and maintaining host metabolic functions potentially mediated by gut microbiota. The differences in the composition of NSPs are an important reason for the diversity of its effects, and also a key factor in their functional evaluation.

4.3 Proteins

Proteins that reach the intestine originate from endogenous and exogenous sources. Endogenous proteins derive from bile, intestinal mucus, and sloughed-off intestinal epithelial cells, and include digestive enzymes, glycoproteins, and mucinous proteins. Exogenous proteins (i.e., dietary proteins) primarily come from food and beverages. Microbiota possess the proteolytic ability to degrade proteins into shorter peptides and amino acids^[410]. These undigested proteins as well as peptides arrive in the colon, and are fermented by the intestinal microbiota to produce metabolites such as SCFAs, branched-chain fatty acids (BCFAs), ammonia salts, phenols, p-cresol, indoles, N-nitrosamines, amines, sulfides and gases, including ammonia, H₂, CO₂, and H₂S^[410,411], which are absorbed into the host or excreted from the body. The content of BCFAs in feces is proposed as a biomarker for colonic protein fermentation^[412]. The fermentation metabolites of proteins in the

colon, apart from a small portion serving as nitrogen sources for intestinal bacteria and amino acids, are mostly harmful to host health, which depends on the concentration and retention time. The amount of protein derivatives in the colon increases with protein intake, and most of it is absorbed by the intestine^[413]. Branched-chain amino acids dysmetabolism in the host and gut microbiome play a key role in the development of obesity and T2DM. It is also evident that modulating dietary components can alter amino acids-derived microbial metabolites and has the potential to modulate the progression of NAFLD^[414]. Long-term exposure of intestinal epithelial cells to protein-derived toxic metabolites may elevate susceptibility to intestinal diseases such as IBD, CRC, and metabolic diseases^[415,416]. Moreover, high consumption of animal-based proteins, as in a traditional Western diet, might exacerbate the growth of sulfate-reducing bacteria such as *Desulfovibrio spp.* that produce H₂S from dietary inorganic sulfur and sulfated amino acids, potentially increasing gut inflammation^[417]. Therefore, dietary protein can influence colonic protein fermentation and host health. Previous studies based on statistical models demonstrate that protein quantity has a more significant effect on shaping gut microbial communities compared to other macronutrients^[418,419].

Different protein sources can affect the structure and metabolites of intestinal microbiota. In animal experiments, rats were fed dietary protein from different sources, including beef, pork, chicken, fish, casein, and soybeans, and it was observed significant differences in the composition of intestinal microbiota^[420]. The primary sources of dietary proteins can be classified into plant-derived and animal-derived. Many studies have reported that plant proteins can improve the structure of intestinal microbiota and promote health. Soy proteins and peptides exhibit prebiotic-like activity, selectively stimulating the growth of probiotic bacteria (*Lactobacilli* and *Bifidobacteria*) while inhibiting *Bacteroidetes* expansion in the intestinal ecosystem^[421]. In an *in vitro* study of intestinal digestion, soy protein extract has been proven to have potential prebiotic functions, promoting the growth of *Lactobacillus*^[422]. The fermented soy whey can alter the gut microbiota in mice, which enhances the abundance of *Bifidobacterium*, *Lactobacillus*, *Butyricicoccus*, *Parabacteroides*, *Lachnospiraceae*, and *Akkermansia muciniphila*, thereby influencing the metabolism and health of mice^[423]. Animal protein in the diet has also been revealed to promote the growth of *Lactobacillus* in growing rats^[424]. However, chicken protein elicited distinct microbial responses in young versus middle-aged rats, revealing age-dependent microbiota modulation^[425]. Casein and red meat proteins show similar effects on postweaning growth performance; casein specifically increased the abundance of *Lactococcus lactis*^[426]. L-carnitine is an amino acid in significant quantities in animal foods such as red meat. A diet rich in animal proteins could increase the abundance of bile-tolerant anaerobic bacteria such as *Bacteroides*, *Alistipes*, and *Bilophila*, and increase proteolytic fermentation and microbial-generated TMA, subsequently leading to an increase of TMAO, a metabolite associated with increased risk of CVDs and dementia^[427].

Moreover, the plant-derived and animal-derived proteins show different impacts on the structure and metabolites of the intestinal microbiota. Higher intake of animal protein results in a reduction in beneficial gut bacteria and an enrichment in harmful microbial taxa, typically in obesity. Conversely, plant-based protein consumption promotes substantial enrichment of anti-inflammatory and butyrate-producing microbial taxa,

and reduces pro-inflammatory bacteria^[428]. Dietary assessments show that dietary proteins from plant and animal sources oppositely affect the abundances of *pathobionts* *Bilophila* and *Lachnoclostridium*^[429]. Compared to the animal-based diet, microbial profiling revealed significant decreases in the intestinal prevalence of *Fusobacterium*, *Bacteroides*, and *Campylobacter* species in adult healthy dogs fed a plant-based diet^[430]. Regular consumption of both animal-based and plant-based proteins may differentially modulate gut microbiota composition, thereby potentially affecting the onset of puberty^[431]. Although both hen egg white and duck egg white belong to animal-derived proteins, they have different effects on gut microbiota, which further highlights the importance of protein sources^[432]. Compared to animal proteins, plant proteins can increase the levels of intestinal SCFAs^[433]. Similar results have also been observed in some short-term animal model studies^[424,434]. BCFAs are specifically fermented from branched-chain amino acids, such as valine, leucine, and isoleucine, which are found mostly in animal protein. Therefore, animal protein can lead to an increase in BCFAs content produced by gut microbiota^[426,435]. Additionally, other gut microbiota metabolites, such as ammonia nitrogen content, are also related to the source of protein^[426,436]. Currently, there is insufficient research on the quantity and types of microbial metabolites produced from different protein sources, especially metabolites such as amines, hydrogen sulfide, phenols, and indoles.

The amount of protein intake affects the composition and metabolites of gut microbiota. In an *in vitro* intestinal model, a high protein diet results in an increase in intestinal pH and SCFAs production, and leads to a series of changes in gut microbiota composition and activity^[437]. Compared with a normal-protein diet, the high-protein diet negatively changed the gut microbiota by increasing *Escherichia*, *Shigella*, *Enterococcus*, *Streptococcus*, and sulfate-reducing microbiota^[438]. A high-protein diet mainly affects the microbial community in the colon by microbial species replacement^[439]. Diets rich in protein may compromise gut microbial diversity, potentially exacerbating neuroinflammation and contributing to central nervous system disorders through pro-inflammatory mechanisms^[440]. High-protein-low-fiber diets enriched the abundance of Proteobacteria and shifted the microbial catabolism of tryptophan, resulting in a higher concentration of Ind, TA, Kyn, and Oxi^[441]. The gut microbiota is also adversely affected by a low-protein diet. For example, compared to mice on a standard protein diet, mice on a low protein diet have a lower abundance of other mycorrhizal genera in their gut^[442].

The diversity of dietary proteins can impact the structure of intestinal microbiota. The gut microbial diversity of rats fed with the black soybean-whey blended protein diet was significantly higher than that of the other groups with a single protein diet. Dietary protein variations were associated with shifts in fecal amino acids and their metabolites, with tryptophan and tyrosine metabolism emerging as pivotal pathways driving alterations in gut microbial composition^[443].

The differences in amino acid profiles are also an important factor in altering the composition of gut microbiota. Compared to plant proteins, animal proteins provide a more complete and balanced composition of essential amino acids^[444] and higher digestibility in the human gastrointestinal tract^[445]. The current approach for assessing protein quality is the Digestible Indispensable Amino Acid Score (DIAAS). DIAAS

focuses solely on the amino acid profile and considers the digestibility of each essential amino acid. The DIAAS of plant-based proteins is typically lower than that of animal-based proteins^[446]. It is considered to be a more accurate measure of protein quality than the Protein Digestibility Corrected Amino Acids Score (PDCAAS). In addition, the structural properties and biological activity of proteins are severely affected by processing and storage^[447,448], which further affect protein fermentation, absorption, and functional properties in the gut, consequently impacting the composition of gut microbiota and human health^[449]. Besides, the gut microbiome generally prioritizes the fermentation of carbohydrates over proteins. But the interactive effects of protein and non-digestible carbohydrate consumption on gut microbiota composition and human health remain poorly understood. Although many studies have noted the impact of different protein sources on the gut microbiome, the proteins used in these studies are still mixed, and they do not essentially explore the impact of different types of proteins.

4.4 Fats

Fat digestion primarily occurs in the upper segment of the small intestine, where bile from the liver and enzymes from the pancreas work together to break down fat molecules into smaller components. Limited quantities of unabsorbed fats transit to the large intestine, where they exert direct effects on microbiota composition and metabolic activity. Significantly, the intestinal microbiota plays a pivotal role in lipid metabolism, as well as breaks down dietary lipids to produce bioactive metabolites that influence host physiology. The fat type and quantity can impact the gut microbiota.

Although fats are not the main energy source for the gut microbiota^[419], the amount of fat intake can modulate the microbial ecology and bacterial metabolic activity. Excessive intake of dietary fat leads to excess energy, which can contribute to obesity, diabetes, fatty liver, and other metabolic diseases and cardiovascular diseases. Gut lymphoid cells impacted by high-fat diets (HFD) or low fiber diets induced microbiota dysbiosis highly proliferate in mesenteric lymph nodes (MLNs) and migrate from MLNs to the periphery, which fuels T cell accumulation within atherosclerotic plaques. MLN resection or lymphocyte deficiency abrogates the pro-atherogenic effects of a microbiota shaped by low fiber diet^[450]. In addition, the Western HFD is rich in choline that the gut microbiota can transform to induce an increase in TMAO levels, thereby promoting the development of CVDs^[451]. It is widely reported that there are significant differences in gut microbiota between an HFD and a baseline diet. When mice were shifted to HFD, the gut microbiota composition was altered within one day^[452]. The changes in gut microbial composition are reproducible due to HFD, and taxonomic investigation revealed that the most reproducible signals are *Lactococcus* species^[453]. A distinct shift in intestinal microbe composition with increased pathogenic bacteria *Alistipes* sp. Marseille-P5997 and *Alistipes* sp.5CPEGH6, and depleted probiotic *Parabacteroides distasonis*, along with impaired gut barrier function, metabolomic dysregulation were identified in HFD group^[454]. Small intestinal microbes are particularly sensitive to HFD and activate host processes regulating fat digestion and transport^[455,456]. HFD generally reduces microbial diversity and richness, but altered alpha diversity is not a consistent feature of HFD across studies with considerable heterogeneity^[453]. Although the F/B ratio is frequently used in the literature, it is an

inconsistent feature of the HFD and is generally higher in both animals and humans with HFD^[180,453,457–459]. Unlike alpha diversity, the F/B ratio was significantly correlated with fat content^[453]. Interestingly, ketogenic diets reversed this trend and altered the intestinal bacteria in a way different from HFD, with a reproducible depletion of *Bifidobacteria*. Experimental evidence from both *in vitro* and *in vivo* models demonstrated that ketone bodies selectively inhibited *Bifidobacteria* growth^[460]. Chronic exposure to HFD disrupts colonic epithelial mitochondrial function, increasing luminal oxygen and nitrate availability. This altered microenvironment promotes the expansion of facultative anaerobic Gram-negative bacteria, ultimately reshaping microbial metabolic activity^[451]. BA biotransformation is an essential metabolic characteristic of the gut microbiota; dietary fat and BA supplementation also modulate the mouse cecal microbiota^[461].

Dietary fats are generally categorized into three subsets, saturated fatty acids (SFAs), MUFAs, and polyunsaturated fatty acids (PUFAs) according to the presence of double bonds between carbon molecules. The diversity of gut bacteria differs significantly by intake of all types of fatty acids^[458,462]. High intake of SFAs negatively affects microbiota richness and diversity, and diets high in MUFAs may decrease total bacterial numbers, whereas PUFAs have no effect on richness and diversity^[458]. It has been reported that HFD high in PUFAs significantly increases microbial community richness compared to the other HFD high in SFAs and MUFAs^[459]. The gut microbiota in adolescents responds differently to dietary fats even at a normal dose^[463].

SFAs contribute to dysbiosis and increase gut barrier permeability, chronic low-grade inflammation, and oxidative stress. Extensive evidence demonstrates that saturated fat-rich diets change gut microbiota composition, typically decrease the abundance of *Bacteroidetes*, and elevate the abundance of Firmicutes and Proteobacteria independently of obesity^[464]. Further, at the genus level, SFA consumption has been revealed to increase gram-negative bacteria, including *Fusobacterium*, *Tyzzereella*, *Anaerotruncus*, *Lachnospiraceae*, *Eisenbergiella*, and *Escherichia*^[462,465,466]. The SFA diet can stimulate the production of sulfate-reducing bacteria, leading to defects in the mucous layer and increasing intestinal inflammation. Interestingly, poorly absorbed dietary long-chain SFA, particularly stearic acid, induces a shift in BA profile and improved metabolism and steatosis in mice. These benefits are dependent on the gut microbiota, as they are transmitted by microbial transfer^[467]. Stearic and oleic acids have been shown to selectively alter the growth of certain bacterial strains *in vitro*^[468]. When fat intake is constant, only at a high-fat level can palm stearin favor the growth of Firmicutes over Bacteroidetes in the cecum and feces^[457].

The consumption of a MUFAs-rich diet can increase the gut microbiota diversity in healthy and unhealthy animal models^[469,470]. A MUFAs-rich diet decreased the F/B ratio, and the increase in Bacteroidetes and *Bifidobacterium spp.* is correlated with high SCFAs production^[458,471]. Animal study indicates that the intake of oleic acid promotes the expansion of beneficial bacteria in the gut microbiota, such as the *Bifidobacterium* group and *Lactobacillus* group^[472].

PUFAs are unsaturated fats that present two or up to six double bonds in their structure. Recent studies have also indicated that PUFAs exert beneficial effects on gut microbiota composition and decrease the F/B

ratio in humans^[473]. More specifically, the shift of gut microbiota is presented in increasing abundances of butyrate-producing genera, including *Roseburia*, *Eubacterium*, *Lactobacillus*, and *Bifidobacterium*, along with decreases in *Veillonella* and *Phascolarctobacterium*^[473–475]. Omega-3 PUFA supplementation can increase the abundance of Bacteroidetes and butyrate-producing bacteria belonging to the Lachnospiraceae family. Importantly, these two taxa are significantly associated with the severity of neurological diseases^[476]. The conjugated linoleic acids (CLAs) family represents a unique class of PUFA, which show anti-atherosclerotic, anti-obesogenic, and anti-cancer properties. Murine model studies have demonstrated that dietary supplemented with *cis*-12 CLA can alter gut microbiota at the phylum level, such as a decrease in Firmicutes and an increase in Bacteroidetes^[477], and at the species level with enrichment of *Butyrivibrio*, *Roseburia*, and *Lactobacillus*, resulting in a distinct increase of butyrate in the feces and acetate in plasma^[478]. The metabolic responses of HFD rich in PUFAs are different compared with HFD rich in MUFAs; intake of an HFD rich in MUFAs leads to greater fat oxidation and lower carbohydrate oxidation. Besides, the impact of PUFAs or MUFAs consumption on metabolism is associated with the meal pattern, whether long-term or acute^[479].

The intake of TFAs reduces the diversity of the gut microbiota in mice fed an HFD, and increases the abundance of the Proteobacteria phylum and Desulfovibrionaceae family, whereas it reduces the abundance of *Bacteroidetes*, *Lachnospiraceae*, *Bacteroidales* S24-7, and *Tyzzereella*^[462,480,481]. Surprisingly, the intake of TFAs increases the abundance of the probiotic *Lactobacillaceae*. Additionally, the intake of TFAs increases inflammatory parameters, as well as a numerical decrease in fecal butyric acid and valeric acid^[481]. However, other studies show that TFAs intake does not affect alpha diversity but change beta diversity of gut microbiota. Hua et al. reported that the TFAs did not decrease gut microbial diversity or richness, but the clustering of the TFA groups in the principal component analysis was distinctly different from the basal diet group^[482]. The differences in conclusions of the impact of TFAs on gut microbiota and fecal metabolites might be due to using different proportions and types of TFAs^[483].

Dietary fat overconsumption modulates microbial gene expression patterns, particularly upregulating lipid biosynthesis pathways, including the fatty acid regulator *fadR*. This microbial metabolic shift toward enhanced fatty acid production contributes to obesity^[484]. Interestingly, alterations in gut microbiota composition are primarily driven by dietary fat intake rather than obesity levels. Alterations in gut microbe structure were observed exclusively with the high-fat/SFAs diet. A high-fat/MUFAs diet did not alter gut microbiota composition but induced greater obesity than an energy-matched low-fat/SFAs diet. Therefore, the altered gut microbiota composition appears to be driven by excessive dietary fat intake rather than by the obese phenotype^[458,464]. However, the mechanisms by which dietary fatty acids affect the gut microbiota are still not well defined. Current understanding of specific gut microbial strains and their enzymatic machinery involved in saturated fat metabolism remains limited^[485,486].

4.5 Minerals

Compared to macronutrients, relatively little is known about the effects of micronutrients on gut

microbiota composition and metabolic activity. Minerals play various roles in metabolism and normal tissue functioning. The absorption of minerals mainly occurs in the small intestine through both active and passive transport, and the exact absorption mechanisms vary depending on the elements.

The gut microbiota affects mineral metabolism in both disease and healthy conditions. For instance, gut microbiota produce 1,3-diaminopropane and reuterin that suppress hypoxia-inducible factor 2a (HIF-2a), a master transcription factor of intestinal iron absorption, and increase the iron-storage protein ferritin, resulting in decreased intestinal iron absorption by the host^[487]. On the other hand, they secrete a variety of enzymes, which degrade chelators such as tannins or phytates, to release usable forms of minerals from food^[488]. Besides, these SCFAs produced by them can lower the luminal pH, enhancing the solubility of minerals and allowing for better absorption^[489]. Therefore, the bioavailability of minerals partially depends on gut microbiota.

Both deficiency and excess of minerals can change the composition and diversity of gut microbiota. An iron deficient diet leads to a decline in the gut microbiota diversity and an increase in potential opportunistic pathogens in rats. More specifically, iron deficient diet decreases the abundance of *Roseburia*, *Bacteroides* and *Eubacterium rectale* and increase the abundance of *Lactobacillus*, and *Enterobacteriaceae*^[490]. *In vitro* colonic fermentation, a decrease in iron availability to the human gut microbiota reduces the growth of potentially pathogenic gut bacteria^[491]. Compared to healthy volunteers, there was a significant difference in the gut microbiota of the patients with iron deficiency anemia^[492]. While experimental outcomes vary between model systems, a recurring observation is iron-mediated suppression of beneficial Lactobacillaceae and Bifidobacteria and an increase in Enterobacteriaceae^[493]. Interestingly, Lactic acid bacteria were traditionally thought to be iron-independent, as various *Lactobacillus* strains showed no growth differences when cultured in either iron-replete or iron-depleted media^[494]. The results from *in vitro* models also show that supplementary iron caused higher levels of *Roseburia* and *Prevotella*^[495]. Iron-enriched diets reduce microbial activity, leading to an increased number of Proteobacteria and decreased colonization of Firmicutes^[496]. On the one hand, gut microbiota needs to tightly regulate the acquisition of iron due to the inherent redox potential of free iron at high concentration^[497]. On the other hand, given the absence of alternative iron transporters in *Bifidobacterium spp.*, elevated luminal iron concentrations from supplementation may disrupt microbial homeostasis, preferentially promoting pathogenic over commensal bacterial growth. Besides, the different types of iron supplements and fortification, as well as different forms of iron, used in supplementation prompt unique modulation of gut microbiota^[490,498,499], due to their different bioavailability to intestinal microbiota. Dietary iron attenuates CDI via modulation of intestinal immune response and gut microbiota. *E. coli* AVS0501, enriched in the gut microbiota of iron-treated CDI mice, showed prophylactic and therapeutic effects on CDI. Moreover, the production of L-proline and tauroursodeoxycholic acid in CDI mice treated with high dietary iron influences *C. difficile* colonization, toxin production, and in turn regulates the intestinal neutrophil response^[500]. Ferroptosis, characterized by ROS-dependent accumulation of lipid peroxides, has been implicated in various diseases etiologies. Gut microbes influence the level of hepcidin, a primary regulator of Fe homeostasis, while disturbed gut microbes can induce ferroptosis within the intestinal tract^[501]. Besides,

supplementation of probiotics can prevent Bacteroidaceae-mediated ferroptosis^[502]. Therefore, it is a potential strategy that dietary intervention suppresses ferroptosis via reshaping the gut microbiota, thereby providing effective countermeasures for prevention.

Zinc deficiency also changes the composition and function of the intestinal microbiota, as well as the production of SCFAs^[503,504]. Zinc deficiency in chickens was associated with an expansion of Proteobacteria, particularly *Enterobacteriaceae* and *Enterococcus*, which were significantly enriched under zinc-limiting conditions^[504]. In Zn-deficient children, they exhibited a significantly higher Shannon index. At the genus level, *Coprobacter*, *Acetivibrio*, *Paraprevotella*, and *Clostridium_XI* showed significantly more abundant than in controls^[505]. Excess dietary zinc substantially alters the gut microbiota^[506]. Long-term and high-dose zinc supplementation significantly reduced both the prevalence of SCFA-producing bacterial taxa and their metabolites^[507]. The existing data demonstrate that both Zn deficiency and excess have adverse effects on gut microbiota.

Unlike other nutrients, specific elements rather than specific compounds are emphasized for minerals. In fact, the substances introduced in experiments and daily life are not single compounds, which may introduce confounding factors when studying the impact of minerals on the microbiome.

4.6 Vitamins

There are 13 vitamins that the human body needs, but humans cannot synthesize these vitamins except for vitamin D. So, other vitamins need to be obtained exogenously. In addition to obtaining vitamins through diet, vitamins can also be produced de novo by human gut bacteria, especially the K and B group^[508], and the yield has been estimated to be up to 50% and 30% of the recommended daily intake, respectively^[508,509], which depends on the gut microbiota composition and the host's diet.

Gut bacteria directly participate in the metabolism of vitamin A. Multiple bacteria, including gut commensals, have been proposed to metabolize carotenoids to retinoids, *Bacillus cereus* being the first example to directly convert retinal to retinoic acid (RA) or retinol using aldehyde dehydrogenase (ALDH). Recent work shows that gut microbes, including SFB, express ALDH and produce RA^[510]. Both FMT and *in vitro* fermentation experiments showed that intestinal bacteria can convert dietary vitamin A into active retinoids, and *Lactobacillus intestinalis* specifically restored RA levels in the gut of vancomycin-treated mice^[511]. Gut bacteria also participate in vitamin D metabolism. In *Streptomyces griseolus*, the CYP105A1 enzyme catalyzes the sequential hydroxylation of vitamin D3^[512]. This indicates that the bacterial populations possessed homologous proteins such as CYP27A1 (*Ruminococcus torques*) and CYP27B1 (*Mycobacterium tuberculosis*), which may be associated with vitamin D metabolism. Vitamin K exists in the intestinal tract primarily in the form of long-chain menaquinones. Menaquinone biosynthesis is restricted to specific taxa within the intestinal microbiota, such as *Bacteroides fragilis*, *Eubacterium*, *Propionibacterium*, and *Arachnia* groups^[508,513]. Computational analysis identified that the *Burkholderia*, *Pseudomonas*, and *Erwinia* may possess the capacity to generate ascorbate, and Chang et al. validated the production of ascorbate in the *Pseudomonas* group, *Pseudomonas aeruginosa*^[514]. Genomic analyses reveal that 40-65% of human gut

microbiota possess biosynthetic pathways for one or more B vitamins, with *Bacteroides* species disproportionately represented among the 12.5% capable of producing all eight essential B vitamins^[509]. However, experimental evidence currently confirms B1 and B12 biosynthesis capabilities in only select gut bacterial species. Partial gut bacteria are unable to synthesize all vitamins required for growth or have no de novo vitamin synthesis capacity. Consequently, these microbial species rely on host-derived or bacterial cross-feeding mechanisms to obtain essential vitamins for proliferation^[515].

Intriguingly, vitamins have also been shown to modulate the metabolic activity and structure of the intestinal microbiota in both deficiency and supplementation. The vitamin A-deficient diet (VAD) led to increased mucin Muc2 expression and goblet cell hyperplasia, and reduced SFB in the gut microbiota^[516]. Acute VAD significantly altered gut microbiota composition and meta-transcriptome profiles, with *Bacteroides vulgatus* emerging as a key responder that markedly increased in abundance under vitamin A-depleted conditions^[517]. Notably, metagenomic functional prediction revealed a significant decline in GABAergic synapse activity and retinol metabolism following VAD intervention^[518]. Vitamin B6 deficiency did not alter the alpha diversity of cecal contents in rats, but microbial beta-diversity differed significantly compared to control. Microbial analysis revealed *Lachnospiraceae_NK4A136_group* and *Bacteroides* as key discriminators between vitamin B6-deficient and control groups, concomitant with significant decreases in cecal propionate and butyrate concentrations^[519]. Vitamin D3 exhibits strain-dependent microbiota modulatory effects, with C57BL/6 mice demonstrating greater microbial community plasticity in response to varying vitamin D3 levels compared to BALB/c mice^[520].

Increased vitamin supplementation levels significantly modified the intestinal microbiota profile. It was reported that water-soluble vitamins increased the abundance of ileal *Lactobacillus* and reduced the richness of ileal *Romboutsia*, *Turicibacter*, and cecal *Faecalibacterium*, whereas lipid-soluble vitamins increased cecal *Megasphaera* and *Phascolarctobacterium* compared with the control group^[521]. In a human clinical study and batch fermentation experiments, Pham et al. examined how colon-targeted delivery of vitamins A, B2, C, D, and E influences the gut microbiota. The results showed that vitamin C exerted the most pronounced effect, significantly enhancing microbial alpha diversity and fecal SCFA levels compared to placebo. The other tested vitamins also modulated microbial diversity, composition, and metabolic activity in vitro, though to varying extents^[522]. Otten et al. found that two weeks of high-dose vitamin C can modulate the gut microbiota in healthy individuals, promoting potentially beneficial bacterial changes. Notably, these affected bacterial groups possess anti-inflammatory properties and are closely linked to gut health^[523]. Mice treated with vitamin A displayed significantly greater gut microbial diversity and altered flora composition. Targeted metabolomics revealed elevated levels of SCFAs in these mice. Furthermore, gut microbiota depletion and FMT experiments confirmed that vitamin A alleviates UC in a gut microbiota-dependent manner—promoting SCFA-producing bacteria while suppressing UC-associated genera^[524].

Vitamin B12 (Cobalamin) exists in multiple chemical forms, including cyanocobalamin, hydroxycobalamin, and methylcobalamin, and the structural variations influence the modulation of gut

microbial communities. Cyanocobalamin supplementation in zebrafish induced significant modifications to gut redox homeostasis and microbial community composition. These changes were associated with enhanced ecological network stability, improved intestinal barrier integrity through tight junction reinforcement, and increased resistance to pathogenic invasion^[525]. However, Altered vitamin B12 (hydroxycobalamin and cyanocobalamin) in the diet does not affect gut microbial diversity or community composition in disease-free hosts in both infant and mouse studies^[526–528]. An *in vitro* batch fermentation study also indicates that B12 (cyanocobalamin) availability in the medium had no or only a minor impact on total bacterial growth and microbiota structure and diversity^[529]. Though vitamin induced a shift in microbial composition and metabolic activity in an *in vitro* colon simulation, the ecosystem structures of the control and cyanocobalamin groups exhibited high similarity, while the microbial community structure was significantly influenced by methylcobalamin^[530].

On one hand, the gut microbiota has specific metabolic requirements for vitamins^[531], and deficiencies in vitamins can significantly affect their composition and function. On the other hand, the microbial community depends on dynamic cross-species metabolic exchanges that form interconnected metabolic networks. High doses of vitamins could change the competitive or syntrophic balance between intestinal microbiota. In addition, the gut immune system is profoundly influenced by vitamins from dietary sources and bacterial production, which may in turn impact gut microbes. Certain vitamins, including A, C, and E, have been demonstrated to have direct antimicrobial activity *in vitro* or *in vivo* experiments^[532–535]. Besides, metabolites derived from vitamins, such as active retinoids, also present antimicrobial properties and primes innate defense^[510,511,534].

4.7 Food additives

The category of food additives mainly includes sweeteners, emulsifiers, preservatives, antioxidants, flavor enhancers, and colorants, which have been extensively employed to improve the taste, texture, color, aroma, and shelf-life of foods. The long-term exposure to these additives could change gut microbial communities.

Sweeteners can be classified based on their origin as either synthetic or natural. Current research has observed alterations in intestinal microbes and metabolites induced by artificial sweeteners. The consumption of artificial sweeteners may cause microbiome-dependent glycemic changes. Common artificial sweeteners (acesulfame potassium, aspartame, saccharin, sucralose) may promote metabolic dysregulation through microbiota-mediated mechanisms, potentially contributing to glucose intolerance and adiposity^[536]. Artificial sweeteners promote oxidative stress in the gut environment and enhance the horizontal transfer of antibiotic resistance genes between commensal microbiota and pathogenic species^[537]. Aspartame can increase bacterial metabolites, with propionate dominating. The production of propionate may increase liver gluconeogenesis, thereby increasing the output of glucose from the liver^[538]. Sweeteners may act on the glucose transport system on bacterial cell membranes, thereby inhibiting bacterial glucose fermentation^[539]. Acesulfame K can increase the abundance of various Bacteroidetes^[540], which have a wide range of polysaccharide abilities. Those

alterations in gut microbiota communities after the consumption of acesulfame K present sex-specific effects. The evidence suggests that sweeteners (saccharin, sucralose, and aspartame) enhance bacterial biofilm formation capacity. Co-culturing with human intestinal epithelial cells enhances bacterial adhesion, invasion, and cytotoxicity toward the host epithelium^[541]. Although most of the results illustrate negative outcomes, a few studies present neutral effects of sweeteners on the microbiota. Suez et al. observed that Acesulfame potassium administration showed no significant effect on gut microbial composition in mice^[542]. Frankenfeld found neither bacterial abundance patterns nor predicted functional gene profiles showed significant associations with recent high-intensity sweetener intake^[543].

An important class of natural sweeteners is polyols, also known as sugar alcohols. Due to the substitution of the carbonyl group with a hydroxyl group, polyols are poorly metabolized in the small intestine and are usually catabolized by the gut microbiota in the large intestine. Metabolic studies indicate that a minor fraction (5-10%) of circulating erythritol undergoes sequential oxidation, first to erythrose and subsequently to erythronate^[544]. Polyol consumption does not stimulate pancreatic β -cell activity or elevate plasma glucose levels. These polyols also bear similarity with the corresponding sugars in fermenting into gas and acids. Excessive polyols generate higher osmotic pressure, thereby altering the microenvironment, which may influence the gut microbiota.

Low- and no-calorie sweeteners (LNCS) serve as sugar alternatives in dietary interventions aimed at mitigating chronic disease risks associated with excessive sugar consumption. Fermentation kinetics of LNCS exhibit significant compound-specific variability, which means results obtained for one LNCS are difficult to generalize^[545]. *In vitro* and *in vivo* studies confirm the bacteriostatic effects of xylitol and sorbitol against *Streptococcus mutans* and *Streptococcus sobrinus*, likely mediated by intracellular accumulation of toxic sugar-phosphate derivatives following polyol uptake^[546]. Notably, nearly all of the absorbed erythritol was not metabolized, and the unabsorbed portion that transitioned to the colon was not metabolized by gut microbiota. The human gut microbial community is not significantly affected by erythritol due to the lack of ability to utilize erythritol^[547]. Although pathogenic *Brucella abortus* strains can metabolize erythritol^[548], there is no evidence that *Brucella abortus* is a symbiotic bacterium in the human gut. However, a significant increase in butyric acids was observed after the addition of erythritol^[549]. One possible reason is that low-dose erythritol intake may not substantially alter gut microbiota composition, but it could influence microbial functionality. A recent study shows that sorbitol consumption activates intestinal macrophages by altering the gut microbiome and metabolites, which in turn promotes intestinal inflammation^[550].

Even at low exposure levels, both carboxymethylcellulose (CMC) and polysorbate-80 were sufficient to induce metabolic syndrome and subclinical inflammation in wild-type hosts, while exacerbating colitis severity in genetically susceptible mice^[104]. The metabolic syndrome triggered by emulsifiers was linked to microbial encroachment, shifts in species composition, and heightened pro-inflammatory activity. Experiments using germ-free mice and FMT demonstrated that these microbiota alterations were both necessary and sufficient to induce low-grade inflammation and metabolic syndrome. Particularly stark

detrimental impacts were observed in response to various carrageenans and gums, which altered microbiota density, composition, and the expression of pro-inflammatory molecules. Emulsifiers can directly alter gut microbiota by promoting intestinal inflammation^[551]. CMC intake led to mild postprandial abdominal discomfort and altered gut microbiota composition characterized by decreased diversity. The ingestion of CMC led to greater microbial infiltration into the typically sterile inner mucus layer—a hallmark of intestinal inflammation—along with significant shifts in microbiota composition. These changes disrupted the gut microbiome and metabolome, thereby elevating the risk of various chronic inflammatory disorders^[552].

Preservatives can have both positive and negative effects on the gut microbiota. These effects can be direct or indirect through the stimulation/inhibition of microbial growth or production of metabolites/degradation products that affect the microbiota, with effects varying depending on the specific preservative and its concentration. β -Diversity analysis showed distinct gut microbiota profiles in mice fed different preservatives in recommended levels, including benzoic acid, potassium sorbate, and sodium nitrite. These preservatives cause specific patterns of microbial diversity and unique microbial signatures. Benzoate increased the proportion of *Bacteroides*, *Blautia*, *Ruminococcus*, *Oscillospira*, and *Dorea*; sodium nitrate increased the abundance of Firmicutes, *Turicibacter*, and *Alkaliphilus*; and potassium sorbate increased the proportion of *Parabacteroides* and *Adlercreutzia*^[553]. Antimicrobial preservatives (APs) promoted glucose intolerance and disrupted gut microbiota, regardless of their origin. Notably, biogenic APs were not consistently safer than synthetic counterparts^[554]. Ruiz-Rico et al. assessed the influence of novel phenolic immobilization-based food preservatives on the gut microbiota and identified free eugenol as the most influential phenolic compound, significantly altering gut microbiota composition by markedly increasing the relative abundance of Lachnospiraceae and Akkermansiaceae families. Unlike free phenolics, the immobilized forms promoted the growth of *Bacteroides* and lowered the F/B ratio^[555]. Potassium sorbate, sodium bisulfite, sodium benzoate, and saccharin showed greater antimicrobial activity against the studied species. *Lactococcus lactis* and *Lactobacillus acidophilus* bacteria had decreased SCFAs production after exposure to saccharin and sorbate, and *Bifidobacterium longum* after exposure to sorbate, in comparison to controls^[556,557].

Food additives permitted by regulations are generally not considered to exert direct harmful effects on humans; however, they can alter the gut microbiota and its metabolism, which may indirectly affect host health. Notably, if low doses of food additives are sufficient to induce changes in the gut microbiome over a short period, intestinal health should be taken into consideration when evaluating their safety. Incorporating assessments of gut microbiota-related effects, such as in vitro fermentation experiments and metabolic studies, would provide a more comprehensive understanding of food additive safety. Nevertheless, the impact of food additives on the human gut microbiota remains poorly understood, as most existing studies have been conducted in animal models. Importantly, differences in experimental animals and model systems limit the direct extrapolation of findings from animals to humans. For example, animal studies have reported that long-term intake of sweeteners can induce intestinal cancer in mice; however, such associations have not been confirmed in large-scale epidemiological studies to date. In addition, how food additives are metabolized by

the gut microbiota remains largely unclear.

4.8 Dietary patterns

Dietary patterns refer to the combination and proportion of foods and nutrients that individuals consume regularly over time. Although studies have widely assessed the impact of different nutrients on the gut microbiota, the effects of diet patterns on the modulation of the gut microbiota also need to be taken into consideration. Because the complex interactions of the dietary compounds cannot be reflected in the analysis of a single nutrient. Each dietary pattern has its own characteristics and exerts different effects on the intestinal microbiota. There are dietary patterns emphasizing single nutrients, such as high-sugar, high-fiber, high-protein, and high-fat, and their impact on gut microbiota has been highlighted in previous sections. Table 2 summarizes other dietary patterns and their influence on gut microbiota.

Table 2. Effects of different dietary patterns on gut microbiota.

Dietary patterns	Dietary features	Gut microbiota signature	Reference
Ketogenic diet	High-fat, very low-carbohydrate, and moderate-protein dietary pattern designed to promote fat metabolism and ketone production by mimicking a fasting state.	Actinobacteria↓ Bacteroidetes↑ Firmicutes↓ <i>Bifidobacterium</i> ↓	[460]
Mediterranean diet	Emphasizing plant-based foods, healthy fats, and moderate consumption of animal products.	<i>Bacteroides</i> ↑ <i>Butyricoccus</i> ↑ <i>Coprococcus</i> .1↑ <i>Lachnoclostridium</i> <i>Lachnospiraceae</i> UCG 001↑ <i>Parasutterella</i> ↑ <i>Lachnospira</i> ↑	[558]
Western diet	High consumption of processed foods, refined sugars, unhealthy fats, and low intake of fruits, vegetables, and whole grains.	<i>Blautia</i> ↑ <i>Akkermansia</i> ↑ <i>Alistipes</i> ↓ <i>Muribaculaceae</i> ↓	[559]
Vegetarian diet	Plant-based dietary pattern that excludes meat, poultry, and seafood but may include animal-derived products such as dairy and eggs.	<i>Prevotella</i> ↑ <i>Clostridium</i> ↑ <i>Lactobacillus</i> ↑ <i>Ruminococcus</i> ↑ <i>Eubacterium rectale</i> ↑ <i>Faecalibacterium prausnitzii</i> ↑ <i>Bacteroides</i> ↓ <i>Bifidobacterium</i> ↓	[560]
Intermittent fasting diet	A framework for regulating meal timing. Alternating between periods of fasting and eating.	<i>Bacteroides</i> ↑ <i>Fusicatenibacter</i> ↑ <i>Parabacteroides</i> ↑ <i>Agathobacter</i> ↓ <i>Clostridium</i> ↓ <i>Coprococcus</i> ↓ <i>Enterocloster</i> ↓	[561]
Gluten-free diet	Excluding gluten, a protein found in wheat, barley, rye, and their derivatives.	<i>Lachnospiraceae</i> ↑ <i>Bifidobacterium</i> ↓ <i>Dorea</i> ↓ <i>Blautia wexlerae</i> ↓ <i>Lachnospiraceae</i> ↓ <i>Anaeostipes hadrus</i> ↓ <i>Eubacterium hallii</i> ↓	[562]
DASH diet ¹	Emphasizing nutrient-rich foods that are low in sodium, saturated fat, and cholesterol while being high in	<i>Clostridium</i> ↑ <i>Ruminococcus</i> ↑	[563]

	potassium, calcium, magnesium, and fiber.	<i>Lactobacillus</i> ↑ <i>Fusobacterium</i> ↓ <i>Porphyromonas</i> ↓ <i>Bacteroides</i> ↓ <i>Bifidobacterium</i> ↓ <i>Succinivibrio</i> ↓	
Very low-calorie diet	Consuming 800 calories or fewer per day.	<i>Akkermansia</i> ↑ <i>Christensenellaceae</i> R-7 group↑ <i>Pseudobutyrvibrio</i> ↓ <i>Blautia</i> ↓ <i>Bifidobacterium spp.</i> ↓	[564]
Low FODMAP	The temporary elimination of fermentable carbohydrates.	<i>Erysipelotrichia</i> ↑ <i>Anaerostipes</i> ↓	[565]

¹ DASH (Dietary approaches to stop hypertension)

There is no doubt that food composition and dietary patterns can alter gut microbiota structure and metabolism. Long-term dietary patterns can induce specific gut microbial enterotypes^[566], and gut microbial enterotypes are linked to a number of diseases, which may help in elucidating variability in treatment outcomes and direct personalized intervention strategies^[117]. Diets high in animal protein foster *Bacteroides* enterotype and other species associated with proatherogenic metabolites and CVDs^[566]. High salt treatment depleted *Lactobacillus spp.* from the gut microbiota, resulting in an increase in Th17 cells and salt-sensitive hypertension both in humans and animals^[567]. Interestingly, other studies demonstrated that either reduced salt or increasing *Lactobacillus spp.* with probiotic treatment improved blood pressure regulation, arterial compliance, vascular function, and insulin sensitivity^[568]. Besides, the gut microbiota modulates the equilibrium between pro- and anti-inflammatory signaling pathways in the intestinal mucosa. Assessing how dietary patterns influence gut microbiota linked to mucosal barrier integrity and immune regulation is valuable. Bolte et al. demonstrated consistent associations between specific dietary patterns and functionally similar bacterial clusters across health and disease states. Their findings further revealed particular food components linked to microbial species exhibiting mucosal protective and anti-inflammatory properties^[569]. Moreover, dietary modulation of the gut microbiome can serve as an immunoregulatory intervention and improve the efficacy of checkpoint blockade therapy. Intermittent fasting, high fiber, and low sugar consumption are significantly associated with better immune checkpoint inhibitors outcomes^[570]. More broadly, dietary interventions have the potential to alter the gut microbiota and impact on systemic inflammation^[571]. Thus, it is plausible that dietary interventions targeting inflammatory responses could be developed to treat cancer and autoimmune diseases. Caloric restriction and caloric restriction mimetics are emerging as additional tools to modulate the gut microbiota and thereby promote health. Intermittent fasting and molecules such as polyphenols and beta-hydroxybutyrate decrease blood pressure by modulating the gut microbiota and attenuating inflammatory pathways. Thus, available evidence supports modulating the gut microbiota via calorie restriction modalities that improve health through mechanisms such as BA signaling^[568]. Previous studies observed an attenuating effect of the ketogenic diet on CRC cell growth. Tsenkova et al. further demonstrated a mediating role of the gut microbiota in this effect. In ketogenic conditions, bacterial species that produce stearic acid are enriched, resulting in elevated levels of free stearate in the gut lumen. This

microbial product demonstrates tumor-suppressing properties by inducing apoptosis in cancer cells and decreasing colonic Th17 immune cell populations^[572]. Evidence from seizure studies highlights the vital role of the gut microbiome in the neuroprotective effects of a ketogenic diet. Transplantation of the ketogenic diet gut microbiome can confer seizure protection to mice via reducing systemic gamma-glutamylated amino acids and increasing hippocampal γ -aminobutyric acid (GABA)/glutamate levels^[573].

Existing human studies of short-term dietary interventions have documented only temporary microbial changes, typically lasting from several days to a few weeks. Current understanding of long-term dietary effects on gut microbiota remains constrained by insufficient longitudinal studies and interventions incorporating serial fecal sampling with extended follow-up periods. Besides, the synergistic effects and interactions of nutrients on the gut microbiome need to be emphasized because the nutrients in daily diets are mixed. For example, dietary fiber can suppress microbial amino acid metabolism, as carbohydrates generally serve as the primary energy substrate for most gut microbiota species^[574]. Saturated fat showed more pronounced effects than protein source in modulating taxon abundances, but protein source exhibited independent significant effects when fat-related variation was statistically removed^[469].

Elucidating dietary modulation of gut microbiota composition and function, and thus regulating human health, has led to targeted dietary strategies. In fact, the concept of microbiota-directed food (MDF) was first proposed in 2017^[575]. Gehrig et al. designed microbiota-directed complementary food, based on which both the abundance and functional expression of growth-promoting bacterial taxa showed progressive enrichment during microbiota development^[576]. A clinical trial demonstrated the efficacy of microbiota-directed complementary food (MDCF-2) as a nutritional intervention for moderately malnourished young children, and it further elucidated potential mechanisms linking targeted microbiota modulation to growth enhancement^[577]. The MDCF-2 treatment also reduced stunting during two years of follow-up^[578]. Li et al. designed a non-industrialized-type diet to restore the industrialized gut microbiome to improve health. The restore diet enhanced the persistence of *Limosilactobacillus reuteri* from rural Papua New Guinea and redressed several microbiome features altered by industrialization. The diet also beneficially altered microbiota-derived plasma metabolites implicated in the etiology of chronic non-communicable diseases and obtained considerable cardiometabolic benefits^[579]. These findings indicate that incorporating microbiota-supporting ingredients could enhance the efficacy of nutritional interventions for undernutrition.

Although the general influence of diet on gut microbial composition is well established, the consequent functional shifts within the microbiota, their effects on host health outcomes, and the overall dynamic processes still require further elucidation. This point is strongly supported by varying results in similar studies, with few dose-response or structure-activity relationships between diet and gut microbiota being clearly established. Incorporating personalized factors is key to achieving precise gut microbiota modulation and precise nutrition, which includes intrinsic factors such as gut microbiota, genetics, and extrinsic factors such as diet and physical activity, which enables a quantitative description of variable responses to the same dietary intervention at both gut microbiota and health outcome levels. Notably, the consideration of dietary patterns

and enterotypes is the starting point for this process. For food components, it is essential to clarify their dose-response and structure-activity relationship. Besides, the definition of dietary patterns needs to be more precisely quantified rather than described vaguely. Similarly, communities of gut bacteria may be treated as a spectrum rather than distinct groups (i.e., enterotypes). Based on these, a targeted diet plan can be designed to achieve accurate prediction and precise regulation^[580]. Last but not least, it is also necessary to assess whether dietary interventions, in addition to regulating the gut microbiome, may introduce other health risks.

In summary, the impact of diet on the gut microbiota is complex. It can directly influence the microbiota through food components or indirectly affect it by modulating the host's immune system (Figure 4). In microbiome-based dietary interventions, it is crucial to identify microbiota-mediated pathways and to determine their effect sizes on health outcomes. Each species may have specific metabolic mechanisms that respond to dietary patterns and influence health, which remain largely unknown. Decoding microbial genomes has become essential for revealing their identities and functions. Using advanced technologies such as genome sequencing, culturomics, humanized animal organ-on-chip models, and multi-omics, our understanding of the function of the gut microbiota can be further enhanced. Considering the enormous impact of diet on the microbiota and the underlying mechanisms remaining unclear, building a comprehensive database that reflects diet-microbiome-host interactions is necessary, which could provide the basis for personalized nutritional interventions. In addition, most research findings are inconsistent. Therefore, we propose employing data mining techniques to uncover potential mechanisms underlying diet-microbiome-host interactions, enabling precise gut microbiota modulation and advancing the applications of precision nutrition.

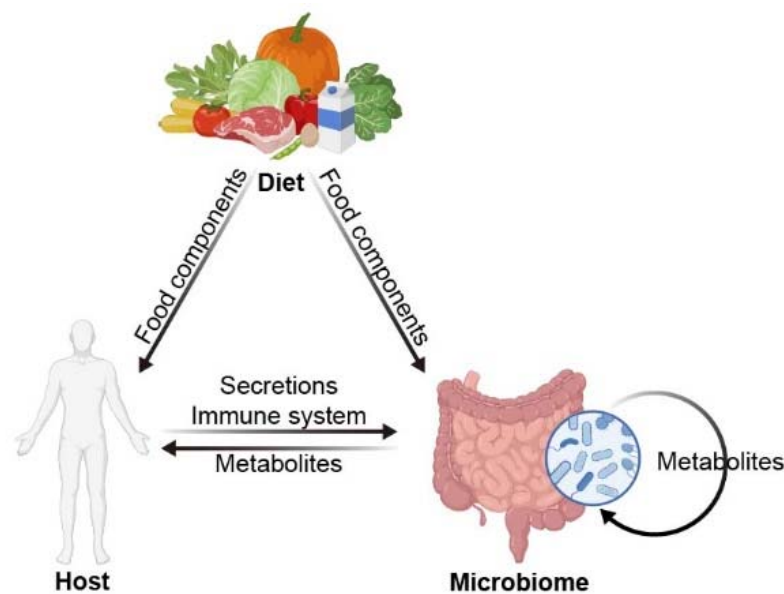


Figure 4. The complex, multidirectional interactions among diet, gut microbiome, and host.

5. Big data drives precise nutrition

The differences in genetic background, physiological status, and lifestyle among individuals can affect their nutritional needs, metabolism, and response to dietary interventions, and further bring different health outcomes^[581]. This has given rise to precision nutrition, also referred to as personalized nutrition, which aims to preserve or ameliorate health and well-being through dietary interventions, products, or services that

leverage human variability^[582].

As mentioned in previous sections, the metabolic activity of intestinal microbes is closely related to human physiology and digestion, and microbes interact strongly with dietary nutrition. Therefore, the heterogeneity in dietary response among individuals with different metabolic profiles could be partly explained by pre-intervention variations in gut microbiota structure and function. Indeed, microbiome characterization has emerged as a critical focus in nutritional science^[583], with current research extensively examining how dietary components modulate gut microbial diversity. Microbiome profiling now serves as a critical determinant for predicting personalized dietary responses and formulating tailored nutritional strategies. Contemporary nutritional interventions increasingly target gut microbiome optimization, emphasizing both taxonomic richness and diversity. Growing evidence supports microbial profiling as an essential component of precision nutrition strategies^[584]. Hence, it is possible to design personalized response prediction frameworks and feasible intervention strategies to achieve more accurate health management through approaches that target or are mediated by gut microbiota^[585,586].

With the development of multi-omics technologies, we have gained a deeper understanding of the functions of gut microbiota and metabolites, as well as their role in human health and disease. The integration of wearable sensors with mobile platforms has advanced dietary monitoring, allowing for extensive dataset generation and instantaneous evaluation. Technological advancements in big data analytics and AI represent fundamental pillars in the development of precision nutrition. This has enabled precision nutrition to integrate these large volumes of data, thereby enhancing investigations into the connections between gut microbiota, diet, and disease, enabling more accurate profiling of individual dietary responses to support tailored nutritional recommendations and interventions (Figure 5). The integration of mechanistic insights, data-driven approaches, and translational nutrition provides a systems-level framework for future microbiome research and clinical practice.

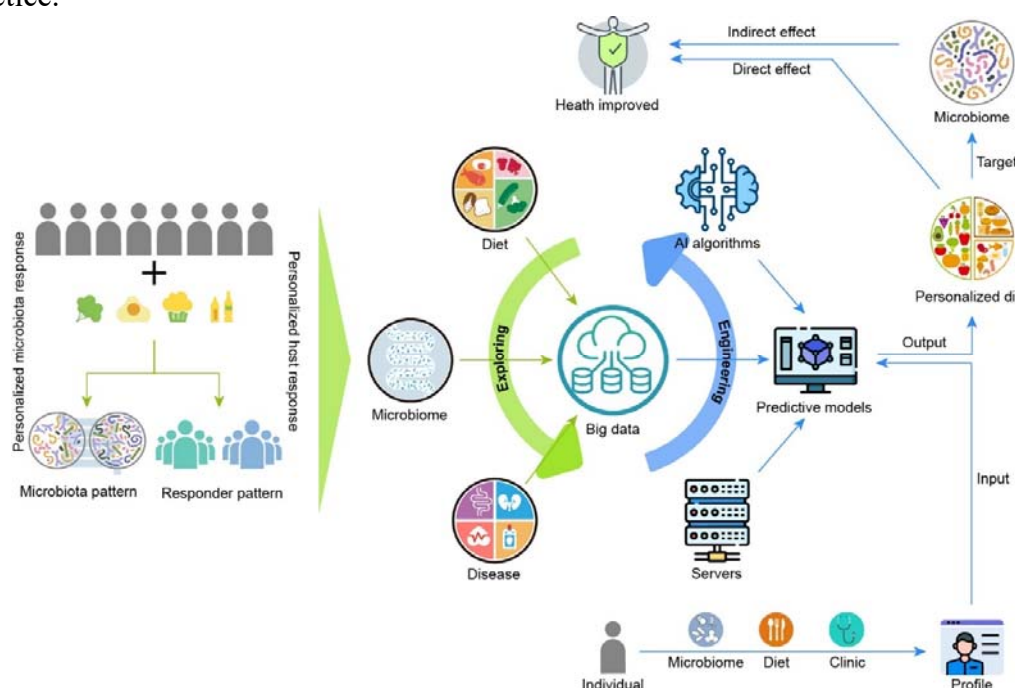


Figure 5. A framework of precise nutrition driven by big data from gut microbiome, diet, and disease.

From a translational perspective, a precision nutrition pipeline includes: (i) identifying inter-individual variability in responses to dietary interventions during specific biological or pathological processes; (ii) standardized collection of dietary, microbiome, and host phenotype data; (iii) predictive modeling using machine learning algorithms; (iv) post hoc interpretation of machine learning models to elucidate key variables, their biological relevance, and underlying mechanisms; and (v) iterative validation through dietary interventions and longitudinal follow-up. Such an approach shifts microbiome research from associative observations toward actionable, individualized dietary recommendations.

5.1 Data source and integration

The simple way to obtain big data is by using large sample sizes in cross-sectional studies or cohort studies. This allows for higher variability in data, thereby allowing for more robust statistical analyses and more accurate conclusions. Meanwhile, multi-dimensional data can be collected from each sample, such as information on the gut microbiome, diet, and individual phenotype, which are the focus of this review. Other data, such as metabolomics, lifestyle habits, medication use (especially antibiotics), exercise, psychological stress, and sleep quality, can also be combined. Adding new data sources may reveal previously unrecognized determinants that account for observed response variability^[587]. The comprehensive data collection is essential for creating a detailed health profile for each individual.

There are several data types in gut microbiota, including composition, diversity, genes, functions, metabolism, and enterotype, which are mainly obtained with multi-omics technologies. Identifying microorganisms, genes, and metabolites offers a holistic assessment of both nutritional consumption and physiological status. In addition, gut microenvironmental factors that profoundly influence the gut microbiota can also be taken into consideration. Similarly, dietary intake data can also be represented in different ways, such as nutrient content, energy, food type, digestive index, and diet patterns. Conventional dietary investigation methods, such as food frequency questionnaires, diet records, and recalls, are extensively applied in nutritional studies^[588]. These assessment approaches exhibit inherent limitations due to inaccurate reporting of dietary intake, and the results are influenced by individual characteristics such as age, gender, and body mass index (BMI)^[589]. Therefore, these methods offer limited precision in quantifying dietary intake and impose a significant participant burden. Emerging mobile technologies incorporating image-based meal quantification, wearable nutrient sensors, and barcode scanning capabilities could enable more accurate, real-time dietary monitoring with improved user experience^[41]. Precise, objective dietary assessment in free-living populations continues to present significant methodological challenges for nutritional science, and the intricate dietary pattern, combined with substantial intra-individual daily variation, creates significant challenges for precise nutritional quantification. Food nutrition composition database is another form of dietary data, such as the USDA National Nutrient Database^[444], AI4FoodDB^[590], and FOODB^[591], which can be used for building recommender systems. As for diseases and phenotypes, i.e., clinical data, their physiological and biochemical indicators depend on specific ones. Anthropometric data include weight, height, BMI, and body fat rate. These data could be used to develop personalized dietary response prediction models and dietary

recommendation models to improve gut microbiota homeostasis and enhance the overall outcomes of individuals. However, expanded data requirements will impose a burden on the participants, so understanding what information helps and what does not is important during the process of data collection.

Isolated analysis of individual datasets yields fragmentary biological insights, failing to capture critical mechanistic pathways and dynamic interactions. On the contrary, integrating diverse, large-scale datasets enables a more holistic understanding of complex biological processes at multiple levels, which enables the identification of key driving factors, facilitating the development of prediction models and nutritional intervention strategies. In summary, large cohorts with multidimensional and longitudinal analyses are needed to understand and implement precision nutrition. AI algorithms enable the integration of multi-scale individual characteristics spanning molecular profiles to population-level clinical data, which supports virtual screening of nutritional strategies through predictive simulation and allows for pre-clinical efficacy assessment.

5.2 Data mining with machine learning

Data mining is a process of employing computational algorithms and modeling technologies to extract meaningful patterns, correlations, and structural insights from extensive datasets. Conventional statistical methods suffice for examining individual biomarkers but lack the capacity to model complex diet-omics interactions. Machine learning, a subset of AI, offers powerful tools for data-driven analysis, enabling the integration of multi-omics data, diet data, and clinical information. It aims to detect data patterns and generate predictive models based on mathematical relationships between features and targets from the given dataset, which enables the development of predictive models for personalized dietary recommendations in precision nutrition. The general steps in a machine learning process include data collection, data cleaning, feature engineering, model building, evaluating the model, and deployment.

Data cleaning involves removing noise and errors from data, ensuring that the data is accurate, consistent, and complete for modeling. Containing erroneous data may cause machine learning algorithms to learn from artifactual patterns, potentially yielding invalid predictions. Gut microbiota raw sequence data need to undergo a series of processing steps to be transferred into taxonomic composition tables. Some machine learning algorithms cannot handle non-numerical data directly, which need to be converted into numerical formats, i.e., feature encoding.

Feature engineering involves extracting meaningful features from data or transforming existing features to improve the predictive power of a model. In-depth knowledge of input data characteristics is fundamental to both of the validity of selected features and result interpretation. The transformation of raw data into model-ready formats constitutes the complex stage in building predictive models. Part of the raw data contains non-informative or duplicative elements that lack predictive utility, which will increase the noise that potentially leads to inaccurate or unreliable predictions. Eliminating redundant and irrelevant features will reduce computational complexity and errors in the models. Data exploration and visualization can help to discover these redundancies, such as descriptive statistics, boxplots, scatterplots, and correlation heatmaps. Feature selection methods are also employed to remove redundant and non-informative features. Numerous robust

feature selection algorithms have been established, such as principal component analysis (PCA), and recursive feature elimination (RFE). Multiple methods should be applied to select features. Machine learning algorithms employ feature importance metrics to evaluate and rank variables based on their predictive influence within models. Feature importance methods provide useful insights into understanding the data-generating process under certain conditions^[592] and finding the potential biomarkers.

Features with the greatest impact on the prediction output are analyzed by the algorithms to create prediction models. There are numerous machine learning prediction algorithms, which can be broadly split into 4 types based on learning paradigms, including supervised, unsupervised, semi-supervised, and reinforcement learning (Table 3). Algorithm selection should be guided by both dataset characteristics and specific research objectives. Additionally, these algorithms have been well established in R packages and Python libraries that are easy to carry out.

Table 3. Different machine learning paradigms and algorithms.

paradigms	Description	Tasks	Algorithms	Key Points
Supervised Learning	Learns a mapping function between the input and the outputs from labeled data.	Classification	Logistic Regression, K-Nearest Neighbors, Decision Trees, Support Vector Machine, Random Forests, Naive Bayes, Neural Networks	Highly dependent on data quality; prone to overfitting
		Regression	Linear Regression, Decision Trees Regression, Support Vector Regression, Neural Networks Regression	
Unsupervised Learning	Discovers hidden structures or patterns in unlabeled data.	Clustering	K-means, Hierarchical Clustering, Gaussian Mixture Model, Spectral Clustering, DBSCAN	Results are less interpretable; used for exploratory analysis
		Association	Apriori, FP-Growth, Eclat	
		Dimensionality Reduction	PCA, ICA, t-SNE, UMAP, MDS	
Semi-Supervised Learning	Combines supervised and unsupervised learning by using labeled and unlabeled data.	Classification, Regression, Clustering, Dimensionality Reduction	Self-Training, Co-Training, Label Propagation, Semi-Supervised GAN, Semi-Supervised VAE	Reduces labeling effort; improves generalization
Reinforcement Learning	Agents learn optimal policies by interacting with an environment to maximize cumulative rewards.	Decision making	Q-learning, R-learning, TD-learning, Deep Q Network	Delayed rewards; balances exploration and exploitation

Supervised learning algorithms establish predictive relationships between input variables and specified known target outcomes. Some algorithms are designed exclusively for continuous variables and are

incompatible with categorical inputs. Some methods, such as decision trees, allow both categorical and continuous inputs. Depending on the type of target variable, supervised machine learning can be further divided into classification tasks (discrete values, usually categories or labels) and regression tasks (continuous values, usually real numbers), which can be converted into each other by segmenting or mapping the target variable. The availability of annotated labels enables supervised methods to learn effectively from less data compared to unsupervised techniques that must discover patterns independently. In precision nutrition applications, supervised algorithms can be utilized to 1) assess the risk of chronic disease; 2) predict gut microbiota responses to diets; 3) forecast health outcome responses to diet; 4) predict dietary plans for individuals. For example, supervised learning algorithms leverage labeled training data to learn patterns and relationships between metabolomics data and dietary outcomes. These algorithms can predict individual responses to dietary interventions, discover metabolic biomarkers linked to specific dietary patterns or health conditions, and stratify individuals based on their metabolic phenotypes.

Since no target labels are available, unsupervised learning algorithms identify relationships exclusively from characteristics of input features. Instead, the goal is to reveal hidden relations and patterns within the data with methods such as clustering. In precision nutrition, unsupervised learning algorithms are mainly applied to group individuals based on their health and dietary data, categorize foods into different groups based on their nutritional content, and detect unusual patterns in nutrition-related data. For example, unsupervised learning can be used to identify patterns and group individuals based on their dietary and biological characteristics without pre-defined labels, allowing researchers to discover hidden subgroups within a population and generate new hypotheses. Examining these groups may show that individuals consume distinct dietary patterns. Upon further analysis, we might discover that the dietary patterns are associated with metabolic syndrome. Unsupervised clustering techniques can categorize biosensor data (e.g., heart rate, blood glucose, oxygen saturation) from wearables, enabling real-time health monitoring, detection of disease progression patterns, and tailored therapeutic strategies.

Reinforcement learning can optimize personalized dietary recommendations by incorporating reward signals from either nutritionist evaluations or user feedback, enabling adaptive lifestyle suggestions. Deep learning employs multi-layered artificial neural networks, biologically inspired by human cognition, to perform sophisticated analysis of high-dimensional data, which can be applied across the above learning paradigm. Such networks exhibit inherent feature extraction capabilities, enabling optimal performance when processing complex, multidimensional datasets.

Algorithm performance is critically determined by factors, including training data quality, dataset size, and specific research objectives. Machine learning modeling practices indicate that multiple algorithms need to be tried, and comparisons of their performance need to be made, which allows us to identify which model works best for specific datasets.

Machine learning applications frequently require balancing model precision with explanatory transparency. Many models exhibit substantial complexity that obscures their decision-making processes,

which are often described as “black boxes”. Although such models demonstrate predictive capability, they often fail to elucidate the biological pathways linking dietary factors, gut microbiota, and disease etiology. The reduced explanatory capacity impedes translation of model outputs into actionable dietary guidance. Explainable AI techniques enable the identification of key predictive drivers within complex models. For instance, feature importance analysis enables researchers to quantify and rank variables by their relative contribution to model predictions, which can facilitate the discovery of biomarkers and candidate intervention targets. SHAP (SHapley Additive exPlanations) is a method to explain individual predictions[593,594]. An alternative strategy involves constructing intrinsically interpretable models. Conventional machine learning approaches (e.g., decision trees, random forests) offer two key advantages: 1) intrinsic feature importance quantification and 2) superior interpretability compared to deep neural networks, particularly with limited training data. The reduced complexity and enhanced interpretability of these models facilitate mechanistic understanding of the interplay among intestinal microbes, diet, and disease. In summary, while predictive accuracy represents a crucial performance metric, the interpretability and generalizability also should be taken into account in machine learning. To advance our comprehension of gut microbiome-diet-disease interactions, developing biologically interpretable models is required, which can accelerate progress toward precision nutrition.

Specifically, mechanistic insights derived from studies of microbial metabolism, and diet–microbiome–host interactions provide the biological foundation for understanding individualized dietary responses. These mechanistic principles are increasingly complemented by data-driven approaches that leverage large-scale datasets, longitudinal cohort studies, and machine learning algorithms to identify patterns, generate predictive models, and stratify individuals based on microbiome-related features. Besides, mechanistic insights further enhance model robustness and biological relevance. Importantly, the integration of these two dimensions enables translational nutrition strategies that move beyond descriptive associations toward actionable, personalized dietary interventions, with potential applications in disease prevention, risk stratification, and therapeutic optimization (Table 4).

Table 4. Applications of machine learning in precision nutrition based on gut microbiota.

Scenario	Underlying Principle	Machine Learning Objective	Precision Nutrition Strategy	Reference
Disease diagnosis	Associations between gut microbiota and disease	Predict disease presence and severity	Identify potential diagnostic biomarkers or dietary intervention targets	[595–597]
Disease prevention and risk assessment	Associations between gut microbiota and physiological disease indicators; Associations between gut microbiota and dietary metabolism; Associations between dietary metabolism and physiological disease indicators	Predict individual disease susceptibility and risk level; Predict the rationality of dietary structure; predict individual metabolic phenotypes; Predict physiological indicators following dietary interventions	Personalized dietary recommendations from a dietary perspective to reduce disease risk; Personalized dietary recommendations from a microbiota perspective to modulate gut microbial profiles and reduce disease risk	[598,599]
Disease treatment and management	Associations between gut microbiota and physiological disease indicators; Associations between gut microbiota and dietary metabolism; Associations between dietary metabolism and physiological disease indicators	Predict the impact of dietary interventions on disease treatment and management processes; Identify responders and non-responders	Develop personalized dietary recommendations for responders and non-responders	[571,600,601] [602]
Targeted modulation of gut microbiota	Associations between gut microbiota and dietary metabolism	Predict microbial community structure and metabolic responses to dietary interventions	Personalized dietary recommendations to enable targeted modulation of the gut microbiota	[577–579]

Overall, leveraging big data and AI to integrate diet, gut microbiota, and disease context provides a translational framework for precision nutrition. This strategy has the potential not only to elucidate generalizable principles underlying host–microbe–diet interactions across diverse populations, thereby improving the interpretability and predictive power of microbiome-based models, but also to improve disease prevention and management.

5.3 Current and potential applications

The common applications of machine learning algorithms in medicine and nutrition include biomarker identification, pattern recognition, predictive model development, and recommendations to optimize health outcomes.

At present, the scientific community reports multiple microbial biomarker candidates each year, but the main concern about transferring them into clinical practice involves the validation of analytical methods (accuracy, precision, specificity, range, and robustness) and demonstration of clinical relevance^[603]. The first scenario is to directly utilize disease labels, gut microbiota data, and machine learning to construct classification models for accurate diagnosis, identifying key microbial biomarkers and potential therapeutic targets. Zheng et al. utilize 10 gut microbiota species for UC and 9 gut microbiota species for CD to construct diagnostic models. The diagnostic models demonstrated high discriminative power ($AUC > 0.90$) for IBD detection in the discovery cohort, with robust performance maintained across eight ethnically diverse validation populations^[596]. Ferreira et al. discovered distinct gut microbial signatures linked to preclinical AD. Incorporating these microbial markers enhanced machine learning model performance, boosting prediction accuracy, sensitivity, and specificity for early-stage AD detection^[597]. Lee et al. conducted a comprehensive cross-cohort assessment of gut microbiome-derived machine learning classifiers across twenty distinct disease conditions from 69 projects; and the models achieved more robust performance in gastrointestinal diseases than other diseases^[595]. These studies revealed the potential of using gut microbe characteristics to construct models for diagnosing diseases. Despite the desire to elucidate the mechanisms of specific bacteria in diseases, it is difficult to use a single strain as a biomarker for disease diagnosis or risk assessment. In fact, the models constructed with AI algorithms are more inclined to pattern recognition. The diagnostic models can be further transformed into tools for risk assessment through probability interpretation or risk scoring based on features^[598]. The second scenario is to link physiological indicators with gut microbiota to reveal susceptibility and severity, such as BMI and blood glucose, which emphasize disease risk assessment and prevention. Through integration of microbiome-derived biomarkers associated with health perturbations, we could systematically analyze health status and the impact of environmental parameters and individual behavior on health. This may advance our comprehension of disease pathogenesis, associated risk factors, and preventive approaches, potentially enhancing public health.

Except for disease diagnosis and risk assessment, the combination of machine learning and gut microbiome is also a path to personalized health management. Gut microbiome information can be utilized to investigate the physiological and pathological reactions to diets, which facilitate to formulate customized dietary guidance through identifying microbial features linked to health outcomes coupled with diet.

Two primary strategies could be applied in designing personalized dietary interventions based on gut microbiota and diets. The first strategy focuses on determining key relationships between host metabolic attributes and intestinal microbes, which is prior knowledge. One of the classic examples is the variation between meat consumers and excluders in the production of TMAO, a microbial metabolite associated with

cardiovascular complications, following ingestion of L-carnitine^[227]. A random forest classification model based on gut microbiome information was developed to predict TMAO-producing phenotypes^[604]. Based on these findings, individuals exhibiting elevated blood TMAO concentrations and harboring TMAO-producing gut bacteria may benefit from dietary interventions limiting TMAO precursor intake. Another example is that heterogeneity in response to fiber interventions can be attributed to interindividual variations in gut microbial composition. By integrating knowledge of fiber metabolism with machine learning algorithms, it is possible to a priori identify responders and non-responders to fiber interventions^[605], while also predicting subsequent SCFA production levels^[606]. The ideal strategy for personalized nutrition development involves utilizing evidence-based predictive models of individual responses to specific dietary interventions. However, this dietary personalization strategy may be restricted to controlling simple and a few traits, because the knowledge of the metabolic pathways through which gut microbiota utilize diet to produce beneficial/harmful metabolites is limited.

Another strategy is to use AI algorithms to train models that forecast the impacts of specific diets on individual physiology, and the data derives from clinical features, microbial features, and individual physiological reactions to diets. Unlike the first strategy, this method does not require prior mechanistic knowledge of the interaction among intestinal microbiota, diet, and individual physiology. However, it emphasizes the observation of different physiological responses to the same diet intervention, which is potentially related to host health outcomes. Notably, this is both an advantage and a disadvantage. On the one hand, this strategy, in theory, is an exploratory application and is feasible for any measurable biological parameters; on the other hand, as the complexity of the model increases, the interpretability of machine learning algorithms deteriorates, which hinders biologists from discovering mechanisms and the factors responsible for the model's output^[607].

The second strategy has been widely explored in predicting postprandial glycemic responses after interindividual variability was observed. An example is the illustration of the impact of gut microbiota on personalized dietary responses to artificial sweeteners. Furthermore, machine learning models using baseline microbiome data successfully predicted individual glycemic responses to saccharin^[542]. But there is controversy over the use of excessive doses of artificial sweeteners in the study. Similarly, glycemic response varied notably across different bread types, and the bread triggering a higher glycemic response in every individual can be forecasted just from gut microbial information prior to dietary intervention^[608]. A landmark work was conducted by Zeevi et al.^[38]. By continuous monitoring of glucose levels in a large cohort, they found substantial inter-individual variation in glycemic response to the same diet. Furthermore, a gradient boosting regression model was devised that achieved precise forecasting of meal-induced glucose fluctuations through multimodal integration of nutritional patterns, anthropometrics, and microbial profiles. Based on this model, individually tailored dietary advice significantly lower postprandial responses for a new group of 26 individuals^[38]. This study also revealed that dietary carbohydrate intake accounts for merely 15% of glycemic response variation, whereas models integrating clinical and microbial features achieve 50% explanatory power.

Besides, two randomized crossover trials show that a personalized postprandial-targeting diet relying on the ML algorithm led to significantly greater improvements in glycemic measures compared to a Mediterranean-style diet for prediabetes^[609] and newly diagnosed T2DM^[610], providing evidence for the clinical effectiveness of this approach. This personalized method for prediction of postprandial blood glucose fluctuations to diets was further confirmed in a non-diabetic cohort study^[611], and results show that the personalized predictive model that incorporates individual factors, including the gut microbiome, alongside food characteristics, presents superior predictive power than conventional dietary methods that rely solely on caloric or carbohydrate quantities. Likewise, the Personalised REsponses to Dietary Composition Trial (PREDICT) 1, a study cohort involving over 1,000 healthy UK individuals, revealed substantial interindividual variability in postprandial blood sugar, triglyceride, and insulin responses to identical diets. A machine-learning model was developed using multi-omics data to predict both triglyceride and glycemic responses^[612]. Person-specific factors, including the gut microbiome, influenced postprandial lipemia more than meal macronutrients, whereas postprandial glycemia was less affected; genetic variants had only a modest impact on predictions. Schüssler-Fiorenza Rose et al. developed predictive models for insulin resistance and oral glucose tolerance test based on multi-omics measurements^[613].

The successful in developing microbiota-based personalized diets managing blood glucose levels have also brought insights and applications to other health management fields. Baseline gut microbiota proved to be the strongest predictor of individual weight loss trajectories, surpassing other factors. Incorporating intestinal microbe signatures can enhance the predictive accuracy of the gradient boosting regression model to predict weight loss outcomes after dietary intervention^[614]. Random forest models integrating multi-omics data showed that the most predictive weight loss models incorporated diet features, gut microbiota, and urine metabolites, outperforming models based solely on diet^[601]. These results indicate that more personalized nutrition strategies have the potential to improve individual health^[615]. The beneficial effects of dietary treatment for IBD were also reflected in the intestinal microbiota structure. Nichols et al. used a random forest model to investigate the influence of baseline factors on exclusive enteral nutrition response, and found that gut metabolome and microbes signatures could serve as predictors of exclusive enteral nutrition response^[600]. Resorting to machine learning algorithms to develop prediction models based on clinical parameters, intestinal microbiome profiles, and metabolic signatures could also be an effective approach for achieving precision dietary restriction intervention for anti-aging^[602]. A longitudinal investigation tracked gut microbiota composition, host phenotypic characteristics, and plasma metabolomic profiles in 338 participants across a 4-year period. Analysis revealed that dynamic taxa (e.g., *Lachnospiraceae bacterium*, *Blautia obeum*, *Collinsella spp.*) correlated with metabolite-mediated phenotypic variations. In addition, deep neural networks show optimal accuracy for predicting the host's age based on intestinal microbial signatures^[616]. Therefore, the gut microbiota and metabolites can serve as host fingerprints employed to build models and discern the potentially effective individuals for the dietary restriction intervention.

Leveraging machine learning algorithms to analyze critical factors and create a prediction model with

big data could be a well practice in precise nutrition. This approach paves the way for designing more effective recommendations of diets and preventive strategies customized to individual gut microbiota profiles. These studies support that the integration of biological information, including genetic, epigenetic, metabolomic, gut microbiota data, and AI algorithms, could be critical in the development of data-driven precision nutrition. It is noteworthy that these studies primarily focused on individual responses to short-term diet interventions. While results for long-term interventions remain limited, the predictive potential of the intestinal microbes is becoming increasingly obvious. Personalized health management based on gut microbiota still needs further exploration in other diseases, particularly in chronic diseases, because the etiology of chronic diseases is often multifactorial, and gut microbiota and diet are the key factors. To transfer these precise strategies into healthcare practices, we should thoroughly understand why individuals respond differently to the same diet, whether the differential responses and phenotypes persist over time, and the degree to which the developed algorithms and models are reproducible.

6. Challenges and outlook

It is well acknowledged that the gut microbiota is closely related to host health in microbial ecology. Accumulating evidence, including findings from both animal and human studies, reveals that microbiota affects susceptibility to diseases in observational and interventional designs. The gut microbiota is also recognized as an important intermediary role in diet and human health. Modulating the intestinal microbes with diet to improve health is an easily accepted, implemented, and safe approach for the general public. Therefore, targeting or leveraging the gut microbiota as a mediator holds promise for achieving precise diet-based health management. However, several challenges remain to be addressed.

The causal relationship between gut microbiota and diseases is largely unclear. Advances in culture-independent sequencing and bioinformatics have enabled most gut microbiome research to focus on microbial community shifts linked to disease. While this has generated extensive associative data, it offers limited insight into causality. A correlation does not necessarily imply causation, and evidence of causality usually requires several experimental methods, such as FMT, and clinical randomized controlled trials (RCT), which are expensive, time-consuming, laborious, and present ethical challenges^[601]. It seems to be difficult to define pathogenic bacterial strains or communities in gut microbiota-related diseases. Jumping out from taxonomic groups and analyzing from the perspective of functional groups may be another way. Coupling multi-omics technologies with the isolation, cultivation, and functional analyses of gut microbiota will help to move beyond associations to understand how gut microbes regulate health and disease. Although causal discovery in observational microbiome data faces many challenges, Recent progress in causal structure learning methods enhances data-driven causal inference capabilities between the microbiota and diseases, such as causal network modeling, structural equation modeling, and mediation analysis[617–620]. Besides, Mendelian randomization (MR) has been employed to investigate the relation between the intestinal microbes and related diseases in recent years[621,622]. However, a key challenge in applying MR to microbiome studies is the inconsistent replication of host genetic variants linked to gut microbiota across different studies. Those studies

currently lack well-validated genetic markers linked to gut microbiome composition, and the biological pathways through which host genetics influence microbial traits remain poorly understood. In fact, environmental factors exert substantially stronger influence on gut microbiome composition than host genetics. This indicates larger cohorts and collaborative consortia are required to achieve sufficient statistical power in MR analyses examining causal relationships of the gut microbiome on disease. The gut microbiota is impacted by many factors; thus, large-scale longitudinal investigations are required to accurately reflect the association and causal relationship between gut microbiota and health. This is also helpful in validating the predictive power of microbiome-based models. The intestinal microbes may be one of the factors contributing to various diseases, or may primarily exacerbate rather than initiate disease. Of note, this was observed in ZAP70 mutated mice model that is used to simulate human SLE^[623]. Therefore, it is significant to assess and quantify the importance and proportion of gut microbiota in diseases^[624]. For example, multi-omics data from large clinical plasma samples indicate that diet and microbiota play a prominent role in shaping metabolic health compared to genetics^[625]. To take a step back, the strong correlation between intestinal microbes and diseases can still be leveraged in predictive modeling though the mechanisms remains unclear.

The gut microbiota acts as a target that diet can directly influence, which in turn generates crucial bioactive compounds that modulate the host's health. However, the causal relationship issue makes it difficult to further identify gut microbiota targets for dietary intervention. The gut microbiota remained an underexplored target for developing innovative diagnostic, therapeutic, and preventive strategies. Existing knowledge of diet-microbe-host relationships remains insufficient to clearly distinguish between health-promoting and harmful gut microbial species, and it seems too oversimplified to divide bacteria into probiotics, harmful, neutral, and conditional pathogenic bacteria. Meanwhile, given the extensive cross-feeding networks among gut bacteria, physiological benefits likely emerge from complex microbial consortia rather than isolated species. Moreover, no standardized criteria currently exist for characterizing a normal gut microbiota regarding its taxonomic diversity and metabolism, nor the specific attributes that identify dysbiotic states, though attempts have already been made in this aspect^[626,627]. Notably, high species richness and diversity are insufficient criteria for assessing gut microbial health due to individual variability and functional redundancy in intestinal microbiota. The functional group may be another potential target compared to taxonomic groups. Studies demonstrate that bacterial abundance poorly predicts functional significance, as both dominant and rare taxa contribute to host physiology. The intestinal microbiome demonstrates considerable taxonomic diversity coupled with metabolic redundancy; microbial communities with distinct compositions may exhibit functional overlap, producing comparable protein and metabolite profiles. These findings are essential for developing microbiota-targeted therapies. Big data and AI algorithms can identify biomarkers and recognize patterns in the taxonomic and functional profile of gut microbes. These biomarkers and patterns may contain potential causal relationships and can further serve as targets or directions for gut microbiome modulation. Moreover, the computational approaches for causal inference can also provide potential modulation targets and help to construct clinical prediction models^[628,629].

In addition, effective and precise strategies to modulate gut microbiota have not yet been developed for the prevention and supportive treatment of diseases, though there are interventions targeting gut microbiota such as diet, probiotics, prebiotics, synbiotics, postbiotics, pharmabiotics, and FMT. It is easy to detect changes in the structure of gut microbiota resulting from interventions, but there is no information quantifying the extent to which these changes contribute to end-products of microbiota metabolism and how these changes are linked to health physiology^[401]. In addition, the composition of the food matrix is complex, and other active ingredients, aside from nutrients, may also impact the gut microbiota. Moreover, there are potential synergistic or antagonistic effects between these components^[469,630]. The dynamic factors in the food digestion process, as well as the timing of meals, also need to be considered. Dietary interventions induce temporary gut microbial changes, but whether prolonged dietary modifications can lead to lasting alterations remains uncertain. In the context of individual differences, the host and gut microbiota's response to the same interventions also exhibits personalization. Emerging evidence suggests that baseline microbial composition critically influences the final gut microbiome outcomes as well as the impact of diet^[39,631,632], which may help explain the inconsistency and poor reproducibility of gut microbiota intervention studies. But few studies explored the mechanisms behind personalized factors. Therefore, it is necessary to include individual data and establish the dose-response and structure-activity relationship of dietary components in randomized controlled trials in order to achieve predictable and precise personalized interventions. For example, the consumption of fiber induces distinct biochemical responses and microbial shifts linked to its degradation^[633], a recent study also revealed significant variability across individuals in microbiota reactions to different dietary fibers^[634], and the genome analysis enables prediction of microbial fiber degradation capabilities^[635]. Thus, recommending suitable types and amounts of dietary fiber could be based on gut microbiota. Developing predictive models based on diet and gut microbiota data holds promise for precise gut microbiota regulation, but extensive datasets and experimental validation are required. In the future, more sophisticated techniques for modulating the microbiota could appear, including precisely targeted microbial colonization/elimination techniques and novel functional modulation strategies.

The gut microbiota is an important mediator, and the influences of diet on host metabolism partially depend on the intestinal microbes, which not only reveal the limitations of universal nutritional interventions but also highlighting the necessity of personalized interventions. Novel mediation analysis approaches for microbiome data have emerged recently to test the mediated effects of environmental and host factors mediated by gut microbiota^[620]. Such investigations could reveal microbial contributions to disease mechanisms and health maintenance, potentially enabling microbiome-based and diet-based clinical interventions with a clear and sensible causal path. Chen et al. carried out a mediation analysis and found that microbial-derived metabolites may mediate the gut microbiome's impact on cardiometabolic function^[114]. In addition, machine learning and causal inference have been used to evaluate the importance of intestinal microbes and metabolites in the classification of neonatal jaundice and potential causal relationships^[629]. During the implementation of precision nutrition, gut microbiota may undergo changes, so it is necessary to

continuously monitor and evaluate it to adjust nutritional strategies accordingly, rather than only using baseline data.

Clinical evidence from interventions such as probiotics, prebiotics, synbiotics, postbiotics, FMT, and next-generation microbial therapeutics demonstrates that modulating the gut ecosystem can meaningfully influence metabolic, inflammatory, and immune outcomes. These therapies highlight the feasibility of reshaping microbial functions—such as SCFA production, BA metabolism, or mucosal barrier regulation—which are also key pathways through which diet exerts its effects. Integrating insights from these clinical interventions into precision nutrition frameworks may enable more targeted dietary designs, in which specific foods or nutrients are chosen to support beneficial microbial functions already shown to be therapeutically relevant. Moreover, understanding patient-specific factors that determine responsiveness to microbiota-directed therapies, including baseline microbial composition and functional potential, can guide the personalization of nutritional strategies to maximize efficacy and minimize adverse effects. Ultimately, bridging microbiota-targeted therapeutics with precision nutrition offers an opportunity to move from generalized dietary recommendations to mechanistically informed, patient-tailored interventions that improve clinical outcomes.

Precision nutrition strategies built on the interplay among the gut microbiome, diet, and disease will be reflected in several scenarios (Table 4). For example, microbiome profiling can guide personalized dietary interventions for obesity and type 2 diabetes—such as increasing fermentable fibers to enhance short-chain fatty acid-producing bacteria and improve metabolic homeostasis. Individuals with a high microbial capacity for TMAO production may benefit from tailored reductions in choline- and carnitine-rich foods to lower cardiovascular risk. In IBD, characteristic dysbiosis can inform individualized exclusion or enrichment diets, combined with targeted prebiotics or postbiotics to modulate inflammatory pathways. For people with food intolerances or post-antibiotic dysbiosis, identifying specific deficits in carbohydrate-fermenting microbes can support customized low-FODMAP plans and structured microbiome restoration. In oncology, microbial signatures associated with immunotherapy responses may be used to design high-fiber or polyphenol-rich dietary strategies that enhance treatment efficacy. Additionally, in healthy aging, longitudinal monitoring of microbiome changes can guide personalized diets that restore beneficial taxa, reduce inflammation, and strengthen metabolic resilience. Together, these scenarios highlight the translational potential of precision nutrition in disease management, therapeutic support, and long-term health maintenance.

Big data research provides new avenues for personalized nutrition, but in current practice, the lack of large-scale, high-quality data on diverse populations and diets may still restrict its robust application. In addition to the dataset, advanced statistical and modeling methods are needed to adjust for potential confounders and sort out the importance of different factors. We should also admit that personalized dietary response likely involves complex multifactorial interactions beyond simple microbial characteristics, including genetics, epigenetics, habitual, environmental, and clinical factors, which also provides valuable insights for developing successful personalized diets. The challenge is how to integrate these data and identify

key individual parameters and further translate them into clinical practice.

Personalized nutritional services for targeted individuals, such as those with obesity, diabetes, and gastrointestinal diseases, hold promising commercial potential. A growing number of companies now provide personalized nutrition services. However, major questions remain regarding the inadequate scientific evidence and clinical validation of current commercial claims. Further exploration of the molecular mechanisms of cross-talk between the microbiota, host, and diet is pivotal for advancing personalized nutrition strategies. As personalized nutrition heavily relies on data, ethical concerns and privacy issues need to be addressed. There is a need to create and adhere to regulatory frameworks for the collection, use, and protection of data in the context of personalized nutrition.

Despite current limitations, gut microbiota holds great promise for personalized and precision nutrition, and current management systems is required to utilize artificial intelligence technologies that incorporates microbiome, diet, and clinical data, which is expected to improve our understanding of the complex interactions among diet, gut microbiota and host; and further to explore the potential applications. Developing a model that describes the regulation of energy and nutrition metabolism, intestinal function, and their relationship with human health and diseases from a global perspective can help effectively regulate metabolism in diseases and assist in disease intervention and treatment for different populations.

Conflict of interest

The authors report there are no competing interests to declare.

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