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The human microbiome and its role in health and disease

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Summary

The human microbiome encompasses trillions of microorganisms, including bacteria, archaea, fungi, viruses, and protozoa, colonizing virtually every body surface. These communities contribute to digestion, immune regulation, metabolic homeostasis, and protection against pathogens. Disruption of microbial balance, termed dysbiosis, is associated with conditions spanning gastrointestinal, metabolic, neurological, psychiatric, immune-mediated, cardiovascular, and renal diseases. This narrative review synthesizes current evidence on microbiome composition, function, and clinical significance across health and disease. We address early-life microbiome establishment, site-specific microbial communities, and mechanisms linking microbial imbalance to disease pathogenesis, including the gut-brain, gut-skin, and gut-kidney axes. We distinguish microbial associations from causal relationships, acknowledge research limitations, and outline emerging therapeutic strategies, including probiotics, prebiotics, Fecal Microbiota Transplantation (FMT), and precision microbiome-based medicine. Future research should prioritize longitudinal multi-omics studies, diverse population sampling, and standardized methodologies.

Key words: disease, dysbiosis, fecal microbiota transplantation, gut-brain axis, human health, microbiome, microbiota, short-chain fatty acids.

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Introduction

The human body harbors an estimated 37 trillion human cells alongside an approximately equal number of microorganisms, collectively termed the microbiome [100]. These organisms colonize the gastrointestinal tract, skin, oral cavity, respiratory mucosa, and urogenital tract [32,38]. For much of medical history, microorganisms were regarded primarily as agents of disease, and commensal microbes received comparatively little scientific attention [2,79].

This view changed fundamentally in the late twentieth and early twenty-first centuries with the advent of culture-independent molecular techniques. The development of 16S ribosomal RNA (rRNA) gene sequencing enabled species identification directly from clinical samples, overcoming the limitation that most gut microbes are not cultivable under standard conditions [55,57,89]. Subsequent advances in whole-genome metagenomics, metatranscriptomics, metaproteomics, and metabolomics have provided an increasingly detailed view of both microbial identity and function [99,105]. The Human Microbiome Project (HMP), launched in 2007, catalogued microbial composition across multiple body sites in healthy individuals, establishing a foundational reference dataset and revealing substantial interpersonal variation [43,99].

The gut microbiome has emerged as the most clinically significant microbial community. It functions as a "virtual organ," contributing to digestion, vitamin synthesis, immune maturation, and pathogen resistance [61,98]. Its metabolic outputs, including Short-Chain Fatty Acids (SCFAs), secondary bile acids, and neurotransmitter precursors, influence the liver, cardiovascular system, brain, and kidneys [25,51,71]. Dysbiosis has been linked to inflammatory bowel disease, metabolic syndrome, neurological and psychiatric disorders, cardiovascular disease, autoimmune conditions, and renal disease [76,98].

Despite the volume of observational data, most microbiome-disease associations remain correlative rather than causal. Establishing causality faces methodological challenges, including inter-individual variability, dietary and lifestyle confounding, and the absence of long-term interventional studies in humans. This review synthesizes current evidence on microbiome composition and function while carefully distinguishing established correlations from demonstrated causal mechanisms, and identifies priorities for future research.

Review methodology

This narrative review searched PubMed and Google Scholar using the terms "human microbiome," "gut microbiota," "dysbiosis," "microbiome and disease," "gut-brain axis," "fecal microbiota transplantation," and related terms. Articles published in English from 2000 to 2026 were considered, prioritizing randomized controlled trials, systematic reviews, meta-analyses, and original research. Historically significant studies published before 2000 were included where relevant. Given the breadth of microbiome research, this review aims to provide a balanced synthesis of key evidence across major disease categories rather than exhaustive coverage.

Overview of the human microbiome

Joshua Lederberg defined the microbiome as the ecological community of commensal, symbiotic, and pathogenic microorganisms sharing the human body [58]. Early microbiology focused on pathogens, leaving the physiological role of commensal organisms largely unexplored [79]. As the twentieth century progressed, investigators recognized that microorganisms are essential partners in human physiology, a paradigm shift accelerated by molecular biology [24].

Culture-based techniques could identify fewer than 30% of gut microbes, severely constraining knowledge of microbial diversity [55]. Molecular methods, particularly 16S rRNA gene sequencing, transformed this picture by enabling taxonomic profiling of uncultured organisms [89]. Metagenomics extended the approach by sequencing all DNA in a sample, revealing not only microbial identity but also metabolic potential [99]. Metatranscriptomics characterizes active microbial genes, metaproteomics identifies expressed proteins, and metabolomics detects metabolites linking microbial activity to host physiology [105]. Culturomics, applying high-throughput culture conditions, has further expanded the known microbial repertoire [14]. Integration of these approaches into multi-omics frameworks now enables systems-level understanding of host-microbiome interactions [44].

Microbial diversity varies significantly by body site, reflecting local differences in pH, oxygen tension, nutrient availability, and moisture [43]. The colon harbors the largest and most dense community. Firmicutes and Bacteroidetes together constitute approximately 90% of intestinal microbial mass, with Actinobacteria, Proteobacteria, and Verrucomicrobia present in smaller proportions [4,60]. The skin microbiome is site-dependent; sebaceous regions favour *Cutibacterium acnes*, moist areas support *Staphylococcus* and *Corynebacterium*, and dry areas host more diverse communities [17]. The oral cavity harbors over 700 microbial species organized into complex biofilms [50]. Though once considered sterile, the lower respiratory tract contains low-biomass microbial communities [65]. The vaginal microbiome is dominated by *Lactobacillus* species, which maintain an acidic protective environment [78].

Functional diversity

Gut microbes are taxonomically and functionally heterogeneous, collectively contributing to digestion, immune regulation, hormone metabolism, and xenobiotic transformation. Functional redundancy, the capacity of distinct taxa to perform the same biological function, confers resilience against perturbations such as antibiotic use or dietary change [68]. Diet, age, genetics, environment, and lifestyle all shape microbial composition, and shifts in these parameters can alter host physiology in ways only beginning to be characterized [29]. Microbial metabolites entering systemic circulation influence the liver, cardiovascular system, kidneys, and brain, establishing the microbiome as a body-wide regulatory system [71].

Early-life microbiome

Microbiome establishment begins in early life and follows a developmental trajectory shaped by maternal, environmental, and postnatal factors [67]. Whether any microbial colonization occurs in the uterus remains debated; reports of microbial DNA in the placenta, amniotic fluid, and meconium have been challenged on the grounds of sampling contamination, and the functional relevance of prenatal microbial exposure is not established [1,30].

Delivery mode is among the most influential determinants of neonatal microbiome composition. Vaginally delivered infants acquire *Lactobacillus, Prevotella*, and *Sneathia* species from the maternal vaginal and fecal microbiota [34], whereas infants born by cesarean section are initially colonized by skin and hospital-derived *Staphylococcus, Corynebacterium*, and *Propionibacterium* [91]. These differences may persist for months to years. Cesarean delivery has been epidemiologically associated with higher risks of asthma, allergies, obesity, and type 1 diabetes, though causation remains tentative given the multifactorial nature of these outcomes [90].

Breastfeeding supplies both nutritional substrates and live microorganisms. Human Milk Oligosaccharides (HMOs) selectively promote *Bifidobacterium* growth in the neonatal gut [13]. Breastfed infants accordingly show microbiomes enriched in *Bifidobacterium* and *Lactobacillus,* while formula-fed infants harbor more *Clostridium* and *Enterobacteriaceae* [75]. Introduction of solid foods drives a substantial increase in microbial diversity and the gradual emergence of adult-like community structure [103].

Antibiotic exposure in early life reduces microbial diversity and causes lasting community alterations [25,54]. Animal studies demonstrate that antibiotic administration during critical developmental windows can induce obesity and metabolic dysregulation. Analogous associations have been reported in human cohort studies, though confounding remains a challenge [26]. The infant microbiome shapes immune system maturation. Germ-free animals show deficient immune development partially restored by colonization with specific microbial communities [84]. Balanced early microbial exposure promotes regulatory T-cell differentiation, strengthens mucosal immunity, and fosters immunological tolerance that reduces later susceptibility to allergic and autoimmune conditions [3,6,36].

Role in normal physiology

The gut microbiome makes indispensable contributions to host physiology. Gut microbes ferment indigestible dietary fibers into SCFAs, principally acetate, propionate, and butyrate, since humans lack enzymes to break down complex polysaccharides [35,51]. Butyrate is the primary energy source for colonocytes (absorptive epithelial cells) and exerts anti-inflammatory effects by inhibiting NF-κB signalling and promoting regulatory T-cell differentiation [37,102]. Propionate and acetate modulate liver metabolism, adipogenesis, and insulin sensitivity [27,51]. Gut microbes also transform primary bile acids into secondary forms and modulate lipid metabolism [7,81], while contributing to the synthesis of vitamin K, B-complex vitamins, folate, and biotin [9,62].

The microbiome is essential for immune system development. Microbial colonization stimulates maturation of Gut-Associated Lymphoid Tissue (GALT), regulatory T-cell expansion, and calibration of Toll-Like Receptor (TLR) signalling [5,41,66]. *Bacteroides fragilis*, for example, produces polysaccharide A, which induces IL-10-secreting regulatory T-cells and prevents excessive inflammatory responses [16]. Commensals also mediate colonization resistance through nutrient competition, bacteriocin production, and stimulation of innate immune responses [34,47,97]. Disruption of this resistance following broad-spectrum antibiotic treatment dramatically increases susceptibility to *Clostridioides difficile* [82].

The microbiome communicates with the host through diverse metabolites and signalling molecules. SCFAs stimulate the release of gut hormones, including Glucagon-Like Peptide-1 (GLP-1) and Peptide YY (PYY), regulating appetite, intestinal transit, and glucose homeostasis [27]. Microbial metabolites interact with the nervous system via the gut-brain axis, influencing mood, cognition, and

stress responsiveness through vagal afferent pathways, immune mediators, and neuroactive metabolites [28,71], underscoring the concept of the microbiome as a distributed metabolic organ whose outputs extend far beyond the intestinal lumen.

Microbiome in health

The gut communicates with the brain through bidirectional neural, immune, and endocrine pathways collectively termed the gut-brain axis [20]. SCFAs, tryptophan derivatives, and GABA precursors serve as key molecular mediators [28]. Germ-free mice display altered behavior, heightened stress responses, and impaired social interactions, partially normalized by colonization with specific bacterial strains [23,39]. In humans, gut bacteria produce GABA, serotonin precursors, and dopamine intermediates influencing central neurotransmission [94]; over 90% of the body's serotonin is synthesized in the gut, underscoring its influence on mood and mental health [72].

The microbiome regulates fat storage, insulin sensitivity, and energy balance [8]. Obesity is associated with reduced microbial diversity and an altered Firmicutes-to-Bacteroidetes ratio, though whether this reflects cause or consequence remains debated [24]. Microbiome-targeted interventions, including prebiotic supplementation, dietary fiber, and fermented foods, have shown promise in improving metabolic parameters, though effect sizes in human trials have generally been modest [31]. The skin microbiome protects against pathogen colonization through competitive exclusion and antimicrobial peptide production [69,85], while the oral microbiome maintains oral homeostasis; its disruption is causally linked to dental caries, gingivitis, and periodontitis [52,56,101].

Colonization resistance, the capacity of the resident microbiota to prevent pathogen establishment, is among the most clinically significant functions of a healthy microbiome [48]. Gut microbes inhibit *Salmonella, Clostridioides difficile*, and pathogenic *Escherichia coli* through bacteriocin production, competitive nutrient utilization, and stimulation of mucosal defences [15,86]. Probiotic supplementation has demonstrated efficacy in reducing infection risk in specific clinical contexts [73].

Microbiome in disease

Dysbiosis, characterized by loss of beneficial species, enrichment of potentially harmful taxa, or reduced diversity, is implicated in numerous diseases [21,76]. In most cases, however, the relationship between dysbiosis and disease represents a correlation rather than proven causation. Demonstrating microbial causality requires interventional evidence, such as germ-free animal colonization experiments or well-controlled clinical trials, and such evidence remains limited across many disease areas. Table 1 and Figure 1 summarize the current state of evidence.

Gastrointestinal disorders

Inflammatory Bowel Disease (IBD), encompassing Crohn's Disease (CD) and Ulcerative Colitis (UC), is among the most extensively studied microbiome-associated conditions. IBD patients consistently display reduced microbial diversity, depletion of butyrate-producing Firmicutes including *Faecalibacterium prausnitzii*, and enrichment of pathobionts such as adherent-invasive *Escherichia coli* [70,93], impairing intestinal barrier integrity

Table 1. Summary of microbiome-disease associations, evidence levels, and clinical implications.

Disease	Key microbial changes	Evidence level	Clinical implications
IBD	Low *Faecalibacterium prausnitzii*; elevated *E. coli*; low Firmicutes	High (RCTs, cohort)	FMT efficacy; dysbiosis as therapeutic target
Obesity and type 2 diabetes	Elevated Firmicutes/Bacteroidetes; low butyrate producers; elevated TMAO	Moderate (human cohorts, animal)	Microbiome modulation for metabolic control
Colorectal cancer	Elevated Fusobacterium nucleatum; elevated secondary bile acids	Moderate (case-control)	Biomarker potential; microbiome-based screening
Cardiovascular disease	Elevated TMAO producers; elevated PAGln; elevated *Enterobacteriaceae*	High (meta-analysis, cohort)	Dietary modulation; reduce red meat intake
Depression and anxiety	Low *Bifidobacterium*; low *Lactobacillus*; elevated pro-inflammatory genera	Moderate (observational, animal)	Psychobiotic interventions; ongoing FMT research
Parkinson's disease	Elevated *Enterobacteriaceae*; low SCFA producers; gut-origin alpha-synuclein	Moderate (observational)	Gut-first hypothesis; vagus nerve as pathway
Chronic kidney disease	Low *Lactobacillus*; elevated uremic toxin producers (IS, PCS, TMAO)	Moderate (cohort, animal)	Probiotics and synbiotics to reduce uremic burden
Autoimmune diseases (RA, MS, T1D)	Elevated *Prevotella copri* (RA); gut dysbiosis alters Tregs; low SCFA producers	Moderate (observational, animal)	Microbiome-based immune modulation
Skin diseases (AD, psoriasis)	Elevated *Staphylococcus aureus*; low *S. epidermidis*; gut dysbiosis via gut-skin axis	Moderate (observational)	Topical and oral microbiome therapies

IBD, Inflammatory Bowel Disease; RA, Rheumatoid Arthritis; MS, Multiple Sclerosis; T1D, Type 1 Diabetes; IS, Indoxyl Sulfate; PCS, p-Cresol Sulfate; TMAO, Trimethylamine-N-Oxide; PAGln, Phenylacetylglutamine; AD, Atopic Dermatitis; FMT, Fecal Microbiota Transplantation; SCFA, Short-Chain Fatty Acid.

and sustaining a pro-inflammatory mucosal environment. A recent randomized controlled trial of FMT for mild-to-moderate CD found that patients achieving remission in the FMT arm showed greater microbiome similarity to their donors, suggesting bacterial engraftment may be a prerequisite for efficacy [49]. Phage community profiling in UC patients undergoing FMT revealed that transplantation increases phage richness and shifts compositions toward donor profiles; responders were enriched in specific viral operational taxonomic units linked to bacteria producing vitamin B complex [63].

Irritable Bowel Syndrome (IBS) is associated with reductions in *Bifidobacterium* and increases in gas-producing taxa, which alter visceral sensitivity and gut motility [22]. Colorectal Cancer (CRC) development is influenced by *Fusobacterium nucleatum*, which is consistently enriched in CRC tumour tissue, and by secondary bile acids generated through microbial transformation of primary bile acids [12].

Metabolic disorders

Obesity, Type 2 Diabetes Mellitus (T2DM), and Non-Alcoholic Fatty Liver Disease (NAFLD) are strongly associated with microbiome alterations, though causal directionality is not fully established. Obesity is linked to an elevated Firmicutes-to-Bacteroidetes ratio and reduced microbial diversity; germ-free mice colonized with microbiota from obese donors gain more fat than those receiving lean donor microbiota [80]. T2DM is associated with reduced butyrate-producing species; SCFAs and lipopolysaccharides modulate insulin receptor signalling and systemic inflammation [19]. NAFLD involves microbial translocation across a compromised intestinal barrier to the liver, where endogenous ethanol produced by

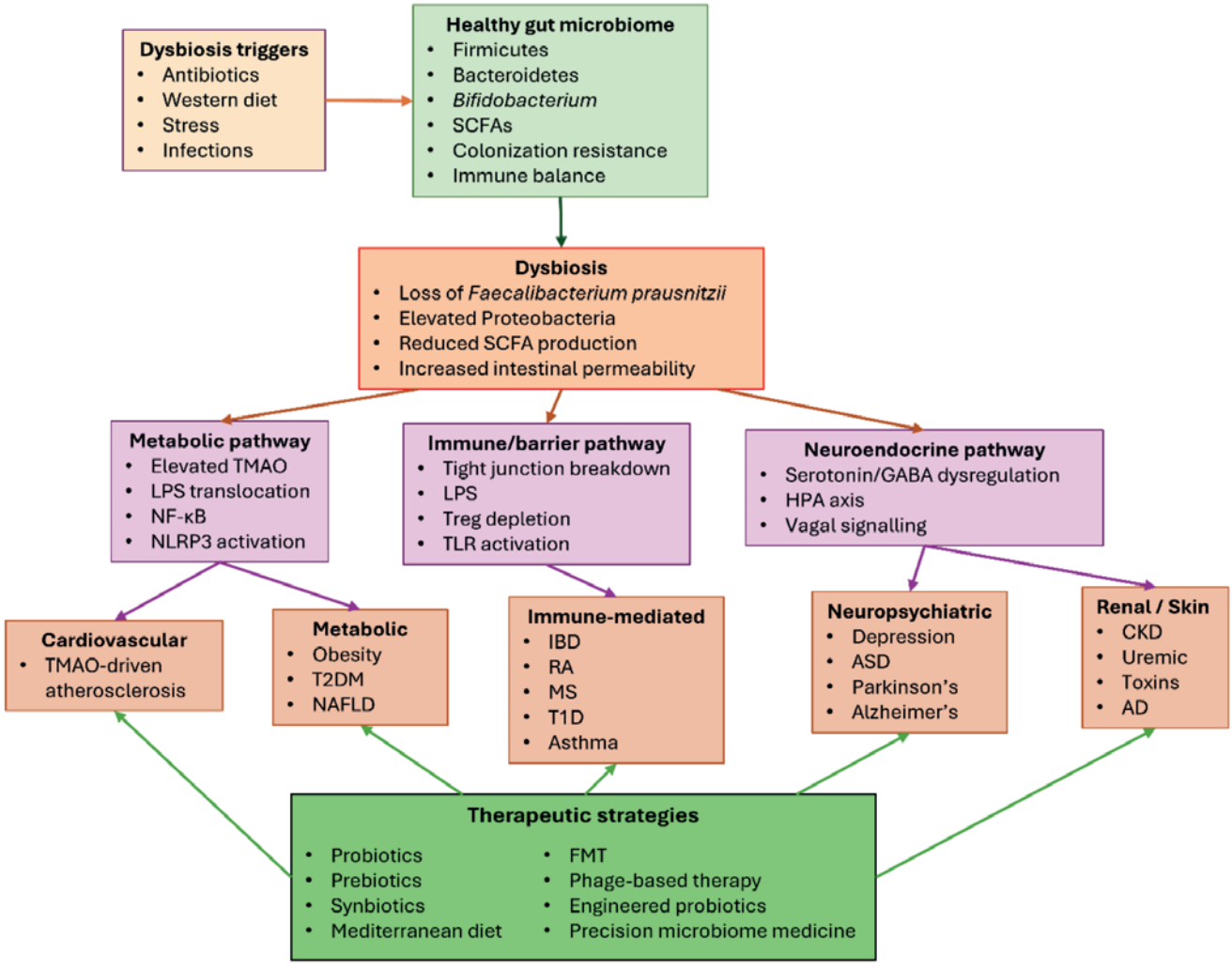

Figure 1. Mechanistic pathways linking gut microbiome dysbiosis to systemic disease. Dysbiosis triggers three overlapping core mechanisms (metabolite imbalance, immune/barrier dysfunction, and neuroendocrine dysregulation) that collectively drive cardiovascular, metabolic, immune, neuropsychiatric, renal, and skin disease. Therapeutic strategies targeting these pathways are shown at the bottom in the green box.
AD, Atopic Dermatitis; ASD, Autism Spectrum Disorder; CKD, Chronic Kidney Disease; FMT, Fecal Microbiota Transplantation; HPA, Hypothalamic-Pituitary-Adrenal; IBD, Inflammatory Bowel Disease; LPS, Lipopolysaccharide; MS, Multiple Sclerosis; NAFLD, Non-Alcoholic Fatty Liver Disease; RA, Rheumatoid Arthritis; SCFA, Short-Chain Fatty Acid; T1D, Type 1 Diabetes; T2DM, Type 2 Diabetes Mellitus; TMAO, Trimethylamine-N-Oxide.

Klebsiella strains activates hepatic inflammatory cascades [95,104]. The microbiome-oxidative stress-inflammation triad is increasingly recognized as a central mechanism linking gut dysbiosis to metabolic pathology: reactive oxygen species generated under dysbiotic conditions activate NF-κB and the NLRP3 inflammasome, amplifying cytokine-mediated organ damage [40].

Immune-mediated diseases

The early-life microbiome is critical for immune tolerance; reduced microbial diversity and exposure in infancy are associated with increased risk of allergic diseases and asthma, consistent with the hygiene hypothesis [42]. Autoimmune conditions, including Multiple Sclerosis (MS), Rheumatoid Arthritis (RA), and Type 1 Diabetes (T1D) share gut dysbiosis characterized by depletion of regulatory immune cell-promoting taxa. In MS, transplantation of MS patient microbiota into germ-free mice can precipitate autoimmune encephalomyelitis [11]. In RA, expansion of *Prevotella copri* correlates with disease activity, though whether this precedes or follows joint inflammation remains unclear [88]. In T1D, reduced microbial diversity and decreased abundance of butyrate-producing species are consistently reported in pre-clinical and newly diagnosed patients.

Neurological disorders

The gut-brain axis is increasingly implicated in neurodegenerative disease pathogenesis [71,72]. The "gut-first" hypothesis for Parkinson's Disease (PD) proposes that misfolded alpha-synuclein aggregates originate in the enteric nervous system and propagate to the brain via the vagus nerve; animal studies demonstrate that injection of alpha-synuclein fibrils into gut tissue can induce brain pathology [72,87]. PD patients display elevated *Enterobacteriaceae* and reduced butyrate-producing species, with dysbiosis severity correlating with motor symptom severity [87]. In AD, gut bacteria produce amyloid-like proteins that cross-seed with amyloid-beta, potentially accelerating protein misfolding; altered bile acid profiles and disrupted one-carbon metabolism have also been mechanistically linked to AD pathology [72]. Most evidence in human neurodegeneration remains observational, and interventional data are limited.

Psychiatric disorders

Growing evidence links gut microbiome composition to Major Depressive Disorder (MDD), anxiety disorders, and Autism Spectrum Disorder (ASD). In MDD, studies consistently report reduced microbial diversity, depletion of butyrate-producing genera including *Roseburia* and *Faecalibacterium*, and enrichment of pro-inflammatory taxa [45]. A meta-analysis of 44 studies found consistent depletion of butyrate-producing genera in patients with depression [72]. Importantly, transplantation of fecal microbiota from depressed patients into germ-free rodents induces depressive and anxiety-like behaviors, providing preclinical support for a contributory role of the microbiome in mood dysregulation [45]. Gut bacteria influence psychiatric function through the production of serotonin precursors, GABA, and BDNF-modulating metabolites; regulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis; and modulation of neuroinflammation via the vagal-immune pathway. Psychobiotic strains are under active clinical investigation, and *Lactobacillus* and *Bifidobacterium* supplementation has reduced anxiety and depression scores in several clinical trials [72]. ASD patients frequently display gut dysbiosis, and microbiome-targeted therapies have shown preliminary benefits in some studies, though larger well-controlled trials are needed [92].

Infectious diseases

The microbiome significantly modulates susceptibility to, severity of, and recovery from infectious diseases. In HIV infection, dysbiosis characterized by increased microbial translocation, elevated Lipopolysaccharide (LPS) levels, and systemic immune activation occurs early and persists in virologically suppressed patients on antiretroviral therapy, driving HIV-associated comorbidities through chronic inflammation. SARS-CoV-2 infection induces substantial gut dysbiosis with reduced *Bifidobacterium bifidum*, *Lactobacillus*, and *Faecalibacterium prausnitzii*, and elevated *Ruminococcus gnavus* and *Clostridium ramosum.* COVID-19 severity correlates with the degree of gut dysbiosis, and microbiome alterations may persist beyond acute infection, potentially contributing to post-COVID syndrome. A microbiome rich in butyrate-producing bacteria appears protective, possibly by supporting mucosal barrier integrity and moderating inflammatory cytokine release [37].

A healthy gut microbiome provides colonization resistance against *Clostridioides difficile*, carbapenem-resistant *Enterobacteriaceae*, and vancomycin-resistant *Enterococcus*, organisms that frequently cause life-threatening hospital-acquired infections after antibiotic exposure. FMT achieves approximately 90% clinical resolution in recurrent *C. difficile* infection across multiple trials, the most compelling demonstration of microbiome-based therapeutic efficacy to date [37]. Antibiotic-induced dysbiosis also permits *Candida* overgrowth, underscoring the importance of considering the full microbial ecosystem in infectious disease management.

Cardiovascular disease

The gut microbiome contributes to Cardiovascular Disease (CVD) through bioactive metabolites that influence vascular function, platelet aggregation, and lipid metabolism [96]. Trimethylamine-N-Oxide (TMAO), generated when gut bacteria convert dietary choline, betaine, and L-carnitine into trimethylamine, which is then hepatically oxidized, is the most studied microbiome-derived cardiovascular risk factor. An umbrella review and updated meta-analysis incorporating data from over 80 studies found that elevated TMAO was associated with a 74% increased risk of major adverse cardiovascular events (HR: 1.74) and a 60% increased risk of all-cause mortality (HR: 1.60); each 1 μmol/L increment in TMAO corresponded to a 9% increase in all-cause mortality risk and an 11% increase in MACE risk [59].

Phenylacetylglutamine (PAGln), produced when gut microbes metabolize dietary phenylalanine, has emerged as an independent cardiovascular risk metabolite. In two independent cohorts comprising over 4,000 patients, PAGln levels were significantly elevated across all heart failure phenotypes and correlated inversely with left ventricular ejection fraction and positively with NT-proBNP. Mechanistic studies demonstrated that PAGln blunts epinephrine-mediated inotropic responses in cardiomyocytes and increases BNP gene expression, mirroring the attenuated adrenergic responsiveness of clinical heart failure [83]. These findings position PAGln and TMAO as promising targets for cardiovascular risk stratification and intervention.

Cancer beyond the gut

While the microbiome's role in colorectal cancer is well-established, accumulating evidence implicates dysbiosis in carcinogene-

sis at sites distant from the gut. In Hepatocellular Carcinoma (HCC), increased intestinal permeability allows microbial products, particularly LPS and bacterial DNA, to reach the liver via portal circulation, where they activate TLR4 and inflammatory cascades promoting fibrosis and malignant transformation. In breast cancer, gut microbial beta-glucuronidase activity deconjugates estrogens in the gut and increases enterohepatic estrogen recirculation, potentially elevating breast tissue estrogen exposure. *Fusobacterium nucleatum* has also been detected in breast tumor tissue [40].

In lung cancer, pre-treatment gut microbiome composition predicts responses to anti-PD-1 therapy, with higher *Ruminococcaceae* and lower *Bacteroidaceae* abundance associated with better outcomes. In pancreatic cancer, intratumoral Gammaproteobacteria can metabolize gemcitabine to its inactive form, conferring chemotherapy resistance. The microbiome-oxidative stress-inflammation axis underpins cancer carcinogenesis across organ systems, as dysbiosis drives reactive oxygen species overproduction, causing genomic instability, activating oncogenic signalling, and suppressing antitumor immune surveillance [40,74]. These findings collectively indicate that the tumor microbiome and the systemic gut microbiome are important and potentially modifiable determinants of cancer development and treatment response.

Renal disease and the gut-kidney axis

The gut-kidney axis describes a bidirectional relationship in which gut microbial dysbiosis contributes to kidney disease progression, while renal dysfunction in turn alters gut microbial ecology. Butyrate-producing bacteria, including *Faecalibacterium prausnitzii, Lactobacillus*, and *Bifidobacterium*, maintain intestinal barrier integrity in healthy individuals. In Chronic Kidney Disease (CKD), dysbiosis reduces SCFA production while increasing urease- and indole-producing bacteria. Accumulating uremic toxins, particularly Indoxyl Sulfate (IS), p-Cresol Sulfate (PCS), and TMAO, cross the compromised intestinal barrier and activate TGF-β/Smad, NF-κB, Aryl Hydrocarbon Receptor (AHR), and Keap1/Nrf2 signalling pathways, driving renal inflammation, oxidative stress, and fibrosis [46]. FMT has demonstrated reductions in circulating PCS and uremic toxin burden in dialysis patients [37,46]. Diabetic kidney disease, IgA nephropathy, and lupus nephritis each exhibit characteristic gut microbial disruption patterns linked to immune dysregulation and accelerated renal pathology [46].

Skin diseases and the gut-skin axis

The gut-skin axis represents a bidirectional communication pathway through which gut dysbiosis influences skin health. Systemic inflammation originating from gut dysbiosis, mediated by increased intestinal permeability, elevated LPS levels, and altered SCFA production, promotes skin barrier dysfunction and immune dysregulation. Atopic Dermatitis (AD) is associated with gut dysbiosis in early infancy, predicting subsequent AD development; patients demonstrate reduced gut *Bifidobacterium* and increased *Clostridium difficile* alongside skin dominance of *Staphylococcus aureus* [10]. Psoriasis patients exhibit reduced *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*, implicating reduced mucosal barrier integrity and systemic immune activation in cutaneous pathology. Acne vulgaris is influenced by both *Cutibacterium acnes* dysbiosis on the skin and gut microbial imbalances modulating systemic inflammation and IGF-1 signalling. Skin diseases cannot be fully understood without consideration of the gut microbial environment, and interventions targeting the gut-skin axis, including dietary modification, probiotics, and synbiotics, may offer benefits beyond conventional treatments.

Therapeutic approaches

Growing understanding of microbiome-disease relationships has catalysed microbiome-targeted therapies [37]. Probiotics and prebiotics have been evaluated across IBD, IBS, metabolic syndrome, and mood disorders, with modest but meaningful benefits [37,73]. Synbiotics combining both approaches may offer additive benefits. Mediterranean-style diets rich in fiber, polyphenols, and fermented foods reliably increase microbial diversity and reduce systemic inflammation [37,72].

FMT is the most effective microbiome-based intervention currently available, achieving approximately 90% clinical resolution in recurrent *C. difficile* infection. In IBD, FMT response rates average approximately 50%, with remission rates of 24 to 53% in mild-to-moderate UC [37]. Phage-based therapies, leveraging the phageome's capacity to selectively modulate bacterial populations, represent a promising next frontier, particularly given evidence that specific viral communities are enriched in FMT responders [63]. Engineered next-generation probiotics developed using CRISPR-based tools to target microbial pathways represent a longer-term but potentially transformative approach. Natural compounds, including polyphenol-rich dietary components, have demonstrated microbiome-modulating properties, reducing uremic toxin burden and restoring SCFA production in preclinical models [40,46].

Limitations of current research

Several fundamental limitations constrain the translation of microbiome research into clinical practice. First, the majority of published studies are observational and cross-sectional, establishing associations but not causality. Inter-individual variability driven by genetics, geography, diet, and lifestyle complicates the identification of universal microbial disease signatures. Second, findings from animal models, particularly germ-free mouse experiments, do not translate directly to humans given profound differences in physiology, diet, and immune context. Third, standardization remains incomplete: differences in DNA extraction protocols, sequencing platforms, bioinformatic pipelines, and reference databases generate inconsistency across studies. Fourth, the current literature is heavily biased toward high-income, Western populations, limiting generalizability. Fifth, reproducibility of reported associations across independent cohorts has been inconsistent, partly reflecting the dynamic and context-dependent nature of the microbiome. Addressing these limitations requires longitudinal cohort studies, standardized methodological frameworks, diverse demographic sampling, and robust interventional trial designs.

Conclusions

The human microbiome has been transformed from a scientific curiosity into one of the most consequential frontiers in biomedical research. It is now recognized as an active participant in virtually every dimension of human physiology, from digestive metabolism and immune calibration to mood regulation, cardiovascular homeostasis, and cancer biology. Across gastrointestinal, metabolic, neurological, psychiatric, cardiovascular, renal, and dermatological conditions, microbial dysbiosis is a consistent correlate and, in a growing number of instances, a demonstrated contributor to disease pathogenesis.

Yet the field stands at an inflection point. The descriptive phase of cataloguing microbiome-disease associations must increasingly give way to mechanistic and interventional science. For most conditions, we can describe how the microbiome differs in disease but cannot yet fully explain why it changes, whether it causes the disease, or how precisely to restore a health-promoting community. Reproducibility, inter-individual variation, and global under-representation of non-Western populations are critical limitations requiring urgent attention. Future research should prioritize longitudinal, multi-omics, and internationally diverse cohort studies; clinical trials with sufficient power to detect microbiome-mediated effects; and standardized methodological protocols enabling cross-study comparison.

Microbiome-targeted interventions hold expanding promise. FMT has demonstrated transformative efficacy in *C. difficile* infection, and ongoing trials are testing its potential across IBD, metabolic syndrome, neuropsychiatric conditions, and oncology. Precision microbiome medicine aims to tailor interventions to an individual's microbial profile, genetic background, and disease context, and represents the ultimate aspiration of the field. Realizing this vision will require scientific rigor, careful ethical consideration of equity and access, and attention to the safety of microbiome manipulation. With these imperatives in mind, the microbiome stands as one of the most promising territories in twenty-first century medicine.

References

1. Aagaard K, Ma J, Antony KM, et al. The placenta harbors a unique microbiome. Sci Transl Med 2014;6:237ra65.
2. Amann RI, Ludwig W, Schleifer KH. Phylogenetic identification and in situ detection of individual microbial cells without cultivation. Microbiological Reviews 1995;59:143-69.
3. Arrieta MC, Stiemsma LT, Amenyogbe N, et al. The intestinal microbiome in early life: health and disease. Front Immunol 2014;5:427.
4. Arumugam M, Raes J, Pelletier E, et al. Enterotypes of the human gut microbiome. Nature 2011;473:174-80.
5. Atarashi K, Tanoue T, Oshima K, et al. Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. Nature 2013;500:232-6.
6. Atarashi K, Tanoue T, Shima T, et al. Induction of colonic regulatory T cells by indigenous Clostridium species. Science 2011;331:337-41.
7. Backhed F, Ding H, Wang T, et al. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci 2004;101:15718-23.
8. Backhed F, Manchester JK, Semenkovich CF, Gordon JI. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. Proc Natl Acad Sci 2007;104:979-84.
9. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell 2014;157:121-41.
10. Belkaid Y, Segre JA. Dialogue between skin microbiota and immunity. Science 2014;346:954-9.
11. Berer K, Gerdes LA, Cekanaviciute E, et al. Gut microbiota from multiple sclerosis patients enables spontaneous autoimmune encephalomyelitis in mice. Proc Natl Acad Sci 2017;114:10719-24.
12. Bernstein H, Bernstein C, Payne CM, et al. Bile acids as carcinogens in human gastrointestinal cancers. Mutat Res 2005; 589:47-65.
13. Bode L. Human milk oligosaccharides: every baby needs a sugar mama. Glycobiology 2012;22:1147-62.
14. Browne HP, Forster SC, Anonye BO, et al. Culturing of 'unculturable' human microbiota reveals novel taxa and extensive sporulation. Nature 2016;533:543-6.
15. Buffie CG, Bucci V, Stein RR, et al. Precision microbiome reconstitution restores bile acid mediated resistance to Clostridium difficile. Nature 2015;517:205-8.
16. Buffie CG, Pamer EG. Microbiota-mediated colonization resistance against intestinal pathogens. Nat Rev Immunol 2013;13:790-801.
17. Byrd AL, Belkaid Y, Segre JA. The human skin microbiome. Nat Rev Microbiol 2018;16:143-55.
18. Canfora EE, Jocken JW, Blaak EE. Short-chain fatty acids in control of body weight and insulin sensitivity. Nat Rev Endocrinol 2015;11:577-91.
19. Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 2007;56: 1761-72.
20. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol 2015;28:203.
21. Carding S, Verbeke K, Vipond DT, et al. Dysbiosis of the gut microbiota in disease. Microb Ecol Health Dis 2015;26:26191.
22. Carroll IM, Ringel-Kulka T, Keku TO, et al. Molecular analysis of the luminal- and mucosal-associated intestinal microbiota in diarrhea-predominant IBS. Am J Physiol Gastrointest Liver Physiol 2011;301:G799-807.
23. Clarke G, Grenham S, Scully P, et al. The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. Mol Psychiatry 2013;18:666-73.
24. Clarridge JE III. Impact of 16S rRNA gene sequence analysis for identification of bacteria on clinical microbiology and infectious diseases. Clin Microbiol Rev 2004;17:840-62.
25. Cox LM, Blaser MJ. Antibiotics in early life and obesity. Nat Rev Endocrinol 2015;11:182-90.
26. Cox LM, Yamanishi S, Sohn J, et al. Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. Cell 2014;158:705-21.
27. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci 2012;13:701-12.
28. Cryan JF, O'Riordan KJ, Cowan CS, et al. The microbiota-gut-brain axis. Physiol Rev 2019;99:1877-2013.
29. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature 2014;505:559-63.
30. de Goffau MC, Lager S, Salter SJ, et al. Recognizing the reagent microbiome. Nat Microbiol 2018;3:851-3.
31. Delzenne NM, Bindels LB. Microbiome metabolomics reveals new drivers of human liver steatosis. Nat Med 2018;24:906-7.
32. Dewhirst FE, Chen T, Izard J, et al. The human oral microbiome. J Bacteriol 2010;192:5002-17.
33. Dobson A, Cotter PD, Ross RP, Hill C. Bacteriocin production: a probiotic trait? Appl Environ Microbiol 2012;78:1-6.
34. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci 2010;107:11971-5.
35. Flint HJ, Scott KP, Louis P, Duncan SH. The role of the gut

microbiota in nutrition and health. Nat Rev Gastroenterol Hepatol 2012;9:577-89.
36. Gensollen T, Iyer SS, Kasper DL, Blumberg RS. How colonization by microbiota in early life shapes the immune system. Science 2016;352:539-44.
37. Goetzl EJ. Microbiomes in health, diseases and therapeutics. Am J Med 2026;139:145-9.
38. Grice EA, Segre JA. The skin microbiome. Nat Rev Microbiol 2011;9:244-53.
39. Heijtz RD, Wang S, Anuar F, et al. Normal gut microbiota modulates brain development and behavior. Proc Natl Acad Sci 2011;108:3047-52.
40. Herrera-Quintana L, Iturbe-Sanz P, Olivares-Arancibia J, et al. Interplay of microbiome, oxidative stress and inflammation in health and disease. Antioxidants 2026;15:222.
41. Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. Science 2012;336: 1268-73.
42. Huang YJ, Boushey HA. The microbiome in asthma. J Allergy Clin Immunol 2015;135:25-30.
43. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature 2012;486:207-14.
44. The integrative human microbiome project. Nature. 2019;569: 641-8.
45. Jiang H, Ling Z, Zhang Y, et al. Altered fecal microbiota composition in patients with major depressive disorder. Brain Behav Immun 2015;48:186-94.
46. Jin Y, Zhang SJ, Zhuang S, et al. Microbiota-gut-kidney axis in health and renal disease. Int J Biol Sci 2026;22:750-70.
47. Johansson ME, Hansson GC. Immunological aspects of intestinal mucus and mucins. Nat Rev Immunol 2016;16:639-49.
48. Kamada N, Chen GY, Inohara N, Nunez G. Control of pathogens and pathobionts by the gut microbiota. Nat Immunol 2013;14:685-90.
49. Kao D, Wong K, Jijon H, et al. Preliminary results from a multicenter, randomized trial using fecal microbiota transplantation to induce remission in patients with mild-to-moderate Crohn's disease. Am J Gastroenterol 2025;120:1334-44.
50. Kilian M, Chapple IL, Hannig M, et al. The oral microbiome: an update for oral healthcare professionals. Br Dent J 2016;221:657-66.
51. Koh A, De Vadder F, Kovatcheva-Datchary P, Backhed F. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell 2016;165:1332-45.
52. Kolenbrander PE, Palmer RJ Jr, Periasamy S, Jakubovics NS. Oral multispecies biofilm development and the key role of cell-cell distance. Nat Rev Microbiol 2010;8:471-80.
53. Koren O, Goodrich JK, Cullender TC, et al. Host remodeling of the gut microbiome and metabolic changes during pregnancy. Cell 2012;150:470-80.
54. Korpela K, Salonen A, Virta LJ, et al. Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children. Nat Commun 2016;7:10410.
55. Lagier JC, Hugon P, Khelaifia S, et al. The rebirth of culture in microbiology through the example of culturomics to study human gut microbiota. Clin Microbiol Rev 2015;28:237-64.
56. Lamont RJ, Koo H, Hajishengallis G. The oral microbiota: dynamic communities and host interactions. Nat Rev Microbiol 2018;16:745-59.
57. Lane DJ, Pace B, Olsen GJ, et al. Rapid determination of 16S ribosomal RNA sequences for phylogenetic analyses. Proceedings of the National Academy of Sciences 1985;82: 6955-9.
58. Lederberg J, McCray AT. Ome Sweet Omics: a genealogical treasury of words. The Scientist 2001;15:8.
59. Li D, Lu Y, Yuan S, et al. Gut microbiota-derived metabolite trimethylamine-N-oxide and multiple health outcomes: an umbrella review and updated meta-analysis. Am J Clin Nutr 2022;116:230-43.
60. Lozupone CA, Stombaugh JI, Gordon JI, et al. Diversity, stability and resilience of the human gut microbiota. Nature 2012;489:220-30.
61. Lynch SV, Pedersen O. The human intestinal microbiome in health and disease. N Engl J Med 2016;375:2369-79.
62. Magnusdottir S, Ravcheev D, de Crecy-Lagard V, Thiele I. Systematic genome assessment of B-vitamin biosynthesis suggests co-operation among gut microbes. Front Genet 2015;6:148.
63. Majzoub ME, Paramsothy S, Haifer C, et al. The phageome of patients with ulcerative colitis treated with donor fecal microbiota reveals markers associated with disease remission. Nat Commun 2024;15:8979.
64. Mammen MJ, Sethi S. COPD and the microbiome. Respirology 2016;21:590-9.
65. Man WH, de Steenhuijsen Piters WA, Bogaert D. The microbiota of the respiratory tract: gatekeeper to respiratory health. Nat Rev Microbiol 2017;15:259-70.
66. Mazmanian SK, Round JL, Kasper DL. A microbial symbiosis factor prevents intestinal inflammatory disease. Nature 2008;453:620-5.
67. Milani C, Duranti S, Bottacini F, et al. The first microbial colonizers of the human gut. Microbiol Mol Biol Rev 2017;81:10-128.
68. Moya A, Ferrer M. Functional redundancy-induced stability of gut microbiota subjected to disturbance. Trends Microbiol 2016;24:402-13.
69. Naik S, Bouladoux N, Wilhelm C, et al. Compartmentalized control of skin immunity by resident commensals. Science 2012;337:1115-9.
70. Ni J, Wu GD, Albenberg L, Tomov VT. Gut microbiota and IBD: causation or correlation? Nat Rev Gastroenterol Hepatol 2017;14:573-84.
71. Nicholson JK, Holmes E, Kinross J, et al. Host-gut microbiota metabolic interactions. Science 2012;336:1262-7.
72. Olasunkanmi OI, Zheng L, Zheng P. Gut-brain axis in health and brain disease. Chin Med J 2026;139:799-827.
73. Ouwehand AC, Salminen S, Isolauri E. Probiotics: an overview of beneficial effects. Antonie Van Leeuwenhoek 2002;82:279-89.
74. Pagliaro R, Scialo F, Schiattarella A, et al. Mechanisms of lung cancer development in cystic fibrosis patients: the role of inflammation, oxidative stress, and lung microbiome dysbiosis. Biomolecules 2025;15:828.
75. Pannaraj PS, Li F, Cerini C, et al. Association between breast milk bacterial communities and establishment and development of the infant gut microbiome. JAMA Pediatr 2017;171:647-54.
76. Petersen C, Round JL. Defining dysbiosis and its influence on host immunity and disease. Cell Microbiol 2014;16:1024-33.
77. Qin J, Li R, Raes J, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature 2010;464:59-65.

78. Ravel J, Gajer P, Abdo Z, et al. Vaginal microbiome of reproductive-age women. Proc Natl Acad Sci 2011;108:4680-7.
79. Relman DA. The human microbiome: ecosystem resilience and health. Nutr Rev 2012;70:S2-9.
80. Ridaura VK, Faith JJ, Rey FE, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science 2013;341:1241214.
81. Ridlon JM, Kang DJ, Hylemon PB, Bajaj JS. Bile acids and the gut microbiome. Curr Opin Gastroenterol 2014;30:332-8.
82. Rios-Covian D, Ruas-Madiedo P, Margolles A, et al. Intestinal short chain fatty acids and their link with diet and human health. Front Microbiol 2016;7:185.
83. Romano KA, Nemet I, Saha PP, et al. Gut microbiota-generated phenylacetylglutamine and heart failure. Circ Heart Fail 2023;16:e009972.
84. Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. Nat Rev Immunol 2009;9:313-23.
85. Sanford JA, Gallo RL. Functions of the skin microbiota in health and disease. Semin Immunol 2013;25:370-7.
86. Sassone-Corsi M, Raffatellu M. No vacancy: how beneficial microbes cooperate with immunity to provide colonization resistance to pathogens. J Immunol 2015;194:4081-7.
87. Schloss PD, Handelsman J. Status of the microbial census. Microbiol Mol Biol Rev 2004;68:686-91.
88. Scheperjans F, Aho V, Pereira PA, et al. Gut microbiota are related to Parkinson's disease and clinical phenotype. Mov Disord 2015;30:350-8.
89. Scher JU, Sczesnak A, Longman RS, et al. Expansion of intestinal Prevotella copri correlates with enhanced susceptibility to arthritis. eLife 2013;2:e01202.
90. Sevelsted A, Stokholm J, Bonnelykke K, Bisgaard H. Cesarean section and chronic immune disorders. Pediatrics 2015;135:e92-8.
91. Shao Y, Forster SC, Tsaliki E, et al. Stunted microbiota and opportunistic pathogen colonization in caesarean-section birth. Nature 2019;574:117-21.
92. Sharon G, Cruz NJ, Kang DW, et al. Human gut microbiota from autism spectrum disorder promotes behavioral symptoms in mice. Cell 2019;177:1600-18.
93. Sokol H, Pigneur B, Watterlot L, et al. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. Proc Natl Acad Sci 2008;105:16731-6.
94. Strandwitz P. Neurotransmitter modulation by the gut microbiota. Brain Res 2018;1693:128-33.
95. Szabo G, Bala S. Alcoholic liver disease and the gut-liver axis. World J Gastroenterol 2010;16:1321.
96. Tang WW, Wang Z, Levison BS, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. N Engl J Med 2013;368:1575-84.
97. Theriot CM, Young VB. Microbial and metabolic interactions between the gastrointestinal tract and Clostridium difficile infection. Gut Microbes 2014;5:86-95.
98. Thursby E, Juge N. Introduction to the human gut microbiota. Biochem J 2017;474:1823-36.
99. Turnbaugh PJ, Ley RE, Hamady M, et al. The human microbiome project. Nature 2007;449:804-10.
100. Ursell LK, Metcalf JL, Parfrey LW, Knight R. Defining the human microbiome. Nutr Rev 2012;70:S38-44.
101. Wade WG. The oral microbiome in health and disease. Pharmacol Res 2013;69:137-43.
102. Wahlstrom A, Sayin SI, Marschall HU, Backhed F. Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism. Cell Metab 2016;24:41-50.
103. Yatsunenko T, Rey FE, Manary MJ, et al. Human gut microbiome viewed across age and geography. Nature 2012;486:222-7.
104. Yuan J, Chen C, Cui J, et al. Fatty liver disease caused by high-alcohol-producing Klebsiella pneumoniae. Cell Metab 2019;30:675-88.
105. Zhang X, Deeke SA, Ning Z, et al. Metaproteomics reveals associations between microbiome and intestinal extracellular vesicle proteins in pediatric inflammatory bowel disease. Nat Commun 2018;9:2873.

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