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Gut microbiota: origin or panacea for all ills? Immune and metabolic diseases, nutrition, and microbiota-based interventions

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ABSTRACT

Chronic non-communicable diseases (CNCDs), including obesity, type 2 diabetes, allergies, and autoimmune conditions, represent a significant global health burden, exacerbated by the interplay between genetic and environmental factors, such as diet, and the gut microbiota.

The gut microbiota is a complex and dynamic microbial community that influences host immune and metabolic systems from birth through adulthood. Dysbiosis – an imbalance in gut microbial composition – has been implicated in the development of low-grade inflammation, insulin resistance, and metabolic and immune disorders.

This paper reviews the critical role of gut microbiota in CNCDs, emphasizing its interactions with the immune system, including regulatory T cell induction and the Th1/Th2 balance. Furthermore, it explores the influence of birth mode, diet, and xenobiotics on microbiota composition and function. Finally, the study highlights the potential of microbiota-targeted interventions – such as prebiotics, probiotics, synbiotics, and fecal microbiota transplantation – to modulate gut ecology and mitigate disease risk.

From literature revision emerges the need for integrative approaches in disease prevention and management, considering microbiota as a key player in health and disease.

1. Introduction

Chronic non-communicable diseases (CNCDs) encompass a range of conditions, including cardiovascular, chronic respiratory, neurodegenerative, and rheumatic diseases, as well as cancer, obesity, type 2 diabetes, and various renal and mental health disorders.

These diseases were officially acknowledged by the 66th United Nations General Assembly in 2011. According to World Health Organization (WHO) estimates, CNCDs account for 41 million deaths annually, representing approximately 74 % of global mortality. Europe bears the highest global burden of CNCDs (Fig. 1).

The alarming rise in CNCDs prevalence presents one of the most pressing health and socioeconomic challenges of the 21st century [1,2]. For this reason, the WHO has developed strategies to reduce premature mortality due to chronic diseases by 25 % by 2025. These measures focus on ensuring access to medications, health technologies, and counselling while addressing the primary risk factors (or determinants) of CNCDs.

A distinguishing characteristic of CNCDs is a sustained state of low-grade inflammation caused by immune system activation [3].

In the realm of CNCDs, conditions such as obesity, type 2 diabetes, and allergies represent significant health concerns globally, particularly within Western nations. While genetic predisposition plays a role in their development, accumulating evidence highlights the importance of environmental influences, such as diet, on gut microbiota in shaping systemic inflammation and triggering metabolic imbalances. The interconnectedness between diet, the immune system, and gut microbiota significantly impacts systemic inflammation and contributes to the emergence of issues like insulin resistance, obesity, cardiovascular risks, and immune dysfunction [4,5]. It is important to differentiate between microbiota and microbiome; the former refers to microbial communities associated with organisms – like humans – while the latter encompasses

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those microbes, their genetic material [6,7], and their associated biological milieu, including structural elements (proteins, peptides, lipids, polysaccharides), nucleic acids (structural DNA/RNA), mobile genetic components (viruses and phages), and microbial metabolites (signal molecules, toxins, organic and inorganic compounds) [8]. The mammals' microbiota consists of an array of microorganisms, including bacteria, fungi, and viruses, which reside in and on the body (Table 1).

This community significantly influences physiological processes such as digestion, immunity, and metabolism. Most of these microorganisms reside in the gut, with bacterial species being the most extensively studied [9]. Historically regarded solely as a digestive organ, the human gastrointestinal tract is now recognized as a multifunctional system possessing profound regulatory capabilities with local and systemic repercussions. Indeed, it significantly influences metabolism, immunity, inflammatory processes, behavior, and mood [10].

The multifactorial origins of CNCDs are linked to disruptions in postnatal colonization patterns of gut microbes and reduced microbial diversity, both of which may contribute to immune-metabolic imbalances and chronic low-grade inflammation characteristic of many CNCDs [11–13]. Although a definitive "healthy" microbiota composition remains elusive [14], observational studies consistently associate dysbiosis—imbalances in microbial diversity and abundance—with various CNCDs [15].

Emerging evidence further suggests that dysbiotic microbiota could contribute to disease progression [16]; microbiota transplantation studies have indicated that transferring dysbiotic communities from affected individuals to healthy animals can trigger disease and that microbiota composition is influenced by close contact with others. In 2020, Finlay proposed that certain CNCDs might have a microbial component and could even be communicable through microbiota transmission [9].

The gut microbiota – a highly dynamic yet robustly self-regulating microbial ecosystem – plays a pivotal role in the development and functioning of immune and metabolic systems throughout life. Its interactions with the host occur via metabolic, immune-related, and structural pathways. Microbial family's dysbiosis is finally identified as a characteristic sign of many CNCDs.

Despite substantial variation in taxonomic composition between individuals, functional redundancy ensures that distinct microbial taxa can fulfil identical metabolic roles, thereby maintaining core physiological functions across divergent microbiomes [17]. Indeed, the composition of gut microbiota varies significantly between individuals as well as within the same individual across different life stages. In healthy adults, the phyla Firmicutes (e.g., *Enterococcus, Lactobacillus, Clostridiales, Bacillus*, and *Ruminococcus*) and Bacteroidetes (e.g., *Bacteroides* and *Prevotella*) dominate, while phyla like Actinobacteria (*Bifidobacteria*), Fusobacteria, Proteobacteria (*Escherichia coli*), and Verrucomicrobia are less prevalent [18].

Gut microbiota development begins in utero and undergoes rapid colonization after birth [19]. An individual's initial microbial composition reflects that of their mother (including influences from delivery method) but evolves during adulthood due to factors such as social interactions. For example, cohabitants or spouses often exhibit microbiota similarities that may surpass those found between genetically related but geographically separated siblings. The microbiota is transmissible both within family and social networks and marital relationships can be determined based on the analysis of intestinal bacteria [20].

Throughout its long evolutionary history, man has had an inseparable relationship with his "old friends" bacteria. Over time, in fact, humans have co-evolved with microorganisms in a relationship characterized by interdependence and mutual benefit. The term *"homo bacteriens"*, introduced by Henderson and Wilson, aptly captures this symbiotic relationship [21]. This long-standing association underscores the integral role microbes play in shaping human physiology and health.

The "endosymbiosis theory", originally proposed by American geneticist Lynn Margulis, suggests that mitochondria evolved from ancestral bacteria [22]. Once integrated into human cells, these bacteria transitioned from potential threats to symbiotic partners, thanks to their beneficial oxidative metabolism [23].

The human body is widely regarded as a "superorganism" or holobiont, composed of its own eukaryotic cells along with an extensive population of microorganisms, predominantly bacteria, collectively referred to as the microbiota. From birth, various bacterial species colonize specific regions of the body – such as the skin, oral cavity, respiratory system, urogenital tract, and especially the gastrointestinal tract. The intestinal microbiota develops through a gradual process and reaches full composition within the first two years of life [24].

Primarily concentrated in the colon, the intestinal microbiota represents a massive bacterial biomass, with cell numbers exceeding those of the eukaryotic cells in the human body by tenfold [25,26].

While relatively stable over time, the microbiota's composition can shift due to physiological or pathological factors [27]. This complex ecosystem, along with its collective genetic material (microbiome), interacts closely with the host in a relationship characterized by symbiosis.

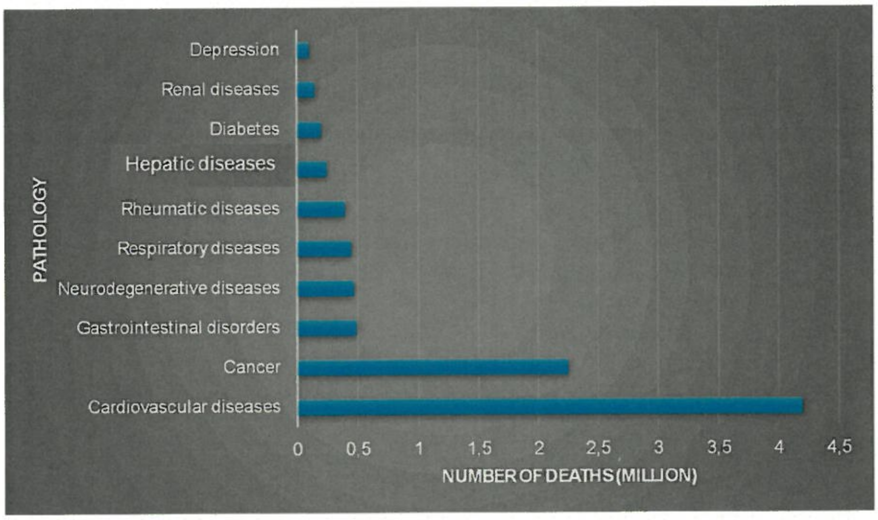


Fig. 1. The ten main causes of death in Europe. Data from Global Burden of Disease Collaborative Network, Global Burden of Disease Study 2019 (GBD 2019) Results (2020, Institute for Health Metrics and Evaluation – IHME) https://vizhub.healthdata.org/gbd-results/.

Table 1
Taxonomy of principal mammals' microbiota organisms.

MICROBIOTA TAXA OF MAMMALS					
PHYLUM	CLASS	ORDER	FAMILY	GENDER	SPECIES
Firmicutes or Bacillota	Bacilli	Bacillales	Bacillaceae	*Bacillus*	*Bacillus clausii, subtilis*
			Lactobacellaceae	*Lactobacillus*	*Lactobacillus fermentum, plantarum, casei, rhamnosus, acidophilus, johnsoni, jensenii, fornicalis, gasseri, delbruecki, brevis, bulgaricus*
			Listeriaceae	*Listeria*	*Listeria monocytogenes*
	Clostridia	Clostridiales	Lachnospiraceae	*Clostridium*	*Clostridium difficile*
				Roseburia	*Roseburia intestinalis, hominis*
				Lachnoclostridium	
				Blautia	
				Pseudobutyrivibrio	
				Coprococcus	
				Lachnospira	
			Oscillospiraceae or Ruminococcacee	*Ruminicoccus*	*Ruminococcus gnavus*
				Faecalibacterium	*Faecalibacterium prausnitzii*
				Oscillospira	
			Eubacteriaceae	*Eubacterium*	*Eubacterium rectale*
			Acidaminococcacee	*Megasphaera*	
				Veillonella	*Veillonella dispar*
				Acidaminococcus	
		Peptostreptococcales-Tissierellales	Peptostreptococcaceae	*Peptostreptococcus*	
				Romboutsia	
		Eubacteriales	Clostridiaceae	*Intestinibacter*	
			Butyricoccaceae	*Butyricicoccus*	
			Enterococcaceae	*Enterococcus*	*Enterococcus faecium*
			Streptococcaceae	*Streptococcus*	*Streptococcus salivarius, bradycosus*
			Staphylococcaceae	*Staphylococcus*	
	Erysipelotrichia	Erysipelotrichales	Erysipelotrichaceae	*Holdemania*	
Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidacee	*Bacteroides*	*Bacteroides fragilis*
				Prevotella	*Prevotella copri*
			Prevotellaceae	*Alloprevotella*	
			Tannerellaceae	*Parabacteroides*	
			Rikenellaceae	*Alistipes*	
			Porphyromonadaceae	*Porphyromonas*	*Porphyromonas gingivalis*
Actinobacteria or Actinomycetota	Actinobacteria or Actinomycetia	Actinomycetales	Actinomycetaceae	*Actinomyces*	*Aggregatibacter actinomycetemcomitans*
		Propionibacteriales	Propionibacteriaceae	*Propionibacterium*	
		Bifidobacteriales	Bifidobacteriaceae	*Bifidobacterium*	*Bifidobacterium adolescentis, bifidum, infantum, animalis, longum, lattis*
				Gardnerella	*Gardnerella vaginalis*
		Micrococcales	Micrococcaceae	*Rothia*	
	Coriobacteriia	Coriobacteriales	Coriobacteriaceae	*Collinsella*	
		Eggerthellales	Eggerthellaceae	*Eggerthella*	*Eggerthella lenta*
Fusobacteriota	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacteria*	*Fusobacterium nucleatum*
Proteobacteria or Pseudomonadota	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	*Enterobacteria*	*Escherichia coli*
				Klebsiella	*Klebsiella pneumoniae*
				Shigella	
				Devosia	*Devosia riboflavina*
				Salmonella	*Salmonella enterica*
				Serratia	
			Morganellaceae	*Proteus*	*Proteus mirabilis, vulgari, penneri*
		Alteromonadales	Alteromonadaceae	*Alteromonas*	*Candida albicans*
		Pseudomonadales	Pseudomonadaceae	*Pseudomonas*	*Pseudomonas aeruginosa*
		Pasteurellales	Pasturellaceae	*Haemophylus*	*Haempphylus influenzae*
	Epsilonproteobacteria	Campylobacterales	Helicobacteraceae	*Helicobacter*	*Helicobacter pilori*
			Campylobacteraceae	*Campylobacter*	*Campylobacter jejuni*
	Betaproteobacteria	Burkholderiales	Oxalobacteriaceae	*Oxalobacter*	*Oxalicibacterium*
	Deltaproteobacteria	Desulfovibrionales	Desulfovibrionaceae	*Desulfovibrio*	
		Neisseriales	Neisseriaceae	*Neisseria*	
Ascomycota	Saccharomycetes	Saccharomycetales	Saccharomycetaceae	*Candida*	*Rhodotorula glutinis*
	Eurotiomycetes	Eurotiales	Trichocomaceae	*Aspergillus*	
Basidiomycota	Microbotryomycetes	Sporidiobolales	Sporidiobolaceae	*Rhodotorula*	*Akkermansia muciniphila*
	Malasseziomycetes	Malasseziales	Malasseziaceae	*Malassezia*	*Malassezia restricta, globosa*
Verrucomicrobia	Verrucomicrobiae	Verrucomicrobiales	Verrucomicrobialaceae	*Akkermansia*	
Spirochaetota	Spirochaetia	Brachyspirales	Brachispiraceae	*Brachyspira*	
		Brevinematales	Brevinemataceae		
		Leptospirales	Leptospiraceae	*Leptospira*	
		Spirochaetales	Spirachaetaceae	*Spirocheta*	*Treponema pallidum*
				Treponema	
			Borreliaceae	*Borrelia*	
Thermodesulfo bacteriota	Desulfovibronia	Desulfovibrionales	Desulfovibrionaceae	*Bilophila*	*Bilophila wadsworthia*
Euryarchaeota o Methanogens	Methanomicrobia	Methanosarcynales	Methanosarcina		
			Methanococcoides		
			Methanolobus		

(continued on next page)

Table 1 (*continued*)

MICROBIOTA TAXA OF MAMMALS					
PHYLUM	CLASS	ORDER	FAMILY	GENDER	SPECIES
			Methanothrix		
		Methanomicrobiales	Methanoculleus,		
			Methanogenium		
			Methanolinea		
			Methanomicrobium		
			Methanoregula		
			Methanospirillum		
			Methanocorpusculum		
	Methanobacteria	Methanobacteriales	Methanobrevibacter	*Methanobrevibacter smithii*	
			Methanobacterium		
			Methanothermobacter		
			Methanosphaera		
	Methanococci	Methanococcales	Methanocaldococcus		
			Methanococcus		
			Methanothermococcus		
	Methanopyri	Methanopyrales		*Methanopyrus*	

The makeup of this bacterial community reflects a dynamic commensal balance with the host organism.

Despite significant individual variability, researchers hypothesize the existence of a shared “core microbiota” and associated “core microbiome” that provide essential metabolic and trophic functions [28]. This “microbial control room” thus emerges as a critical mediator of overall organismal homeostasis [29]. A healthy microbiota is defined by its ecological stability and resilience, which refers to its capacity to resist disruptions or recover its composition under stress. It is also characterized by the presence of specific bacterial patterns associated with health and beneficial functional profiles, such as trophic, metabolic, immune, and protective roles that are fostered by commensal microorganisms [30].

Recently, the idea of a universal core within human microbiota, crucial for basic trophic and metabolic functions and described as “functional stability”, has been reexamined. This reconsideration incorporates environmental influences, addressing anatomical regions, nutrition, ethnicity, and geographical factors [31].

Advancements in meta-omics technologies have deepened our understanding of intestinal microbiota and its role in human health and disease. These scientific methods analyze different biological components: DNA (metagenomics), RNA (meta-transcriptomics), proteins (meta-proteomics), metabolites (metabolomics), lipids (meta-lipidomics), and carbohydrate-protein interactions (meta-glycomics) [32, 33].

Given that 70–80 % of symbiotic microorganisms cannot be cultivated using traditional methods, these cultivation-independent techniques have revolutionized the study of the human microbiota. They have also strengthened theories regarding its involvement in the prevention and pathogenesis of chronic inflammatory and immune-mediated diseases [34].

To date, more than 1000 bacterial species belonging to various phyla have been identified in the human gastrointestinal tract, including Bacteroides, Firmicutes (e.g., *lactobacillus, clostridium, enterococcus*), Actinobacteria (e.g., *bifidobacteria*), and Proteobacteria (e.g., *Enterobacteriaceae, Escherichia coli*). The intestinal microbial genome is estimated to comprise around 3 million genes – approximately 150 times the size of the human genome. This estimate also includes the virome, a term describing the substantial presence of viruses, which often outnumber bacteria at ratios ranging from 1:1 to 10:1 [35].

Historically viewed as solely focused on digestion, the gastrointestinal tract is now understood as playing a far more comprehensive role. Microbiota's presence facilitates numerous regulatory processes with extensive systemic effects, influencing local and overall inflammation [25], metabolism [36], and even behavior [37]. Consequently, interactions between the intestinal microbiota and its metabolites are crucial for maintaining host health [38–40].

The intestinal microbiota is critical to the host organism due to its diverse protective, trophic-metabolic, detoxifying, structural, and immunomodulatory roles [41].

Its protective function helps prevent pathogenic bacteria from colonizing and invading the bloodstream. Mechanisms supporting this resistance include competitive inhibition (e.g., competition for nutrients or blocking receptor sites), physical displacement of pathogens from intestinal epithelial receptors or mucus layers, and the production of antimicrobial substances (amensalism) [42].

Though the human body produces only a few dozen gastrointestinal enzymes, microbial biomass contributes hundreds more, both complementary and unique. These microbial enzymes are fundamental to numerous metabolic processes [43]. Through this collaboration, the intestinal microbiome enhances human biochemical flexibility by offering an expansive repertoire of enzymes that complement the human genome. This evolutionary partnership is thought to be the result of selective pressures that shaped bacteria into symbiotic allies [44].

The trophic-metabolic role of microbiota includes synthesizing polyphenols [45] derived by digesting polysaccharides [46] and essential vitamins such as biotin, folic acid, vitamin K, and B vitamins, as well as facilitating ion absorption (Mg^{++}, Ca^{++}, Fe^{++}). It also plays a key role in producing compounds necessary for enterocyte growth – such as short-chain fatty acids (SCFAs), amino acids, polyamines, and growth factors – and ferments indigestible dietary components like oligosaccharides, polysaccharides, and epithelial mucus. Additionally, energy recovery from dietary fibers via microbial fermentation compensates for processes that humans cannot independently perform. The regulation of this process by specific commensal bacterial groups highlights the intricate relationship between microbiota composition and the multifactorial etiology of obesity [47,48].

The altered qualitative makeup of the microbiota is now understood as a significant factor influenced by the interplay of genetic, environmental, and lifestyle factors. The detoxification abilities of the microbiota, attributed to its enzymatic synthesis capabilities for processing and neutralizing xenobiotics such as drugs (particularly antibiotics), environmental toxins, and agricultural residues, provide further evidence of its critical physiological functions [49].

Recent research highlights how microbial-derived metabolites (such as short-chain fatty acids (SCFAs), secondary bile acids, and tryptophan catabolites) serve as pivotal signaling molecules influencing host metabolism, immune regulation, inflammation, and gene expression. This research positions the gut microbiota not simply as a group of passive residents but as active contributors to systemic health. When dysbiosis occurs, it can compromise intestinal barrier integrity, provoke endotoxemia, and elicit systemic immune responses that are often implicated in metabolic and inflammatory diseases [50].

Emerging evidence demonstrates a strong connection between gut microbial alterations and immune-metabolic disorders (Table 2), necessitating a paradigm shift in the way disease etiology, prevention, and treatment are approached. Modulating the gut microbiota has gained recognition as a potential transformative strategy to enhance metabolic health, reduce systemic inflammation, and improve immune regulation. In this evolving context, dietary interventions, microbiota-targeted therapies (like fecal microbiota transplantation, FMT), and personalized medical approaches stand as promising areas with significant translational and clinical implications [51].

2. Gut microbiota and immunity

The human gastrointestinal tract represents one of the planet's most intricate ecosystems, characterized by an extensive microbial

Table 2
Microbiota's alterations in metabolic diseases. Abbr. legenda: SCFAs (short-chain fatty acids); TLR (toll-like receptor); Treg (T regulatory) cells; GPR (G protein-coupled receptor).

MICROBIOTA'S ALTERATIONS IN METABOLIC DISEASES			
Condition	Microbiota alteration	Proposed action's mechanisms	Studies
Obesity	↑ Firmicutes (*clostridia*), ↑ Proteobacteria, ↓ Bacteroidetes, ↓*Bifidobacterium*, ↓*Lactobacillus* ↑*Bacteroides fragilis* ↔*Actinomycetes*	Greater energy extraction from food, SCFAs, Promotion of fat storage, altered intestinal permeability, increased plasma levels of lipopolysaccharides, production of proinflammatory cytokines, persistent low-grade inflammation, and dysregulation of the endocannabinoid system.	58, 59, 129–136 139, 140, 150, 151
Type 2 Diabetes	↓ *Faecalibacterium prausnitzii*, ↓ *Akkermansia muciniphila.* ↓*Roseburia intestinalis* ↓*L. fermentum, plantarum, casei* ↓*Bacteroides fragilis* ↓*Blautia* ↓*Butyricicoccus* ↔Bacteroidetes/Firmicutes	Reduced butyrate-production and gut barrier function, systemic inflammation, insulin resistance, glucose metabolism and insulin sensitivity decrease, proinflammatory cytokines increase, gastrointestinal tolerance of metformin decrease, intestinal permeability and endotoxemia increase, TLR signalling decrease, angiopoietin-like protein 4 dysregulation.	151, 153, 154, 156- 159, 163–166
Diabetic nephropathy	↓*Prevotella*, ↓*Ruminococcaceae*, ↓*Roseburia*, ↓*Faecalibacterium* ↑*Parabacteroides*, ↑*Enterococcus*, ↑*Enterobacteriaceae* ↑*Klebsiella*		167
Diabetic retinopathy	↓*Bacteroidetes* ↓*Actinobacteria* ↑*Acidaminococcus*, ↑*Escherichia*, ↑*Enterobacter*		168
Diabetic neuropathy	↓*Bacteroidetes* ↓*Faecalibacterium* ↑*Firmicutes*, ↑*Actinobacteria*, ↑*Escherichia-Shigella*, ↑*Lachnoclostridium*, ↑*Blautia*, ↑*Megasphaera* ↑*Rumincoccus*		169
Caesarean section	↑*Clostridium* ↑*Escherichia coli* ↓*Lactobacillus jensenii*	Pro-inflammatory cytokines production, Th17 lymphocytes expansion, tight junctions opening, intestinal permeability increase, immunosuppressive effect.	57 98
Asthma	↓*Lactobacillus*	SCFAs synthesis that stimulate Treg cells and CD4 precursors production, activate GPR and inhibit histone deacetylase.	96, 99, 100
Allergies	*Lactobacillus jensenii* ↑*L. fornicalis* ↑*G. vaginalis* ↑*Clostridium* ↑*Bifidobacterium* ↑*Escherichia coli*	Immunosuppressive effect Stimulate lipopolysaccharide production. Food allergies. Production of specific SCFAs	98, 104, 105, 107, 119- 121, 124, 127
Food allergies	↓*Holdemania*	Increased allergies risk.	113, 115- 118, 122, 123, 125, 126

community spanning diverse ecological niches. This interconnected system has coevolved with its human host over millennia under complex yet delicate regulatory dynamics. In this symbiotic relationship, the human body is no longer considered an isolated entity but rather an integrated superorganism, a union with the microbial universe identified as "non-self", that makes it a "metaorganism" [52].

One notable role of the intestinal microbiota, in fact, is its influence on the development and polarization of the immune system during early life [53,54]. The microbial community within the gut provides an essential antigenic load that activates regulatory mechanisms pivotal for establishing non-atopic immune profiles and fostering oral tolerance [55].

2.1. Gut microbiota, enterocytes, and gut-associated lymphoid tissues signalling

The single layer of intestinal epithelial cells, serving as a dynamic boundary between luminal contents and the gut-associated lymphoid tissues (GALT), plays a critical role in maintaining homeostasis. This interface represents a sophisticated defense barrier, mediating antigen trafficking and facilitating discrimination between self and non-self to ensure mucosal integrity [56]. The perpetual exchange among the microbiota, enterocytes, and GALT translates into an immunomodulatory function that strengthens the mucosal barrier while supporting immune homeostasis [57]. Disruption of this finely tuned interaction can initiate a cascade of pathogenetic events, including increased intestinal permeability, loss of oral tolerance, inflammation, and subsequent tissue damage [58]. These disruptions are implicated in the development of immune-mediated conditions such as allergies and autoimmune diseases [59].

The host organism influences its microbiota through specific factors such as miRNAs and non-specific factors like antimicrobial peptides, mucus, and IgA. These elements encourage the proliferation of certain bacterial genera while suppressing others [60]. The regulation of (microRNA) miRNA expression is particularly important for maintaining intestinal homeostasis and preventing pathological conditions. Although non-coding, endogenous and exogenous (food-derived) miRNAs play significant roles in modulating bacterial gene expression, supporting epithelial barrier integrity, managing apoptosis, and controlling enterocyte proliferation and differentiation [61,62].

The alteration of this integrated system underscores its pivotal role in maintaining systemic immune balance. Helper T cells (CD4 Th cells) play a central role in adaptive immunity by producing cytokines that regulate the activity of other immune cells. Differentiation into Th1 or Th2 subtypes is influenced by environmental cues and antigen-presenting cells (APCs). Cytokines like interferon-gamma (IFN-γ) and interleukin-12 (IL-12) favor Th1 differentiation, while interleukins such as IL-4, IL-2, and IL-13 promote Th2 cell differentiation; in healthy individuals, Th1-oriented immune responses predominate against specific environmental antigens, whereas individuals with an allergic phenotype exhibit a dominant Th2 cytokine pattern [63].

2.2. A sophisticated balance between the lymphocyte populations

In utero, the maternal immune system confronts the presence of fetal antigens derived partially from paternal genetics. This non-self-antigenic profile places the fetus at potential risk of immunological rejection mediated by Th1 cytokine responses. However, this is circumvented due to the fetus's Th2 polarization during gestation. Postnatally, this immune orientation becomes insufficient for combating viral and intracellular pathogens, necessitating an immune transition from a Th2-dominant profile to a Th1-oriented state during early childhood. Individuals with atopic tendencies may experience incomplete or defective immune shifts due to insufficient levels of cytokines like IFN-γ or IL-12 required to drive this process [64].

The "hygiene hypothesis", proposed by Strachan in 1989, posits that exposure to infectious agents and antigenic challenges during early life is critical for catalyzing the Th2-to-Th1 immunological conversion process [65].

The dramatic epidemiological rise in allergic diseases in industrialized nations has been partly attributed to reduced exposure to infections, particularly those transmitted via the fecal-oral route. Improved sanitation practices, widespread vaccination programs, and the extensive use of antibiotics have collectively diminished such exposures. Gerrard provocatively describes this rise in allergic disease prevalence as the cost society pays for liberation from childhood infections and parasitic infestations [66].

The biological mechanisms underlying immune responses, however, are more complicated than the Th1/Th2 paradigm initially prompted by the "hygiene hypothesis". Antigenic stimuli do not exclusively provoke either Th1 or Th2 responses, highlighting the multifaceted nature of the immune system. Furthermore, alongside the dramatic rise in allergic conditions predominantly mediated by Th2 responses, there has been a concomitant and noteworthy increase in disorders linked to Th1 overactivation, such as type 1 diabetes (T1D), celiac disease, and chronic inflammatory bowel diseases. To address these observations, the hygiene hypothesis has been revised and expanded into what is now termed the "revisited hygiene hypothesis" [67].

Within the framework of postnatal microbial colonization, the early interaction between the intestinal microbiota and gut-associated lymphoid tissue (GALT) dendritic cells triggers mechanisms that regulate tolerance versus immune activation. This dynamic involves a sophisticated equilibrium among various lymphocyte populations [68]. In such homeostatic contexts, regulatory T lymphocytes (Tregs) emerge as central players, supported by their production of key immunomodulatory cytokines such as IL-10 and TGF-β [69,70].

Tregs have a critical role among the T helper cell subsets; in fact, they are defined by distinct cytokine expression profiles and can be further categorised into natural Tregs (nTregs), which are derived from the thymus, and inducible Tregs (iTregs) that come from peripheral tissues. These inducible Tregs are primarily responsible for secreting TGF-β and IL-10, cytokines essential for curbing inflammation and exerting immunosuppressive effects [71].

The gut's colonization by an extensive and diverse population of bacterial cells – whose collective genome exceeds the human genome by 150-fold – provides a beneficial antigenic repertoire. This microbiota and its genetic content (termed the microbiome) activate a regulatory network orchestrated by Tregs, which serves to prevent immune polarization toward either a Th2-dominant (allergic) or Th1-dominant (autoimmune) response [72]. This regulatory function of microbiota surpasses that of infections, historically highlighted in the original hygiene hypothesis as catalysts for maturation of an immune system that is still … in the running-in process [73,74].

2.3. Gut microbiota and birth modality

The intestinal microbiota functions as an immunologically active "bacterial organ", contributing to both innate and adaptive immune programming during early development [75]. During early life, numerous intrinsic and extrinsic factors significantly shape the composition of the microbiota. These factors include genetics, delivery method (vaginal or cesarean), perinatal antibiotic use, gestational age, APGAR score, delivery location (hospital or home), infant feeding practices (breastfeeding, formula use, or mixed), duration and quality of alternative feeding, maternal milk oligosaccharide residues, weight gain during pregnancy, atopy level, BMI, and finally the exposition to pets [76].

Through the process of vaginal birth, mothers pass a "microbial inheritance" to their newborns, facilitating colonization by maternal and environmental microorganisms on the skin and mucosal surfaces such as the oral cavity, respiratory tract, urogenital tract, and alimentary canal. Therefore, in full-term neonates born via vaginal delivery, the microbiota exhibits favorable species diversity dominated by genera such as *Bacteroides* (*Bacteroidetes*), *Bifidobacteria* (*Actinobacteria*), *Lactobacilli* (*Firmicutes*), and *Enterobacteria* (*Proteobacteria*), which coexist in a balanced state of symbiosis termed eubiosis. By contrast, neonates delivered by cesarean section experience significant microbiota compositional disturbances (dysbiosis), characterized by qualitative and quantitative alterations that impact functional outcomes [77,78].

This inadequate postnatal colonization – contributed to by cesarean deliveries, extended hospital stays, and early or prolonged antibiotic use – acts as a determinant factor in dysbiotic states implicated in the pathogenesis of various immune-mediated and metabolic diseases [79,80]. During dysbiosis takes place a series of adverse events, including delayed intestinal barrier maturation ("gut closure"), bacterial and food antigens translocation, immune dysregulation and local inflammation [81] (Fig. 2).

During eubiosis, tolerogenic dendritic cells secrete a cytokine called TGF-β. This cytokine induces Treg populations that, in turn, stop the overactivation of both Th2-mediated allergic pathways and the Th1-driven autoimmune responses [82]. In contrast, dysbiosis associated with cesarean births frequently involves an overrepresentation of *Clostridia* and *Escherichia coli*, which promote the production of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. These cytokines further facilitate the expansion of Th17 lymphocytes, disrupt tight junction integrity, and enhance intestinal permeability [83]. Emerging evidence implicates microbiota not only in immune regulation but also in critical physiological processes such as body weight control, energy homeostasis, and systemic inflammation, with profound relevance for the pathophysiology of obesity [84,85].

3. Gut microbiota and allergies

The immune system (IS) itself represents an intricately integrated network comprised of chemical mediators, cellular elements, biological structures, and dynamic processes developed throughout evolution to protect the organism against external threats – be they physical, chemical, or biological. The IS can be subdivided into subsystems representative of the innate versus adaptive immunity or humoral versus cell-mediated immunity. Its core function lies in distinguishing self-molecules from non-self entities, a category encompassing a diverse array of agents including pathogenic metabolites from viruses, bacteria, fungi, and helminths [86].

The immune system (IS) serves as a critical regulator of host homeostasis, enabling the maintenance and restoration of tissue functionality when encountering microbial or environmental factors [87]. The emergence of IS subsystems associated with adaptive immunity has paralleled the development of a complex microbiota, reinforcing the idea that much of this system evolved to sustain symbiotic interactions with diverse microbial communities. These communities, in turn, influence and regulate various aspects of the immune system [88].

The IS operates as a finely tuned dynamic balance, adjusting its activity as needed. A downturn in this balance results in immunodeficiency, leading to recurrent and potentially life-threatening infections. This condition may stem from genetic factors, diseases like AIDS, or the use of immunosuppressive therapies. Conversely, an upward shift in the balance triggers immune hyperactivation, manifesting as autoimmunity, where the body's own tissues become targets of immune attacks. Common autoimmune conditions include type 1 diabetes (T1D), rheumatoid disorders, and allergies [89].

Allergies are widespread health concerns. In developed nations, about 15–25 % of individuals experience allergic rhinitis [90], approximately 6 % have at least one food allergy [91], and around 20 % suffer from atopic dermatitis [92]. Otherwise, depending on the region, 1–18 % of the population [93] suffers from asthma, while 0.05–2 % from anaphylaxis [94].

3.1. The role of exposome

Over recent decades, epidemiological studies have shown a growing

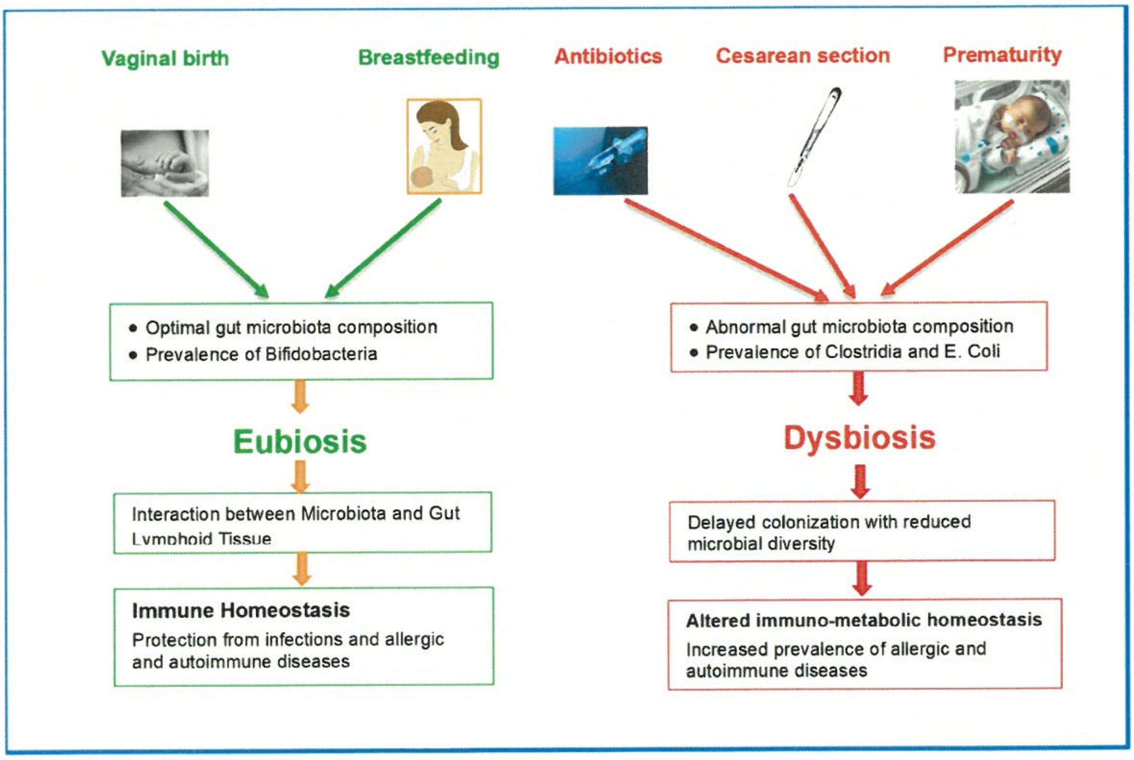


Fig. 2. Eubiosis and dysbiosis (images from https://pixabay.com/it/).

prevalence of allergies, particularly in industrialized nations [95]. Beyond genetic predisposition, environmental factors collectively referred to as the exposome play a decisive role. The exposome encompasses all environmental influences encountered from early intrauterine stages onward [96] and can be divided into three overlapping domains: the general external environment (e.g., urbanization, social conditions, stress, noise, artificial light); the specific external environment (e.g., chemical pollutants, diet, physical activity, tobacco exposure, infections); and the internal environment (e.g., metabolic processes, gut microbiota composition, inflammation, oxidative stress) [97] (see flow chart). These domains are highly dynamic and continue to evolve throughout life [98]. Among these factors, the intestinal microbiota appears to play a predominant role [99] due to its significant biodiversity changes over just a few decades – a mere instant compared to the millions of years of evolution.

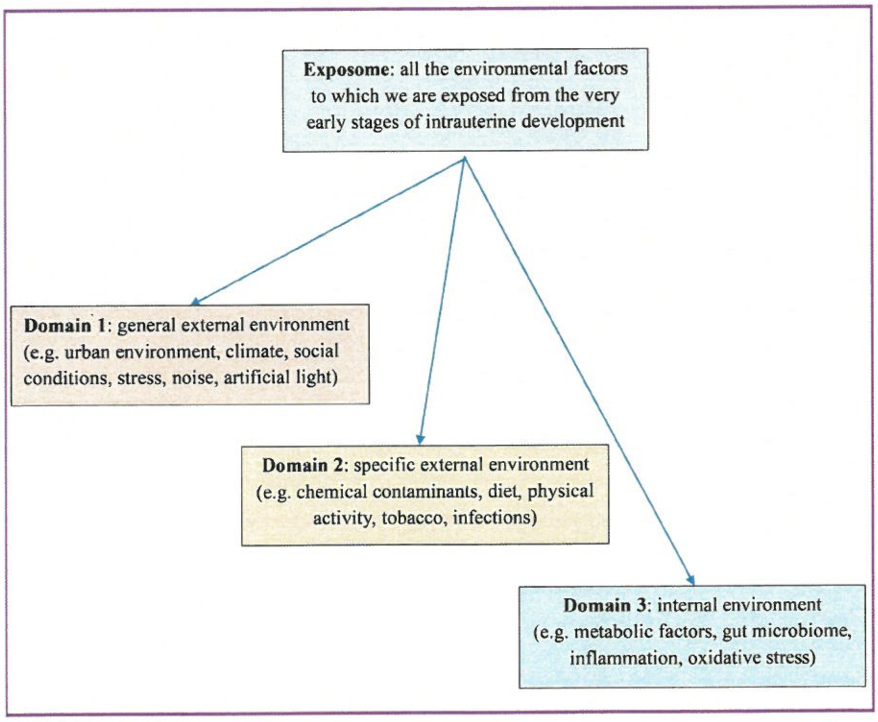
Selective pressures promoting metabolic efficiency have likely shaped the coevolution of hosts and their microbiota. This prolonged integration has formed intricate physiological connections between microbial communities – even outside the gastrointestinal tract – and their hosts, extending beyond metabolism. These interconnections are particularly evident in the interplay between microbiota and the immune system. This interaction influences immune responses, metabolic activity, and endocrine pathways through complex interkingdom signaling processes and metabolic modulation. Depending on its composition and functional dynamics in response to dietary and environmental factors, the gut microbiota can either protect or harm the host.

The establishment of gut microbiota from the fetal stage and through early life is critical for equipping the host's immune system to handle external stimuli and respond appropriately. Alterations in the fetal gut microbiota can begin in utero due to maternal factors such as lifestyle choices, diet, or medication use – especially antibiotics [100] – and continue postnatally based on delivery mode (vaginal vs. cesarean) [101] and feeding method (breastfeeding vs. bottle-feeding) [102]. Within three years of age, microbial composition undergoes a rapid transformation; it resembles that of an adult by the first year and stabilizes into a mature community by the third year [103,104]. This perinatal phase is thus essential for fostering a healthy microbiota and a resilient immune system. Dysbiosis – or disequilibrium – of the gut microbiome can evolve in metabolic and immunological disadvantages in babies and children. These disruptions contribute to metabolic issues as well as allergic and autoimmune conditions such as obesity [105], T1D [106], allergies [107], autism spectrum disorders [108], non-specific inflammatory bowel diseases (IBD) [109], and stunted growth [110].

A connection between gut microbiota dysbiosis and immune responses in the gut, systemic circulation, other organs, and peripheral tissues is firmly established [56]. Notably, there is a substantial correlation between intestinal dysbiosis and allergy development. For instance, about 80 % of infants and young children diagnosed with atopic dermatitis later develop allergic rhinitis or asthma [111]. This progression aligns with the so-called "allergic march", which details a sequential development of allergic conditions during childhood, starting with atopic dermatitis or food allergies and advancing to asthma and allergic rhinitis [112].

3.2. Microbiota and the immunological component of asthma

Asthma is a chronic inflammatory condition of the respiratory system, marked by recurring symptoms such as shortness of breath, coughing, and wheezing [113]. While the immune response mechanisms involved in asthma are not fully understood [114], it is clear that inflammation and allergen sensitivity play key roles in its pathophysiology [115]. Research has suggested that microbial metabolites – mainly SCFAs produced by lactobacilli – may have protective and immunomodulatory effects. SCFAs stimulate the generation of regulatory T cells (Treg) from CD4 precursors and dendritic T cells, activate G protein-coupled receptors (GPR), and inhibit histone deacetylase, thereby exerting significant influence [116]. The microbiota is central to the inflammatory response associated with asthma [117]. Factors like maternal smoking during pregnancy [118], a history of maternal asthma [119], antibiotic use during gestation [120], diet [121], and prenatal



Exposome's representative flowchart.

stress [122] are linked to an increased risk of asthma.

Additionally, research has documented an association between reduced microbial diversity (dysbiosis) and respiratory diseases [123]. Dysbiosis in both the gastrointestinal and respiratory systems significantly contributes to asthma's pathophysiology by altering the response of the IS [124]. Studies have shown connections between bacteria transferred from the mother's vaginal microbiota, newborn IgE levels, and allergic immune modulation [125]. The presence of specific antigens like *Lactobacillus jensenii* in meconium suggests they could suppress certain immune functions in utero, promoting better immune tolerance to allergens during early childhood [126]. Interestingly, the predominance of *Lactobacillus* species in the vaginal microbiota is associated with susceptibility to asthma development, as it may trigger IgE production during an infant's first year of life [127]. Furthermore, genetic factors also seem to play a role in shaping the intestinal microbiota and the subsequent development of asthma [128].

3.3. Microbiota and atopic dermatitis

Scientific evidence also highlights that 60 % of atopic dermatitis cases emerge within the first year of life, often presenting as infantile eczema [129]. Intestinal dysbiosis, along with its regulatory effects on immune processes, plays a considerable role in the onset of atopic dermatitis. The microbiota's beneficial properties include stimulating the production of regulatory T cells, which protect against inflammation-related allergic and autoimmune conditions [130]. In allergic rhinitis and sensitization, bacterial diversity is often reduced; however, this phenomenon does not appear to be closely linked with atopic dermatitis.

3.4. Dysbiosis and allergies

A healthy vaginal microbiota correlated with lower allergy incidence in children [131], while the prevalence of species like *L. fornicalis* or *G. vaginalis* is linked to vaginal dysbiosis and inflammation, promoting allergy development through lipopolysaccharide production [132]. Postnatal factors such as lifestyle choices significantly shape the gastrointestinal microbial environment, contributing to dysbiosis and increasing susceptibility to allergies over time [133]. Exposure to parasites and other microorganisms also affects immune system reactivity and allergen development [134]. Studies underscore how a mother's microbiota closely influences the baby's microbiota depending on various factors such as mode of delivery [135]. Additionally, nutrition [136], probiotic use [137], and antibiotic administration [138] significantly impact microbiota development and early colonization – factors that help shape immune responses and eventually influence health outcomes [51].

The increasing prevalence of food allergies presents considerable public health and economic concerns [91]. Evidence suggests that the intestinal microbiota can act either as a protective barrier or a trigger for food allergies by modulating immune responses [139]. As several times mentioned, the intestinal microbiota comprises trillions of bacteria across hundreds of species, varying widely among individuals [140]. A healthy intestinal immune system typically maintains tolerance to commensal microbes, but disruptions can lead to pro-inflammatory states that contribute to food allergies, these are linked to pro-inflammatory changes that disrupt the homeostatic balance of the gut's immune environment [141]. Both protective and allergy-inducing bacteria have been identified for their ability to modulate immune responses through stimulation of Th1 helper lymphocytes and suppression of Th2-mediated pathways [142]. Mechanisms mediated by microbiota, such as microbiota-specific regulatory T cells (Tregs), play a vital role in suppressing allergic inflammation [143]. However, the processes by which immune cells orchestrate the formation of dietary antigen-specific Tregs and the microbiota's contribution to their functionality remain partially understood [144].

The gut microbiota is a principal part of the newborn intestinal immune system's shape and maturation. Specific fecal microbial profiles have been associated with allergic predispositions in infants and children [145–147]. Observational studies have examined longitudinal changes in bacterial abundance across different age groups among food-allergic children, uncovering distinctions in bacterial phyla that could inform correlations with developing allergies [148]. For instance, analyses have associated maternal concentrations of *Holdemania* spp. with reduced food allergy risks in offspring, suggesting its potential protective role [149]. Additionally, imbalances in the microbial composition, such as increased *Clostridium* spp., certain *Bifidobacterium* species [150], and elevated *Escherichia coli* abundance [151], alongside shifts in short-chain fatty acid production tied to diet, delivery mode, environmental exposure, and the timing of bacterial colonization, have been linked to allergic diseases [152]. The evidence strongly supports the premise that a maternal microbiota characterized by balance and diversity (eubiosis) is fundamental to ensuring proper immune development in the fetus and neonate, thereby mitigating allergy risk [153].

4. Gut microbiota and obesity

Aberrant microbial patterns have been associated with low-grade inflammation, a hallmark of obesity and other non-communicable diseases [154]. Dysbiosis and obesity share a well-documented association, supported by both human and animal studies [155]. For example, laboratory animals on a Western-style diet exhibit significant shifts in dominant bacterial phyla – namely, an increase in *Firmicutes* (e.g., *clostridia*) and a reduction in *Bacteroidetes* [156] – a pattern similarly observed in obese individuals [157].

Evidence from prospective studies indicates that childhood compositional shifts in the microbiota often precede the development of overweight and obesity [158,159]. The prevalence of specific bacterial genera appears critical; for instance, higher levels of *Bifidobacteria*, prevalent in breastfed and vaginally delivered infants, are associated with a reduced risk of being overweight, while the dominance of *Bacteroides fragilis* correlates with heightened obesity risk [160].

High-fat diets further exacerbate dysbiosis, promoting reductions in *Bifidobacteria* and *Lactobacilli* alongside increased proportions of *Firmicutes* and *Proteobacteria* [161]. Dysbiotic patterns in obese children and adults are characterised by diminished *Bacteroidetes*, elevated *Firmicutes*, and altered frequencies of bacterial phyla like *Actinomycetes* [162,163].

4.1. Obesity's dysbiosis mechanisms

The complex mechanisms linking gut dysbiosis to obesity are gradually being elucidated [164,165].

Dysbiosis induces altered intestinal permeability, elevated plasma levels of lipopolysaccharides (LPS) – a structural component of gram-negative bacterial cell walls – and increased systemic proinflammatory cytokines such as interleukins (IL-1β, IL-6) and tumor necrosis factor-alpha (TNF-α). These factors contribute to persistent low-grade inflammation and dysregulation of the endocannabinoid system (ECS), which collectively influence energy homeostasis and adiposity [166,167].

LPS mediates intestinal permeability by downregulating tight junction proteins like zonulin-1 and occludin via nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) activation, proinflammatory cytokines, such as interleukins (IL-1β, IL-6) and tumor necrosis factor alpha (TNF-α), on the other hand, are responsible for local and systemic inflammation [168]. The resulting proinflammatory milieu supports the "metabolic infection" hypothesis, which posits that dysbiosis-driven inflammation propagates systemic consequences, including adipose tissue inflammation [169]. Patients with metabolic syndrome (MS) develop serious endotoxemia [170]. ECS hyperactivation, in association with dysbiosis, stimulates adipogenesis by increasing intestinal permeability and amplifying LPS-mediated inflammation [171] (Fig. 3a).

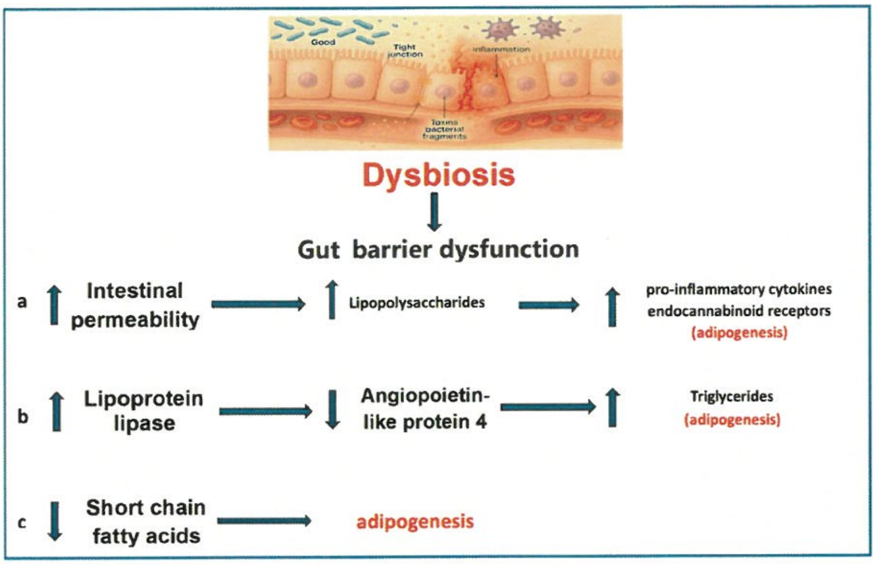


Fig. 3. Mechanisms between intestinal dysbiosis and obesity. (Modified from PEDIATRIA PREVENTIVA & SOCIALE ANNO XI - Numero 2–2016 ISSN 1970–8165 https://www.sipps.it/pdf/rivista/2016_02.pdf).

4.2. The link between obesity and diabetes

Research using murine models has linked the intestinal microbiome to energy management and weight regulation [172]. These processes appear to involve the regulation of angiopoietin-like protein 4 (ANGPTL4) expression in the intestinal epithelium. ANGPTL4, also known as the fasting-induced adipose factor (FIAF), plays various roles, including the regulation of lipid and glucose homeostasis and supporting angiogenesis [173]. By inhibiting lipoprotein lipase (LPL) activity, ANGPTL4 reduces triglyceride uptake and storage in tissues, particularly adipose tissue, where it promotes lipolysis [174] (Fig. 3b). Lower serum levels of ANGPTL4 have been observed in individuals with diabetes [175] and obesity [176]. Studies on animals and *in vitro* experiments suggest that gut microbiota significantly influences intestinal ANGPTL4 expression, thereby affecting lipid storage and body mass [177].

SCFAs are metabolites produced by bacterial fermentation of indigestible dietary carbohydrates [178]. Metabolomic analyses reveal that SCFAs profiles reflect the synergy among various bacterial genera within the intestinal ecosystem. As indirect nutrients, SCFAs (including acetate, propionate, and butyrate) play a critical role in energy metabolism and adipose tissue expansion, functioning as metabolic modulators [179] (Fig. 3c).

Metagenomic research has emphasized the strong correlation between specific gut bacteria, their genes, and intestinal metabolites with type 2 diabetes (T2D). Notably, lower levels of butyrate-producing bacteria, such as *Roseburia intestinalis* and *Faecalibacterium prausnitzii*, have been detected in individuals with T2D, suggesting that reduced SCFA production may contribute to obesity, diabetes, and related metabolic disorders [179].

5. Gut microbiota and diabetes

T2D (diabetes mellitus) is responsible for 80 % of early deaths all over the world. Projections estimate that by 2045, approximately 700 million people will suffer from T2D, despite available drug therapies [180]. This condition is marked by elevated blood glucose levels due to defective pancreatic insulin production or reduced insulin sensitivity [181]. Poorly managed diabetes and its related metabolic dysfunctions, including hypertension, impaired lipid metabolism, and oxidative stress, can lead to a wide range of macrovascular complications (e.g., coronary heart disease, stroke, peripheral vascular disease) and microvascular complications (e.g., nephropathy, neuropathy, diabetic retinopathy) [182], alongside disruptions in interconnected metabolic pathways [183].

Individuals with T2D exhibit altered gut microbial communities compared to healthy counterparts [184], showing reduced diversity of symbiotic bacteria and increased levels of opportunistic pathogens [185]. These microbiota shifts promote diabetes onset and progression by influencing critical mechanisms such as glucose metabolism, insulin resistance, and chronic inflammation [186]. Certain gut bacteria also directly impact insulin sensitivity by regulating SCFAs production [187]. Additionally, the gut microbiota modulates the host's metabolic response to diet through the breakdown of various dietary components [181].

5.1. Metabolism's regulation by gut bacteria

Beyond digesting food, gut microbiota interacts with Enteroendocrine Cells (EECs), a small but diverse population making up about 1 % of intestinal epithelial cells. Distributed along the digestive tract, EECs produce and release up to 20 different hormones that regulate host metabolism, digestion, gut motility, gastric emptying, and overall intestinal health [188]. These cells interact closely with gut microbiota and their metabolites – produced through the fermentation or enzymatic degradation of proteins, carbohydrates, and bile acids – including SCFAs, branched-chain fatty acids, secondary bile acids, and tryptophan-derived catabolites like indole, which affects bowel motility [189]. The interplay between gut microbiota, EECs, and metabolism is highly intricate, as these components mutually influence one another. This dynamic relationship governs many physiological processes such as gastric emptying, intestinal motility, dietary habits, and energy metabolism. Because of this, a breakdown in microbiota-EEC communication can develop toward metabolic alterations like insulin resistance, an antechamber to diabetes [190].

5.2. Dysbiosis and diabetes

Numerous investigations have identified a significant relationship between modifications in the intestinal microbiota and the pathogenesis of diabetes. Notably, alterations in the ratio of the phyla Bacteroidetes to Firmicutes have been linked to increased intestinal permeability [191]. This disruption facilitates the translocation of microbial by-products across the compromised intestinal barrier, subsequently initiating inflammatory processes characteristic of diabetes. A notable decrease in SCFAs-producing bacteria, particularly butyrate producers, has also been correlated with T2D, as these metabolites are critical for modulating insulin sensitivity [192].

Certain bacterial strains have demonstrated protective effects against diabetes by reducing pro-inflammatory markers and preserving intestinal barrier integrity. Among these good microorganisms are *Lactobacilli fermentum, plantarum*, and *casei, Roseburia intestinalis, Bacteroides fragilis*, and *Akkermansia muciniphila*. These species have shown potential in enhancing glucose metabolism, improving insulin sensitivity, and mitigating the production of pro-inflammatory cytokines [182]. Additionally, the gut microbiome is integral to modulating both the efficacy and gastrointestinal tolerance of metformin, an antidiabetic medication that functions by suppressing hepatic glucose production, improving insulin sensitivity, and facilitating glucose uptake in muscle and liver tissues [193]. Animal and human studies suggest that metformin supplementation is associated with an increase in several SCFAs-producing taxa, such as *Blautia, Butyricicoccus*, and in *A. muciniphila*, that notably promote the proliferation of ileal goblet cells, reduce intestinal permeability, lower endotoxemia, and enhance toll-like receptor signalling pathways [194].

In the context of diabetic nephropathy, recent findings underscore the impact of intestinal dysbiosis, specifically characterized by a reduction in beneficial bacteria such as *Prevotella, Ruminococcaceae, Roseburia*, and *Faecalibacterium*. Concurrently, an expansion of potentially pathogenic taxa, including *Parabacteroides, Enterococcus, Enterobacteriaceae*, and *Klebsiella*, has been documented [195].

Similarly, altered gut microbiota has been observed in individuals with diabetic retinopathy, marked by decreased abundance of *Bacteroidetes* and *Actinobacteria* and an increased prevalence of *Acidaminococcus, Escherichia*, and *Enterobacter* [196].

Diabetic neuropathy has also been associated with distinct microbial dysbiosis, manifesting as an elevated abundance of *Firmicutes, Actinobacteria, Escherichia-Shigella, Lachnoclostridium, Blautia, Megasphaera*, and *Ruminococcus* in conjunction with a decline in *Bacteroidetes* and *Faecalibacterium* [197].

6. Gut microbiota and biomodulators

The perinatal period represents a critical window during which the developing immune system exhibits heightened susceptibility to environmental influences. Prevailing strategies for immune system modulation during this stage have shifted from allergen exclusion (restrictive approaches) to more proactive interventions targeting the intestinal microbiota to shape naïve immune responses (promotional approaches) [77,78]. Advances in understanding the intricate interactions between the gut microbiota and immune system have driven efforts to optimise maternal immunity during pregnancy and neonatal immune development in early infancy via nutritional interventions involving prebiotics and probiotics [198].

The concept of 'manipulating' gut microbial composition traces its scientific origins to Ilja Metchnikoff, a Ukrainian Nobel laureate who ascribed therapeutic benefits to fermented foods containing live lactic acid bacteria in the early 20th century. Metchnikoff's pioneering insights underpin the modern framework for employing microbiota-targeted therapies – collectively termed "biomodulators" – which include prebiotics, probiotics (including psychobiotics), synbiotics, paraprobiotics, metabiotics, and postbiotics [199] (Table 3).

Each of these categories encompasses different strategies for maintaining or restoring intestinal microbial balance, with the ultimate goal of preventing or treating chronic diseases linked to dysbiosis.

Fecal microbiota transplantation (FMT), a technique involving the transfer of microbiota from rigorously screened healthy donors to recipients with dysbiotic conditions, exemplifies another promising strategy for modifying gut microbial communities. FMT aims to restore a healthy ecosystem and, in turn, promote clinical recovery. Although the precise mechanisms underlying its efficacy remain only partially understood, evidence increasingly supports its therapeutic potential not only in recurrent *Clostridioides difficile* [200,201] infection but also across a spectrum of chronic non-communicable diseases (CNCDs) [202,203].

Table 3
The different types of gut microbiota biomodulators.

GUT MICROBIOTA BIOMODULATORS	
Prebiotics	Non-digestible food constituents which selectively promote the growth and activity of one or more bacterial species present in the intestinal tract
Probiotics (included Psychobiotics)	Live microorganisms which confer beneficial effects on the host organism
Synbiotics	A combination of prebiotics and probiotics
Paraprobiotics	Set of dead probiotic microbial cells and cell constituents
Metabiotics	Structural components of probiotic microorganisms that can optimise host-specific physiological functions and responses
Postbiotics	Healthy metabolic products or secreted components of probiotics

6.1. Gut microbiota and prebiotics

The International Scientific Association for Probiotics and Prebiotics (ISAPP) defines a prebiotic as a substance that is selectively utilized by host microorganisms to provide health benefits [204]. Prebiotics positively influence the host's health due to their resistance to digestion and absorption in the gastrointestinal tract; instead, they are fermented by intestinal bacteria [205]. This fermentation process produces compounds that lower the pH of the intestinal environment and promote the growth of beneficial bacteria in the small intestine, including Lactobacillus, Bifidobacterium, and Bacteroides families [206]. Naturally occurring in many plant-based foods and certain animal-based sources like honey and cow's milk, prebiotics, along with antimicrobials produced by lactic acid bacteria (LAB), help shape gut microbiota composition and metabolic functions, supporting health and preventing disease [207]. Common examples of prebiotics include inulin, galactooligosaccharides (GOS), fructooligosaccharides (FOS), human milk oligosaccharides (HMO), xylooligosaccharides (XOS), mannanoligosaccharides (MOS), lactulose, galactose derivatives, and β-glucans [208]. Additionally, polyphenols such as flavonoids [209], polyunsaturated fatty acids (PUFAs) [210], and glucooligosaccharides [211] are considered potential prebiotics.

The clinical significance of prebiotics extends beyond gut ecology. By supporting SCFA production and fostering eubiosis, prebiotics contribute to immune tolerance, improved gut barrier function, and metabolic regulation. Emerging evidence links prebiotic supplementation with reduced risk or alleviation of several chronic conditions, including obesity, type 2 diabetes, inflammatory bowel disease, and allergic disorders [206]. Moreover, specific prebiotics such as HMOs appear to play a pivotal role in shaping the infant gut microbiota, potentially influencing susceptibility to immune-mediated diseases later in life [212].

From a preventive and therapeutic standpoint, prebiotics illustrate how targeted dietary strategies can sustain microbiota health and reduce disease risk. However, clinical studies show heterogeneous outcomes, largely due to differences in prebiotic type, dosage, treatment duration, and patient characteristics. Addressing these methodological challenges will be essential to fully establish prebiotics as reliable tools for microbiota-centred prevention and therapy.

6.2. Gut microbiota and probiotics

Probiotics are defined as live microorganisms that, when consumed in adequate amounts, provide health benefits to the host [213]. These microorganisms can produce antimicrobial substances, enhance immune responses, protect against the adhesion of harmful bacteria to the epithelium, stimulate mucosal IgA production, and inhibit the production of bacterial toxins [214]. Lactic acid-producing bacteria (LAB) are particularly significant among gastrointestinal bacteria as they ferment saccharides to produce lactic acid. Probiotics also contribute to the production of short-chain fatty acids (SCFAs), vitamins, bactericidins, and are involved in bile acid metabolism. Found abundantly in fermented foods like kefir, yoghurt, pickles, miso, and kimchi [215].

Clinically, probiotics have been explored across a broad spectrum of chronic non-communicable diseases. Evidence supports their role in gastrointestinal disorders, such as antibiotic-associated diarrhoea and irritable bowel syndrome, as well as in immune-mediated conditions, including atopic dermatitis and allergic rhinitis. Their capacity to modulate the gut–brain axis has also generated interest in psychiatry, where certain strains, termed *psychobiotics* [216], have been shown to alleviate anxiety [217] and depressive symptoms [218]. In preliminary trials, moreover, probiotic supplementation has been linked to improvements in metabolic regulation, cardiovascular risk profiles, and even cancer prevention strategies through immunomodulation [219] and anti-inflammatory pathways. Despite these promising findings, the therapeutic use of probiotics is challenged by substantial variability in clinical outcomes. Efficacy appears to depend on strain-specific properties, dosage, duration of intervention, and host-related factors such as baseline microbiota composition and immune status. Furthermore, in vulnerable populations (e.g., immunocompromised patients, preterm infants), probiotics may carry risks, highlighting the importance of careful strain selection and safety evaluation [220].

Taken together, probiotics exemplify how targeted microbial supplementation can be harnessed for disease prevention and treatment by maintaining or restoring eubiosis. Yet, to translate their potential into consistent clinical practice, large-scale, standardised trials are required to clarify optimal strains, treatment regimens, and patient selection criteria.

6.3. *Gut microbiota and synbiotics*

Synbiotics combine probiotics and prebiotics to create a synergistic effect on host health [215]. In agreement with ISAPP, synbiotics represent a combination of living microorganisms and substrates that bring beneficial effects when ingested by host microorganisms [221]. This dual approach is designed to both supply beneficial microbes and provide them with substrates that enhance their survival, colonization, and metabolic activity.

Their functional roles include regulating gut microbial imbalances, enhancing immune function, and preventing obesity [222]. While the combination of probiotics and prebiotics represents a promising area of research, there is still limited scientific literature supporting their efficacy in dietary supplements. Common synbiotic formulations include *Lactobacillus GG* and/or *Bifidobacteria* combined with omega-3 fatty acids, fructooligosaccharides (FOS), or inulin [223].

Clinically, synbiotics are under investigation in diverse contexts, including allergy prevention, metabolic disorders, and gastrointestinal diseases. Preliminary studies suggest that they may improve glycaemic control in type 2 diabetes, enhance immunological tolerance in allergic conditions, and support weight management in obesity. Their potential also extends to oncology and cardiometabolic disease, where systemic anti-inflammatory effects are particularly relevant [224].

However, despite their theoretical appeal, scientific evidence on synbiotics remains limited compared to that for probiotics or prebiotics alone. Clinical outcomes vary widely depending on the specific strains, prebiotic substrates, and patient populations studied. Standardisation of formulations and rigorous clinical trials are therefore essential to clarify their efficacy and to identify contexts in which synbiotics offer clear advantages over probiotics or prebiotics administered separately.

From a translational perspective, synbiotics illustrate how tailored combinations of microbiota-directed strategies could enhance therapeutic and preventive interventions. Their success, however, will depend on overcoming methodological heterogeneity and on advancing towards precision medicine approaches that integrate dietary, microbial, and host factors.

6.4. *Gut microbiota and paraprobiotics*

The term paraprobiotic refers to non-viable probiotic microorganisms or their cellular components, coined in 2011 [225]. Paraprobiotics are particularly useful in scenarios where live probiotics could pose risks, such as for premature infants, immunocompromised individuals, or patients with sepsis or weakened intestinal barrier [226]. In such cases, administering bacterial fragments or metabolites offers similar therapeutic benefits without the risks associated with live bacterial cells [227]. Paraprobiotics are non-living agents and, for this reason, are easier to produce and store with respect to probiotics [228]. They also pose no risk of bacterial translocation or transfer of antibiotic resistance genes [229] and allow for more precise dosing for reproducible therapeutic effects [225,230].

The production process involves cultivating specific microbial strains followed by deactivation through methods like ionising radiation, ultraviolet light, high-pressure drying, or pH adjustments. Paraprobiotic species with promoting health effects include *Bifidobacterium lactis* Bb12, *Bifidobacterium longum*, *Lactobacillus gasseri* OLL2716, *Saccharomyces cerevisiae*, *Lactobacillus brevis* SBC8803, and *Lactobacillus delbrueckii* subsp. *bulgaricus* OLL1073R-1.

These strains exert effects such as immunomodulation [231] through proteins, peptides, peptidoglycans, lipoteichoic acids, polysaccharides (like glucans), or fragments of genetic material such as AT-rich DNA. Some proteins derived from paraprobiotics can also support intestinal mucosa regeneration and repair the intestinal barrier [230]. Components of yeast cell walls, including β-(1,3)-D-glucan, β-(1,6)-D-glucan, chitin, and mannoproteins, enhance digestion [232].

Although still an emerging field, para-probiotics hold promise for applications in populations where conventional probiotics are contraindicated. Early studies suggest potential benefits in modulating inflammation, reducing infections, and supporting metabolic regulation. Nevertheless, more robust clinical trials are required to establish their efficacy across different chronic disease contexts.

6.5. *Gut microbiota and metabiotics*

Metabiotics consist of structural elements of probiotics, their metabolites, or specific signaling molecules that optimise host-specific physiological functions and influence metabolic, regulatory, and/or behavioral responses connected to the activity of native microbiota [233]. These compounds are present in fermented foods like kefir, kimchi, sauerkraut, tempeh, yoghurt, certain pickles, and in the human body [234]. Metabiotics have gained attention as a biotechnological advancement to mitigate the side effects of live probiotics and are applied in health treatments and functional food development [235]. They include a broad range of bioactive compounds with numerous benefits for the host. Metabiotics can reduce oxidative stress, regulate blood pressure, provide immunomodulatory effects, and exhibit anti-inflammatory and anticancer properties [235,236]. Key components of metabiotics include signaling molecules, dead cells or cell fragments post-metabolism, SCFAs, PUFAs, bacteriocins, polyamines, surface molecules, polysaccharides, peptidoglycans, proteins, and peptides [237].

Research on gut microbiota has underscored the role of biomodulators in maintaining overall health. They influence various systems such as the nervous system, inflammation response, oncology, the gastrointestinal tract, the endocrine system, the urinary tract, the respiratory system, the cardiovascular system, and IS. Recent studies also highlight their potential in combating antibiotic resistance caused by misuse. When antimicrobials are paired with probiotics, healing accelerates through reduced drug dosages. This combined approach improves pathogen elimination while reducing side effects. Such synergy has proven effective in treating oral and vaginal candidiasis, periodontitis, and *Helicobacter pylori* infections [238].

Clinical studies and meta-analyses evaluating probiotic biomodulators for preventing allergic pathologies have yielded conflicting results [239]. Variability in factors such as probiotic strain diversity, treatment duration, study methodology, primary and secondary outcomes evaluated, allergic phenotypes addressed, and patient characteristics (e.g., age and atopy) complicates data interpretation.

Clinically, metabiotics are being investigated as therapeutic agents in chronic conditions such as obesity [240,241], type 2 diabetes, cardiovascular disease, and neurodegenerative disorders [237]. For example, butyrate [242] has shown promise in reducing intestinal inflammation and enhancing gut barrier integrity, while propionate has been linked to improved insulin sensitivity [243]. Furthermore, bioactive metabolites derived from *Lactobacillus* and *Bifidobacterium* species demonstrated immunomodulatory and antioxidant properties relevant to both gastrointestinal [244] and systemic health.

Despite these advances, the translation of metabiotics into clinical practice is still limited. Challenges include the complexity of identifying active metabolites, inter-individual variability in microbial metabolism, and the need for controlled trials to validate efficacy. Nevertheless, metabiotics hold strong potential as precision therapeutics, capable of targeting specific pathways implicated in chronic disease pathogenesis.

6.6. *Gut microbiota and postbiotics*

Postbiotics are a complex blend of beneficial metabolic byproducts or secreted substances from probiotics, found in cell-free supernatants [245]. These may include enzymes, secreted proteins, short-chain fatty acids (SCFAs), vitamins, amino acids, peptides, and organic acids [246]. The term postbiotic, which means after life, refers to substances derived from the metabolism of living microorganisms. Postbiotics are stable, easily transported, and offer extended shelf life while simplifying packaging. Their active components remain intact during delivery to the intestine, where they exert physiological effects [247]. Studies on postbiotics have highlighted their ability to modulate inflammation, reduce pathogen adhesion in the gastrointestinal tract, and address conditions such as obesity [222], hypertension, coronary artery diseases, cancer, and oxidative stress [248]. In addition, postbiotics present strong immunomodulatory and anti-tumour effects. The specific mechanisms at the basis of their action are still unclear. A few experimental studies have been made. Nowadays, postbiotics are often added as functionals to food derivatives such as dairy, vegetables, bread, meat, fish, and other ingredients.

Moreover, postbiotics often preserve the metabolic by-products of probiotics, such as SCFAs, which further contribute to metabolic and immunological benefits.

Clinically, postbiotics have been investigated in the prevention of respiratory and gastrointestinal infections, in allergy modulation, and in the management of chronic inflammatory disorders. Their non-viable nature makes them particularly suitable for vulnerable populations—such as infants, the elderly, and immunocompromised patients—where probiotics might pose safety concerns. Some studies also suggest potential applications in metabolic syndrome, obesity, and neuroinflammatory diseases, although larger and more standardised trials are needed.

Despite these advantages, limitations remain. The precise bioactive components responsible for the observed benefits are not always clearly identified, and inter-individual variability in response persists. Furthermore, most studies to date have been short-term and focused on surrogate outcomes rather than long-term disease endpoints.

6.7. *Fecal microbiota transplantation*

FMT consists of the transplantation of processed fecal material from a healthy donor into a receiver who has suffered from dysbiosis to rebuild a healthy microbial equilibrium. This procedure primarily addresses conditions driven or exacerbated by disturbed microbiota [249] (Fig. 4).

FMT has become the gold standard for treating recurrent or refractory *Clostridioides difficile* infection (rCDI), particularly in patients resistant to antibiotics. Beyond rCDI treatment, its experimental applications are being assessed in other dysbiosis-related conditions [201, 250].

Various protocols have been developed for FMT using different administration methods [251]. These include upper gastrointestinal routes like capsules or nasoenteric tubes targeting the stomach or small intestine (duodenum or jejunum) and lower gastrointestinal routes like enemas or procedures such as flexible sigmoidoscopy and colonoscopy.

Donor screening serves as a critical step in ensuring FMT safety. This process involves a comprehensive review of clinical history alongside an extensive array of laboratory tests aimed at minimizing pathogen transmission risks [252]. Additional donor characteristics linked to a healthy microbiome, such as vaginal delivery, breastfeeding, or adherence to a Mediterranean diet, have been proposed to enhance the effectiveness of FMT in addressing CNCDs [253].

At present, the primary clinical application of FMT lies in treating rCDI [254,255], where its efficacy can reach up to 90 %. This treatment not only quickly restores the recipient's intestinal microbiota but also inhibits the germination and vegetative growth of *C. difficile* [256,257]. Over time, numerous studies have expanded the scope of FMT's potential, demonstrating its effectiveness in managing other chronic conditions. These findings highlight the intricate role of the intestinal microbiota in infectious, metabolic, and inflammatory diseases, with FMT showing promise in influencing microbiota-host interactions through pathways involving immuno-metabolic mechanisms [258].

A notable insight into the efficacy of FMT stemmed from a pilot study that utilized a sterile fecal filtrate, created by passing an FMT suspension through increasingly finer filters down to 0.2 mm. Administering this filtrate to five patients with rCDI yielded outcomes comparable to conventional FMT [259]. This finding suggested that the success of FMT might not be solely dependent on viable bacteria but rather on soluble factors present in the filtrate – viruses, fungi, metabolites, microRNAs (miRNAs), and immune signaling molecules.

Research on bacteriophages (viruses that infect bacteria or archaea) has revealed changes in the virome following FMT across various disease contexts [260]. Notably, recipients' intestinal viromes shifted to resemble those of donors, with these changes persisting for over a year [261].

The theory of niche competition also underpins FMT's efficacy in rCDI treatment. Gut commensals reintroduced through FMT compete with *C. difficile* for essential nutrient sources and some molecules such as succinate, interleukins, and certain amino acids like proline. Additionally, some post-FMT bacteria actively catabolize these nutrients, thereby preventing their availability to *C. difficile*. FMT success has also been linked to the restoration of SCFAs levels, particularly valerate demonstrated dose-dependent inhibitory effects on *C. difficile* growth [262]. Moreover, FMT helps curtail the pathogenicity of *C. difficile* by restoring bile-metabolizing bacteria, enabling processes such as the degradation of taurocholic acid – a germination trigger for *C. difficile* – and increasing production of secondary bile acids like deoxycholic acid, which inhibit vegetative growth.

Beyond rCDI contexts, SCFAs, bile acids, and other microbial metabolites have proven critical for FMT's success in conditions like ulcerative colitis [263]. Dietary approaches have further bolstered outcomes, with studies showing that adhering to anti-inflammatory diets during therapy significantly improves remission rates compared to standard medical protocols [264].

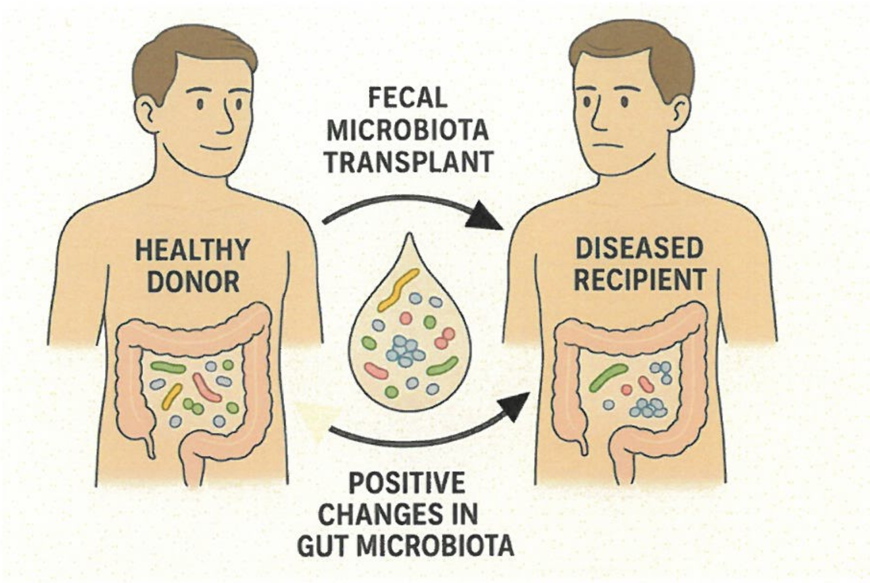


Fig. 4. Fecal microbiota transplant restores eubiosis (Image created with the help of artificial intelligence).

The efficacy of FMT may also hinge on other factors, such as transferring antimicrobial compounds from donor bacteria, like cathelicidins, or inducing changes in host miRNAs, which can influence inflammatory gene expression or reduce intestinal permeability by improving autophagy and addressing intestinal barrier dysfunction. Restoration of the gut barrier has been documented in various contexts, including nonalcoholic fatty liver disease [265] and HIV infections [266]. Additionally, in cases of rCDI, multidrug-resistant bacteria, and severe alcoholic hepatitis, FMT has been associated with reduced invasive infections and bacteremia by limiting the translocation of harmful intestinal bacteria into systemic circulation [267].

Lastly, FMT underscores the dynamic and reciprocal relationship between the gut microbiota and the immune system [83,268], emphasizing its expansive therapeutic potential across diverse health conditions.

In subjects with rCDI receiving FMT, the targeting of secretory immunoglobulin A aligned more closely with that of healthy donor profiles [269,270]. Additionally, immunosenescence markers in the innate and adaptive immune systems appeared to be reversed, and the complexity of serum N-glycan structures, potentially linked to changes in immune function, was reduced.

FMT's immunological effects have also been evaluated in non-CDI contexts. For instance, colonic inflammation can be modulated via IL-10 [270], IBD through Treg cells [144], and bacterial sepsis through alterations in interferon regulatory factor 3 [271].

In animal studies, it has been demonstrated that gut microbiota remodeled by prebiotics as donors for FMT can improve metabolic syndrome. One clinical trial assessing the benefits of FMT in adolescents with metabolic syndrome revealed enhanced insulin sensitivity and glucose metabolism [272]. Moreover, a novel approach known as washed microbiota transplantation (WMT) [273], a method involving added safety measures like bacterial isolation, rinsing, and donor stool quantification, was carried out on a cohort of 237 patients with functional bowel diseases (42 with metabolic syndrome and 195 without). It significantly improved outcomes for patients with metabolic syndrome [274].

Evidence from several studies exploring the role of gut microbiota and FMT in T1D shows that the progression of T1D was either halted or meaningfully slowed [275,276]. Small intestinal levels of *Prevotella* also appeared inversely correlated with residual β-cell function [275]. In a 12-week randomized study of 61 obese participants with T2D, three groups were investigated: FMT plus lifestyle intervention (LSI), FMT alone, and a sham procedure with LSI. The first milestone was obtained by 100 % of the FMT + LSI group, 88.2 % of the FMT-only group, and 22 % of the LSI-only group. Furthermore, FMT increased butyrate-producing bacteria in all cases, while the combination of FMT + LSI also stimulated growth in Bifidobacterium and Lactobacillus compared to FMT alone. Improvements in lipid profiles and liver functions were also observed. Repeated FMT applications demonstrated a sustained and enhanced impact on T2D patients' metabolic outcomes [277]. Another study with 17 T2D patients undergoing FMT reported significant improvements in 11 participants. There was a notable reduction in glycated hemoglobin, fasting glucose, postprandial glucose, and uric acid levels, along with higher postprandial C-peptide (an indicator of insulin secretion). Participants with higher abundances of anaerobic bacteria linked to insulin resistance showed more robust clinical responses [278]. Additionally, FMT or WMT helped diabetic patients by improving distal symmetric polyneuropathy [279] and glycemic variability [280] through modulation of gut microbiota.

In neonates delivered vaginally, maternal gut microbiota colonizes the newborns effectively [77], unlike cesarean-delivered babies [54] who have distinct microbiota compositions [281]. These differences contribute to higher susceptibility to allergic diseases among cesarean-delivered newborns, especially if they are formula-fed rather than breastfed [282]. One study, which utilized maternal stool transplantation in newborns delivered via cesarean section, found that their gut microbiota closely resembled that of vaginally delivered infants [283]. This suggests that FMT could potentially prevent allergies in infants and offers a promising therapeutic strategy for treating pediatric allergic conditions [284].

In spite of positive results from research and clinical practice confirming the efficacy of FMT, critical questions are still without answers. Factors such as disease-specific responses to FMT, ideal dosing regimens, treatment frequency, repeatability, and sustained effectiveness need further exploration. Most available evidence comes from studies with small sample sizes, necessitating larger, high-quality trials. Comprehensive investigations are essential to better understand mechanisms of action, effective therapeutic concentrations, potential side effects, cost feasibility, and long-term implications before FMT can be widely adopted in routine clinical care.

The strategies reviewed in this chapter – ranging from various biomodulators to FMT – illustrate the expanding therapeutic landscape of microbiota modulation. Together, they reflect a paradigm shift from symptom-centred approaches to interventions aimed at restoring ecological balance within the gut.

As regards biomodulators, pre-, pro-, and synbiotics highlight how diet and supplementation can shape microbial communities to promote resilience, immune tolerance, and metabolic health. Para- and post-biotics offer safe and standardised alternatives, extending the use of microbiota-derived benefits to fragile populations. Metabiotics, with their focus on defined bioactive molecules, bring microbiota science closer to precision pharmacology.

As far as it concerns FMT, this technique represents the most comprehensive approach, reconstituting entire microbial ecosystems with transformative potential for both gastrointestinal and extra-intestinal diseases.

Yet, across all these strategies, common challenges remain heterogeneity of clinical outcomes, lack of standardisation, and the need for long-term, high-quality trials. Moreover, their efficacy is influenced by diet, lifestyle, host genetics, and baseline microbiota composition – factors that call for personalized approaches.

Ultimately, maintaining a healthy gut microbiota emerges not only as a therapeutic target but also as a cornerstone of disease prevention. Integrating microbiota-based interventions into broader health strategies may reduce the burden of chronic non-communicable diseases and open new avenues for precision and preventive medicine.

7. Gut microbiota and nutrition

Historically, the colon was considered primarily a storage organ for fluids and indigestible materials [285]. However, research now highlights its role as a fully functioning metabolic organ containing more bioactive cells than any other part of the body [286]. Initial breakthroughs in the 1970s revealed that stool mass comprises mostly bacteria rather than undigested material. A key discovery following this was the realization that the primary energy source for colonic epithelial cells is not glucose but SCFAs, marking a significant shift in understanding its metabolic role [287]. A distinctive characteristic of mucosal epithelia lies in their capability to directly derive and utilize nutrients from dietary intake or the digestion process, circumventing the reliance on blood circulation. However, by the point at which chyle reaches the colon, more than 90 % of proteins and carbohydrates have already been absorbed, leaving behind undigested components such as fiber, starch, and "resistant" proteins. The colon itself does not produce enzymes capable of breaking down these residues. This is where the gut microbiota becomes critical, functioning as a key example of host-microbe symbiosis. The microbiota ferments these indigestible residues to produce SCFAs and gases, including hydrogen and methane, which are primarily absorbed or excreted through respiration [288]. SCFAs contribute substantially to colonic health; for instance, substantial experimental evidence demonstrates that butyrate, a specific SCFA, can reduce tumorigenesis [289]. Moreover, the interplay between diet and gut microbiota leads to the synthesis of various other metabolites with beneficial effects, including vitamins [290]. Nonetheless, it is important to note that microbial metabolism in the gut can also generate compounds detrimental to the mucosa [291].

Emerging evidence from research in animal models and human studies underscores the significant role of the gut microbiota in regulating energy metabolism and influencing the propensity for obesity. Variations in the composition of colonic microbiota between lean and obese individuals, encompassing changes in the relative abundance of *Bacteroidetes* and *Firmicutes* [292], have been identified as determinants of the host's ability to harvest energy from dietary sources [293]. Beyond its role in mucosal health, the metabolic function of the colon can serve as a critical survival mechanism in cases of severe intestinal malabsorption. In such scenarios, gut microbiota-mediated fermentation can recover up to 1000 kilocalories of energy from unabsorbed dietary residues. Additionally, this metabolic activity supports survival in nutrient-deprived states by synthesizing essential vitamins such as folic acid, biotin, and vitamin K [294,295].

One of the earliest studies into the protective effects of dietary patterns on colonic disorders found an absence of non-infectious colonic diseases among Africans consuming a 'traditional' diet rich in fiber from home-ground grains [296]. The study proposed that increased gut transit facilitated by high fiber intake reduces exposure to toxins and carcinogens while increasing stool bulk, this effect decreases constipation and lowers the risk of conditions such as diverticulosis [297].

Diet influences CNCDs risk via multiple mechanisms. First, it may introduce non-absorbable pro-inflammatory molecules derived from food processing or environmental pollutants. Besides, determinates nutrients are important for health and cellular metabolism. The Western diet has been implicated in promoting an aberrant mucosal immune response to commensal bacteria and disrupting intestinal barrier integrity, thereby initiating inflammation in the gut [298]. In contrast, adherence to a Mediterranean diet has demonstrated beneficial outcomes on gut physiology by fostering eubiosis, bolstering intestinal barrier function, and supporting immune health. This restoration of gut health through dietary intervention often creates a positive feedback loop that improves long-term dietary compliance [298].

Unique among tissues in the body, intestinal mucosa is capable of utilizing dietary nutrients directly to sustain structural integrity and functionality [299]. Nutrients, furthermore, regulate metabolic processes essential for maintaining a robust immune system capable of warding off infections and inflammation. Evidence supporting this can be observed in the health and longevity of populations adhering to fiber- and antioxidant-rich diets such as the Mediterranean diet (distinguished by its high content of polyphenols) [300] and traditional Japanese diets [301]. These dietary models exemplify one of the most actionable strategies for preserving overall health through their profound impact on gut microbial composition [302]. Healthy diets are linked not only to reductions in CNCDs but also to deceleration in aging by promoting diverse and balanced gut microbiota populations [303]. Such diets typically minimize ultra-processed foods, refined carbohydrates, and animal-based foods rich in saturated fats while emphasizing plant-based foods such as legumes, whole grains, nuts, fruits, vegetables, and herbs – sources rich in biologically active phytochemicals [304].

7.1. Microbiota and phytochemicals

Phytochemicals constitute a diverse group of bioactive, non-nutritive compounds synthesized by plants, responsible for plant pigmentation, flavor profiles, and aromatic properties. Over 100,000 phytochemicals have been identified to date, including polyphenols, carotenoids, isothiocyanates, alkaloids, phytosterols, and saponins [305]. The bioavailability of these compounds in human diets varies depending on several factors: molecular size, lipophilicity, chemical stability, interaction within the food matrix, and metabolic transformation by the gut microbiota [306]. Phytochemicals, particularly polyphenols [307], are often poorly absorbed in the digestive system, which enables them to reach the large intestine intact. Here, they interact with the gut microbiota and undergo metabolism to form new bioactive microbial metabolites [308]. Both dietary phytochemicals and these metabolites play a beneficial role in maintaining intestinal health by positively impacting intestinal tissues [309]. Once microbial metabolites enter systemic circulation, they act as signaling molecules that mediate host-microbiota interactions and influence immune, metabolic, and neurological functions across various tissues and organs [310]. The balance between the local mucosal immune system and the gut microbiota is crucial for controlling pathogens, encouraging beneficial microbes, and preventing bacterial overgrowth. It is known that gut persistent inflammation leads to the destruction of local and systemic activities [311]. Foods and dietary supplements containing phytochemicals are essential for modulating inflammation, owing to their anti-inflammatory, antioxidant, and immunomodulatory properties. These compounds derive their effectiveness from enhancing the body's natural defenses and indirectly influencing the gut microbiota composition.

7.2. Microbiota's metabolites

Among dietary components produced by bacterial metabolism, SCFAs [312] and amino acids (AAs) [313] serve as key regulators of host physiology.

GPR43, a receptor for SCFAs, has been shown to link bacterial metabolic activity to energy homeostasis in the host [314]. SCFAs, such as acetate, propionate, and butyrate (produced during the fermentation of dietary fibers by anaerobic gut bacteria, together with gases such as H_2 and CO_2) [315], demonstrate numerous health benefits. These include maintaining immune balance, supporting metabolic functions, stabilizing glucose levels, strengthening intestinal barrier integrity, and regulating appetite [316]. SCFAs also contribute positively to the prevention and management of CNCDs [186], in fact, their levels are known to decline in dysbiotic conditions associated with disease [317].

As reported above, AAs also play an integral role in sustaining gut microbiota growth and activity during digestion and absorption. The microbiota contributes to modulating both the total quantity (AA pool) and structural characteristics (AA profile) of amino acids within the gastrointestinal tract [318]. Furthermore, interactions between gut microbes and dietary nitrogenous components, including AAs, are critical for host health and nutrition. These interactions influence the effectiveness of dietary supplementation with AAs [319]. Gut bacteria impact AAs metabolism in ways such as modifying glutathione metabolism [320]. Recent studies have identified specific bacterial species active in the human colon that are involved in protein and amino acid fermentation. For instance, *Clostridium* species metabolize proline and lysine, while *Peptostreptococcus* species process tryptophan and glutamate. Other genera like *Bacteroides*, *Fusobacterium*, and *Veillonella* also play key roles in AAs catabolism within the colon [321]. Advanced molecular research has revealed that some interactions between gut microbiota and AAs metabolism can have either beneficial or harmful effects on host nutrition and overall health [322].

The composition of an individual's gut microbiota significantly influences the metabolism and pharmacokinetics of dietary phytochemicals [304]. Consequently, a person's ability to produce beneficial microbial metabolites from functional foods depends on the specific microbial communities present in their gut [306]. Several factors – such as intestinal permeability, age, disease conditions, drug use (e.g., antibiotics), genetics, and environmental influences – may further impact this process.

Microbial metabolites represent a rapidly advancing area of research that holds promise for discovering new compounds capable of preventing or delaying the onset of CNCDs.

8. Gut microbiota and xenobiotics

Humans are frequently exposed to xenobiotics – environmentally released substances by humans' activities – foreign to biological systems. These include drugs (among these antibiotics), pesticides, heavy metals, and micro- and nano-plastics (Table 4).

Environmental pollutants, aside from drugs, primarily reach humans through food. Living organisms tend to absorb these pollutants at a faster rate than they can eliminate or metabolize them [323]. Host genetics only minimally influences microbiota composition (less than 2 %) compared to environmental factors [324], underscoring the significant role of these factors in causing dysbiosis. Changes in the gut microbiota due to xenobiotics can influence immune system development, thereby increasing the risk of chronic conditions such as IBD [325]. One primary function of the gut microbiota is converting xenobiotic compounds and dietary molecules into bioactive metabolites [326]. Exposure to these compounds affects the interactions between microbial and human metabolites, often leading to changes in microbial physiology and diversity

Table 4
Xenobiotics induced dysbiosis. Abbr. legenda: PCBs (polychlorinated biphenyls); CNCDs (chronic non communicable diseases); SCFAs (short-chain fatty acids); Aas (amino acids); TPA (terephthalic acid, a Polyethylene terephthalate – PET – monomer); BPA (bisphenol A, a Polycarbonate – PC – monomer).

XENOBIOTICS' EFFECTS ON MICROBIOTA			
Xenobiotic	Microbiota alteration	Action's mechanisms	Studies
Antibiotics	Decrease in levels of bacterial diversity and changes in relative abundances	Alter intestinal lipid and plasma metabolic profiles, affect immune system functions and infection resistance.	362, 365, 370,
Phytopharmaceuticals (pesticides)	54 % of the bacterial species sensitive ↑*Bacillalles* ↑*Propionibacteriales* ↑*Propionibacteriaceae*	PCBs exposure during pregnancy causes a long-lasting alteration in the relative abundance of some fetus gut microbiota species.	381, 384, 386
Heavy metals Cadmium Nickel Arsenic Lead Mercury	Gut microbiota's diversity and structure alteration ↑*Collinsella* ↑*Proteobacteria*, ↑*Enterobacteriaceae* ↓*Bifidobacterium* ↑*Firmicutes* ↓*Bacteroides* ↓*Bifidobacterium bifidum* and *longum* ↓*Penicillium* ↑*Bilophila*, ↑*Collinsella*, ↑*Proteobacteri*, ↑*Burkholderiales* ↑*Malassezia restricta* and *globosa* ↑*Actinobacteria*, ↑*Desulfovibrio*, ↑*Methanogens*	Inflammation and CNCDs development, neurotoxicity, intestinal epithelial barrier damage, immune and microbial homeostasis loss, oxidative stress, inflammation, cytotoxic, genotoxic, and carcinogenic effects, cholesterol alteration, glycogenesis decrease, and triglyceride increase, tight junction proteins reduction, leaky gut, metabolic endotoxemia, intestinal and metabolic disorders, neurodegenerative diseases, brain and muscle abscesses, structural alterations, increased permeability, bile acids synthesis, SCFAs, and Aas synthesis interference.	390, 395, 396, 397, 401, 403–407
Micro and nano plastics	Alteration in bacterial diversity and relative abundance ↑*Proteobacteria*	TPA and BPA (plastic-derived metabolites) in the feces – PET and PC biodegradation derived products, additives release into the systemic circulation	431, 432, 435

[327].

8.1. Antibiotics-induced dysbiosis

Research on the impact of antibiotics on gut microbiota began shortly after the discovery of penicillin [328]. Advances in molecular techniques, particularly those independent of culture and based on 16S rRNA gene analysis, have greatly enhanced our understanding of the intestinal microbiota. The 16S rRNA sequence includes conserved regions (common across all bacteria), semi-conserved regions (similar within bacteria of the same phylum), and variable regions, which are used for identifying bacterial species [329]. 16S rDNA sequencing of these regions has uncovered antibiotic-induced dysbiosis, revealing qualitative and quantitative alterations in microbiota composition [330]. Major projects like the Human Microbiome Project [331] and Metagenomics of the Human Intestinal Tract [332] have produced substantial datasets that enrich our understanding of the microbial world, though much of this data remains complex to interpret. Metagenomic approaches have demonstrated associations between dysbiosis and changes in both intestinal lipid profiles and plasma metabolomes [333]. Antibiotics have a profound effect on gut microbiota, causing a sharp decline in bacterial diversity and shifts in relative abundance.

The higher pH in the colon corresponds to its rich microbial diversity and density [334]. In healthy individuals, the Firmicutes and Bacteroidetes phyla dominate (comprising over 90 %), followed by Verrucomicrobia and Actinobacteria [335]. A healthy gut microbiota performs essential roles such as vitamin production, nutrient metabolism, immunomodulation, and protecting against infections by preventing pathogen colonization [336]. Comparative studies across populations from different countries revealed variations in microbiota composition tied to differences in diet, geography, early-life exposures, and genetics [337]. Factors such as age, diet, antibiotics, probiotics, and prebiotics all contribute to shaping dynamic and evolving microbiota throughout life [335].

Antibiotics, however, can disrupt this balance by causing dysbiosis, and growing evidence links such disruptions to altered immune function and reduced infection resistance [338]. Dysbiosis resulting from antibiotic use has been linked to numerous health issues, including neurodegenerative diseases [339], neurological disorders [340], obesity and diabetes [341], IBD [342], Crohn's disease [343], celiac disease [344], and autoimmune conditions such as allergies, juvenile idiopathic arthritis, and asthma [345]. These effects are especially pronounced when antibiotics are taken within the first two years of life, with potential cumulative consequences [346]. While the microbiota shows some resilience (ability to return to a composition close to its original state following antibiotic treatment) [347], this recovery process can take months or even years and is still not fully understood [348].

8.2. Phytopharmaceuticals-induced dysbiosis

The widespread use of pesticides in agriculture has a long history, but their application surged with industrialized farming practices. According to data from the Food and Agriculture Organization of the United Nations (FAO), over four million tons of pesticides are used annually, with China, the United States, and Brazil being the largest consumers. Decades of intensive pesticide use have left residues in soil, sediment, and water samples. Some endocrine-disrupting pesticides, like dichlorodiphenyltrichloroethane (DDT), have been banned in most countries after accumulating evidence of their harm. However, not all nations have phased out these harmful substances entirely [349]. Numerous studies have investigated the occupational hazards associated with pesticide exposure, yet only recently has attention shifted to the health risks posed by regular consumption of agricultural products and water tainted with pesticide residues. Evidence from various studies reveals that pesticides can jeopardize consumer health, particularly through disruptions in the gut microbiota's balance [350].

Recent findings even suggest that gut microbiota could serve as a biomarker for exposure to environmental chemical hazards like pesticides [351]. Notably, common herbicides such as 2,4-dichlorophenoxyacetic acid (2,4-D) and glyphosate, often used in combination due to resistance developed by transgenic crops, have significant effects [352]. Research has shown that glyphosate potentially impacts 54 % of the bacterial species within the human gut microbiota [353]. Despite being banned in 1977 due to their toxic nature, polychlorinated biphenyls (PCBs) persist extensively in the environment and continue to pose risks. Human exposure to PCBs, mainly through ingestion, has been linked to gastrointestinal disruptions, dysbiosis, and heightened susceptibility to neurodevelopmental disorders like autism spectrum disorder [354]. Exposure during pregnancy has been shown to alter the fetal intestinal microbiota for years, increasing certain bacterial groups such as *Bacillalles*, *Propionibacteriales*, and *Propionibacteriaceae* [355].

Despite the gut being colonized at birth, many studies in mice have suggested that the maternal gut microbiota can influence fetal nervous cells' development by placental passage [356]. In addition, breastfeeding influences the earliest intestinal microbiota population; the breast milk may transfer pesticide residues [357]. Recent studies have revealed DDT metabolites and DDT itself, often at higher concentrations respect to the recommended daily limits [358].

8.3. Heavy metals induced dysbiosis

Pollution from heavy metals (HMs), such as arsenic (As), cadmium (Cd), lead (Pb), and mercury (Hg), represents a pervasive and enduring threat, known to disrupt gut microbiota balance [359]. Human exposure occurs through environmental pollution, contaminated food, dental procedures, and industrial or agricultural activities [360]. Dysbiosis caused by HMs can impair physiological and metabolic functions, trigger inflammation, and contribute to CNCDs [361]. HMs act as potent neurotoxins, particularly harmful during critical periods such as early pregnancy [362]. Xenobiotics – including phthalates, bisphenol A, particulate matter, and HMs – are known to interfere with the microbiota-gut-brain axis [323], potentially affecting mental and neurological health [363]. While findings sometimes vary, research consistently shows that HMs exposure alters gut microbiota diversity and structure [364]. Moreover, exposure to environmental pollutants such as HMs damages the intestinal epithelial barrier, disrupting immune and microbial balance [365] while impairing metabolic activity and triggering inflammatory responses and cellular damage [366]. Animal studies have demonstrated that HMs exert toxic effects by altering gut bacterial composition and function. These changes impact metabolites, leading to pathological conditions [367]. Intestinal dysbiosis linked to HMs can damage the intestinal lining, heightening oxidative stress and inflammation while causing cytotoxic, genotoxic, and carcinogenic effects that contribute to CNCDs [367]. Recent studies highlight the ability of intestinal bacteria and host signaling systems to regulate immunity and strengthen intestinal barrier defenses through microbial metabolites [368]. The gut microbiota plays a crucial role in mitigating HMs toxicity and maintaining homeostasis [369]. Consequently, utilizing intestinal biomodulators offers promising potential for treating intestinal barrier dysfunction caused by xenobiotics [370]. Notably, exposure to elevated HM levels (with the exception of Cd) has been associated with an increased abundance of *Collinsella*, a proinflammatory bacterial genus from the Coriobacteriaceae family known as pathobionts [371]. This genus influences metabolic pathways by altering cholesterol absorption in the gut, reducing liver glycogenesis, and increasing triglyceride synthesis [372]. Dietary fiber intake has been shown to lower HM concentrations in the blood [373], while low dietary fiber correlates with higher *Collinsella* abundance [374]. Furthermore, *Collinsella* contributes to leaky gut by reducing tight junction protein expression in intestinal cells, a hallmark of metabolic endotoxemia [375].

The prevalence of certain pathogenic bacteria linked to inflammation, such as *Collinsella*, *Proteobacteria*, and *Enterobacteriaceae*, has been observed to increase under As exposure. Conversely, a reduction in *Bifidobacterium*, some strains of which are considered probiotics, has been noted. Notably, this negative effect on *Bifidobacterium* populations can be reversed by simultaneous Zn exposure [369]. A related study found that urinary As levels in newborns exhibited a direct correlation with *Firmicutes* and an inverse correlation with *Bacteroides*. These two dominant intestinal phyla are also closely associated with conditions like obesity and cancer [376].

Pb exposure has similarly adverse effects, causing a decline in the beneficial bacteria *Bifidobacterium bifidum* and *longum*, as well as in the fungal genus *Penicillium*. Concurrently, it promotes the proliferation of pathogenic groups such as *Bilophila*, *Collinsella*, *Proteobacteria*, and *Burkholderiales*, along with pathogenic fungi like *Malassezia restricta* and *globosa*. Some species of *Malassezia* are known to contribute to conditions such as seborrheic dermatitis, pityriasis versicolor, folliculitis, and may exacerbate atopic dermatitis [377]. Pb also compromises the integrity of the intestinal barrier, facilitating the entry of microbial metabolites, including bile acids and SCFAs, into the intrahepatic circulation, which can subsequently trigger systemic damage in both animals and humans [378].

Hg exposure, particularly through dietary sources such as fish compared to rice, has been linked to an increase in three specific bacterial taxa: Actinobacteria, Desulfovibrio, and Methanogens. Fish consumption remains the primary route of Hg exposure in humans due to widespread aquatic contamination [379]. Among these bacteria, Desulfovibrio functions as a pathobiont implicated not only in gut-related disorders but also in neurodegenerative diseases such as Parkinson's disease [380]. Methanogens, on the other hand, have been associated with brain and muscle abscess formation, dysbiosis, metabolic abnormalities, and colorectal cancer [381].

Cd demonstrates pronounced negative effects on the gut microbiota, including structural disruption, enhanced permeability, and interference with the biosynthesis of bile acids, SCFAs, and Aas [382]. When combined with other toxins, Cd exacerbates gut dysbiosis, thereby causing dysfunction across multiple organ systems [383]. Similar impacts have also been reported for Ni [384].

To counteract these detrimental effects of HMs exposure on the gut microbiome and overall health, several dietary interventions have been proposed. These include increased consumption of fiber (particularly pectin from whole grains) antioxidant-rich foods, and intestinal biomodulators. A moderate intake of animal-derived fat and protein is also recommended [385]. Additionally, diets enriched with essential nutrients, vitamins, high-quality proteins, bioactive peptides, and phytochemicals abundant in antioxidants may serve as effective strategies to mitigate HM-induced toxicity and gut dysbiosis [386].

8.4. Micro and nano plastics induced dysbiosis

Plastics play an indispensable role in modern society due to their versatility and application across diverse sectors – from consumer goods like cosmetics, kitchenware, and food packaging to advanced domains such as medical devices and construction. Despite increasing global efforts to phase out single-use plastics and promote recyclable or plastic-free alternatives, plastic waste continues to pose a significant threat to environmental sustainability. Its accumulation in soil and marine ecosystems has reached unprecedented levels, leading some experts to refer to the current epoch as the "Plasticene" [387]. Projections suggest that an additional 33 billion tons of plastic could be introduced to the environment by 2050 [388].

In natural ecosystems, plastics undergo biodegradation via physical, chemical, or biological mechanisms, or through a combination thereof [389]. These degradation processes produce particles classified into four size categories: macroplastics (>25 mm), mesoplastics (5–25 mm), microplastics (<5 mm), and nanoplastics (<1 μm or <100 nm) [390]. Although the distinction between microplastics and nanoplastics remains contentious, they are often collectively referred to as micro- and nano-plastics (MNPs). Plastics and MNPs can absorb metals and persistent organic pollutants [391]. Additionally, their hydrophobic nature, durability, and buoyancy make MNPs potential carriers for a range of pathogens [392]. A significant concern regarding MNPs in the environment is their entry into the food chain and eventual impact on diet, posing risks to both food safety and human health. While recent studies have explored interactions between plastics, environmental microorganisms, and microbiomes, limited research has addressed how MNPs interact with the gut microbiome or how these interactions may influence human physiology and health [393]. Human exposure to MNPs occurs primarily through ingestion, followed by inhalation and skin absorption.

Considering ingestion as the primary route, the interaction between MNPs and the gut microbiota warrants closer examination. Ingesting MNPs through food chains has been shown to affect intestinal microbial populations. While a healthy individual's microbiota exhibits resilience by quickly restoring balance after disturbances, chronic disruptions can lead to an imbalance, or dysbiosis, which is linked to various CNCDs [394,395]. Animal models are commonly used to study intestinal ecosystems; however, due to physiological differences between animals and humans, such results are not always directly applicable. *In vitro* gastrointestinal models thus offer an alternative method to provide more reliable insights [396]. The distribution of ingested MNPs within the body remains poorly understood. The chemical stability of plastics makes enzymatic or chemical degradation challenging, especially as mammalian intestines lack specialized enzymes to break them down. As a result, digestion does not significantly degrade plastic particles. Larger microplastics (>150 μm) tend to adhere to the intestinal mucus layer and come into direct contact with epithelial cells. Smaller particles (<150 μm) are capable of penetrating the mucus layer. MNP uptake depends on particle size and occurs through several mechanisms, including transcytosis via microfold cells, endocytosis through enterocytes, perabsorption through intestinal villus clefts (following enterocyte loss), and paracellular uptake [397]. Prolonged exposure to high quantities of MNPs may lead to systemic toxicity as these particles can reach deep into organs due to their small size [398].

MNPs also have a high surface area relative to their volume, which facilitates organic matter adsorption and creates new habitats for microbial species collectively termed the "Plastisphere" [389]. Many microorganisms within this plastisphere can consume MNPs and transform them into environmentally friendly carbon compounds [399]. Beyond environmental microbiomes, gut microbiota also plays a role in potentially degrading MNPs [400]. Although there is substantial evidence about insect gut bacteria capable of breaking down MNPs, much less is known about these mechanisms in mammals. Simulations of human intestinal environments have shown biofilm formation that may support biotransformation of microplastics by human fecal microbiota, hinting at the gut microbiome's potential to biodegrade plastics [401]. These findings suggest that dietary microplastics may be reduced into nano-sized particles within the digestive system, where they could linger temporarily. Certain members of the gut microbiota, particularly pathogenic-capable bacteria like Proteobacteria and other pathobionts, may adapt to environmental changes brought about by plastic accumulation in the gut. These bacteria could not only survive but also exploit MNPs as a novel carbon source. Moreover, such metabolic processes might involve degrading MNPs into monomers, which other microbial groups may assimilate and further break down. However, direct evidence of these capabilities in humans remains lacking. There is currently no definitive understanding of enzymatic activities, microbial functions, or plastic metabolites involved in MNP biodegradation within the human gut. A recent study has identified terephthalic acid (TPA), a monomer of polyethylene terephthalate (PET), and bisphenol A (BPA), a monomer of polycarbonate (PC), in the feces of both adults and infants. This finding indicates a potential association between plastic-derived metabolites and the biodegradation of PET and PC polymers by gut microbiota [402].

Beyond synthetic polymers, plastics also incorporate numerous additives designed to confer specific physical and chemical properties required for various commercial applications. For this reason, it is crucial to consider the diverse degradation products resulting from plastics, as they vary based on the type of polymer, additives, and degradation conditions. Many of these products can detrimentally impact human health, notably formaldehyde, benzene, and furan, which are recognized for their carcinogenic and mutagenic properties [403]. The particularly high bioavailability of degradation byproducts from micro- and nanoplastics (MNPs) in the intestine, facilitated by gut microbiota, raises significant concerns for human and animal health. For instance, para-nonylphenol, one of the most extensively studied plastic degradation compounds, has been implicated in various pathologies due to its inhibitory effects on cell growth and physiological functions across multiple organisms [404]. The metabolism of environmental chemical substances by human gut microbiota plays a pivotal role in releasing such additives into the system [405]. The microbial transformations within the intestine can yield byproducts that are either absorbed into systemic circulation or exert localized effects on epithelial cells of the gastrointestinal tract. These interactions may have implications for both host physiology and microbial ecology [406]. Although further research is required, emerging *in vitro* and *in vivo* evidence underscores the gut microbiota as a biological conduit linking exposure to MNPs with implications for human health. This connection consequently extends to environmental health, emphasizing its reliance on anthropogenic activities.

9. Conclusion

The human gastrointestinal tract is home to complex and dynamic populations of microorganisms, collectively known as the gut microbiota, which exist in a mutually beneficial relationship with the host through intricate biochemical interactions. This symbiotic correlation between host and microbiota arises from the dynamic interplay among microorganisms and between the microbiota and the host. A balanced and diverse microbial community, referred to as eubiosis, is vital for maintaining immune and metabolic stability in the host. This balance also helps counteract the growth of pathogenic organisms. Under conditions of eubiosis, in fact, microbiota exerts regulatory effects on various organ systems and physiological functions through complex and finely tuned mechanisms. Conversely, disruptions in the microbiota's composition, known as dysbiosis, are increasingly linked to the development of numerous diseases. While further advancements in fields such as 'omics' are necessary, the ability to influence gut microbial populations through biomodulators, such as probiotics, psychobiotics, prebiotics, symbiotics, paraprobiotics, metabiotics, and postbiotics, presents an intriguing opportunity to restore or maintain eubiosis.

There is ample scientific evidence supporting the designation of the intestinal microbiota as a "bacterial organ" with vital local and systemic functions. Intestinal commensal microorganisms, indeed, play a key role in regulating immune responses, making it theoretically possible to mitigate or even prevent related diseases by addressing microbial imbalances. This intricate integration transforms the human body into a holobiont, a "superorganism" composed of eukaryotic cells alongside a multitude of microbial entities. As Henderson and Wilson aptly proposed through the term "*Homo bacteriens*", this concept captures the mutualistic relationship between humans and their resident microbes [21].

Early life represents a critical window for immunometabolic programming, and for infants who are not breastfed, supplementing their formulas with tailored biomodulators targeting the gut microbiota can be a valuable step toward mirroring the benefits provided by breast milk. Despite the exciting potential of this approach, additional scientific validation is required before such strategies can be fully integrated into clinical practice on a broad scale.

Dietary interventions targeting the gut microbiota are rapidly gaining recognition as essential tools for managing metabolic and immune-mediated disorders. Fiber-rich foods, polyphenols, and fermented products have been shown to promote beneficial bacterial groups like Bifidobacteria and Lactobacilli. Prebiotics such as inulin and fructooligosaccharides selectively encourage the growth of health-promoting microbes, while probiotics introduce live strains directly into the gut ecosystem. Postbiotics (non-living bacterial byproducts) also provide therapeutic benefits, including anti-inflammatory effects. Synbiotics combine prebiotics and probiotics for enhanced microbial resilience and functionality.

FMT has shown notable success in reestablishing eubiosis in cases of rCDIs and is being investigated as a treatment option for conditions like metabolic syndrome and IBD. Personalized nutrition strategies, informed by microbiome analysis, aim to customize dietary interventions according to individual microbial profiles, potentially enhancing both prevention and treatment outcomes. These advancements highlight the promising role of microbiota modulation in managing CNCDs.

The gut microbiota has also emerged as a critical factor in the development and management of conditions such as allergies, obesity, diabetes, and gastrointestinal diseases. It serves both as a reflection of the host's overall health and as a potential mediator of physiological processes. Recognizing microbiota as a therapeutic target emphasizes the need for interdisciplinary collaboration across fields such as microbiology, nutrition science, immunology, and systems medicine.

Restoring eubiosis through strategic interventions such as diet modification, prebiotics, probiotics, or microbiota-targeted therapies like FMT holds significant promise for managing CNCDs. Achieving these advancements will require collaborative efforts spanning research initiatives, clinical applications, and public health strategies.

Considering the above, one of the primary challenges in microbiota research lies in the substantial variability in its composition among individuals. This variability is largely shaped by an interplay of factors encompassed within the exposome, such as diet, genetics, and lifestyle. Such diversity complicates efforts to establish clear cause-and-effect relationships between CNCDs and specific microbial components. Furthermore, while correlations between intestinal microbiota composition and CNCDs are now well-documented, the underlying biological mechanisms remain unclear, posing another significant hurdle. The limited insights gained from cross-sectional studies further highlight this issue, as these studies lack the depth to capture the dynamic nature of host-microbiota interactions over time. Large-scale, longitudinal research efforts incorporating multi-omics approaches are needed to unravel microbiota changes, their relevance to disease progression, and microbiota-host dynamics. To address this complexity, research must prioritize exploring how diet, biomodulators assumption, and lifestyle influence microbiota composition and associated disease outcomes [407]. This includes the development of effective biomodulators targeting the gut microbiome with the potential to transform therapeutic strategies. Investigating dietary patterns, lifestyle habits, and emerging therapies can help tailor recommendations based on individual microbiota profiles, fostering improved prevention and management of various diseases [408].

Despite significant progress, challenges persist. Factors such as interindividual variability in genetic background, environmental exposure, and microbial diversity make it difficult to establish a standard "healthy" microbiome. The absence of defined microbial reference ranges and inconsistencies in findings across populations further impede causal inference. Consequently, there is an urgent need for standardized methodologies and longitudinal studies to better establish causation and assess therapeutic efficacy. The adoption of multi-omics technologies – spanning metagenomics, metabolomics, transcriptomics, and proteomics – represents a revolutionary step forward in identifying microbial functions and their impact on host physiology.

Simultaneously, advancements in machine learning and systems biology provide powerful tools for modeling complex microbiota-host networks, enabling the identification of predictive biomarkers for disease progression or therapeutic response. International collaborations and open-access microbiome databases are also vital to facilitate breakthroughs and accelerate clinical applications.

Human health should be approached holistically as it is intricately connected to our environment and lifestyle. All components of the exposome interact dynamically and influence each other in ways that can determine overall well-being or contribute to the development of CNCDs (Fig. 5). Achieving better health outcomes necessitates considering this broader perspective on human-environment interactions.

Personalized nutrition, precise microbiota modulation, and next-generation probiotics hold immense promises for revolutionizing health outcomes. Future strategies will likely integrate microbiome profiles with individual genetic, metabolic, and immune data to create precision-based therapies. Microbiota-driven diagnostics and companion tools will pave the way for tailored treatments ranging from dietary interventions to engineered microbial consortia targeting specific health challenges.

Beyond personalized care, public health initiatives focused on population-level strategies (such as promoting breastfeeding, minimizing antibiotic misuse, and encouraging diets rich in fiber and diversity) offer opportunities to enhance overall microbial resilience and reduce the prevalence of CNCDs. Meanwhile, research on microbiota-modulating molecules, live biotherapeutic agents, and developments in synthetic biology represent a transformative potential to redesign microbial ecosystems with accuracy.

Capitalizing on the microbiome's potential will require collective research efforts, technological progress, and the integration of microbiota science into healthcare and public health frameworks. As we transition into an era where microbiome-informed medicine becomes a reality, the gut microbiota is poised to play a central role in both disease prevention and personalized treatment approaches. In this regard, microbiota engineering techniques such as precision microbiome editing and synthetic ecology stand out as promising avenues for intervention. These emerging methods show great potential for manipulating microbiota composition and functionality to treat diseases and promote long-term health [409]. Advanced multi-omics research will be essential for achieving a more comprehensive understanding of microbiota-host interactions. Integrative approaches combining genomics, transcriptomics, proteomics, metabolomics, and microbiomics will help uncover key microbial biomarkers, therapeutic targets, and molecular mechanisms underlying CNCDs. Such advances will strengthen the foundation for personalized medicine tailored to individual microbiota characteristics, heralding a new era of preventive and therapeutic innovation.

In conclusion, the significance of the gut microbiome for human health is only beginning to be understood. Current knowledge represents just the surface of an expansive field. With further exploration of approximately 800 bacterial species and their 7000 distinct strains, our capability to prevent and treat chronic non-communicable diseases is expected to grow exponentially.

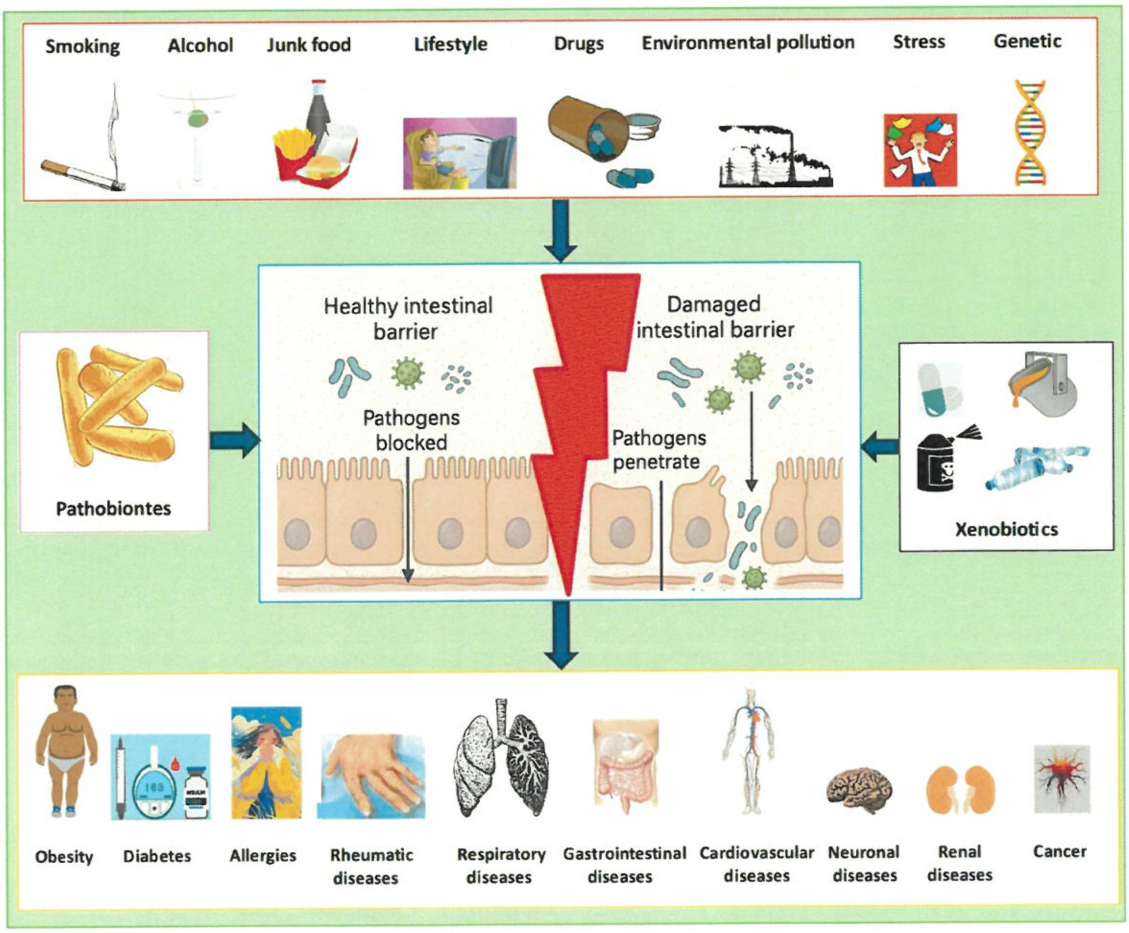


Fig. 5. External and internal factors determining intestinal barrier impairment and consequent systemic diseases (images from: https://pixabay.com/it/; https://chatgpt.com/; https://posturafacile.it/).

CRediT authorship contribution statement

Carmela Colica: Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Data curation, Conceptualization. **Immacolata Vecchio:** Writing – review & editing, Visualization, Supervision, Data curation.

Declarations

During the preparation of this work the authors used plagiarism removal software in order to improve language and readability and AI to create some figures or parts of them. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Abbreviations

CNCDs	Chronic non-communicable diseases
WHO	World Health Organization
GALT	Gut-Associated Lymphoid Tissues
APCs	antigen-presenting cells
IFN	interferon
IL	interleukin
T1D	type 1 diabetes
Treg	regulatory T lymphocytes
IS	immune system
IBD	irritable bowel disease
SCFAs	short-chain fatty acids
GPR	G protein-coupled receptor
LPS	lipopolysaccharides
ECS	endocannabinoid system
TNF-α	tumour necrosis factor alpha
MS	metabolic syndrome
ANGPTL4	angiopoietin-like protein 4
FIAF	fasting-induced adipose factor
T2D	type 2 diabetes
EECs	Enteroendocrine Cells
FMT	Faecal microbiota transplantation
PUFAs	polyunsaturated fatty acids
LAB	lactic acid-producing bacteria
rCDI	recurrent or refractory *Clostridioides difficile* infection
WMT	Washed microbiota transplantation
LSI	lifestyle intervention
AAs	amino acids
FAO	Food and Agriculture Organization of the United Nations
PCBs	polychlorinated biphenyls
HMs	Heavy metals
MNPs	micro-nano-plastics
TPA	terephthalic acid
BPA	bisphenol A
PET	Polyethylene terephthalate
PC	Polycarbonate

Data availability

No data was used for the research described in the article.

References

[1] S.M.S. Islam, T.D. Purnat, N.T.A. Phuong, U. Mwingira, K. Schacht, G. Fröschl, Non-communicable diseases (NCDs) in developing countries: a symposium report, Glob. Health 10 (1) (Dec. 2014) 81, https://doi.org/10.1186/s12992-014-0081-9.

[2] R. Geneau, et al., Raising the priority of preventing chronic diseases: a political process, Lancet 376 (9753) (Nov. 2010) 1689–1698, https://doi.org/10.1016/S0140-6736(10)61414-6.

[3] D.J. Raiten, et al., Inflammation and nutritional science for programs/policies and interpretation of research evidence (INSPIRE), J. Nutr. 145 (5) (May 2015) 1039S–1108S, https://doi.org/10.3945/jn.114.194571.

[4] C.E. West, et al., The gut microbiota and inflammatory noncommunicable diseases: associations and potentials for gut microbiota therapies, J. Allergy Clin. Immunol. 135 (1) (Jan. 2015) 3–13, https://doi.org/10.1016/j.jaci.2014.11.012.

[5] L. Di Renzo, et al., Role of personalized nutrition in chronic-degenerative diseases, Nutrients 11 (8) (Jul. 2019) 1707, https://doi.org/10.3390/nu11081707.

[6] M.H. Mohajeri, et al., The role of the microbiome for human health: from basic science to clinical applications, Eur. J. Nutr. 57 (S1) (May 2018) 1–14, https://doi.org/10.1007/s00394-018-1703-4.

[7] L.K. Ursell, J.L. Metcalf, L.W. Parfrey, R. Knight, Defining the human microbiome, Nutr. Rev. 70 (Aug. 2012) S38–S44, https://doi.org/10.1111/j.1753-4887.2012.00493.x.

[8] G. Berg, et al., Microbiome definition re-visited: old concepts and new challenges, Microbiome 8 (1) (Dec. 2020) 103, https://doi.org/10.1186/s40168-020-00875-0.

[9] B.B. Finlay, Are noncommunicable diseases communicable? Science 367 (6475) (Jan. 2020) 250–251, https://doi.org/10.1126/science.aaz3834 (1979).

[10] Y. Belkaid, T.W. Hand, Role of the microbiota in immunity and inflammation, Cell 157 (1) (Mar. 2014) 121–141, https://doi.org/10.1016/j.cell.2014.03.011.

[11] S.L. Prescott, Early-life environmental determinants of allergic diseases and the wider pandemic of inflammatory noncommunicable diseases, J. Allergy Clin. Immunol. 131 (1) (Jan. 2013) 23–30, https://doi.org/10.1016/j.jaci.2012.11.019.

[12] P.D. Cani, M. Osto, L. Geurts, A. Everard, Involvement of gut microbiota in the development of low-grade inflammation and type 2 diabetes associated with obesity, Gut Microbes 3 (4) (Jul. 2012) 279–288, https://doi.org/10.4161/gmic.19625.

[13] X. Ke, Presence of multiple independent effects in risk loci of common complex human diseases, Am. J. Hum. Genet. 91 (1) (Jul. 2012) 185–192, https://doi.org/10.1016/j.ajhg.2012.05.020.

[14] D. Rojo, et al., Exploring the human microbiome from multiple perspectives: factors altering its composition and function, FEMS Microbiol. Rev. 41 (4) (Jul. 2017) 453–478, https://doi.org/10.1093/femsre/fuw046.

[15] A. Noce, et al., Impact of gut microbiota composition on onset and progression of chronic non-communicable diseases, Nutrients 11 (5) (May 2019) 1073, https://doi.org/10.3390/nu11051073.

[16] M. Khalil, et al., Unraveling the role of the human gut microbiome in health and diseases, Microorganisms 12 (11) (Nov. 2024) 2333, https://doi.org/10.3390/microorganisms12112333.

[17] V. Vinelli, et al., Effects of dietary fibers on short-chain fatty acids and gut microbiota composition in healthy adults: a systematic review, Nutrients 14 (13) (Jun. 2022) 2559, https://doi.org/10.3390/nu14132559.

[18] E. Miko, A. Csaszar, J. Bodis, K. Kovacs, The maternal–fetal gut microbiota axis: physiological changes, dietary influence, and modulation possibilities, Life 12 (3) (Mar. 2022) 424, https://doi.org/10.3390/life12030424.

[19] F. Bäckhed, R.E. Ley, J.L. Sonnenburg, D.A. Peterson, J.I. Gordon, Host-bacterial mutualism in the human intestine, Science 307 (5717) (Mar. 2005) 1915–1920, https://doi.org/10.1126/science.1104816 (1979).

[20] I.L. Brito, et al., Transmission of human-associated microbiota along family and social networks, Nat. Microbiol. 4 (6) (Mar. 2019) 964–971, https://doi.org/10.1038/s41564-019-0409-6.

[21] B. Henderson, M. Wilson, Homo bacteriens and a network of surprise, J. Med. Microbiol. 45 (6) (Dec. 1996) 393–394, https://doi.org/10.1099/00222615-45-6-393.

[22] L. Margulis, Symbiotic theory of the origin of eukaryotic organelles; criteria for proof, Symp. Soc. Exp. Biol. 29 (1975) 21–38.

[23] R. Cazzolla Gatti, Endogenosymbiosis: from hypothesis to empirical evidence towards a unified symbiogenetic theory (UST), Theor Biol Forum 111 (1–2) (Jan. 2018) 13–26, https://doi.org/10.19272/201811402002.

[24] E.C. Davis, M. Wang, S.M. Donovan, The role of early life nutrition in the establishment of gastrointestinal microbial composition and function, Gut Microbes 8 (2) (Mar. 2017) 143–171, https://doi.org/10.1080/19490976.2016.1278104.

[25] I. Sekirov, S.L. Russell, L.C.M. Antunes, B.B. Finlay, Gut microbiota in health and disease, Physiol. Rev. 90 (3) (Jul. 2010) 859–904, https://doi.org/10.1152/physrev.00045.2009.

[26] G.M. Nava, T.S. Stappenbeck, Diversity of the autochthonous colonic microbiota, Gut Microbes 2 (2) (Mar. 2011) 99–104, https://doi.org/10.4161/gmic.2.2.15416.

[27] J. Penders, et al., Factors influencing the composition of the intestinal microbiota in early infancy, Pediatrics 118 (2) (Aug. 2006) 511–521, https://doi.org/10.1542/peds.2005-2824.

[28] T. Jost, C. Lacroix, C. Braegger, C. Chassard, Stability of the maternal gut microbiota during late pregnancy and early lactation, Curr. Microbiol. 68 (4) (Apr. 2014) 419–427, https://doi.org/10.1007/s00284-013-0491-6.

[29] V.L. Miniello, et al., Gut immunobiosis and biomodulators, Nutrients 15 (9) (Apr. 2023) 2114, https://doi.org/10.3390/nu15092114.

[30] M. Fassarella, E.E. Blaak, J. Penders, A. Nauta, H. Smidt, E.G. Zoetendal, Gut microbiome stability and resilience: elucidating the response to perturbations in order to modulate gut health, Gut 70 (3) (Mar. 2021) 595–605, https://doi.org/10.1136/gutjnl-2020-321747.

[31] I. Sharon, et al., The core human microbiome: does it exist and how can we find it? A critical review of the concept, Nutrients 14 (14) (Jul. 2022) 2872, https://doi.org/10.3390/nu14142872.

[32] S.S. Yoon, E.-K. Kim, W.-J. Lee, Functional genomic and metagenomic approaches to understanding gut microbiota–animal mutualism, Curr. Opin. Microbiol. 24 (Apr. 2015) 38–46, https://doi.org/10.1016/j.mib.2015.01.007.

[33] F. Carbone, et al., Metabolomics, Lipidomics, and Immunometabolism, 2021, pp. 319–328, https://doi.org/10.1007/978-1-0716-1311-5_24.

[34] T. Clavel, et al., Intestinal microbiota in metabolic diseases, Gut Microbes 5 (4) (Jul. 2014) 544–551, https://doi.org/10.4161/gmic.29331.

[35] H.W. Virgin, The virome in mammalian physiology and disease, Cell 157 (1) (Mar. 2014) 142–150, https://doi.org/10.1016/j.cell.2014.02.032.

[36] G. Musso, R. Gambino, M. Cassader, Interactions between gut microbiota and host metabolism predisposing to obesity and diabetes, Annu. Rev. Med. 62 (1) (Feb. 2011) 361–380, https://doi.org/10.1146/annurev-med-012510-175505.

[37] R.D. Heijtz, et al., Normal gut microbiota modulates brain development and behavior, Proc. Natl. Acad. Sci. 108 (7) (Feb. 2011) 3047–3052, https://doi.org/10.1073/pnas.1010529108.

[38] N. Cerf-Bensussan, V. Gaboriau-Routhiau, The immune system and the gut microbiota: friends or foes? Nat. Rev. Immunol. 10 (10) (Oct. 2010) 735–744, https://doi.org/10.1038/nri2850.

[39] A. Korecka, V. Arulampalam, The gut microbiome: scourge, sentinel or spectator? J. Oral Microbiol. 4 (1) (Jan. 2012) 9367, https://doi.org/10.3402/jom.v4i0.9367.

[40] A.M. O'Hara, F. Shanahan, The gut flora as a forgotten organ, EMBO Rep. 7 (7) (Jul. 2006) 688–693, https://doi.org/10.1038/sj.embor.7400731.

[41] R. Luoto, M.C. Collado, S. Salminen, E. Isolauri, Reshaping the gut microbiota at an early age: functional impact on obesity risk? Ann. Nutr. Metab. 63 (Suppl. 2) (2013) 17–26, https://doi.org/10.1159/000354896.

[42] H.A. Swain Ewald, P.W. Ewald, Natural selection, the microbiome, and public health, Yale J. Biol. Med. 91 (4) (Dec. 2018) 445–455.

[43] S. Possemiers, et al., The intestinal environment in health and disease – recent insights on the potential of intestinal bacteria to influence human health, Curr. Pharm. Des. 15 (18) (Jun. 2009) 2051–2065, https://doi.org/10.2174/138161209788489159.

[44] M.J. McFall-Ngai, Unseen forces: the influence of bacteria on animal development, Dev. Biol. 242 (1) (Feb. 2002) 1–14, https://doi.org/10.1006/dbio.2001.0522.

[45] M. V Selma, J.C. Espín, F.A. Tomás-Barberán, Interaction between phenolics and gut microbiota: role in human health, J. Agric. Food Chem. 57 (15) (Aug. 2009) 6485–6501, https://doi.org/10.1021/jf902107d.

[46] K. Venema, Role of gut microbiota in the control of energy and carbohydrate metabolism, Curr. Opin. Clin. Nutr. Metab. Care 13 (4) (Jul. 2010) 432–438, https://doi.org/10.1097/MCO.0b013e32833a8b60.

[47] G. Escobedo, E. López-Ortiz, I. Torres-Castro, Gut microbiota as a key player in triggering obesity, systemic inflammation and insulin resistance, Rev. Invest. Clin. 66 (5) (2014) 450–459.

[48] S. Matamoros, C. Gras-Leguen, F. Le Vacon, G. Potel, M.-F. de La Cochetiere, Development of intestinal microbiota in infants and its impact on health, Trends Microbiol. 21 (4) (Apr. 2013) 167–173, https://doi.org/10.1016/j.tim.2012.12.001.

[49] A. Pant, T.K. Maiti, D. Mahajan, B. Das, Human gut microbiota and drug metabolism, Microb. Ecol. 86 (1) (Jul. 2023) 97–111, https://doi.org/10.1007/s00248-022-02081-x.

[50] I.D. Iliev, et al., Microbiota-mediated mechanisms of mucosal immunity across the lifespan, Nat. Immunol. (Sep. 2025), https://doi.org/10.1038/s41590-025-02281-w.

[51] I.I. López-Tenorio, et al., Primary prevention strategy for non-communicable diseases (NCDs) and their risk factors: the role of intestinal microbiota, Biomedicines 12 (11) (Nov. 2024) 2529, https://doi.org/10.3390/biomedicines12112529.

[52] E. Guven-Maiorov, C.-J. Tsai, R. Nussinov, Structural host-microbiota interaction networks, PLoS Comput. Biol. 13 (10) (Oct. 2017) e1005579, https://doi.org/10.1371/journal.pcbi.1005579.

[53] D.A. Chistiakov, Y.V. Bobryshev, E. Kozarov, I.A. Sobenin, A.N. Orekhov, Intestinal mucosal tolerance and impact of gut microbiota to mucosal tolerance, Front. Microbiol. 5 (Jan. 2015), https://doi.org/10.3389/fmicb.2014.00781.

[54] F. Bäckhed, et al., Dynamics and stabilization of the human gut microbiome during the first year of life, Cell Host Microbe 17 (6) (Jun. 2015) 852, https://doi.org/10.1016/j.chom.2015.05.012.

[55] R.M. Torrazza, J. Neu, The developing intestinal microbiome and its relationship to health and disease in the neonate, J. Perinatol. 31 (S1) (Apr. 2011) S29–S34, https://doi.org/10.1038/jp.2010.172.

[56] T. Takiishi, C.I.M. Fenero, N.O.S. Câmara, Intestinal barrier and gut microbiota: shaping our immune responses throughout life, Tissue Barriers 5 (4) (Oct. 2017) e1373208, https://doi.org/10.1080/21688370.2017.1373208.

[57] N. Fukasawa, et al., The gut–organ axis: clinical aspects and immune mechanisms, Allergol. Int. (Feb. 2025), https://doi.org/10.1016/j.alit.2025.01.004.

[58] D.C. Baumgart, A.U. Dignass, Intestinal barrier function, Curr. Opin. Clin. Nutr. Metab. Care 5 (6) (Nov. 2002) 685–694, https://doi.org/10.1097/00075197-200211000-00012.

[59] J. Penders, E.E. Stobberingh, P.A. van den Brandt, C. Thijs, The role of the intestinal microbiota in the development of atopic disorders, Allergy 62 (11) (Nov. 2007) 1223–1236, https://doi.org/10.1111/j.1398-9995.2007.01462.x.

[60] N. Hasan, H. Yang, Factors affecting the composition of the gut microbiota, and its modulation, PeerJ 7 (Aug. 2019) e7502, https://doi.org/10.7717/peerj.7502.

[61] A. Masotti, Interplays between gut microbiota and gene expression regulation by miRNAs, Front. Cell. Infect. Microbiol. 2 (2012), https://doi.org/10.3389/fcimb.2012.00137.

[62] L.B. McKenna, et al., MicroRNAs control intestinal epithelial differentiation, architecture, and barrier function, Gastroenterology 139 (5) (Nov. 2010) 1654–1664.e1, https://doi.org/10.1053/j.gastro.2010.07.040.

[63] L.V. Rizzo, R.H. Dekruyff, D.T. Umetsu, R.R. Caspi, Regulation of the interaction between Th1 and Th2 T cell clones to provide help for antibody production *in vivo*, Eur. J. Immunol. 25 (3) (Mar. 1995) 708–716, https://doi.org/10.1002/eji.1830250312.

[64] S.L. Friedlander, et al., Viral infections, cytokine dysregulation and the origins of childhood asthma and allergic diseases, Pediatr. Infect. Dis. J. 24 (11) (Nov. 2005) S170–S176, https://doi.org/10.1097/01.inf.0000187273.47390.01.

[65] D.P. Strachan, Hay fever, hygiene, and household size, Br. Med. J. 299 (6710) (Nov. 1989) 1259–1260, https://doi.org/10.1136/bmj.299.6710.1259.

[66] J.W. Gerrard, C.A. Geddes, P.L. Reggin, C.D. Gerrard, S. Horne, Serum IgE levels in white and metis communities in Saskatchewan, Ann. Allergy 37 (2) (Aug. 1976) 91–100.

[67] J.D. Bufford, J.E. Gern, The hygiene hypothesis revisited, Immunol. Allergy Clin. 25 (2) (May 2005) 247–262, https://doi.org/10.1016/j.iac.2005.03.005.

[68] E.M. Brown, M. Sadarangani, B.B. Finlay, The role of the immune system in governing host-microbe interactions in the intestine, Nat. Immunol. 14 (7) (Jul. 2013) 660–667, https://doi.org/10.1038/ni.2611.

[69] A. Taylor, J. Verhagen, K. Blaser, M. Akdis, C.A. Akdis, Mechanisms of immune suppression by interleukin-10 and transforming growth factor-β: the role of T regulatory cells, Immunology 117 (4) (Apr. 2006) 433–442, https://doi.org/10.1111/j.1365-2567.2006.02321.x.

[70] S. Sakaguchi, K. Wing, Y. Onishi, P. Prieto-Martin, T. Yamaguchi, Regulatory T cells: how do they suppress immune responses? Int. Immunol. 21 (10) (Oct. 2009) 1105–1111, https://doi.org/10.1093/intimm/dxp095.

[71] X. Meng, J.A. Layhadi, S.T. Keane, N.J.K. Cartwright, S.R. Durham, M.H. Shamji, Immunological mechanisms of tolerance: central, peripheral and the role of T and B cells, Asia Pac Allergy 13 (4) (Dec. 2023) 175–186, https://doi.org/10.5415/apallergy.0000000000000128.

[72] C.E. West, M.C. Jenmalm, S.L. Prescott, The gut microbiota and its role in the development of allergic disease: a wider perspective, Clin. Exp. Allergy 45 (1) (Jan. 2015) 43–53, https://doi.org/10.1111/cea.12332.

[73] A. Shreiner, G. B. Huffnagle, and M. C. Noverr, 'The "Microflora Hypothesis" of allergic disease', in GI Microbiota and Regulation of the Immune System, New York, NY: Springer New York, pp. 113–134. doi: 10.1007/978-0-387-09550-9_10.

[74] S.L. Russell, B.B. Finlay, The impact of gut microbes in allergic diseases, Curr. Opin. Gastroenterol. 28 (6) (Nov. 2012) 563–569, https://doi.org/10.1097/MOG.0b013e3283573017.

[75] H. Chung, D.L. Kasper, Microbiota-stimulated immune mechanisms to maintain gut homeostasis, Curr. Opin. Immunol. 22 (4) (Aug. 2010) 455–460, https://doi.org/10.1016/j.coi.2010.06.008.

[76] G. Galazzo, et al., Development of the microbiota and associations with birth mode, diet, and atopic disorders in a longitudinal analysis of stool samples, collected from infancy through early childhood, Gastroenterology 158 (6) (May 2020) 1584–1596, https://doi.org/10.1053/j.gastro.2020.01.024.

[77] M.G. Dominguez-Bello, et al., Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns, Proc. Natl. Acad. Sci. 107 (26) (Jun. 2010) 11971–11975, https://doi.org/10.1073/pnas.1002601107.

[78] S.J. Song, M.G. Dominguez-Bello, R. Knight, How delivery mode and feeding can shape the bacterial community in the infant gut, Can. Med. Assoc. J. 185 (5) (Mar. 2013) 373–374, https://doi.org/10.1503/cmaj.130147.

[79] H.E. Jakobsson, et al., Decreased gut microbiota diversity, delayed bacteroidetes colonisation and reduced Th1 responses in infants delivered by caesarean section, Gut 63 (4) (Apr. 2014) 559–566, https://doi.org/10.1136/gutjnl-2012-303249.

[80] E. Esteve, W. Ricart, J.-M. Fernández-Real, Gut microbiota interactions with obesity, insulin resistance and type 2 diabetes, Curr. Opin. Clin. Nutr. Metab. Care 14 (5) (Sep. 2011) 483–490, https://doi.org/10.1097/MCO.0b013e328348c06d.

[81] V.L. Miniello, et al., Gut microbiota biomodulators, when the stork comes by the scalpel, Clin. Chim. Acta 451 (Dec. 2015) 88–96, https://doi.org/10.1016/j.cca.2015.01.022.

[82] S. Sakaguchi, K. Wing, T. Yamaguchi, Dynamics of peripheral tolerance and immune regulation mediated by treg, Eur. J. Immunol. 39 (9) (Sep. 2009) 2331–2336, https://doi.org/10.1002/eji.200939688.

[83] C.L. Maynard, C.O. Elson, R.D. Hatton, C.T. Weaver, Reciprocal interactions of the intestinal microbiota and immune system, Nature 489 (7415) (Sep. 2012) 231–241, https://doi.org/10.1038/nature11551.

[84] R.E. Ley, P.J. Turnbaugh, S. Klein, J.I. Gordon, Human gut microbes associated with obesity, Nature 444 (7122) (Dec. 2006) 1022–1023, https://doi.org/10.1038/4441022a.

[85] G.S. Hotamisligil, Inflammation and metabolic disorders, Nature 444 (7121) (Dec. 2006) 860–867, https://doi.org/10.1038/nature05485.
[86] D.J. Dudley, 1 the immune system in health and disease, Baillieres Clin Obstet Gynaecol 6 (3) (Sep. 1992) 393–416, https://doi.org/10.1016/S0950-3552(05)80003-3.
[87] J.L. Linehan, et al., Non-classical immunity controls microbiota impact on skin immunity and tissue repair, Cell 172 (4) (Feb. 2018) 784–796.e18, https://doi.org/10.1016/j.cell.2017.12.033.
[88] X. Cui, Y. Cong, Role of gut microbiota in the development of some autoimmune diseases, J. Inflamm. Res. 18 (Mar. 2025) 4409–4419, https://doi.org/10.2147/JIR.S515618.
[89] P.J. Delves, I.M. Roitt, The immune system, N. Engl. J. Med. 343 (1) (Jul. 2000) 37–49, https://doi.org/10.1056/NEJM200007063430107.
[90] J. Genuneit, et al., Overview of systematic reviews in allergy epidemiology, Allergy 72 (6) (Jun. 2017) 849–856, https://doi.org/10.1111/all.13123.
[91] J.P. Lopes, S. Sicherer, Food allergy: epidemiology, pathogenesis, diagnosis, prevention, and treatment, Curr. Opin. Immunol. 66 (Oct. 2020) 57–64, https://doi.org/10.1016/j.coi.2020.03.014.
[92] S.F. Thomsen, Atopic dermatitis: natural history, diagnosis, and treatment, ISRN Allergy 2014 (Apr. 2014) 1–7, https://doi.org/10.1155/2014/354250.
[93] Z. Wang, et al., Global, regional, and national burden of asthma and its attributable risk factors from 1990 to 2019: a systematic analysis for the global burden of disease study 2019, Respir. Res. 24 (1) (Jun. 2023) 169, https://doi.org/10.1186/s12931-023-02475-6.
[94] P.J. Turner, E. Jerschow, T. Umasunthar, R. Lin, D.E. Campbell, R.J. Boyle, Fatal anaphylaxis: mortality rate and risk factors, J. Allergy Clin. Immunol. Pract. 5 (5) (Sep. 2017) 1169–1178, https://doi.org/10.1016/j.jaip.2017.06.031.
[95] J. Zheng, et al., Global, regional, and national epidemiology of allergic diseases in children from 1990 to 2021: findings from the global burden of disease study 2021, BMC Pulm. Med. 25 (1) (Jan. 2025) 54, https://doi.org/10.1186/s12890-025-03518-y.
[96] C.P. Wild, Complementing the genome with an "Exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology, Cancer Epidemiol. Biomarkers Prev. 14 (8) (Aug. 2005) 1847–1850, https://doi.org/10.1158/1055-9965.EPI-05-0456.
[97] H. Mostafavi Abdolmaleky, J.-R. Zhou, Gut microbiota dysbiosis, oxidative stress, inflammation, and epigenetic alterations in metabolic diseases, Antioxidants 13 (8) (Aug. 2024) 985, https://doi.org/10.3390/antiox13080985.
[98] M. Vrijheid, The exposome: a new paradigm to study the impact of environment on health, Thorax 69 (9) (Sep. 2014) 876–878, https://doi.org/10.1136/thoraxjnl-2013-204949.
[99] L. Di Renzo, et al., Exploring the exposome spectrum: unveiling endogenous and exogenous factors in non-communicable chronic diseases, Diseases 12 (8) (Aug. 2024) 176, https://doi.org/10.3390/diseases12080176.
[100] C. Milani, et al., The first microbial colonizers of the human gut: composition, activities, and health implications of the infant gut microbiota, Microbiol. Mol. Biol. Rev. 81 (4) (Dec. 2017), https://doi.org/10.1128/MMBR.00036-17.
[101] G. Rigon, C. Vallone, V. Lucantoni, F. Signore, Maternal factors Pre- and during delivery contribute to gut microbiota shaping in newborns, Front. Cell. Infect. Microbiol. 2 (2012), https://doi.org/10.3389/fcimb.2012.00093.
[102] L.C. Roger, A. Costabile, D.T. Holland, L. Hoyles, A.L. McCartney, Examination of faecal bifidobacterium populations in breast- and formula-fed infants during the first 18 months of life, Microbiology (N. Y.) 156 (11) (Nov. 2010) 3329–3341, https://doi.org/10.1099/mic.0.043224-0.
[103] J.E. Koenig, et al., Succession of microbial consortia in the developing infant gut microbiome, Proc. Natl. Acad. Sci. 108 (supplement_1) (Mar. 2011) 4578–4585, https://doi.org/10.1073/pnas.1000081107.
[104] A. Bergström, et al., Establishment of intestinal microbiota during early life: a longitudinal, explorative study of a large cohort of Danish infants, Appl. Environ. Microbiol. 80 (9) (May 2014) 2889–2900, https://doi.org/10.1128/AEM.00342-14.
[105] L.R. Dugas, et al., Gut microbiota, short chain fatty acids, and obesity across the epidemiologic transition: the METS-microbiome study protocol, BMC Public Health 18 (1) (Dec. 2018) 978, https://doi.org/10.1186/s12889-018-5879-6.
[106] P.G. Gavin, E.E. Hamilton-Williams, The gut microbiota in type 1 diabetes: friend or foe? Curr. Opin. Endocrinol. Diabetes Obes. 26 (4) (Aug. 2019) 207–212, https://doi.org/10.1097/MED.0000000000000483.
[107] M. Dzidic, T.R. Abrahamsson, A. Artacho, M.C. Collado, A. Mira, M.C. Jenmalm, Oral microbiota maturation during the first 7 years of life in relation to allergy development, Allergy 73 (10) (Oct. 2018) 2000–2011, https://doi.org/10.1111/all.13449.
[108] P. Andreo-Martínez, N. García-Martínez, E.P. Sánchez-Samper, A.E. Martínez-González, An approach to gut microbiota profile in children with autism spectrum disorder, Environ Microbiol Rep 12 (2) (Apr. 2020) 115–135, https://doi.org/10.1111/1758-2229.12810.
[109] Y. Hirata, S. Ihara, K. Koike, Targeting the complex interactions between microbiota, host epithelial and immune cells in inflammatory bowel disease, Pharmacol. Res. 113 (Nov. 2016) 574–584, https://doi.org/10.1016/j.phrs.2016.09.044.
[110] C.R. Mareş, M.O. Săsăran, C.O. Mărginean, Small intestinal bacterial overgrowth and childhood malnutrition: a comprehensive review of available evidence, Nutrients 16 (24) (Dec. 2024) 4319, https://doi.org/10.3390/nu16244319.
[111] S.G. Plötz, M. Wiesender, A. Todorova, J. Ring, What is new in atopic dermatitis/eczema? Expet Opin. Emerg. Drugs 19 (4) (Dec. 2014) 441–458, https://doi.org/10.1517/14728214.2014.953927.
[112] J. Spergel, Atopic dermatitis and the atopic march, J. Allergy Clin. Immunol. 112 (6) (Dec. 2003) S118–S127, https://doi.org/10.1016/j.jaci.2003.09.033.
[113] A. Weinstein, Asthma, a comprehensive clinical review, Dela J Public Health 3 (1) (Mar. 2017) 10–22, https://doi.org/10.32481/djph.2017.03.003.
[114] I. Tarrant, B.B. Finlay, Like mother, like child: the maternal microbiome impacts offspring asthma, Cell Rep. Med. 3 (8) (Aug. 2022) 100722, https://doi.org/10.1016/j.xcrm.2022.100722.
[115] A. Bush, Pathophysiological mechanisms of asthma, Front. Pediatr. 7 (Mar) (2019), https://doi.org/10.3389/fped.2019.00068.
[116] Y. Yao, X. Cai, W. Fei, Y. Ye, M. Zhao, C. Zheng, The role of short-chain fatty acids in immunity, inflammation and metabolism, Crit. Rev. Food Sci. Nutr. 62 (1) (Jan. 2022) 1–12, https://doi.org/10.1080/10408398.2020.1854675.
[117] D. Zheng, T. Liwinski, E. Elinav, Interaction between microbiota and immunity in health and disease, Cell Res. 30 (6) (Jun. 2020) 492–506, https://doi.org/10.1038/s41422-020-0332-7.
[118] R. Moradzadeh, M.A. Mansournia, T. Baghfalaki, H. Nadrian, P. Gustafson, L. C. McCandless, The impact of maternal smoking during pregnancy on childhood asthma: adjusted for exposure misclassification; results from the national health and nutrition examination survey, 2011–2012, Ann. Epidemiol. 28 (10) (Oct. 2018) 697–703, https://doi.org/10.1016/j.annepidem.2018.07.011.
[119] A.M. García-Serna, E. Martín-Orozco, T. Hernández-Caselles, E. Morales, Prenatal and perinatal environmental influences shaping the neonatal immune system: a focus on asthma and allergy origins, Int. J. Environ. Res. Publ. Health 18 (8) (Apr. 2021) 3962, https://doi.org/10.3390/ijerph18083962.
[120] M.M. Alhasan, et al., Antibiotic use during pregnancy increases offspring asthma severity in a dose-dependent manner, Allergy 75 (8) (Aug. 2020) 1979–1990, https://doi.org/10.1111/all.14234.
[121] L.E.K. Gray, M. O'Hely, S. Ranganathan, P.D. Sly, P. Vuillermin, The maternal diet, gut bacteria, and bacterial metabolites during pregnancy influence offspring asthma, Front. Immunol. 8 (Mar) (2017), https://doi.org/10.3389/fimmu.2017.00365.
[122] K. Douros, M. Moustaki, S. Tsabouri, A. Papadopoulou, M. Papadopoulos, K. N. Priftis, Prenatal maternal stress and the risk of asthma in children, Front. Pediatr. 5 (Sep. 2017), https://doi.org/10.3389/fped.2017.00202.
[123] J.G. Natalini, S. Singh, L.N. Segal, The dynamic lung microbiome in health and disease, Nat. Rev. Microbiol. 21 (4) (Apr. 2023) 222–235, https://doi.org/10.1038/s41579-022-00821-x.
[124] A. Ver Heul, J. Planer, A.L. Kau, The human microbiota and asthma, Clin. Rev. Allergy Immunol. 57 (3) (Dec. 2019) 350–363, https://doi.org/10.1007/s12016-018-8719-7.
[125] A. Jagodzinski, E. Zielinska, L. Laczmanski, L. Hirnle, The early years of life. Are they influenced by our microbiome? Ginekol. Pol. 90 (4) (Apr. 2019) 228–232, https://doi.org/10.5603/GP.2019.0041.
[126] K.E. Fujimura, S. V Lynch, Microbiota in allergy and asthma and the emerging relationship with the gut microbiome, Cell Host Microbe 17 (5) (May 2015) 592–602, https://doi.org/10.1016/j.chom.2015.04.007.
[127] J. Penders, et al., New insights into the hygiene hypothesis in allergic diseases, Gut Microbes 5 (2) (Mar. 2014) 239–244, https://doi.org/10.4161/gmic.27905.
[128] D. Galeana-Cadena, et al., Winds of change a tale of: asthma and microbiome, Front. Microbiol. 14 (Dec. 2023), https://doi.org/10.3389/fmicb.2023.1295215.
[129] T. Bieber, Atopic dermatitis, N. Engl. J. Med. 358 (14) (Apr. 2008) 1483–1494, https://doi.org/10.1056/NEJMra074081.
[130] N. Arpaia, et al., Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation, Nature 504 (7480) (Dec. 2013) 451–455, https://doi.org/10.1038/nature12726.
[131] K.E. McCauley, et al., Heritable vaginal bacteria influence immune tolerance and relate to early-life markers of allergic sensitization in infancy, Cell Rep. Med. 3 (8) (Aug. 2022) 100713, https://doi.org/10.1016/j.xcrm.2022.100713.
[132] S. Morrill, N.M. Gilbert, A.L. Lewis, Gardnerella vaginalis as a cause of bacterial vaginosis: appraisal of the evidence from in vivo models, Front. Cell. Infect. Microbiol. 10 (Apr. 2020), https://doi.org/10.3389/fcimb.2020.00168.
[133] E. Zubeldia-Varela, T.C. Barker-Tejeda, D. Obeso, A. Villaseñor, D. Barber, M. Pérez-Gordo, Microbiome and allergy: new insights and perspectives, J Investig. Allergol. Clin. Immunol. 32 (5) (Oct. 2022) 327–344, https://doi.org/10.18176/jiaci.0852.
[134] J.-F. Bach, Revisiting the hygiene hypothesis in the context of autoimmunity, Front. Immunol. 11 (Jan. 2021), https://doi.org/10.3389/fimmu.2020.615192.
[135] L. Xiao, F. Zhao, Microbial transmission, colonisation and succession: from pregnancy to infancy, Gut 72 (4) (Apr. 2023) 772–786, https://doi.org/10.1136/gutjnl-2022-328970.
[136] R.C. Robertson, A.R. Manges, B.B. Finlay, A.J. Prendergast, The human microbiome and child growth – first 1000 days and beyond, Trends Microbiol. 27 (2) (Feb. 2019) 131–147, https://doi.org/10.1016/j.tim.2018.09.008.
[137] P. Kleniewska, R. Pawliczak, The link between dysbiosis, inflammation, oxidative stress, and asthma—the role of probiotics, prebiotics, and antioxidants, Nutrients 17 (1) (Dec. 2024) 16, https://doi.org/10.3390/nu17010016.
[138] J. Wurm, N. Curtis, P. Zimmermann, The effect of antibiotics on the intestinal microbiota in children - a systematic review, Frontiers in Allergy 5 (Oct. 2024), https://doi.org/10.3389/falgy.2024.1458688.
[139] E. Ionescu, C.R. Nagler, The role of intestinal bacteria in promoting tolerance to food, Curr. Opin. Immunol. 91 (Dec. 2024) 102492, https://doi.org/10.1016/j.coi.2024.102492.
[140] Human Microbiome Project Consortium, Structure, function and diversity of the healthy human microbiome, Nature 486 (7402) (Jun. 2012) 207–214, https://doi.org/10.1038/nature11234.

[141] H.A. Brough, et al., Early intervention and prevention of allergic diseases, Allergy 77 (2) (Feb. 2022) 416–441, https://doi.org/10.1111/all.15006.
[142] V. Notarbartolo, M. Carta, S. Accomando, M. Giuffrè, The first 1000 days of life: how changes in the microbiota can influence food allergy onset in children, Nutrients 15 (18) (Sep. 2023) 4014, https://doi.org/10.3390/nu15184014.
[143] O.I. Iweala, C.R. Nagler, The microbiome and food allergy, Annu. Rev. Immunol. 37 (1) (Apr. 2019) 377–403, https://doi.org/10.1146/annurev-immunol-042718-041621.
[144] B. Akagbosu, et al., Novel antigen-presenting cell imparts Treg-dependent tolerance to gut microbiota, Nature 610 (7933) (Oct. 2022) 752–760, https://doi.org/10.1038/s41586-022-05309-5.
[145] T. Feehley, et al., Healthy infants harbor intestinal bacteria that protect against food allergy, Nat. Med. 25 (3) (Mar. 2019) 448–453, https://doi.org/10.1038/s41591-018-0324-z.
[146] E. Crestani, et al., Untargeted metabolomic profiling identifies disease-specific signatures in food allergy and asthma, J. Allergy Clin. Immunol. 145 (3) (Mar. 2020) 897–906, https://doi.org/10.1016/j.jaci.2019.10.014.
[147] R. Bao, L.A. Hesser, Z. He, X. Zhou, K.C. Nadeau, C.R. Nagler, Fecal microbiome and metabolome differ in healthy and food-allergic twins, J. Clin. Investig. 131 (2) (Jan. 2021), https://doi.org/10.1172/JCI141935.
[148] S. Wang, et al., Relationship between maternal–infant gut microbiota and infant food allergy, Front. Microbiol. 13 (Nov. 2022), https://doi.org/10.3389/fmicb.2022.933152.
[149] K. Su, et al., Early infancy dysbiosis in food protein-induced enterocolitis syndrome: a prospective cohort study, Allergy 78 (6) (Jun. 2023) 1595–1604, https://doi.org/10.1111/all.15644.
[150] M. Kalliomäki, P. Kirjavainen, E. Eerola, P. Kero, S. Salminen, E. Isolauri, Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing, J. Allergy Clin. Immunol. 107 (1) (Jan. 2001) 129–134, https://doi.org/10.1067/mai.2001.111237.
[151] J. Penders, et al., Molecular fingerprinting of the intestinal microbiota of infants in whom atopic eczema was or was not developing, Clin. Exp. Allergy 36 (12) (Dec. 2006) 1602–1608, https://doi.org/10.1111/j.1365-2222.2006.02599.x.
[152] M.F. Böttcher, E.K. Nordin, A. Sandin, T. Midtvedt, B. Björkstén, Microflora-associated characteristics in faeces from allergic and nonallergic infants, Clin. Exp. Allergy 30 (11) (Nov. 2000) 1591–1596, https://doi.org/10.1046/j.1365-2222.2000.00982.x.
[153] N. Dera, et al., Impact of early-life microbiota on immune system development and allergic disorders, Biomedicines 13 (1) (Jan. 2025) 121, https://doi.org/10.3390/biomedicines13010121.
[154] V. Tremaroli, F. Bäckhed, Functional interactions between the gut microbiota and host metabolism, Nature 489 (7415) (Sep. 2012) 242–249, https://doi.org/10.1038/nature11552.
[155] P.J. Turnbaugh, et al., A core gut microbiome in obese and lean twins, Nature 457 (7228) (Jan. 2009) 480–484, https://doi.org/10.1038/nature07540.
[156] R.E. Ley, F. Bäckhed, P. Turnbaugh, C.A. Lozupone, R.D. Knight, J.I. Gordon, Obesity alters gut microbial ecology, Proc. Natl. Acad. Sci. 102 (31) (Aug. 2005) 11070–11075, https://doi.org/10.1073/pnas.0504978102.
[157] P.J. Turnbaugh, F. Bäckhed, L. Fulton, J.I. Gordon, Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome, Cell Host Microbe 3 (4) (Apr. 2008) 213–223, https://doi.org/10.1016/j.chom.2008.02.015.
[158] M. Kalliomäki, M. Carmen Collado, S. Salminen, E. Isolauri, Early differences in fecal microbiota composition in children may predict overweight, Am. J. Clin. Nutr. 87 (3) (Mar. 2008) 534–538, https://doi.org/10.1093/ajcn/87.3.534.
[159] S. Dogra, et al., Dynamics of infant gut microbiota are influenced by delivery mode and gestational duration and are associated with subsequent adiposity, mBio 6 (1) (Feb. 2015), https://doi.org/10.1128/mBio.02419-14.
[160] C. Vael, S.L. Verhulst, V. Nelen, H. Goossens, K.N. Desager, Intestinal microflora and body mass index during the first three years of life: an observational study, Gut Pathog. 3 (1) (2011) 8, https://doi.org/10.1186/1757-4749-3-8.
[161] E.A. Murphy, K.T. Velazquez, K.M. Herbert, Influence of high-fat diet on gut microbiota, Curr. Opin. Clin. Nutr. Metab. Care 18 (5) (Sep. 2015) 515–520, https://doi.org/10.1097/MCO.0000000000000209.
[162] M.A. Hildebrandt, et al., High-fat diet determines the composition of the murine gut microbiome independently of obesity, Gastroenterology 137 (5) (Nov. 2009) 1716–1724.e2, https://doi.org/10.1053/j.gastro.2009.08.042.
[163] F. Borgo, et al., Relative abundance in bacterial and fungal gut microbes in obese children: a case control study, Child. Obes. 13 (1) (Feb. 2017) 78–84, https://doi.org/10.1089/chi.2015.0194.
[164] Y.-R. Chae, Y.R. Lee, Y.-S. Kim, H.-Y. Park, Diet-induced gut dysbiosis and leaky gut syndrome, J. Microbiol. Biotechnol. 34 (4) (Apr. 2024) 747–756, https://doi.org/10.4014/jmb.2312.12031.
[165] F. Di Vincenzo, A. Del Gaudio, V. Petito, L.R. Lopetuso, F. Scaldaferri, Gut microbiota, intestinal permeability, and systemic inflammation: a narrative review, Intern Emerg Med 19 (2) (Mar. 2024) 275–293, https://doi.org/10.1007/s11739-023-03374-w.
[166] N. Kobyliak, O. Virchenko, T. Falalyeyeva, Pathophysiological role of host microbiota in the development of obesity, Nutr. J. 15 (1) (Dec. 2015) 43, https://doi.org/10.1186/s12937-016-0166-9.
[167] P. Cani, N. Delzenne, The role of the gut microbiota in energy metabolism and metabolic disease, Curr. Pharm. Des. 15 (13) (May 2009) 1546–1558, https://doi.org/10.2174/138161209788168164.
[168] N. Kamada, S.-U. Seo, G.Y. Chen, G. Núñez, Role of the gut microbiota in immunity and inflammatory disease, Nat. Rev. Immunol. 13 (5) (May 2013) 321–335, https://doi.org/10.1038/nri3430.
[169] R. Burcelin, Regulation of metabolism: a cross talk between gut microbiota and its human host, Physiology 27 (5) (Oct. 2012) 300–307, https://doi.org/10.1152/physiol.00023.2012.
[170] M.I. Lassenius, et al., Bacterial endotoxin activity in human serum is associated with dyslipidemia, insulin resistance, obesity, and chronic inflammation, Diabetes Care 34 (8) (Aug. 2011) 1809–1815, https://doi.org/10.2337/dc10-2197.
[171] F. Bäckhed, J.K. Manchester, C.F. Semenkovich, J.I. Gordon, Mechanisms underlying the resistance to diet-induced obesity in germ-free mice, Proc. Natl. Acad. Sci. 104 (3) (Jan. 2007) 979–984, https://doi.org/10.1073/pnas.0605374104.
[172] C. Grootaert, T. Van de Wiele, W. Verstraete, M. Bracke, B. Vanhoecke, Angiopoietin-like protein 4: health effects, modulating agents and structure–function relationships, Expert Rev. Proteomics 9 (2) (Apr. 2012) 181–199, https://doi.org/10.1586/epr.12.12.
[173] S. Mandard, et al., The fasting-induced adipose Factor/angiopoietin-like protein 4 is physically associated with lipoproteins and governs plasma lipid levels and adiposity, J. Biol. Chem. 281 (2) (Jan. 2006) 934–944, https://doi.org/10.1074/jbc.M506519200.
[174] A. Xu, et al., Angiopoietin-like protein 4 decreases blood glucose and improves glucose tolerance but induces hyperlipidemia and hepatic steatosis in mice, Proc. Natl. Acad. Sci. 102 (17) (Apr. 2005) 6086–6091, https://doi.org/10.1073/pnas.0408452102.
[175] M.R. Robciuc, et al., Serum angiopoietin-like 4 protein levels and expression in adipose tissue are inversely correlated with obesity in monozygotic twins, J. Lipid Res. 52 (8) (Aug. 2011) 1575–1582, https://doi.org/10.1194/jlr.P015867.
[176] F. Bäckhed, et al., The gut microbiota as an environmental factor that regulates fat storage, Proc. Natl. Acad. Sci. 101 (44) (Nov. 2004) 15718–15723, https://doi.org/10.1073/pnas.0407076101.
[177] A. Korecka, et al., ANGPTL4 expression induced by butyrate and rosiglitazone in human intestinal epithelial cells utilizes independent pathways, Am. J. Physiol. Gastrointest. Liver Physiol. 304 (11) (Jun. 2013) G1025–G1037, https://doi.org/10.1152/ajpgi.00293.2012.
[178] Y. Peng, D. Hu, Q. Luo, D. Peng, Angiopoietin-like protein 4 may be an interplay between serum uric acid and triglyceride-rich lipoprotein cholesterol, Front. Cardiovasc. Med. 9 (May 2022), https://doi.org/10.3389/fcvm.2022.863687.
[179] M.J. Khan, K. Gerasimidis, C.A. Edwards, M.G. Shaikh, Role of gut microbiota in the aetiology of obesity: proposed mechanisms and review of the literature, J Obes 2016 (2016) 1–27, https://doi.org/10.1155/2016/7353642.
[180] P. Saeedi, et al., Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the international diabetes Federation diabetes Atlas, 9th edition, Diabetes Res. Clin. Pract. 157 (Nov. 2019) 107843, https://doi.org/10.1016/j.diabres.2019.107843.
[181] Y. Sanz, M. Olivares, Á. Moya-Pérez, C. Agostoni, Understanding the role of gut microbiome in metabolic disease risk, Pediatr. Res. 77 (1–2) (Jan. 2015) 236–244, https://doi.org/10.1038/pr.2014.170.
[182] C.O. Iatcu, A. Steen, M. Covasa, Gut microbiota and complications of Type-2 diabetes, Nutrients 14 (1) (Dec. 2021) 166, https://doi.org/10.3390/nu14010166.
[183] N. Larsen, et al., Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults, PLoS One 5 (2) (Feb. 2010) e9085, https://doi.org/10.1371/journal.pone.0009085.
[184] Z. Zhou, B. Sun, D. Yu, C. Zhu, Gut microbiota: an important player in type 2 diabetes mellitus, Front. Cell. Infect. Microbiol. 12 (Feb. 2022), https://doi.org/10.3389/fcimb.2022.834485.
[185] R.K. Al-Ishaq, S.M. Samuel, D. Büsselberg, The influence of gut microbial species on diabetes mellitus, Int. J. Mol. Sci. 24 (9) (May 2023) 8118, https://doi.org/10.3390/ijms24098118.
[186] G. den Besten, K. van Eunen, A.K. Groen, K. Venema, D.-J. Reijngoud, B. M. Bakker, The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism, J. Lipid Res. 54 (9) (Sep. 2013) 2325–2340, https://doi.org/10.1194/jlr.R036012.
[187] J.K. Paul, M. Azmal, A.S.N.B. Haque, M. Meem, O.F. Talukder, A. Ghosh, Unlocking the secrets of the human gut microbiota: comprehensive review on its role in different diseases, World J. Gastroenterol. 31 (5) (Feb. 2025), https://doi.org/10.3748/wjg.v31.i5.99913.
[188] F.M. Gribble, F. Reimann, Enteroendocrine cells: chemosensors in the intestinal epithelium, Annu. Rev. Physiol. 78 (1) (Feb. 2016) 277–299, https://doi.org/10.1146/annurev-physiol-021115-105439.
[189] J. Chao, R.A. Coleman, D.J. Keating, A.M. Martin, Gut microbiome regulation of gut hormone secretion, Endocrinology 166 (4) (Feb. 2025), https://doi.org/10.1210/endocr/bqaf004.
[190] R.K. Meyer, F.A. Duca, Rising stars: endocrine regulation of metabolic homeostasis via the intestine and gut microbiome, J. Endocrinol. 258 (2) (May 2023), https://doi.org/10.1530/JOE-23-0019.
[191] M. Gurung, et al., Role of gut microbiota in type 2 diabetes pathophysiology, EBioMedicine 51 (Jan. 2020) 102590, https://doi.org/10.1016/j.ebiom.2019.11.051.
[192] W. Massey, J.M. Brown, The gut microbial endocrine organ in type 2 diabetes, Endocrinology 162 (2) (Feb. 2021), https://doi.org/10.1210/endocr/bqaa235.
[193] G. Rena, D.G. Hardie, E.R. Pearson, The mechanisms of action of metformin, Diabetologia 60 (9) (Sep. 2017) 1577–1585, https://doi.org/10.1007/s00125-017-4342-z.
[194] X. Zhang, et al., Modulation of gut microbiota by berberine and metformin during the treatment of high-fat diet-induced obesity in rats, Sci. Rep. 5 (1) (Sep. 2015) 14405, https://doi.org/10.1038/srep14405.

[195] B. Das, G.B. Nair, Homeostasis and dysbiosis of the gut microbiome in health and disease, J. Biosci. 44 (5) (Oct. 2019).
[196] R. Fernandes, S.D. Viana, S. Nunes, F. Reis, Diabetic gut microbiota dysbiosis as an inflammaging and immunosenescence condition that fosters progression of retinopathy and nephropathy, Biochim. Biophys. Acta Mol. Basis Dis. 1865 (7) (Jul. 2019) 1876–1897, https://doi.org/10.1016/j.bbadis.2018.09.032.
[197] A.I. Vinik, M.-L. Nevoret, C. Casellini, H. Parson, Diabetic neuropathy, Endocrinol Metab. Clin. N. Am. 42 (4) (Dec. 2013) 747–787, https://doi.org/10.1016/j.ecl.2013.06.001.
[198] J. Penders, et al., Factors influencing the composition of the intestinal microbiota in early infancy, Pediatrics 118 (2) (Aug. 2006) 511–521, https://doi.org/10.1542/peds.2005-2824.
[199] A.M. Mowat, Historical perspective: metchnikoff and the intestinal microbiome, J. Leukoc. Biol. 109 (3) (Mar. 2021) 513–517, https://doi.org/10.1002/JLB.4RI0920-599.
[200] F. Deutschbein, G. Ianiro, Fecal microbiota transplantation for primary Clostridioides difficile infection. Ready for prime time? Gastroenterology (Sep. 2025) https://doi.org/10.1053/j.gastro.2025.09.017.
[201] J.S. Bakken, et al., Treating Clostridium difficile infection with fecal microbiota transplantation, Clin. Gastroenterol. Hepatol. 9 (12) (Dec. 2011) 1044–1049, https://doi.org/10.1016/j.cgh.2011.08.014.
[202] B.H. Mullish, et al., The role of faecal microbiota transplantation in chronic noncommunicable disorders, J. Autoimmun. 141 (Dec. 2023) 103034, https://doi.org/10.1016/j.jaut.2023.103034.
[203] R.E. Ooijevaar, E.M. Terveer, H.W. Verspaget, E.J. Kuijper, J.J. Keller, Clinical application and potential of fecal microbiota transplantation, Annu. Rev. Med. 70 (1) (Jan. 2019) 335–351, https://doi.org/10.1146/annurev-med-111717-122956.
[204] G.R. Gibson, et al., Expert consensus document: the international scientific association for probiotics and prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics, Nat. Rev. Gastroenterol. Hepatol. 14 (8) (Aug. 2017) 491–502, https://doi.org/10.1038/nrgastro.2017.75.
[205] A. Martyniak, M. Wójcicka, I. Rogatko, T. Piskorz, P.J. Tomasik, A comprehensive review of the usefulness of prebiotics, probiotics, and postbiotics in the diagnosis and treatment of small intestine bacterial overgrowth, Microorganisms 13 (1) (Jan. 2025) 57, https://doi.org/10.3390/microorganisms13010057.
[206] D. Davani-Davari, et al., Prebiotics: definition, types, sources, mechanisms, and clinical applications, Foods 8 (3) (Mar. 2019) 92, https://doi.org/10.3390/foods8030092.
[207] Ö.C.O. Umu, K. Rudi, D.B. Diep, Modulation of the gut microbiota by prebiotic fibres and bacteriocins, Microb. Ecol. Health Dis. 28 (1) (Jan. 2017) 1348886, https://doi.org/10.1080/16512235.2017.1348886.
[208] J.A.E. Van Loo, Prebiotics promote good health, J. Clin. Gastroenterol. 38 (Supplement 2) (Jul. 2004) S70–S75, https://doi.org/10.1097/01.mcg.0000128928.99037.e6.
[209] S. Taherkhani, P. Ahmadi, L.R. Nasiraie, A. Janzadeh, M. Honardoost, S. Sedghi Esfahani, Flavonoids and the gut microbiome: a powerful duo for brain health, Crit. Rev. Food Sci. Nutr. (Dec. 2024) 1–16, https://doi.org/10.1080/10408398.2024.2435593.
[210] A.B. Marcari, A.D. Paiva, C.R. Simon, M.E.S.M. dos Santos, Leaky gut syndrome: an interplay between nutrients and dysbiosis, Curr Nutr Rep 14 (1) (Jan. 2025) 25, https://doi.org/10.1007/s13668-025-00614-7.
[211] M. Zeng, J. van Pijkeren, X. Pan, Gluco-oligosaccharides as potential prebiotics: synthesis, purification, structural characterization, and evaluation of prebiotic effect, Compr. Rev. Food Sci. Food Saf. 22 (4) (Jul. 2023) 2611–2651, https://doi.org/10.1111/1541-4337.13156.
[212] T. Amin, M.M. Amin, A.A.D.I. Adikari, X. Zheng, Y. Ning, B. Wang, Clinical evidence and mechanistic pathways of human milk oligosaccharide supplementation for health benefits: an updated review, Front. Nutr. 12 (Jul. 2025), https://doi.org/10.3389/fnut.2025.1599678.
[213] S. Salminen, A. Ouwehand, Y. Benno, Y.K. Lee, Probiotics: how should they be defined? Trends Food Sci. Technol. 10 (3) (Mar. 1999) 107–110, https://doi.org/10.1016/S0924-2244(99)00027-8.
[214] D. Wolvers, J.-M. Antoine, E. Myllyluoma, J. Schrezenmeir, H. Szajewska, G. T. Rijkers, Guidance for substantiating the evidence for beneficial effects of probiotics: prevention and management of infections by probiotics, J. Nutr. 140 (3) (Mar. 2010) 698S–712S, https://doi.org/10.3945/jn.109.113753.
[215] D. Dahiya, P.S. Nigam, Probiotics, prebiotics, synbiotics, and fermented foods as potential biotics in nutrition improving health via microbiome-gut-brain axis, Fermentation 8 (7) (Jun. 2022) 303, https://doi.org/10.3390/fermentation8070303.
[216] T.G. Dinan, J.F. Cryan, Brain-gut-microbiota axis and mental health, Psychosom. Med. 79 (8) (Oct. 2017) 920–926, https://doi.org/10.1097/PSY.0000000000000519.
[217] P. Gualtieri, et al., Psychobiotics regulate the anxiety symptoms in carriers of allele A of IL-1 β gene: a randomized, placebo-controlled clinical trial, Mediat. Inflamm. 2020 (Jan. 2020) 1–11, https://doi.org/10.1155/2020/2346126.
[218] I. Al Kassaa, M. Fuad, Effects of Lacticaseibacillus rhamnosus HN001 on happiness and mental well-being: findings from a randomized controlled trial, Nutrients 16 (17) (Sep. 2024) 2936, https://doi.org/10.3390/nu16172936.
[219] V. Taverniti, S. Guglielmetti, The immunomodulatory properties of probiotic microorganisms beyond their viability (ghost probiotics: proposal of paraprobiotic concept), Gene Nutr. 6 (3) (Aug. 2011) 261–274, https://doi.org/10.1007/s12263-011-0218-x.
[220] S.S. Kruth, C. Willers, E. Persad, E.S. Sjöström, S.R. Lagerström, A. Rakow, Probiotic supplementation and risk of necrotizing enterocolitis and mortality among extremely preterm Infants—the probiotics in extreme prematurity in scandinavia (PEPS) trial: study protocol for a multicenter, double-blinded, placebo-controlled, and registry-based randomized controlled trial, Trials 25 (1) (Apr. 2024) 259, https://doi.org/10.1186/s13063-024-08088-8.
[221] K.S. Swanson, et al., The international scientific association for probiotics and prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics, Nat. Rev. Gastroenterol. Hepatol. 17 (11) (Nov. 2020) 687–701, https://doi.org/10.1038/s41575-020-0344-2.
[222] H.-Y. Li, et al., Effects and mechanisms of probiotics, prebiotics, synbiotics, and postbiotics on metabolic diseases targeting gut microbiota: a narrative review, Nutrients 13 (9) (Sep. 2021) 3211, https://doi.org/10.3390/nu13093211.
[223] A.C. Ford, L.A. Harris, B.E. Lacy, E.M.M. Quigley, P. Moayyedi, Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome, Aliment. Pharmacol. Ther. 48 (10) (Nov. 2018) 1044–1060, https://doi.org/10.1111/apt.15001.
[224] B.A. Napier, et al., Multi-species synbiotic supplementation enhances gut microbial diversity, increases urolithin A and butyrate production, and reduces inflammation in healthy adults: a randomized, placebo-controlled trial, Nutrients 17 (17) (Aug. 2025) 2734, https://doi.org/10.3390/nu17172734.
[225] N. Lee, Y.-S. Park, D.-K. Kang, H.-D. Paik, Paraprobiotics: definition, manufacturing methods, and functionality, Food Sci. Biotechnol. 32 (14) (Dec. 2023) 1981–1991, https://doi.org/10.1007/s10068-023-01378-y.
[226] S. Akter, J.-H. Park, H.K. Jung, Potential health-promoting benefits of paraprobiotics, inactivated probiotic cells, J. Microbiol. Biotechnol. 30 (4) (Apr. 2020) 477–481, https://doi.org/10.4014/jmb.1911.11019.
[227] R.A. Siciliano, A. Reale, M.F. Mazzeo, S. Morandi, T. Silvetti, M. Brasca, Paraprobiotics: a new perspective for functional foods and nutraceuticals, Nutrients 13 (4) (Apr. 2021) 1225, https://doi.org/10.3390/nu13041225.
[228] V. Taverniti, S. Guglielmetti, The immunomodulatory properties of probiotic microorganisms beyond their viability (ghost probiotics: proposal of paraprobiotic concept), Gene Nutr. 6 (3) (Aug. 2011) 261–274, https://doi.org/10.1007/s12263-011-0218-x.
[229] S.S. Monteiro, C.E. Schnorr, M.A. de B. Pasquali, Paraprobiotics and postbiotics—current state of scientific research and future trends toward the development of functional foods, Foods 12 (12) (Jun. 2023) 2394, https://doi.org/10.3390/foods12122394.
[230] C.N. de Almada, C.N. Almada, R.C.R. Martinez, A.S. Sant'Ana, Paraprobiotics: evidences on their ability to modify biological responses, inactivation methods and perspectives on their application in foods, Trends Food Sci. Technol. 58 (Dec. 2016) 96–114, https://doi.org/10.1016/j.tifs.2016.09.011.
[231] V. Taverniti, S. Guglielmetti, The immunomodulatory properties of probiotic microorganisms beyond their viability (ghost probiotics: proposal of paraprobiotic concept), Gene Nutr. 6 (3) (Aug. 2011) 261–274, https://doi.org/10.1007/s12263-011-0218-x.
[232] A. Martyniak, A. Medyńska-Przęczek, A. Wędrychowicz, S. Skoczeń, P.J. Tomasik, Prebiotics, probiotics, synbiotics, paraprobiotics and postbiotic compounds in IBD, Biomolecules 11 (12) (Dec. 2021) 1903, https://doi.org/10.3390/biom11121903.
[233] B.A. Shenderov, Metabiotics: novel idea or natural development of probiotic conception, Microb. Ecol. Health Dis. 24 (Apr. 2013), https://doi.org/10.3402/mehd.v24i0.20399.
[234] H.J. Jang, N.-K. Lee, H.-D. Paik, A narrative review on the advance of probiotics to metabiotics, J. Microbiol. Biotechnol. 34 (3) (Mar. 2024) 487–494, https://doi.org/10.4014/jmb.2311.11023.
[235] M.-O. Cristina, B.-R. Elizabeth, R.-A.M. Jose, P.-G. Berenice, Z. Diego, C.-S.J. Luis, Mechanisms and therapeutic potential of key anti-inflammatory metabiotics: trans-vaccenic acid, Indole-3-Lactic acid, thiamine, and butyric acid, Probiotics Antimicrob. Proteins (Feb. 2025), https://doi.org/10.1007/s12602-025-10475-9.
[236] M. Sharma, G. Shukla, Metabiotics: one step ahead of probiotics; an insight into mechanisms involved in anticancerous effect in colorectal cancer, Front. Microbiol. 7 (Dec. 2016), https://doi.org/10.3389/fmicb.2016.01940.
[237] I. Biswas, P.K. Das Mohapatra, Recent advancement in metabiotics: a consortium with bioactive molecules after fermentation by probiotic bacteria with multidisciplinary application potential and future solution in health sector, Bioresour. Technol. Rep. 23 (Sep. 2023) 101583, https://doi.org/10.1016/j.biteb.2023.101583.
[238] J.M.B. Vítor, F.F. Vale, Alternative therapies for helicobacter pylori: probiotics and phytomedicine, FEMS Immunol. Med. Microbiol. 63 (2) (Nov. 2011) 153–164, https://doi.org/10.1111/j.1574-695X.2011.00865.x.
[239] M.V. Kopp, I. Hennemuth, A. Heinzmann, R. Urbanek, Randomized, double-blind, placebo-controlled trial of probiotics for primary prevention: no clinical effects of lactobacillus GG supplementation, Pediatrics 121 (4) (Apr. 2008) e850–e856, https://doi.org/10.1542/peds.2007-1492.
[240] Y. Wu, Q. Zhang, Y. Ren, Z. Ruan, Effect of probiotic lactobacillus on lipid profile: a systematic review and meta-analysis of randomized, controlled trials, PLoS One 12 (6) (Jun. 2017) e0178868, https://doi.org/10.1371/journal.pone.0178868.
[241] B. Kapoor, et al., Orchestration of obesolytic activity of microbiome: metabiotics at centre stage, Curr. Drug Metabol. 23 (2) (Feb. 2022) 90–98, https://doi.org/10.2174/1389200223666220211095024.
[242] P. Gonçalves, F. Martel, Butyrate and colorectal cancer: the role of butyrate transport, Curr. Drug Metabol. 14 (9) (Oct. 2013) 994–1008, https://doi.org/10.2174/1389200211314090006.
[243] P. Louis, H.J. Flint, Formation of propionate and butyrate by the human colonic microbiota, Environ. Microbiol. 19 (1) (Jan. 2017) 29–41, https://doi.org/10.1111/1462-2920.13589.

[244] V. Mishra, D. Dash, A.K. Panda, S.K. Pathak, Efficacy of lactobacillus spp. supplementation in Helicobacter pylori eradication: a systematic meta-analysis of randomized controlled trials with trial sequential analysis, Helicobacter 29 (6) (Nov. 2024), https://doi.org/10.1111/hel.70006.
[245] S. Salminen, et al., The international scientific association of probiotics and prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics, Nat. Rev. Gastroenterol. Hepatol. 18 (9) (Sep. 2021) 649–667, https://doi.org/10.1038/s41575-021-00440-6.
[246] B.H. Nataraj, S.A. Ali, P. V Behare, H. Yadav, Postbiotics-parabiotics: the new horizons in microbial biotherapy and functional foods, Microb. Cell Fact. 19 (1) (Dec. 2020) 168, https://doi.org/10.1186/s12934-020-01426-w.
[247] C.A.M. Wegh, S.Y. Geerlings, J. Knol, G. Roeselers, C. Belzer, Postbiotics and their potential applications in early life nutrition and beyond, Int. J. Mol. Sci. 20 (19) (Sep. 2019) 4673, https://doi.org/10.3390/ijms20194673.
[248] Q. Xie, J. Liu, P. Yu, T. Qiu, S. Jiang, R. Yu, Unlocking the power of probiotics, postbiotics: targeting apoptosis for the treatment and prevention of digestive diseases, Front. Nutr. 12 (Mar. 2025), https://doi.org/10.3389/fnut.2025.1570268.
[249] S.M. Vindigni, C.M. Surawicz, Fecal microbiota transplantation, Gastroenterol. Clin. N. Am. 46 (1) (Mar. 2017) 171–185, https://doi.org/10.1016/j.gtc.2016.09.012.
[250] P.C. Konturek, et al., Successful therapy of Clostridium difficile infection with fecal microbiota transplantation, J. Physiol. Pharmacol. 67 (6) (Dec. 2016) 859–866.
[251] L.J. Brandt, O.C. Aroniadis, An overview of fecal microbiota transplantation: techniques, indications, and outcomes, Gastrointest. Endosc. 78 (2) (Aug. 2013) 240–249, https://doi.org/10.1016/j.gie.2013.03.1329.
[252] S. Bibbò, et al., Fecal microbiota transplantation: screening and selection to choose the optimal donor, J. Clin. Med. 9 (6) (Jun. 2020) 1757, https://doi.org/10.3390/jcm9061757.
[253] S. Hamamah, R. Gheorghita, A. Lobiuc, I.-O. Sirbu, M. Covasa, Fecal microbiota transplantation in non-communicable diseases: recent advances and protocols, Front. Med. 9 (Dec. 2022), https://doi.org/10.3389/fmed.2022.1060581.
[254] A.F. Peery, et al., AGA clinical practice guideline on fecal microbiota–based therapies for select gastrointestinal diseases, Gastroenterology 166 (3) (Mar. 2024) 409–434, https://doi.org/10.1053/j.gastro.2024.01.008.
[255] E. Mattila, et al., Fecal transplantation, through colonoscopy, is effective therapy for recurrent Clostridium difficile infection, Gastroenterology 142 (3) (Mar. 2012) 490–496, https://doi.org/10.1053/j.gastro.2011.11.037.
[256] A.R. Weingarden, et al., Microbiota transplantation restores normal fecal bile acid composition in recurrent *Clostridium difficile* infection, Am. J. Physiol. Gastrointest. Liver Physiol. 306 (4) (Feb. 2014) G310–G319, https://doi.org/10.1152/ajpgi.00282.2013.
[257] T.A. Rubin, C.E. Gessert, J. Aas, J.S. Bakken, Fecal microbiome transplantation for recurrent Clostridium difficile infection: report on a case series, Anaerobe 19 (Feb. 2013) 22–26, https://doi.org/10.1016/j.anaerobe.2012.11.004.
[258] D.E. Hoffmann, G.H. Javitt, C.R. Kelly, J.J. Keller, S.M.D. Baunwall, C.L. Hvas, Fecal microbiota transplantation: a tale of two regulatory pathways, Gut Microbes 17 (1) (Dec. 2025), https://doi.org/10.1080/19490976.2025.2493901.
[259] S.J. Ott, et al., Efficacy of sterile fecal filtrate transfer for treating patients with Clostridium difficile infection, Gastroenterology 152 (4) (Mar. 2017) 799–811.e7, https://doi.org/10.1053/j.gastro.2016.11.010.
[260] A. Weingarden, et al., Dynamic changes in short- and long-term bacterial composition following fecal microbiota transplantation for recurrent Clostridium difficile infection, Microbiome 3 (1) (Dec. 2015) 10, https://doi.org/10.1186/s40168-015-0070-0.
[261] S. Kedia, et al., Faecal microbiota transplantation with anti-inflammatory diet (FMT-AID) followed by anti-inflammatory diet alone is effective in inducing and maintaining remission over 1 year in mild to moderate ulcerative colitis: a randomised controlled trial, Gut 71 (12) (Dec. 2022) 2401–2413, https://doi.org/10.1136/gutjnl-2022-327811.
[262] J.A.K. McDonald, et al., Inhibiting growth of Clostridioides difficile by restoring valerate, produced by the intestinal microbiota, Gastroenterology 155 (5) (Nov. 2018) 1495–1507.e15, https://doi.org/10.1053/j.gastro.2018.07.014.
[263] S. Paramsothy, et al., Specific bacteria and metabolites associated with response to fecal microbiota transplantation in patients with ulcerative colitis, Gastroenterology 156 (5) (Apr. 2019) 1440–1454.e2, https://doi.org/10.1053/j.gastro.2018.12.001.
[264] E. Varela, et al., Colonisation by <scp>F</scp> *aecalibacterium prausnitzii* and maintenance of clinical remission in patients with ulcerative colitis, Aliment. Pharmacol. Ther. 38 (2) (Jul. 2013) 151–161, https://doi.org/10.1111/apt.12365.
[265] K.T. Suk, H. Koh, New perspective on fecal microbiota transplantation in liver diseases, J. Gastroenterol. Hepatol. 37 (1) (Jan. 2022) 24–33, https://doi.org/10.1111/jgh.15729.
[266] S. Serrano-Villar, et al., Fecal microbiota transplantation in HIV: a pilot placebo-controlled study, Nat. Commun. 12 (1) (Feb. 2021) 1139, https://doi.org/10.1038/s41467-021-21472-1.
[267] S.M. Kim, et al., Fecal microbiota transplant rescues mice from human pathogen mediated sepsis by restoring systemic immunity, Nat. Commun. 11 (1) (May 2020) 2354, https://doi.org/10.1038/s41467-020-15545-w.
[268] T.W. Hand, I. Vujkovic-Cvijin, V.K. Ridaura, Y. Belkaid, Linking the microbiota, chronic disease, and the immune system, Trends Endocrinol. Metabol. 27 (12) (Dec. 2016) 831–843, https://doi.org/10.1016/j.tem.2016.08.003.
[269] K.E. Huus, et al., Changes in IgA-targeted microbiota following fecal transplantation for recurrent *Clostridioides difficile* infection, Gut Microbes 13 (1) (Jan. 2021), https://doi.org/10.1080/19490976.2020.1862027.
[270] Y. Wang, et al., Combination of probiotics with different functions alleviate DSS-induced colitis by regulating intestinal microbiota, IL-10, and barrier function, Appl. Microbiol. Biotechnol. 104 (1) (Jan. 2020) 335–349, https://doi.org/10.1007/s00253-019-10259-6.
[271] O.Y. Kim, et al., Bacterial outer membrane vesicles suppress tumor by interferon-γ-mediated antitumor response, Nat. Commun. 8 (1) (Sep. 2017) 626, https://doi.org/10.1038/s41467-017-00729-8.
[272] K.S.W. Leong, et al., Effects of fecal microbiome transfer in adolescents with obesity, JAMA Netw. Open 3 (12) (Dec. 2020) e2030415, https://doi.org/10.1001/jamanetworkopen.2020.30415.
[273] Nanjing consensus on methodology of washed microbiota transplantation, Chin Med J (Engl) 133 (19) (Oct. 2020) 2330–2332, https://doi.org/10.1097/CM9.0000000000000954.
[274] L. Wu, et al., Washed microbiota transplantation improves patients with metabolic syndrome in South China, Front. Cell. Infect. Microbiol. 12 (Nov. 2022), https://doi.org/10.3389/fcimb.2022.1044957.
[275] P. de Groot, et al., Faecal microbiota transplantation halts progression of human new-onset type 1 diabetes in a randomised controlled trial, Gut 70 (1) (Jan. 2021) 92–105, https://doi.org/10.1136/gutjnl-2020-322630.
[276] K.L. Høyer, et al., Faecal microbiota transplantation for patients with diabetes type 1 and severe gastrointestinal neuropathy (FADIGAS): a randomised, double-blinded, placebo-controlled trial, eClinicalMedicine 79 (Jan. 2025) 103000, https://doi.org/10.1016/j.eclinm.2024.103000.
[277] S.C. Ng, et al., Microbiota engraftment after faecal microbiota transplantation in obese subjects with type 2 diabetes: a 24-week, double-blind, randomised controlled trial, Gut 71 (4) (Apr. 2022) 716–723, https://doi.org/10.1136/gutjnl-2020-323617.
[278] D. Ding, et al., Prospective study reveals host microbial determinants of clinical response to fecal microbiota transplant therapy in type 2 diabetes patients, Front. Cell. Infect. Microbiol. 12 (Mar. 2022), https://doi.org/10.3389/fcimb.2022.820367.
[279] J. Yang, et al., Gut microbiota modulate distal symmetric polyneuropathy in patients with diabetes, Cell Metab. 35 (9) (Sep. 2023) 1548–1562.e7, https://doi.org/10.1016/j.cmet.2023.06.010.
[280] Y. Li, et al., Washed microbiota transplantation reduces glycemic variability in unstable diabetes, J. Diabetes 16 (2) (Feb. 2024), https://doi.org/10.1111/1753-0407.13485.
[281] A. Sai, G.B. Shetty, P. Shetty, N. H L, Influence of gut microbiota on autoimmunity: a narrative review, Brain Behavior and Immunity Integrative 5 (Jan. 2024) 100046, https://doi.org/10.1016/j.bbii.2024.100046.
[282] J.O. Warner, J.A. Warner, The foetal origins of allergy and potential nutritional interventions to prevent disease, Nutrients 14 (8) (Apr. 2022) 1590, https://doi.org/10.3390/nu14081590.
[283] K. Korpela, et al., Maternal fecal microbiota transplantation in cesarean-born infants rapidly restores normal gut microbial development: a proof-of-concept study, Cell 183 (2) (Oct. 2020) 324–334.e5, https://doi.org/10.1016/j.cell.2020.08.047.
[284] D. Ishikawa, X. Zhang, A. Nagahara, Current applications and future prospects of fecal microbiota transplantation, Juntendo Medical Journal 71 (2) (2025), https://doi.org/10.14789/ejmj.JMJ24-0045-R pp. JMJ24-0045-R.
[285] I. Nordgaard, P.B. Mortensen, Digestive processes in the human colon, Nutrition 11 (1) (1995) 37–45.
[286] S.J. O'Keefe, The colon as a metabolic organ, S. Afr. Med. J. 84 (7) (Jul. 1994) 376–377.
[287] W.E. Roediger, Utilization of nutrients by isolated epithelial cells of the rat colon, Gastroenterology 83 (2) (Aug. 1982) 424–429.
[288] S.J.D. O'Keefe, Nutrition and colonic health: the critical role of the microbiota, Curr. Opin. Gastroenterol. 24 (1) (Jan. 2008) 51–58, https://doi.org/10.1097/MOG.0b013e3282f323f3.
[289] C.C. Roy, C.L. Kien, L. Bouthillier, E. Levy, Short-chain fatty acids: ready for prime time? Nutr. Clin. Pract. 21 (4) (Aug. 2006) 351–366, https://doi.org/10.1177/0115426506021004351.
[290] J.G. LeBlanc, C. Milani, G.S. de Giori, F. Sesma, D. van Sinderen, M. Ventura, Bacteria as vitamin suppliers to their host: a gut microbiota perspective, Curr. Opin. Biotechnol. 24 (2) (Apr. 2013) 160–168, https://doi.org/10.1016/j.copbio.2012.08.005.
[291] S.I. Sitkin, E.I. Tkachenko, T.Y. Vakhitov, Metabolic dysbiosis of the gut microbiota and its biomarkers, Eksp Klin Gastroenterol 12 (12) (Jul. 2016) 6–29.
[292] S.F. Clarke, et al., The gut microbiota and its relationship to diet and obesity, Gut Microbes 3 (3) (May 2012) 186–202, https://doi.org/10.4161/gmic.20168.
[293] P.J. Turnbaugh, R.E. Ley, M.A. Mahowald, V. Magrini, E.R. Mardis, J.I. Gordon, An obesity-associated gut microbiome with increased capacity for energy harvest, Nature 444 (7122) (Dec. 2006) 1027–1031, https://doi.org/10.1038/nature05414.
[294] F. Shanahan, The host–microbe interface within the gut, Best Pract. Res. Clin. Gastroenterol. 16 (6) (Dec. 2002) 915–931, https://doi.org/10.1053/bega.2002.0342.
[295] D.L. O'Connor, T.H. Kim, J. Yang, P.B. Darling, A large pool of available folate exists in the large intestine of human infants and piglets, J. Nutr. 134 (6) (Jun. 2004) 1389–1394, https://doi.org/10.1093/jn/134.6.1389.
[296] C. De Filippo, et al., Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa, Proc. Natl. Acad. Sci. 107 (33) (Aug. 2010) 14691–14696, https://doi.org/10.1073/pnas.1005963107.

[297] D.P. Burkitt, Epidemiology of large bowel disease: the role of fibre, Proc. Nutr. Soc. 32 (3) (Dec. 1973) 145–149, https://doi.org/10.1079/PNS19730032.
[298] M. Florio, L. Crudele, F. Sallustio, A. Moschetta, M. Cariello, R.M. Gadaleta, Disentangling the nutrition-microbiota liaison in inflammatory bowel disease, Mol. Aspect. Med. 102 (Apr. 2025) 101349, https://doi.org/10.1016/j.mam.2025.101349.
[299] S.J.D. O'Keefe, R.B. Lee, J. Li, W. Zhou, B. Stoll, Q. Dang, Trypsin and splanchnic protein turnover during feeding and fasting in human subjects, Am. J. Physiol. Gastrointest. Liver Physiol. 290 (2) (Feb. 2006) G213–G221, https://doi.org/10.1152/ajpgi.00170.2005.
[300] J. Godos, et al., Mediterranean diet and quality of life in adults: a systematic review, Nutrients 17 (3) (Feb. 2025) 577, https://doi.org/10.3390/nu17030577.
[301] K. Eto, T. Sakamoto, T. Ainuki, A review on eating together and its health, diet, and lifestyle influences among Japanese, J. Nutr. Sci. Vitaminol. 68 (Supplement) (Nov. 2022) S52–S54, https://doi.org/10.3177/jnsv.68.S52.
[302] L.M. DeVito, et al., Extending human healthspan and longevity: a symposium report, Ann. N. Y. Acad. Sci. 1507 (1) (Jan. 2022) 70–83, https://doi.org/10.1111/nyas.14681.
[303] A.M. Armet, et al., Rethinking healthy eating in light of the gut microbiome, Cell Host Microbe 30 (6) (Jun. 2022) 764–785, https://doi.org/10.1016/j.chom.2022.04.016.
[304] L.M. Beaver, P.E. Jamieson, C.P. Wong, M. Hosseinikia, J.F. Stevens, E. Ho, Promotion of healthy aging through the nexus of gut microbiota and dietary phytochemicals, Adv. Nutr. 16 (3) (Mar. 2025) 100376, https://doi.org/10.1016/j.advnut.2025.100376.
[305] L. Guo, et al., Natural products of medicinal plants: biosynthesis and bioengineering in post-genomic era, Hortic. Res. 9 (Jan. 2022), https://doi.org/10.1093/hr/uhac223.
[306] J.M. Laparra, Y. Sanz, Interactions of gut microbiota with functional food components and nutraceuticals, Pharmacol. Res. 61 (3) (Mar. 2010) 219–225, https://doi.org/10.1016/j.phrs.2009.11.001.
[307] P.E. Jamieson, F. Carbonero, J.F. Stevens, Dietary (poly)phenols mitigate inflammatory bowel disease: therapeutic targets, mechanisms of action, and clinical observations, Curr. Res. Food Sci. 6 (2023) 100521, https://doi.org/10.1016/j.crfs.2023.100521.
[308] H. Cheng, et al., Interactions between gut microbiota and polyphenols: a mechanistic and metabolomic review, Phytomedicine 119 (Oct. 2023) 154979, https://doi.org/10.1016/j.phymed.2023.154979.
[309] A. Cortés-Martín, M.V. Selma, F.A. Tomás-Barberán, A. González-Sarrías, J. C. Espín, Where to look into the puzzle of polyphenols and health? The postbiotics and gut microbiota associated with human metabotypes, Mol. Nutr. Food Res. 64 (9) (May 2020), https://doi.org/10.1002/mnfr.201900952.
[310] Y. Zhang, R. Chen, D. Zhang, S. Qi, Y. Liu, Metabolite interactions between host and microbiota during health and disease: which feeds the other? Biomed. Pharmacother. 160 (Apr. 2023) 114295, https://doi.org/10.1016/j.biopha.2023.114295.
[311] R. Okumura, K. Takeda, Maintenance of intestinal homeostasis by mucosal barriers, Inflamm. Regen. 38 (1) (Dec. 2018) 5, https://doi.org/10.1186/s41232-018-0063-z.
[312] Y.P. Silva, A. Bernardi, R.L. Frozza, The role of short-chain fatty acids from gut microbiota in gut-brain communication, Front. Endocrinol. 11 (Jan. 2020), https://doi.org/10.3389/fendo.2020.00025.
[313] G.V. Sridharan, et al., Prediction and quantification of bioactive microbiota metabolites in the mouse gut, Nat. Commun. 5 (1) (Nov. 2014) 5492, https://doi.org/10.1038/ncomms6492.
[314] I. Kimura, D. Inoue, K. Hirano, G. Tsujimoto, The SCFA receptor GPR43 and energy metabolism, Front. Endocrinol. 5 (Jun. 2014), https://doi.org/10.3389/fendo.2014.00085.
[315] H.D. Holscher, Dietary fiber and prebiotics and the gastrointestinal microbiota, Gut Microbes 8 (2) (Mar. 2017) 172–184, https://doi.org/10.1080/19490976.2017.1290756.
[316] A. Koh, F. De Vadder, P. Kovatcheva-Datchary, F. Bäckhed, From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites, Cell 165 (6) (Jun. 2016) 1332–1345, https://doi.org/10.1016/j.cell.2016.05.041.
[317] C. Duvallet, S.M. Gibbons, T. Gurry, R.A. Irizarry, E.J. Alm, Meta-analysis of gut microbiome studies identifies disease-specific and shared responses, Nat. Commun. 8 (1) (Dec. 2017) 1784, https://doi.org/10.1038/s41467-017-01973-8.
[318] Z.-L. Dai, Amino acid metabolism in intestinal bacteria: links between gut ecology and host health, Front. Biosci. 16 (1) (2011) 1768, https://doi.org/10.2741/3820.
[319] W.G. Bergen, G. Wu, Intestinal nitrogen recycling and utilization in health and disease, J. Nutr. 139 (5) (May 2009) 821–825, https://doi.org/10.3945/jn.109.104497.
[320] A. Abdallah, E. Elemba, Q. Zhong, Z. Sun, Gastrointestinal interaction between dietary amino acids and gut microbiota: with special emphasis on host nutrition, Curr. Protein Pept. Sci. 21 (8) (Nov. 2020) 785–798, https://doi.org/10.2174/1389203721666200212095503.
[321] A. Mardinoglu, et al., The gut microbiota modulates host amino acid and glutathione metabolism in mice, Mol. Syst. Biol. 11 (10) (Oct. 2015), https://doi.org/10.15252/msb.20156487.
[322] R. Lin, W. Liu, M. Piao, H. Zhu, A review of the relationship between the gut microbiota and amino acid metabolism, Amino Acids 49 (12) (Dec. 2017) 2083–2090, https://doi.org/10.1007/s00726-017-2493-3.
[323] S. Singh, et al., Impact of environmental pollutants on gut microbiome and mental health via the gut-brain axis, Microorganisms 10 (7) (Jul. 2022), https://doi.org/10.3390/microorganisms10071457.
[324] D. Rothschild, et al., Environment dominates over host genetics in shaping human gut microbiota, Nature 555 (7695) (Mar. 2018) 210–215, https://doi.org/10.1038/nature25973.
[325] S. Altajar, A. Moss, Inflammatory bowel disease environmental risk factors: Diet and gut microbiota, Curr. Gastroenterol. Rep. 22 (12) (Dec. 2020) 57, https://doi.org/10.1007/s11894-020-00794-y.
[326] N. Koppel, V. Maini Rekdal, E.P. Balskus, Chemical transformation of xenobiotics by the human gut microbiota, Science 356 (6344) (Jun. 2017), https://doi.org/10.1126/science.aag2770 (1979).
[327] C.F. Maurice, H.J. Haiser, P.J. Turnbaugh, Xenobiotics shape the physiology and gene expression of the active human gut microbiome, Cell 152 (1–2) (Jan. 2013) 39–50, https://doi.org/10.1016/j.cell.2012.10.052.
[328] J.M. Di Caprio, Effects of terramycin on the bacterial flora of the bowel in man, Arch. Intern. Med. 86 (5) (Nov. 1950) 649, https://doi.org/10.1001/archinte.1950.00230170002001.
[329] C.R. Woese, O. Kandler, M.L. Wheelis, Towards a natural system of organisms: proposal for the domains Archaea, bacteria, and Eucarya, Proc. Natl. Acad. Sci. 87 (12) (Jun. 1990) 4576–4579, https://doi.org/10.1073/pnas.87.12.4576.
[330] G. Greene, et al., Effect of doxycycline use in the early broiler production cycle on the microbiome, Front. Microbiol. 13 (Jul. 2022), https://doi.org/10.3389/fmicb.2022.885862.
[331] P.J. Turnbaugh, R.E. Ley, M. Hamady, C.M. Fraser-Liggett, R. Knight, J.I. Gordon, The human microbiome project, Nature 449 (7164) (Oct. 2007) 804–810, https://doi.org/10.1038/nature06244.
[332] J. Qin, et al., A human gut microbial gene catalogue established by metagenomic sequencing, Nature 464 (7285) (Mar. 2010) 59–65, https://doi.org/10.1038/nature08821.
[333] J. Armetta, S.S. Li, T.H. Vaaben, R. Vazquez-Uribe, M.O.A. Sommer, Metagenome-guided culturomics for the targeted enrichment of gut microbes, Nat. Commun. 16 (1) (Jan. 2025) 663, https://doi.org/10.1038/s41467-024-55668-y.
[334] S.M. Jandhyala, Role of the normal gut microbiota, World J. Gastroenterol. 21 (29) (2015) 8787, https://doi.org/10.3748/wjg.v21.i29.8787.
[335] E.B. Hollister, C. Gao, J. Versalovic, Compositional and functional features of the gastrointestinal microbiome and their effects on human health, Gastroenterology 146 (6) (May 2014) 1449–1458, https://doi.org/10.1053/j.gastro.2014.01.052.
[336] Z.F. Ma, Y.Y. Lee, The role of the gut microbiota in health, diet, and disease with a focus on obesity, Foods 14 (3) (Feb. 2025) 492, https://doi.org/10.3390/foods14030492.
[337] J. Lloyd-Price, G. Abu-Ali, C. Huttenhower, The healthy human microbiome, Genome Med. 8 (1) (Dec. 2016) 51, https://doi.org/10.1186/s13073-016-0307-y.
[338] A. Langdon, N. Crook, G. Dantas, The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation, Genome Med. 8 (1) (Dec. 2016) 39, https://doi.org/10.1186/s13073-016-0294-z.
[339] H. Tremlett, K.C. Bauer, S. Appel-Cresswell, B.B. Finlay, E. Waubant, The gut microbiome in human neurological disease: a review, Ann. Neurol. 81 (3) (Mar. 2017) 369–382, https://doi.org/10.1002/ana.24901.
[340] I. Lurie, Y.-X. Yang, K. Haynes, R. Mamtani, B. Boursi, Antibiotic exposure and the risk for depression, anxiety, or psychosis, J. Clin. Psychiatry 76 (11) (Nov. 2015) 1522–1528, https://doi.org/10.4088/JCP.15m09961.
[341] K.H. Mikkelsen, K.H. Allin, F.K. Knop, Effect of antibiotics on gut microbiota, glucose metabolism and body weight regulation: a review of the literature, Diabetes Obes. Metabol. 18 (5) (May 2016) 444–453, https://doi.org/10.1111/dom.12637.
[342] O.F. Ahmad, A. Akbar, Microbiome, antibiotics and irritable bowel syndrome, Br. Med. Bull. 120 (1) (Dec. 2016) 91–99, https://doi.org/10.1093/bmb/ldw038.
[343] J.D. Lewis, et al., Inflammation, antibiotics, and diet as environmental stressors of the gut microbiome in pediatric crohn's disease, Cell Host Microbe 18 (4) (Oct. 2015) 489–500, https://doi.org/10.1016/j.chom.2015.09.008.
[344] R.E. Rossi, G. Dispinzieri, A. Elvevi, S. Massironi, Interaction between gut microbiota and celiac disease: from pathogenesis to treatment, Cells 12 (6) (Mar. 2023) 823, https://doi.org/10.3390/cells12060823.
[345] M. Li, M. Wang, S. Donovan, Early development of the gut microbiome and immune-mediated childhood disorders, Semin. Reprod. Med. 32 (1) (Jan. 2014) 74–86, https://doi.org/10.1055/s-0033-1361825.
[346] A. Attiq, Early-life antibiotic exposures: paving the pathway for dysbiosis-induced disorders, Eur. J. Pharmacol. 991 (Mar. 2025) 177298, https://doi.org/10.1016/j.ejphar.2025.177298.
[347] M.P. Francino, Antibiotics and the human gut microbiome: dysbioses and accumulation of resistances, Front. Microbiol. 6 (Jan. 2016), https://doi.org/10.3389/fmicb.2015.01543.
[348] K. Korpela, et al., Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children, Nat. Commun. 7 (1) (Jan. 2016) 10410, https://doi.org/10.1038/ncomms10410.
[349] P. Forbes, Y. Naudé, J. Strumpher, Ongoing use and monitoring of DDT in South Africa, in: Persistent Organic Pollutants in the Environment, CRC Press, Boca Raton, 2021, pp. 203–235, https://doi.org/10.1201/9781003053170-8-8.
[350] M. Zhou, J. Zhao, A review on the health effects of pesticides based on host gut microbiome and metabolomics, Front. Mol. Biosci. 8 (Feb. 2021), https://doi.org/10.3389/fmolb.2021.632955.
[351] P.C. Kandel Gambarte, M.J. Wolansky, The gut microbiota as a biomarker for realistic exposures to pesticides: a critical consideration, Neurotoxicol. Teratol. 91 (May 2022) 107074, https://doi.org/10.1016/j.ntt.2022.107074.
[352] J. Gama, B. Neves, A. Pereira, Chronic effects of dietary pesticides on the gut microbiome and neurodevelopment, Front. Microbiol. 13 (2022) 931440, https://doi.org/10.3389/fmicb.2022.931440.

[353] L. Leino, et al., Classification of the glyphosate target enzyme (5-enolpyruvylshikimate-3-phosphate synthase) for assessing sensitivity of organisms to the herbicide, J. Hazard. Mater. 408 (Apr. 2021) 124556, https://doi.org/10.1016/j.jhazmat.2020.124556.
[354] M.M. Mitchell, et al., Levels of select PCB and PBDE congeners in human postmortem brain reveal possible environmental involvement in 15q11-q13 duplication autism spectrum disorder, Environ. Mol. Mutagen. 53 (8) (Oct. 2012) 589–598, https://doi.org/10.1002/em.21722.
[355] H.E. Laue, et al., Associations of prenatal exposure to polybrominated diphenyl ethers and polychlorinated biphenyls with long-term gut microbiome structure: a pilot study, Environmental Epidemiology 3 (1) (Feb. 2019) e039, https://doi.org/10.1097/EE9.0000000000000039.
[356] H.E. Vuong, et al., The maternal microbiome modulates fetal neurodevelopment in mice, Nature 586 (7828) (Oct. 2020) 281–286, https://doi.org/10.1038/s41586-020-2745-3.
[357] S. Mekonen, A. Ambelu, M. Wondafrash, P. Kolsteren, P. Spanoghe, Exposure of infants to organochlorine pesticides from breast milk consumption in southwestern Ethiopia, Sci. Rep. 11 (1) (Nov. 2021) 22053, https://doi.org/10.1038/s41598-021-01656-x.
[358] Y. Dong, et al., Exposure patterns, chemical structural signatures, and health risks of pesticides in breast milk: a multicenter study in China, Sci. Total Environ. 830 (Jul. 2022) 154617, https://doi.org/10.1016/j.scitotenv.2022.154617.
[359] L. Järup, Hazards of heavy metal contamination, Br. Med. Bull. 68 (1) (Dec. 2003) 167–182, https://doi.org/10.1093/bmb/ldg032.
[360] D. Witkowska, J. Słowik, K. Chilicka, Heavy metals and human health: possible exposure pathways and the competition for protein binding sites, Molecules 26 (19) (Oct. 2021) 6060, https://doi.org/10.3390/molecules26196060.
[361] S. Assefa, G. Köhler, Intestinal microbiome and metal toxicity, Curr Opin Toxicol 19 (Feb. 2020) 21–27, https://doi.org/10.1016/j.cotox.2019.09.009.
[362] T.W. Clarkson, L. Magos, The toxicology of mercury and its chemical compounds, Crit. Rev. Toxicol. 36 (8) (Jan. 2006) 609–662, https://doi.org/10.1080/10408440600845619.
[363] S. Delaney, M. Hornig, Environmental exposures and neuropsychiatric disorders: what role does the gut–immune–brain axis play? Curr. Environ. Health Rep. 5 (1) (Mar. 2018) 158–169, https://doi.org/10.1007/s40572-018-0186-z.
[364] H. Duan, L. Yu, F. Tian, Q. Zhai, L. Fan, W. Chen, Gut microbiota: a target for heavy metal toxicity and a probiotic protective strategy, Sci. Total Environ. 742 (Nov. 2020) 140429, https://doi.org/10.1016/j.scitotenv.2020.140429.
[365] F. Giambò, et al., Influence of toxic metal exposure on the gut microbiota, World Acad Sci J 3 (2) (Feb. 2021) 19, https://doi.org/10.3892/wasj.2021.90.
[366] S. Ghosh, S.P. Nukavarapu, V.R. Jala, Effects of heavy metals on gut barrier integrity and gut microbiota, Microbiota and Host 2 (1) (Dec. 2023), https://doi.org/10.1530/MAH-23-0015.
[367] P. Bist, S. Choudhary, Impact of heavy metal toxicity on the gut microbiota and its relationship with metabolites and future probiotics strategy: a review, Biol. Trace Elem. Res. 200 (12) (Dec. 2022) 5328–5350, https://doi.org/10.1007/s12011-021-03092-4.
[368] N. Gasaly, P. de Vos, M.A. Hermoso, Impact of bacterial metabolites on gut barrier function and host immunity: a focus on bacterial metabolism and its relevance for intestinal inflammation, Front. Immunol. 12 (May 2021), https://doi.org/10.3389/fimmu.2021.658354.
[369] M. Rezazadegan, B. Forootani, Y. Hoveyda, N. Rezazadegan, R. Amani, Major heavy metals and human gut microbiota composition: a systematic review with nutritional approach, J. Health Popul. Nutr. 44 (1) (Jan. 2025) 21, https://doi.org/10.1186/s41043-025-00750-4.
[370] K.B. Arun, et al., Probiotics and gut microbiome – Prospects and challenges in remediating heavy metal toxicity, J. Hazard. Mater. 420 (Oct. 2021) 126676, https://doi.org/10.1016/j.jhazmat.2021.126676.
[371] J. Chow, H. Tang, S.K. Mazmanian, Pathobionts of the gastrointestinal microbiota and inflammatory disease, Curr. Opin. Immunol. 23 (4) (Aug. 2011) 473–480, https://doi.org/10.1016/j.coi.2011.07.010.
[372] J.M. Ridlon, D.-J. Kang, P.B. Hylemon, Bile salt biotransformations by human intestinal bacteria, J. Lipid Res. 47 (2) (Feb. 2006) 241–259, https://doi.org/10.1194/jlr.R500013-JLR200.
[373] Y. Román-Ochoa, et al., Specific dietary fibers prevent heavy metal disruption of the human gut microbiota in vitro, Food Res. Int. 176 (Jan. 2024) 113858, https://doi.org/10.1016/j.foodres.2023.113858.
[374] L.F. Gomez-Arango, et al., Low dietary fiber intake increases *Collinsella* abundance in the gut microbiota of overweight and obese pregnant women, Gut Microbes 9 (3) (May 2018) 189–201, https://doi.org/10.1080/19490976.2017.1406584.
[375] P.D. Cani, et al., Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability, Gut 58 (8) (Aug. 2009) 1091–1103, https://doi.org/10.1136/gut.2008.165886.
[376] J. An, H. Kwon, Y.J. Kim, The firmicutes/bacteroidetes ratio as a risk factor of breast cancer, J. Clin. Med. 12 (6) (Mar. 2023) 2216, https://doi.org/10.3390/jcm12062216.
[377] D.M.L. Saunte, G. Gaitanis, R.J. Hay, Malassezia-associated skin diseases, the use of diagnostics and treatment, Front. Cell. Infect. Microbiol. 10 (Mar. 2020), https://doi.org/10.3389/fcimb.2020.00112.
[378] W. Liu, et al., Pb toxicity on gut physiology and microbiota, Front. Physiol. 12 (Mar. 2021), https://doi.org/10.3389/fphys.2021.574913.
[379] P. Li, X. Feng, G. Qiu, Methylmercury exposure and health effects from rice and fish consumption: a review, Int. J. Environ. Res. Publ. Health 7 (6) (Jun. 2010) 2666–2691, https://doi.org/10.3390/ijerph7062666.
[380] S.B. Singh, A. Carroll-Portillo, H.C. Lin, Desulfovibrio in the gut: the enemy within? Microorganisms 11 (7) (Jul. 2023) 1772, https://doi.org/10.3390/microorganisms11071772.
[381] E. Sogodogo, M. Drancourt, G. Grine, Methanogens as emerging pathogens in anaerobic abscesses, Eur. J. Clin. Microbiol. Infect. Dis. 38 (5) (May 2019) 811–818, https://doi.org/10.1007/s10096-019-03510-5.
[382] Z.S. Nehzomi, K. Shirani, The gut microbiota: a key player in cadmium toxicity - implications for disease, interventions, and combined toxicant exposures, J. Trace Elem. Med. Biol. 88 (Apr. 2025) 127570, https://doi.org/10.1016/j.jtemb.2024.127570.
[383] G. Genchi, M.S. Sinicropi, G. Lauria, A. Carocci, A. Catalano, The effects of cadmium toxicity, Int. J. Environ. Res. Publ. Health 17 (11) (May 2020) 3782, https://doi.org/10.3390/ijerph17113782.
[384] G. Genchi, A. Carocci, G. Lauria, M.S. Sinicropi, A. Catalano, Nickel: human health and environmental toxicology, Int. J. Environ. Res. Publ. Health 17 (3) (Jan. 2020) 679, https://doi.org/10.3390/ijerph17030679.
[385] G.N. Ayodeji-Fapohunda, E. Ugwoha, E.O. Nwaichi, Nutrition as A therapeutic intervention for metal toxicity, Current Journal of Applied Science and Technology 42 (46) (Dec. 2023) 72–84, https://doi.org/10.9734/cjast/2023/v42i464296.
[386] M.A. Peraza, F. Ayala-Fierro, D.S. Barber, E. Casarez, L.T. Rael, Effects of micronutrients on metal toxicity, Environ. Health Perspect. 106 (suppl 1) (Feb. 1998) 203–216, https://doi.org/10.1289/ehp.98106s1203.
[387] C. Reed, Dawn of the plasticene age, New Sci. 225 (3006) (Jan. 2015) 28–32, https://doi.org/10.1016/S0262-4079(15)60215-9 (1956).
[388] T.S. Galloway, Micro- and nano-plastics and human health, in: Marine Anthropogenic Litter, Springer International Publishing, Cham, 2015, pp. 343–366, https://doi.org/10.1007/978-3-319-16510-3_13.
[389] E.R. Zettler, T.J. Mincer, L.A. Amaral-Zettler, Life in the "Plastisphere": microbial communities on plastic marine debris, Environ. Sci. Technol. 47 (13) (Jul. 2013) 7137–7146, https://doi.org/10.1021/es401288x.
[390] B. Toussaint, et al., Review of micro- and nanoplastic contamination in the food chain, Food Addit. Contam. 36 (5) (May 2019) 639–673, https://doi.org/10.1080/19440049.2019.1583381.
[391] O.S. Alimi, J. Farner Budarz, L.M. Hernandez, N. Tufenkji, Microplastics and nanoplastics in aquatic environments: aggregation, deposition, and enhanced contaminant transport, Environ. Sci. Technol. 52 (4) (Feb. 2018) 1704–1724, https://doi.org/10.1021/acs.est.7b05559.
[392] F.K. Mammo, et al., Microplastics in the environment: interactions with microbes and chemical contaminants, Sci. Total Environ. 743 (Nov. 2020) 140518, https://doi.org/10.1016/j.scitotenv.2020.140518.
[393] C. Jiménez-Arroyo, A. Tamargo, N. Molinero, M.V. Moreno-Arribas, The gut microbiota, a key to understanding the health implications of micro(nano)plastics and their biodegradation, Microb. Biotechnol. 16 (1) (Jan. 2023) 34–53, https://doi.org/10.1111/1751-7915.14182.
[394] L. Lu, T. Luo, Y. Zhao, C. Cai, Z. Fu, Y. Jin, Interaction between microplastics and microorganism as well as gut microbiota: a consideration on environmental animal and human health, Sci. Total Environ. 667 (Jun. 2019) 94–100, https://doi.org/10.1016/j.scitotenv.2019.02.380.
[395] M. Teles, J.C. Balasch, M. Oliveira, J. Sardans, J. Peñuelas, Insights into nanoplastics effects on human health, Sci. Bull. 65 (23) (Dec. 2020) 1966–1969, https://doi.org/10.1016/j.scib.2020.08.003.
[396] L. Rubio, R. Marcos, A. Hernández, Potential adverse health effects of ingested micro- and nanoplastics on humans. Lessons learned from *in vivo* and *in vitro* mammalian models, J. Toxicol. Environ. Health, Part A B 23 (2) (Feb. 2020) 51–68, https://doi.org/10.1080/10937404.2019.1700598.
[397] J.J. Powell, N. Faria, E. Thomas-McKay, L.C. Pele, Origin and fate of dietary nanoparticles and microparticles in the gastrointestinal tract, J. Autoimmun. 34 (3) (May 2010) J226–J233, https://doi.org/10.1016/j.jaut.2009.11.006.
[398] C. Covello, F. Di Vincenzo, G. Cammarota, M. Pizzoferrato, Micro(nano)plastics and their potential impact on human gut health: a narrative review, Curr. Issues Mol. Biol. 46 (3) (Mar. 2024) 2658–2677, https://doi.org/10.3390/cimb46030168.
[399] O. García-Depraect, et al., Inspired by nature: microbial production, degradation and valorization of biodegradable bioplastics for life-cycle-engineered products, Biotechnol. Adv. 53 (Dec. 2021) 107772, https://doi.org/10.1016/j.biotechadv.2021.107772.
[400] M.W.K. So, L.D. Vorsatz, S. Cannicci, C. Not, Fate of plastic in the environment: from macro to nano by macrofauna, Environ. Pollut. 300 (May 2022) 118920, https://doi.org/10.1016/j.envpol.2022.118920.
[401] A. Tamargo, et al., PET microplastics affect human gut microbiota communities during simulated gastrointestinal digestion, first evidence of plausible polymer biodegradation during human digestion, Sci. Rep. 12 (1) (Jan. 2022) 528, https://doi.org/10.1038/s41598-021-04489-w.
[402] J. Zhang, L. Wang, L. Trasande, K. Kannan, Occurrence of polyethylene terephthalate and polycarbonate microplastics in infant and adult feces, Environ. Sci. Technol. Lett. 8 (11) (Nov. 2021) 989–994, https://doi.org/10.1021/acs.estlett.1c00559.
[403] M.O. Rodrigues, N. Abrantes, F.J.M. Gonçalves, H. Nogueira, J.C. Marques, A.M. M. Gonçalves, Impacts of plastic products used in daily life on the environment and human health: what is known? Environ. Toxicol. Pharmacol. 72 (Nov. 2019) 103239 https://doi.org/10.1016/j.etap.2019.103239.
[404] Y. Okai, et al., Effects of an environmental endocrine disruptor, *para* -nonylphenol on the cell growth of *Euglena gracilis* : association with the cellular oxidative stress, Environ Microbiol Rep 14 (1) (Feb. 2022) 25–33, https://doi.org/10.1111/1758-2229.13032.

[405] X. Zhang, et al., Effect of microplastics on nasal and gut microbiota of high-exposure population: protocol for an observational cross-sectional study, Medicine 101 (34) (Aug. 2022) e30215, https://doi.org/10.1097/MD.0000000000030215.
[406] Z. Li, et al., Effects of metabolites derived from gut microbiota and hosts on pathogens, Front. Cell. Infect. Microbiol. 8 (Sep. 2018), https://doi.org/10.3389/fcimb.2018.00314.
[407] M. Conlon, A. Bird, The impact of diet and lifestyle on gut microbiota and human health, Nutrients 7 (1) (Dec. 2014) 17–44, https://doi.org/10.3390/nu7010017.
[408] G. Lagoumintzis, G.P. Patrinos, Triangulating nutrigenomics, metabolomics and microbiomics toward personalized nutrition and healthy living, Hum. Genom. 17 (1) (Dec. 2023) 109, https://doi.org/10.1186/s40246-023-00561-w.
[409] M.E. Inda, E. Broset, T.K. Lu, C. de la Fuente-Nunez, Emerging frontiers in microbiome engineering, Trends Immunol. 40 (10) (Oct. 2019) 952–973, https://doi.org/10.1016/j.it.2019.08.007.