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The Human Gut Microbiome in the Development of Chronic Disease: A Comprehensive Review

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Abstract: The human gut microbiome, comprising trillions of microorganisms, functions as an "essential organ" with metabolic, immunological, and protective roles critical to host health. This review synthesizes current evidence on the relationship between gut microbiota and chronic disease pathogenesis, drawing from 50 high-impact studies identified through a comprehensive literature search. Dysbiosis microbial imbalance is strongly associated with metabolic disorders (obesity, type 2 diabetes, NAFLD), cardiovascular disease, inflammatory bowel disease, autoimmune conditions, neurodegenerative diseases, and certain cancers. Key mechanisms include immune modulation, regulation of intestinal barrier integrity, and production of bioactive metabolites (short-chain fatty acids, trimethylamine N-oxide) that influence host physiology. Environmental factors, particularly diet and lifestyle, shape microbial composition, while therapeutic interventions including dietary modification, probiotics, and faecal microbiota transplantation show promise but variable efficacy. Despite significant advances in understanding microbiome-disease associations through high-throughput sequencing, challenges remain in establishing causality due to confounding variables and inter-individual variability. This review highlights the gut microbiome's pivotal role in chronic disease pathogenesis while identifying critical research gaps requiring longitudinal studies, standardised dysbiosis definitions, and rigorous validation of personalised therapeutic approaches.

Keywords: *Gut microbiome, dysbiosis, chronic disease, metabolic disorders, inflammation, therapeutic interventions*.

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Introduction

Microbiomes exist in every human ecological niche that has been examined: the oral cavity, skin surface, intestinal tract, oesophagus, lungs, and others. The microbiota they comprise include bacteria, archaea, viruses, phages and fungi. Bacteria are the most prominent members of the microbiota, particularly in terms of species (Manos, 2022). More than 100 trillion symbiotic microorganisms live on and within human beings, playing an important role in human health and disease. The human microbiota, especially the gut microbiota, has even been considered to be an “essential organ”, carrying approximately 150 times more genes than are found in the entire human genome (O'Hara & Shanahan, 2006; Ursell *et al*., 2014; Afzaal et al., 2022). Important advances have shown that the gut microbiota is involved in basic human biological processes, including modulating the metabolic phenotype, regulating epithelial development, and influencing innate immunity (Wang & Li, 2015). Chronic diseases such as obesity, inflammatory bowel disease (IBD), diabetes mellitus, metabolic syndrome, atherosclerosis, alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), cirrhosis, and hepatocellular carcinoma have been associated with the human microbiota (see Fig. 1) (Ley *et al*., 2006; Hyun & , Cheon, 2025).

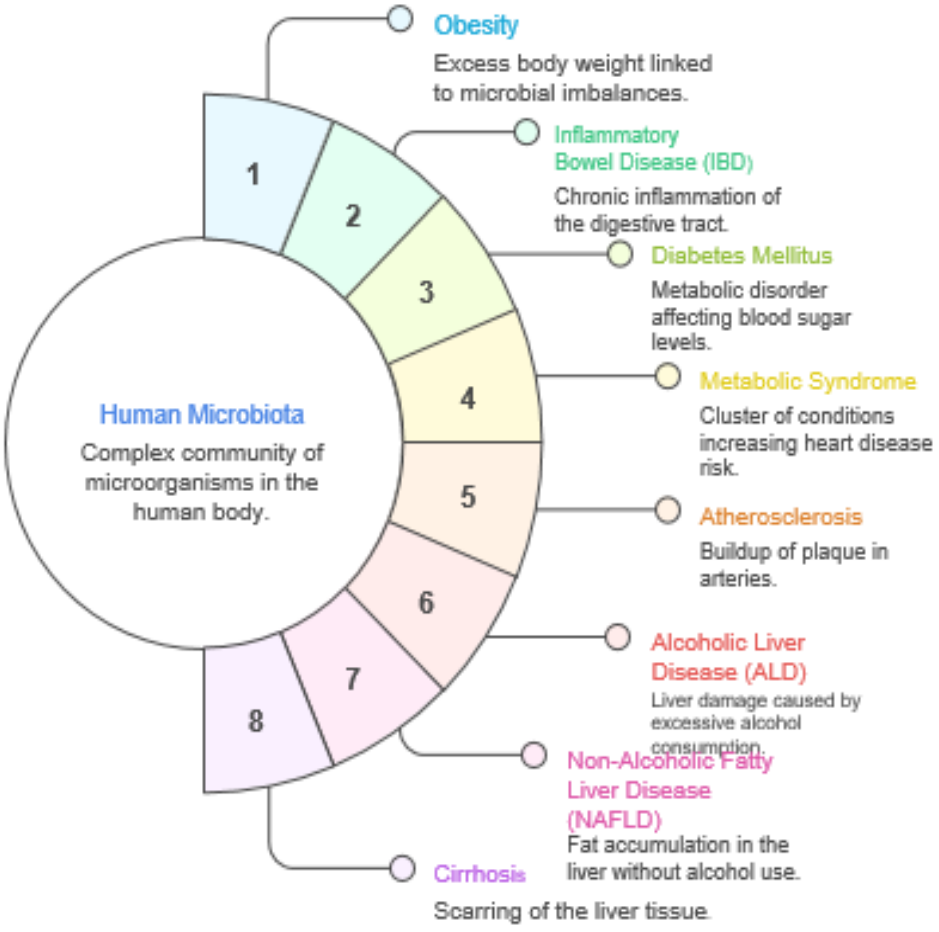


Fig. 1. Unveiling the human gut microbial role in chronic diseases

In recent decades, a tremendous amount of evidence has strongly suggested a crucial role of the human microbiota in human health and disease (Wang *et al*., 2016) via several mechanisms. First, the microbiota can increase energy extraction from food (Turnbaugh *et al*., 2006), enhance nutrient harvesting (Gill *et al*., 2006), and alter appetite signalling (Perry *et al*., 2016). The microbiota contains far more versatile metabolic genes than are found in the human genome, and provides humans with unique and specific enzymes and biochemical pathways (Gill *et al*., 2006). In addition, a large proportion of the microbiome's beneficial metabolic processes are involved in either nutrient acquisition or xenobiotic processing, including the metabolism of undigested carbohydrates and the biosynthesis of vitamins (Roberfrod *et al*., 1995). Second, the human microbiota also provides a physical barrier, protecting its host against foreign pathogens through competitive exclusion and the Production of antimicrobial substances (Cash *et al*., 2006). Finally, the microbiota is essential for the development of the host's intestinal mucosa and immune system (Bouskra *et al*., 2008). For example, germ-free (GF) animals have abnormal numbers of several immune cell types, deficits in local and systemic lymphoid structures, poorly formed spleens and lymph nodes, and perturbed cytokine levels (Macpherson & Harris, 2004). Studies on GF animals have suggested that the immune-modulatory functions of the microbiota primarily promote the maturation of immune cells and the normal development of immune function (Bouskra *et al*., 2008). In addition, studies have revealed the central role of microbial symbiosis in the development of many diseases, such as infection, liver diseases (Liu *et al*., 2004), gastrointestinal (GI) malignancy, metabolic disorders, respiratory diseases, mental or psychological diseases, and autoimmune diseases (Finegold *et al*., 2002; Ley *et al*., 2006; Sartor *et al*., 2008; Wen *et al*., 2008; Verhulst *et al*., 2008; Sekirov *et al*., 2010; Scanlan *et al*., 2018).

Whether as part of a microbiome or not, bacteria prefer to live in communities called biofilms in most hosts and many environmental settings. This preference for 'community living' and their 'communication skills' gives them an advantage within a microbiome. In order to build a community, bacteria communicate and interact with one another via small molecules known as autoinducers to assess numbers of 'self' (intraspecies communication) and to determine whether other bacterial species are present in the community (interspecies communication) by the process known as quorum sensing (QS) (Frederix & Downie, 2011). With interspecies communication, several species can work in unison, contributing to the community and forming an enclosed microbiome. While microbiomes exist in all environments, this review will concentrate on the relationship between the bacterial community within microbiomes and disease pathology in the human host (Manos, 2022).

Looking briefly at some of the most prominent human microbiomes, the most studied is that of the intestinal tract (gut). The gut microbiota are integral to host digestion and nutrition, and they can generate nutrients from substrates which are not accessible to host processes, such as xyloglucans found in onions

and lettuce. The gut microbiome exhibits greater diversity than that of other body sites (Manos, 2022).

According to data compiled by the Human Microbiome Project and the metagenomic analysis database MetaHIT, approximately 3000 bacterial species have been isolated from human faeces. The species have been classified into 11 phyla, with Proteobacteria, Firmicutes, Actinobacteria, and Bacteroidetes accounting for over 90% of the gut microbiome (Li *et al*., 2014).

Gut Microbiome and Chronic Disease

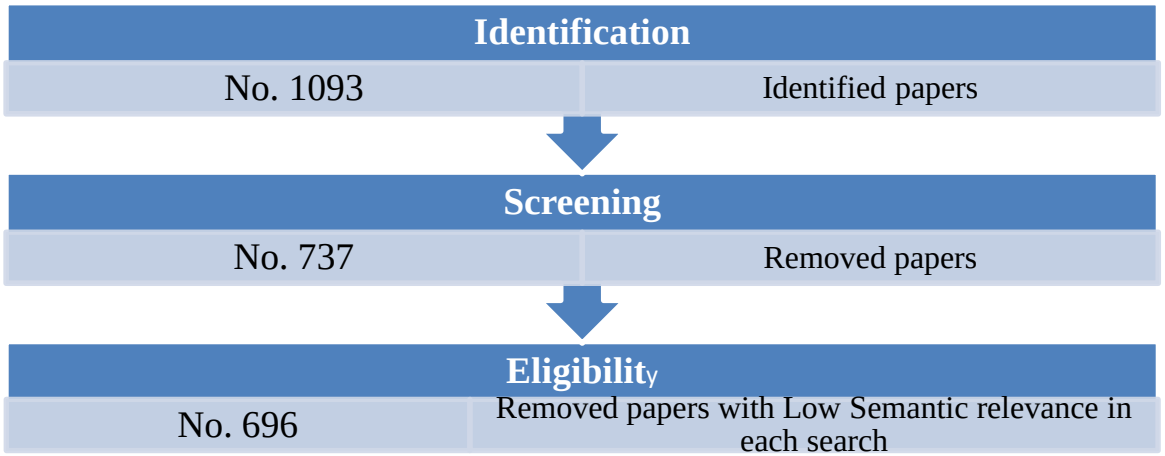
The human gut microbiome, a complex community of microorganisms residing in the gastrointestinal tract, plays a crucial role in maintaining health and influencing disease development. It is a vast and dynamic community of bacteria, viruses, fungi, and other microorganisms that plays a crucial role in maintaining health and is increasingly recognised as a key factor in the development of chronic diseases. Recent research has highlighted its significant impact on various chronic diseases, including metabolic disorders like type 2 diabetes and obesity, cardiovascular diseases, inflammatory bowel diseases (IBD), and even neurodegenerative conditions (Hills et al., 2019; Chen et al., 2021; Afraal et al., 2022). Dysbiosis, or microbial imbalance, is often linked to these conditions through mechanisms that modulate the immune system, regulate metabolism, and involve interactions between the gut and the brain (Cani et al., 2018; Shabani et al., 2025). While evidence supports the pivotal role of the gut microbiome in chronic disease development through complex interactions with host physiology (Martel et al., 2022), establishing causality across various conditions remains challenging due to confounding factors such as diet and genetics (Partel et al., 2025). The quality of the research varies; however, high-throughput sequencing technologies have significantly advanced our understanding. The human gut microbiome plays a critical role in the pathogenesis of various chronic diseases through mechanisms that modulate the immune system and regulate metabolism. While significant progress has been made in understanding these interactions, further research is needed to translate findings into clinical applications. This review synthesises current findings on how gut microbiota contribute to chronic disease pathogenesis and explores potential therapeutic interventions targeting microbial communities.

The imbalance in gut microbiota has been linked to a wide range of conditions, including metabolic disorders (such as obesity and type 2 diabetes), cardiovascular diseases, inflammatory bowel disease (IBD), autoimmune disorders, neurological diseases, and even certain cancers (Durack et al., 2018; Fan et al., 2020; Afzaal et al., 2022; Shaabani et al., 2025). Mechanistically, the gut microbiome influences host metabolism, immune function, intestinal barrier integrity, and systemic inflammation through its metabolites (e.g., short-chain fatty acids, trimethylamine N-oxide) and interactions with host pathways (Fan et al., 2022; Pires et al., 2024; Liu et al., 2025). Environmental factors, including diet, antibiotics, lifestyle, and genetics, shape the composition and function of the gut microbiota (Illiano et al., 2020; Martel et al., 2022; Shaabani et al., 2025). While advances in sequencing technologies have deepened our understanding of these complex relationships, challenges remain in establishing causality and translating findings into clinical interventions (Cani et al., 2018; Liu et al., 2025). This review synthesises current knowledge on how the human gut microbiome contributes to the development of chronic disease and highlights emerging therapeutic strategies.

Methods

A comprehensive literature search was conducted across over 170 million research papers indexed by Consensus, including Semantic Scholar, PubMed, and additional sources. The search strategy targeted foundational theories, mechanistic pathways, disease-specific links (e.g., IBD, cardiovascular disease, diabetes), therapeutic interventions (dietary modulation, probiotics/prebiotics/FMT), methodological critiques, environmental determinants, age-related differences, and computational modelling. In total, 1093 papers were identified; after de-duplication and screening for relevance/quality, 737 were screened; 696 met eligibility criteria; and the top 50 most relevant papers were included for this review.

Search Strategy



Inclusion	
No. 50	Highest quality papers selected

Results

The included studies span high-impact reviews and original research from leading journals published between 2012 and 2025. They cover diverse chronic diseases, metabolic (obesity/diabetes), cardiovascular (atherosclerosis/heart failure), gastrointestinal (IBD/colorectal cancer), neurological (Alzheimer's/Parkinson's), and autoimmune disorders and address both mechanistic insights and clinical implications (Durack et al., 2018; Fan et al., 2020; Afzaal et al., 2022; Rahman et al., 2022; Shaabani et al., 2025).

Microbiome–Disease Links

Dysbiosis is associated with metabolic disorders such as obesity, type 2 diabetes (T2D), and nonalcoholic fatty liver disease (NAFLD), often via altered energy harvest/metabolism and immune modulation (Hills et al., 2019; Fan et al., 2020; Gurung et al., 2020; Pires et al., 2024; Liu et al., 2025). Gut-derived metabolites like TMAO are implicated in atherosclerosis/hypertension; reduced SCFA production is linked to increased inflammation and Cardiovascular disease outcomes (Tang et al., 2017; Rahman et al., 2022; Trøseid et al., 2020; Nesci et al., 2023; Hemmati et al., 2023). Altered microbial diversity/composition is consistently observed in patients with Inflammatory Bowel Disease (IBD); specific taxa, such as Proteobacteria, are enriched during active inflammation (Qui et al., 2020; Zhang et al., 2022; Haneishi et al., 2023). Other chronic disease associations extend to cancer risk (especially colorectal cancer), neurodegenerative diseases (via gut-brain axis), autoimmune conditions (via immune dysregulation), respiratory illnesses (COPD/asthma), kidney disease, and more (Kho et al., 20; Manos, 2022; Di Vincenzo et al., 2023).

Key mechanisms include modulation of host immunity/inflammation, Regulation of intestinal barrier ("leaky gut") integrity, Production of bioactive metabolites (SCFAs/bile acids/TMAO), and interaction with host metabolic/endocrine/neural signalling pathways (Hills et al., 2017; Tang et al., 2019; Di Vincenzo et al., 2023). Interventions targeting the microbiome dietary changes (fibre/prebiotics/probiotics), faecal microbiota transplantation (FMT), and next-generation probiotics show promise for prevention/treatment but require further validation (Tsai et al., 2019; Illiano et al., 2020).

Discussion

The evidence strongly supports the view that the human gut microbiome is intricately involved in chronic disease pathogenesis through multiple mechanisms, particularly via immune modulation/inflammation, and metabolic regulation (Fan et al., 2020). However, distinguishing causality from correlation remains challenging due to confounding factors such as diet/lifestyle/medications/genetics (Cani et al., 2018). While animal models provide mechanistic insights, especially regarding microbial metabolites such as SCFAs/TMAO, translating these findings to humans is complicated by inter-individual variability and environmental influences (Du et al., 2025). Large-scale multi-omics studies have improved our understanding but have also highlighted substantial heterogeneity across populations (Jie et al., 2017).

Therapeutic interventions targeting dysbiosis show promise but are not universally effective; traditional probiotics/prebiotics yield mixed results, while FMT holds promise for select conditions, such as recurrent C. difficile infection or IBD flares (Tsai et al., 2019). Personalised approaches based on individual microbial profiles may enhance efficacy but require further research.

Claims and Evidences

Dysbiosis is strongly associated with increased risk for multiple chronic diseases, as evidenced by consistent associations across large-scale human studies for metabolic, CVD, IBD, and cancer outcomes (Hills et al., 2019; Fan et al., 2020; Afraal et al., 2022). Gut-derived metabolites have been shown to strongly modulate host metabolism and inflammation, as observed in mechanistic animal/human data linking SCFAs/TMAO/bile acids to metabolic/CVD risk (Nesci et al., 2023; Liu et al., 2025). Numerous studies have reported strong evidence that dietary/lifestyle factors shape gut microbiota composition, as evidenced by various epidemiological/interventional studies showing rapid shifts in microbiota composition in response to diet/exercise/antibiotics (Illiano et al., 2020; Shabani et al., 2025). Although there is moderate evidence linking microbiome-targeted therapies to the amelioration of some chronic diseases, results from clinical trials show benefit for some interventions, but the effects are variable (Tsai et al., 2019; Shabani et al., 2025).

Research Gaps

Despite rapid advances, causal relationships between specific microbial changes and chronic disease onset/progression remain unclear. The definitions of "healthy" vs "dysbiotic" microbiomes lack Consensus. There are limited longitudinal/interventional human studies. The efficacy/safety of personalised or next-generation therapies also needs further validation.

Conclusion

In conclusion, substantial evidence supports the gut microbiome's involvement in the development of chronic disease. Current research demonstrates that the human gut microbiome plays a pivotal role in modulating risk for and potentially driving the development of numerous chronic diseases through complex interactions involving metabolism, immunity, barrier function, and environmental exposures. While strong associations exist between dysbiosis and disease states across metabolic, cardiovascular, gastrointestinal, and neurological domains, and mechanistic pathways are increasingly understood, definitive proof of causality remains elusive due to confounding variables and methodological limitations.

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