Correlating the Gut Microbiome to Health and Disease

The Gut-Brain Axis, Second Edition

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CHAPTER

Correlating the Gut Microbiome to Health and Disease

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Introduction

The human gut microbiota is a complex microbial ecosystem that consists of a diverse population of mainly prokaryotes that have a symbiotic relationship with the human host. Most of these have a (facultative) anaerobic lifestyle and belong to a few abundant phyla, including Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, and Verrucomicrobia (Hugon et al., 2015; de Vos et al., 2022). The Firmicutes and Bacteroidetes phyla accommodate the most abundant species and constitute over 90% of the human gut microbiota (Bäckhed et al., 2005; Eckburg et al., 2005).

The gut microbiota exerts a considerable influence on the host, being involved in food metabolism and the production of numerous bioactive compounds, immunomodulation, regulation of endocrinological functions and neurological signaling, pathogen exclusion, and elimination of toxins. Thus, the microbiome has a significant potential to affect our health by affecting our physiological, immunological, and nutritional status (Hooper et al., 1998; Neish, 2009; Van Treuren and Dodd, 2020).

From being sterile at birth, our gut is rapidly colonized in the first few days of life, being affected by such factors as mode of delivery (Grölund et al., 1999), type of feeding (Orrhage and Nord, 1999), and antibiotic therapy (Gibson et al., 2015). Although the gut microbiome develops rapidly in diversity and complexity in the first few years after birth, it becomes relatively stable in adulthood, and specific microbiota signatures have been detected in longitudinal analysis over 10 years (Rajilić-Stojanović et al., 2013). In addition, the composition of our microbiome is highly individual (Gacesa et al., 2022), is similar in genetically related subjects (Turnbaugh et al., 2009), and differs among individuals of different ethnicities (Deschasaux et al., 2018). Moreover, interindividual differences in the composition of the gut microbiome can be overwhelmingly explained by an individual's geographic location as shown in a large-scale clinical microbiome study conducted in China (He et al., 2018).

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Although our microbiome is relatively stable, it may be modified by various factors such as food components, major dietary changes, and pharmaceutical treatments that target the composition, stability, and activity of the microbiota (Sommer et al., 2017). After the discovery of microbial life, Antonie van Leeuwenhoek reported in 1681 the first observation relating a disturbed microbial composition to the diarrhea he was experiencing, possibly after drinking dirty Amsterdam canal water (Dobell, 1932). More than two centuries later, Metchnikoff hypothesized that replacing the "bad" bacteria in the gut with lactic acid bacteria could normalize bowel health and thus prolong life (Metchnikoff and Mitchell, 1907). Hence, it has long been speculated that the gut microbiota bears a significant functional role in maintaining gut health and numerous studies have been performed to elucidate what role the human gut microbiome plays in human health. Most of our knowledge about this microbial organ and what role it plays in our physiology is becoming clearer, thanks to recent advances in sequencing technology, and "omics" tools which have helped us to reveal the complexity and composition of the gut microbiota and its functionality. Dysbiosis is often used to designate an alteration of the composition of the gut microbiota, but this term is a misnomer because a healthy gut microbiota has not been well defined because it is also highly personalized, affected by diet, and extremely complex (Gacesa et al., 2022; Zoetendal et al., 2008; Zoetendal and de Vos, 2014). However, the presence of changes in gut microbiota composition has been described as the major hallmark that is associated with, or contributes to, diseases that have been linked to the gut microbiome. Although these are associations and not causalities in most cases, microbiota changes have been linked with diseases occurring within and outside of the gut, including inflammatory bowel disease (IBD; Lee and Chang, 2021), irritable bowel syndrome (IBS; Hou et al., 2022; Pittayanon et al., 2019), obesity (Barczynska et al., 2018), type II diabetes (Gurung et al., 2019), colorectal cancer (CRC; Cheng et al., 2020; Thomas et al., 2019), and cardiovascular diseases (Fromentin et al., 2022; Talmor-Barkan et al., 2022). Therefore, the aim of this chapter is to give an overview of the extensive role of our gut microbiome in health and disease.

Gut Microbiota and Immune System-Related Diseases

Millions of years of coevolution have created a complex mutualistic relationship between the commensal microbiota and its host that begins at birth. The immune system shapes the microbiota composition and, in turn, the microbiota induces the maturation of the immune system and directs the development of immune responses. The immune system has evolved, recognizing commensal bacteria and responding and adapting to foreign and self-molecules, hence protecting the host from pathogens while preserving the symbiotic relationship (Hooper et al., 2012). In turn, the gut bacterial community has developed to modulate structures and cells of the immune system, all of which have important roles in the process of tolerance and susceptibility to inflammation (Belkaid and Harrison, 2017).

Studies using germ-free (GF) animals have shown that the gut microbiota is required for the normal generation and maturation of gut-associated lymphoid

tissues (Cebra et al., 1998) to regulate the development of specific immune cells in the gut, such as the T helper 17 (Th17) and Foxp3+ regulatory T cells (Ivanov et al., 2008; Lathrop et al., 2011), and to induce the differentiation of immunoglobulin A− producing B cells (Strugnell and Wijburg, 2010), and to promote CD8+ T cells differentiation into memory cells (Bachem et al., 2019). Therefore early-life exposure to microbial antigens is critical for proper immune development. By recognizing self from nonself, presenting a broad range of antigens during the first days of life and at weaning (critical window) will lower the risk for autoimmune diseases and exacerbated responsiveness to allergens later in life that may increase the susceptibility to inflammatory pathologies, including allergies and asthma (Al Nabhani et al., 2019; Fujimura and Lynch, 2015; Hooper et al., 2012).

Allergies and Asthma

The prevalence of allergic diseases, such as atopic dermatitis (eczema), food allergies, and asthma, has increased over the last decades, becoming a major health problem in high-income countries. This increase has coincided with lifestyle-associated environmental changes that may affect the host microbiota, such as increased hygiene, smaller family sizes, dietary changes, and excessive antibiotic use (von Mutius and Smits, 2020).

Early life environmental exposures are critical to immune system training and function and, consequently, allergy and asthma pathogenesis (Lynch and Vercelli, 2021). Indeed, epidemiological studies have shown an inverse relationship between rates of childhood allergies and exposure to microbial-rich environments, suggesting that exposure to high levels of certain allergens and bacteria early in life might be beneficial. In a study conducted by Ege et al. (2011), school children growing up in predominantly rural areas were shown to be protected from asthma and atopy, whereas a study by Ownby et al. (2002) demonstrated that exposure to two or more dogs or cats in the first year of life reduced subsequent allergic sensitization. A birth cohort study in an inner-city environment conducted by Lynch et al. (2014) found the lowest rates of atopy and wheezing in children with higher bacterial diversity that had been exposed to high levels of cockroach, mouse, and cat allergen if compared with children with lower exposure to these allergens. Moreover, dust microbiota composition was shown to be a reproducible predictor of asthma risk in a modeling study conducted by Kirjavainen et al. (2019). By comparing data collected in two Finnish birth cohorts, Lukas 1 (farm home model) and Lukas 2 (non-farm home model), and validating the model using a German cohort, it was shown that children living in a non-farm home with a rich indoor dust microbiota, similar to the microbiota of a farm, have decreased risk to develop asthma.

Several clinical studies have shown that reduced diversity of intestinal microbiota in early life is associated with an increased risk of developing atopic diseases and asthma in infants (Abrahamsson et al., 2012, 2014; Bisgaard et al., 2011; Forno et al., 2008; Wang et al., 2008). Vancomycin treatment of newborn mice has been shown to reduce gut microbiota diversity and disrupt the balance of pro-

inflammatory and regulatory immune response, enhancing the susceptibility to experimental allergic asthma (Russel et al., 2012), whereas asthma in children has been positively associated with prenatal and postnatal antibiotic prescriptions in an English birth cohort (Souza da Cunha et al., 2021). Moreover, a retrospective cohort study using twin pairs discordant for eczema/asthma has shown that early-life antibiotic use is associated with asthma, independently of genetic and environmental factors. However, the antibiotic effect on eczema onset could not be dissociated from familial and genetic factors (Slob et al., 2020).

Substantial effort has been devoted to identifying specific bacterial species or taxa that correlate with the development of, or protection against, allergy-related disorders. However, the results are still conflicting and differ significantly depending on the study, probably because of differences in sample populations and the methods applied for microbiota analysis. Although Lynch et al. (2014) described the presence of allergy-protective bacteria, particularly from the Prevotellaceae, Lachnospiraceae, and Ruminococcaceae families, in the house dust of urban neighbourhoods; Ege et al. (2011) did not identify any protective microorganisms in the rural environment studied. Abrahamsson et al. (2012) reported a lower diversity of Bacteroidetes and Proteobacteria in infants with atopic eczema, but the same group did not find associations between asthma and the relative abundance of any phylum or genus in a second study (Abrahamsson et al., 2014). A study by Arrieta et al. (2015) found that babies that had low or undetectable levels of the bacterial genera *Lachnospira*, *Veillonella*, *Faecalibacterium*, and *Rothia* at 3 months of age had an elevated risk to develop asthma-like symptoms by their first birthday, whereas infants at lower asthma risk had relatively robust levels of these bacteria in their intestine when they were 3 months old. It is interesting to note that the group confirmed the protective effect of these bacteria in a second experiment that showed an improvement in airway inflammation in GF mice inoculated with these four bacterial taxa. It is of interest to note that the absence of similar bacteria, including *Rothia* spp., were included in a classifier predicting later-life asthma in a large cohort of Finnish infants that had been exposed to unusually high levels of antibiotics earlier in life (Korpela et al., 2016). An increasing body of evidence has identified maternal weight gain and maternal and child obesity to be related to asthma development and severity, with alterations in the gut microbiome as a potential mechanism linking both diseases (Peters et al., 2018). In adults, pronounced deviations in the gut microbiota have been reported in notably obese subjects with asthma in comparison with healthy controls (Michalovich et al., 2019). This study found that asthma severity was inversely correlated to the abundance of *Akkermansia muciniphila*, which upon addition in a murine asthma model appeared to reduce hyperactivity and inflammation.

Rheumatoid Arthritis

The gut microbiota and its interactions with the host mucosal immune system may also play a role in rheumatoid arthritis (RA) onset and progression in genetically predisposed individuals (Bergot and Giri, 2019). RA is a systemic autoimmune inflammatory disease, and its development is associated with the dysregulation of normal

immune function with increased production of proinflammatory cytokines and activation of autoreactive B and T lymphocytes (Brandl et al., 2021). Animal models of inflammatory arthritis have demonstrated that bacterial colonization can be an environmental trigger for the development of the disease. Wu et al. (2010) showed that segmented filamentous bacteria (SFB) introduced into GF animals can induce Th17 cells to produce IL-17, a cytokine that stimulates the production of auto-antibodies, provoking the onset of arthritis. However, it should be emphasized that SFB have only anecdotally been described to be present in humans. Hence, a study that further embarked on the molecular mechanism of SFB in inducing Th17 cell accumulation in mice also described the isolation of human bacteria that could mimic this signaling system (Atarashi et al., 2015). In other animal studies, Abdollahi-Roodsaz et al. (2008) demonstrated that contamination of IL1rn−/− GF mice with a single species, *Lactobacillus bifidus*, results in the activation of toll-like receptor (TLR)-2 and TLR4 with the rapid development of arthritis, whereas Jubair et al. (2018) demonstrated that modification of the gut microbiota through the administration of broad-spectrum antibiotics modulates mucosal inflammation, reducing the severity of arthritis in collagen-induced arthritis (CIA) animal model. Furthermore, clinical studies have been done to investigate if intestinal microbiota composition in patients with RA differs from healthy subjects. Scher et al. (2013) demonstrated that the species *Prevotella copri* was more abundant in patients suffering from untreated RA than in healthy subjects, but this discrepancy was not observed in chronic RA patients receiving treatment. And in this same study, colonization of mice with *P. copri* exacerbated the severity of dextran sulfate sodium−induced colitis, suggesting that this organism has a potential proinflammatory function. Zhang et al. (2015) also reported alterations in the microbiota composition of RA patients when compared with healthy controls, which was partially resolved after RA treatment. Bacteria from the *Haemophilus* species were depleted, whereas *Lactobacillus salivarius* was overrepresented in individuals with RA, and this deviation was most marked in patients suffering from very active RA. In a recent study, Chen et al. (2021) reported that alterations in the gut microbiota were mainly in abundance but not in composition in a small cohort of Chinese subjects. Bacteria from the genus *Bacteroides, Faecalibacterium,* and *Bifidobacterium* were decreased, whereas 97 other genera, including *Lactobacillus*, *Streptococcus*, and *Akkermansia*, were increased in the RA group compared to the healthy group. Moreover, fecal metabolic profiles suggested that RA can lead to significant changes in metabolites, as observed for the two long-chain fatty acids 9,12-octadecadiynoic acid and 10Z-nonadecenoic acid, which were increased in the RA patients and strongly positively correlated with the phylum Verrucomicrobia and the genus *Akkermansia*.

SCFA have also been shown to have a role in RA development. In a study by Lucas et al. (2018) SCFA treatment significantly attenuated the severity of inflammation and modulated bone metabolism in two mouse models of inflammatory arthritis (CIA model and K/BxN serum-induced (SIA) model), whereas Tajik et al. (2020) demonstrated that the administration of butyrate can restore intestinal barrier function inhibiting the onset of arthritis in mice. Moreover, Rosser et al.

(2020) reported that butyrate levels were reduced in feces from RA patients compared to healthy controls, and in an animal model of antigen-induced of arthritis (AIA). Moreover, this study demonstrated that supplementation with butyrate can reduce arthritis severity in AIA mice by influencing B cell development and Breg function. Altogether these studies suggest that modulation of gut microbiota composition and manipulation of microbial end-products may be a potential therapeutic approach to ameliorate RA.

Gut Microbiota and Intestinal Diseases

Recurrent *Clostridioides Difficile* Infections

Clostridioides difficile infection (CDI) is a possibly life-threatening condition with symptoms ranging from mild diarrhea and abdominal pain to severe colitis and sepsis. CDI manifests commonly after some perturbation to the existing gut microbiota, such as antibiotic treatment, allowing the rapid expansion of a spore-forming, toxin-producing pathogenic bacterium *Clostridioides difficile*. Although certain antibiotics, such as vancomycin, may effectively treat bouts of CDI, continued exposure to antibiotics prevents the re-establishment of gut microbiota and the cessation of antibiotic treatment eventually leads to the recurrence of CDI. First described in 1958 as a treatment for pseudomembranous enterocolitis, inoculation of new microbes to the intestinal environment via a process called fecal microbiota transplantation (FMT) has since proved effective at treating recurrent CDI (rCDI) (Guery et al., 2019). In the first randomized clinical trial comparing the efficacies of FMT, vancomycin, and vancomycin with bowel lavage in the treatment of rCDI, duodenal infusion of donor feces to rCDI patients resulted in the resolution of symptoms in 15/16 of patients whereas only 4/13 patients receiving vancomycin and 3/13 patients receiving vancomycin with bowel lavage went into remission (van Nood et al., 2013). Subsequent clinical trials have reported similar findings with efficacy rates varying from 80% to 94% depending on the FMT protocol (Guery et al., 2019; Li et al., 2016). These successes have led to numerous investigations into using FMT to treat other diseases and disorders but so far, its clinical application has been limited to the treatment of rCDI. The exact biological mechanisms behind FMT's effectiveness in treating rCDI remain unclear albeit it likely involves multiple complementary processes (Khoruts and Sadowsky, 2016). The intestinal microbiota composition of rCDI patients pre-FMT is characterized by a low diversity of bacterial species coupled with the overgrowth of inflammatory bacteria (Fuentes et al., 2014), a state frequently described as gut dysbiosis. FMT reverts this aberrant state back to a healthy microbial ecosystem that inhibits *C. difficile* by competing for nutrients, activating host defenses, and limiting the pool of certain bile acids that stimulate the growth of *C. difficile* (Fuentes et al., 2014; Khoruts and Sadowsky, 2016; Mullish et al., 2019). Further highlighting the role of the microbial ecosystem in resisting the colonization of pathogenic bacteria, recent studies have shown that the decreased abundance of certain key bacterial species is what allows *C. difficile* to colonize the

intestinal milieu in the first place which thus increases the risk for CDI after antibiotic treatment (Berkell et al., 2021; Haran et al., 2021). Overall, FMT's success in treating rCDI is a unique example showing how bugs can be better than drugs although a lot of uncertainty remains (Hanssen et al., 2021). Recent studies based on deep metagenomic analysis revealing strain-specific signatures have identified the basic principles relating to the successful establishment of newly administered microbes in the complex gut ecosystem (Lee et al., 2022; Schmidt et al., 2022). Hence, it may be expected that innovative products based on synthetic microbial consortia will be developed that can be used to treat recurrent CDI and other diseases.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is an umbrella term for several immune disorders of the gastrointestinal tract characterized by chronic mucosal inflammation. The two most common clinical phenotypes of IBD are Crohn's disease (CD) and ulcerative colitis (UC). The causes of IBD are still incompletely understood but cumulative evidence suggests that the development of these diseases involves genetic, environmental, immunological, and microbial factors (Lee and Chang, 2021). Currently, the main hypothesis states that IBD arises in genetically susceptible individuals due to an abnormal immune reaction against intestinal microbiota. However, although microbial changes are evident in IBD patients, it remains unclear whether intestinal microbiota alterations are the cause, or the consequence of the disease and which microbial species act as the main contributors to disease development (Lee and Chang, 2021).

Because IBD is a heterogeneous disease with varying phenotypes affecting different parts of the gastrointestinal tract, it is difficult to establish all-encompassing microbial changes applicable to all IBD phenotypes. Nevertheless, evidence from human studies suggests that, compared to healthy controls, decreased microbial diversity, reduced abundance of *Bacillota* (*Firmicutes*), and increased abundance of *Pseudomonadota* (*Proteobacteria*) are common features in IBD-associated microbiota (Halfvarson et al., 2017; Machiels et al., 2014; Ni et al., 2017; Rashed et al., 2022; Russo et al., 2019; Zhang et al., 2022). Considering that the *Bacillota* phylum includes several notable butyrate-producing bacteria, such as *Faecalibacterium prausnitzii*, and *Roseburia* spp, whereas the *Pseudomonadota* phylum consists mainly of Gram-negative, proinflammatory bacterial species, it seems likely that the microbial alterations contribute to the overt inflammatory processes present in IBD. These microbial findings have raised the question of whether IBD patients could benefit from FMT. However, although some studies have shown promising results, especially in the treatment of UC, the overall efficacy of FMT in the treatment of IBD remains unclear and appears to be highly dependent on the donor microbiota, and the chosen FMT protocol (Haifer et al., 2022; Rashed et al., 2022; Zhang et al., 2022).

Microscopic colitis (MC) is a chronic inflammatory disease of the colon that primarily manifests as chronic watery diarrhea and abdominal pain (Zabana et al.,

2022). Compared to CD and UC where mucosal inflammation is visible to the naked eye, MC diagnosis is based on a microscopic evaluation of colonic mucosal biopsies (hence the name "microscopic"). MC is divided into two main subtypes: collagenous colitis (CC) and lymphocytic colitis (LC). Both subtypes show increased inflammatory infiltrate underneath the colonic epithelial layer, but CC also features a thickened subepithelial collagen layer. The cause of MC remains unclear but as in CD and UC, the pathophysiological processes likely involve an aberrant immune response to luminal antigens in predisposed individuals (Zabana et al., 2022). Although the intestinal microbiota changes in MC are less well-characterized than in CD or UC, the current evidence suggests that microbiota could play a role in the pathophysiology of MC. For example, recent studies have reported a reduced abundance of bacteria in the Ruminococcaceae family (Carstens et al., 2019; Hertz et al., 2022) which includes butyrate-producing *F. prausnitzii*, decreased abundance of mucin-degrading *Akkermansia* (Carstens et al., 2019; Fischer et al., 2015; Rindom Krogsgaard et al., 2019), and increased abundance of proinflammatory, sulfur-reducing bacteria *Desulfovibrionales* (Millien et al., 2019). Interestingly, the microbiota composition in MC patients appears to resemble the disease state as individuals with active disease display more microbial alterations than individuals in remission (Carstens et al., 2019) and corticosteroid treatment shifts microbiota composition toward healthy controls (Rindom Krogsgaard et al., 2019). Regarding MC and FMT, one case study (Günaltay et al., 2017) and one small pilot study (Holster et al., 2019) have shown that a subset of CC patients may benefit from FMT but reports have also described new onset MC cases following FMT (Zabana et al., 2022) which highlights the uncertainty in our current knowledge of microbial interactions.

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a multifactorial functional gastrointestinal disorder with a prevalence of 10%−20%. IBS patients suffer from various symptoms, such as pain and cramps, diarrhea and/or constipation, bloating, flatulence, feelings of incomplete defecation, and relief of pain or discomfort upon defecation. The etiology of IBS is still not well understood, and IBS diagnosis is often based on the exclusion of other intestinal diseases such as IBD. However, it is generally accepted that dysregulation along the microbe-gut-brain axis is present in IBS, as shown by the high prevalence of psychological comorbidities and an increased visceral hypersensitivity in IBS patients (Kennedy et al., 2014). In addition, low-grade intestinal inflammation is present in the intestinal mucosa of some patients, and there is evidence that the immune system reacts abnormally to the commensal microbiota, especially in the case of postinfectious IBS (Sundin et al., 2015a, 2015b).

Ample evidence from human studies shows that IBS patients' intestinal microbiota not only differs from healthy controls but also within different IBS subtypes (Hou et al., 2022; Pozuelo et al., 2015; Rangel et al., 2015; Sundin et al., 2015a; Sundin et al., 2020; Tana et al., 2010). A recent systematic review including 24 studies

comparing specific microbial species between IBS patients and healthy controls (Pittayanon et al., 2019) reported that IBS patients consistently appear to display increased abundance of the Enterobacteriaceae family that includes several pathogenic bacteria and the family Lactobacillaceae that includes organic acid -producing genus *Lactobacillus* previously linked to IBS symptoms (Tana et al., 2010). In addition, the IBS-associated microbiota seems to have reduced abundance of *Faecalibacterium prausnitzii* and *Bifidobacterium* (Pittayanon et al., 2019) which are both considered beneficial for maintaining intestinal health. It should be noted that many of these findings arise from analyses using fecal samples, not mucosal samples where the microbial composition might differ substantially (Hou et al., 2022; Sundin et al., 2020). Nevertheless, several of the aforementioned studies have reported correlations between IBS symptoms and both mucosa-associated and fecal microbiota suggesting that microbiota-modifying treatments might provide solutions for IBS symptom management. For example, certain probiotic combinations have shown beneficial effects on IBS symptoms although no consensus exists on which probiotic strain or combination would be universally effective (Ford et al., 2018). Similarly, individual studies on FMT have reported improvements in IBS symptoms following FMT (Holster et al., 2019; Holvoet et al., 2021; Lahtinen et al., 2020) but due to the heterogeneity of IBS symptoms, IBS subtypes, and FMT protocols, the overall efficacy of FMT on alleviating IBS symptoms remains unclear (Zhao et al., 2022).

Colorectal Cancer

An imbalance between the colonic microbiota and the intestinal epithelium might lead to an immune cell invasion and chronic inflammation, which in turn might result in colorectal carcinogenesis. Animal studies have shown that the presence of microbiota is necessary for the development of colorectal cancer (CRC) (Keku et al., 2015). Considering the significant individual and societal disease burden of CRC, extensive research efforts have attempted to find the microbial alterations that possibly drive tumorigenesis in CRC patients. Perhaps the most consistent finding in these studies is the increased abundance of *Fusobacterium nucleatum* in CRC patients compared to healthy controls (Cheng et al., 2020; Kong et al., 2022; Thomas et al., 2019; Wirbel et al., 2019; Yachida et al., 2019). *Fusobacterium nucleatum* are Gram-negative bacteria that are prevalent in the oral cavity where it is associated with periodontal disease. Interestingly, a recent meta-analysis found that CRC patients also display higher abundancies of oral bacterial species in general in their fecal microbiota than healthy controls (Thomas et al., 2019). Other bacterial species associated with CRC development and progression include for example *Bacteroides fragilis* and *Peptostreptococcus stomatis*, among others (Cheng et al., 2020; Obón-Santacana et al., 2022; Thomas et al., 2019; Wirbel et al., 2019). In addition to characterizing changes in CRC-associated microbiota, metagenomic analyses have revealed microbial species that could be used to predict and diagnose early-onset CRC and disease progression as studies have shown cancer-stage specific changes in microbiota composition and

function (Thomas et al., 2019; Yachida et al., 2019; Yu et al., 2017). However, some of the microbial changes might just reflect the presence of the tumor itself, and not necessarily the pathological processes (Obón-Santacana et al., 2022). In addition, a recent metagenomic analysis showed marked differences between early-onset CRC (<50 years) and late-onset CRC with late-onset CRC being associated with increased abundance of *Fusobacterium nucleatum* and the depletion of short-chain fatty acids (SCFA) (Kong et al., 2022). Overall, these findings suggest that the intestinal microbiota is an important factor for CRC risk and development although the role of microbiota as a clinical prognostic test is still unclear.

Gut Microbiota and Diseases of the Nervous System

Anxiety and Depression

Psychological disorders, such as anxiety and depression, are to some degree comorbidities in all the diseases previously mentioned. The microbe−gut−brain axis is a well-accepted entity and is involved in these disorders. However, it remains uncertain whether mental and microbial factors are a cause or consequence.

A direct connection between intestinal microbiota and mood disorders is well documented in animal models. GF mice show less anxiety-like behavior compared with conventionalized mice, suggesting that the development of this behavior can be affected by the intestinal microbiota (Neufeld et al., 2011). In addition, the colonization of GF mice with microbiota of a different species resulted in behavioral changes (Bercik et al., 2011). FMT from mice with depressive-like features showed recipient mice to express similar depressive-like features and decreased neuromodulatory signaling via the endocannabinoid system, due to a low amount of ligands originating from fatty acid precursors (Chevalier et al., 2020). Enhancing the endocannabinoid signaling and complementing the microbiota with the probiotic *Lactobacillus plantarum* normalized behavior and triggered neurogenesis.

In humans it is known that enteropathogens may affect mood, probably via the immune system. Reichenberg et al. (2001) showed in a placebo-controlled study that healthy volunteers experienced increased anxiety and depressive mood after intravenous infusion with *Salmonella abortusequi* endotoxins. The authors hypothesized that this effect on emotional perception was probably generated because of the host's immune system release of cytokines. Moreover, the common observation that many patients with chronic hepatitis C develop depression during interferon treatment led to the theory that depression is an inflammatory state (Udina et al., 2012). However, a recent body of studies shows conflicting results on whether microbial composition, in terms of diversity, is altered in patient groups suffering from depression and/or anxiety (Simpson et al., 2021).

Unfortunately, not many human studies on the effect of altered intestinal microbiota composition on brain function have been performed yet, but a few studies using probiotics showed an effect on mental factors. A milky drink containing the probiotic *Lactobacillus casei Shirota* improved the mood of volunteers with initially

poor mood, but it had no effect on the general study populations (Benton et al., 2007). In addition, the administration of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 was studied in a double-blind, placebo-controlled, randomized trial (Messaoudi et al., 2011). Taking this mix of probiotics for 30 days improved psychological distress in healthy subjects. Many more studies have been conducted over the past 10 years and a recent meta-analysis of probiotic intervention studies showed high variability in results with only some minor detectable improvements for psychiatric distress and depression with probiotic interventions (Le Morvan de Sequeira et al., 2022).

Autistic Spectrum Disorder

Children with autistic spectrum disorder (ASD) are more likely to suffer from intestinal problems than children in the general population (Horvath et al., 1999). Several studies reported an altered microbiota composition in children with autism, indicating that microbiota possibly plays a role in this disorder. For instance, Wang et al. (2011) showed that children with autism have lower relative abundance of *Bifidobacterium* species and mucolytic bacterium *A. muciniphila* in their feces compared with children without autism. It should be mentioned that the altered bowel habits per se could be the reason for altered microbiota composition. In addition, altered microbiota composition in ileal and cecal mucosa has been reported (Williams et al., 2011, 2012). However, results are equivocal, probably because of different sampling and analysis methods as well as small patient numbers (König et al., 2015). A comprehensive study that investigated the causality between altered gut microbiota composition and ASD progression in children found that ASD behavior led to less diverse dietary patterns that were reflected in decreased microbiota diversity (Yap CX et al., 2021). This study places previous findings on the role of gut microbiota in ASD pathophysiology under a new light, though replication studies are needed to verify the results. However, even though altering microbial composition could potentially reduce bowel symptoms and improve ASD behavior, the findings so far are inconclusive. One small pilot study investigated the effect of vancomycin, an antibiotic that is poorly absorbed in the intestine, in children with autism and reported that autistic behavior was improved during the 8 weeks of intervention (Sandler et al., 2000). Although this result did not persist after treatment, it showed that the intestinal microbiota-brain connection might be of importance in ASD. In addition, the metabolites that are produced by gut microbiota, such as propionate, acetate, and valerate, were found in lower levels in patients with autism than in children from the general population, suggesting that in addition to the microbiota, metabolites could also play an important role in ASD (Adams et al., 2011). Meta-analysis of intervention studies with prebiotics, probiotics, and synbiotics do not, however, clearly support the early findings of beneficial effects (Tan et al., 2021). The effects of FMT are not well characterized but one trial found significant improvements to both ASD—and bowel symptom outcomes after FMT treatment (Kang et al., 2017, 2019).

Alzheimer's Disease

There is increasing evidence of impaired gastrointestinal function in Alzheimer's disease (AD). Using an AD male transgenic mouse model, Karri et al. (2010) showed that alterations in gastrointestinal tract morphology, a shift in microbiota composition, and an increase of amyloid protein expression in the gut could play a key role in the pathophysiology of this disease. The amyloid precursor protein (APP) is found in many tissues in the body. Proteolysis of this protein results in the generation of misfolded β-amyloid, which forms the amyloid plaques in the brain of AD patients. Fecal transplantation from AD patients into mice was shown to increase markers of stress for the endoplasmic reticulum in the brain (Wang et al., 2022), a process that can lead to protein misfolding. In mice, APP expression increased after repeated injection of lipopolysaccharide (LPS; Lee et al., 2008), and systemic administration of LPS in mice leads to acute neurodegeneration (Qin et al., 2007). In addition, increased plasma levels of LPS were found in AD patients (Zhang et al., 2009). The authors suggested that plasma LPS originates from the translocation of commensal and pathogenic bacteria and may play an important role in the pathology of AD, possibly through neuroinflammation. However, these findings need to be carefully interpreted as microbial contamination from the gut during autopsy handling could interfere with the results. In a study it was reported that in the microbiota of a mouse model for AD, certain microbes were depleted, including *A. muciniphila* (Harach et al., 2017). Interestingly, mice models of AD treated with *A. muciniphila* showed improved intestinal barrier function and reduced β-amyloid formation in the brain (Ou et al., 2020). Mounting evidence further supports a potentially important role for the gut microbiota in AD pathophysiology, where GF mice versus specific-pathogen-free AD mice models show a reduction of AD pathology in the former compared to the latter (Chen et al., 2021). FMT from AD patients into animal models of AD further exacerbates AD hallmark pathologies (Chen et al., 2021). Human studies are very limited but do show that the gut microbiota is different at different stages of AD (mild, moderate) (Chen et al., 2022a).

Parkinson's Disease

In addition to a dysfunctional motor system, most Parkinson's disease (PD) patients suffer from constipation. It was long thought that gastrointestinal problems in PD patients were a consequence of the disease (Abbott et al., 2001). However, a study found almost half of all PD patients in a cohort of 200 patients to suffer from constipation before the onset of the actual disease (Savica et al., 2009), suggesting a relation between early gastrointestinal problems and later development of PD (König et al., 2015). It has been shown that PD patients have significantly increased gut permeability and an increased amount of *Escherichia coli* in sigmoid colon biopsies (Forsyth et al., 2011). Hypothetically, the *E. coli* could translocate to the epithelium and lamina propria because of this increased epithelial permeability. A study investigating the microbiota in PD patients showed that the abundance of Prevotellaceae is reduced compared with healthy controls (Scheperjans et al., 2015). Recent studies have found certain

butyrate-producing bacteria reduced in patients with PD (Romano et al., 2021), this could render the intestinal barrier weakened and at higher risk for microbial translocation. The level of fecal SCFA, including butyrate, has been shown to negatively correlate with PD (motor) severity (Chen et al., 2022b). Another study found that the abundance of *Enterobacteriacea* correlated with the severity of gait difficulty and postural instability, suggesting that the microbiota could be associated with motor symptoms in PD (Scheperjans et al., 2015). The most recent metagenomic study (Wallen et al., 2022) showed PD patients to harbor a gut microbiota that is significantly increased in the amount of pathogens and microbial components that can trigger inflammation, toxicity, and dysregulation of neurotransmitters. Interestingly, a bacterial component called curli, produced by *Escherichia coli*, could induce α-synuclein (hallmark protein of PD) pathology and lead to neurodegeneration. This study significantly highlights the important role of gut microbiota in PD pathophysiology.

Gut Microbiota and Metabolic Diseases

Obesity

Obesity is a worldwide public health concern with multifactorial origins involving genetic, metabolic, and environmental factors. It is interesting to note that some individuals seem to be more susceptible to "obesogenic" environmental factors, such as sedentary lifestyles and high-calorie intake, than others (Tims et al., 2013). Although genome-wide association studies have identified several loci associated with obesity susceptibility, human genome variation itself cannot explain the observed variance in energy homeostasis and the apparent heritability of body mass index (BMI; Xia and Grant, 2013).

Numerous studies have revealed that the gut microbiota is strongly associated with host energy regulation and homeostasis and may play a critical role in the development of obesity. Bäckhed et al. (2004) were one of the first groups to suggest that the microbiota may be an environmental factor affecting the host predisposition toward adiposity. They showed that the gut microbiota regulates the host capacity for harvesting energy from the diet as well as energy storage in mice. In 2006, Turnbaugh et al. (2006) demonstrated that germ-free (GF) C57BL/6J mice colonized with a microbiota obtained from obese (ob/ob) donors exhibited a greater increase in body fat than mice colonized with microbiota from lean donors. In addition, numerous animal studies have shown that microbiota-related metabolites, in particular, SCFA may play an important role in obesity. Results from these studies have indicated that SCFAs can regulate host energy metabolism in the development of diet-induced obesity, e.g., by increasing de novo lipogenesis, inhibiting lipolysis, and increasing circulating levels of gut hormones involved in appetite and food intake regulation (Ge et al., 2008; Hong et al., 2005; Karaki et al., 2008; Samuel et al., 2008). However, in clinical studies there are mixed results regarding the relationship between SCFAs and obesity with some studies reporting a positive correlation between fecal SCFA concentrations and obesity (Rahat-Rozenbloom et al.,

2014; Riva et al., 2017) and others reporting a negative correlation (Barczynska et al., 2018). It should be noted, however, that the higher fecal butyrate levels observed in individuals with obesity may reflect a difference in absorption or microbial utilization and not necessarily a higher production.

Although there are some conflicting results, an obesity-associated gut microbiota has been characterized by a decline in Bacteroidetes and a compensatory increase of the Firmicutes phylum (Armougom et al., 2009; Kasai et al., 2015; Ley et al., 2005; Turnbaugh et al., 2009) and by a reduction in microbial diversity and richness (Cotillard et al., 2013). Ley et al. demonstrated a lower abundance of Bacteroidetes and a proportional increase in Firmicutes in genetically obese ob/ob mice (Ley et al., 2005) and in a small cohort of obese people (Ley et al., 2006) when compared with lean controls. Moreover, in the clinical study by Ley et al. (2006), the proportion of Bacteroidetes was shown to increase with weight loss when people followed low-calorie diets. These results led the group to hypothesize that the increased ratio of Firmicutes to Bacteroidetes could promote the accumulation of adipose tissue and that manipulation of gut microbial communities could be an alternative approach in the treatment of obesity. Another study found that the Firmicutes/Bacteroidetes ratio increased with increasing BMI (Koliada et al., 2017). In addition, several other clinical studies have reported a significant reduction in the proportion of Bacteroidetes in obese patients compared with lean individuals (Armougom et al., 2009; Kasai et al., 2015; Turnbaugh et al., 2009). However, other studies have contradicted these findings. Schwiertz et al. (2010) reported a lower ratio of Firmicutes to Bacteroidetes in obese adults compared with lean controls and several other studies have found no correlation between human obesity and the proportions of Bacteroidetes and Firmicutes (Duncan et al., 2008; Galley et al., 2014; Hu et al., 2015; Tims et al., 2013). One study showed that Bacteroidetes were depleted in the intestinal samples of morbidly obese patients as compared with lean subjects (Verdam et al., 2013). Further analysis of this cohort using a metaproteomics approach showed that although their numbers were decreased, the activity of the Bacteroidetes was highly increased in morbidly obese patients, most likely as a consequence of their pH sensitivity (Kolmeder et al., 2015). This finding highlights the fact that it is the activity rather than the mere presence of intestinal microbes that determines their functionality.

Other studies have associated obesity with specific bacterial groups. It has been shown that the abundance of SCFA producers including *Eubacterium ventriosum* is associated with obesity (Tims et al., 2013), while other studies have shown that butyrate producers may be associated with leanness (Gophna et al., 2017; Remely et al., 2014). Another study demonstrated that the abundance of *Bacteroides thetaiotaomicron*, a glutamate-fermenting commensal, was markedly decreased in individuals with obesity and that this was inversely correlated with glutamate concentrations in serum (Liu et al., 2017). Recently, the family Christensenellaceae was found to be associated with weight loss and its relative abundance was inversely related to host BMI (Waters and Ley, 2019). Another recent study showed an inverse association between the presence of the genus *Blautia* and visceral fat accumulation in Japanese adults (Ozato et al., 2019).

Type II Diabetes

Type II diabetes (T2D) is a complex metabolic disorder influenced by genetic and environmental components and aggravated by several risk factors, including age, family history, diet, sedentary lifestyle, and obesity (Karlsson et al., 2013; Qin et al., 2012). Similar to obesity, T2D has become a major public health issue throughout the world. Both diseases are characterized by a state of chronic low-grade inflammation with abnormal expression and production of multiple inflammatory mediators accompanied by gut microbiota changes (Larsen et al., 2010).

In a large metagenomics study by Qin et al. (2012), Chinese patients with T2D were shown to have a moderate degree of gut microbial aberrations, with a decrease in the abundance of some universal butyrate-producing bacteria and an increase in various opportunistic pathogens, such as *Bacteroides caccae*, *Clostridium hathewayi*, *Clostridium ramosum*, *Clostridium symbiosum*, *Eggerthella lenta*, and *E. coli*. In addition, mucin-degrading species *A. muciniphila* and sulfate-reducing species *Desulfovibrio* sp. were also enriched in the samples of the T2D patients. In retrospect, the abundance of *A. muciniphila* could be attributed to the use of metformin in T2D patients and the fact that metformin is stimulating the growth of this mucolytic bacterium (Lee and Ko, 2014). The functional changes in the T2D patients were characterized by an enrichment of markers of membrane transport of sugars, branched-chain amino acid, methane, and xenobiotic metabolism, and sulfate reduction. By contrast, a decreased level of bacterial chemotaxis, flagellar assembly, butyrate biosynthesis, and metabolism of cofactors and vitamins was observed in T2D patients. Markers related to oxidative stress resistance and drug resistance were greatly enriched, suggesting that T2D patients may have a more hostile gut environment. Another large metagenomics study, conducted by Karlsson et al. (2013), also demonstrated compositional and functional alterations in the gut microbiome of European women with T2D. Increased numbers of *Lactobacillus* species and decreased numbers of *Clostridium* species were observed in the T2D group, and these changes were not correlated with BMI. The pathways that showed the highest scores for enrichment in T2D metagenomes were related to glycerol−lipid metabolism, fatty acid biosynthesis, and, as also observed by Qin et al., membrane transport and oxidative stress resistance. Both studies developed mathematical models based on the metagenomic profiles gathered and used that to identify individuals with T2D. However, when Karlsson et al. applied their European-cohort model to the Chinese cohort described by Qin et al., they discovered that the discriminant metagenomic markers for T2D found by them differed from the ones found by the Chinese group. This led the authors to suggest that, although both studies have found functional alterations of the gut microbiome directly linked to T2D development, metagenomic predictive tools for T2D should be specific for the age and geographical location of the populations studied. However, after correcting for the confounding use of metformin and other drugs, a series of robust signatures associated with T2D were found (Lee and Ko, 2014).

An altered microbiota in T2D may induce inflammatory processes and, in support of such a concept, several studies have demonstrated that patients with T2D

exhibit remarkable endotoxemia. In a study by Larsen et al. (2010), T2D was associated with a higher abundance of Gram-negative bacteria, belonging to the phyla Bacteroidetes and Proteobacteria, and a lower abundance of Firmicutes. Higher levels of *Bacilli* and the *Lactobacillus* group were also observed in the diabetic subjects compared with controls. Of note, these compositional changes in the intestinal microbiota were not related to the individual's body mass. Although T2D is considered an attribute of obesity, in this study a higher *Bacteroidetes* to *Firmicutes* ratio correlated positively with higher blood glucose levels but negatively with higher body mass. These findings led the authors to suggest that overweight and diabetes are associated with different groups of intestinal microbiota and that levels of glucose tolerance should be considered when linking microbiota with obesity and other metabolic diseases. Correspondingly, Membrez et al. (2008) demonstrated that modulation of gut microbiota with antibiotics influences whole-body glucose homeostasis, independent of body weight/body fat mass. In antibiotic-treated mice, reduced liver TGs correlated with improved insulin resistance, suggesting that the influence of gut microbiota on glucose and liver metabolism may have similar mechanisms. Both groups hypothesized that higher amounts of Gram-negative bacteria, as seen in cases of reduced glucose tolerance, increase the load of circulating LPS, which is known to cause acute whole-body insulin resistance and is a potent stimulator of inflammation (Cani et al., 2007). To further confirm this hypothesis, a clinical study by Jayashree et al. (2014) revealed increased levels of circulating LPS and LPS activity, associated with poor glycemic/lipid control and subclinical inflammation, in patients with T2D compared with control subjects. Moreover, Sato et al. (2014) also observed higher levels of LPS binding protein in plasma samples of Japanese T2D patients compared with control subjects. However, most of the gut bacteria detected at a higher rate in the blood of diabetic patients were Gram-positive, not Gram-negative. Similar to the data presented by others, counts of total *Lactobacillus* were significantly higher, whereas fecal counts of the *Clostridium coccoides* group were significantly lower in T2D patients.

Specific bacterial groups with relatively high abundances in T2D subjects have also been identified. These bacterial groups include, e.g., *Blautia*, *Sporobacter*, *Parasutterella*, *Collinsella*, *Abiotrophia*, *Coprococcus*, and *Peptostreptococcus* (Lambeth et al., 2015; Zhang et al., 2013; Zhao et al., 2019). Of note, and mentioned earlier, opportunistic pathogenic bacterial species with a proinflammatory functional potential are frequently described in T2D, including *Escherichia coli* and *Bacteroides caccae* (Furet et al., 2010; Lambeth et al., 2015; Qin et al., 2012).

Butyrate-producing bacteria have particularly been shown to be depleted in subjects with T2D, specifically the species *Faecalibacterium prausnitzii*, *Eubacterium rectale,* and *Roseburia intestinalis* (Forslund et al., 2015; Furet et al., 2010; Qin et al., 2012; Sedighi et al., 2017; Zhang et al., 2019). In a recently published systematic review, the potential role of different bacterial taxa in T2D was investigated. Among the commonly reported findings, the genera of *Bifidobacterium*, *Bacteroides*, *Faecalibacterium*, *Akkermanisa,* and *Roseburia* were negatively associated with T2D, while the genera *Ruminococcus*, *Fusobacterium,* and *Blautia* were

positively associated with T2D (Gurung et al., 2019). In a recent study, several novel microbial metabolites related to the gut microbiota, including, e.g., creatine, urate, and kynureate were associated with decreased insulin secretion and insulin sensitivity and thus, an increased risk of T2D (Vangipurapu et al., 2020).

Overall, the microbiome in subjects with prediabetes and T2D appears to be relatively depleted in bacterial butyrate producers and to exhibit an increase in species with a pro-inflammatory functional potential.

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome and the leading cause of chronic liver disease in the Western world. It is defined as the presence of fat accumulation in the hepatic cells in the absence of any secondary causes of liver injury, such as significant alcohol consumption, the use of steatogenic medications, or hereditary disorders (Aqel and DiBaise, 2015). NAFLD is characterized by a broad spectrum of hepatic pathology that ranges from simple steatosis to nonalcoholic steatohepatitis (NASH) and even cirrhosis, fibrosis, and hepatocellular carcinoma. Most individuals with NAFLD remain asymptomatic without any histological or biochemical injury, but 20% progress to develop NASH, a chronic hepatic inflammation, characterized by steatosis, inflammation, and hepatocyte injury with or without cirrhosis (Henao-Mejia et al., 2012; Jiang et al., 2015).

There is growing recognition that a disturbed gut microbiota may be one of several crucial factors in the pathophysiology of NAFLD and NASH (Festi et al., 2014; Gupta et al., 2022). Henao-Mejia et al. (2012) observed that inflammasome-deficient mice develop massive hepatic steatosis and liver inflammation accompanied by changes in the configuration of the gut microbiota. They found that *Porphyromonas*, a type of bacteria that has been associated with complications of chronic liver disease and with several components of the metabolic syndrome in mice and humans, was increased in the inflammasome-deficient mouse model. Inflammasome depletion was associated with a potentially pathogenic microbiota resulting in increased influx and accumulation of bacterial products, such as LPS in the liver. This led to the stimulation of TLR4 and TLR9 and increased the expression of hepatic TNF-α expression, which drives NASH progression. Miele et al. (2009) also investigated the mechanisms underlying the transition from steatosis to NASH. They provided the first evidence that NAFLD in humans is associated with increased gut permeability and that this abnormality is related to the increased prevalence of small intestinal bacterial overgrowth (SIBO). In this study, tight junction integrity disruption was shown, as evidenced by a lower expression of zona occludens-1 in the duodenal mucosa of patients with NAFLD compared with healthy subjects. The prevalence of SIBO in patients with NAFLD was more than twice as high compared with healthy subjects; however, the characteristics of the microbiota were not assessed in this study. The composition of gut microbiota in patients with NAFLD was investigated in a comprehensive clinical study by Jiang et al. (2015). In this study, subjects with NAFLD had

an increased abundance of species assigned to *Clostridium*, *Streptococcus*, *Escherichia*, *Anaerobacter*, and *Lactobacillus*, whereas *Oscillobacter*, *Odoribacter*, and *Allistipes* spp. were less abundant. Gut microbiota changes were also accompanied by increased intestinal permeability and inflammation in subjects with NAFLD (Jiang et al., 2015). In alignment with the results by Jiang et al. (2015), Zhu et al. (2013) also reported increased levels of *Escherichia* spp. in NASH patients when compared with controls. Moreover, NASH patients exhibited significantly elevated blood ethanol levels. Ethanol activates nuclear factor-κβ (NF-κβ) signaling pathways and causes tissue damage by impairing gut barrier function and contributing to portal endotoxemia (Rao et al., 2004; Xu et al., 2011). Children with steatosis or NASH have also been reported to be depleted in *Oscillospira* spp. and to have higher abundance of *Dorea* and *Ruminococcus* spp. when compared with controls (Chierico et al., 2017). It was recently also demonstrated that a high abundance of the alcohol-producing bacteria *Klebsiella pneumoniae* in the gut accelerates the pathogenesis of NAFLD (Yuan et al., 2019). A recent integrative multi-omics approach also demonstrated that subjects with liver steatosis have low microbial gene richness and increased genetic potential for the processing of dietary lipids and endotoxin biosynthesis (notably from Proteobacteria), hepatic inflammation and dysregulation of aromatic and branched-chain amino acid metabolism (Hoyles et al., 2018).

Overview of Some Potential Therapies That Are Currently Being Used to Re-Establish a Healthy Gut Microbiota

Given that a disturbed gut microbiota has been associated with numerous diseases, several therapeutic options are currently being used with the aim to re-establish a healthy, beneficial ecosystem within the gut. Such potential therapies include the use of probiotics and prebiotics, which act by increasing the numbers and/or activity of beneficial bacteria within the gut, and fecal transplantation, which introduces a healthy, diverse microbiota by replacing the existing microbiota. More than 1000 cultured bacterial isolates have been described in detail (Rajilić-Stojanović et al., 2012), a number that is ever increasing (Bilen et al., 2018). This is of significant interest because culturing the intestinal microbiota has rather been neglected when the fast DNA-based approaches have been developed. A culturing renaissance is indeed taking place because it turns out that insight into cultures is needed when trying to develop new therapies (Browne et al., 2016; Lagier et al., 2018).

To date, many examples of beneficial effects have been associated with the use of probiotic bacteria in health and various diseases, including *Clostridium difficile*-associated diarrhea, IBD, IBS, obesity, and depression (Goldenberg et al., 2017; Saez-Lara et al., 2015; Sanders et al., 2013). Beneficial effects of probiotics can be due to the direct effect of the bacterium itself, or the products it produces, as well as the effects that the probiotic bacterium has on the composition and/or activity of the resident microbiota (Plaza-Diaz et al., 2019). Indeed, probiotics can interact with the host's epithelial cells and other cells in the human body through

physicochemical, enteroendocrine, and immune signals in the same way as the commensal gut microbiota, and although the use of a probiotic bacterium does not give rise to detectable changes in the composition of the fecal microbiota, its metabolic activity may be altered (McNulty et al., 2011). However, several studies showing positive effects of different probiotic strains are obtained from animal models, and despite convincing and reproducible results from such studies, data from clinical trials are still uncertain. Reasons for this may partly include poor study design (dosage, time, etc.) and poor choice of strain. In addition, it should be pointed out that humans and mice have different microbiota. This is exemplified in the recent metagenomic comparison that revealed extensive functional similarity between mouse and man microbiota but indicated that only 4% of the mouse microbial genes were found with high identity in the human microbiome (Xiao et al., 2015). Moreover, although numerous probiotic strains have been identified, there is a current need to discover organisms that elicit more robust therapeutic responses, that are compatible with the host, and that can affect the host in a well-controlled, physiological manner. Therefore, potential new microbial therapeutics, so-called "next-generation probiotics" or "live biotherapeutic products," are being investigated using advanced "omics" technologies and more sophisticated culturing methodologies, tools that are massively increasing our knowledge of the composition and function of the human gut microbiome (O'Toole et al., 2017).

Prebiotics are growth substrates (e.g., fructooligosaccharides, galactooligosaccharides, inulin, resistant starch) that act as enhancers for bacteria that are already present in the human colon by stimulating their growth and/or activity (Cunningham et al., 2021; Sanders et al., 2013). The most used prebiotics specifically act as growth enhancers for lactobacilli and bifidobacteria; however, this concept of prebiotics has been expanded from solely focusing on the "bifidogenic effect" and nowadays it also includes other beneficial members of the gut microbiota. One example of this is the butyrate-producing bacterium *F. prausnitzii*, which currently is regarded as an important, functionally active bacterium within the human gut. For example, reduced numbers of *F. prausnitzii* have been detected in patients with Crohn's disease (Sokol et al., 2009), and given that this bacterium is also associated with antiinflammatory effects (Sokol et al., 2008), it makes it a strong target for disease therapy. *F. prausnitzii* has been shown to respond to inulin supplements and to pectins as growth substrates (Ramirez-Farias et al., 2009; Lopez-Silas et al., 2012). Thus, increasing our knowledge about which bacterial species are present at lower abundance in a diseased state compared with a healthy state, will enable us to selectively target these repressed bacteria by using a prebiotic substrate that we know can boost the growth and the activity of these bacteria. Prebiotic fibers, in addition to other nondigestible carbohydrates that we cannot break down with our own enzymes, can also give rise to SCFAs. SCFAs (acetate, propionate, and butyrate) are not only important for gut health, but they also act as signaling molecules, for example by stimulating the production of gut and neuroactive peptides (Parnell and Relmer, 2009; Psichias et al., 2015). In addition, they can enter our circulatory system and thereby they may directly affect metabolism and the

function of peripheral tissues (Smith et al., 2013; Gao et al., 2009). It has been shown that SCFA released in the distal and not the proximal colon reach circulation and reduce insulin resistance in prediabetic subjects (Canfora et al., 2019). Most prebiotic supplements consist of highly purified fibers that are fermented in the proximal colon while fibers included in plant cells may reach the distal colon (Puhlmann and de Vos, 2022). Hence these latter, so called intrinsic fibers, may have beneficial effects beyond purified fibers. Indeed, a recent intervention in subjects at risk for T2D consuming intact plant cells delivering a complex fiber showed high levels of fecal SCFA, increased bowel function and improvement of glycemic control (Puhlmann et al., 2022).

An increasing number of diseases have been reported to be cured by using FMT (Biazzo and Deidda, 2022; Smits et al., 2013). As previously described, in this treatment the intestinal microbiota of a patient is removed via lavage and largely replaced by the fecal microbiota of a healthy donor. The success of FMT in recurrent CDI enormously stimulated the field, notably because it showed the power of microbes (van Nood et al., 2013). In a more sophisticated comparative study aimed to address the role of the intestinal microbiota in metabolic disease, not only transplantation with a lean donor fecal microbiota was performed but also autologous transplantation with the patient's own microbiota was performed in a blinded way. In this way, it was shown that intestinal microbiota can affect host energy metabolism and insulin sensitivity (Vrieze et al., 2012). By using a similar approach, patients suffering from UC could be maintained in remission after transplantation with a healthy donor sample (Rossen et al., 2015). All of these FMT studies are highly relevant and demonstrate the impact of the intestinal microbiota. In some cases, such as in recurrent CDI, transplantations are becoming mainstream. However, several issues associated with safety, delivery mode, and storage are limiting factors for large-scale treatments (Cammarota et al., 2017; DeFilipp et al., 2019; Wang et al., 2016). Hence, considerable efforts are dedicated to designing so-called synthetic microbiomes (Clark et al., 2021; Petrof et al., 2013; Shetty et al., 2019). Other diseases are more complex and other avenues are taken, including reverse engineering, in which microbial taxa are identified based on careful analysis of the microbial changes in successful fecal transplantations (de Vos, 2013). These and other approaches of single intestinal strains that may improve health are currently under development. One is the intestinal mucosal inhabitant *A. muciniphila* (Belzer and de Vos, 2012). Mouse experiments have shown this unusual representative of the Verrucomicrobia to be capable of preventing diet-induced obesity and inflammation as well as regulatory T cell stimulation (Everard et al., 2013; Shin et al., 2014). The basis for this effect is an increased barrier function that was determined in human cell lines (Reunanen et al., 2015). Of note this barrier improving effect of *A. muciniphila* was also demonstrated in a proof-of-concept trial in obese humans (Depommier et al., 2019). These and other intestinal strains hold great promise to be developed into new therapeutic strains that can be used to improve human health and treat patients with deviations in the intestinal microbiota (Cani et al., 2022).

Conclusion

There is increasing evidence that changes in the gut microbiota are involved in common gut diseases such as IBS and IBD, that it is a partaker in systemic diseases such as allergies and metabolic diseases, and that it also may play a critical role in the development of stress-related disorders, such as anxiety and depression. However, understanding these microbiota changes and defining a healthy microbiome is challenging because of the tremendous complexity of the gut ecosystem and the huge variability between healthy individuals. Rapid advances in sequencing technology, made predominantly during the past decade, have expanded our knowledge about this second genome; nonetheless, further research is required to get new and deeper insights into what actual role the human gut microbiome plays in health and disease. A combination of classical microbiology (i.e., culturing bacterial isolates of the gut microbiota), high-throughput sequencing techniques (including metatranscriptomics and metaproteomics), carefully designed animal experiments, and notably clinical trials are needed to establish cause-and-effect relationships and to establish interactions with key human cellular functions (i.e., to understand microbiota-host relationships). On the basis of this, tailor-made treatment strategies, designed to target specific deviations in microbiome structure and functioning, may be developed.

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References

Abbott, R.D., Petrovitch, H., White, L.R., Masaki, K.H., Tanner, C.M., Curb, J.D., et al., 2001. Frequency of bowel movements and the future risk of Parkinson's disease. Neurology 57 (3), 456–462.

Abdollahi-Roodsaz, S., Joosten, L.A., Koenders, M.I., Devesa, I., Roelofs, M.F., Radstake, T.R., et al., 2008. Stimulation of TLR2 and TLR4 differentially skews the balance of T cells in a mouse model of arthritis. J. Clin. Investig. 118 (1), 205.

Abrahamsson, T.R., Jakobsson, H.E., Andersson, A.F., Björkstén, B., Engstrand, L., Jenmalm, M.C., 2012. Low diversity of the gut microbiota in infants with atopic eczema. J. Allergy Clin. Immunol. 129 (2), 434–440.

Abrahamsson, T.R., Jakobsson, H.E., Andersson, A.F., Björkstén, B., Engstrand, L., Jenmalm, M.C., 2014. Low gut microbiota diversity in early infancy precedes asthma at school age. Clin. Exp. Allergy 44 (6), 842–850.

Adams, J.B., Johansen, L.J., Powell, L.D., Quig, D., Rubin, R.A., 2011. Gastrointestinal flora and gastrointestinal status in children with autism—comparisons to typical children and correlation with autism severity. BMC Gastroenterol. 11 (1), 22.

Al Nabhani, Z., Dulauroy, S., Marques, R., Cousu, C., Al Bounny, S., Déjardin, F., et al., 2019. A weaning reaction to microbiota is required for resistance to immunopathologies in the adult. Immunity 50 (5), 1276—1288.e5.

Aqel, B., DiBaise, J.K., 2015. Role of the gut microbiome in nonalcoholic fatty liver disease. Nutr. Clin. Pract. 30 (6), 780—786.

Armougom, F., Henry, M., Vialettes, B., Raccah, D., Raoult, D., 2009. Monitoring bacterial community of human gut microbiota reveals an increase in *Lactobacillus* in obese patients and Methanogens in anorexic patients. PLoS One 4 (9), e7125.

Arrieta, M.C., Stiemsma, L.T., Dimitriu, P.A., Thorson, L., Russell, S., Yurist-Doutsch, S., et al., 2015. Early infancy microbial and metabolic alterations affect risk of childhood asthma. Sci. Transl. Med. 7 (307), 307ra152.

Atarashi, K., Tanoue, T., Ando, M., Kamada, N., Nagano, Y., Narushima, S., et al., 2015. Th17 cell induction by adhesion of microbes to intestinal epithelial cells. Cell 163 (2), 367—380.

Bachem, A., Makhlouf, C., Binger, K.J., de Souza, D.P., Tull, D., Hochheiser, K., et al., 2019. Microbiota-Derived short-chain fatty acids promote the memory potential of antigen-activated $CD8^+$ T cells. Immunity 51 (2), 285—297.e5.

Bäckhed, F., Ding, H., Wang, T., Hooper, L.V., Koh, G.Y., Nagy, A., et al., 2004. The gut microbiota as an environmental factor that regulates fat storage. Proc. Natl. Acad. Sci. U.S.A. 101 (44), 15718—15723.

Bäckhed, F., Ley, R.E., Sonnenburg, J.L., Peterson, D.A., Gordon, J.I., 2005. Host-bacterial mutualism in the human intestine. Science 307 (5717), 1915—1920.

Barczynska, R., Litwin, M., Slizemska, K., Szalecki, M., Berdowska, A., Bandurska, K., et al., 2018. Bacterial microbiota and fatty acids in faeces of overweight and obese children. Pol. J. Microbiol. 67, 339—345.

Belkaid, Y., Harrison, O.J., 2017. Homeostatic immunity and the microbiota. Immunity 46 (4), 562—576.

Belzer, C., de Vos, W.M., 2012. Microbes inside—from diversity to function: the case of Akkermansia. ISME J. 6 (8), 1449—1458.

Benton, D., Williams, C., Brown, A., 2007. Impact of consuming a milk drink containing a probiotic on mood and cognition. Eur. J. Clin. Nutr. 61 (3), 355—361.

Bercik, P., Denou, E., Collins, J., Jackson, W., Lu, J., Jury, J., et al., 2011. The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. Gastroenterology 141 (2), 599—609.

Bergot, A.S., Giri, R., 2019. Thomas, R. The microbiome and rheumatoid arthritis. Best Pract. Res. Clin. Rheumatol. 33 (6), 101497.

Berkell, M., Mysara, M., Xavier, B.B., van Werkhoven, C.H., Monsieurs, P., Lammens, C., , et al.ANTICIPATE study group, 2021. Microbiota-based markers predictive of development of *Clostridioides difficile* infection. Nat. Commun. 12, 2241.

Biazzo, M., Deidda, G., 2022. Fecal microbiota transplantation as new therapeutic avenue for human diseases. J. Clin. Med. 11 (14), 4119.

Bilen, M., Dufour, J.C., Lagier, J.C., Cadoret, F., Daoud, Z., Dubourg, G., Raoult, D., 2018. The contribution of culturomics to the repertoire of isolated human bacterial and archaeal species. Microbiome 6 (1), 1—11.

Bisgaard, H., Li, N., Bonnelykke, K., Chawes, B.L.K., Skov, T., Paludan-Müller, G., et al., 2011. Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. J. Allergy Clin. Immunol. 128 (3), 646−652.

Brandl, C., Bucci, L., Schett, G., Zaiss, M.M., 2021. Crossing the barriers: revisiting the gut feeling in rheumatoid arthritis. Eur. J. Immunol. 51 (4), 798−810.

Browne, H.P., Forster, S.C., Anonye, B.O., Kumar, N., Neville, B.A., Stares, M.D., et al., 2016. Culturing of 'unculturable'human microbiota reveals novel taxa and extensive sporulation. Nature 533 (7604), 543−546.

Cammarota, G., Ianiro, G., Tilg, H., Rajilić-Stojanović, M., Kump, P., Satokari, R., et al., 2017. European consensus conference on faecal microbiota transplantation in clinical practice. Gut 66 (4), 569−580.

Canfora, E.E., Meex, R.C., Venema, K., Blaak, E.E., 2019. Gut microbial metabolites in obesity, NAFLD and T2DM. Nat. Rev. Endocrinol. 15 (5), 261−273.

Cani, P.D., Amar, J., Iglesias, M.A., Poggi, M., Knauf, C., Bastelica, D., et al., 2007. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 56 (7), 1761−1772.

Cani, P.D., Depommier, C., Derrien, M., Everard, A., de Vos, W.M., 2022. *Akkermansia muciniphila*: paradigm for next-generation beneficial microorganisms. Nat. Rev. Gastroenterol. Hepatol. 19 (10), 625−637.

Carstens, A., Dicksved, J., Nelson, R., Lindqvist, M., Andreasson, A., Bohr, J., et al., 2019. The gut microbiota in collagenous colitis shares characteristics with inflammatory bowel disease-associated dysbiosis. Clin. Transl. Gastroenterol. 10, e00065.

Cebra, J.J., Periwal, S.B., Lee, G., Lee, F., Shroff, K.E., 1998. Development and maintenance of the gut-associated lymphoid tissue (GALT): the roles of enteric bacteria and viruses. J. Immunol. Res. 6 (1−2), 13−18.

Chen, Y., Ma, C., Liu, L., He, J., Zhu, C., Zheng, F., et al., 2021. Analysis of gut microbiota and metabolites in patients with rheumatoid arthritis and identification of potential biomarkers. Aging (Albany NY) 13 (20), 23689−23701.

Chen, L., Xu, X., Wu, X., Cao, H., Li, X., Hou, Z., et al., 2022a. A comparison of the composition and functions of the oral and gut microbiotas in Alzheimer's patients. Front. Cell. Infect. Microbiol. 12, 942460.

Chen, S.J., Chen, C.C., Liao, H.Y., Lin, Y.T., Wu, Y.W., Liou, J.M., et al., 2022b. Association of fecal and plasma levels of short-chain fatty acids with gut microbiota and clinical severity in patients with Parkinson disease. Neurology 98 (8), e848−e858.

Cheng, Y., Ling, Z., Li, L., 2020. The intestinal microbiota and colorectal cancer. Front. Immunol. 11, 615056.

Chevalier, G., Siopi, E., Guenin-Macé, L., Pascal, M., Laval, T., Rifflet, A., et al., 2020. Effect of gut microbiota on depressive-like behaviors in mice is mediated by the endocannabinoid system. Nat. Com. 11 (1), 6363.

Chierico, F.D., Nobili, V., Vernocchi, P., Russo, A., De Stefanis, C., Gnani, D., 2017. Gut microbiota profiling of pediatric nonalcoholic fatty liver disease and obese patients unveiled by an integrated meta-omics-based approach. Hepatology 65 (2), 451−464.

Clark, R.L., Connors, B.M., Stevenson, D.M., Hromada, S.E., Hamilton, J.J., Amador-Noguez, D., Venturelli, O.S., 2021. Design of synthetic human gut microbiome assembly and butyrate production. Nat. Com. 12 (1), 1−16.

Cotillard, A., Kennedy, S.P., Kong, L.C., Prifti, P., Pons, F., et al., 2013. Dietary intervention impact on gut microbial gene richness. Nature 500, 585−588.

Cunningham, M., Azcarate-Peril, M.A., Barnard, A., Benoit, V., Grimaldi, R., Guyonnet, D., et al., 2021. Shaping the Future of Probiotics and Prebiotics. Trends Microbiol 29 (8), 667−685. https://doi.org/10.1016/j.tim.2021.01.003. Epub 2021 Feb 4.

DeFilipp, Z., Bloom, P.P., Torres Soto, M., Mansour, M.K., Sater, M.R., Huntley, M.H., et al., 2019. Drug-resistant *E. coli* bacteremia transmitted by fecal microbiota transplant. N. Engl. J. Med. 381 (21), 2043−2050.

Depommier, C., Everard, A., Druart, C., Plovier, H., Van Hul, M., Vieira-Silva, S., et al., 2019. With *Akkermansia muciniphila* in overweight and obese human volunteers: a proof-of-concept exploratory study. Nat. Med. 25, 1096−1103.

Deschasaux, M., Bouter, K.E., Prodan, A., Levin, E., Groen, A.K., Herrema, H., et al., 2018. Depicting the composition of gut microbiota in a population with varied ethnic origins but shared geography. Nat. Med. 24 (10), 1526−1531.

Dobell, C., 1932. Anthony Van Leeuwenhoek and His Little Animals. Harcourt Brace & Company, New York.

Duncan, S.H., Lobley, G.E., Holtrop, G., Ince, J., Johnstone, A.M., Louis, P., Flint, H.J., 2008. Human colonic microbiota associated with diet, obesity and weight loss. Int. J. Obes. 32 (11), 1720−1724.

Eckburg, P.B., Bik, E.M., Bernstein, C.N., Purdom, E., Dethlefsen, L., Sargent, M., et al., 2005. Diversity of the human intestinal microbial flora. Science 308 (5728), 1635−1638.

Ege, M.J., Mayer, M., Normand, A.C., Genuneit, J., Cookson, W.O., Braun-Fahrländer, C., et al., 2011. Exposure to environmental microorganisms and childhood asthma. N. Engl. J. Med. 364 (8), 701−709.

Everard, A., Belzer, C., Geurts, L., Ouwerkerk, J.P., Druart, C., Bindels, L.B., et al., 2013. Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. Proc. Natl. Acad. Sci. U.S.A. 110 (22), 9066−9071.

Festi, D., Schiumerini, R., Eusebi, L.H., Marasco, G., Taddia, M., Colecchia, A., 2014. Gut microbiota and metabolic syndrome. World J. Gastroenterol. 20 (43), 16079.

Fischer, H., Holst, E., Karlsson, F., Benoni, C., Toth, E., Olesen, M., Let, al., 2015. Altered microbiota in microscopic colitis. Gut 64, 1185−1186.

Ford, A.C., Harris, L.A., Lacy, B.E., Quigley, E.M.M., Moayyedi, P., 2018. Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. Aliment. Pharmacol. Ther. 48, 1044−1060.

Forno, E., Onderdonk, A.B., McCracken, J., Litonjua, A.A., Laskey, D., Delaney, M.L., et al., 2008. Diversity of the gut microbiota and eczema in early life. Clin. Mol. Allergy 6 (11), 11.

Forslund, K., Hildebrand, F., Nielsen, T., Falony, G., Le Chantelier, E., Sunagawa, S., et al., 2015. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. Nature 528 (7581), 262−266.

Forsyth, C.B., Shannon, K.M., Kordower, J.H., Voigt, R.M., Shaikh, M., Jaglin, J.A., et al., 2011. Increased intestinal permeability correlates with sigmoid mucosa alpha-synuclein staining and endotoxin exposure markers in early Parkinson's disease. PLoS One 6 (12), e28032.

Fromentin, S., Forslund, S.K., Chechi, K., Aron-Wisnewsky, J., Chakaroun, R., Nielsen, T., et al., 2022. Microbiome and metabolome features of the cardiometabolic disease spectrum. Nat Med 28 (2), 303−314.

Fuentes, S., van Nood, E., Tims, S., Heikamp-de Jong, I., ter Braak, C.J., Keller, J.J., et al., 2014. Reset of a critically disturbed microbial ecosystem: faecal transplant in recurrent *Clostridium difficile* infection. ISME J. 8, 1621−1633.

Fujimura, K.E., Lynch, S.V., 2015. Microbiota in allergy and asthma and the emerging relationship with the gut microbiome. Cell Host Microbe 17 (5), 592−602.

Furet, J.P., Kong, L.C., Tap, J., Poitou, C., Basdevant, A., Bouillot, J.L., et al., 2010. Differential adaptation of human gut microbiota to bariatric surgery-induced weight loss: links with metabolic and low-grade inflammation markers. Diabetes 59 (12), 3049−3057.

Gacesa, R., Kurilshikov, A., Vich, V.A., Sinha, T., Klaassen, M.A.Y., Bolte, L.A., et al., 2022. Environmental factors shaping the gut microbiome in a Dutch population. Nature 604 (7907), 732−739.

Galley, J.D., Bailey, M., Dush, C.K., Schoppe-Sullivan, S., Christian, L.M., 2014. Maternal obesity is associated with alterations in the gut microbiome in toddlers. PLoS One 9 (11), e113026.

Gao, Z., Yin, J., Zhang, J., Ward, R.E., Martin, R.J., Lefevre, M., Cefalu, W.T., Ye, J., 2009. Butyrate improves insulin sensitivity and increases energy expenditure in mice. Diabetes 58 (7), 1509−1517.

Ge, H., Li, X., Weiszmann, J., Wang, P., Baribault, H., Chen, J.L., et al., 2008. Activation of G protein-coupled receptor 43 in adipocytes leads to inhibition of lipolysis and suppression of plasma free fatty acids. Endocrinology 149 (9), 4519−4526.

Gibson, M.K., Crofts, T.S., Dantas, G., 2015. Antibiotics and the developing infant gut microbiota and resistome. Curr. Opin. Microbiol. 27, 51−56.

Goldenberg, J.Z., Yap, C., Lytvyn, L., Lo, C.K.F., Beardsley, J., Mertz, D., Johnston, B.C., 2017. Probiotics for the prevention of clostridium difficile-associated diarrhea in adults and children. Cochrane Database Syst. Rev. (12).

Gopna, U., Konikoff, T., Nielsen, H.B., 2017. Oscillospira and related bacteria−from metagenomic species to metabolic features. Environ. Microbiol. 19 (3), 835−841.

Grölund, M.M., Lehtonen, O.P., Eerola, E., Kero, P., 1999. Fecal microflora in healthy infants born by different methods of delivery: permanent changes in intestinal flora after cesarean delivery. J. Pediatr. Gastroenterol. Nutr. 28 (1), 19−25.

Guery, B., Galperine, T., Barbut, F., 2019. *Clostridioides difficile*: diagnosis and treatments. Br. Med. J. 366, l4609.

Günaltay, S., Rademacher, L., Hultgren Hörnquist, E., Bohr, J., 2017. Clinical and immunologic effects of faecal microbiota transplantation in a patient with collagenous colitis. World J. Gastroenterol. 23, 1319−1324.

Gupta, H., Min, B.H., Ganesan, R., Gebru, Y.A., Sharma, S.P., Par, E., et al., 2022. Gut microbiome in non-alcoholic fatty liver disease: from mechanisms to therapeutic role. Bioedicines 10 (3), 550.

Gurung, M., Li, Z., Rodriques, R., Jump, D.B., Morgun, A., et al., 2019. Role of gut microbiota in type 2 diabetes pathophysiology. EBioMedicine 51, 102590.

Haifer, C., Luu, L.D.W., Paramsothy, S., Borody, T.J., Leong, R.W., Kaakoush, N.O., 2022. Microbial determinants of effective donors in faecal microbiota transplantation for UC. Gut gutjnl 2022−327742.

Halfvarson, J., Brislawn, C.J., Lamendella, R., Vázquez-Baeza, Y., Walters, W.A., Bramer, L.M., et al., 2017. Dynamics of the human gut microbiome in inflammatory bowel disease. Nat. Microbiol. 2, 17004.

Hanssen, N.M.J., de Vos, W.M., Nieuwdorp, M., 2021. Fecal microbiota transplantation in human metabolic diseases: from a murky past to a bright future? Cell Metabol. 33, 1098−1110.

Harach, T., Marungruang, N., Dutilleul, N., Cheatham, V., Mc Coy, K.D., Neher, J.J., Jucker, M., Fåk, F., Lasser, T., Bolmont, T., 2017. Reduction of Alzheimer's disease beta-amyloid pathology in the absence of gut microbiota. Sci. Rep. 7, 41802.

Haran, J.P., Ward, D.V., Bhattarai, S.K., Loew, E., Dutta, P., Higgins, A., et al., 2021. The high prevalence of *Clostridioides difficile* among nursing home elders associates with a dysbiotic microbiome. Gut Microb. 13, 1897209.

He, Y., Wu, W., Zheng, H.M., Li, P., McDonald, D., Sheng, H.F., et al., 2018. Regional variation limits applications of healthy gut microbiome reference ranges and disease models. Nat Med 24 (10), 1532−1535.

Henao-Mejia, J., Elinav, E., Jin, C., Hao, L., Mehal, W.Z., Strowig, T., Flavell, R.A., 2012. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. Nature 482 (7384), 179−185.

Hertz, S., Durack, J., Kirk, K.F., Nielsen, H.L., Lin, D.L., Fadrosh, D., et al., 2022. Microscopic colitis patients possess a perturbed and inflammatory gut microbiota. Dig. Dis. Sci. 67, 2433−2443.

Holster, S., Lindqvist, C.M., Repsilber, D., Salonen, A., de Vos, W.M., König, J., Brummer, R.J., 2019. The effect of allogenic versus autologous fecal microbiota transfer on symptoms, visceral perception and fecal and mucosal microbiota in irritable bowel syndrome: a randomized controlled study. Clin. Transl. Gastroenterol. 10, e00034.

Holvoet, T., Joossens, M., Vázquez-Castellanos, J.F., Christiaens, E., Heyerick, L., Boelens, J., et al., 2021. Fecal microbiota transplantation reduces symptoms in some patients with irritable bowel syndrome with predominant abdominal bloating: short- and long-term results from a placebo-controlled randomized trial. Gastroenterology 160, 145−157.e8.

Hong, Y.H., Nishimura, Y., Hishikawa, D., Tsuzuki, H., Miyahara, H., Gotoh, C., et al., 2005. Acetate and propionate short chain fatty acids stimulate adipogenesis via GPCR43. Endocrinology 146 (12), 5092−5099.

Hooper, L.V., Bry, L., Falk, P.G., Gordon, J.I., 1998. Host−microbial symbiosis in the mammalian intestine: exploring an internal ecosystem. Bioessays 20 (4), 336−343.

Hooper, L.V., Littman, D.R., Macpherson, A.J., 2012. Interactions between the microbiota and the immune system. Science 336 (6086), 1268−1273.

Horvath, K., Papadimitriou, J.C., Rabsztyn, A., Drachenberg, C., Tildon, J.T., 1999. Gastrointestinal abnormalities in children with autistic disorder. J. Pediatr. 135 (5), 559−563.

Hou, Y., Dong, L., Lu, X., Shi, H., Xu, B., Zhong, W., et al., 2022. Distinctions between fecal and intestinal mucosal microbiota in subgroups of irritable bowel syndrome. Dig. Dis. Sci. 67 (12), 5580−5592.

Hoyles, L., Fernandez-Real, J.M., Federici, M., Serino, M., Abbott, J., Charpentier, J., 2018. Molecular phenomics and metagenomics of hepatic steatosis in non-diabetic obese women. Nat. Med. 24, 1070−1080.

Hu, H.J., Park, S.G., Jang, H.B., Choi, M.K., Park, K.H., Kang, J.H., et al., 2015. Obesity alters the microbial community profile in Korean adolescents. PLoS One 10 (7), e0134333.

Hugon, P., Dufour, J.C., Colson, P., Fournier, P.E., Sallah, K., Raoult, D., 2015. A comprehensive repertoire of prokaryotic species identified in human beings. Lancet Infect. Dis. 15 (10), 1211−1219.

Ivanov, I.I., de Llanos Frutos, R., Manel, N., Yoshinaga, K., Rifkin, D.B., Sartor, R.B., et al., 2008. Specific microbiota direct the differentiation of IL-17-producing T-helper cells in the mucosa of the small intestine. Cell Host Microbe 4 (4), 337−349.

Jayashree, B., Bibin, Y.S., Prabhu, D., Shanthirani, C.S., Gokulakrishnan, K., Lakshmi, B.S., et al., 2014. Increased circulatory levels of lipopolysaccharide (LPS) and zonulin signify novel biomarkers of proinflammation in patients with type 2 diabetes. Mol. Cell. Biochem. 388 (12), 203−210.

Jiang, W., Wu, N., Wang, X., Chi, Y., Zhang, Y., Qiu, X., et al., 2015. Dysbiosis gut microbiota associated with inflammation and impaired mucosal immune function in intestine of humans with non-alcoholic fatty liver disease. Sci. Rep. 5, 8096.

Jubair, W.K., Hendrickson, J.D., Severs, E.L., Schulz, H.M., Adhikari, S., Ir, D., 2018. Modulation of inflammatory arthritis in mice by gut microbiota through mucosal inflammation and autoantibody generation. Arthritis Rheumatol. 70 (8), 1220−1233.

Kang, D.W., Adams, J.B., Gregory, A.C., Borody, T., Chittick, L., Fasano, A., et al., 2017. Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. Microbiome 5 (1), 10.

Kang, D.W., Adams, J.B., Coleman, D.M., Pollard, E.L., Maldonado, J., McDonough-Means, S., et al., 2019. Long-term benefit of microbiota transfer therapy on autism symptoms and gut microbiota. Sci. Rep. 9 (1), 5821.

Karaki, S.I., Tazoe, H., Hayashi, H., Kashiwabara, H., Tooyama, K., Suzuki, Y., Kuwahara, A., 2008. Expression of the short-chain fatty acid receptor, GPR43, in the human colon. J. Mol. Histol. 39 (2), 135−142.

Karlsson, F.H., Tremaroli, V., Nookaew, I., Bergström, G., Behre, C.J., Fagerberg, B., et al., 2013. Gut metagenome in European women with normal, impaired and diabetic glucose control. Nature 498 (7452), 99−103.

Karri, S., Martinez, V.A., Coimbatore, G., 2010. Effect of dihydrotestosterone on gastrointestinal tract of male Alzheimer's disease transgenic mice. Indian J. Exp. Biol. 48 (5), 453−465.

Kasai, C., Sugimoto, K., Moritani, I., Tanaka, J., Oya, Y., Inoue, H., et al., 2015. Comparison of the gut microbiota composition between obese and non-obese individuals in a Japanese population, as analyzed by terminal restriction fragment length polymorphism and next generation sequencing. BMC Gastroenterol. 15 (1), 100.

Keku, T.O., Dulal, S., Deveaux, A., Jovov, B., Han, X., 2015. The gastrointestinal microbiota and colorectal cancer. Am. J. Physiol. Gastrointest. Liver Physiol. 308, G351−G363.

Kennedy, P.J., Cryan, J.F., Dinan, T.G., Clarke, G., 2014. Irritable bowel syndrome: a microbiome-gut-brain axis disorder? World J. Gastroenterol. 20, 14105−14125.

Khoruts, A., Sadowsky, M.J., 2016. Understanding the mechanisms of faecal microbiota transplantation. Nat. Rev. Gastroenterol. Hepatol. 13, 508−516.

Kirjavainen, P.V., Karvonen, A.M., Adams, R.I., Täubel, M., Roponen, M., Tuoresmäki, P., et al., 2019. Farm-like indoor microbiota in non-farm homes protects children from asthma development. Nat Med 25 (7), 1089−1095.

Koliada, A., Syzenko, G., Moseiko, V., Budovska, L., Puchkov, K., Perederiy, V., et al., 2017. Association between body mass index and Firmicutes/Bacteroidetes ratio in an adult Ukrainian population. BMC Microbiol. 17, 120.

Kolmeder, C.A., Ritari, J., Verdam, F.J., Muth, T., Keskitalo, S., Varjosalo, M., et al., 2015. Colonic metaproteomic signatures of active bacteria and the host in obesity. Proteomics 15 (20), 3544−3552.

Kong, C., Liang, L., Liu, G., Du, L., Yang, Y., Liu, J., et al., 2022. Integrated metagenomic and metabolomic analysis reveals distinct gut-microbiome-derived phenotypes in early-onset colorectal cancer. Gut 72 (6), 1129−1142. Aug 11:gutjnl-2022-327156.

König, J., Ganda-Mall, J.P., Rangel, I., Edebol-Carlman, H., Brummer, R.J., 2015. The role of the gut microbiota in brain function. In: Venema, K., do Carmo, A.P. (Eds.), Probiotics and Prebiotics: Current Research and Future Trends. Caister Academic Press, Poole, UK.

Korpela, K., Salonen, A., Virta, L.J., Kekkonen, R.A., Forslund, K., Bork, P., de Vos, W.M., 2016. Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children. Nat. Com. 7, 10410.

Lagier, J.C., Dubourg, G., Million, M., Cadoret, F., Bilen, M., Fenollar, F., et al., 2018. Culturing the human microbiota and culturomics. Nat. Rev. Microbiol. 16 (9), 540−550.

Lahtinen, P., Jalanka, J., Hartikainen, A., Mattila, E., Hillilä, M., Punkkinen, J., et al., 2020. Randomised clinical trial: faecal microbiota transplantation versus autologous placebo administered via colonoscopy in irritable bowel syndrome. Aliment. Pharmacol. Ther. 51, 1321−1331.

Lambeth, S.M., Carson, T., Lowe, J., Ramaraj, T., Leff, J.W., et al., 2015. Composition, diversity and abundance of gut microbiome in prediabetes and type 2 diabetes. J. Diabetes. Obes. 2 (3), 1−7.

Larsen, N., Vogensen, F.K., Van Den Berg, F.W., Nielsen, D.S., Andreasen, A.S., Pedersen, B.K., et al., 2010. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS One 5 (2), e9085.

Lathrop, S.K., Bloom, S.M., Rao, S.M., Nutsch, K., Lio, C.W., Santacruz, N., et al., 2011. Peripheral education of the immune system by colonic commensal microbiota. Nature 478 (7368), 250−254.

Lee, M., Chang, E.B., 2021. Inflammatory bowel diseases (IBD) and the microbiome-searching the crime scene for clues. Gastroenterology 160, 524−537.

Lee, H., Ko, G., 2014. Effect of metformin on metabolic improvement and gut microbiota. Appl. Environ. Microbiol. 80 (19), 5935−5943.

Lee, J.W., Lee, Y.K., Yuk, D.Y., Choi, D.Y., Ban, S.B., Oh, K.W., Hong, J.T., 2008. Neuro-inflammation induced by lipopolysaccharide causes cognitive impairment through enhancement of beta-amyloid generation. J. Neuroinflammation 5 (1), 37.

Lee, K.A., Thomas, A.M., Bolte, L.A., Björk, J.R., de Ruijter, L.K., Armanini, F., et al., 2022. Cross-cohort gut microbiome associations with immune checkpoint inhibitor response in advanced melanoma. Nat. Med. 28, 535−544.

Ley, R.E., Bäckhed, F., Turnbaugh, P., Lozupone, C.A., Knight, R.D., Gordon, J.I., 2005. Obesity alters gut microbial ecology. Proc. Natl. Acad. Sci. U.S.A. 102 (31), 11070−11075.

Ley, R.E., Turnbaugh, P.J., Klein, S., Gordon, J.I., 2006. Microbial ecology: human gut microbes associated with obesity. Nature 444 (7122), 1022−1023.

Li, Y.T., Cai, H.F., Wang, Z.H., Xu, J., Fang, J.Y., 2016. Systematic review with meta-analysis: long-term outcomes of faecal microbiota transplantation for *Clostridium difficile* infection. Aliment. Pharmacol. Ther. 43, 445−457.

Liu, R., Hong, J., Xu, X., Feng, Q., Zhang, D., Gu, Y., et al., 2017. Gut microbiome and serum metabolome alterations in obesity and after weight loss intervention. Nat. Med. 23, 859−868.

Lopez-Siles, M., Khan, T.M., Duncan, S.H., Harmsen, H.J., Garcia-Gil, L.J., Flint, H.J., 2012. Cultured representatives of two major phylogroups of human colonic *Faecalibacterium prausnitzii* can utilize pectin, uronic acids, and host-derived substrates for growth. Appl. Environ. Microbiol. 78 (2), 420−428.

Lucas, S., Omata, Y., Hofmann, J., Böttcher, M., Iljazovic, A., Sarter, K., et al., 2018. Short-chain fatty acids regulate systemic bone mass and protect from pathological bone loss. Nat. Commun. 9 (1), 55.

Lynch, S.V., Vercelli, D., 2021. Microbiota, epigenetics, and trained immunity. Convergent drivers and mediators of the asthma trajectory from pregnancy to childhood. Am. J. Respir. Crit. Care Med. 203 (7), 802−808.

Lynch, S.V., Wood, R.A., Boushey, H., Bacharier, L.B., Bloomberg, G.R., Kattan, M., et al., 2014. Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children. J. Allergy Clin. Immunol. 134 (3), 593−601.

Machiels, K., Joossens, M., Sabino, J., De Preter, V., Arijs, I., Eeckhaut, V., et al., 2014. A decrease of the butyrate-producing species Roseburia hominis and Faecalibacterium prausnitzii defines dysbiosis in patients with ulcerative colitis. Gut 63, 1275−1283.

McNulty, N.P., Yatsunenko, T., Hsiao, A., Faith, J.J., Muegge, B.D., Goodman, A.L., et al., 2011. The impact of a consortium of fermented milk strains on the gut microbiome of gnotobiotic mice and monozygotic twins. Sci. Transl. Med. 3 (106), 106ra106.

Membrez, M., Blancher, F., Jaquet, M., et al., 2008. Gut microbiota modulation with norfloxacin and ampicillin enhances glucose tolerance in mice. Faseb. J. 22, 2416−2426.

Messaoudi, M., Lalonde, R., Violle, N., Javelot, H., Desor, D., Nejdi, A., et al., 2011. Assessment of psychotropic-like properties of a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) in rats and human subjects. Br. J. Nutr. 105 (05), 755−764.

Metchnikoff, E., Mitchell, P.C., 1907. The Prolongation of Life: Optimistic Studies. W. Heinemann, GP Putnam's Sons, London New York.

Michalovich, D., Rodriguez-Perez, N., Smolinska, S., Pirozynski, M., Mayhew, D., Uddin, S., et al., 2019. Obesity and disease severity magnify disturbed microbiome-immune interactions in asthma patients. Nat. Commun. 10 (1), 1−14.

Miele, L., Valenza, V., La Torre, G., Montalto, M., Cammarota, G., Ricci, R., et al., 2009. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. Hepatology 49 (6), 1877−1887.

Millien, V., Rosen, D., Hou, J., Shah, R., 2019. Proinflammatory sulfur-reducing bacteria are more abundant in colonic biopsies of patients with microscopic colitis compared to healthy controls. Dig. Dis. Sci. 64, 432−438.

Le Morvan de Sequeira, C., Hengstberger, C., Enck, P., Mack, I., 2022. Effect of probiotics on psychiatric symptoms and central nervous system functions in human health and disease: a systematic review and meta-analysis. Nutrients 14 (3), 621.

Mullish, B.H., McDonald, J.A.K., Pechlivanis, A., Allegretti, J.R., Kao, D., Barker, G.F., et al., 2019. Microbial bile salt hydrolases mediate the efficacy of faecal microbiota transplant in the treatment of recurrent Clostridioides difficile infection. Gut 68, 1791−1800.

von Mutius, E., Smits, H.H., 2020. Primary prevention of asthma: from risk and protective factors to targeted strategies for prevention. Lancet 396 (10254), 854−866.

Neish, A.S., 2009. Microbes in gastrointestinal health and disease. Gastroenterology 136 (1), 65−80.

Neufeld, K.M., Kang, N., Bienenstock, J., Foster, J.A., 2011. Reduced anxiety-like behavior and central neurochemical change in germ-free mice. Neuro Gastroenterol. Motil. 23 (3), 255−264, e119.

Ni, J., Wu, G.D., Albenberg, L., Tomov, V.T., 2017. Gut microbiota and IBD: causation or correlation? Nat. Rev. Gastroenterol. Hepatol. 14, 573−584.

van Nood, E., Vrieze, A., Nieuwdorp, M., Fuentes, S., Zoetendal, E.G., de Vos, W.M., et al., 2013. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. N. Engl. J. Med. 368, 407−415.

Obón-Santacana, M., Mas-Lloret, J., Bars-Cortina, D., Criado-Mesas, L., Carreras-Torres, R., Díez-Villanueva, A., et al., 2022. Meta-analysis and validation of a colorectal cancer risk prediction model using deep sequenced fecal metagenomes. Cancers 14, 4214.

Orrhage, K., Nord, C.E., 1999. Factors controlling the bacterial colonization of the intestine in breastfed infants. Acta Paediatr. 88 (s430), 47−57.

Ou, Z., Deng, L., Lu, Z., Wu, F., Liu, W., Huang, D., Peng, Y., 2020. Protective effects of Akkermansia muciniphila on cognitive deficits and amyloid pathology in a mouse model of Alzheimer's disease. Nutr. Diabetes 10 (1), 12.

Ownby, D.R., Johnson, C.C., Peterson, E.L., 2002. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. JAMA 288 (8), 963−972.

Ozato, N., Saito, S., Yamaguchi, T., Katashima, M., Tokuda, I., Sawada, K., et al., 2019. Et al. Blautia genus associated with visceral fat accumulation in adults 20−76 years of age. NPJ Biofilms Microbiomes 5.

O'Toole, P.W., Marchesi, J.R., Hill, C., 2017. Next-generation probiotics: the spectrum from probiotics to live biotherapeutics. Nat. Microbiol. 2 (5), 1−6.

Parnell, J.A., Relmer, R.A., 2009. Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. Am. J. Clin. Nutr. 89 (6), 1751−1759.

Peters, U., Dixon, A.E., Forno, E., 2018. Obesity and asthma. J. Allergy Clin. Immunol. 141 (4), 1169−1179.

Petrof, E.O., Gloor, G.B., Vanner, S.J., Weese, S.J., Carter, D., Daigneault, M.C., et al., 2013. Stool substitute transplant therapy for the eradication of *Clostridium difficile* infection: 'RePOOPulating' the gut. Microbiome 1 (1), 1−12.

Pittayanon, R., Lau, J.T., Yuan, Y., Leontiadis, G.I., Tse, F., Surette, M., Moayyedi, P., 2019. Gut microbiota in patients with irritable bowel syndrome-A systematic review. Gastroenterology 157, 97−108.

Plaza-Diaz, J., Ruiz-Ojeda, F.J., Gil-Campos, M., Gil, A., 2019. Mechanisms of action of probiotics. Adv. Nutr. 10 (Suppl. l_1), S49−S66.

Pozuelo, M., Panda, S., Santiago, A., Mendez, S., Accarino, A., Santos, J., et al., 2015. Reduction of butyrate- and methane-producing microorganisms in patients with Irritable Bowel Syndrome. Sci. Rep. 5, 12693.

Psichias, A., Sleeth, M.L., Murphy, K.G., Brook, L., Bewick, G.A., Hanyaloglu, A.C., et al., 2015. The short chain fatty acid propionate stimulates GLP-1 and PYY secretion via free fatty acid receptor 2 in rodents. Int. J. Obes. 39 (3), 424−429.

Puhlmann, M.L., de Vos, W.M., 2022. Intrinsic dietary fibers and the gut microbiome: rediscovering the benefits of the plant cell matrix for human health. Front. Immunol. 13.

Puhlmann, M.L., Jokela, R., van Dongen, K.C.W., Bui, T.P.N., van Hangelbroek, R.W.J., Smidt, H., et al., 2022. Dried chicory root improves bowel function, benefits intestinal microbial trophic chains and increases faecal and circulating short chain fatty acids in subjects at risk for type 2 diabetes. Gut Microb. 3.

Qin, L., Wu, X., Block, M.L., Liu, Y., Breese, G.R., Hong, J.S., et al., 2007. Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. Glia 55 (5), 453−462.

Qin, J., Li, Y., Cai, Z., Li, S., Zhu, J., Zhang, F., et al., 2012. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature 490 (7418), 55−60.

Rahat-Rozenbloom, S., Fernandes, J., Gloor, G.B., Wolever, T.M., 2014. Evidence for greater production of colonic short-chain fatty acids in overweight than lean humans. Int. J. Obes. 38, 1525−1531.

Rajilić-Stojanović, M., Heilig, H.G., Tims, S., Zoetendal, E.G., Vos, W.M., 2012. Long-term monitoring of the human intestinal microbiota composition. Environ. Microbiol. 15 (4), 1146−1159.

Rajilić-Stojanović, M., Shanahan, F., Guarner, F., de Vos, W.M., 2013. Phylogenetic analysis of dysbiosis in ulcerative colitis during remission. Inflamm. Bowel Dis. 19 (3), 481−488.

Ramirez-Farias, C., Slezak, K., Fuller, Z., Duncan, A., Holtrop, G., Louis, P., 2009. Effect of inulin on the human gut microbiota: stimulation of *Bifidobacterium adolescentis* and *Faecalibacterium prausnitzii*. Br. J. Nutr. 101 (4), 541−550.

Rangel, I., Sundin, J., Fuentes, S., Repsilber, D., de Vos, W.M., Brummer, R.J., 2015. The relationship between faecal-associated and mucosal-associated microbiota in irritable bowel syndrome patients and healthy subjects. Aliment. Pharmacol. Ther. 42, 1211−1221.

Rao, R., Seth, A., Sheth, P., 2004. Recent advances in alcoholic liver diease I. Role of intestinal permeability and endotoxemia in alcoholic liver disease. Am. J. Physiol. Gastrointest. Liver Physiol. 286, G881−G884.

Rashed, R., Valcheva, R., Dieleman, L.A., 2022. Manipulation of gut microbiota as a key target for Crohn's disease. Front. Med. 9, 887044.

Reichenberg, A., Yirmiya, R., Schuld, A., Kraus, T., Haack, M., Morag, A., Pollmächer, T., 2001. Cytokine-associated emotional and cognitive disturbances in humans. Arch. Gen. Psychiatr. 58 (5), 445−452.

Remely, M., Aumueller, E., Merold, C., Dworzak, S., Hippe, B., Zanner, J., et al., 2014. Effects of short chain fatty acid producing bacteria on epigenetic regulation of FFAR3 in type 2 diabetes and obesity. Gene 537 (1), 85−92.

Reunanen, J., Kainulainen, V., Huuskonen, L., Ottman, N., Belzer, C., Huhtinen, H., et al., 2015. *Akkermansia muciniphila* adheres to enterocytes and strengthens the integrity of the epithelial cell layer. Appl. Environ. Microbiol. 81 (11), 3655−3662.

Rindom Krogsgaard, L., Kristian Munck, L., Bytzer, P., Wildt, S., 2019. An altered composition of the microbiome in microscopic colitis is driven towards the composition in healthy controls by treatment with budesonide. Scand. J. Gastroenterol. 1−7.

Riva, A., Borgo, F., Lassando, C., Verduci, E., Morace, G., Borghi, E., Berry, D., 2017. Pediatric obesity is associated with an altered gut microbiota and discordant shifts in Firmicutes populations. Environ. Microbiol. 19, 95−105.

Romano, S., Savva, G.M., Bedarf, J.R., Charles, I.G., Hildebrand, F., Narbad, A., 2021. Meta-analysis of the Parkinson's disease gut microbiome suggests alterations linked to intestinal inflammation. NPJ Parkinsons Dis 7 (1), 27.

Rossen, N.G., Fuentes, S., van der Spek, M.J., Tijssen, J., Hartman, J.H., Duflou, A., et al., 2015. Findings from a randomized controlled trial of fecal transplantation for patients with ulcerative colitis. Gastroenterology 149 (1), 110−118.e4.

Rosser, E.C., Piper, C.J.M., Matei, D.E., Blair, P.A., Rendeiro, A.F., Orford, M., 2020. Microbiota-derived metabolites suppress arthritis by amplifying aryl-hydrocarbon receptor activation in regulatory B cells. Cell Metabol. 31 (4), 837−851.e10.

Russell, S.L., Gold, M.J., Hartmann, M., Willing, B.P., Thorson, L., Wlodarska, M., et al., 2012. Early life antibiotic-driven changes in microbiota enhance susceptibility to allergic asthma. EMBO Rep. 13 (5), 440−447.

Russo, E., Giudici, F., Fiorindi, C., Ficari, F., Scaringi, S., Amedei, A., 2019. Immunomodulating activity and therapeutic effects of short chain fatty acids and tryptophan post-biotics in inflammatory bowel disease. Front. Immunol. 10, 2754.

Saez-Lara, M.J., Gomez-Llorente, C., Plaza-Diaz, J., Gil, A., 2015. The role of probiotic lactic acid bacteria and bifidobacteria in the prevention and treatment of inflammatory bowel disease and other related diseases: a systematic review of randomized human clinical trials. BioMed Res. Int. 2015.

Samuel, B.S., Shaito, A., Motoike, T., Rey, F.E., Backhed, F., Manchester, J.K., et al., 2008. Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor. Gpr41. Proc. Natl. Acad. Sci. U.S.A. 105 (43), 16767−16772.

Sanders, M.E., Guarner, F., Guerrant, R., Holt, P.R., Quigley, E.M., Sartor, R.B., et al., 2013. An update on the use and investigation of probiotics in health and disease. Gut 62 (5), 787−796.

Sandler, R.H., Finegold, S.M., Bolte, E.R., Buchanan, C.P., Maxwell, A.P., Väisänen, M.L., et al., 2000. Short-term benefit from oral vancomycin treatment of regressive-onset autism. J. Child Neurol. 15 (7), 429−435.

Sato, J., Kanazawa, A., Ikeda, F., Yoshihara, T., Goto, H., Abe, H., et al., 2014. Gut dysbiosis and detection of "live gut bacteria" in blood of Japanese patients with type 2 diabetes. Diabetes Care 37 (8), 2343−2350.

Savica, R., Carlin, J.M., Grossardt, B.R., Bower, J.H., Ahlskog, J.E., Maraganore, D.M., et al., 2009. Medical records documentation of constipation preceding Parkinson disease: a case-control study. Neurology 73 (21), 1752−1758.

Scheperjans, F., Aho, V., Pereira, P.A., Koskinen, K., Paulin, L., Pekkonen, E., et al., 2015. Gut microbiota are related to Parkinson's disease and clinical phenotype. Mov. Disord. 30 (3), 350−358.

Scher, J.U., Sczesnak, A., Longman, R.S., Segata, N., Ubeda, C., Bielski, C., et al., 2013. Expansion of intestinal *Prevotella copri* correlates with enhanced susceptibility to arthritis. Elife 2, e01202.

Schmidt, T.S.B., Li, S.S., Maistrenko, O.M., Akanni, W., Coelho, L.P., Dolai, S., et al., 2022. Drivers and determinants of strain dynamics following fecal microbiota transplantation. Nat. Med. 1−11.

Schwiertz, A., Taras, D., Schäfer, K., Beijer, S., Bos, N.A., Donus, C., Hardt, P.D., 2010. Microbiota and SCFA in lean and overweight healthy subjects. Obesity 18 (1), 190−195.

Sedighi, M., Razavi, S., Navab-Moghadam, F., Khamseh, m.E., Alaei-Shahmri, F., Mehrtash, A., et al., 2017. Comparison of gut microbiota in adult patients with type 2 diabetes and healthy individuals. Microb. Pathog. 111, 362−369.

Shetty, S.A., Smidt, H., de Vos, W.M., 2019. Reconstructing functional networks in the human intestinal tract using synthetic microbiomes. Curr. Opin. Biotechnol. 58, 146−154.

Shin, N., Lee, J.W., Lee, B., Kim, M.S., Wong, T.B., et al., 2014. An increase in the *Akkermansia* spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. Gut 63, 727−735.

Simpson, C.A., Diaz-Arteche, C., Eliby, D., Schwartz, O.S., Simmons, J.G., Cowan, C.S.M., 2021. The gut microbiota in anxiety and depression - a systematic review. Clin. Psychol. Rev. 83, 101943.

Slob, E.M.A., Brew, B.K., Vijverberg, S.J.H., Kats, C.J.A.R., Longo, C., Pijnenburg, M.W., et al., 2020. Early-life antibiotic use and risk of asthma and eczema: results of a discordant twin study. Eur. Respir. J. 55 (4), 1902021.

Smith, P.M., Howitt, M.R., Panikov, N., Michaud, M., Gallini, C.A., Bohlooly-Y, M., et al., 2013. The microbial metabolites short-chain fatty acids, regulate colonic T_{reg} cell homeostasis. Science 341 (6145), 569−573.

Smits, L.P., Bouter, K.E., de Vos, W.M., Borody, T.J., Nieuwdorp, M., 2013. Therapeutic potential of fecal microbiota transplantation. Gastroenterology 145 (5), 946−953.

Sokol, H., Pigneur, B., Watterlot, L., Lakhdari, O., Bermúdez-Humarán, L.G., Gratadoux, J.J., et al., 2008. *Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. Proc. Natl. Acad. Sci. U.S.A. 105 (43), 16731−16736.

Sokol, H., Seksik, P., Furet, J., Firmesse, O., Nion-Larmurier, I., Beaugerie, L., et al., 2009. Low counts of *Faecalibacterium prausnitzii* in colitis microbiota. Inflamm. Bowel Dis. 15 (8), 1183−1189.

Sommer, F., Anderson, J.M., Bharti, R., Raes, J., Rosenstiel, P., 2017. The resilience of the intestinal microbiota influences health and disease. Nat. Rev. Microbiol. 15 (10), 630−638.

Souza da Cunha, S., Santorelli, G., Pearce, N., Wright, J., Oddie, S., Petherick, E., et al., 2021. Evidence for causal associations between prenatal and postnatal antibiotic exposure and asthma in children, England. Clin. Exp. Allergy 51 (11), 1438−1448.

Strugnell, R.A., Wijburg, O.L., 2010. The role of secretory antibodies in infection immunity. Nat Rev Microbiol 8 (9), 656−667.

Sundin, J., Rangel, I., Fuentes, S., Heikamp-de Jong, I., Hultgren-Hörnquist, E., de Vos, W.M., Brummer, R.J., 2015a. Altered faecal and mucosal microbial composition in post-infectious irritable bowel syndrome patients correlates with mucosal lymphocyte phenotypes and psychological distress. Aliment. Pharmacol. Ther. 41, 342−351.

Sundin, J., Rangel, I., Repsilber, D., Brummer, R.-J., 2015b. Cytokine response after stimulation with key commensal bacteria differ in post-infectious irritable bowel syndrome (PI-IBS) patients compared to healthy controls. PLoS One 10, e0134836.

Sundin, J., Aziz, I., Nordlander, S., Polster, A., Hu, Y.O.O., Hugerth, L.W., et al., 2020. Evidence of altered mucosa-associated and fecal microbiota composition in patients with Irritable Bowel Syndrome. Sci. Rep. 10, 593.

Tajik, N., Frech, M., Schulz, O., Schälter, F., Lucas, S., Azizov, V., et al., 2020. Targeting zonulin and intestinal epithelial barrier function to prevent onset of arthritis. Nat. Commun. 11 (1), 1995.

Talmor-Barkan, Y., Bar, N., Shaul, A.A., Shahaf, N., Godneva, A., et al., 2022. Metabolomic and microbiome profiling reveals personalized risk factors for coronary artery disease. Nat Med 28 (2), 295−302.

Tan, Q., Orsso, C.E., Deehan, E.C., Kung, J.Y., Tun, H.M., Wine, E., et al., 2021. Probiotics, prebiotics, synbiotics, and fecal microbiota transplantation in the treatment of behavioral symptoms of autism spectrum disorder: a systematic review. Autism Res. 14 (9), 1820−1836.

Tana, C., Umesaki, Y., Imaoka, A., Handa, T., Kanazawa, M., Fukudo, S., 2010. Altered profiles of intestinal microbiota and organic acids may be the origin of symptoms in irritable bowel syndrome. Neurogastroenterol. Motil. Off. J. Eur. Gastrointest. Motil. Soc. 22 (512−519), e114−e115.

Thomas, A.M., Manghi, P., Asnicar, F., Pasolli, E., Armanini, F., Zolfo, M., et al., 2019. Metagenomic analysis of colorectal cancer datasets identifies cross-cohort microbial diagnostic signatures and a link with choline degradation. Nat. Med. 25, 667−678.

Tims, S., Derom, C., Jonkers, D.M., Vlietinck, R., Saris, W.H., Kleerebezem, M., et al., 2013. Microbiota conservation and BMI signatures in adult monozygotic twins. ISME J. 7 (4), 707−717.

Van Treuren, W., Dodd, D., 2020. Microbial contribution to the human metabolome: implications for health and disease. Annu. Rev. Pathol. 24 (15), 345−369.

Turnbaugh, P.J., Ley, R.E., Mahowald, M.A., Magrini, V., Mardis, E.R., Gordon, J.I., 2006. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 444 (7122), 1027−1131.

Turnbaugh, P.J., Hamady, M., Yatsunenko, T., Cantarel, B.L., Duncan, A., Ley, R.E., et al., 2009. A core gut microbiome in obese and lean twins. Nature 457 (7228), 480−484.

Udina, M., Castellví, P., Moreno-España, J., Navinés, R., Valdés, M., Forns, X., et al., 2012. Interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis. J. Clin. Psychiatry 73 (8), 1128−1138.

Vangipurapu, J., Silva, L.F., Kuulasmaa, T., Smith, U., Laakso, M., 2020. Microbiota-related metabolites and the risk of type 2 diabetes. Diabetes Care 43 (6), 1319−1325.

Verdam, F.J., Fuentes, S., de Jonge, C., Zoetendal, E.G., Erbil, R., Greve, J.W., et al., 2013. Human intestinal microbiota composition is associated with local and systemic inflammation in obesity. Obesity 21 (12), E607−E615.

de Vos, W.M., 2013. Fame and future of faecal transplantations−developing next-generation therapies with synthetic microbiomes. Microb. Biotechnol. 6 (4), 316−325.

de Vos, W.M., Tilg, H., Van Hul, M., Cani, P.D., 2022. Gut microbiome and health: mechanistic insights. Gut 71 (5), 1020−1032.

Vrieze, A., Van Nood, E., Holleman, F., Salojärvi, J., Kootte, R.S., Bartelsman, J.F., et al., 2012. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology 143 (4), 913−916.

Wallen, Z.D., Demirkan, A., Twa, G., Cohen, G., Dean, M.N., Standaert, D.G., et al., 2022. Metagenomics of Parkinson's disease implicates the gut microbiome in multiple disease mechanisms. Nat. Commun. 13 (1), 6958.

Wang, M., Karlsson, C., Olsson, C., Adlerberth, I., Wold, A.E., Strachan, D.P., et al., 2008. Reduced diversity in the early fecal microbiota of infants with atopic eczema. J. Allergy Clin. Immunol. 121 (1), 129−134.

Wang, L., Christophersen, C.T., Sorich, M.J., Gerber, J.P., Angley, M.T., Conlon, M.A., 2011. Low relative abundances of the mucolytic bacterium *Akkermansia muciniphila* and *Bifidobacterium* spp. in feces of children with autism. Appl. Environ. Microbiol. 77 (18), 6718−6721.

Wang, S., Xu, M., Wang, W., Cao, X., Piao, M., Khan, S., et al., 2016. Systematic review: adverse events of fecal microbiota transplantation. PLoS One 11 (8), e0161174.

Wang, F., Gu, Y., Xu, C., Du, K., Zhao, C., Zhao, Y., Liu, X., 2022. Transplantation of fecal microbiota from APP/PS1 mice and Alzheimer's disease patients enhanced endoplasmic reticulum stress in the cerebral cortex of wild-type mice. Front. Aging Neurosci. 14, 858130.

Waters, J.L., Ley, R.E., 2019. The human gut bacteria *Christensenellaceae* are widespread, heritable, and associated with health. BMC Biol. 17, 83.

Williams, B.L., Hornig, M., Buie, T., Bauman, M.L., Cho Paik, M., Wick, I., et al., 2011. Impaired carbohydrate digestion and transport and mucosal dysbiosis in the intestines of children with autism and gastrointestinal disturbances. PLoS One 6 (9), e24585.

Williams, B.L., Hornig, M., Parekh, T., Lipkin, W.I., 2012. Application of novel PCR-based methods for detection, quantitation, and phylogenetic characterization of *Sutterella* species in intestinal biopsy samples from children with autism and gastrointestinal disturbances. mBio 3 (1) e00261−11.

Wirbel, J., Pyl, P.T., Kartal, E., Zych, K., Kashani, A., Milanese, A., et al., 2019. Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer. Nat. Med. 25, 679−689.

Wu, H.J., Ivanov, I.I., Darce, J., Hattori, K., Shima, T., Umesaki, Y., et al., 2010. Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells. Immunity 32 (6), 815−827.

Xia, Q., Grant, S.F., 2013. The genetics of human obesity. Ann. N. Y. Acad. Sci. 1281 (1), 178−190.

Xiao, L., Feng, Q., Liang, S., Sonne, S.B., Xia, Z., Qiu, X., et al., 2015. A catalog of the mouse gut metagenome. Nat. Biotechnol. 33 (10), 1103−1108.

Xu, J., Lai, K.K.Y., Verlinsky, A., Lugea, A., French, S.W., Cooper, M.P., 2011. Synergistic steatohepatitis by moderate obesity and alcohol in mice despite increased adiponectin and p-AMPK. J. Hepatol. 55 (3), 673−682.

Yachida, S., Mizutani, S., Shiroma, H., Shiba, S., Nakajima, T., Sakamoto, T., et al., 2019. Metagenomic and metabolomic analyses reveal distinct stage-specific phenotypes of the gut microbiota in colorectal cancer. Nat. Med. 25, 968−976.

Yap, C.X., Henders, A.K., Alvares, G.A., Wood, D.L.A., Krause, L., Tyson, G.W., et al., 2021. Autism-related dietary preferences mediate autism-gut microbiome associations. Cell 184 (24), 5916−5931 e17.

Yu, J., Feng, Q., Wong, S.H., Zhang, D., Liang, Q.Y., Qin, Y., et al., 2017. Metagenomic analysis of faecal microbiome as a tool towards targeted non-invasive biomarkers for colorectal cancer. Gut 66, 70−78.

Yuan, J., Chen, C., Cui, J., Lu, J., Yan, C., Wei, X., 2019. Fatty liver disease caused by high-alcohol-producing *Klebsiella pneumoniae*. Cell Metabol. 30 (4), 675−688.

Zabana, Y., Tontini, G., Hultgren-Hörnquist, E., Skonieczna-Żydecka, K., Latella, G., Østvik, A.E., et al., 2022. Pathogenesis of microscopic colitis: a systematic review. J. Crohns Colitis 16, 143−161.

Zhang, R., Miller, R.G., Gascon, R., Champion, S., Katz, J., Lancero, M., et al., 2009. Circulating endotoxin and systemic immune activation in sporadic amyotrophic lateral sclerosis (sALS). J. Neuroimmunol. 206 (1), 121−124.

Zhang, X., Shen, D., Fang, Z., Jie, Z., Qiu, X., Zhang, C., et al., 2013. Human gut microbiota changes reveal the progression of glucose intolerance. PLoS One 8 (8), e71108.

Zhang, X., Zhang, D., Jia, H., Feng, Q., Wang, D., Liang, D., et al., 2015. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. Nat. Med. 21, 895−905.

Zhang, F., Wang, M., Yang, J., Xu, Q., Liang, C., Chen, B., et al., 2019. Response of gut microbiota in type 2 diabetes to hypoglycemic agents. Endocrine 66 (3), 485−493.

Zhang, J., Guo, Y., Duan, L., 2022. Features of gut microbiome associated with responses to fecal microbiota transplantation for inflammatory bowel disease: a systematic review. Front. Med. 9, 773105.

Zhao, L., Lou, H., Peng, Y., Chen, S., Zhang, Y., Li, X., 2019. Comprehensive relationships between gut microbiome and faecal metabolome in individuals with type 2 diabetes and its complications. Endocrine 66 (3), 526−537.

Zhao, H.-J., Zhang, X.-J., Zhang, N.-N., Yan, B., Xu, K.-K., Peng, L.-H., Pan, F., 2022. Fecal microbiota transplantation for patients with irritable bowel syndrome: a meta-analysis of randomized controlled trials. Front. Nutr. 9, 890357.

Zhu, L., Baker, S.S., Gill, C., Liu, W., Alkhouri, R., Baker, R.D., Gill, S.R., 2013. Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: a connection between endogenous alcohol and NASH. Hepatology 57 (2), 601−609.

Zoetendal, E.G., de Vos, W.M., 2014. Effect of diet on the intestinal microbiota and its activity. Curr. Opin. Gastroenterol. 30 (2), 189−195.

Zoetendal, E.G., Rajilić-Stojanović, M., De Vos, W.M., 2008. High-throughput diversity and functionality analysis of the gastrointestinal tract microbiota. Gut 57 (11), 1605−1615.