REVIEW

The gut microbiome: a core regulator of metabolism

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Abstract

The human body is inhabited by numerous bacteria, fungi, and viruses, and each part has a unique microbial community structure. The gastrointestinal tract harbors approximately 100 trillion strains comprising more than 1000 bacterial species that maintain symbiotic relationships with the host. The gut microbiota consists mainly of the phyla Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria. Of these, Firmicutes and Bacteroidetes constitute 70–90% of the total abundance. Gut microbiota utilize nutrients ingested by the host, interact with other bacterial species, and help maintain healthy homeostasis in the host. In recent years, it has become increasingly clear that a breakdown of the microbial structure and its functions, known as dysbiosis, is associated with the development of allergies, autoimmune diseases, cancers, and arteriosclerosis, among others. Metabolic diseases, such as obesity and diabetes, also have a causal relationship with dysbiosis. The present review provides a brief overview of the general roles of the gut microbiota and their relationship with metabolic disorders.

Key Words

- obesity
- diabetes
- metabolism

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Physiological role of the gut microbiota

Nutrient metabolism and absorption

Degradation of indigestible polysaccharides

Short-chain fatty acids (SCFAs) are metabolites generated from the fermentation of insoluble dietary fiber and indigestible polysaccharides by the gut microbiota. Linear monovalent carboxylic acids with fewer than six carbons, such as acetate (C2), propionate (C3), and butyrate (C4), are the most abundant SCFAs, with average ratios of ~60%:20%:20%. Total intestinal SCFA concentrations can reach 100 mM (Cummings *et al.* 1987). Butyrate is the main nutrient source for colonocytes. Acetate has the highest intestinal concentration of all SCFAs. It enters the liver via the portal vein, undergoes oxidation, and is used mainly by hepatocytes. Propionate participates in hepatic gluconeogenesis. These SCFAs maintain the barrier function of the intestinal tract, are bioactive substances in energy metabolism (Morrison and Preston 2016), regulate immunocyte development, and are anti-inflammatory (Louis *et al.* 2014, Richards *et al.* 2016). Various pathways are involved in SCFA synthesis (Koh *et al.* 2016). Acetate is synthesized from pyruvate during glycolysis and by acetogenic bacteria via the Wood–Ljungdahl pathway, which produces acetyl-CoA from CO_2. Acetoacetyl-CoA is converted to butyryl-CoA, which, in turn, is transformed into butyrate. Major butyrate-producing bacterial taxa include the Ruminococcaceae, Lachnospiraceae, Erysipelotrichaceae, and Clostridiaceae of the Firmicutes phylum (Barcenilla *et al.* 2000, Louis *et al.* 2004). *Clostridium* spp. (such as *C. butyricum*) and *Butyrivibrio* spp. (such as *B. fibrisolvens*) also produce butyrate. *Acetobacter* spp. and *Gluconobacter* spp. produce acetate (Louis *et al.* 2014, Knip & Siljander 2016, Koh *et al.* 2016). SCFAs are interconverted, and 24% of all acetate is

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converted to butyrate (Boets *et al.* 2017). Pathways involved in propionate synthesis include the acrylate pathway mediated by lactate metabolism, the succinate pathway mediated by succinate, and the propanediol pathway utilizing deoxy sugars such as fucose and rhamnose (Fig. 1) (Louis & Flint 2017). *Akkermansia muciniphila* and other species are propionate-producing, mucin-degrading bacteria (Derrien *et al.* 2004). SCFAs are important not only for energy and glucose metabolism, inflammation, and immune function regulation (Koh *et al.* 2016) but also for intestinal environment maintenance. For example, butyrate is important for maintaining an anaerobic environment in the intestinal tract and activating PPARγ by promoting mitochondrial β-oxidation in intestinal epithelial cells (IECs), maintaining hypoxia for epithelial cells and inhibiting oxygen transfer into the intestinal lumen (Rivera-Chavez *et al.* 2016, Byndloss *et al.* 2017). Acetate and propionate produced in the intestine also play an important role in intestinal homeostasis. They induce colonic Treg to protect against experimentally induced colitis (Smith *et al.* 2013). Another group reported that acetate suppresses intestinal inflammation via G protein-coupled receptor (GPR) 43 signaling expressed on neutrophils (Maslowski *et al.* 2009). It also enhances intestinal barrier function and contributes to defense against pathogens (Fukuda *et al.* 2011).

Bile acids and lipid metabolism

Secondary bile acids are major bacterial metabolites affecting host physiology. Hepatocytes produce cholic acid and chenodeoxycholic acid from cholesterol. These lipid-soluble bile acids are conjugated to glycine or taurine to form water-soluble bile salts and are stored in the gallbladder and released into the intestine during digestion. Gut bacteria dehydroxylate primary bile salts into secondary bile salts. These bile acids are actively resorbed along the proximal and distal ileum into the hepatic portal circulation. Bacteria also deconjugate certain primary and secondary conjugated bile salts into lipid-soluble bile acids that are passively absorbed into the hepatic portal circulation. Approximately 95% of bile acids delivered to the duodenum are recycled via enterohepatic circulation. Bile acids emulsify and facilitate the absorption of dietary lipids. They are also ligands for bile acid receptors, such as transmembrane G protein-coupled receptor 5 (TGR5) and farnesoid X receptor (FXR), which regulate energy and cholesterol metabolism and bile acid transporter gene expression (Wahlstrom *et al.* 2016) (Fig. 2). Deoxycholic acid is associated with hepatocellular carcinoma (Yoshimoto *et al.* 2013) and the inhibition of bacterial overgrowth. Recently, centenarians were found to have a distinct gut microbiome enriched in *Parabacteroides merdae*, *Odoribacter laneus*, and Odoribacteraceae. These microbiota synthesize

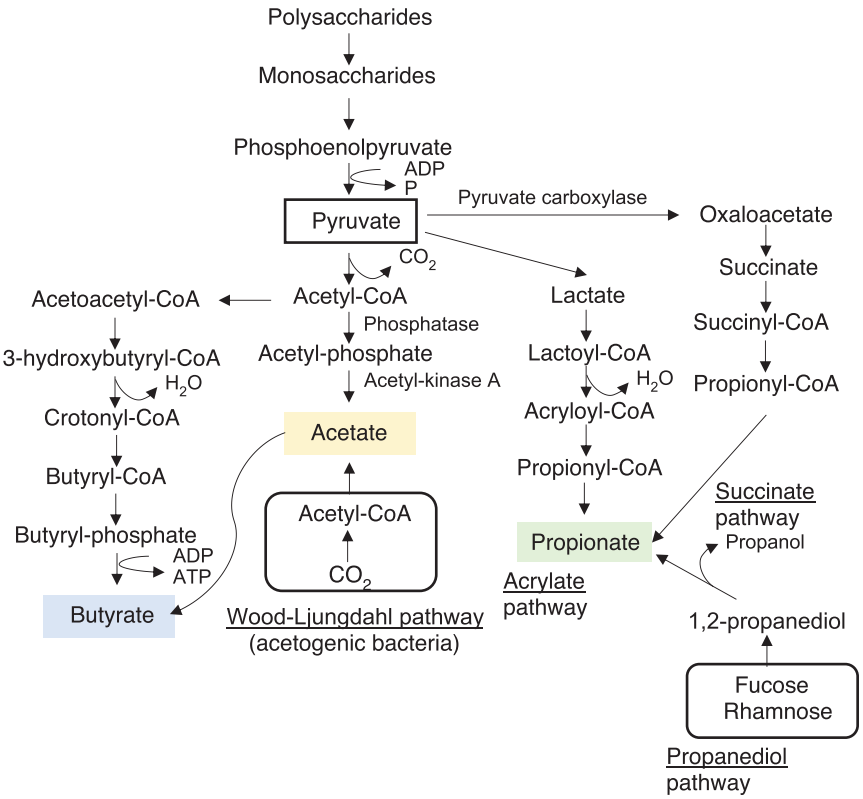

Figure 1
Short-chain fatty acid (SCFA) biosynthesis pathways.

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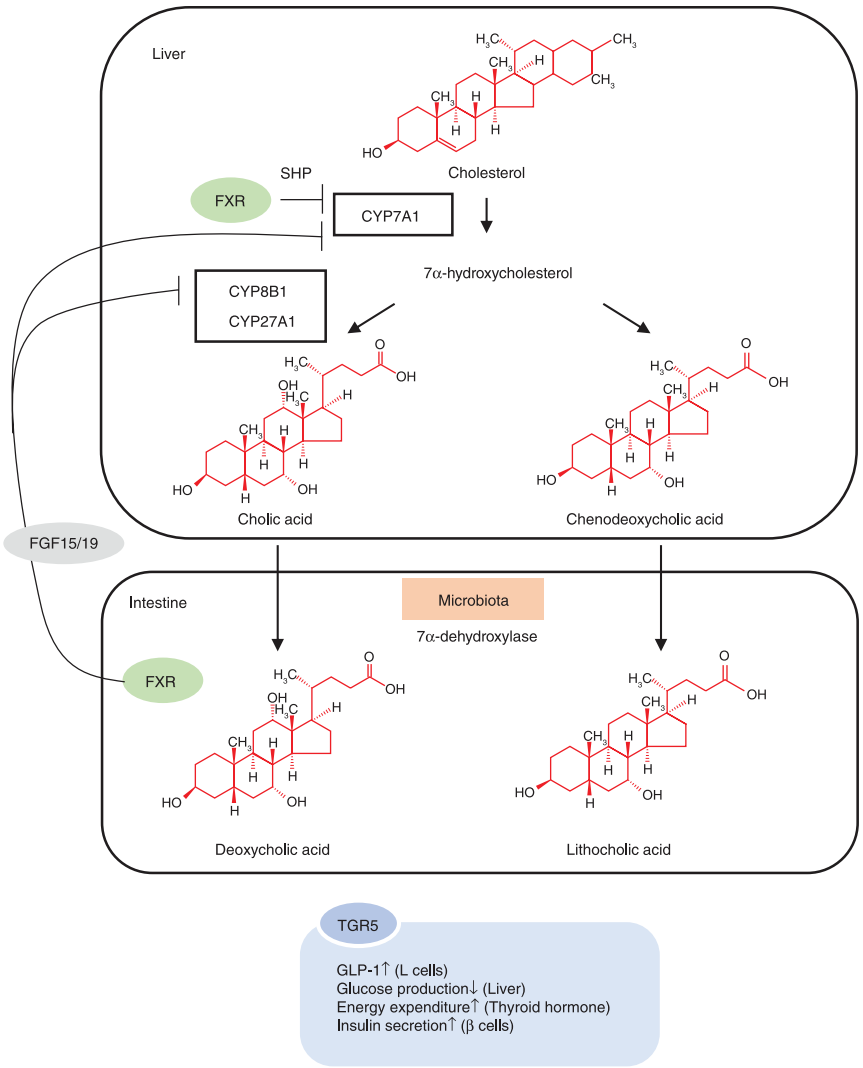

Figure 2
Bile acid metabolism. The microbiota dehydroxylate primary bile acids, such as cholic acid and chenodeoxycholic acid, to secondary bile acids with 7a-dehydroxylase. Activation of the bile acid receptor FXR suppresses the expression of CYP7A1, a bile acid rate-limiting enzyme, via the induction of small heterodimer partner (SHP) expression in the liver to control bile acid synthesis. In addition, FXR activation in the intestine suppresses CYP7A1 and CYP8B1 expression via the induction of FGF15/19 expression.

isoallolithocholic acid, which has antibacterial efficacy against Gram-positive bacteria (Sato *et al.* 2021). Hence, this gut bacteria-derived bile acid might be conducive to human longevity.

Additionally, gut microbiota produces lipids. The genes encoding sphingolipid biosynthesis mediators are distributed mainly in eukaryotes. Nevertheless, certain bacterial species in the Bacteroides phylum also have genes that regulate sphingolipid biosynthesis. *Bacteroides fragilis* produces α-galactosylceramide, which suppresses intestinal natural killer T (NKT) cell activation (An *et al.* 2014). Patients with inflammatory bowel disease (IBD) present with relatively low fecal *Bacteroides* sphingolipid concentrations and are negatively correlated with inflammation. The colonization of germ-free (GF) mice by genetically engineered *Bacteroides thetaiotaomicron*, which lacks sphingolipid synthesis, results in intestinal inflammation and altered host ceramide pools (Brown *et al.* 2019). Thus, sphingolipids produced by *Bacteroides* might maintain intestinal homeostasis.

Gut bacteria also saturate dietary unsaturated fatty acids. *Lactobacillus plantarum* enzymatically metabolizes unsaturated fatty acids via catalysts of hydration and catalysts of dehydration to produce hydroxy-, oxo-, and conjugated fatty acids and partially saturated trans-fatty acids (Kishino *et al.* 2013). Linoleic acid administration activates the arachidonic acid cascade, which induces chronic inflammation in adipose tissue. *Lactobacillus salivarius* and *Lactobacillus gasseri* produce 10-hydroxy-*cis*-12-octadecenoic acid via linoleic acid hydroxylation, which improves obesity, increases GLP-1 secretion, and improves glucose metabolism (Miyamoto *et al.* 2019). Dietary nutrients are major drivers that determine microbial composition. Plasma lipidomic analysis of GF or colonized mice fed different nutrient compositions revealed that the microbiota have dynamic effects on systemic lipid

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profiles, and the magnitude of this influence is related to metabolic disorders (Watanabe *et al.* 2021). Thus, the gut microbiota comprises a regulator of bile acid metabolism, lipid absorption, inflammatory signals via lipid synthesis, and energy metabolism. Therefore, its disruption can cause metabolic disorders through these mechanisms, which will be discussed in more detail later in this article.

Vitamins

Vitamins are either fat soluble (A, D, E, and K) or water soluble (B-complex and C). Fat-soluble vitamins are transported to various tissues and act as signaling molecules and bioactive effectors, whereas water-soluble vitamins act as coenzymes. Vitamin administration alters gut bacteria, increases their biodiversity, and elevates SCFA levels (Pham *et al.* 2021). However, gut bacteria themselves synthesize vitamins (Steinert *et al.* 2020).

Humans cannot synthesize any vitamin, except D. Thus, the human vitamin supply depends on diet and gut bacteria. Gut microbiota produce C, K, and B-complex vitamins. Thiele *et al.* analyzed the microbial genome and assessed the ability of bacteria to synthesize thiamine (B1), riboflavin (B2), niacin (B3), pantothenate (B5), pyridoxine (B6), biotin (B7), folate (B9), and cobalamin (B12). Approximately 40–65% of 256 human commensal bacteria possess a B-complex synthesis pathway (Magnusdottir *et al.* 2015). Interactions occur between vitamins and gut microbiota, and the former affect microbial community structures (Pham *et al.* 2021). Vitamin A administration to neonates within 2 days after birth affects the gut bacterial composition in a sex-dependent manner. It increases *Bifidobacterium* abundance in boys but increases Actinobacteria and *A. muciniphila* abundance in girls (Huda *et al.* 2019). Dietary vitamin A intake and plasma concentrations affect the gut bacterial composition (Wu *et al.* 2011, Li *et al.* 2017), which could aid in protection against various pathogens (Long *et al.* 2007, 2011).

Vitamin D also modifies the gut microbial community structure, and supplementation is associated with significant changes in Firmicutes, Actinobacteria, and Bacteroidetes abundances. Veillonellaceae and Oscillospiraceae (Firmicutes) are negatively associated with 25(OH)-D levels and vitamin D supplementation (Bellerba *et al.* 2021). Vitamin D may protect against IBD by suppressing immunocyte activation, strengthening intestinal barrier functions, and enhancing antibacterial peptide production (Pham *et al.* 2021). Certain bacterial species regulate vitamin D receptors (VDRs). Wu *et al.* reported that the probiotics *Lactobacillus rhamnosus* and *L. plantarum* increase VDR in the IECs and protect against colitis in a VDR signaling-dependent manner (Wu *et al.* 2015). A genome-wide association analysis revealed that variations in VDR affect β-diversity and Parabacteroides abundance (Wang *et al.* 2016). This evidence suggests that gut microbiota regulate vitamin D signaling and help to maintain intestinal homeostasis.

Amino acid metabolism

Gut microbiota degrade proteins, produce amino acids (AAs), and metabolize the choline and L-carnitine in red meat to trimethylamine (TMA). The latter enters circulation and is metabolized in the liver to trimethylamine-*N*-oxide (TMAO). In an animal model, TMAO was found to promote atherosclerosis. Plasma TMAO could increase cardiovascular disease (CVD) risk and mortality in a dose-dependent manner (Koeth *et al.* 2013, Tang *et al.* 2013, Schiattarella *et al.* 2017). Wang *et al.* showed that a structural analog of choline, 3,3-dimethyl-1-butanol (DMB), inhibits microbial TMA production. Oral DMB administration reduces TMAO levels and inhibits choline diet-induced macrophage foam cell formation to suppress the development of arteriosclerosis in apolipoprotein E knockout (KO) mice. Therefore, microbial intervention might help to prevent arteriosclerosis (Wang *et al.* 2015).

Gut microbiota also metabolize other AAs. Plasma levels of the branched-chain amino acids (BCAAs) valine, leucine, and isoleucine are correlated with insulin resistance in diabetic patients (Newgard *et al.* 2009, Batch *et al.* 2013, Jang *et al.* 2016). Pedersen *et al.* integrated analyses of serum metabolomics and metagenomics and showed that elevated BCAA levels in insulin-resistant individuals are associated with microbiota, which are enriched in BCAA biosynthesis pathways. *Prevotella copri* and *Bacteroides vulgatus* are the major BCAA synthesizers. The oral administration of *P. copri* to mice fed a high-fat diet results in increased serum BCAAs and aggravates glucose intolerance. Thus, BCAAs produced by gut microbiota could contribute to insulin resistance (Pedersen *et al.* 2016).

The aromatic AAs tyrosine, phenylalanine, and tryptophan are correlated with diabetes risk (Wang *et al.* 2011, Chen *et al.* 2016). Bacteria harbor genes encoding mediators of aromatic AA metabolism. Antibiotic administration strongly affects these metabolic pathways. Hence, aromatic AA metabolism by gut microbiota affects the host AA profile (Fujisaka *et al.* 2018).

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Immune function maintenance and protection against pathogens

SCFAs exert various bioactive effects that help maintain the immune system (Shibata *et al.* 2017). Butyrate is an energy source for IECs and has anti-inflammatory and immunomodulatory effects (den Besten *et al.* 2013). Butyrate interacts with IECs, induces antimicrobial peptide and cytokine production, inhibits pathogen overgrowth, and strengthens intestinal barrier functions (Raqib *et al.* 2006, Singh *et al.* 2014, Shibata *et al.* 2017). The predominant phylum Firmicutes consists mainly of butyrate-producing *Clostridium* clusters IV and XIV (Eckburg *et al.* 2005). Clostridiales bacteria induce regulatory T-cell differentiation in the intestinal mucosa, which helps suppress the immune response (Atarashi *et al.* 2011). Furusawa *et al.* reported that butyrate derived from Clostridiales leads to butyrate-enhanced histone H3 acetylation in both the promoter and conserved non-coding sequence regions of *Foxp3* (Furusawa *et al.* 2013), suggesting that butyrate is an epigenetic modifier for Treg induction.

Bifidobacteria are major producers of acetate, which has immunoregulatory effects. Acetate fortifies the gut barrier function against *Escherichia coli* O157 (Fukuda *et al.* 2011). Acetate induces apoptosis via neutrophil GPR43 and suppresses colitis in a mouse colorectal cancer model (Maslowski *et al.* 2009). Acetate also alleviates allergic airway disease (AAD) in a mouse model. The oral administration of a high-fiber diet or acetate to pregnant mice delays the onset of AAD in their offspring, possibly by inducing Tregs via *Foxp3* acetylation at its promoter and HDAC9 inhibition (Thorburn *et al.* 2015). Succinate, produced by neonate intestinal bacteria, promotes gut microbiota maturation by establishing Clostridiales in the intestinal tract, thereby preventing *Salmonella* and pathogenic *E. coli* growth (Kim *et al.* 2017). Thus, certain bacteria suppress immunocyte activation. In contrast, other bacteria can activate certain immunocytes. Atarashi *et al.* reported that salivary *Klebsiella* spp. ectopically colonizing the intestine activate the Th1 immune response and exacerbate intestinal inflammation in a mouse IBD model (Atarashi *et al.* 2017). In rodents, segmented filamentous bacteria strongly induce Th17cells (Atarashi *et al.* 2015), trigger the production of the proinflammatory cytokines IL-17 and IL-22, and promote antimicrobial peptide production in IECs (Shale *et al.* 2013). In contrast, some bacteria such as *Gordonibacter pamelaeae*, *Eggerthella lenta*, and *Raoultibacter massiliensis* negatively regulate Th17 cell differentiation by producing the secondary bile acid metabolites 3-oxolithocholic acid (3-oxoLCA) and isolithocholic acid (isoLCA). These bile acids inhibit retinoic acid receptor-related orphan nuclear receptor-γ t (RORγt), a key transcription factor that promotes Th17 cell differentiation. Since 3-oxoLCA and isoLCA levels are reduced in patients with IBD and inversely correlated with Th17 cell/IL-17-related genes, decreased 3-oxoLCA and isoLCA in dysbiosis could contribute to IBD pathophysiology (Paik *et al.* 2022). In general, Tregs have anti-inflammatory effects, whereas Th17 cells act in a pro-inflammatory manner in IBD, and the Th17/Treg balance is important to maintain intestinal immune homeostasis, with its dysregulation contributing to IBD development (Ueno *et al.* 2018). Thus, although the mechanisms are complex, it is important to elucidate the interaction between gut commensal bacteria and immunocyte functions.

Regulation of intestinal motility

Intestinal motility is vital to digestion, absorption, and excretion. Gut bacteria regulate intestinal motility by helping to develop and maintain the intestinal nervous system. Intestinal motility is seldom observed in fetuses with little or no intestinal bacteria (Kien 1996). GF mice present with decreased colonic neuron density and intestinal motility compared with those in specific pathogen-free (SPF) mice. Fecal microbiota transplantation promotes serotonin (5-HT) production in the intestinal mucosa and neurons and increases neuron density and motility (De Vadder *et al.* 2018). Deoxycholic acid produced by spore-forming bacteria enhances 5-HT biosynthesis from colonic enterochromaffin cells and activate platelet functions and intestinal peristalsis (Yano *et al.* 2015). Obata *et al.* compared RNA sequencing of the intestinal tracts of conventionally raised mice with GF mice and found a transcription factor, aryl hydrocarbon receptor (AhR), was induced by microbiota. AhR was expressed in colonic neurons and promoted peristalsis of the intestinal tract, indicating a close link between microbiota and the enteric nervous system (Obata *et al.* 2020). These findings show that intestinal microbiota help to regulate intestinal motility. Therefore, gut dysbiosis can cause chronic constipation and irritable bowel syndrome, which are associated with dysregulated peristalsis. In summary, the gut microbiota play an important role in maintaining systemic homeostasis through the metabolism of nutrients, such as indigestible polysaccharides, lipids, vitamins, and AAs, and regulation of the immune system

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and intestinal function. In the latter part of this article, we outline the relationship between dysbiosis and obesity/glucose metabolism.

History of GF animals

Next-generation sequencing technologies such as 16S rRNA sequencing and shotgun metagenomic sequencing have been developed to obtain microbial information. Details of these technologies are described in other reviews (Wensel *et al.* 2022). The transplantation of gut bacteria into GF animals is a powerful tool to investigate the effects of the gut microbiota of interest on biological functions and disease. In this section, we briefly introduce the significance and history of the development of GF animals.

GF animals harbor no detectable microorganisms and can help clarify the roles and significance of the gut microbiota. Gnotobiotic animals are GF and colonized by a single strain or a specific bacterial community comprising various species. They help demonstrate the physiological effects of certain bacteria on the host.

The development of GF animals began in 1885 through the advocacy of Louis Pasteur in France (Pasteur 1885). In 1895, Nuttal and Thierfelder obtained Guinea pigs via aseptic Caesarean section and maintained them in a sterile environment for 13 days (Nuttal & Thierfelder 1985). In 1989, Schottelius *et al.* created the first reported GF chickens. In the early 1900s, Kuster *et al.* established GF goats. Later, GF rats, chickens, and guinea pigs were bred as experimental animals.

GF mice were first weaned in 1954 (Reyniers *et al.* 1946, Reyniers *et al.* 1949, Miyakawa *et al.* 1954). The goal of early GF animal research was to determine whether bacterial symbiosis was beneficial or detrimental to the survival of host organisms. GF animal research is used in physiology, nutrition, bacteriology, and immunology. Current microbiota study tools and techniques have revealed close associations between bacteria and metabolic diseases.

However, maintenance of a gnotobiotic status is expensive and requires experienced staff, and the available facilities for GF animals are limited. Furthermore, as GF animals have not innately experienced immunological stimulation by microorganisms, their nutritional status and immune systems are quite different from those of SPF animals. Therefore, we should be cautious in interpreting results of such studies.

Gut microbiota in obesity

Obesity is one of the most serious and common medical conditions in modern society. According to World Health Organization data, the obese population is increasing annually. In 2016, 39% of all adults (1.9 billion people) were overweight and 13% of all adults (650 million people) were obese. Obesity causes metabolic disorders, hypertension, glucose intolerance, dyslipidemia, and hyperuricemia and is a risk factor for atherosclerosis, ischemic heart disease, and CVD. Therefore, the pathogenesis, prevention, and treatment of obesity merit further investigation. Recent studies have revealed a close relationship between gut microbiota and obesity. The latter alters the gut microbiota, which is in turn closely related to obesity pathogenesis, as it affects host immunity and metabolism. Thus, interventions involving gut microbiota could be used to prevent and treat obesity.

The gut microbiota is inextricably linked to obesity

Bäckhed *et al.* first found that fecal microbiota transplantation of normal microbiota from the cecum of conventionally raised mice into GF C57/BL6 mice increased fat mass and insulin resistance. The increase in fat storage was not due to an increased food intake but a decreased expression of the fasting-induced adipose factor (Fiaf), a fat accumulation inhibitory factor (Backhed *et al.* 2004). Several years later, they showed the mechanisms by which GF mice are resistant to obesity compared to conventionally raised mice. They found that (1) GF mice had elevated intestinal Fiaf levels, which activated PGC1α in the skeletal muscle, and (2) AMPK in skeletal muscle is activated in GF mice independently of Fiaf signaling. These two phenotypes can lead to enhanced fatty acid oxidation in GF animals, suggesting that the gut microbiota plays an important role in promoting energy accumulation (Backhed *et al.* 2007). Subsequently, several studies showed that the transplantation of gut microbiota from obese human or mouse models into GF mice results in obesity (Turnbaugh *et al.* 2006, Vijay-Kumar *et al.* 2010, Ridaura *et al.* 2013). Furthermore, microbial perturbation via antibiotic administration in childhood has been shown to elevate the risk of obesity in adulthood (Cox *et al.* 2014, Cox & Blaser 2015, Schwartz *et al.* 2016). This led us to recognize that disruption of the microbiota (dysbiosis) is a cause, and not a consequence, of obesity and is closely associated with metabolic diseases (Le Chatelier *et al.* 2013). Thus, the gut microbiota is inextricably linked to obesity.

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In 2006, it was first shown that gut bacteria differ with obesity. These findings showed a relative increase in the Firmicutes/Bacteroides (F/B) ratio in obese humans and rodents (Ley *et al.* 2006, Turnbaugh *et al.* 2006). Since then, numerous studies have reported on the gut microbiota of obese patients to clarify this dysbiosis among various ethnic groups and different geographic regions (Table 1). However, the pattern of microbial structure changes with obesity is not constant, and some reports show no change or a decrease in the F/B ratio (Schwiertz *et al.* 2010, Tims *et al.* 2013). Interactions among multiple factors such as race, region, diet, and cultural background might account for these discrepancies. Some human studies have revealed that *Oscillospira* is reduced with obesity (Konikoff & Gophna 2016, Yang *et al.* 2021) and is expected to be a candidate for next-generation probiotics as it produces SCFAs such as butyrate. However, several reports showed that this bacterium is associated with gallstones and chronic constipation, suggesting complex interactions between the bacterium and host physiology (Yang *et al.* 2021). Goodrich *et al.* analyzed the gut microbiota of 416 pairs of twins and found that the abundance of Christensenellaceae was correlated with low BMI and that the transplantation of *Christensenella minuta* into GF mice reduces weight gain (Goodrich *et al.* 2014). Everard *et al.* showed that the relative abundance of *A. muciniphila*, which has been linked to a favorable effect on glucose metabolism, is reduced in obese and diabetic mice and humans (Everard *et al.* 2013). The metabolic ameliorating effects of *A. muciniphila* are described later in the 'Impaired gut barrier function' section.

More recently, metabolomics has been used to elucidate the effects of metabolites produced by the gut microbiota. In China, a metagenome-wide association analysis and serum metabolomic profiling revealed that the abundance of glutamate-fermenting *B. thetaiotaomicron* is reduced with obesity and associated with an elevation in serum glutamine (Gln). Bariatric surgery and *B. thetaiotaomicron* administration decrease Gln levels in mice. Hence, *B. thetaiotaomicron* affects AA cycling and has anti-obesity effects (Liu *et al.* 2017). In contrast, other researchers reported that *B. thetaiotaomicron* upregulates intestinal lipid absorption transporters, promotes hepatic lipid biosynthesis, and causes obesity and impaired glucose tolerance in high-fat diet-fed mice (Cho *et al.* 2022). Further research is required to identify the mechanism through which gut bacteria help to improve obesity and metabolic disorders.

Obesity treatment alters the gut microbiota

Bariatric surgery is a well-established obesity treatment. It promotes weight loss and improves obesity-related metabolic disorders such as hypertension, diabetes, and dyslipidemia (Courcoulas *et al.* 2018) by reducing food intake and altering gut hormone and bile acid levels, energy metabolism, and the gut microbiota (Debedat *et al.* 2019). Several studies have shown that the microbial community structure is altered after bariatric surgery. Nevertheless, the results and conclusions were inconsistent among reports possibly because of differences in study designs, sample sizes, subject races, geography, and diet (Table 2). Ryan *et al.* demonstrated that the metabolic effects of sleeve gastrectomy are abolished in FXR-disrupted mice, suggesting that FXR signaling contributes to body weight reduction and improvement in glycemic control after bariatric surgery (Ryan *et al.* 2014). Another group elucidated the mechanism by which Roux-en-Y gastric bypass (RYBG) improves metabolism in rodents. Specifically, it decreases bile acids and increases glucagon-like peptide 1 (GLP-1) via L-cell proliferation. The decrease in bile acids, associated with a decline in *Lactobacillus* abundance, results in intestinal L-cell proliferation, an increase in GLP-1 secretory capacity, and improvements in glycemic control (Dang *et al.* 2021). Torsten *et al.* analyzed 40 pre-RYBG and post-RYBG cases and showed that RYBG improved chronic inflammation but increased proinflammatory Proteobacteria. Lipopolysaccharide (LPS) and flagellin-specific immunoglobulin A (IgA) were increased, but the total fecal IgA content remained unchanged. Hence, an increase in intestinal IgA after bariatric surgery neutralized immunogenic bacteria and their components, leading to the improved systemic inflammation (Scheithauer *et al.* 2022). Thus, metabolic improvements mediated by bariatric surgery are mainly associated with changes in incretin secretion and immune activities that are mediated by microbial alterations.

Gut microbiota and glucose metabolism

Research on the relationships among gut microbiota, diabetes, and obesity has progressed. Gut microbiota differ by nationality and race in patients with type 2 diabetes (T2DM). A metagenomic analysis of a Chinese T2DM cohort conducted by Qin *et al.* revealed decreased butyrate-producing bacteria, increased methane metabolism and hydrogen sulfide production, and upregulation of the

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Table 1 Characteristics of microbiota associated with obesity among different countries. Characteristics of the microbial composition in obese individuals vary by race and region.

Age	Number	Country	Obese vs normal (excerpted bacteria is shown)		Other phenotype	References
Adults	10 obese/20 lean	Japan	↑*Firmicutes* ↑*Fusobacteria* ↑*Alistipes* ↑*Anaerococcus* ↑*Corpococcus* ↑*Fusobacterium* ↑*Parvimonas*	↓*Bacteroides* ↓*Desulfovibrio* ↓*Faecalibacterium* ↓*Lachnoanaerobaculum* ↓*Olsenella* ↓*Faecalibacterium prausnitzii*	*Bacteroidetes/Firmicutes* (*B/F*) ratio not significant	Andoh *et al.* (2016)
Adults	20 normal weight/20 obese/9 anorexic	France	↑*Lactobacillus* (not significant)	↓*Bacteroidetes*	*Firmicutes* data are similar in the three categories	Armougom *et al.* (2009)
Adults	20 obese/20 normal weight	Italy	↑*Veillonellaceae* ↑*Dialister spp.*	↓*Oscillospira* genus	↓a-diversity	Borgo *et al.* (2013)
Adults	17 obese/25 obese with metabolic syndrome/ 25 healthy	Mexico	↑*Faecalibacterium* ↑*Roseburia* ↑*Lachnospira* ↑*Coprococcus* ↑*Bilophila*	↓*Erysipelotrichaceae*		Chávez-Carbajal *et al.* (2019)
Adults	3 obese/24 overweight/106 normal weight/7 underweight	Italy	↑*Selenomonas* ↑*Megasphaera* ↑*Streptococcus* ↑*Dorea* ↑*Lachnobacterium* ↑*Jannaschia* ↑*Dialister* ↑*Eubacterium*	↓*Paraprevotella*	*Firmicutes/Bacteroidetes* (*F/B*) ratio not significant	Gallè *et al.* (2020)
Adults	24 obese/28 overweight/31 normal weight/21 underweight	Saudi Arabia	↑*Lentisphaerae*			Harakeh *et al.* (2020)
Adults	1674 subjects	USA	↑*Acidaminococcus* ↑*Megasphaera* ↑*Catenibacterium* ↑*Prevotella* ↑*Streptococcus*	↓*Oscillospira* ↓*Cloacibacillus* ↓*Anaerotruncus* ↓*Ruminococcus* ↓*Coprobacillus* ↓*Eggerthella*		Kaplan *et al.* (2019)
Adults	33 obese/23 non-obese	Japan	↑*Blautia hydrogenotorophica* ↑*Coprococcus catus* ↑*Eubacterium ventriosum* ↑*Ruminococcus bromii* ↑*Ruminococcus obeum*	↓*Bacteroides* ↓*Bacteroides faecichinchillae* ↓*Bacteroides thetaiotaomicron* ↓*Blautia wexlerae* ↓*Clostridium bolteae* ↓*Flavonifractor plautii*	↑*F/B* ratio, ↑Shannon–Wiener index	Kasai *et al.* (2015)
Adults	167 normal/396 overweight or obese with different BMI history	Finland	↑*Roseburia* ↑*Blautia*	↓*Rikenellaceae* ↓*Oscillospira*	↓Shannon index	Loftfield *et al.* (2020)
Adults	52 African American/46 Caucasian American	USA			*Bacteroidetes* numbers not significant	Mai *et al.* (2009)
Adults	170 HIV-negative women	South Africa	↑*Prevotella*			Oduaran *et al.* (2020)
Adults	531 subjects (132 obese/100 normal weight)	Finland	↑*Tissierellacea* ↑*Blautia*	↓*Archaea (Methanobrevibacter)*	*F/B* ratio not significant	Org *et al.* (2017)
Adults	248 subjects (83 obese or overweight/83 normal weight/82 underweight)	Bangladesh	↑*Acidaminococcus*	↓*Oscillospira*	↓Chao1 richness, ↓Shannon diversity index	Osborne *et al.* (2020)

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Table 1 (Continued).

Age	Number	Country	**Obese vs normal** (excerpted bacteria is shown)		Other phenotype	References
Adults	767 subjects	Japan		↓*Alistipes* ↓*Clostridium XlVb* ↓*Erysipelotrichaceae incertae sedis* ↓*Lactobacillus*	*Blautia hansenii* and *Blautia producta* were negatively associated with changes in VFA	Ozato *et al.* (2022)
Adults	1001 subjects	Japan	↑*Prevotella* in men ↑*Clostridium sensu stricto, Roseburia* ↑*Ruminococcus,* and *Megasphaera* in women	↓*Blautia* and *Bifidobacterium* in men ↓*Blautia, Bifidobacterium, Eggerthella, Sutterella*, and *Erysipelotrichaceae incertae sedis* in women	*Blautia* was the only microbiota significantly and negatively associated with VFA, regardless of sex	Ozato *et al.* (2019)
Adults	5 obese/5 surgically treated/5 obese/5 lean	India	↑*Bacteroides*			Patil *et al.* (2012)
Adults	599 subjects (142 obese/246 overweight/211 normal weight)	USA	↑*Bacilli* ↑*Streptococcaceae* ↑*Lactobacillaceae*	↓*Clostridia* including *Christensenellaceae* ↓*Clostridiaceae* and *Dehalobacteriaceae*	↓Number of OTUs, ↓Shannon index	Peters *et al.* (2018)
Adults	32 obese/32 normal weight	Mexico	↑*Clostridum leptum* ↑*Lactobacillus*	↓*Prevotella* ↓*Escherichia coli*		Radilla-Vazquez *et al.* (2016)
Adults	60 subjects (25 obese with T2D/25 obese non-diabetic/5 non-obese with T2D/5 control)	Egypt	↑*Prevotella* ↑*Clostridium* ↑*Faecalibacterium* ↑*Staphylococcus*	↓*Akkermansia*	↑*F/B* ratio	Salah *et al.* (2019)
Adults	33 obese/35 overweight/30 normal weight	Germany	↑*Bacteroidetes*	↓*Bifidobacterium* ↓*Methanobrevibacter spp.* ↓*Ruminococcus flavefaciens* subgroup	↓*F/B* ratio	Schwiertz *et al.* (2010)
Adults	20 twin pairs	Finland			The abundance and diversity of the bacterial groups not significant	Simoes *et al.* (2013)
Adults	1280 subjects (633 lean non-diabetic/494 obese non-diabetic/153 obese with T2D)	Germany	↑*Bacteroides thetaiotaomicron*	↓*Faecalibacterium prausnitzii*		Thingholm *et al.* (2019)
Adults	20 concordant/20 discordant BMI twin pairs	Netherlands	↑*Eubacterium ventriosum*, ↑*Roseburia intestinalis*	↓*Oscillospiraguillermondii*	*B/F* ratio not significant	Tims *et al.* (2013)
Adults	52 obese/52 normal weight	China		↓*Clostridium perfringens*, ↓*Bacteroides*		Zuo *et al.* (2011)
Children	15 obese/13 normal weight	India	↑*Fecalibacterium prausntzi*			Balamurugan *et al.* (2010)
Children	25 overweight/7 obese/24 normal weight	Finland	↑*Staphylococcus aureus*	↓*Bifidobacteria*		Kalliomaki *et al.* (2008)
Children	15 obese/15 normal weight	Swiss			No significant quantitative differences	Payne *et al.* (2011)
Children	138 subjects	Flanders	↑*Bacteroides fragilis*	↓*Staphylococcus*		Vael *et al.* (2011)

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expression of genes regulating oxidative stress resistance (Qin *et al.* 2012). A shotgun metagenomic analysis conducted by Karlsson *et al.* on a cohort of 145 European women with a normal status, impaired glucose tolerance, and T2DM characterized compositional and functional alterations in the gut microbiota. They established a random forest model based on the metagenomic data that could be applied to patients with impaired glucose tolerance. However, this model could not be consistently applied to the cohort of Qin *et al.* (Karlsson *et al.* 2013). Hence, metagenomic profiles differ between diabetic and healthy individuals and can be a good predictive tool for impaired glucose metabolism, but regional and racial differences in gut microbiota must be considered. There is nonetheless a strong link between microbial dysfunction and impaired glucose metabolism. Moreover, gut dysbiosis is already present at the impaired glucose tolerance stage, even before T2DM onset. A metagenomic analysis conducted by Wu *et al.* on ~1500 Swedish subjects showed that prediabetes and T2DM are characterized by alterations in the gut microbiota and their functional genes and decreases in the abundance of butyrate-producing bacteria. The authors constructed a machine learning model using a random forest algorithm to distinguish individuals with prediabetes or diabetes and showed that bacterial compositional/functional alterations are associated with insulin resistance at the impaired glucose tolerance stage (Wu *et al.* 2020). Gut microbiota analysis could help diagnose early-stage glucose intolerance and improve early intervention. Based on these studies, the construction of a machine learning model to predict the development of T2DM in healthy and prediabetic patients has been challenging (Aasmets *et al.* 2021). However, it could serve as a predictive marker for individual risks of metabolic disorders.

Gut microbiota are also implicated in type 1 diabetes (T1DM). Gavin *et al.* proteomically analyzed stool samples of patients with T1DM and detected proteins associated with intestinal inflammation, reduced intestinal barrier functions, and changes in gut microbiota even before disease onset (Gavin *et al.* 2018). Tracking the gut microbiota of children congenitally predisposed to T1DM revealed reduced microbial diversity and transient spikes in *Ruminococcus gnavus* and *Streptococcus infantarius* abundance before disease onset (Kostic *et al.* 2015). A metagenomic analysis of 74 T1DM patients and 296 healthy controls showed microbial differences between groups; *P. copri* and *Eubacterium siraeum* were more common in T1DM, whereas Firmicutes and *Faecalibacterium prausnitzii* were more prevalent in controls. In this study, altered bacterial species and metabolic pathways were associated with host glycemic control (Shilo *et al.* 2022). Thus, changes in gut microbiota and the ambient environment might be associated with T1DM development. As an immunological mechanism, the commensal gut bacterium *Parabacteroides distasonis* has an epitope similar to the insulin beta chain, the target protein of the autoimmune response in T1DM. The presence of this bacteria could cause the production of autoimmune antibodies leading to the pathogenesis of T1DM (Girdhar *et al.* 2022). However, some reports suggest that the microbiota inhibit the development of T1DM. MyD88-KO NOD mice develop T1DM in a GF environment but not in the presence of intestinal bacteria (Wen *et al.* 2008). Shimokawa *et al.* reported that *Ruminococcus* spp. might prevent the onset of T1DM by inducing CD8+ regulatory T cells (Shimokawa *et al.* 2020), suggesting a close interaction between the microbiota and immune system and the onset of T1DM. This evidence clearly implicates the involvement of microbiota in glucose metabolism. The mechanisms by which microbiota contribute to glucose metabolism are described in the following sections.

Short-chain fatty acids

SCFAs exert their metabolic effects through G protein-coupled fatty acid receptors such as GPR41 and GPR43. GPRs are involved in GLP-1 and peptide YY (PYY) secretion in intestinal L cells (Samuel *et al.* 2008, Tolhurst *et al.* 2012) to regulate insulin secretion by stimulating pancreatic β-cells and energy balance (Natarajan & Pluznick 2014, McNelis *et al.* 2015). Mice lacking these receptors exhibit reduced GLP-1 and PYY secretion after SCFA administration (Psichas *et al.* 2015, Koh *et al.* 2016, Brooks *et al.* 2017). Butyrate enhances thermogenesis in skeletal muscle and brown adipose tissue (BAT), improves glucose metabolism by upregulating PGC-1α, AMPK, and p38 expression (Gao *et al.* 2009), promotes energy expenditure via GPR41 in sympathetic ganglia, and contributes to *in vivo* energy homeostasis (Inoue *et al.* 2012). Kimura *et al.* also reported that SCFAs regulate energy metabolism by promoting sympathetic activation via GPR41 signaling (Kimura *et al.* 2011). SCFA-mediated GPR43 activation in adipocytes inhibits insulin signaling by suppressing Akt phosphorylation to reduce fat accumulation (Kimura *et al.* 2013). This evidence suggests that increasing SCFAs in the body might be metabolically beneficial. In addition to the intake of non-digestible polysaccharides, physical activity (Magzal *et al.* 2022) and cold stimuli (Ichikawa *et al.* 2021) are implicated in SCFA production. Prior attempts have been made to ameliorate

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Table 2 Characteristics of microbiota after bariatric surgery in different countries.

Operation	Number	Country	Major bacterial changes after surgery		Diversity after surgery	References
Roux-en-Y gastric bypass	14	Brazil	↓F/B ratio		↑OTUs richness	Al Assal *et al.* (2020)
Gastric banding or Roux-en-Y gastric bypass	24	France	↑*Butyricimonas virosa* , 11 altered after Roux-en-Y and 2 altered after gastric banding		↑Microbial gene richness	Aron-Wisnewsky *et al.* (2019)
Roux-en-Y gastric bypass or sleeve gastrectomy	53	China	33 altered after sleeve and 19 altered after Roux-en-Y		↑Richness and evenness	Chen *et al.* (2020)
Roux-en-Y gastric bypass	24	China	↑*Bacteroidetes* ↑*Bifidobacterium*			Chen *et al.* (2017)
Roux-en-Y gastric bypass or sleeve gastrectomy	197	France, Switzerland, USA	↑*Akkermansia muciniphila*		↑Shannon index and gene richness	Farin *et al.* (2020)
Sleeve gastrectomy	10	Japan	↑*Bacteroidetes* ↑*Fusobacteria*		↑Faith PD ↑Chao1 ↑Shannon index	Fukuda *et al.* (2022)
Roux-en-Y gastric bypass	30	France	↑*Bacteroides/Prevotella* ↑*E. coli*	↓*Bifidobacterium/ Lactobacillus/ Leuconostoc* ↓*Pediococcus*		Furet *et al.* (2010)
Roux-en-Y gastric bypass or sleeve gastrectomy	31	Korea	↑*Streptococcus* ↑*Oscillospira* ↑*Akkermansia*	↓*Prevotella* ↓*Turicibacter* ↓*Bifidobacterium*	↑Observed species	Han *et al.* (2022)
Sleeve gastrectomy or sleeve with duodenojejunal bypass or gastric banding	44	Japan	↑*Bacteroidetes* ↑*Lactobacillales* ↑*Enterobacteriales*			Kikuchi *et al.* (2018)
Roux-en-Y gastric bypass	30	France	↑*Proteobacteria* ↑*Bacteroides* ↑*Escherichia*	↓*Lactobacillus* ↓*Dorea* ↓*Blautia* ↓*Bifidobacterium*	↑Richness	Kong *et al.* (2013)
Sleeve gastrectomy	23	China			↑α-diversity	Liu *et al.* (2017)
Roux-en-Y gastric bypass or sleeve gastrectomy	28	Spain	(Sleeve) ↑*Akkermansia* ↑*Haemophilus* (Roux-en-Y) ↑*Clostridium* ↑*Fusobacterium*	(Sleeve) ↓*Anaerostip* ↓*Bifidobacterium* (Roux-en-Y) ↓*Bifidobacterium* ↓*Collinsella*		Sanchez-Alcoholado *et al.* (2019)
Roux-en-Y gastric bypass or sleeve gastrectomy	45	Poland	↑*Bacteroidetes* ↑*Bacteroidales* ↑*Bacteroidia* ↑*Prevotellaceae* ↑*Rikenellaceae*	↓*Firmicutes* ↓*Clostridiales* ↓*Clostridia* ↓*Lachnospiraceae* ↓*Blautia*		Stefura *et al.* (2022)
Roux-en-Y gastric bypass	40	Netherlands	↑*Proteobacteria* ↑*Akkermansia*	↓*Roseburia* ↓*Bacteroides* ↓*Faecallibacterium*	↑α-diversity	Scheithauer *et al.* (2022)

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metabolic diseases using SCFA-related interventions. Emanuel *et al.* reported that infusions of SCFAs, such as acetate, butyrate, and propionate, into the distal colon increase fasting fat oxidation, resting energy expenditure, and PYY concentrations in men (Canfora *et al.* 2017).

FXR/TGR5/bile acids

FXR (NR1H4) is a member of the nuclear receptor superfamily of TFs that senses and regulates bile acid, lipid, and glucose metabolism (Matsubara *et al.* 2013, Sayin *et al.* 2013). Gut microbiota regulate FXR signaling by reducing the FXR antagonist muricholic acid (Sayin *et al.* 2013). Mice lacking FXR signaling exhibit dyslipidemia (Sinal *et al.* 2000). The FXR agonists 6-ethyl-chenodeoxycholic acid, fexaramine, and GW 4064 and FXR overexpression improve the metabolic profile in a mouse obesity model (Zhang *et al.* 2006, Cipriani *et al.* 2010, Fang *et al.* 2015). In contrast, FXR-KO mice display improvements in metabolic disturbances induced by a high-fat diet (Prawitt *et al.* 2011) and increased GLP-1 secretion (Trabelsi *et al.* 2015). Jiang *et al.* reported that oral administration of the selective high-affinity FXR inhibitor glycine-β-muricholic acid ameliorates obesity, insulin resistance, and fatty liver (Jiang *et al.* 2015). These conflicting results suggest that FXR plays complex roles in the etiology of metabolic dysfunction and that its effects on metabolism vary in an organ-dependent manner. Future research should aim to clarify the significance of FXR in glucose metabolism.

TGR5 is a membrane-bound or G-protein bile acid-activated receptor (Kawamata *et al.* 2003). *TGR5* expression is ubiquitous in human and rodent tissues and is upregulated in the lungs, liver, gallbladder, spleen, adipose tissue, CNS, and intestine (Duboc *et al.* 2014). Bile acids stimulate the secretion of intestinal hormones that regulate blood glucose and appetite (Adrian *et al.* 2012), such as GLP-1 and PYY. The latter is a centrally acting appetite suppressant (Kuhre *et al.* 2018). Bile acids also affect metabolism via TGR5 receptors in BAT. In mice, bile acid-induced TGR5 activation in BAT increases energy expenditure by inducing the cAMP-dependent thyroid hormone-activating enzyme known as type 2

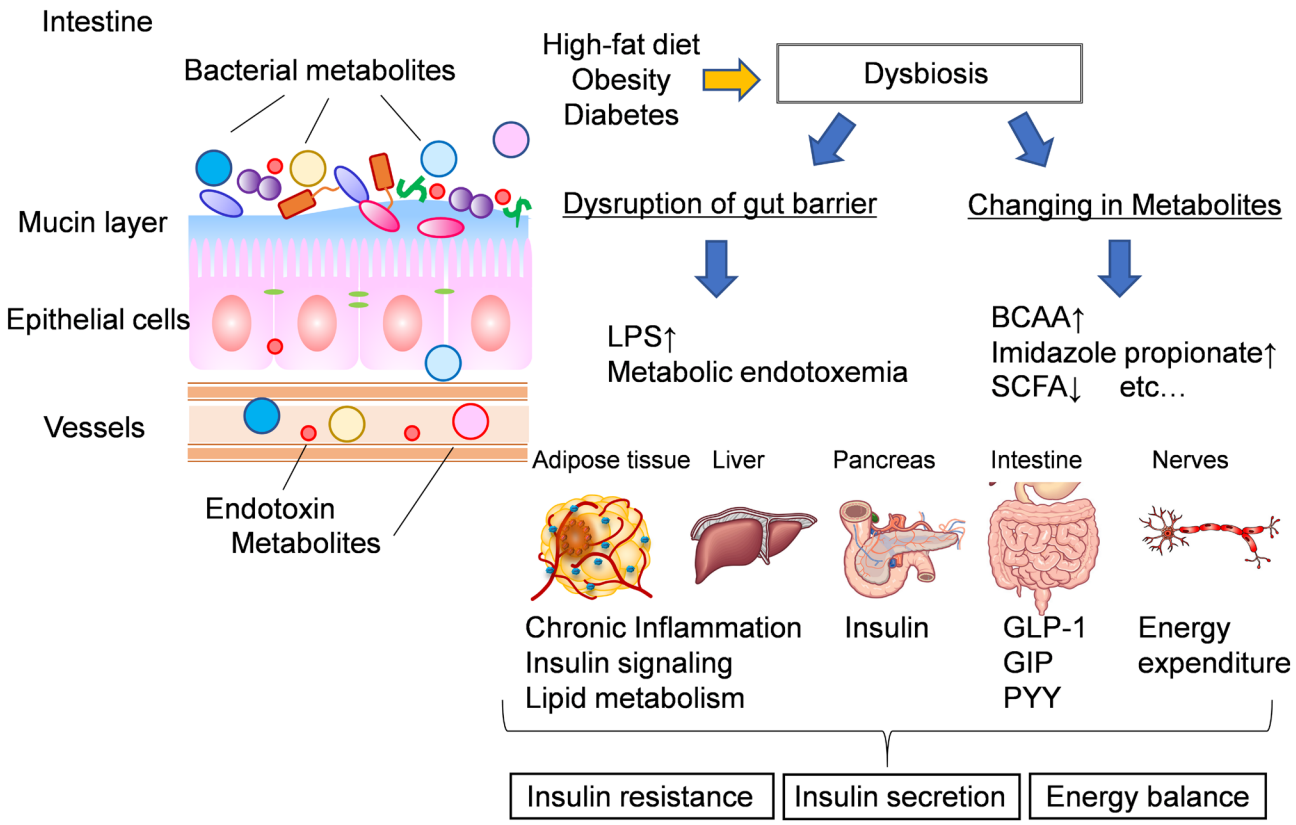

Figure 3
Mechanisms of dysbiosis-induced impaired glucose metabolism. There are two major mechanisms of impaired glucose metabolism mediated by dysbiosis. One is the disruption of the intestinal barrier function, which causes LPS to enter circulation, inducing chronic inflammation and exacerbating insulin resistance, and the other is the effect of microbial metabolites. Increased branched-chain amino acids (BCAAs), imidazole propionate, and decreased short-chain fatty acids, such as butyrate, can affect insulin resistance in various organs, insulin secretion, and energy expenditure.

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iodothyronine deiodinase (D2), leading to improved obesity tolerance and metabolic disease. This increase in TGR5-mediated energy expenditure is abolished in D2$^{-/-}$ mice. The authors also confirmed that bile acid induces D2 expression and elevated oxygen consumption in a TGR-dependent fashion in human skeletal muscle cells. Hence, bile acid-TGR5-cAMP-D2 signaling might be protective against obesity in humans (Watanabe *et al.* 2006).

In vitro, bile acids could decrease endoplasmic reticulum (ER) stress, which is increased in obesity and closely related to insulin resistance etiology. ER stress blocks insulin signaling by overactivating c-Jun N-terminal kinase and promoting the serine phosphorylation of insulin receptor substrate-1 (Ozcan *et al.* 2004), inducing β-cell dysfunction and diabetes onset. Ozcan *et al.* reported that taurine-bound ursodeoxycholic acid reduces ER stress in cultured cells and whole animals. The administration of this conjugated bile acid to obese and diabetic mice normalizes hyperglycemia, restores systemic insulin sensitivity, improves fatty liver, and enhances insulin actions in liver, muscle, and adipose tissues (Ozcan *et al.* 2006). Alterations to the bile acid profile through microbiota modification have been investigated for the improvement of metabolic disorders. Jielong *et al.* reported that phenolic blueberry extracts increase energy expenditure in BAT and improve hepatic lipid metabolism via TGR5 and FXR. These effects are strongly correlated with bile acid regulation, reduction of the FXR inhibitors TαMCA and TβMCA, and expansion of the gut microbiota, including *Bifidobacterium* spp. and *Lactobacillus* spp. Antibiotic administration attenuates the aforementioned metabolic effects (Guo *et al.* 2019).

Chronic antibiotic treatments such as vancomycin or metronidazole change bile acid composition due to a loss of intestinal bacteria harboring bile acid-converting enzymes and resulted in the inhibition of inflammatory secondary bile acids production. Furthermore, the changes in the bile acid composition induced anti-inflammatory TGR5 in the liver. As a result, antibiotic treatment mitigated high-fat diet-induced systemic inflammation in C57BL6 mice. However, these effects were not observed in 129S1 or 129S6 mice. Hence, antibiotic modification of the gut microbiota and changes in bile acid and inflammatory signaling can improve glucose metabolism. However, these effects vary by host genetic background and inflammatory potential (Fujisaka *et al.* 2016).

Imidazole propionate

Imidazole propionate (ImP) is a histidine (His) metabolite produced by the gut microbiota. A study on 1990 subjects in 3 European countries showed elevated ImP levels in the serum of prediabetic and T2DM patients. Nevertheless, there was no correlation between His consumption and ImP levels, suggesting that the gut microbiota is largely responsible for increases in ImP (Molinaro *et al.* 2020). ImP exacerbates insulin resistance by activating the mTOR pathway and inhibiting insulin signaling (Koh *et al.* 2018). Thus, ImP might contribute to metabolic disease progression. *Clostridium bolteae*, *Cenarchaeum symbiosum*, and *R. gnavus* might affect ImP levels. High saturated fatty acid, low fiber, and low unsaturated fatty acid diets are associated with elevated ImP. Furthermore, ImP levels are high in patients with poorly controlled T2DM, and ImP inhibits the action of metformin. The glucose-lowering effect of metformin is abolished in mice pretreated with ImP, via the inhibition of AMPK phosphorylation in a p38γ-dependent manner (Koh *et al.* 2020). Thus, metabolites produced from AAs by gut microbiota not only modulate insulin signaling but also influence drug action.

Impaired gut barrier function

Dysbiosis causes so-called 'leaky gut' syndrome wherein the intestinal barrier function is impaired, with increased permeability, via decreases in intestinal mucus and tight junction protein content in the intestinal epithelium. With increased intestinal permeability, the bacterial cell wall component endotoxin enters circulation and causes hyper-endotoxemia. Endotoxin activates Toll-like receptor (TLR) 4, which in turn promotes chronic inflammation in the adipose tissue and liver and exacerbates obesity-induced insulin resistance (Amar *et al.* 2008, Gummesson *et al.* 2011, Lassenius *et al.* 2011). Impaired barrier functions can be treated by microbial intervention. Amer *et al.* found that administration of the probiotic *Bifidobacterium animalis* prevents LPS invasion into circulation and improves the inflammatory and metabolic status of diet-induced obese mice (Amar *et al.* 2011). In humans, supplementation with the probiotics *Bacillus indicus*, *Bacillus subtilis*, *Bacillus coagulans*, *Bacillus licheniformis*, and *Bacillus clausii* reduces serum endotoxin levels by 42% (McFarlin *et al.* 2017). Thus, intervention with gut bacteria, to strengthen gut barrier functions, is a novel therapeutic approach.

A. muciniphila is an oval, nonmotile, Gram-negative bacterium of phylum Verrucomicrobia. In 2004, Derrien isolated it from healthy human feces inoculated on media containing mucin as the nutrient source (Derrien *et al.* 2004). The genus *Akkermansia* (of *A. muciniphila*) is derived from that of the Dutch microbial ecologist Antoon Akkermans. In both obese humans and rodents,

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reductions in *A. muciniphila* abundance have been reported (Everard *et al.* 2013, Le Chatelier *et al.* 2013). By contrast, therapeutic interventions that increase *A. muciniphila* are associated with improvements in obesity or glucose metabolism. For example, when mice fed a high-fat, high-sucrose diet are treated with polyphenol-rich cranberry extract, the abundance of *A. muciniphila* is increased, which is associated with improved obesity, insulin resistance, and intestinal inflammation (Anhe *et al.* 2015). Bofutsushosan is a Chinese herbal medicine that improves insulin resistance by increasing *A. muciniphila* and improving intestinal barrier functions (Fujisaka *et al.* 2020). Metformin also modulates the gut microbiota, promotes *A. muciniphila* growth, and improves glucose metabolism (Shin *et al.* 2014, de la Cuesta-Zuluaga *et al.* 2017). Prebiotics such as isomalto-oligosaccharides and red pitaya betacyanin significantly increase *A. muciniphila* and improve glucose metabolism (Song *et al.* 2016, Singh *et al.* 2017). *A. muciniphila* helps maintain intestinal and mucosal epithelial cell functions and suppresses intestinal inflammation leading to improved metabolism in diabetic and obese patients (Everard *et al.* 2013, Plovier *et al.* 2017, Ansaldo *et al.* 2019). Crala *et al.* reported that pasteurized *A. muciniphila* administration decreases body weight in a mouse diet-induced obesity model by increasing systemic energy expenditure and fecal energy excretion (Depommier *et al.* 2020). In a randomized, double-blind, controlled trial on *A. muciniphila* in humans, *A. muciniphila* transplantation improved weight loss, total cholesterol levels, and insulin resistance compared to those with a placebo. Furthermore, pasteurized *A. muciniphila* had higher efficacy than live *A. muciniphila*. Hence, *A. muciniphila* administration might be both a safe and effective treatment (Plovier *et al.* 2017, Depommier *et al.* 2019). Kim *et al.* demonstrated that whereas live *A. muciniphila* suppresses diet-induced fatty liver (Kim *et al.* 2020), pasteurized *A. muciniphila* improves intestinal barrier functions but does not impede the progression of nonalcoholic steatohepatitis (Morrison *et al.* 2022). These results suggest that live and pasteurized *A. muciniphila* are beneficial for obesity-related metabolic disorders but have different effects on the host, and further research is required to clarify them.

Gut microbiota and hepatic diseases

The liver receives >70% of its blood flow from the portal vein and is continuously exposed to nutrients and bacteria-related substances from the intestine. Therefore, compositional and functional changes in microbiota play important roles in hepatic disease pathogenesis. A healthy intestinal barrier maintains its function and prevents gut microbiota from reaching the liver. However, when the barrier is impaired by various environmental factors, such as an unbalanced diet, gut bacteria and/or their components can be translocated to the liver. TLRs and pathogen recognition receptors, such as the inflammasome, recognize bacterial antigens and enhance the production of proinflammatory cytokines by activating hepatic macrophages and the immune response (Regnier *et al.* 2021). Dysbiosis is associated with the pathological conditions of various hepatic diseases such as alcoholic hepatitis, nonalcoholic fatty liver disease (NAFLD), cirrhosis, and hepatocellular carcinoma (HCC). Chronic alcohol intake has been reported to cause dysbiosis and impair intestinal barrier functions in animals and humans (Yan *et al.* 2011, Mutlu *et al.* 2012). *Enterococcus faecalis* is increased in alcoholic hepatitis patients and secretes cytolysin, which causes hepatocyte death and liver injury. In one study, bacteriophages targeting cytolysin-producing *E. faecalis* abolished ethanol-induced liver damage (Duan *et al.* 2019). Future research should establish whether this approach improves alcoholic hepatitis in humans.

Loomba *et al.* assessed hepatic fibrosis severity based on biopsies of 86 American patients with NAFLD. Whole-genome shotgun sequencing of stool samples revealed that advanced hepatic fibrosis is associated with increased Proteobacteria and decreased Firmicutes, *Ruminococcus obeum*, and *Eubacterium rectale* abundance (Loomba *et al.* 2017). In contrast, Boursier *et al.* showed that the relative abundances of Bacteroides and *Ruminococcus* were increased and that of *Prevotella* was decreased in French patients with advanced hepatic fibrosis (Boursier *et al.* 2016). Race, geographical factors, diet, and patient enrollment criteria also substantially influence gut microbial responses and must be considered. However, changes in gut microbiota can cause hepatic fibrosis. In the future, gut microbiota could be used to predict the risk of hepatic diseases.

Gut microbiota are also implicated in the development of HCC. Deoxycholic acid is increased in obesity-induced gut dysbiosis, induces the senescence-associated secretory phenotype in hepatic stellate cells, and is associated with various proinflammatory and tumor-promoting factors in the liver. These processes promote HCC development in mice exposed to chemical carcinogens (Yoshimoto *et al.* 2013). Ma *et al.* demonstrated that hepatic CXCR-positive NKT cells have antitumor

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efficacy in mouse spontaneous HCC and metastatic liver cancer models. Primary bile acids upregulate, whereas bacteria-derived secondary bile acids downregulate, CXCL16 expression, which in turn induces hepatic NKT cells. *Clostridium scindens* produces secondary bile acids that inhibit hepatic NKT cells (Ma *et al.* 2018). These studies demonstrate that the gut microbiota is vital in regulating hepatocarcinogenesis through bile acid signaling.

Conclusions

In recent years, as our understanding of the physiological role of the gut microbiota has advanced, the mechanisms by which its dysfunction can cause metabolic disorders have gained clarity (Fig. 3). Future research should aim to elucidate the complex roles of the gut microbiota in these processes. These discoveries might lead to the application of the gut microbiota and their metabolites for the future treatment of metabolic diseases.

Declaration of interest

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References

Aasmets O, Lull K, Lang JM, Pan C, Kuusisto J, Fischer K, Laakso M, Lusis AJ & Org E 2021 Machine learning reveals time-varying microbial predictors with complex effects on glucose regulation. *mSystems* **6** e01191-20. (https://doi.org/10.1128/mSystems.01191-20)

Adrian TE, Gariballa S, Parekh KA, Thomas SA, Saadi H, Al Kaabi J, Nagelkerke N, Gedulin B & Young AA 2012 Rectal taurocholate increases L cell and insulin secretion, and decreases blood glucose and food intake in obese type 2 diabetic volunteers. *Diabetologia* **55** 2343–2347. (https://doi.org/10.1007/s00125-012-2593-2)

Al Assal K, Prifti E, Belda E, Sala P, Clement K, Dao MC, Dore J, Levenez F, Taddei CR, Fonseca DC, *et al.* 2020 Gut microbiota profile of obese diabetic women submitted to Roux-en-Y gastric bypass and its association with food intake and postoperative diabetes remission. *Nutrients* **12** 278. (https://doi.org/10.3390/nu12020278)

Amar J, Burcelin R, Ruidavets JB, Cani PD, Fauvel J, Alessi MC, Chamontin B & Ferrieres J 2008 Energy intake is associated with endotoxemia in apparently healthy men. *American Journal of Clinical Nutrition* **87** 1219–1223. (https://doi.org/10.1093/ajcn/87.5.1219)

Amar J, Chabo C, Waget A, Klopp P, Vachoux C, Bermudez-Humaran LG, Smirnova N, Berge M, Sulpice T, Lahtinen S, *et al.* 2011 Intestinal mucosal adherence and translocation of commensal bacteria at the early onset of type 2 diabetes: molecular mechanisms and probiotic treatment. *EMBO Molecular Medicine* **3** 559–572. (https://doi.org/10.1002/emmm.201100159)

An D, Oh SF, Olszak T, Neves JF, Avci FY, Erturk-Hasdemir D, Lu X, Zeissig S, Blumberg RS & Kasper DL 2014 Sphingolipids from a symbiotic microbe regulate homeostasis of host intestinal natural killer T cells. *Cell* **156** 123–133. (https://doi.org/10.1016/j.cell.2013.11.042)

Andoh A, Nishida A, Takahashi K, Inatomi O, Imaeda H, Bamba S, Kito K, Sugimoto M & Kobayashi T 2016 Comparison of the gut microbial community between obese and lean peoples using 16S gene sequencing in a Japanese population. *Journal of Clinical Biochemistry and Nutrition* **59** 65–70. (https://doi.org/10.3164/jcbn.15-152)

Anhe FF, Roy D, Pilon G, Dudonne S, Matamoros S, Varin TV, Garofalo C, Moine Q, Desjardins Y, Levy E, *et al.* 2015 A polyphenol-rich cranberry extract protects from diet-induced obesity, insulin resistance and intestinal inflammation in association with increased Akkermansia spp. population in the gut microbiota of mice. *Gut* **64** 872–883. (https://doi.org/10.1136/gutjnl-2014-307142)

Ansaldo E, Slayden LC, Ching KL, Koch MA, Wolf NK, Plichta DR, Brown EM, Graham DB, Xavier RJ, Moon JJ, *et al.* 2019 Akkermansia muciniphila induces intestinal adaptive immune responses during homeostasis. *Science* **364** 1179–1184. (https://doi.org/10.1126/science.aaw7479)

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** e7125. (https://doi.org/10.1371/journal.pone.0007125)

Aron-Wisnewsky J, Prifti E, Belda E, Ichou F, Kayser BD, Dao MC, Verger EO, Hedjazi L, Bouillot JL, Chevallier JM, *et al.* 2019 Major microbiota dysbiosis in severe obesity: fate after bariatric surgery. *Gut* **68** 70–82. (https://doi.org/10.1136/gutjnl-2018-316103)

Atarashi K, Suda W, Luo C, Kawaguchi T, Motoo I, Narushima S, Kiguchi Y, Yasuma K, Watanabe E, Tanoue T, *et al.* 2017 Ectopic colonization of oral bacteria in the intestine drives TH1 cell induction and inflammation. *Science* **358** 359–365. (https://doi.org/10.1126/science.aan4526)

Atarashi K, Tanoue T, Ando M, Kamada N, Nagano Y, Narushima S, Suda W, Imaoka A, Setoyama H, Nagamori T, *et al.* 2015 Th17 cell induction by adhesion of microbes to intestinal epithelial cells. *Cell* **163** 367–380. (https://doi.org/10.1016/j.cell.2015.08.058)

Atarashi K, Tanoue T, Shima T, Imaoka A, Kuwahara T, Momose Y, Cheng G, Yamasaki S, Saito T, Ohba Y, *et al.* 2011 Induction of colonic regulatory T cells by indigenous Clostridium species. *Science* **331** 337–341. (https://doi.org/10.1126/science.1198469)

Backhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF & Gordon JI 2004 The gut microbiota as an environmental factor that regulates fat storage. *PNAS* **101** 15718–15723. (https://doi.org/10.1073/pnas.0407076101)

Backhed F, Manchester JK, Semenkovich CF & Gordon JI 2007 Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *PNAS* **104** 979–984. (https://doi.org/10.1073/pnas.0605374104)

Balamurugan R, George G, Kabeerdoss J, Hepsiba J, Chandragunasekaran AM & Ramakrishna BS 2010 Quantitative differences in intestinal Faecalibacterium prausnitzii in obese Indian children. *British Journal of Nutrition* **103** 335–338. (https://doi.org/10.1017/S0007114509992182)

Barcenilla A, Pryde SE, Martin JC, Duncan SH, Stewart CS, Henderson C & Flint HJ 2000 Phylogenetic relationships of butyrate-producing bacteria from the human gut. *Applied and Environmental Microbiology* **66** 1654–1661. (https://doi.org/10.1128/AEM.66.4.1654-1661.2000)

Batch BC, Shah SH, Newgard CB, Turer CB, Haynes C, Bain JR, Muehlbauer M, Patel MJ, Stevens RD, Appel LJ, *et al.* 2013 Branched chain amino acids are novel biomarkers for discrimination of metabolic wellness. *Metabolism: Clinical and Experimental* **62** 961–969. (https://doi.org/10.1016/j.metabol.2013.01.007)

Bellerba F, Muzio V, Gnagnarella P, Facciotti F, Chiocca S, Bossi P, Cortinovis D, Chiaradonna F, Serrano D, Raimondi S, *et al.* 2021 The association between vitamin D and gut microbiota: a systematic review of human studies. *Nutrients* **13** 3378. (https://doi.org/10.3390/nu13103378)

Boets E, Gomand SV, Deroover L, Preston T, Vermeulen K, De Preter V, Hamer HM, Van den Mooter G, De Vuyst L, Courtin CM, *et al.* 2017 Systemic availability and metabolism of colonic-derived short-chain fatty acids in healthy subjects: a stable isotope study. *Journal of Physiology* **595** 541–555. (https://doi.org/10.1113/JP272613)

Borgo F, Garbossa S, Riva A, Severgnini M, Luigiano C, Benetti A, Pontiroli AE, Morace G & Borghi E 2018 Body mass index and sex affect diverse microbial niches within the gut. *Frontiers in Microbiology* **9** 213. (https://doi.org/10.3389/fmicb.2018.00213)

Boursier J, Mueller O, Barret M, Machado M, Fizanne L, Araujo-Perez F, Guy CD, Seed PC, Rawls JF, David LA, *et al.* 2016 The severity of nonalcoholic fatty liver disease is associated with gut dysbiosis and shift in the metabolic function of the gut microbiota. *Hepatology* **63** 764–775. (https://doi.org/10.1002/hep.28356)

Brooks L, Viardot A, Tsakmaki A, Stolarczyk E, Howard JK, Cani PD, Everard A, Sleeth ML, Psichas A, Anastasovskaj J, *et al.* 2017 Fermentable carbohydrate stimulates FFAR2-dependent colonic PYY cell expansion to increase satiety. *Molecular Metabolism* **6** 48–60. (https://doi.org/10.1016/j.molmet.2016.10.011)

Brown EM, Ke X, Hitchcock D, Jeanfavre S, Avila-Pacheco J, Nakata T, Arthur TD, Fornelos N, Heim C, Franzosa EA, *et al.* 2019 Bacteroides-derived sphingolipids are critical for maintaining intestinal homeostasis and symbiosis. *Cell Host and Microbe* **25** 668–680.e7. (https://doi.org/10.1016/j.chom.2019.04.002)

Byndloss MX, Olsan EE, Rivera-Chavez F, Tiffany CR, Cevallos SA, Lokken KL, Torres TP, Byndloss AJ, Faber F, Gao Y, *et al.* 2017 Microbiota-activated PPAR-gamma signaling inhibits dysbiotic Enterobacteriaceae expansion. *Science* **357** 570–575. (https://doi.org/10.1126/science.aam9949)

Canfora EE, van der Beek CM, Jocken JWE, Goossens GH, Holst JJ, Olde Damink SWM, Lenaerts K, Dejong CHC & Blaak EE 2017 Colonic infusions of short-chain fatty acid mixtures promote energy metabolism in overweight/obese men: a randomized crossover trial. *Scientific Reports* **7** 2360. (https://doi.org/10.1038/s41598-017-02546-x)

Chavez-Carbajal A, Nirmalkar K, Perez-Lizaur A, Hernandez-Quiroz F, Ramirez-Del-Alto S, Garcia-Mena J & Hernandez-Guerrero C 2019 Gut Microbiota and Predicted Metabolic Pathways in a Sample of Mexican Women Affected by Obesity and Obesity Plus Metabolic Syndrome. *International Journal of Molecular Science* **20** 438. (https://doi.org/10.3390/ijms20020438)

Chen T, Zheng X, Ma X, Bao Y, Ni Y, Hu C, Rajani C, Huang F, Zhao A, Jia W, *et al.* 2016 Tryptophan predicts the risk for future Type 2 diabetes. *PLoS One* **11** e0162192. (https://doi.org/10.1371/journal.pone.0162192)

Chen H, Qian L, Lv Q, Yu J, Wu W & Qian H 2017 Change in gut microbiota is correlated with alterations in the surface molecule expression of monocytes after Roux-en-Y gastric bypass surgery in obese type 2 diabetic patients. *American Journal of Translational Research* **9** 1243–1254.

Chen G, Zhuang J, Cui Q, Jiang S, Tao W, Chen W, Yu S, Wu L, Yang W, Liu F, *et al.* 2020 Two bariatric surgical procedures differentially alter the intestinal microbiota in obesity patients. *Obesity Surgery* **30** 2345–2361. (https://doi.org/10.1007/s11695-020-04494-4)

Cho SH, Cho YJ & Park JH 2022 The human symbiont Bacteroides thetaiotaomicron promotes diet-induced obesity by regulating host lipid metabolism. *Journal of Microbiology* **60** 118–127. (https://doi.org/10.1007/s12275-022-1614-1)

Cipriani S, Mencarelli A, Palladino G & Fiorucci S 2010 FXR activation reverses insulin resistance and lipid abnormalities and protects against liver steatosis in Zucker (fa/fa) obese rats. *Journal of Lipid Research* **51** 771–784. (https://doi.org/10.1194/jlr.M001602)

Courcoulas AP, King WC, Belle SH, Berk P, Flum DR, Garcia L, Gourash W, Horlick M, Mitchell JE, Pomp A, *et al.* 2018 Seven-year weight trajectories and health outcomes in the longitudinal assessment of bariatric surgery (LABS) study. *JAMA Surgery* **153** 427–434. (https://doi.org/10.1001/jamasurg.2017.5025)

Cox LM & Blaser MJ 2015 Antibiotics in early life and obesity. *Nature Reviews. Endocrinology* **11** 182–190. (https://doi.org/10.1038/nrendo.2014.210)

Cox LM, Yamanishi S, Sohn J, Alekseyenko AV, Leung JM, Cho I, Kim SG, Li H, Gao Z, Mahana D, *et al.* 2014 Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. *Cell* **158** 705–721. (https://doi.org/10.1016/j.cell.2014.05.052)

Cuesta-Zuluaga J, Mueller NT, Corrales-Agudelo V, Velasquez-Mejia EP, Carmona JA, Abad JM & Escobar JS 2017Metformin is associated with higher relative abundance of mucin-degrading akkermansia muciniphila and several short-chain fatty acid-producing microbiota in the gut. *Diabetes Care* **40** 54–62. (https://doi.org/10.2337/dc16-1324)

Cummings JH, Pomare EW, Branch WJ, Naylor CP & Macfarlane GT 1987 Short chain fatty acids in human large intestine, portal, hepatic and venous blood. *Gut* **28** 1221–1227. (https://doi.org/10.1136/gut.28.10.1221)

Dang JT, Mocanu V, Park H, Laffin M, Tran C, Hotte N, Karmali S, Birch DW & Madsen K 2021 Ileal microbial shifts after Roux-en-Y gastric bypass orchestrate changes in glucose metabolism through modulation of bile acids and L-cell adaptation. *Scientific Reports* **11** 23813. (https://doi.org/10.1038/s41598-021-03396-4)

De Vadder F, Grasset E, Manneras Holm L, Karsenty G, Macpherson AJ, Olofsson LE & Backhed F 2018 Gut microbiota regulates maturation of the adult enteric nervous system via enteric serotonin networks. *PNAS* **115** 6458–6463. (https://doi.org/10.1073/pnas.1720017115)

Debedat J, Clement K & Aron-Wisnewsky J 2019 Gut microbiota dysbiosis in human obesity: impact of bariatric surgery. *Current Obesity Reports* **8** 229–242. (https://doi.org/10.1007/s13679-019-00351-3)

den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud DJ & Bakker BM 2013 The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. *Journal of Lipid Research* **54** 2325–2340. (https://doi.org/10.1194/jlr.R036012)

Depommier C, Everard A, Druart C, Plovier H, Van Hul M, Vieira-Silva S, Falony G, Raes J, Maiter D, Delzenne NM, *et al.* 2019 Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: a proof-of-concept exploratory study. *Nature Medicine* **25** 1096–1103. (https://doi.org/10.1038/s41591-019-0495-2)

Depommier C, Van Hul M, Everard A, Delzenne NM, De Vos WM & Cani PD 2020 Pasteurized Akkermansia muciniphila increases whole-body energy expenditure and fecal energy excretion in diet-induced obese mice. *Gut Microbes* **11** 1231–1245. (https://doi.org/10.1080/19490976.2020.1737307)

Derrien M, Vaughan EE, Plugge CM & de Vos WM 2004 Akkermansia muciniphila gen. nov., sp. nov., a human intestinal mucin-degrading bacterium. *International Journal of Systematic and Evolutionary Microbiology* **54** 1469–1476. (https://doi.org/10.1099/ijs.0.02873-0)

Duan Y, Llorente C, Lang S, Brandl K, Chu H, Jiang L, White RC, Clarke TH, Nguyen K, Torralba M, *et al.* 2019 Bacteriophage targeting of gut bacterium attenuates alcoholic liver disease. *Nature* **575** 505–511. (https://doi.org/10.1038/s41586-019-1742-x)

Duboc H, Tache Y & Hofmann AF 2014 The bile acid TGR5 membrane receptor: from basic research to clinical application. *Digestive and Liver Disease* **46** 302–312. (https://doi.org/10.1016/j.dld.2013.10.021)

Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, Gill SR, Nelson KE & Relman DA 2005 Diversity of the human intestinal microbial flora. *Science* **308** 1635–1638. (https://doi.org/10.1126/science.1110591)

Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, Guiot Y, Derrien M, Muccioli GG, Delzenne NM, *et al.* 2013 Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *PNAS* **110** 9066–9071. (https://doi.org/10.1073/pnas.1219451110)

Fang S, Suh JM, Reilly SM, Yu E, Osborn O, Lackey D, Yoshihara E, Perino A, Jacinto S, Lukasheva Y, *et al.* 2015 Intestinal FXR agonism promotes adipose tissue browning and reduces obesity and insulin resistance. *Nature Medicine* **21** 159–165. (https://doi.org/10.1038/nm.3760)

Farin W, Onate FP, Plassais J, Bonny C, Beglinger C, Woelnerhanssen B, Nocca D, Magoules F, Le Chatelier E, Pons N, *et al.* 2020 Impact of laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy on gut microbiota: a metagenomic comparative analysis. *Surgery for Obesity and Related Diseases: Official Journal of the American Society for Bariatric Surgery* **16** 852–862. (https://doi.org/10.1016/j.soard.2020.03.014)

Fujisaka S, Avila-Pacheco J, Soto M, Kostic A, Dreyfuss JM, Pan H, Ussar S, Altindis E, Li N, Bry L, *et al.* 2018 Diet, genetics, and the gut microbiome drive dynamic changes in plasma metabolites. *Cell Reports* **22** 3072–3086. (https://doi.org/10.1016/j.celrep.2018.02.060)

Fujisaka S, Ussar S, Clish C, Devkota S, Dreyfuss JM, Sakaguchi M, Soto M, Konishi M, Softic S, Altindis E, *et al.* 2016 Antibiotic effects on gut microbiota and metabolism are host dependent. *Journal of Clinical Investigation* **126** 4430–4443. (https://doi.org/10.1172/JCI86674)

Fujisaka S, Usui I, Nawaz A, Igarashi Y, Okabe K, Furusawa Y, Watanabe S, Yamamoto S, Sasahara M, Watanabe Y, *et al.* 2020 Bofutsushosan improves gut barrier function with a bloom of Akkermansia muciniphila and improves glucose metabolism in mice with diet-induced obesity. *Scientific Reports* **10** 5544. (https://doi.org/10.1038/s41598-020-62506-w)

Fukuda S, Toh H, Hase K, Oshima K, Nakanishi Y, Yoshimura K, Tobe T, Clarke JM, Topping DL, Suzuki T, *et al.* 2011 Bifidobacteria can protect from enteropathogenic infection through production of acetate. *Nature* **469** 543–547. (https://doi.org/10.1038/nature09646)

Fukuda N, Ojima T, Hayata K, Katsuda M, Kitadani J, Takeuchi A, Goda T, Ueda Y, Iwakura H, Nishi M, *et al.* 2022 Laparoscopic sleeve gastrectomy for morbid obesity improves gut microbiota balance, increases colonic mucosal-associated invariant T cells and decreases circulating regulatory T cells. *Surgical Endoscopy* **36** 7312–7324. (https://doi.org/10.1007/s00464-022-09122-z)

Furet JP, Kong LC, Tap J, Poitou C, Basdevant A, Bouillot JL, Mariat D, Corthier G, Dore J, Henegar C, *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** 3049–3057. (https://doi.org/10.2337/db10-0253)

Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, Nakanishi Y, Uetake C, Kato K, Kato T, *et al.* 2013 Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* **504** 446–450. (https://doi.org/10.1038/nature12721)

Galle F, Valeriani F, Cattaruzza MS, Gianfranceschi G, Liguori R, Antinozzi M, Mederer B, Liguori G & Romano Spica V 2020 Mediterranean diet, physical activity and gut microbiome composition: a cross-sectional study among healthy young italian adults. *Nutrients* **12** 2164. (https://doi.org/10.3390/nu12072164)

Gao Z, Yin J, Zhang J, Ward RE, Martin RJ, Lefevre M, Cefalu WT & Ye J 2009 Butyrate improves insulin sensitivity and increases energy expenditure in mice. *Diabetes* **58** 1509–1517. (https://doi.org/10.2337/db08-1637)

Gavin PG, Mullaney JA, Loo D, Cao KL, Gottlieb PA, Hill MM, Zipris D & Hamilton-Williams EE 2018 Intestinal metaproteomics reveals host-microbiota interactions in subjects at risk for type 1 diabetes. *Diabetes Care* **41** 2178–2186. (https://doi.org/10.2337/dc18-0777)

Girdhar K, Huang Q, Chow IT, Vatanen T, Brady C, Raisingani A, Autissier P, Atkinson MA, Kwok WW, Kahn CR, *et al.* 2022 A gut microbial peptide and molecular mimicry in the pathogenesis of type 1 diabetes. *PNAS* **119** e2120028119. (https://doi.org/10.1073/pnas.2120028119)

Goodrich JK, Waters JL, Poole AC, Sutter JL, Koren O, Blekhman R, Beaumont M, Van Treuren W, Knight R, Bell JT, *et al.* 2014 Human genetics shape the gut microbiome. *Cell* **159** 789–799. (https://doi.org/10.1016/j.cell.2014.09.053)

Gummesson A, Carlsson LM, Storlien LH, Backhed F, Lundin P, Lofgren L, Stenlof K, Lam YY, Fagerberg B & Carlsson B 2011 Intestinal permeability is associated with visceral adiposity in healthy women. *Obesity* **19** 2280–2282. (https://doi.org/10.1038/oby.2011.251)

Guo J, Han X, Tan H, Huang W, You Y & Zhan J 2019 Blueberry extract improves obesity through regulation of the gut microbiota and bile acids via pathways involving FXR and TGR5. *iScience* **19** 676–690. (https://doi.org/10.1016/j.isci.2019.08.020)

Han Y, Kim G, Ahn E, Jung S, Jung Y, Kim Y, Ha E, Heo Y, Ryu DH, Park H, *et al.* 2022 Integrated metagenomics and metabolomics analysis illustrates the systemic impact of the gut microbiota on host metabolism after bariatric surgery. *Diabetes, Obesity & Metabolism* **24** 1224–1234. (https://doi.org/10.1111/dom.14689)

Harakeh S, Angelakis E, Karamitros T, Bachar D, Bahijri S, Ajabnoor G, Alfadul SM, Farraj SA, Al Amri T, Al-Hejin A, *et al.* 2020 Impact of smoking cessation, coffee and bread consumption on the intestinal microbial composition among Saudis: a cross-sectional study. *PLoS One* **15** e0230895. (https://doi.org/10.1371/journal.pone.0230895)

Huda MN, Ahmad SM, Kalanetra KM, Taft DH, Alam MJ, Khanam A, Raqib R, Underwood MA, Mills DA & Stephensen CB 2019 Neonatal vitamin A supplementation and vitamin A status are associated with gut microbiome composition in Bangladeshi infants in early infancy and at 2 years of age. *Journal of Nutrition* **149** 1075–1088. (https://doi.org/10.1093/jn/nxz034)

Ichikawa N, Sasaki H, Lyu Y, Furuhashi S, Watabe A, Imamura M, Hayashi K & Shibata S 2021 Cold exposure during the active phase affects the short-chain fatty acid production of mice in a time-specific manner. *Metabolites* **12** 20. (https://doi.org/10.3390/metabo12010020)

Inoue D, Kimura I, Wakabayashi M, Tsumoto H, Ozawa K, Hara T, Takei Y, Hirasawa A, Ishihama Y & Tsujimoto G 2012 Short-chain fatty acid receptor GPR41-mediated activation of sympathetic neurons involves synapsin 2b phosphorylation. *FEBS Letters* **586** 1547–1554. (https://doi.org/10.1016/j.febslet.2012.04.021)

Jang C, Oh SF, Wada S, Rowe GC, Liu L, Chan MC, Rhee J, Hoshino A, Kim B, Ibrahim A, *et al.* 2016 A branched-chain amino acid metabolite drives vascular fatty acid transport and causes insulin resistance. *Nature Medicine* **22** 421–426. (https://doi.org/10.1038/nm.4057)

Jiang C, Xie C, Lv Y, Li J, Krausz KW, Shi J, Brocker CN, Desai D, Amin SG, Bisson WH, *et al.* 2015 Intestine-selective farnesoid X receptor inhibition improves obesity-related metabolic dysfunction. *Nature Communications* **6** 10166. (https://doi.org/10.1038/ncomms10166)

Kalliomaki M, Collado MC, Salminen S & Isolauri E 2008 Early differences in fecal microbiota composition in children may predict overweight. *American Journal of Clinical Nutrition* **87** 534–538. (https://doi.org/10.1093/ajcn/87.3.534)

Kaplan RC, Wang Z, Usyk M, Sotres-Alvarez D, Daviglus ML, Schneiderman N, Talavera GA, Gellman MD, Thyagarajan B, Moon JY, *et al.* 2019 Gut microbiome composition in the Hispanic Community Health Study/Study of Latinos is shaped by geographic relocation, environmental factors, and obesity. *Genome Biology* **20** 219. (https://doi.org/10.1186/s13059-019-1831-z)

Karlsson FH, Tremaroli V, Nookaew I, Bergstrom G, Behre CJ, Fagerberg B, Nielsen J & Backhed F 2013 Gut metagenome in European women with normal, impaired and diabetic glucose control. *Nature* **498** 99–103. (https://doi.org/10.1038/nature12198)

Kasai C, Sugimoto K, Moritani I, Tanaka J, Oya Y, Inoue H, Tameda M, Shiraki K, Ito M, Takei Y, *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 Gastroenterology* **15** 100. (https://doi.org/10.1186/s12876-015-0330-2)

Kawamata Y, Fujii R, Hosoya M, Harada M, Yoshida H, Miwa M, Fukusumi S, Habata Y, Itoh T, Shintani Y, *et al.* 2003 A G protein-

coupled receptor responsive to bile acids. *Journal of Biological Chemistry* **278** 9435–9440. (https://doi.org/10.1074/jbc.M209706200)
Kien CL 1996 Digestion, absorption, and fermentation of carbohydrates in the newborn. *Clinics in Perinatology* **23** 211–228. (https://doi.org/10.1016/S0095-5108(18)30239-2)
Kikuchi R, Irie J, Yamada-Goto N, Kikkawa E, Seki Y, Kasama K & Itoh H 2018 The impact of laparoscopic sleeve gastrectomy with duodenojejunal bypass on intestinal microbiota differs from that of laparoscopic sleeve gastrectomy in Japanese patients with obesity. *Clinical Drug Investigation* **38** 545–552. (https://doi.org/10.1007/s40261-018-0638-0)
Kim S, Lee Y, Kim Y, Seo Y, Lee H, Ha J, Lee J, Choi Y, Oh H & Yoon Y 2020 Akkermansia muciniphila prevents fatty liver disease, decreases serum triglycerides, and maintains gut homeostasis. *Applied and Environmental Microbiology* **86** e03004-19. (https://doi.org/10.1128/AEM.03004-19)
Kim YG, Sakamoto K, Seo SU, Pickard JM, Gillilland MG, 3rd, Pudlo NA, Hoostal M, Li X, Wang TD, Feehley T, *et al.* 2017 Neonatal acquisition of Clostridia species protects against colonization by bacterial pathogens. *Science* **356** 315–319. (https://doi.org/10.1126/science.aag2029)
Kimura I, Inoue D, Maeda T, Hara T, Ichimura A, Miyauchi S, Kobayashi M, Hirasawa A & Tsujimoto G 2011 Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41 (GPR41). *PNAS* **108** 8030–8035. (https://doi.org/10.1073/pnas.1016088108)
Kimura I, Ozawa K, Inoue D, Imamura T, Kimura K, Maeda T, Terasawa K, Kashihara D, Hirano K, Tani T, *et al.* 2013 The gut microbiota suppresses insulin-mediated fat accumulation via the short-chain fatty acid receptor GPR43. *Nature Communications* **4** 1829. (https://doi.org/10.1038/ncomms2852)
Kishino S, Takeuchi M, Park SB, Hirata A, Kitamura N, Kunisawa J, Kiyono H, Iwamoto R, Isobe Y, Arita M, *et al.* 2013 Polyunsaturated fatty acid saturation by gut lactic acid bacteria affecting host lipid composition. *PNAS* **110** 17808–17813. (https://doi.org/10.1073/pnas.1312937110)
Knip M & Siljander H 2016 The role of the intestinal microbiota in type 1 diabetes mellitus. *Nature Reviews. Endocrinology* **12** 154–167. (https://doi.org/10.1038/nrendo.2015.218)
Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, Britt EB, Fu X, Wu Y, Li L, *et al.* 2013 Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nature Medicine* **19** 576–585. (https://doi.org/10.1038/nm.3145)
Kong LC, Tap J, Aron-Wisnewsky J, Pelloux V, Basdevant A, Bouillot JL, Zucker JD, Dore J & Clement K 2013 Gut microbiota after gastric bypass in human obesity: increased richness and associations of bacterial genera with adipose tissue genes. *American Journal of Clinical Nutrition* **98** 16–24. (https://doi.org/10.3945/ajcn.113.058743)
Koh A, De Vadder F, Kovatcheva-Datchary P & Backhed F 2016 From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. *Cell* **165** 1332–1345. (https://doi.org/10.1016/j.cell.2016.05.041)
Koh A, Manneras-Holm L, Yunn NO, Nilsson PM, Ryu SH, Molinaro A, Perkins R, Smith JG & Backhed F 2020 Microbial imidazole propionate affects responses to metformin through p38gamma-dependent inhibitory AMPK phosphorylation. *Cell Metabolism* **32** 643–653.e4. (https://doi.org/10.1016/j.cmet.2020.07.012)
Koh A, Molinaro A, Stahlman M, Khan MT, Schmidt C, Manneras-Holm L, Wu H, Carreras A, Jeong H, Olofsson LE, *et al.* 2018 Microbially produced imidazole propionate impairs insulin signaling through mTORC1. *Cell* **175** 947–961.e17. (https://doi.org/10.1016/j.cell.2018.09.055)
Konikoff T & Gophna U 2016 Oscillospira: a central, enigmatic component of the human gut microbiota. *Trends in Microbiology* **24** 523–524. (https://doi.org/10.1016/j.tim.2016.02.015)
Kostic AD, Gevers D, Siljander H, Vatanen T, Hyotylainen T, Hamalainen AM, Peet A, Tillmann V, Poho P, Mattila I, *et al.* 2015 The dynamics of the human infant gut microbiome in development and in progression toward type 1 diabetes. *Cell Host Microbe* **17** 260–273. (https://doi.org/10.1016/j.chom.2015.01.0010)
Kuhre RE, Wewer Albrechtsen NJ, Larsen O, Jepsen SL, Balk-Moller E, Andersen DB, Deacon CF, Schoonjans K, Reimann F, Gribble FM, *et al.* 2018 Bile acids are important direct and indirect regulators of the secretion of appetite- and metabolism-regulating hormones from the gut and pancreas. *Molecular Metabolism* **11** 84–95. (https://doi.org/10.1016/j.molmet.2018.03.007)
Lassenius MI, Pietilainen KH, Kaartinen K, Pussinen PJ, Syrjanen J, Forsblom C, Porsti I, Rissanen A, Kaprio J, Mustonen J, *et al.* 2011 Bacterial endotoxin activity in human serum is associated with dyslipidemia, insulin resistance, obesity, and chronic inflammation. *Diabetes Care* **34** 1809–1815. (https://doi.org/10.2337/dc10-2197)
Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, Almeida M, Arumugam M, Batto JM, Kennedy S, *et al.* 2013 Richness of human gut microbiome correlates with metabolic markers. *Nature* **500** 541–546. (https://doi.org/10.1038/nature12506)
Ley RE, Turnbaugh PJ, Klein S & Gordon JI 2006 Microbial ecology: human gut microbes associated with obesity. *Nature* **444** 1022–1023. (https://doi.org/10.1038/4441022a)
Li L, Krause L & Somerset S 2017 Associations between micronutrient intakes and gut microbiota in a group of adults with cystic fibrosis. *Clinical Nutrition* **36** 1097–1104. (https://doi.org/10.1016/j.clnu.2016.06.029)
Liu R, Hong J, Xu X, Feng Q, Zhang D, Gu Y, Shi J, Zhao S, Liu W, Wang X, *et al.* 2017 Gut microbiome and serum metabolome alterations in obesity and after weight-loss intervention. *Nature Medicine* **23** 859–868. (https://doi.org/10.1038/nm.4358)
Loftfield E, Herzig KH, Caporaso JG, Derkach A, Wan Y, Byrd DA, Vogtmann E, Mannikko M, Karhunen V, Knight R, *et al.* 2020 Association of body mass index with fecal microbial diversity and metabolites in the Northern Finland Birth Cohort. *Cancer Epidemiolology, Biomarkers & Prevention* **29** 2289–2299. (https://doi.org/10.1158/1055-9965.EPI-20-0824)
Long KZ, Garcia C, Santos JI, Rosado JL, Hertzmark E, Dupont HL & Ko G 2007 Vitamin A supplementation has divergent effects on Norovirus infections and clinical symptoms among Mexican children. *Journal of Infectious Diseases* **196** 978–985. (https://doi.org/10.1086/521195)
Long KZ, Santos JI, Rosado JL, Estrada-Garcia T, Haas M, Al Mamun A, DuPont HL & Nanthakumar NN 2011 Vitamin A supplementation modifies the association between mucosal innate and adaptive immune responses and resolution of enteric pathogen infections. *American Journal of Clinical Nutrition* **93** 578–585. (https://doi.org/10.3945/ajcn.110.003913)
Loomba R, Seguritan V, Li W, Long T, Klitgord N, Bhatt A, Dulai PS, Caussy C, Bettencourt R, Highlander SK, *et al.* 2017 Gut microbiome-based metagenomic signature for non-invasive detection of advanced fibrosis in human nonalcoholic fatty liver disease. *Cell Metabolism* **25** 1054–1062.e5. (https://doi.org/10.1016/j.cmet.2017.04.001)
Louis P, Duncan SH, McCrae SI, Millar J, Jackson MS & Flint HJ 2004 Restricted distribution of the butyrate kinase pathway among butyrate-producing bacteria from the human colon. *Journal of Bacteriology* **186** 2099–2106. (https://doi.org/10.1128/JB.186.7.2099-2106.2004)
Louis P & Flint HJ 2017 Formation of propionate and butyrate by the human colonic microbiota. *Environmental Microbiology* **19** 29–41. (https://doi.org/10.1111/1462-2920.13589)
Louis P, Hold GL & Flint HJ 2014 The gut microbiota, bacterial metabolites and colorectal cancer. *Nature Reviews. Microbiology* **12** 661–672. (https://doi.org/10.1038/nrmicro3344)
Ma C, Han M, Heinrich B, Fu Q, Zhang Q, Sandhu M, Agdashian D, Terabe M, Berzofsky JA, Fako V, *et al.* 2018 Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. *Science* **360** eaan5931. (https://doi.org/10.1126/science.aan5931)
Magnusdottir S, Ravcheev D, de Crecy-Lagard V & Thiele I 2015 Systematic genome assessment of B-vitamin biosynthesis suggests co-operation among gut microbes. *Frontiers in Genetics* **6** 148. (https://doi.org/10.3389/fgene.2015.00148)
Magzal F, Shochat T, Haimov I, Tamir S, Asraf K, Tuchner-Arieli M, Even C & Agmon M 2022 Increased physical activity improves gut microbiota

composition and reduces short-chain fatty acid concentrations in older adults with insomnia. *Scientific Reports* **12** 2265. (https://doi.org/10.1038/s41598-022-05099-w)

Mai V, McCrary QM, Sinha R & Glei M 2009 Associations between dietary habits and body mass index with gut microbiota composition and fecal water genotoxicity: an observational study in African American and Caucasian American volunteers. *Nutrition Journal* **8** 49. (https://doi.org/10.1186/1475-2891-8-49)

Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, Yu D, Schilter HC, Rolph MS, Mackay F, Artis D, *et al.* 2009 Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature* **461** 1282–1286. (https://doi.org/10.1038/nature08530)

Matsubara T, Li F & Gonzalez FJ 2013 FXR signaling in the enterohepatic system. *Molecular and Cellular Endocrinology* **368** 17–29. (https://doi.org/10.1016/j.mce.2012.05.004)

McFarlin BK, Henning AL, Bowman EM, Gary MA & Carbajal KM 2017 Oral spore-based probiotic supplementation was associated with reduced incidence of post-prandial dietary endotoxin, triglycerides, and disease risk biomarkers. *World Journal of Gastrointestinal Pathophysiology* **8** 117–126. (https://doi.org/10.4291/wjgp.v8.i3.117)

McNelis JC, Lee YS, Mayoral R, van der Kant R, Johnson AM, Wollam J & Olefsky JM 2015 GPR43 potentiates beta-cell function in obesity. *Diabetes* **64** 3203–3217. (https://doi.org/10.2337/db14-1938)

Miyakawa M, Iijima R, Kobayashi R, Tajima M, Isomura N, Shimizu T, Kobayashi I & Asano M 1954 Report on success of long duration rearing of Germfree Guinea Pigs. *Trans Society of Pathology Japan* **43** 450–452.

Miyamoto J, Igarashi M, Watanabe K, Karaki SI, Mukouyama H, Kishino S, Li X, Ichimura A, Irie J, Sugimoto Y, *et al.* 2019 Gut microbiota confers host resistance to obesity by metabolizing dietary polyunsaturated fatty acids. *Nature Communications* **10** 4007. (https://doi.org/10.1038/s41467-019-11978-0)

Molinaro A, Bel Lassen P, Henricsson M, Wu H, Adriouch S, Belda E, Chakaroun R, Nielsen T, Bergh PO, Rouault C, *et al.* 2020 Imidazole propionate is increased in diabetes and associated with dietary patterns and altered microbial ecology. *Nature Communications* **11** 5881. (https://doi.org/10.1038/s41467-020-19589-w)

Morrison DJ & Preston T 2016 Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes* **7** 189–200. (https://doi.org/10.1080/19490976.2015.1134082)

Morrison MC, Gart E, Duyvenvoorde WV, Snabel J, Nielsen MJ, Leeming DJ, Menke A & Kleemann R 2022 Heat-inactivated Akkermansia muciniphila improves gut permeability but does not prevent development of non-alcoholic steatohepatitis in diet-induced obese Ldlr-/-.Leiden mice. *International Journal of Molecular Sciences* **23** 2325. (https://doi.org/10.3390/ijms23042325)

Mutlu EA, Gillevet PM, Rangwala H, Sikaroodi M, Naqvi A, Engen PA, Kwasny M, Lau CK & Keshavarzian A 2012 Colonic microbiome is altered in alcoholism. *American Journal of Physiology. Gastrointestinal and Liver Physiology* **302** G966–G978. (https://doi.org/10.1152/ajpgi.00380.2011)

Natarajan N & Pluznick JL 2014 From microbe to man: the role of microbial short chain fatty acid metabolites in host cell biology. *American Journal of Physiology. Cell Physiology* **307** C979–C985. (https://doi.org/10.1152/ajpcell.00228.2014)

Newgard CB, An J, Bain JR, Muehlbauer MJ, Stevens RD, Lien LF, Haqq AM, Shah SH, Arlotto M, Slentz CA, *et al.* 2009 A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. *Cell Metabolism* **9** 311–326. (https://doi.org/10.1016/j.cmet.2009.02.002)

Nuttal GHF & Thierfelder H 1895 Thierisches leben ohne bakterien im verdauungskanal. *Zeitschrift für Physiologische Chemie* **21** 109.(https://doi.org/10.1515/bchm2.1897.23.3.231)

Obata Y, Castano Á, Boeing S, Bon-Frauches AC, Fung C, Fallesen T, de Aguero MG, Yilmaz B, Lopes R, Huseynova A, *et al.* 2020 Neuronal programming by microbiota regulates intestinal physiology. *Nature* **578** 284–289. (https://doi.org/10.1038/s41586-020-1975-8)

Oduaran OH, Tamburini FB, Sahibdeen V, Brewster R, Gomez-Olive FX, Kahn K, Norris SA, Tollman SM, Twine R, Wade AN, *et al.* 2020 Gut microbiome profiling of a rural and urban South African cohort reveals biomarkers of a population in lifestyle transition. *BMC Microbiology* **20** 330. (https://doi.org/10.1186/s12866-020-02017-w)

Org E, Blum Y, Kasela S, Mehrabian M, Kuusisto J, Kangas AJ, Soininen P, Wang Z, Ala-Korpela M, Hazen SL, *et al.* 2017 Relationships between gut microbiota, plasma metabolites, and metabolic syndrome traits in the METSIM cohort. *Genome Biology* **18** 70. (https://doi.org/10.1186/s13059-017-1194-2)

Osborne G, Wu F, Yang L, Kelly D, Hu J, Li H, Jasmine F, Kibriya MG, Parvez F, Shaheen I, *et al.* 2020 The association between gut microbiome and anthropometric measurements in Bangladesh. *Gut Microbes* **11** 63–76. (https://doi.org/10.1080/19490976.2019.1614394)

Ozato N, Saito S, Yamaguchi T, Katashima M, Tokuda I, Sawada K, Katsuragi Y, Kakuta M, Imoto S, Ihara K, *et al.* 2019 Blautia genus associated with visceral fat accumulation in adults 20-76 years of age. *NPJ Biofilms and Microbiomes* **5** 28. (https://doi.org/10.1038/s41522-019-0101-x)

Ozato N, Yamaguchi T, Mori K, Katashima M, Kumagai M, Murashita K, Katsuragi Y, Tamada Y, Kakuta M, Imoto S, *et al.* 2022 Two blautia species associated with visceral fat accumulation: a one-year longitudinal study. *Biology* (Basel) **11** 318. (https://doi.org/10.3390/biology11020318)

Ozcan U, Cao Q, Yilmaz E, Lee AH, Iwakoshi NN, Ozdelen E, Tuncman G, Gorgun C, Glimcher LH & Hotamisligil GS 2004 Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. *Science* **306** 457–461. (https://doi.org/10.1126/science.1103160)

Ozcan U, Yilmaz E, Ozcan L, Furuhashi M, Vaillancourt E, Smith RO, Gorgun CZ & Hotamisligil GS 2006 Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. *Science* **313** 1137–1140. (https://doi.org/10.1126/science.1128294)

Paik D, Yao L, Zhang Y, Bae S, D'Agostino GD, Zhang M, Kim E, Franzosa EA, Avila-Pacheco J, Bisanz JE, *et al.* 2022 Human gut bacteria produce TauEta17-modulating bile acid metabolites. *Nature* **603** 907–912. (https://doi.org/10.1038/s41586-022-04480-z)

Pasteur L 1885 Observations relatives a la note precooente de M. Duclaux. *Comptes Rendus de l'Académie des Sciences, Paris* **100** 68.

Patil DP, Dhotre DP, Chavan SG, Sultan A, Jain DS, Lanjekar VB, Gangawani J, Shah PS, Todkar JS, Shah S, *et al.* 2012 Molecular analysis of gut microbiota in obesity among Indian individuals. *Journal of Biosciences* **37** 647–657. (https://doi.org/10.1007/s12038-012-9244-0)

Payne AN, Chassard C, Zimmermann M, Muller P, Stinca S & Lacroix C 2011 The metabolic activity of gut microbiota in obese children is increased compared with normal-weight children and exhibits more exhaustive substrate utilization. *Nutrition & Diabetes* **1** e12. (https://doi.org/10.1038/nutd.2011.8)

Pedersen HK, Gudmundsdottir V, Nielsen HB, Hyotylainen T, Nielsen T, Jensen BA, Forslund K, Hildebrand F, Prifti E, Falony G, *et al.* 2016 Human gut microbes impact host serum metabolome and insulin sensitivity. *Nature* **535** 376–381. (https://doi.org/10.1038/nature18646)

Peters BA, Shapiro JA, Church TR, Miller G, Trinh-Shevrin C, Yuen E, Friedlander C, Hayes RB & Ahn J 2018 A taxonomic signature of obesity in a large study of American adults. *Scientific Reports* **8** 9749. (https://doi.org/10.1038/s41598-018-28126-1)

Pham VT, Dold S, Rehman A, Bird JK & Steinert RE 2021 Vitamins, the gut microbiome and gastrointestinal health in humans. *Nutrition Research* **95** 35–53. (https://doi.org/10.1016/j.nutres.2021.09.001)

Plovier H, Everard A, Druart C, Depommier C, Van Hul M, Geurts L, Chilloux J, Ottman N, Duparc T, Lichtenstein L, *et al.* 2017 A purified membrane protein from Akkermansia muciniphila or the pasteurized bacterium improves metabolism in obese and diabetic mice. *Nature Medicine* **23** 107–113. (https://doi.org/10.1038/nm.4236)

Prawitt J, Abdelkarim M, Stroeve JH, Popescu I, Duez H, Velagapudi VR, Dumont J, Bouchaert E, van Dijk TH, Lucas A, *et al.* 2011 Farnesoid X receptor deficiency improves glucose homeostasis in mouse models of obesity. *Diabetes* **60** 1861–1871. (https://doi.org/10.2337/db11-0030)

Psichas A, Sleeth ML, Murphy KG, Brooks L, Bewick GA, Hanyaloglu AC, Ghatei MA, Bloom SR & Frost G 2015 The short chain fatty acid propionate stimulates GLP-1 and PYY secretion via free fatty acid receptor 2 in rodents. *International Journal of Obesity* **39** 424–429. (https://doi.org/10.1038/ijo.2014.153)

Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, Zhang W, Guan Y, Shen D, *et al.* 2012 A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* **490** 55–60. (https://doi.org/10.1038/nature11450)

Radilla-Vazquez RB, Parra-Rojas I, Martinez-Hernandez NE, Marquez-Sandoval YF, Illades-Aguiar B & Castro-Alarcon N 2016 Gut microbiota and metabolic endotoxemia in young obese mexican subjects. *Obesity Facts* **9** 1–11. (https://doi.org/10.1159/000442479)

Raqib R, Sarker P, Bergman P, Ara G, Lindh M, Sack DA, Nasirul Islam KM, Gudmundsson GH, Andersson J & Agerberth B 2006 Improved outcome in shigellosis associated with butyrate induction of an endogenous peptide antibiotic. *PNAS* **103** 9178–9183. (https://doi.org/10.1073/pnas.0602888103)

Regnier M, Van Hul M, Knauf C & Cani PD 2021 Gut microbiome, endocrine control of gut barrier function and metabolic diseases. *Journal of Endocrinology* **248** R67–R82. (https://doi.org/10.1530/JOE-20-0473)

Reyniers JA, Trexler PC & Ervin RF 1946 Rearing germ-free albino rats. *Lobund Reports* **1** 1–84.

Reyniers JA, Trexler PC, Ervin RF, Wagner M, Luckey TD & Gordon HA 1949 Rearing germfree chickens. *Lobund Report* **2** 1-116.

Richards JL, Yap YA, McLeod KH, Mackay CR & Marino E 2016 Dietary metabolites and the gut microbiota: an alternative approach to control inflammatory and autoimmune diseases. *Clinical and Translational Immunology* **5** e82. (https://doi.org/10.1038/cti.2016.29)

Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, Griffin NW, Lombard V, Henrissat B, Bain JR, *et al.* 2013 Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science* **341** 1241214. (https://doi.org/10.1126/science.1241214)

Rivera-Chavez F, Zhang LF, Faber F, Lopez CA, Byndloss MX, Olsan EE, Xu G, Velazquez EM, Lebrilla CB, Winter SE, *et al.* 2016 Depletion of butyrate-producing Clostridia from the gut microbiota drives an aerobic luminal expansion of Salmonella. *Cell Host and Microbe* **19** 443–454. (https://doi.org/10.1016/j.chom.2016.03.004)

Ryan KK, Tremaroli V, Clemmensen C, Kovatcheva-Datchary P, Myronovych A, Karns R, Wilson-Perez HE, Sandoval DA, Kohli R, Backhed F, *et al.* 2014 FXR is a molecular target for the effects of vertical sleeve gastrectomy. *Nature* **509** 183–188. (https://doi.org/10.1038/nature13135)

Salah M, Azab M, Ramadan A & Hanora A 2019 New insights on obesity and aiabetes from gut microbiome alterations in Egyptian adults. *OMICS* **23** 477–485. (https://doi.org/10.1089/omi.2019.0063)

Samuel BS, Shaito A, Motoike T, Rey FE, Backhed F, Manchester JK, Hammer RE, Williams SC, Crowley J, Yanagisawa M, *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. *PNAS* **105** 16767–16772. (https://doi.org/10.1073/pnas.0808567105)

Sanchez-Alcoholado L, Gutierrez-Repiso C, Gomez-Perez AM, Garcia-Fuentes E, Tinahones FJ & Moreno-Indias I 2019 Gut microbiota adaptation after weight loss by Roux-en-Y gastric bypass or sleeve gastrectomy bariatric surgeries. *Surgery for Obesity and Related Diseases*: Official Journal of the American Society for Bariatric Surgery **15** 1888-1895.(https://doi.org/10.1016/j.soard.2019.08.551)

Sato Y, Atarashi K, Plichta DR, Arai Y, Sasajima S, Kearney SM, Suda W, Takeshita K, Sasaki T, Okamoto S, *et al.* 2021 Novel bile acid biosynthetic pathways are enriched in the microbiome of centenarians. *Nature* **599** 458–464. (https://doi.org/10.1038/s41586-021-03832-5)

Sayin SI, Wahlstrom A, Felin J, Jantti S, Marschall HU, Bamberg K, Angelin B, Hyotylainen T, Oresic M & Backhed F 2013 Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist. *Cell Metabolism* **17** 225–235. (https://doi.org/10.1016/j.cmet.2013.01.003)

Scheithauer TPM, Davids M, Winkelmeijer M, Verdoes X, Aydin Ö, de Brauw M, van de Laar A, Meijnikman AS, Gerdes VEA, van Raalte D, *et al.* 2022 Compensatory intestinal antibody response against pro-inflammatory microbiota after bariatric surgery. *Gut Microbes* **14** 2031696. (https://doi.org/10.1080/19490976.2022.2031696)

Schiattarella GG, Sannino A, Toscano E, Giugliano G, Gargiulo G, Franzone A, Trimarco B, Esposito G & Perrino C 2017 Gut microbe-generated metabolite trimethylamine-N-oxide as cardiovascular risk biomarker: a systematic review and dose-response meta-analysis. *European Heart Journal* **38** 2948–2956. (https://doi.org/10.1093/eurheartj/ehx342)

Schwartz BS, Pollak J, Bailey-Davis L, Hirsch AG, Cosgrove SE, Nau C, Kress AM, Glass TA & Bandeen-Roche K 2016 Antibiotic use and childhood body mass index trajectory. *International Journal of Obesity* **40** 615–621. (https://doi.org/10.1038/ijo.2015.218)

Schwiertz A, Taras D, Schafer K, Beijer S, Bos NA, Donus C & Hardt PD 2010 Microbiota and SCFA in lean and overweight healthy subjects. *Obesity* **18** 190–195. (https://doi.org/10.1038/oby.2009.167)

Shale M, Schiering C & Powrie F 2013 CD4(+) T-cell subsets in intestinal inflammation. *Immunological Reviews* **252** 164–182. (https://doi.org/10.1111/imr.12039)

Shibata N, Kunisawa J & Kiyono H 2017 Dietary and microbial metabolites in the regulation of host immunity. *Frontiers in Microbiology* **8** 2171. (https://doi.org/10.3389/fmicb.2017.02171)

Shilo S, Godneva A, Rachmiel M, Korem T, Bussi Y, Kolobkov D, Karady T, Bar N, Wolf BC, Glantz-Gashai Y, *et al.* 2022 The gut microbiome of Adults with type 1 diabetes and its association with the host glycemic control. *Diabetes Care* **45** 555–563. (https://doi.org/10.2337/dc21-1656)

Shimokawa C, Kato T, Takeuchi T, Ohshima N, Furuki T, Ohtsu Y, Suzue K, Imai T, Obi S, Olia A, *et al.* 2020 CD8(+) regulatory T cells are critical in prevention of autoimmune-mediated diabetes. *Nature Communications* **11** 1922. (https://doi.org/10.1038/s41467-020-15857-x)

Shin NR, Lee JC, Lee HY, Kim MS, Whon TW, Lee MS & Bae JW 2014 An increase in the Akkermansia spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. *Gut* **63** 727–735. (https://doi.org/10.1136/gutjnl-2012-303839)

Simoes CD, Maukonen J, Kaprio J, Rissanen A, Pietilainen KH & Saarela M 2013 Habitual dietary intake is associated with stool microbiota composition in monozygotic twins. *Journal of Nutrition* **143** 417–423. (https://doi.org/10.3945/jn.112.166322)

Sinal CJ, Tohkin M, Miyata M, Ward JM, Lambert G & Gonzalez FJ 2000 Targeted disruption of the nuclear receptor FXR/BAR impairs bile acid and lipid homeostasis. *Cell* **102** 731–744. (https://doi.org/10.1016/s0092-8674(00)00062-3)

Singh DP, Singh J, Boparai RK, Zhu J, Mantri S, Khare P, Khardori R, Kondepudi KK, Chopra K & Bishnoi M 2017 Isomalto-oligosaccharides, a prebiotic, functionally augment green tea effects against high fat diet-induced metabolic alterations via preventing gut dysbacteriosis in mice. *Pharmacological Research* **123** 103–113. (https://doi.org/10.1016/j.phrs.2017.06.015)

Singh N, Gurav A, Sivaprakasam S, Brady E, Padia R, Shi H, Thangaraju M, Prasad PD, Manicassamy S, Munn DH, *et al.* 2014 Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. *Immunity* **40** 128–139. (https://doi.org/10.1016/j.immuni.2013.12.007)

Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly M, Glickman JN & Garrett WS 2013 The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science* **341** 569–573. (https://doi.org/10.1126/science.1241165)

Song H, Chu Q, Yan F, Yang Y, Han W & Zheng X 2016 Red pitaya betacyanins protects from diet-induced obesity, liver steatosis and insulin resistance in association with modulation of gut microbiota in mice. *Journal of Gastroenterology and Hepatology* **31** 1462–1469. (https://doi.org/10.1111/jgh.13278)

Stefura T, Zapala B, Gosiewski T, Skomarovska O, Pedziwiatr M & Major P 2022 Changes in the composition of oral and intestinal microbiota

after sleeve gastrectomy and Roux-En-Y gastric bypass and their impact on outcomes of bariatric surgery. *Obesity Surgery* **32** 1439–1450. (https://doi.org/10.1007/s11695-022-05954-9)

Steinert RE, Lee YK & Sybesma W 2020 Vitamins for the gut microbiome. *Trends in Molecular Medicine* **26** 137–140. (https://doi.org/10.1016/j.molmed.2019.11.005)

Tang WH, Wang Z, Levison BS, Koeth RA, Britt EB, Fu X, Wu Y & Hazen SL 2013 Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *New England Journal of Medicine* **368** 1575–1584. (https://doi.org/10.1056/NEJMoa1109400)

Thingholm LB, Ruhlemann MC, Koch M, Fuqua B, Laucke G, Boehm R, Bang C, Franzosa EA, Hubenthal M, Rahnavard A, *et al.* 2019 Obese individuals with and without type 2 diabetes show different gut microbial functional capacity and composition. *Cell Host & Microbe* **26** 252–264 e210. (https://doi.org/10.1016/j.chom.2019.07.004)

Thorburn AN, McKenzie CI, Shen S, Stanley D, Macia L, Mason LJ, Roberts LK, Wong CH, Shim R, Robert R, *et al.* 2015 Evidence that asthma is a developmental origin disease influenced by maternal diet and bacterial metabolites. *Nature Communications* **6** 7320. (https://doi.org/10.1038/ncomms8320)

Tims S, Derom C, Jonkers DM, Vlietinck R, Saris WH, Kleerebezem M, de Vos WM & Zoetendal EG 2013 Microbiota conservation and BMI signatures in adult monozygotic twins. *ISME Journal* **7** 707–717. (https://doi.org/10.1038/ismej.2012.146)

Tolhurst G, Heffron H, Lam YS, Parker HE, Habib AM, Diakogiannaki E, Cameron J, Grosse J, Reimann F & Gribble FM 2012 Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. *Diabetes* **61** 364–371. (https://doi.org/10.2337/db11-1019)

Trabelsi MS, Daoudi M, Prawitt J, Ducastel S, Touche V, Sayin SI, Perino A, Brighton CA, Sebti Y, Kluza J, *et al.* 2015 Farnesoid X receptor inhibits glucagon-like peptide-1 production by enteroendocrine L cells. *Nature Communications* **6** 7629. (https://doi.org/10.1038/ncomms8629)

Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER & Gordon JI 2006 An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* **444** 1027–1031. (https://doi.org/10.1038/nature05414)

Ueno A, Jeffery L, Kobayashi T, Hibi T, Ghosh S & Jijon H 2018 Th17 plasticity and its relevance to inflammatory bowel disease. *Journal of Autoimmunity* **87** 38–49. (https://doi.org/10.1016/j.jaut.2017.12.004)

Vael C, Verhulst SL, Nelen V, Goossens H & Desager KN 2011 Intestinal microflora and body mass index during the first three years of life: an observational study. *Gut Pathogens* **3** 8. (https://doi.org/10.1186/1757-4749-3-8)

Vijay-Kumar M, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, Srinivasan S, Sitaraman SV, Knight R, Ley RE & Gewirtz AT 2010 Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science* **328** 228–231. (https://doi.org/10.1126/science.1179721)

Wahlstrom A, Sayin SI, Marschall HU & Backhed F 2016 Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism. *Cell Metabolism* **24** 41–50. (https://doi.org/10.1016/j.cmet.2016.05.005)

Wang J, Thingholm LB, Skieceviciene J, Rausch P, Kummen M, Hov JR, Degenhardt F, Heinsen FA, Ruhlemann MC, Szymczak S, *et al.* 2016 Genome-wide association analysis identifies variation in vitamin D receptor and other host factors influencing the gut microbiota. *Nature Genetics* **48** 1396–1406. (https://doi.org/10.1038/ng.3695)

Wang TJ, Larson MG, Vasan RS, Cheng S, Rhee EP, McCabe E, Lewis GD, Fox CS, Jacques PF, Fernandez C, *et al.* 2011 Metabolite profiles and the risk of developing diabetes. *Nature Medicine* **17** 448–453. (https://doi.org/10.1038/nm.2307)

Wang Z, Roberts AB, Buffa JA, Levison BS, Zhu W, Org E, Gu X, Huang Y, Zamanian-Daryoush M, Culley MK, *et al.* 2015 Non-lethal inhibition of gut microbial trimethylamine production for the treatment of atherosclerosis. *Cell* **163** 1585–1595. (https://doi.org/10.1016/j.cell.2015.11.055)

Watanabe M, Houten SM, Mataki C, Christoffolete MA, Kim BW, Sato H, Messaddeq N, Harney JW, Ezaki O, Kodama T, *et al.* 2006 Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. *Nature* **439** 484–489. (https://doi.org/10.1038/nature04330)

Watanabe Y, Fujisaka S, Ikeda K, Ishikawa M, Yamada T, Nawaz A, Kado T, Kuwano T, Nishimura A, Bilal M, *et al.* 2021 Gut microbiota, determined by dietary nutrients, drive modification of the plasma lipid profile and insulin resistance. *iScience* **24** 102445. (https://doi.org/10.1016/j.isci.2021.102445)

Wen L, Ley RE, Volchkov PY, Stranges PB, Avanesyan L, Stonebraker AC, Hu C, Wong FS, Szot GL, Bluestone JA, *et al.* 2008 Innate immunity and intestinal microbiota in the development of Type 1 diabetes. *Nature* **455** 1109–1113. (https://doi.org/10.1038/nature07336)

Wensel CR, Pluznick JL, Salzberg SL & Sears CL 2022 Next-generation sequencing: insights to advance clinical investigations of the microbiome. *Journal of Clinical Investigation* **132**. (https://doi.org/10.1172/JCI154944)

Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, Bewtra M, Knights D, Walters WA, Knight R, *et al.* 2011 Linking long-term dietary patterns with gut microbial enterotypes. *Science* **334** 105–108. (https://doi.org/10.1126/science.1208344)

Wu H, Tremaroli V, Schmidt C, Lundqvist A, Olsson LM, Kramer M, Gummesson A, Perkins R, Bergstrom G & Backhed F 2020 The gut microbiota in prediabetes and diabetes: a population-based cross-sectional study. *Cell Metabolism* **32** 379–390.e3 e373. (https://doi.org/10.1016/j.cmet.2020.06.011)

Wu S, Yoon S, Zhang YG, Lu R, Xia Y, Wan J, Petrof EO, Claud EC, Chen D & Sun J 2015 Vitamin D receptor pathway is required for probiotic protection in colitis. *American Journal of Physiology. Gastrointestinal and Liver Physiology* **309** G341–G349. (https://doi.org/10.1152/ajpgi.00105.2015)

Yan AW, Fouts DE, Brandl J, Starkel P, Torralba M, Schott E, Tsukamoto H, Nelson KE, Brenner DA & Schnabl B 2011 Enteric dysbiosis associated with a mouse model of alcoholic liver disease. *Hepatology* **53** 96–105. (https://doi.org/10.1002/hep.24018)

Yang J, Li Y, Wen Z, Liu W, Meng L & Huang H 2021 Oscillospira - a candidate for the next-generation probiotics. *Gut Microbes* **13** 1987783. (https://doi.org/10.1080/19490976.2021.1987783)

Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, Nagler CR, Ismagilov RF, Mazmanian SK & Hsiao EY 2015 Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell* **161** 264–276. (https://doi.org/10.1016/j.cell.2015.02.047)

Yoshimoto S, Loo TM, Atarashi K, Kanda H, Sato S, Oyadomari S, Iwakura Y, Oshima K, Morita H, Hattori M, *et al.* 2013 Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. *Nature* **499** 97–101. (https://doi.org/10.1038/nature12347)

Zhang Y, Lee FY, Barrera G, Lee H, Vales C, Gonzalez FJ, Willson TM & Edwards PA 2006 Activation of the nuclear receptor FXR improves hyperglycemia and hyperlipidemia in diabetic mice. *PNAS* **103** 1006–1011. (https://doi.org/10.1073/pnas.0506982103)

Zuo HJ, Xie ZM, Zhang WW, Li YR, Wang W, Ding XB & Pei XF 2011 Gut bacteria alteration in obese people and its relationship with gene polymorphism. *World Journal of Gastroenterology* **17** 1076–1081. (https://doi.org/10.3748/wjg.v17.i8.1076)

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