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**Significance of gut microbiota in alcoholic and non-alcoholic fatty liver diseases**

Sharma SP *et al.* Gut-microbiota in fatty liver disease

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**Abstract**

Liver-gut communication is vital in fatty liver diseases, and gut microbes are the key regulators in maintaining liver homeostasis. Chronic alcohol abuse and persistent overnutrition create dysbiosis in gut ecology, which can contribute to fatty liver disease. In this review, we discuss the gut microbial compositional changes that occur in alcoholic and nonalcoholic fatty liver diseases and how this gut microbial dysbiosis and its metabolic products are involved in fatty liver disease pathophysiology. We also summarize the new approaches related to gut microbes that might help in the diagnosis and treatment of fatty liver disease.

**Key Words:** Fatty liver disease; Alcoholic fatty liver disease; Non-alcoholic fatty liver disease; Gut microbiome; Dysbiosis

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**Core Tip:** In this review, we compare the gut microbial composition in two different fatty liver diseases: Alcoholic fatty liver and nonalcoholic fatty liver. This review enables readers to recognize the gut microbiota compositional differences that occur in these two histopathologically analogous conditions and to explore these gut microbial compositional variations in their research. Additionally, this review will also be helpful in the design of new experiments aiming to develop new diagnostic and/or therapeutic methodologies.

**INTRODUCTION**

Significant increases in mortality and morbidity due to chronic fatty liver disease have raised great global health concerns. Alcoholic fatty liver disease (AFLD) and nonalcoholic fatty liver disease (NAFLD) are the most common chronic fatty liver illnesses in the Western world, with prevalences of 6% and 25%, respectively**[**1**]**, and are the leading causes of liver transplantation**[**2,3**]**. Both AFLD and NAFLD start with fat accumulation in the liver, known as benign or simple steatosis, which leads to inflammation identified as steatohepatitis. Advanced disease includes fibrosis and cirrhosis, which can lead to a more severe state, including hepatocellular carcinoma and liver failure, and ultimately can cause death. Only 20% of patients with AFLD and NAFLD develop progressive liver disease**[**4,5]. In addition to fat accumulation, increased inflammation, and alcohol consumption, other causes, such as an altered gut microbial composition, gut microbial metabolites, or gut barrier function, are associated with the exacerbation of chronic liver disease[6,7].

The recent increase in the understanding of the microbiota and its metabolites has changed the perspectives of various chronic diseases[8]. The human gut microbiota represents a complex ecosystem with various species of microbes that are approximately 1-2 kg in weight in total[9,10]. The gut microbiota maintains homeostasis by interacting with the host and has important functions, including metabolism, digestion, vitamin production, mucosal immune reaction, and the translocation of microbial-associated molecular patterns[11-14]. Importantly, the gut microbiota is known to have a significant role in liver disease progression, but the associated mechanisms are still not fully established.

The liver is the first organ exposed to gut microbial metabolites through portal vein blood. Therefore, the gut microbial community has a vital role in liver homeostasis, and dysbiosis in gut microbial ecology can produce microbial metabolites and components that can have a direct impact on the liver[15-19]. Similarly, the liver also influences gut microbial ecology, particularly in the intestine, through primary bile acids[20-22]. In this way, the liver and gut share a close bidirectional relationship. Interestingly, fecal microbiota transplantation (FMT) studies showed a proof of concept in alcohol-associated and metabolic disease generation and establishment[19,23,24].

Although AFLD and NAFLD have similar histopathological characteristics, they have different etiologies[25]. Thus, gut microbial composition in AFLD and NAFLD could have some commonalities as well as dissimilarities at various classification levels[16,26]. These gut microbial compositional similarities in AFLD and NAFLD could help not only establish common pathophysiological pathways but also increase the chance of finding common treatments. Conversely, gut microbial compositional variations in AFLD and NAFLD could be helpful for the development of specific disease-based signatural gut microbiota profiles. Additionally, these disease-specific gut microbiota profiles could be valuable for the design of gut-microbiota-based therapies such as probiotics[27], synbiotics[28], postbiotics[29] and/or FMT[30] to ameliorate liver disease. These microbial therapeutics also could provide access for developing personalized patient-based treatments to restore liver functions in AFLD and/or NAFLD. AFLD and/or NAFLD-specific gut microbiota profiles could also be useful in the future as diagnostic biomarker tools for the early diagnosis of these diseases.

Considering the importance of the disease-specific gut microbial signature in AFLD and/or NAFLD, herein, we review the gut microbial compositions related to AFLD and/or NAFLD development, especially focusing on the relationship of these compositions with the progression of both diseases, particularly in humans. We also explicitly focus on the microbial signature pertaining to AFLD and/or NAFLD and common microbes in both fatty liver conditions. This review also helps in the understanding of the deep association between the gut microbiota and fatty liver diseases, which can also be considered microbiota-associated fatty liver diseases.

**GUT MICROBIAL COMMUNITY EUBIOSIS**

The gut microbiota is an endogenous ecosystem that coevolves with the host as a symbiotic organ and regulates the normal physiological functions of the gut, such as food digestion and nutrient absorption, and provides essential micronutrients to the host[31]. The gut microbial ecosystem maintains a balance between the microbial species living inside the gut known as “eubiosis” that is crucial for good health. Microbial colonization in the gastrointestinal tract starts immediately after birth and is dominated by the *Bifidobacterium* genus, and a decline in this dominance is observed in the first year of life[32]. The infant gut microbiota is changeable, as this microbial colonization is affected by multiple external factors, such as the mode of delivery, medications, nourishment[33,34], age, genetic background, and cultural/geographic influence[32,35,36]. Similarly, breastfed infants have a less diverse gut microbiota than formula-fed infants, which is the best possible explanation for the difference in gut microbial composition between United States infants and non-United States infants, as United States infants have 28 operational taxonomic units dominated by the *Prevotella* genus[32]. As children start consuming solid foods, the gut microbiota becomes more diverse and starts stabilizing[32,35,37,38]. Fecal samples collected from different geographical regions showed that the gut microbiota composition took shape toward an adult-like configuration until 3 years of age[32], after which the gut composition became more persistent[39].

Primarily, the *Firmicutes* and *Bacteroidetes phyla* dominated the adult human gut microbial composition, and *Actinobacteria*, *Proteobacteria* and *Verrucomicrobia* were found in lesser abundance. Fecal metagenomic analysis from 4 different countries identified well-classified robust gut microbial communities, named enterotypes, represented through multiple numbers of 3 genera: *Prevotella*, *Ruminococcus* and *Bacteroides*[40], and this classification of enterotype was independent of nationality, age, body mass index (BMI), and sex. However, this enterotype-based classification remains a topic of debate because external factors such as diet are considered primary regulators of gut microbiota composition and functions[41,42] and fail to be identified in healthy and elderly individuals[43]. In addition to diet, aging is also a considerable factor that changes the gut microbiota composition. Bacteria belonging to the *Bacteroidaceae*, *Lachnospiraceae* and *Ruminococcaceae* families are negatively correlated with aging independent of geographical region, lifestyle, and dietary habits[44-46]. Moreover, healthy aging showed increased microbial richness and higher numbers of *Bifidobacterium*, *Oscillospira*, *Akkermansia*, and *Christensenellaceae*[45]. Emerging metagenomic empirical evidence suggests that a healthier gut always has a more diverse microbiota population and that a healthy gut is essential to maintain human health[47,48].

**GUT MICROBIAL COMMUNITY DYSBIOSIS**

A change or alteration in gut microbial composition, which can be related to diseased conditions, is termed “dysbiosis”[49]. Gut microbiota composition varies from birth to death[50] and is influenced by various environmental factors[51-54]. Gut microbial dysbiosis also has a close connection with AFLD and NAFLD.

***Gut microbiota alteration in AFLD***

Persistent high intake of ethanol is the root cause of AFLD[55], as it disrupts the multilayered intestinal defense system involving physical, immunological, and humoral components[56]. Normally, the liver enzyme alcohol dehydrogenase and the ethanol-oxidizing system convert ethanol to acetaldehyde, which is toxic to hepatic cells. Acetaldehyde is immediately metabolized to acetate, released into the bloodstream, and used as a biological fuel by cells for energy production. In a persistently elevated ethanol consumption state, the accumulation of toxic acetaldehyde is increased in the liver, which leads to the production of highly reactive molecules that generate an oxidative stress milieu and contribute to liver injuries[16]. An increase in the flow of ethanol in the liver alters SIRT1 signaling and initiates fat accumulation in hepatocytes[57]. Ethanol reduces SIRT1 expression in the liver, which leads to the fat accumulation in liver cells by disrupting multiple SIRT1-dependent transcription factors and cofactors, such as peroxisome proliferator-activated receptor α, PPARγ coactivator-1α, AMP-activated kinase, lipin-1, β-catenin, forkhead transcription factor O1, sterol regulatory element-binding protein 1, nuclear factor activated T cells c4, and nuclear transcription factor-κB[57-59]. Ethanol facilitates the inhibition of SIRT1, which leads to various signaling network disruptions that increase the accumulation of fat in hepatocytes by decreasing β-oxidation and lipolysis, boosting lipogenesis and inflammation, and collectively leading to AFLD. Recently, human and animal models suggested that even a small intake of alcohol can harm intestinal barrier integrity and raise microbial byproduct levels in the circulation[60,61]. Moreover, there is adequate experimental evidence proving that the interrelationship between alterations in the intestinal microbiota and alcohol abuse and acute and chronic alcohol exposure is primarily responsible for gut microbiota dysbiosis and can lead to AFLD through various pathways, as shown in Figure 1[62]. Animal model-based studies explain that alcohol-induced microbial dysbiosis in the intestine changes homeostasis in the gut-liver axis and that this altered intestinal microbiota plays a crucial role as a mediator in the production of the many negative effects of alcohol.

Animal studies have shown that 3 wk of alcohol exposure causes a ‘leaky gut’, which increases the number of *Bacteroidetes* and *Verrucomicrobia* and decreases the growth of bacteria with anti-inflammatory activity, such as *Firmicutes* (genera such as *Lactobacillus, Lactococcus, Leuconostoc* and *Pediococcus*), in the cecum[63]. Another rodent alcohol-based model showed that changes in intestinal permeability associated with intestinal microbial alterations are related to the decreased expression of hypoxia-induced factor 1α. These studies showed a relative increase in *Actinobacteria* and *Proteobacteria* and a decline in the *Firmicutes* phylum. Moreover, these changes were restored by treatment with probiotic *Lactobacillus rhamnosus* (*L. rhamnosus*) GGtherapy[64-67].

Interestingly, gnotobiotic animals have become an imperative alcoholic model to explore the relationship between the gut and the liver. A comparative study of gnotobiotic and wild-type rats showed less proinflammatory cytokine release and inflammation in gnotobiotic rats than in wild-type rats when treated with alcohol for one week. Moreover, fecal transplantation from alcohol-fed wild-type rats in gnotobiotic animals increased hepatic and intestinal inflammation, indicating the involvement of the intestinal microbiota in AFLD[68]. Chronic alcohol intake also changes the intestinal mucus composition, and mucin knockout animals have less bacterial overgrowth, minimal translocation of the bacteria and reduced intestinal inflammation when administered alcohol[69]. In other studies, the bacterial species *Akkermansia muciniphila* (*A. muciniphila*) from the *Verrucomicrobia* phylum showed potential anti-inflammatory properties in AFLD[70], and the depletion of *A. muciniphila* species was noticed in alcoholic animal models[71,72]. *A. muciniphila* improves intestinal markers such as gut barrier function and mucus thickness and diminishes the liver damage produced by alcohol[73]. Cumulatively, animal studies strongly indicate that alcohol intake considerably changes the intestinal microbial composition (as shown in Table 1), which can be responsible for producing early-onset AFLD by inducing proinflammatory changes, translocating the bacteria and bacterial material by reducing mucus thickness and increasing intestinal permeability.

Likewise, human studies also support the close association between alcohol intake and intestinal microbial dysbiosis in the onset of AFLD, similar to animal models. Prolonged alcohol intake markedly decreases the *Bacteroidetes* population and increases *Proteobacteria*, which leads to compromised intestinal permeability and an increase in the level of bacterial materials such lipopolysaccharides (LPS) and endotoxins in the hepatic circulation and ultimately causes liver injuries[74]. The families *Ruminococcaceae* and *Lachnospiraceae* and their ratio are considered to be protective, whereas *Enterobacteriaceae* to *Bacteroidaceae* and their ratio are believed to be potential pathobionts in the intestine, especially in those with a liver disease with an alcoholic etiology. Therefore, the overgrowth of potentially pathogenic species in the gut in chronic alcohol abuse conditions is related to the initiation of liver injuries[74-76]. The effect of these microbial alterations in the gut is not yet completely understood. However, the administration of *L. rhamnosus* GGimproves the *Lachnospiraceae* population andlimits the growth of *Enterobacteriaceae,* which leads to a decline in proinflammatory cytokines[77]. A reduction in *A. muciniphila* was observed in patients with alcoholic steatohepatitis compared with healthy controls, and this decline in *A. muciniphila* seems to be related to the severity of liver injuries[73]. Additionally, *A. muciniphila* was considered a health-boosting bacterial species along with *Bifidobacterium spp.*, *Roseburia hominis*, and *Feacalibacterium prausnitzii*[78]. However, human and animal empirical data hinted that alcohol-induced gut microbial dysbiosis, especially ethanol consumption, but that some alcoholic beverages, such as red wine, could exert a positive impact on gut microbial ecology. A human crossover study demonstrated that red wine consumption increased the number of *Bacteroides,* *Enterococcus*, and *Bifidobacterium*[79].

Alterations in the gut microbiota due to persistent alcoholic intake are not restricted to bacterial species; the fungal composition also changes. Remarkably, alcoholic liver disease (ALD) patients have a high risk of bacterial infection, and patients with advanced cirrhosis are more prone to fungal infections. Moreover, fungal infections increased the mortality rate in cirrhosis and alcoholic hepatitis patients[80-82]. In an alcoholic murine model, increased fungal growth, particularly *Candida spp.,* was observed and was related to an increase in liver damage[83]. The study results showed that liver inflammation was induced by β-glucan, which is a fungal cell wall component. β-Glucan binds with Kupffer cell C-type lectin-like receptor and upregulates IL-1β. Similarly, ALD patients also showed an increased immune response to intestinal fungi compared to healthy controls. These findings suggest that the composition of nonbacterial gut microbes, such fungi, can also affect AFLD generation, progression, and final outcomes in patients with AFLD.

***Gut microbiota alterations in NAFLD***

The gut microbiota exacerbates and/or alleviates NAFLD conditions through several pathways (Figure 1). Animal and human studies have presented a causal involvement of the gut microbiota in NAFLD establishment[84-86] and its severity[87-89]; however, a robust correlation between the gut microbiota and NAFLD advancement has not yet been established. Differences in gut microbial composition at various hierarchical levels have been recorded in NAFLD patients compared with healthy controls[90,91]. In NAFLD, alterations in the gut microbial community have been shown to start at the phylum level, where increased Proteobacteria have been reported in many studies[90,92,93]. Likewise, altered composition has also been observed at the family level, where an overgrowth of *Enterobacteriaceae*[84,92] and suppression of *Rikenellaceae*[84,94] and *Ruminococcaceae*[91,92,95] have been reported. Moreover, genera such as *Escherichia*[84.90], *Dorea*[94,95], and *Peptoniphilus*[84,94] were overpopulated, and *Anaerosporobacter*[91], *Coprococcus*[84,90,91], *Eubacterium*[84,90], *Faecalibacterium*[84] and *Prevotella*[90,96]were less populated.

In a comparative study, Wang *et al*[91] showed a higher proportion of gram-negative bacteria, including *Bacteroidetes*, and decreased *Firmicutes* in NAFLD patients when the gut microbiota was compared with lean healthy subjects. The decline in *Firmicutes* is associated with short-chain fatty acid (SCFA)-producing bacteria such as *Lactobacillaceae*, *Lachnospiraceae*, and *Ruminococcaceae*. An overgrowth of gram-negative bacterial species was seen in children with NAFLD, with an increased ratio of Gammaproteobacteria and Epsilonproteobacteria compared to their obese and lean counterparts[97]. In contrast, bacteria from the *Firmicutes* phylum (such as *Lactobacillus*, *Roseburia, Dorea*, and *Robinsoniella*)werefound to be increased in the population of NAFLD patients in another study[95]. However, contradictory results were reported in other studies that showed increases in *Dorea* and *Ruminococcus* in NAFLD patients[94,98]. Variability in gut microbial composition was observed with different levels of NAFLD severity. Bacteria belonging to *Firmicutes* were more dominant in moderate NAFLD, while the prevalence of *Proteobacteria* was noted to be associated with the severity of disease, as in fibrosis[93]. The bacterial species that were dominant in mild NAFLD compared to severe NAFLD conditions were *Eubacterium rectale* and *Ruminococcus obeum*[93]. These human study results reflect the conflicting gut microbiota composition in NAFLD, which needs to be evaluated further by implementing a greater number of NAFLD patient-based gut microbial compositional studies.

The gut microbial composition was also assessed in severe NAFLD conditions such as fibrosis and/or in nonalcoholic steatohepatitis (NASH) to examine the functional role of gut microbial dysbiosis in fibrosis progression. The results of these comparative studies exhibited a decline in gram-negative bacterial abundance. Comparative analysis of the gut microbiota between individuals with severe NAFLD and healthy or less severe NAFLD conditions showed a decrease in the *Fusobacteria* phylum population and an increase in *Enterobacteriaceae* family bacteria such as the genera *Shigella*, *Ruminococcin* and *Bacteroides*[92,96]. Similarly, gram-positive bacteria from the *Firmicutes* phylum, the family *Prevotellaceae* and the genus *Prevotella* also showed increases in severe NAFLD conditions[93]. Recently, a study presented a significant alteration based on fibrosis severity in nonobese patients but not in obese patients, where *Ruminococcaceae* and *Veillonellaceae* were the leading microbes related to fibrosis severity in nonobese subjects[99]. Interestingly, oral microbes, including *Streptococcus*[76,100,101], *Veillonella*[91,100], and *Prevotella*[100,102], are discriminatory microbes for advanced NAFLD conditions (especially cirrhosis). Additionally, some microbe representations were constant in NAFLD patients compared with healthy individuals, but some showed conflicting tendencies[103]. Conclusively, microbial composition in NAFLD patients presented a drastic shift in taxonomic group composition by showing an increased ratio of pathogenic microbes and a decline in microbes that are considered metabolically beneficial microbes. Subsequently, this compositional shift in microbial composition might be responsible for NAFLD pathogenesis and exacerbate the severity of the disease from simple steatosis to NASH and from NASH to cirrhosis. Summarized information on gut microbial dysbiosis in NAFLD is listed in Table 2, which provides details regarding the increased and decreased populations of bacteria in NAFLD.

The gut microbiota composition in NAFLD presented a considerable contradiction, where some microbial taxa showed variability in their occurrence, as shown in Table 2. The underlying reasoning behind these contradictory compositional variabilities might be related to study design, clinical study end points, result interpretation, *etc.* Moreover, these underlying reasons could be fundamental restraints in the process of establishing a robust relationship between the gut and NAFLD. Thus, to determine the pathophysiological association between the gut and liver, these fundamental limitations should be resolved.

**GUT ROLE IN FATTY LIVER**

Trillions of microorganisms reside in the gut, including bacteria, archaea, fungi, and viruses, but liver-disease-related research primarily targets the bacterial community, which includes more than 10 bacterial phyla[104,105]. The gut microbiota includes more than 3 million genes collectively, in comparison to the 23000 genes of the human genome; however, human cells and gut bacterial cells are roughly equal in number[106]. This gut microbial genetic material certainly has a defining role in human pathophysiology through multiple mechanisms, especially in liver disease, due to its close relationship with the gut[6,107,108].

***Gut microbial dysbiosis***

Generally, the gut microbiota starts to be shaped at birth and becomes stable in early childhood. This balanced and stable gut microbiota acquires a unique quotient for each microbial species in a healthy state[38]. As discussed above, gut microbial dysbiosis, defined by diminished microbial diversity and distorted gut microbial composition, is observed in both AFLD and NAFLD patients compared to healthy controls[[18](#_ENREF_18),[103](#_ENREF_103)]. Alcohol abuse and overnutrition deplete several bacterial species and shift the microbial composition toward gram-negative bacteria. Microbial species depleted in liver diseases are considered beneficial microbes, and overgrown microbial species are associated with liver pathophysiology and known as pathobionts[[109](#_ENREF_109)]. Alcohol consumption is linked with diminished fungal diversity generated by an increased number of *Candida* species[[83](#_ENREF_83),[110](#_ENREF_110),[111](#_ENREF_111)]. Moreover, gut viruses are the most abundant gut microbes; nonetheless, they have not yet been characterized in liver disease.

This gut compositional proclivity toward gram-negative bacterial species influences multiple pathways directly or indirectly that contribute to AFLD and NAFLD establishment[[16](#_ENREF_16),[91](#_ENREF_91),[92](#_ENREF_92)]. The distorted gut microbiota alters various metabolic processes, such as bile acids, short-chain fatty acids, and energy harvesting, which leads to the initiation of fatty liver disease[[112](#_ENREF_112)]. The distorted gut microbiota also damages gut barrier function, through which microbes and their metabolites can translocate and activate the inflammasome in the liver and cause fatty liver[[112](#_ENREF_112)]. The detailed role of the gut microbiota in fatty liver pathogenesis is presented in Figure 1.

***Leaky gut syndrome***

In the intestine, there are multiple layers of barriers, including physical, biochemical, and immunological barriers, that restrict the translocation of microbes and their products. Chronic alcohol abuse causes gut barrier dysfunction by altering the gut microbial composition[[113](#_ENREF_113)]. Thus, pathogen-associated molecular patterns, such as LPS, are able to translocate from the lumen of the intestine to the liver *via* the portal vein and are recognized by inflammasomes such as Toll-like receptors in the liver to stimulate hepatic inflammation, which leads to hepatocyte injuries and liver fibrosis[[112](#_ENREF_112)]. Likewise, similar pathophysiological pathways are involved in NAFLD progression, but gut disruption and inflammation are stimulated by dietary factors other than alcohol[[112](#_ENREF_112)]. Other types of inflammasomes, including NOD-like receptor protein 3 (NLRP3), also respond to LPS and cause liver inflammation. The activation of NLRP3 triggers the caspase 1 pathway and produces interleukin-1β and several other inflammatory cytokines, which cause apoptosis and fibrosis. Higher levels of inflammasomes such NLRP3 and others were found in severe fatty liver conditions induced by both alcohol and overnutrition[[114](#_ENREF_114),[115](#_ENREF_115)]. The translocation of the microbial metabolites from the intestine to the liver because of the dysfunction of intestinal barriers and increased intestinal permeability could be the contributing factor for AFLD and NAFLD, but more studies are required to establish robust associations.

***Bile acid dysregulation***

Bile acid synthesis and secretion are essential functions performed by liver cells. Importantly, bile acids not only are crucial for dietary fat emulsification but also act as ligands for nuclear and G-protein coupled receptors and regulate various metabolic functions, including glucose and fat metabolism[[116](#_ENREF_116)]. Therefore, smooth regulation of bile acids is important for maintaining a healthy metabolic profile, but gut microbial dysbiosis is associated with bile acid dysregulation and is associated with fatty liver pathogenesis through metabolites[[117](#_ENREF_117)].

Normally, conjugated bile acids are released from hepatocytes, carried by the biliary duct, and secreted into the intestine. After lipid emulsification, the remaining bile acids (primary, hydrophilic, and conjugated) are reabsorbed in the terminal ileum. Bile acid secretion from hepatocytes is primarily regulated by the farnesoid X receptor (FXR) negative feedback mechanism[[118](#_ENREF_118)]. The release of primary bile acids in the intestine activates intestinal FXR, which precedes the transcription of fibroblast growth factor 19 (FGF19). The ileal hormone FGF19 is carried to the liver *via* the portal vein, where FGF19 suppresses CYP7A1 expression and controls bile acid secretion[[119](#_ENREF_119)]. The disruption of bile acid homeostasis is the leading cause of fatty liver[[119-121](#_ENREF_119)].

The change in the gut microbial composition induced by alcohol abuse and a high intake of energy-dense food cause the dysregulation of the bile acid system and instigate fatty liver diseases (AFLD and NAFLD)[[122](#_ENREF_122),[123](#_ENREF_123)]. In AFLD and NAFLD, pathobionts increased in number and were responsible for the conversion of secondary bile acids from primary bile acids and reduced FXR signaling. This downregulation of FXR expression increased insulin resistance and altered glucose and lipid metabolism, which are the key regulatory pathways in AFLD and NAFLD generation. Moreover, AFLD and NAFLD patients showed higher levels of secondary bile acids than primary bile acids in feces and blood. Similarly, the dysregulation of FXR signaling and FGF19 is increased with the severity of the disease in both AFLD and NAFLD[[124-127](#_ENREF_124)]. These outcomes suggest that FXR and bile acid compositional dysregulation are the metabolic features of AFLD and NAFLD and that the dysregulation of both metabolic factors (FXR and bile acids) increases with the severity of AFLD and NAFLD.

Although gut bacteria control bile acid metabolism, the involvement of intestinal bacteria or other gut microbes (including archaea, fungi, and viruses) in bile acid dysregulation in fatty liver patients is not completely understood, and more experimental evidence is required to fill the fundamental gaps.

***Short-chain fatty acid dysregulation***

Nondigestible carbohydrates in food are fermented by gut bacteria, and SCFAs are produced. Butyrate, acetate, and propionate are the most abundant SCFAs found in the intestine. SCFAs have many beneficial effects, including being used as an energy source by colonocytes and enterocytes, maintaining gut barrier function, suppressing hepatic cell proliferation, reducing inflammation, and lowering food intake by increasing satiety[[128](#_ENREF_128)]. Considering the beneficial function of SCFAs in regulating metabolic pathways, their level in the body is crucial to maintain good health.

Chronic alcohol abuse is related to reduced SCFA levels in the stool[[129](#_ENREF_129)]. The SCFA concentration and SCFA-producing bacterial concentration are decreased in the feces of alcoholic hepatitis patients[[109](#_ENREF_109)]. The low circulatory butyrate level is also associated with serum endotoxin, inflammation, and more advanced liver diseases[[130](#_ENREF_130)]. In contrast, a higher level of SCFAs and an increased number of SCFA-producing bacteria were found in NASH patients; however, the study population was small[[131](#_ENREF_131)]. Additionally, increasing levels of SCFAs are related to immune regulation and NAFLD progression[[131](#_ENREF_131)]. Higher fecal concentrations of propionate and butyrate were observed in mild to severe NAFLD patients, whereas higher fecal concentrations of acetate and formate were found in advanced fibrosis patients[[132](#_ENREF_132),[133](#_ENREF_133)]. There is an insufficient amount of empirical proof to establish a concrete relationship between SCFAs and fatty liver diseases, and more studies are required to determine the association between SCFAs and fatty liver diseases.

***Endogenous ethanol production***

Microbial fermentation of dietary sugar increases the endogenous alcohol level in pediatric NASH patients[[84](#_ENREF_84)]. Recently, a *Klebsiella pneumonia* strain was identified in a NASH patient fecal sample and was responsible for producing endogenous ethanol and increasing the blood ethanol level without alcohol consumption[[134](#_ENREF_134)]. FMT from NASH patients to animals results in liver damage, and the elimination of alcohol-producing *Klebsiella pneumoniae* strains reduces liver damage. Additionally, NASH patient weight reduction was also related to a reduced ability to produce ethanol in the gut microbiome[[134](#_ENREF_134)]. Another study focusing on comparing the gut microbial profile in pediatric NAFLD patients showed higher circulatory ethanol levels in diseased patients, which was related to the higher number of *Prevotella* andGammaproteobacterial[[97](#_ENREF_97" \o "Michail, 2015 #2369)]. The results from another study showed that a higher circulatory level of ethanol in NAFLD patients could be the end result of ethanol dehydrogenase activity in insulin-dependent impairment conditions[[135](#_ENREF_135)]. Thus, gut microbial dysbiosis, which can lead to an increasing level of endogenous ethanol in the body, could be an underlying cause of NAFLD and could be responsible for producing the same histopathological characteristics as AFLD. However, some inconsistencies in the results were observed, and establishing an association between this endogenous ethanol phenomenon and NAFLD generation needs more experimental proof[[16](#_ENREF_16),[136](#_ENREF_136),[137](#_ENREF_137)].

***Gut microbial virulence factors***

Virulence factors are microbial proteins and peptides that help pathobionts colonize and are associated with disease generation. A recent study recognized that cytolysin, a protein secreted (exotoxin) by *E. faecalis*, damages hepatocytes and is highly associated with increased mortality in alcoholic hepatitis patients[[18](#_ENREF_18),[138](#_ENREF_138)]. Unfortunately, few studies have shown any further toxins or other proteins related to gut microbiota that can be associated with liver disease.

**FUTURE PERSPECTIVES**

Fatty liver disease (both AFLD and NAFLD) is intricately linked with the gut microbiota and its dysbiosis. Recent advancements in gut microbiome-based metagenomics studies related to liver disease have shown that an increase in and/or depletion of the specific microbial content could contribute greatly to liver injuries and is possibly the key regulator in fatty liver disease establishment and progression[[112](#_ENREF_112)]. Growing evidence regarding the role of the gut microbiota in fatty liver disease generation and progression turns this noncommunicable disease into a communicable disease[[139](#_ENREF_139)]. Therefore, targeting the gut microbiota through various techniques may be an approach for the management of liver disease in the future.

***Prognostic and/or diagnostic biomarkers***

As discussed above, the microbial composition in fatty liver diseases is different from that in healthy individuals. Gut microbes themselves or their microbial metabolites might be useful as prognostic and/or diagnostic tools for the early detection of fatty liver conditions. Generally, constant alcohol intake of more than 60 g per day leads to alcoholic hepatic steatosis, which also presents with higher levels of liver enzymes, such aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and in NAFLD, daily alcohol intake is approximately 30 g per day. Typically, two to three times higher serum AST levels have been observed compared to serum ALT due to alcoholic liver injuries. Patients with AFLD also have higher serum gamma-glutamyltranspeptidase levels[[140](#_ENREF_140)]. Similarly, NAFLD also has noninvasive biomarker detection protocols, such as the NAFLD fibrosis score (including age, BMI, the AST-to-ALT ratio, impaired fasting glucose and diabetes, albumin and platelets), FIB-4 index (including age, ALT, AST, and platelets), and FibroTest (including total bilirubin, α2-macroglobulin, γ-glutamyl transferase, haptoglobin, and apolipoprotein A1 corrected for sex and age)[[141](#_ENREF_141)]. These are the common diagnostic parameters used for AFLD and NAFLD diagnosis. However, there is a lack of conclusive biomarkers that can help in the early diagnosis of hepatic steatosis, and the repertoire of gut microbes and their metabolite profiles might help to fill this gap. Interestingly, a set of gut bacteria combined with age and BMI was used to identify liver disease, and a much more accurate diagnosis was able to be made with its use in patients with advanced fibrosis[[93](#_ENREF_93)]. The gut microbes used as a marker in this study were first identified from NAFLD and advanced fibrosis patients *via* metagenomics analysis and then further used for diagnostic purposes[[93](#_ENREF_93)]. In a separate study, the combination of metagenomic signature microbes with age and serum albumin levels precisely identified cirrhosis in patients with geographically different origins. Additionally, adding serum aspartate aminotransferase levels to these diagnostic tools increased diagnostic efficacy even in the early stage of fibrosis[[142](#_ENREF_142" \o "Oh, 2020 #11)]. In other studies, gut-microbe-derived metabolites showed great potential as diagnostic markers for fatty liver diseases and other liver conditions[[18](#_ENREF_18),[90](#_ENREF_90),[143](#_ENREF_143)].

Although gut microbes and their metabolites have the potential to be noninvasive prognostic and/or diagnostic tools for fatty liver and other liver diseases, larger population-based studies are still required to eliminate constraints related to geographical factors, ethnicity, and dietary factors. Further studies are also warranted to compare the diagnostic ability of gut microbes and their metabolites with contemporary in-use investigative practices such as biopsy and image-based approaches.

**CONCLUSION**

Gut microbiota is crucial in fatty liver diseases (in both AFLD and NAFLD), thus relevance of fatty liver disease specific gut microbial signatures should be further explored in longitudinal human studies. Where, a team of clinician and researchers can prospectively correlate the deterioration of liver with the alteration in the gut microbiota community. Merging fatty liver disease specific gut microbiota with microbial derived metabolites can be helpful in the future to diagnose and treat the AFLD and NAFLD patients.

**REFERENCES**

1 **Xiao J**, Wang F, Wong NK, He J, Zhang R, Sun R, Xu Y, Liu Y, Li W, Koike K, He W, You H, Miao Y, Liu X, Meng M, Gao B, Wang H, Li C. Global liver disease burdens and research trends: Analysis from a Chinese perspective. *J Hepatol* 2019; **71**: 212-221 [PMID: 30871980 DOI: 10.1016/j.jhep.2019.03.004]

2 **Wong RJ**, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, Ahmed A. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology* 2015; **148**: 547-555 [PMID: 25461851 DOI: 10.1053/j.gastro.2014.11.039]

3 **Lee BP**, Vittinghoff E, Dodge JL, Cullaro G, Terrault NA. National Trends and Long-term Outcomes of Liver Transplant for Alcohol-Associated Liver Disease in the United States. *JAMA Intern Med* 2019; **179**: 340-348 [PMID: 30667468 DOI: 10.1001/jamainternmed.2018.6536]

4 **Parker R**, Aithal GP, Becker U, Gleeson D, Masson S, Wyatt JI, Rowe IA; WALDO study group. Natural history of histologically proven alcohol-related liver disease: A systematic review. *J Hepatol* 2019; **71**: 586-593 [PMID: 31173814 DOI: 10.1016/j.jhep.2019.05.020]

5 **Loomba R**, Adams LA. The 20% Rule of NASH Progression: The Natural History of Advanced Fibrosis and Cirrhosis Caused by NASH. *Hepatology* 2019; **70**: 1885-1888 [PMID: 31520407 DOI: 10.1002/hep.30946]

6 **Acharya C**, Bajaj JS. Chronic Liver Diseases and the Microbiome-Translating Our Knowledge of Gut Microbiota to Management of Chronic Liver Disease. *Gastroenterology* 2021; **160**: 556-572 [PMID: 33253686 DOI: 10.1053/j.gastro.2020.10.056]

7 **Reuter B**, Bajaj JS. Microbiome: Emerging Concepts in Patients with Chronic Liver Disease. *Clin Liver Dis* 2020; **24**: 493-520 [PMID: 32620285 DOI: 10.1016/j.cld.2020.04.006]

8 **Jiang W**, Wu N, Wang X, Chi Y, Zhang Y, Qiu X, Hu Y, Li J, Liu Y. Dysbiosis gut microbiota associated with inflammation and impaired mucosal immune function in intestine of humans with non-alcoholic fatty liver disease. *Sci Rep* 2015; **5**: 8096 [PMID: 25644696 DOI: 10.1038/srep08096]

9 **Cui X**, Ye L, Li J, Jin L, Wang W, Li S, Bao M, Wu S, Li L, Geng B, Zhou X, Zhang J, Cai J. Metagenomic and metabolomic analyses unveil dysbiosis of gut microbiota in chronic heart failure patients. *Sci Rep* 2018; **8**: 635 [PMID: 29330424 DOI: 10.1038/s41598-017-18756-2]

10 **Kundu P**, Blacher E, Elinav E, Pettersson S. Our Gut Microbiome: The Evolving Inner Self. *Cell* 2017; **171**: 1481-1493 [PMID: 29245010 DOI: 10.1016/j.cell.2017.11.024]

11 **Lindheim L**, Bashir M, Münzker J, Trummer C, Zachhuber V, Leber B, Horvath A, Pieber TR, Gorkiewicz G, Stadlbauer V, Obermayer-Pietsch B. Alterations in Gut Microbiome Composition and Barrier Function Are Associated with Reproductive and Metabolic Defects in Women with Polycystic Ovary Syndrome (PCOS): A Pilot Study. *PLoS One* 2017; **12**: e0168390 [PMID: 28045919 DOI: 10.1371/journal.pone.0168390]

12 **Prakash S**, Tomaro-Duchesneau C, Saha S, Cantor A. The gut microbiota and human health with an emphasis on the use of microencapsulated bacterial cells. *J Biomed Biotechnol* 2011; **2011**: 981214 [PMID: 21772792 DOI: 10.1155/2011/981214]

13 **Lynch SV**, Pedersen O. The Human Intestinal Microbiome in Health and Disease. *N Engl J Med* 2016; **375**: 2369-2379 [PMID: 27974040 DOI: 10.1056/NEJMra1600266]

14 **Fouhy F**, Ross RP, Fitzgerald GF, Stanton C, Cotter PD. Composition of the early intestinal microbiota: knowledge, knowledge gaps and the use of high-throughput sequencing to address these gaps. *Gut Microbes* 2012; **3**: 203-220 [PMID: 22572829 DOI: 10.4161/gmic.20169]

15 **Mazagova M**, Wang L, Anfora AT, Wissmueller M, Lesley SA, Miyamoto Y, Eckmann L, Dhungana S, Pathmasiri W, Sumner S, Westwater C, Brenner DA, Schnabl B. Commensal microbiota is hepatoprotective and prevents liver fibrosis in mice. *FASEB J* 2015; **29**: 1043-1055 [PMID: 25466902 DOI: 10.1096/fj.14-259515]

16 **Lang S**, Schnabl B. Microbiota and Fatty Liver Disease-the Known, the Unknown, and the Future. *Cell Host Microbe* 2020; **28**: 233-244 [PMID: 32791115 DOI: 10.1016/j.chom.2020.07.007]

17 **Bajaj JS**, Hylemon PB. Gut-liver axis alterations in alcoholic liver disease: Are bile acids the answer? *Hepatology* 2018; **67**: 2074-2075 [PMID: 29272041 DOI: 10.1002/hep.29760]

18 **Duan Y**, Llorente C, Lang S, Brandl K, Chu H, Jiang L, White RC, Clarke TH, Nguyen K, Torralba M, Shao Y, Liu J, Hernandez-Morales A, Lessor L, Rahman IR, Miyamoto Y, Ly M, Gao B, Sun W, Kiesel R, Hutmacher F, Lee S, Ventura-Cots M, Bosques-Padilla F, Verna EC, Abraldes JG, Brown RS Jr, Vargas V, Altamirano J, Caballería J, Shawcross DL, Ho SB, Louvet A, Lucey MR, Mathurin P, Garcia-Tsao G, Bataller R, Tu XM, Eckmann L, van der Donk WA, Young R, Lawley TD, Stärkel P, Pride D, Fouts DE, Schnabl B. Bacteriophage targeting of gut bacterium attenuates alcoholic liver disease. *Nature* 2019; **575**: 505-511 [PMID: 31723265 DOI: 10.1038/s41586-019-1742-x]

19 **Llopis M**, Cassard AM, Wrzosek L, Boschat L, Bruneau A, Ferrere G, Puchois V, Martin JC, Lepage P, Le Roy T, Lefèvre L, Langelier B, Cailleux F, González-Castro AM, Rabot S, Gaudin F, Agostini H, Prévot S, Berrebi D, Ciocan D, Jousse C, Naveau S, Gérard P, Perlemuter G. Intestinal microbiota contributes to individual susceptibility to alcoholic liver disease. *Gut* 2016; **65**: 830-839 [PMID: 26642859 DOI: 10.1136/gutjnl-2015-310585]

20 **Tilg H**, Cani PD, Mayer EA. Gut microbiome and liver diseases. *Gut* 2016; **65**: 2035-2044 [PMID: 27802157 DOI: 10.1136/gutjnl-2016-312729]

21 **Di Ciaula A**, Garruti G, Lunardi Baccetto R, Molina-Molina E, Bonfrate L, Wang DQ, Portincasa P. Bile Acid Physiology. *Ann Hepatol* 2017; **16**: s4-s14 [PMID: 29080336 DOI: 10.5604/01.3001.0010.5493]

22 **Duca FA**, Lam TKT. Bye, bye, bile: how altered bile acid composition changes small intestinal lipid sensing. *Gut* 2020; **69**: 1549-1550 [PMID: 32303610 DOI: 10.1136/gutjnl-2020-320873]

23 **Le Roy CI**, Bowyer RCE, Castillo-Fernandez JE, Pallister T, Menni C, Steves CJ, Berry SE, Spector TD, Bell JT. Dissecting the role of the gut microbiota and diet on visceral fat mass accumulation. *Sci Rep* 2019; **9**: 9758 [PMID: 31278309 DOI: 10.1038/s41598-019-46193-w]

24 **Boulangé CL**, Neves AL, Chilloux J, Nicholson JK, Dumas ME. Impact of the gut microbiota on inflammation, obesity, and metabolic disease. *Genome Med* 2016; **8**: 42 [PMID: 27098727 DOI: 10.1186/s13073-016-0303-2]

25 **Cohen JC**, Horton JD, Hobbs HH. Human fatty liver disease: old questions and new insights. *Science* 2011; **332**: 1519-1523 [PMID: 21700865 DOI: 10.1126/science.1204265]

26 **Jiang L**, Schnabl B. Gut Microbiota in Liver Disease: What Do We Know and What Do We Not Know? *Physiology (Bethesda)* 2020; **35**: 261-274 [PMID: 32490750 DOI: 10.1152/physiol.00005.2020]

27 **Koutnikova H**, Genser B, Monteiro-Sepulveda M, Faurie JM, Rizkalla S, Schrezenmeir J, Clément K. Impact of bacterial probiotics on obesity, diabetes and non-alcoholic fatty liver disease related variables: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open* 2019; **9**: e017995 [PMID: 30928918 DOI: 10.1136/bmjopen-2017-017995]

28 **Sáez-Lara MJ**, Robles-Sanchez C, Ruiz-Ojeda FJ, Plaza-Diaz J, Gil A. Effects of Probiotics and Synbiotics on Obesity, Insulin Resistance Syndrome, Type 2 Diabetes and Non-Alcoholic Fatty Liver Disease: A Review of Human Clinical Trials. *Int J Mol Sci* 2016; **17** [PMID: 27304953 DOI: 10.3390/ijms17060928]

29 **Sharpton SR**, Schnabl B, Knight R, Loomba R. Current Concepts, Opportunities, and Challenges of Gut Microbiome-Based Personalized Medicine in Nonalcoholic Fatty Liver Disease. *Cell Metab* 2021; **33**: 21-32 [PMID: 33296678 DOI: 10.1016/j.cmet.2020.11.010]

30 **Acharya C**, Bajaj JS. Transmitting Diet-Related Microbial Benefit through Fecal Microbiota Transplant in NASH: Can Microbiota Cut Through the Fat? *Hepatol Commun* 2020; **4**: 1559-1561 [PMID: 33163828 DOI: 10.1002/hep4.1596]

31 **Brestoff JR**, Artis D. Commensal bacteria at the interface of host metabolism and the immune system. *Nat Immunol* 2013; **14**: 676-684 [PMID: 23778795 DOI: 10.1038/ni.2640]

32 **Yatsunenko T**, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, Magris M, Hidalgo G, Baldassano RN, Anokhin AP, Heath AC, Warner B, Reeder J, Kuczynski J, Caporaso JG, Lozupone CA, Lauber C, Clemente JC, Knights D, Knight R, Gordon JI. Human gut microbiome viewed across age and geography. *Nature* 2012; **486**: 222-227 [PMID: 22699611 DOI: 10.1038/nature11053]

33 **Bokulich NA**, Chung J, Battaglia T, Henderson N, Jay M, Li H, D Lieber A, Wu F, Perez-Perez GI, Chen Y, Schweizer W, Zheng X, Contreras M, Dominguez-Bello MG, Blaser MJ. Antibiotics, birth mode, and diet shape microbiome maturation during early life. *Sci Transl Med* 2016; **8**: 343ra82 [PMID: 27306664 DOI: 10.1126/scitranslmed.aad7121]

34 **Dominguez-Bello MG**, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, Knight R. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci U S A* 2010; **107**: 11971-11975 [PMID: 20566857 DOI: 10.1073/pnas.1002601107]

35 **Bäckhed F**, Roswall J, Peng Y, Feng Q, Jia H, Kovatcheva-Datchary P, Li Y, Xia Y, Xie H, Zhong H, Khan MT, Zhang J, Li J, Xiao L, Al-Aama J, Zhang D, Lee YS, Kotowska D, Colding C, Tremaroli V, Yin Y, Bergman S, Xu X, Madsen L, Kristiansen K, Dahlgren J, Wang J. Dynamics and Stabilization of the Human Gut Microbiome during the First Year of Life. *Cell Host Microbe* 2015; **17**: 852 [PMID: 26308884 DOI: 10.1016/j.chom.2015.05.012]

36 **Hill CJ**, Lynch DB, Murphy K, Ulaszewska M, Jeffery IB, O'Shea CA, Watkins C, Dempsey E, Mattivi F, Tuohy K, Ross RP, Ryan CA, O' Toole PW, Stanton C. Evolution of gut microbiota composition from birth to 24 weeks in the INFANTMET Cohort. *Microbiome* 2017; **5**: 4 [PMID: 28095889 DOI: 10.1186/s40168-016-0213-y]

37 **Tsuji H**, Oozeer R, Matsuda K, Matsuki T, Ohta T, Nomoto K, Tanaka R, Kawashima M, Kawashima K, Nagata S, Yamashiro Y. Molecular monitoring of the development of intestinal microbiota in Japanese infants. *Benef Microbes* 2012; **3**: 113-125 [PMID: 22683836 DOI: 10.3920/BM2011.0038]

38 **Cheng J**, Ringel-Kulka T, Heikamp-de Jong I, Ringel Y, Carroll I, de Vos WM, Salojärvi J, Satokari R. Discordant temporal development of bacterial phyla and the emergence of core in the fecal microbiota of young children. *ISME J* 2016; **10**: 1002-1014 [PMID: 26430856 DOI: 10.1038/ismej.2015.177]

39 **Zmora N**, Zilberman-Schapira G, Suez J, Mor U, Dori-Bachash M, Bashiardes S, Kotler E, Zur M, Regev-Lehavi D, Brik RB, Federici S, Cohen Y, Linevsky R, Rothschild D, Moor AE, Ben-Moshe S, Harmelin A, Itzkovitz S, Maharshak N, Shibolet O, Shapiro H, Pevsner-Fischer M, Sharon I, Halpern Z, Segal E, Elinav E. Personalized Gut Mucosal Colonization Resistance to Empiric Probiotics Is Associated with Unique Host and Microbiome Features. *Cell* 2018; **174**: 1388-1405.e21 [PMID: 30193112 DOI: 10.1016/j.cell.2018.08.041]

40 **Arumugam M**, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, Fernandes GR, Tap J, Bruls T, Batto JM, Bertalan M, Borruel N, Casellas F, Fernandez L, Gautier L, Hansen T, Hattori M, Hayashi T, Kleerebezem M, Kurokawa K, Leclerc M, Levenez F, Manichanh C, Nielsen HB, Nielsen T, Pons N, Poulain J, Qin J, Sicheritz-Ponten T, Tims S, Torrents D, Ugarte E, Zoetendal EG, Wang J, Guarner F, Pedersen O, de Vos WM, Brunak S, Doré J; MetaHIT Consortium, Antolín M, Artiguenave F, Blottiere HM, Almeida M, Brechot C, Cara C, Chervaux C, Cultrone A, Delorme C, Denariaz G, Dervyn R, Foerstner KU, Friss C, van de Guchte M, Guedon E, Haimet F, Huber W, van Hylckama-Vlieg J, Jamet A, Juste C, Kaci G, Knol J, Lakhdari O, Layec S, Le Roux K, Maguin E, Mérieux A, Melo Minardi R, M'rini C, Muller J, Oozeer R, Parkhill J, Renault P, Rescigno M, Sanchez N, Sunagawa S, Torrejon A, Turner K, Vandemeulebrouck G, Varela E, Winogradsky Y, Zeller G, Weissenbach J, Ehrlich SD, Bork P. Enterotypes of the human gut microbiome. *Nature* 2011; **473**: 174-180 [PMID: 21508958 DOI: 10.1038/nature09944]

41 **David LA**, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA, Biddinger SB, Dutton RJ, Turnbaugh PJ. Diet rapidly and reproducibly alters the human gut microbiome. *Nature* 2014; **505**: 559-563 [PMID: 24336217 DOI: 10.1038/nature12820]

42 **Muegge BD**, Kuczynski J, Knights D, Clemente JC, González A, Fontana L, Henrissat B, Knight R, Gordon JI. Diet drives convergence in gut microbiome functions across mammalian phylogeny and within humans. *Science* 2011; **332**: 970-974 [PMID: 21596990 DOI: 10.1126/science.1198719]

43 **Claesson MJ**, Jeffery IB, Conde S, Power SE, O'Connor EM, Cusack S, Harris HM, Coakley M, Lakshminarayanan B, O'Sullivan O, Fitzgerald GF, Deane J, O'Connor M, Harnedy N, O'Connor K, O'Mahony D, van Sinderen D, Wallace M, Brennan L, Stanton C, Marchesi JR, Fitzgerald AP, Shanahan F, Hill C, Ross RP, O'Toole PW. Gut microbiota composition correlates with diet and health in the elderly. *Nature* 2012; **488**: 178-184 [PMID: 22797518 DOI: 10.1038/nature11319]

44 **Biagi E**, Franceschi C, Rampelli S, Severgnini M, Ostan R, Turroni S, Consolandi C, Quercia S, Scurti M, Monti D, Capri M, Brigidi P, Candela M. Gut Microbiota and Extreme Longevity. *Curr Biol* 2016; **26**: 1480-1485 [PMID: 27185560 DOI: 10.1016/j.cub.2016.04.016]

45 **Kong F**, Hua Y, Zeng B, Ning R, Li Y, Zhao J. Gut microbiota signatures of longevity. *Curr Biol* 2016; **26**: R832-R833 [PMID: 27676296 DOI: 10.1016/j.cub.2016.08.015]

46 **Wang N**, Li R, Lin H, Fu C, Wang X, Zhang Y, Su M, Huang P, Qian J, Jiang F, Wang H, Jiang L, Yu X, Liu J, Chen Y, Jiang Q. Enriched taxa were found among the gut microbiota of centenarians in East China. *PLoS One* 2019; **14**: e0222763 [PMID: 31639130 DOI: 10.1371/journal.pone.0222763]

47 **Bajinka O**, Tan Y, Abdelhalim KA, Özdemir G, Qiu X. Extrinsic factors influencing gut microbes, the immediate consequences and restoring eubiosis. *AMB Express* 2020; **10**: 130 [PMID: 32710186 DOI: 10.1186/s13568-020-01066-8]

48 **Ruan W**, Engevik MA, Spinler JK, Versalovic J. Healthy Human Gastrointestinal Microbiome: Composition and Function After a Decade of Exploration. *Dig Dis Sci* 2020; **65**: 695-705 [PMID: 32067143 DOI: 10.1007/s10620-020-06118-4]

49 **Hooks KB**, O'Malley MA. Dysbiosis and Its Discontents. *mBio* 2017; **8** [PMID: 29018121 DOI: 10.1128/mBio.01492-17]

50 **Rodríguez JM**, Murphy K, Stanton C, Ross RP, Kober OI, Juge N, Avershina E, Rudi K, Narbad A, Jenmalm MC, Marchesi JR, Collado MC. The composition of the gut microbiota throughout life, with an emphasis on early life. *Microb Ecol Health Dis* 2015; **26**: 26050 [PMID: 25651996 DOI: 10.3402/mehd.v26.26050]

51 **Vandeputte D**, Falony G, Vieira-Silva S, Tito RY, Joossens M, Raes J. Stool consistency is strongly associated with gut microbiota richness and composition, enterotypes and bacterial growth rates. *Gut* 2016; **65**: 57-62 [PMID: 26069274 DOI: 10.1136/gutjnl-2015-309618]

52 **Rothschild D**, Weissbrod O, Barkan E, Kurilshikov A, Korem T, Zeevi D, Costea PI, Godneva A, Kalka IN, Bar N, Shilo S, Lador D, Vila AV, Zmora N, Pevsner-Fischer M, Israeli D, Kosower N, Malka G, Wolf BC, Avnit-Sagi T, Lotan-Pompan M, Weinberger A, Halpern Z, Carmi S, Fu J, Wijmenga C, Zhernakova A, Elinav E, Segal E. Environment dominates over host genetics in shaping human gut microbiota. *Nature* 2018; **555**: 210-215 [PMID: 29489753 DOI: 10.1038/nature25973]

53 **Wu GD**, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, Bewtra M, Knights D, Walters WA, Knight R, Sinha R, Gilroy E, Gupta K, Baldassano R, Nessel L, Li H, Bushman FD, Lewis JD. Linking long-term dietary patterns with gut microbial enterotypes. *Science* 2011; **334**: 105-108 [PMID: 21885731 DOI: 10.1126/science.1208344]

54 **Bajaj JS**, Idilman R, Mabudian L, Hood M, Fagan A, Turan D, White MB, Karakaya F, Wang J, Atalay R, Hylemon PB, Gavis EA, Brown R, Thacker LR, Acharya C, Heuman DM, Sikaroodi M, Gillevet PM. Diet affects gut microbiota and modulates hospitalization risk differentially in an international cirrhosis cohort. *Hepatology* 2018; **68**: 234-247 [PMID: 29350768 DOI: 10.1002/hep.29791]

55 **Seitz HK**, Bataller R, Cortez-Pinto H, Gao B, Gual A, Lackner C, Mathurin P, Mueller S, Szabo G, Tsukamoto H. Alcoholic liver disease. *Nat Rev Dis Primers* 2018; **4**: 16 [PMID: 30115921 DOI: 10.1038/s41572-018-0014-7]

56 **Wiest R**, Albillos A, Trauner M, Bajaj JS, Jalan R. Targeting the gut-liver axis in liver disease. *J Hepatol* 2017; **67**: 1084-1103 [PMID: 28526488 DOI: 10.1016/j.jhep.2017.05.007]

57 **You M**, Jogasuria A, Taylor C, Wu J. Sirtuin 1 signaling and alcoholic fatty liver disease. *Hepatobiliary Surg Nutr* 2015; **4**: 88-100 [PMID: 26005675 DOI: 10.3978/j.issn.2304-3881.2014.12.06]

58 **Ding RB**, Bao J, Deng CX. Emerging roles of SIRT1 in fatty liver diseases. *Int J Biol Sci* 2017; **13**: 852-867 [PMID: 28808418 DOI: 10.7150/ijbs.19370]

59 **Liang X**, Hu M, Rogers CQ, Shen Z, You M. Role of SIRT1-FoxO1 signaling in dietary saturated fat-dependent upregulation of liver adiponectin receptor 2 in ethanol-administered mice. *Antioxid Redox Signal* 2011; **15**: 425-435 [PMID: 21194380 DOI: 10.1089/ars.2010.3780]

60 **Bala S**, Marcos M, Gattu A, Catalano D, Szabo G. Acute binge drinking increases serum endotoxin and bacterial DNA levels in healthy individuals. *PLoS One* 2014; **9**: e96864 [PMID: 24828436 DOI: 10.1371/journal.pone.0096864]

61 **Voigt RM**, Forsyth CB, Shaikh M, Zhang L, Raeisi S, Aloman C, Preite NZ, Donohue TM Jr, Fogg L, Keshavarzian A. Diurnal variations in intestinal barrier integrity and liver pathology in mice: implications for alcohol binge. *Am J Physiol Gastrointest Liver Physiol* 2018; **314**: G131-G141 [PMID: 29074484 DOI: 10.1152/ajpgi.00103.2017]

62 **Leung C**, Rivera L, Furness JB, Angus PW. The role of the gut microbiota in NAFLD. *Nat Rev Gastroenterol Hepatol* 2016; **13**: 412-425 [PMID: 27273168 DOI: 10.1038/nrgastro.2016.85]

63 **Yan AW**, Fouts DE, Brandl J, Stärkel P, Torralba M, Schott E, Tsukamoto H, Nelson KE, Brenner DA, Schnabl B. Enteric dysbiosis associated with a mouse model of alcoholic liver disease. *Hepatology* 2011; **53**: 96-105 [PMID: 21254165 DOI: 10.1002/hep.24018]

64 **Bull-Otterson L**, Feng W, Kirpich I, Wang Y, Qin X, Liu Y, Gobejishvili L, Joshi-Barve S, Ayvaz T, Petrosino J, Kong M, Barker D, McClain C, Barve S. Metagenomic analyses of alcohol induced pathogenic alterations in the intestinal microbiome and the effect of Lactobacillus rhamnosus GG treatment. *PLoS One* 2013; **8**: e53028 [PMID: 23326376 DOI: 10.1371/journal.pone.0053028]

65 **Wang Y**, Kirpich I, Liu Y, Ma Z, Barve S, McClain CJ, Feng W. Lactobacillus rhamnosus GG treatment potentiates intestinal hypoxia-inducible factor, promotes intestinal integrity and ameliorates alcohol-induced liver injury. *Am J Pathol* 2011; **179**: 2866-2875 [PMID: 22093263 DOI: 10.1016/j.ajpath.2011.08.039]

66 **Chen P**, Torralba M, Tan J, Embree M, Zengler K, Stärkel P, van Pijkeren JP, DePew J, Loomba R, Ho SB, Bajaj JS, Mutlu EA, Keshavarzian A, Tsukamoto H, Nelson KE, Fouts DE, Schnabl B. Supplementation of saturated long-chain fatty acids maintains intestinal eubiosis and reduces ethanol-induced liver injury in mice. *Gastroenterology* 2015; **148**: 203-214.e16 [PMID: 25239591 DOI: 10.1053/j.gastro.2014.09.014]

67 **Shao T**, Zhao C, Li F, Gu Z, Liu L, Zhang L, Wang Y, He L, Liu Y, Liu Q, Chen Y, Donde H, Wang R, Jala VR, Barve S, Chen SY, Zhang X, Chen Y, McClain CJ, Feng W. Intestinal HIF-1α deletion exacerbates alcoholic liver disease by inducing intestinal dysbiosis and barrier dysfunction. *J Hepatol* 2018; **69**: 886-895 [PMID: 29803899 DOI: 10.1016/j.jhep.2018.05.021]

68 Canesso MCC, Lacerda NL, Ferreira CM, Goncalves JL, Almeida D, Gamba C, Cassali G, Pedroso SH, Moreira C, Martins FS, Nicoli JR, Teixeira MM, Godard ALB, Vieira AT. Comparing the effects of acute alcohol consumption in germ-free and conventional mice: the role of the gut microbiota. *BMC Microbiol* 2014; **14**: 240 [PMID: 25223989 DOI: 10.1186/s12866-014-0240-4]

69 **Hartmann P**, Chen P, Wang HJ, Wang L, McCole DF, Brandl K, Stärkel P, Belzer C, Hellerbrand C, Tsukamoto H, Ho SB, Schnabl B. Deficiency of intestinal mucin-2 ameliorates experimental alcoholic liver disease in mice. *Hepatology* 2013; **58**: 108-119 [PMID: 23408358 DOI: 10.1002/hep.26321]

70 **Derrien M**, Belzer C, de Vos WM. Akkermansia muciniphila and its role in regulating host functions. *Microb Pathog* 2017; **106**: 171-181 [PMID: 26875998 DOI: 10.1016/j.micpath.2016.02.005]

71 **Lowe PP**, Gyongyosi B, Satishchandran A, Iracheta-Vellve A, Ambade A, Kodys K, Catalano D, Ward DV, Szabo G. Alcohol-related changes in the intestinal microbiome influence neutrophil infiltration, inflammation and steatosis in early alcoholic hepatitis in mice. *PLoS One* 2017; **12**: e0174544 [PMID: 28350851 DOI: 10.1371/journal.pone.0174544]

72 **Lowe PP**, Gyongyosi B, Satishchandran A, Iracheta-Vellve A, Ambade A, Cho Y, Kodys K, Catalano D, Ward DV, Szabo G. Correction: Alcohol-related changes in the intestinal microbiome influence neutrophil infiltration, inflammation and steatosis in early alcoholic hepatitis in mice. *PLoS One* 2017; **12**: e0179070 [PMID: 28562651 DOI: 10.1371/journal.pone.0179070]

73 **Grander C**, Adolph TE, Wieser V, Lowe P, Wrzosek L, Gyongyosi B, Ward DV, Grabherr F, Gerner RR, Pfister A, Enrich B, Ciocan D, Macheiner S, Mayr L, Drach M, Moser P, Moschen AR, Perlemuter G, Szabo G, Cassard AM, Tilg H. Recovery of ethanol-induced *Akkermansia muciniphila* depletion ameliorates alcoholic liver disease. *Gut* 2018; **67**: 891-901 [PMID: 28550049 DOI: 10.1136/gutjnl-2016-313432]

74 **Kakiyama G**, Pandak WM, Gillevet PM, Hylemon PB, Heuman DM, Daita K, Takei H, Muto A, Nittono H, Ridlon JM, White MB, Noble NA, Monteith P, Fuchs M, Thacker LR, Sikaroodi M, Bajaj JS. Modulation of the fecal bile acid profile by gut microbiota in cirrhosis. *J Hepatol* 2013; **58**: 949-955 [PMID: 23333527 DOI: 10.1016/j.jhep.2013.01.003]

75 **Bajaj JS**, Heuman DM, Hylemon PB, Sanyal AJ, White MB, Monteith P, Noble NA, Unser AB, Daita K, Fisher AR, Sikaroodi M, Gillevet PM. Altered profile of human gut microbiome is associated with cirrhosis and its complications. *J Hepatol* 2014; **60**: 940-947 [PMID: 24374295 DOI: 10.1016/j.jhep.2013.12.019]

76 **Chen Y**, Yang F, Lu H, Wang B, Chen Y, Lei D, Wang Y, Zhu B, Li L. Characterization of fecal microbial communities in patients with liver cirrhosis. *Hepatology* 2011; **54**: 562-572 [PMID: 21574172 DOI: 10.1002/hep.24423]

77 **Bajaj JS**, Heuman DM, Hylemon PB, Sanyal AJ, Puri P, Sterling RK, Luketic V, Stravitz RT, Siddiqui MS, Fuchs M, Thacker LR, Wade JB, Daita K, Sistrun S, White MB, Noble NA, Thorpe C, Kakiyama G, Pandak WM, Sikaroodi M, Gillevet PM. Randomised clinical trial: Lactobacillus GG modulates gut microbiome, metabolome and endotoxemia in patients with cirrhosis. *Aliment Pharmacol Ther* 2014; **39**: 1113-1125 [PMID: 24628464 DOI: 10.1111/apt.12695]

78 **Bressa C**, Bailén-Andrino M, Pérez-Santiago J, González-Soltero R, Pérez M, Montalvo-Lominchar MG, Maté-Muñoz JL, Domínguez R, Moreno D, Larrosa M. Differences in gut microbiota profile between women with active lifestyle and sedentary women. *PLoS One* 2017; **12**: e0171352 [PMID: 28187199 DOI: 10.1371/journal.pone.0171352]

79 **Queipo-Ortuño MI**, Boto-Ordóñez M, Murri M, Gomez-Zumaquero JM, Clemente-Postigo M, Estruch R, Cardona Diaz F, Andrés-Lacueva C, Tinahones FJ. Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers. *Am J Clin Nutr* 2012; **95**: 1323-1334 [PMID: 22552027 DOI: 10.3945/ajcn.111.027847]

80 **Bajaj JS**, Reddy RK, Tandon P, Wong F, Kamath PS, Biggins SW, Garcia-Tsao G, Fallon M, Maliakkal B, Lai J, Vargas HE, Subramanian RM, Thuluvath P, Thacker LR, OʼLeary JG. Prediction of Fungal Infection Development and Their Impact on Survival Using the NACSELD Cohort. *Am J Gastroenterol* 2018; **113**: 556-563 [PMID: 29257141 DOI: 10.1038/ajg.2017.471]

81 **Lahmer T**, Messer M, Schwerdtfeger C, Rasch S, Lee M, Saugel B, Schmid RM, Huber W. Invasive mycosis in medical intensive care unit patients with severe alcoholic hepatitis. *Mycopathologia* 2014; **177**: 193-197 [PMID: 24710759 DOI: 10.1007/s11046-014-9740-x]

82 **Gustot T**, Maillart E, Bocci M, Surin R, Trépo E, Degré D, Lucidi V, Taccone FS, Delforge ML, Vincent JL, Donckier V, Jacobs F, Moreno C. Invasive aspergillosis in patients with severe alcoholic hepatitis. *J Hepatol* 2014; **60**: 267-274 [PMID: 24055548 DOI: 10.1016/j.jhep.2013.09.011]

83 **Yang AM**, Inamine T, Hochrath K, Chen P, Wang L, Llorente C, Bluemel S, Hartmann P, Xu J, Koyama Y, Kisseleva T, Torralba MG, Moncera K, Beeri K, Chen CS, Freese K, Hellerbrand C, Lee SM, Hoffman HM, Mehal WZ, Garcia-Tsao G, Mutlu EA, Keshavarzian A, Brown GD, Ho SB, Bataller R, Stärkel P, Fouts DE, Schnabl B. Intestinal fungi contribute to development of alcoholic liver disease. *J Clin Invest* 2017; **127**: 2829-2841 [PMID: 28530644 DOI: 10.1172/JCI90562]

84 **Zhu L**, Baker SS, Gill C, Liu W, Alkhouri R, Baker RD, Gill SR. Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: a connection between endogenous alcohol and NASH. *Hepatology* 2013; **57**: 601-609 [PMID: 23055155 DOI: 10.1002/hep.26093]

85 **Mouzaki M**, Comelli EM, Arendt BM, Bonengel J, Fung SK, Fischer SE, McGilvray ID, Allard JP. Intestinal microbiota in patients with nonalcoholic fatty liver disease. *Hepatology* 2013; **58**: 120-127 [PMID: 23401313 DOI: 10.1002/hep.26319]

86 **Jennison E**, Byrne CD. The role of the gut microbiome and diet in the pathogenesis of non-alcoholic fatty liver disease. *Clin Mol Hepatol* 2021; **27**: 22-43 [PMID: 33291863 DOI: 10.3350/cmh.2020.0129]

87 **Eslamparast T**, Eghtesad S, Poustchi H, Hekmatdoost A. Recent advances in dietary supplementation, in treating non-alcoholic fatty liver disease. *World J Hepatol* 2015; **7**: 204-212 [PMID: 25729475 DOI: 10.4254/wjh.v7.i2.204]

88 **Eslamparast T**, Poustchi H, Zamani F, Sharafkhah M, Malekzadeh R, Hekmatdoost A. Synbiotic supplementation in nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled pilot study. *Am J Clin Nutr* 2014; **99**: 535-542 [PMID: 24401715 DOI: 10.3945/ajcn.113.068890]

89 **Rahimlou M**, Ahmadnia H, Hekmatdoost A. Dietary supplements and pediatric non-alcoholic fatty liver disease: Present and the future. *World J Hepatol* 2015; **7**: 2597-2602 [PMID: 26557952 DOI: 10.4254/wjh.v7.i25.2597]

90 **Hoyles L**, Fernández-Real JM, Federici M, Serino M, Abbott J, Charpentier J, Heymes C, Luque JL, Anthony E, Barton RH, Chilloux J, Myridakis A, Martinez-Gili L, Moreno-Navarrete JM, Benhamed F, Azalbert V, Blasco-Baque V, Puig J, Xifra G, Ricart W, Tomlinson C, Woodbridge M, Cardellini M, Davato F, Cardolini I, Porzio O, Gentileschi P, Lopez F, Foufelle F, Butcher SA, Holmes E, Nicholson JK, Postic C, Burcelin R, Dumas ME. Molecular phenomics and metagenomics of hepatic steatosis in non-diabetic obese women. *Nat Med* 2018; **24**: 1070-1080 [PMID: 29942096 DOI: 10.1038/s41591-018-0061-3]

91 **Wang B**, Jiang X, Cao M, Ge J, Bao Q, Tang L, Chen Y, Li L. Altered Fecal Microbiota Correlates with Liver Biochemistry in Nonobese Patients with Non-alcoholic Fatty Liver Disease. *Sci Rep* 2016; **6**: 32002 [PMID: 27550547 DOI: 10.1038/srep32002]

92 **Shen F**, Zheng RD, Sun XQ, Ding WJ, Wang XY, Fan JG. Gut microbiota dysbiosis in patients with non-alcoholic fatty liver disease. *Hepatobiliary Pancreat Dis Int* 2017; **16**: 375-381 [PMID: 28823367 DOI: 10.1016/S1499-3872(17)60019-5]

93 **Loomba R**, Seguritan V, Li W, Long T, Klitgord N, Bhatt A, Dulai PS, Caussy C, Bettencourt R, Highlander SK, Jones MB, Sirlin CB, Schnabl B, Brinkac L, Schork N, Chen CH, Brenner DA, Biggs W, Yooseph S, Venter JC, Nelson KE. Gut Microbiome-Based Metagenomic Signature for Non-invasive Detection of Advanced Fibrosis in Human Nonalcoholic Fatty Liver Disease. *Cell Metab* 2017; **25**: 1054-1062.e5 [PMID: 28467925 DOI: 10.1016/j.cmet.2017.04.001]

94 **Del Chierico F**, Nobili V, Vernocchi P, Russo A, De Stefanis C, Gnani D, Furlanello C, Zandonà A, Paci P, Capuani G, Dallapiccola B, Miccheli A, Alisi A, Putignani L. Gut microbiota profiling of pediatric nonalcoholic fatty liver disease and obese patients unveiled by an integrated meta-omics-based approach. *Hepatology* 2017; **65**: 451-464 [PMID: 27028797 DOI: 10.1002/hep.28572]

95 **Raman M**, Ahmed I, Gillevet PM, Probert CS, Ratcliffe NM, Smith S, Greenwood R, Sikaroodi M, Lam V, Crotty P, Bailey J, Myers RP, Rioux KP. Fecal microbiome and volatile organic compound metabolome in obese humans with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2013; **11**: 868-75.e1-3 [PMID: 23454028 DOI: 10.1016/j.cgh.2013.02.015]

96 **Boursier J**, Mueller O, Barret M, Machado M, Fizanne L, Araujo-Perez F, Guy CD, Seed PC, Rawls JF, David LA, Hunault G, Oberti F, Calès P, Diehl AM. The severity of nonalcoholic fatty liver disease is associated with gut dysbiosis and shift in the metabolic function of the gut microbiota. *Hepatology* 2016; **63**: 764-775 [PMID: 26600078 DOI: 10.1002/hep.28356]

97 **Michail S**, Lin M, Frey MR, Fanter R, Paliy O, Hilbush B, Reo NV. Altered gut microbial energy and metabolism in children with non-alcoholic fatty liver disease. *FEMS Microbiol Ecol* 2015; **91**: 1-9 [PMID: 25764541 DOI: 10.1093/femsec/fiu002]

98 **Jiang C**, Xie C, Li F, Zhang L, Nichols RG, Krausz KW, Cai J, Qi Y, Fang ZZ, Takahashi S, Tanaka N, Desai D, Amin SG, Albert I, Patterson AD, Gonzalez FJ. Intestinal farnesoid X receptor signaling promotes nonalcoholic fatty liver disease. *J Clin Invest* 2015; **125**: 386-402 [PMID: 25500885 DOI: 10.1172/JCI76738]

99 **Lee G**, You HJ, Bajaj JS, Joo SK, Yu J, Park S, Kang H, Park JH, Kim JH, Lee DH, Lee S, Kim W, Ko G. Distinct signatures of gut microbiome and metabolites associated with significant fibrosis in non-obese NAFLD. *Nat Commun* 2020; **11**: 4982 [PMID: 33020474 DOI: 10.1038/s41467-020-18754-5]

100 **Qin N**, Yang F, Li A, Prifti E, Chen Y, Shao L, Guo J, Le Chatelier E, Yao J, Wu L, Zhou J, Ni S, Liu L, Pons N, Batto JM, Kennedy SP, Leonard P, Yuan C, Ding W, Chen Y, Hu X, Zheng B, Qian G, Xu W, Ehrlich SD, Zheng S, Li L. Alterations of the human gut microbiome in liver cirrhosis. *Nature* 2014; **513**: 59-64 [PMID: 25079328 DOI: 10.1038/nature13568]

101 **Caussy C**, Tripathi A, Humphrey G, Bassirian S, Singh S, Faulkner C, Bettencourt R, Rizo E, Richards L, Xu ZZ, Downes MR, Evans RM, Brenner DA, Sirlin CB, Knight R, Loomba R. A gut microbiome signature for cirrhosis due to nonalcoholic fatty liver disease. *Nat Commun* 2019; **10**: 1406 [PMID: 30926798 DOI: 10.1038/s41467-019-09455-9]

102 **Chen Y**, Ji F, Guo J, Shi D, Fang D, Li L. Dysbiosis of small intestinal microbiota in liver cirrhosis and its association with etiology. *Sci Rep* 2016; **6**: 34055 [PMID: 27687977 DOI: 10.1038/srep34055]

103 **Aron-Wisnewsky J**, Vigliotti C, Witjes J, Le P, Holleboom AG, Verheij J, Nieuwdorp M, Clément K. Gut microbiota and human NAFLD: disentangling microbial signatures from metabolic disorders. *Nat Rev Gastroenterol Hepatol* 2020; **17**: 279-297 [PMID: 32152478 DOI: 10.1038/s41575-020-0269-9]

104 **Sender R**, Fuchs S, Milo R. Are We Really Vastly Outnumbered? Revisiting the Ratio of Bacterial to Host Cells in Humans. *Cell* 2016; **164**: 337-340 [PMID: 26824647 DOI: 10.1016/j.cell.2016.01.013]

105 **Sender R**, Fuchs S, Milo R. Revised Estimates for the Number of Human and Bacteria Cells in the Body. *PLoS Biol* 2016; **14**: e1002533 [PMID: 27541692 DOI: 10.1371/journal.pbio.1002533]

106 **Schroeder BO**, Bäckhed F. Signals from the gut microbiota to distant organs in physiology and disease. *Nat Med* 2016; **22**: 1079-1089 [PMID: 27711063 DOI: 10.1038/nm.4185]

107 **Wang R**, Tang R, Li B, Ma X, Schnabl B, Tilg H. Gut microbiome, liver immunology, and liver diseases. *Cell Mol Immunol* 2021; **18**: 4-17 [PMID: 33318628 DOI: 10.1038/s41423-020-00592-6]

108 **Seo YS**, Shah VH. The role of gut-liver axis in the pathogenesis of liver cirrhosis and portal hypertension. *Clin Mol Hepatol* 2012; **18**: 337-346 [PMID: 23323248 DOI: 10.3350/cmh.2012.18.4.337]

109 **Smirnova E**, Puri P, Muthiah MD, Daitya K, Brown R, Chalasani N, Liangpunsakul S, Shah VH, Gelow K, Siddiqui MS, Boyett S, Mirshahi F, Sikaroodi M, Gillevet P, Sanyal AJ. Fecal Microbiome Distinguishes Alcohol Consumption From Alcoholic Hepatitis But Does Not Discriminate Disease Severity. *Hepatology* 2020; **72**: 271-286 [PMID: 32056227 DOI: 10.1002/hep.31178]

110 **Chu H**, Duan Y, Lang S, Jiang L, Wang Y, Llorente C, Liu J, Mogavero S, Bosques-Padilla F, Abraldes JG, Vargas V, Tu XM, Yang L, Hou X, Hube B, Stärkel P, Schnabl B. The Candida albicans exotoxin candidalysin promotes alcohol-associated liver disease. *J Hepatol* 2020; **72**: 391-400 [PMID: 31606552 DOI: 10.1016/j.jhep.2019.09.029]

111 **Lang S**, Duan Y, Liu J, Torralba MG, Kuelbs C, Ventura-Cots M, Abraldes JG, Bosques-Padilla F, Verna EC, Brown RS Jr, Vargas V, Altamirano J, Caballería J, Shawcross D, Lucey MR, Louvet A, Mathurin P, Garcia-Tsao G, Ho SB, Tu XM, Bataller R, Stärkel P, Fouts DE, Schnabl B. Intestinal Fungal Dysbiosis and Systemic Immune Response to Fungi in Patients With Alcoholic Hepatitis. *Hepatology* 2020; **71**: 522-538 [PMID: 31228214 DOI: 10.1002/hep.30832]

112 **Tripathi A**, Debelius J, Brenner DA, Karin M, Loomba R, Schnabl B, Knight R. The gut-liver axis and the intersection with the microbiome. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 397-411 [PMID: 29748586 DOI: 10.1038/s41575-018-0011-z]

113 **Leclercq S**, Matamoros S, Cani PD, Neyrinck AM, Jamar F, Stärkel P, Windey K, Tremaroli V, Bäckhed F, Verbeke K, de Timary P, Delzenne NM. Intestinal permeability, gut-bacterial dysbiosis, and behavioral markers of alcohol-dependence severity. *Proc Natl Acad Sci U S A* 2014; **111**: E4485-E4493 [PMID: 25288760 DOI: 10.1073/pnas.1415174111]

114 **Wree A**, McGeough MD, Peña CA, Schlattjan M, Li H, Inzaugarat ME, Messer K, Canbay A, Hoffman HM, Feldstein AE. NLRP3 inflammasome activation is required for fibrosis development in NAFLD. *J Mol Med (Berl)* 2014; **92**: 1069-1082 [PMID: 24861026 DOI: 10.1007/s00109-014-1170-1]

115 **Voican CS**, Njiké-Nakseu M, Boujedidi H, Barri-Ova N, Bouchet-Delbos L, Agostini H, Maitre S, Prévot S, Cassard-Doulcier AM, Naveau S, Perlemuter G. Alcohol withdrawal alleviates adipose tissue inflammation in patients with alcoholic liver disease. *Liver Int* 2015; **35**: 967-978 [PMID: 24766056 DOI: 10.1111/liv.12575]

116 **Molinaro A**, Wahlström A, Marschall HU. Role of Bile Acids in Metabolic Control. *Trends Endocrinol Metab* 2018; **29**: 31-41 [PMID: 29195686 DOI: 10.1016/j.tem.2017.11.002]

117 **Molinero N**, Ruiz L, Sánchez B, Margolles A, Delgado S. Intestinal Bacteria Interplay With Bile and Cholesterol Metabolism: Implications on Host Physiology. *Front Physiol* 2019; **10**: 185 [PMID: 30923502 DOI: 10.3389/fphys.2019.00185]

118 **Jia W**, Xie G, Jia W. Bile acid-microbiota crosstalk in gastrointestinal inflammation and carcinogenesis. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 111-128 [PMID: 29018272 DOI: 10.1038/nrgastro.2017.119]

119 **Arora T**, Bäckhed F. The gut microbiota and metabolic disease: current understanding and future perspectives. *J Intern Med* 2016; **280**: 339-349 [PMID: 27071815 DOI: 10.1111/joim.12508]

120 **Chow MD**, Lee YH, Guo GL. The role of bile acids in nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Mol Aspects Med* 2017; **56**: 34-44 [PMID: 28442273 DOI: 10.1016/j.mam.2017.04.004]

121 **Arab JP**, Karpen SJ, Dawson PA, Arrese M, Trauner M. Bile acids and nonalcoholic fatty liver disease: Molecular insights and therapeutic perspectives. *Hepatology* 2017; **65**: 350-362 [PMID: 27358174 DOI: 10.1002/hep.28709]

122 **Kakiyama G**, Hylemon PB, Zhou H, Pandak WM, Heuman DM, Kang DJ, Takei H, Nittono H, Ridlon JM, Fuchs M, Gurley EC, Wang Y, Liu R, Sanyal AJ, Gillevet PM, Bajaj JS. Colonic inflammation and secondary bile acids in alcoholic cirrhosis. *Am J Physiol Gastrointest Liver Physiol* 2014; **306**: G929-G937 [PMID: 24699327 DOI: 10.1152/ajpgi.00315.2013]

123 **Jiao N**, Baker SS, Chapa-Rodriguez A, Liu W, Nugent CA, Tsompana M, Mastrandrea L, Buck MJ, Baker RD, Genco RJ, Zhu R, Zhu L. Suppressed hepatic bile acid signalling despite elevated production of primary and secondary bile acids in NAFLD. *Gut* 2018; **67**: 1881-1891 [PMID: 28774887 DOI: 10.1136/gutjnl-2017-314307]

124 **Brandl K**, Hartmann P, Jih LJ, Pizzo DP, Argemi J, Ventura-Cots M, Coulter S, Liddle C, Ling L, Rossi SJ, DePaoli AM, Loomba R, Mehal WZ, Fouts DE, Lucey MR, Bosques-Padilla F, Mathurin P, Louvet A, Garcia-Tsao G, Verna EC, Abraldes JG, Brown RS Jr, Vargas V, Altamirano J, Caballería J, Shawcross D, Stärkel P, Ho SB, Bataller R, Schnabl B. Dysregulation of serum bile acids and FGF19 in alcoholic hepatitis. *J Hepatol* 2018; **69**: 396-405 [PMID: 29654817 DOI: 10.1016/j.jhep.2018.03.031]

125 **Nobili V**, Alisi A, Mosca A, Della Corte C, Veraldi S, De Vito R, De Stefanis C, D'Oria V, Jahnel J, Zohrer E, Scorletti E, Byrne CD. Hepatic farnesoid X receptor protein level and circulating fibroblast growth factor 19 concentration in children with NAFLD. *Liver Int* 2018; **38**: 342-349 [PMID: 28746779 DOI: 10.1111/liv.13531]

126 **Mouzaki M**, Wang AY, Bandsma R, Comelli EM, Arendt BM, Zhang L, Fung S, Fischer SE, McGilvray IG, Allard JP. Bile Acids and Dysbiosis in Non-Alcoholic Fatty Liver Disease. *PLoS One* 2016; **11**: e0151829 [PMID: 27203081 DOI: 10.1371/journal.pone.0151829]

127 **Caussy C**, Hsu C, Singh S, Bassirian S, Kolar J, Faulkner C, Sinha N, Bettencourt R, Gara N, Valasek MA, Schnabl B, Richards L, Brenner DA, Hofmann AF, Loomba R. Serum bile acid patterns are associated with the presence of NAFLD in twins, and dose-dependent changes with increase in fibrosis stage in patients with biopsy-proven NAFLD. *Aliment Pharmacol Ther* 2019; **49**: 183-193 [PMID: 30506692 DOI: 10.1111/apt.15035]

128 **Schwenger KJ**, Clermont-Dejean N, Allard JP. The role of the gut microbiome in chronic liver disease: the clinical evidence revised. *JHEP Rep* 2019; **1**: 214-226 [PMID: 32039372 DOI: 10.1016/j.jhepr.2019.04.004]

129 **Couch RD**, Dailey A, Zaidi F, Navarro K, Forsyth CB, Mutlu E, Engen PA, Keshavarzian A. Alcohol induced alterations to the human fecal VOC metabolome. *PLoS One* 2015; **10**: e0119362 [PMID: 25751150 DOI: 10.1371/journal.pone.0119362]

130 **Juanola O**, Ferrusquía-Acosta J, García-Villalba R, Zapater P, Magaz M, Marín A, Olivas P, Baiges A, Bellot P, Turon F, Hernández-Gea V, González-Navajas JM, Tomás-Barberán FA, García-Pagán JC, Francés R. Circulating levels of butyrate are inversely related to portal hypertension, endotoxemia, and systemic inflammation in patients with cirrhosis. *FASEB J* 2019; **33**: 11595-11605 [PMID: 31345057 DOI: 10.1096/fj.201901327R]

131 **Rau M**, Rehman A, Dittrich M, Groen AK, Hermanns HM, Seyfried F, Beyersdorf N, Dandekar T, Rosenstiel P, Geier A. Fecal SCFAs and SCFA-producing bacteria in gut microbiome of human NAFLD as a putative link to systemic T-cell activation and advanced disease. *United European Gastroenterol J* 2018; **6**: 1496-1507 [PMID: 30574320 DOI: 10.1177/2050640618804444]

132 **Loomba R**, Seguritan V, Li W, Long T, Klitgord N, Bhatt A, Dulai PS, Caussy C, Bettencourt R, Highlander SK, Jones MB, Sirlin CB, Schnabl B, Brinkac L, Schork N, Chen CH, Brenner DA, Biggs W, Yooseph S, Venter JC, Nelson KE. Gut Microbiome-Based Metagenomic Signature for Non-invasive Detection of Advanced Fibrosis in Human Nonalcoholic Fatty Liver Disease. *Cell Metab* 2019; **30**: 607 [PMID: 31484056 DOI: 10.1016/j.cmet.2019.08.002]

133 **Chu H**, Duan Y, Yang L, Schnabl B. Small metabolites, possible big changes: a microbiota-centered view of non-alcoholic fatty liver disease. *Gut* 2019; **68**: 359-370 [PMID: 30171065 DOI: 10.1136/gutjnl-2018-316307]

134 **Yuan J**, Chen C, Cui J, Lu J, Yan C, Wei X, Zhao X, Li N, Li S, Xue G, Cheng W, Li B, Li H, Lin W, Tian C, Zhao J, Han J, An D, Zhang Q, Wei H, Zheng M, Ma X, Li W, Chen X, Zhang Z, Zeng H, Ying S, Wu J, Yang R, Liu D. Fatty Liver Disease Caused by High-Alcohol-Producing Klebsiella pneumoniae. *Cell Metab* 2019; **30**: 675-688.e7 [PMID: 31543403 DOI: 10.1016/j.cmet.2019.08.018]

135 **Engstler AJ**, Aumiller T, Degen C, Dürr M, Weiss E, Maier IB, Schattenberg JM, Jin CJ, Sellmann C, Bergheim I. Insulin resistance alters hepatic ethanol metabolism: studies in mice and children with non-alcoholic fatty liver disease. *Gut* 2016; **65**: 1564-1571 [PMID: 26006114 DOI: 10.1136/gutjnl-2014-308379]

136 **Chen X**, Zhang Z, Li H, Zhao J, Wei X, Lin W, Zhao X, Jiang A, Yuan J. Endogenous ethanol produced by intestinal bacteria induces mitochondrial dysfunction in non-alcoholic fatty liver disease. *J Gastroenterol Hepatol* 2020; **35**: 2009-2019 [PMID: 32150306 DOI: 10.1111/jgh.15027]

137 **Dai X**, Hou H, Zhang W, Liu T, Li Y, Wang S, Wang B, Cao H. Microbial Metabolites: Critical Regulators in NAFLD. *Front Microbiol* 2020; **11**: 567654 [PMID: 33117316 DOI: 10.3389/fmicb.2020.567654]

138 **Lang S**, Demir M, Duan Y, Martin A, Schnabl B. Cytolysin-positive Enterococcus faecalis is not increased in patients with non-alcoholic steatohepatitis. *Liver Int* 2020; **40**: 860-865 [PMID: 31943701 DOI: 10.1111/liv.14377]

139 **Finlay BB**; CIFAR Humans; Microbiome. Are noncommunicable diseases communicable? *Science* 2020; **367**: 250-251 [PMID: 31949069 DOI: 10.1126/science.aaz3834]

140 **Crabb DW**, Im GY, Szabo G, Mellinger JL, Lucey MR. Diagnosis and Treatment of Alcohol-Associated Liver Diseases: 2019 Practice Guidance From the American Association for the Study of Liver Diseases. *Hepatology* 2020; **71**: 306-333 [PMID: 31314133 DOI: 10.1002/hep.30866]

141 **Stefan N**, Häring HU, Cusi K. Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies. *Lancet Diabetes Endocrinol* 2019; **7**: 313-324 [PMID: 30174213 DOI: 10.1016/S2213-8587(18)30154-2]

142 **Oh TG**, Kim SM, Caussy C, Fu T, Guo J, Bassirian S, Singh S, Madamba EV, Bettencourt R, Richards L, Yu RT, Atkins AR, Huan T, Brenner DA, Sirlin CB, Downes M, Evans RM, Loomba R. A Universal Gut-Microbiome-Derived Signature Predicts Cirrhosis. *Cell Metab* 2020; **32**: 878-888.e6 [PMID: 32610095 DOI: 10.1016/j.cmet.2020.06.005]

143 **Caussy C**, Hsu C, Lo MT, Liu A, Bettencourt R, Ajmera VH, Bassirian S, Hooker J, Sy E, Richards L, Schork N, Schnabl B, Brenner DA, Sirlin CB, Chen CH, Loomba R; Genetics of NAFLD in Twins Consortium. Link between gut-microbiome derived metabolite and shared gene-effects with hepatic steatosis and fibrosis in NAFLD. *Hepatology* 2018; **68**: 918-932 [PMID: 29572891 DOI: 10.1002/hep.29892]

144 **Ferrere G**, Wrzosek L, Cailleux F, Turpin W, Puchois V, Spatz M, Ciocan D, Rainteau D, Humbert L, Hugot C, Gaudin F, Noordine ML, Robert V, Berrebi D, Thomas M, Naveau S, Perlemuter G, Cassard AM. Fecal microbiota manipulation prevents dysbiosis and alcohol-induced liver injury in mice. *J Hepatol* 2017; **66**: 806-815 [PMID: 27890791 DOI: 10.1016/j.jhep.2016.11.008]

145 **Wang H**, Yan Y, Yi X, Duan Y, Wang J, Li S, Luo L, Huang T, Inglis B, Li X, Ji W, Tan T, Si W. Histopathological Features and Composition of Gut Microbiota in Rhesus Monkey of Alcoholic Liver Disease. *Front Microbiol* 2019; **10**: 165 [PMID: 30800107 DOI: 10.3389/fmicb.2019.00165]

146 **Zhong X**, Cui P, Jiang J, Ning C, Liang B, Zhou J, Tian L, Zhang Y, Lei T, Zuo T, Ye L, Huang J, Chen H. *Streptococcus*, the Predominant Bacterium to Predict the Severity of Liver Injury in Alcoholic Liver Disease. *Front Cell Infect Microbiol* 2021; **11**: 649060 [PMID: 33816353 DOI: 10.3389/fcimb.2021.649060]

147 **De Minicis S**, Rychlicki C, Agostinelli L, Saccomanno S, Candelaresi C, Trozzi L, Mingarelli E, Facinelli B, Magi G, Palmieri C, Marzioni M, Benedetti A, Svegliati-Baroni G. Dysbiosis contributes to fibrogenesis in the course of chronic liver injury in mice. *Hepatology* 2014; **59**: 1738-1749 [PMID: 23959503 DOI: 10.1002/hep.26695]

148 **Lee NY**, Joung HC, Kim BK, Kim BY, Park TS, Suk KT. *Lactobacillus lactis* CKDB001 ameliorate progression of nonalcoholic fatty liver disease through of gut microbiome: addendum. *Gut Microbes* 2020; **12**: 1829449 [PMID: 33131411 DOI: 10.1080/19490976.2020.1829449]

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**Figure Legends**



**Figure 1 Gut microbiota role in alcoholic fatty liver disease and non**-**alcoholic fatty liver disease pathogenesis.** Intestinal microbes have the potential relationship with fatty liver disease progression. Regular intake of alcohol and overnutrition altered the gut microbial composition which influence the various pathways and induce the liver injuries and produce the alcoholic fatty liver disease (AFLD) and non-alcoholic fatty liver disease (NAFLD). There are some common pathways found in both AFLD and NAFLD diseases (in the purple box) and others are specifically related to a particular disease. AFLD: Alcoholic fatty liver disease; NAFLD: Non-alcoholic fatty liver disease; HDED: High dense energy diet; SCFA: Short chain fatty acids; IgA: Immunoglobulin A; IL22: Interleukin 22; Reg3g: Regenerating islet-derived protein 3 gamma; C4: Precursor 7α-hydroxy-4-cholesten-3-one; FGF19: Fibroblast growth factor 19; PAA: Phenylacetic acid; TMAO: Trimethylamine N-oxide.

**Table 1 Representative studies presenting gut microbial dysbiosis in alcoholic fatty liver disease**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Sequencing method** | **Overgrown microbes** | **Depleted microbes** | **Model**  |
| Yan *et al*[63] (2011) | Pyrosequencing | ↑*Bacteroidales*, ↑*Bacteroides*, ↑*Porphyromonadaceae* | ↓*Lactococcus*, ↓*Pediococcus*, ↓*Lactobacillus*, ↓*Leuconostoc* | Murine |
| Otterson*et al*[64] (2013) | Pyrosequencing | ↑*Corynebacterium*, ↑*Alcaligenes*, ↑*Listeria*, ↑*Acetivibrio*, ↑*Allobaculum* | ↓*Bacteroides*, ↓*Tannerella*, ↓unclassified *Lachnospiraceae*, ↓undefined *Ruminococcaceae* | Murine |
| Lowe *et al*[71] (2017) | 16S rDNA | ↑*Actinobacteria*, ↑*Eubacteriaceae* | ↓*Tenericutes*, ↓*Verrucomicrobia*, ↓*Lachnospiraceae*, ↓*Moraxellaceae*, ↓*Akkermansia* | Murine |
| Grander *et al*[73] (2018) | Illumina MiSeq | ↑*Olsenella*, ↑*Eubacterium*, ↑*Acetivibrio* | ↓*Acinetobacter*, ↓*Anaerotruncus*, ↓*Akkermansia*, ↓*Blautia* | Murine |
| Kakiyama *et al*[74] (2013) | Pyrosequencing | ↑*Enterobacteriaceae*, ↑*Veillonellaceae* | ↓*Blautia*, ↓*Ruminococcaceae*, ↓*Lachnospiraceae*, ↓*Rikenellaceae* | Human |
| Bajaj *et al*[75] (2014) | Pyrosequencing | ↑*Enterococcaeae*, ↑*Staphylococcaceae*, ↑*Enterobacteriaceae* | ↓*Clostridiales XIV*, ↓*Ruminococcaceae*, ↓*Lachnospiraceae* | Human |
| Yang *et al*[83] (2017) | Illumina MiSeq | ↑*Candida spp.,* ↑*Candida albicans,* ↑*Candida dubliniensis* | ↓*Epicoccum*, ↓Unclassified fungi, ↓*Galactomyces*, ↓*Debaryomyces* | Human |
| Ferrere *et al*[144] (2017) | Illumina MiSeq | ↑*Actinobacteria*, ↑*Firmicutes*, ↑*Coriobacteriaceae*, ↑*Odoribacteriacea*, ↑*Clostridiaceae*, ↑*Dorea* | ↓*Bacteroidetes*, ↓*Proteobacteria*  | Murine |
| Wang *et al*[145] (2019) | Illumina MiSeq | ↑*Verrucomicrobia*, ↑*Proteobacteria*, ↑*Optitutus*, ↑*Botrytis*, ↑*Sporothrix* | ↓*Bacteroidetes*, ↓*Cytophagales*, ↓*Flavobacteriales*, ↓*Sphingobacteriales*, ↓*Lactobacillales*, ↓*Nitrosomonadales*, ↓*Opitutales*, ↓*Helotiales*, ↓*Ophiostomatales* | Monkey |
| Zhong *et al*[146] (2021) | Illumina MiSeq | ↑*Proteobacteria*, ↑*Fusobacteria*, ↑*Fusobacteriaceae*, ↑*Enterobacteriaceae*, ↑*Burkholderiaceae*, ↑*Fusobacterium*, ↑*Escherichia-Shigella* | ↓*Ruminococcaceae*, ↓*Faecalibacterium*, ↓*Lachnospira*, ↓*Agathobacter*, ↓*Ruminococcus* | Human |

**Table 2 Representative studies presenting gut microbial dysbiosis in non-alcoholic fatty liver disease**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Sequencing method** | **Overgrown microbes** | **Depleted microbes** | **Model** |
| Michail *et al*[97] (2015) | Ion torrent | ↑*Actinobacteria,* ↑*Prevotella,* ↑*Clostridia,* ↑*Fusobacteria,* ↑*Epsilonproteobacteria,* ↑*Gammaproteobacteria* | ↓*Erysipelotrichia,* ↓*Alphaproteobacteria,* ↓*Verrucomicrobia* | Human |
| Wang *et al*[91] (2016) | Pyrosequencing | ↑*Bacteroidaceae,* ↑*Prevotellaceae,* | ↓*Lachnospiraceae,* ↓*Ruminococcaceae,* ↓*Lactobacillaceae*  | Human |
| Raman *et al*[95] (2013) | Pyrosequencing | ↑*Alphaproteobacteria,* ↑*Lactobacillaceae,* ↑*Lachnospiraceae,* ↑*Veillonellaceae,*  | ↓*Ruminococcaceae,* ↓*Oscillibacter,* ↓*Porphyromonadaceae* | Human |
| Chierico *et al*[94] (2017) | Pyrosequencing | ↑*Actinobacteria,* ↑*Bradyrhizobium,* ↑*Anaerococcus,* ↑*Peptoniphilus,* ↑*Propionibacterium acnes,* ↑*Dorea,* ↑*Ruminococcus* | ↓*Bacteroidetes,* ↓*Oscillospira*, ↓*Rikenellaceae*  | Human |
| Hoyles *et al*[90] (2018) | Shotgun | *↑Proteobacteria, ↑Actinobacteria, ↑Verrucomicrobia* | ↓*Firmicutes*, ↓*Euryarchaeota* | Human |
| Shen *et al*[92] (2017) | 16S rDNA | *↑Proteobacteria, ↑Fusobacteria, ↑Lachnospiraceae, ↑Enterobacteriaceae, ↑Erysipelotrichaceae, ↑Streptococcaceae, ↑Escherichia Shigella* | ↓*Bacteroidetes*, ↓*Prevotellaceae*, ↓*Ruminococcaceae*,↓*Prevotella* | Human |
| Zhu *et al*[84] (2013) | Pyrosequencing | ↑*Bacteroidetes*, ↑*Proteobacteria*, ↑*Alcaligenaceae*, ↑*Campylobacteraceae*, ↑*Enterobacteriaceae* | ↓*Actinobacteria*, ↓*Biﬁdobacteriaceae*, ↓*Clostridiales family XI*, ↓*Lachnospiraceae* | Human |
| Chierico *et al*[94] (2017) | Pyrosequencing | ↑*Coriobacteriaceae*, ↑*Bacteroidaceae* | ↓*Porphyromonadaceae*, ↓*Rikenellaceae* | Human |
| Minicis *et al*[147] (2014)  | Pyrosequencing | ↑*Firmicutes*, ↑*Actinobacteria* | ↓*Bacteroidetes* | Murine |
| Lee *et al*[148] (2020) | 16S rDNA | ↑*Firmicutes*, ↑*Deferribacters*, ↑*Helicobacter japonicus*, ↑*Mucispirillum schaedleri*, ↑*Flintibacter butyricus*  | ↓*Bacteroidetes*, ↓*Lactobacillus murinus* | Murine |