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**Gut microbiota and metabolic syndrome**

Festi D *et al*. Gut microbiota and metabolic syndrome

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**Abstract**

Gut microbiota exerts a significant role in the pathogenesis of the metabolic syndrome, as confirmed by studies conducted both on humans and animal models. Gut microbial composition and functions are strongly influenced by diet. This complex intestinal “superorganism” seems to affect host metabolic balance modulating energy absorption, gut motility, appetite, glucose and lipid metabolism, as well as hepatic fatty storage. An impairment of the fine balance between gut microbes and host’s immune system could culminate in the intestinal translocation of bacterial fragments and the development of “metabolic endotoxemia”, leading to systemic inflammation and insulin resistance. Diet induced weight-loss and bariatric surgery promote significant changes of gut microbial composition, that seem to affect the success, or the inefficacy, of treatment strategies. Manipulation of gut microbiota through the administration of prebiotics or probiotics could reduce intestinal low grade inflammation and improve gut barrier integrity, thus, ameliorating metabolic balance and promoting weight loss. However, further evidence is needed to better understand their clinical impact and therapeutic use.

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**Key words**: Gut microbiota; Metabolic syndrome; Obesity; Diabetes; Non-alcoholic fatty liver disease; Probiotic; Prebiotic; Bariatric surgery

**Core tip**: The present review offers a summary of available studies exploring the pathogenic role of gut microbiota in the development of metabolic syndrome, subdividing experimental evidences coming from animal models and human subjects, since their results are not always comparable. The relative influences of dietary intake on gut microbial composition and functions are also explored, as well as the effects on intestinal microhabitat exerted by diet-induced weight loss and bariatric surgery. Finally a critical evaluation of the available evidences on probiotic and prebiotics is reported, delineating their potential clinical impact.

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**INTRODUCTION**

The metabolic syndrome is defined by a combination of interconnected physiological, biochemical, clinical and metabolic factors linked to an increased risk of cardiovascular diseases and type 2 diabetes mellitus[1]. Raised blood pressure, dyslipidemia (defined by increased triglycerides and reduced high-density lipoprotein cholesterol), raised fasting glucose and central obesity are metabolic syndrome’s main features, as defined by the International Diabetes Federation (IDF)[2].

The worldwide prevalence is variable, ranging from < 10% to 84%, depending on geographical origins and composition of the studied population, as well as the definition criteria applied[1]. However, its high economic and social burden is still growing, thus, clinical research is focusing on understanding the complex pathogenesis of metabolic disorders.

Recent evidences have proposed the potential role of gut microbiota as pathogenic factor affecting host metabolic balance and disorders[3]. In fact, gut microbiota seems to exert a great variety of functional properties impacting human physiology and pathology[4]: modulation of host nutrition and energy harvest by the production of vitamins and fermentation of food components indigestible by the host; influence of intestinal epithelial homeostasis; development of host immune system; protection against pathogens; drug metabolism[4-6].

Initial studies on gut microbial composition and function were limited by the difficulty to culture all intestinal microbes[7]. The recent introduction of analyzing methods, based on bacterial genome sequencing and “metagenome” analysis, has contributed to increase the knowledge about uncultivable microbes, gut microbial functions, its cross-talk with the host and the potential pathogenic role related to host’s diseases[8].

In the present review, the pathogenic role of gut microbiota on the development of metabolic disorders, such as obesity, type 2 diabetes mellitus and non-alcoholic fatty liver disease (NAFLD), as well as the influence of diet on gut microbial composition, will be discussed. Available evidences emerging from studies conducted on animal models and humans are reported separately, thus, underlining that experimental and clinical observations are not always comparable. Finally, the therapeutic implications of gut microbiota manipulation, through the administration of probiotics and prebiotics, is also discussed.

**GUT MICROBIOTA AND OBESITY**

***Experimental studies on animal models***

First evidences about the role of gut microbiota on the development of obesity came from studies conducted on germ free mice (GF-mice) compared to conventionally raised mice (CONV-R)[9]. In basal conditions, the latter have a 40% higher body fat content than GF-mice and this phenomenon was independent from the food intake. Moreover, after colonization of GF-mice with intestinal flora coming from CONV-R mice, a significant increase of body weight, in particular a 60% increase of body fat, a significant increase of hepatic triglycerides synthesis and the development of insulin resistance were observed in recipients (CONV-D), independently from food intake and total energy expenditure[9]. Several mechanisms have been proposed to explain these observations[9]: the increased secretion of leptin, observed in CONV-D mice, was associated to reduced insulin sensitivity; the increased monosaccharaides absorption in CONV-D mice enhanced hepatic triglyceride synthesis by up-stimulation of lipogenic genes, such as acetyl-CoA carboxylase and fatty acid synthase, through the activation of carbohydrate response element binding protein and sterol response element binding protein-1; moreover, gut microbiota, inoculated in CONV-D mice, seemed to suppress the expression of fasting-induced adipose factor (FIAF), a central regulator of lipid metabolism, that modulate lipoprotein lipase (LPL) activity in adipose tissue[10]. The suppression of FIAF, induced by gut microbiota, resulted in enhanced LPL activity and increased fatty acids storage in adipocytes[9]. Indeed, in their study[9], Bäckhed and colleagues concluded that gut microbiota represents an environmental factor affecting host’s predisposition to develop obesity and increase adiposity.

In a subsequent study[11], Bäckhed and colleagues observed that GF-mice, fed with “high sugar - high fat Western diet”, do not seem to develop obesity[11]. The main mechanisms explaining GF resistance to diet-induced obesity are the enhanced fatty acids oxidation, uncoupled with decreased LPL activity and fatty acids storage[11]. The first mechanism is promoted by increased AMP-activated protein kinase activity, an activator of mitochondrial enzymes, involved in fatty acid oxidation in skeletal muscle and liver. On the other hand, GF-mice showed elevated levels of FIAF, which suppresses LPL activity.[11].

Moreover, GF-mice colonized with intestinal flora coming from obese mice showed a more evident increase of body weight and of fat tissue than those colonized with gut flora deriving from lean mice[12]. The speculated mechanism was the increased energy harvest promoted by gut microbiota metabolism, in particular by microbes deriving from obese subjects[9,12].

The mechanism through which gut microbes contribute to increased energy absorption seems to be the production of short chain fatty acids (SCFAs), resulting from the hydrolysis and the fermentation of dietary polysaccharides. SCFAs, such as propionate, butyrate and acetate, could be absorbed and used as source of energy, but seem to exert more complex metabolic functions influencing host appetite[13,14], intestinal transit time[13], energy absorption and energy harvest[15].

For example, SCFAs increase intestinal absorption of monosaccharides stimulating the expression of sodium/glucose transporter-1[15].

SCFAs also contribute to modulate host appetite and food intake interacting with G-coupled proteins expressed by enteroendocrine cells and promoting the release of glucagon-like peptide-1 (GLP-1) and peptide YY, which directly influence host’s satiety[13,14].

Moreover, SCFAs influence lipid metabolism by increasing lipogenesis[9] and inhibiting fatty acids oxidation[11], as previously reported.

Other studies have reported specific changes of gut microbiota composition in genetically obese mice (*ob/ob* mice), compared to lean counterparts, showing a 50% reduction in the abundance of *Bacteroidetes* and a proportional increase in *Firmicutes*[16]. These specific changes could contribute to the increased SCFAs production and energy harvest observed both in obese mice and in GF-mice colonized with *ob/ob* mice microbiota[12].

However, it’s not clear how and why, in obese subjects, gut microbiota seems to extract more energy from ingested food[17]. Moreover, this mechanism is insufficient to explain the more significant weight gain observed in GF-mice colonized with intestinal flora coming from obese donor, compared to that observed in mice receiving lean donor’s microbiota[12,17]. In genetically obese mice *ob/ob*, leptin deficiency could in part explain the increased efficiency of gut microbiota to extract energy from food; however, it’s not clear why the metabolic activity of “obese-gut microbiota” is still increased, also when transferred to wild-type lean donors[17].

Other putative mechanisms have also been proposed. For example, high-fat diet has shown to increase the proportion of Gram-negative species in gut microbiota, thus, contributing to increased intestinal absorption of bacterial fragments, such as lipopolysaccharides (LPS). As a consequence, the increased levels of circulating LPS lead to a condition defined as “metabolic endotoxemia”[18], in which, however, blood LPS levels are lower than those observed in septic shock. The experimentally induced endotoxemia in mice leads to body weight gain, fasted hyperglycemia and hyperinsulinemia, similar to that observed on high-fat-fed mice[18].

Increasing evidence suggests that high-fat diet promotes changes in gut microbiota composition, but the subsequent development of obese phenotype occurs only in the presence of metabolic endotoxemia[19].

Fei *et al*[20] found that a specific endotoxin-producing bacterium, the *Enterobacter cloacae* B29, isolated from morbidly obese human’s gut, induced obesity and insulin resistance in GF-mice, increasing endotoxin circulating levels. The Authors concluded that an increase of endotoxin-producing bacteria in gut microbiota, represents a cause, rather than a consequence, of the host’s metabolic balance deterioration. Indeed, these two studies[19,20] imply that lowering metabolic endotoxemia, could represent a potential treatment strategy for the metabolic disease, even if additional studies are necessary to confirm this assertion.

Metabolic endotoxemia is promoted by increased intestinal permeability and bacterial translocation related to a low grade intestinal inflammation state, resulting from the interaction between luminal bacteria and host’s immune system[18,19,21].

Bacterial antigens are recognized by specific receptors exposed by intestinal dendritic cells, such as NOD1, CD-14 and Toll-like receptor 4 (TLR-4). The interaction between these receptors and bacterial peptidoglycan or LPS activates mucosal inflammation and bacterial translocation[21], through the activation of the NFkB pathway.

Bacterial translocation is prevented in mice lacking the specific microbial pattern recognition receptors NOD1 or TLR-4[21]. In fact, animal models resistant to high-fat diet induced obesity, showed reduced TLR-4 activation and decreased intestinal translocation[19].

However, even if some studies have explained the role of host immune system in promoting metabolic endotoxemia and bacterial translocation[18,19,21], other studies have underlined the role of immune response in maintain gut homeostasis and prevention of gut dysbiosis[22,23].

For example, TLR-5 seems to exert a central function in the recognition of pathogen-associated molecular patterns (PAMPs) and in the stimulation of inflammatory response in order to maintain mucosal homeostasis[22]. TLR-5 deficient mice develop intestinal dysbiosis, hyperphagia, obesity and insulin resistance[23]; moreover, these tracts could be transmitted by colonizing wild type mice with gut microbiota deriving from TLR-5 knock-out mice.

Another mechanism involved in the regulation of gut echosystem homeostasis is the endocannabinoid system[24]. In fact endocannabinoid receptors expressed in the gut (eCB1) interact with bacterial LPS, modulating gut permeability, LPS translocation and inducing metabolic endotoxemia[24].

On the other hand, gut microbiota is essential for host’s immune system maturation, gut-associated lymphoid tissue development and a well-balanced T-cells differentiation[25]. Indeed, GF-mice show an immature gut-associated lymphoid tissue and several systemic immune system dysfunctions. Moreover, an intestinal dysbiosis contributes to an altered differentiation of T-cells, an imbalance between T-helper and T-regulatory lymphocites, leading to the disruption of immune tolerance and the development of autoimmune diseases[26].

In conclusion, evidences emerging from studies conducted on animal models have confirmed the pathogenic role exerted by gut microbiota on the development of obesity. In fact, microbial products, mainly SCFAs, regulate several host’s metabolic functions, energy absorption and appetite. Moreover, the complex interactions between gut microbes and host’s immune system affect gut microbial homeostasis and composition, intestinal dysbiosis, bacterial translocation and the subsequent development of metabolic endotoxemia, which is essential for the development of obese phenotype and insulin resistance.

***Human clinical studies***

Studies conducted on obese human subjects have confirmed specific changes on gut microbiota composition, such as a reduction of *Bacteroidetes* phylum and a proportional increase of *Firmicutes*[27-29]. Moreover, a reduction of *Bifidobacterium* and *Bacteroides* and an increase of *Staphylococcus*, *Enterobacteriaceae* and *Escherichia coli* were detected in overweight compared to normal-weight pregnant women[29].

However, other studies showed conflicting results: Duncan *et al*[30] reported no significant differences of the *Bacteroidetes/Firmicutes* ratio between obese and lean subjects, as well as no significant changes of fecal *Bacteroidetes* count during diet induced weight loss. On the contrary, Schwiertz *et al*[31] reported a significant increase of *Bacteroidetes* in obese and overweight subjects.

Studies conducted on obese twins have revealed differences on phyla distribution between obese and lean subjects: reduced microbial diversity, such as a relative reduction of *Bacteroidetes* and *Actinobacteria,* were found among obese subjects, but no significant changes in *Firmicutes* proportion emerged[32]. The identification of a “core microbiome” in obese subjects led to the assumption that functional changes, related to different genes and metabolic pathways expression by gut microbiota, rather than the diversity of organismal assemblage, could explain different physiological states (obese or lean)[32]; in particular, a preferential increase of genes involved in sugar and carbohydrate metabolism could be present in overweight subjects[32].

The functional changes in overweight’s gut microbiota lead to an increased production of SCFAs[12,31], with a consequent raised capacity of energy harvest[12] associated to a preferential increase of propionate[31].

A more recent study underlined that low genetic richness in gut microbiota, reflecting a reduced microbial diversity and a preferential expression of few metabolic pathways, is correlated with overall adiposity, insulin resistance and a more pronounced inflammatory phenotype[33]. The qualitative changes in gut microbiota of obese subjects were represented by an increase of *Proteobacteria* and *Bacteroidetes* phyla, a decrease of anti-inflammatory bacteria, such as *Akkermansia muciniphila,* and an increase of pathogens, such as *Campylobacter* and *Shigella*. The changes lead to a decreased production of butyrate, a protective substance affecting intestinal barrier integrity, as well as an increased mucus degradation potential and oxidative stress management [33].

Qualitative changes of gut microbiota composition have been found also in early stages of life. Two studies[34,35] conducted on overweight children demonstrated a reduction of beneficial bacteria, such as *Bifidobacteria*[34], *Desulfovibrio* and *Akkermansia muciniphila*-like bacteria[35], associated with an increase of pathogens or Gram negative bacteria, such as *Staphylococcus aureus*[34] and *Enterobacteriaceae*[35]. Thus, identifying early changes of gut microbiota could predict subsequent development of obesity.

Moreover, gut microbial composition, in overweight adolescents, seems to influence the extent of weight loss, obtained after dietary restriction and increased energy expenditure by physical activity, independently from total food intake[36]. Indeed, increased total bacteria, *Bacteroides fragilis* group, *Clostridium leptum* group, and *Bifidobacterium catenulatum* group counts, associated to decreased levels of *Clostridium coccoides* group, *Lactobacillus* group and *Bifidobacterium* group before and after dietary interventions are associated to a strongly significant weight loss, independently from total food intake. Thus, gut microbiota could potentially influence the efficacy of dietary interventions[36].

Several “non-dietary” factors seem to influence gut microbial composition, since the early stages of life. Indeed, delivery mode[37,38], infant feeding[39], antibiotic use[40], gestational age and infant hospitalization are the most important factors[37]. In fact, term birth, vaginal delivery, short hospitalization, less exposure to antibiotics and breastfeeding are associated to a more "beneficial" gut microbiota, characterized by highest numbers of *Bifidobacteria* and lowest numbers of *Clostridium difficile* and of *Escherichia coli*[37].

In conclusion, studies conducted on human subjects have confirmed the pathogenic role exerted by gut microbiota. However, the observations emerging from these clinical studies are not always comparable to the results reported in experimental studies conducted on animal models. In fact, the alteration of *Bacteroidetes/Firmicutes* ratio in gut microbial composition has not been confirmed in all human studies. The main features characterizing overweight subjects’ microbiota are reduced microbial diversity, decrease of bacteria with potential anti-inflammatory properties and increase of pathogens. Recent evidences have underlined the importance of functional changes of gut microbiota, resulting from the alteration of genetic pathways expression, on the pathogenesis of obesity, rather than the simple organismal assemblage.

**INFLUENCE OF DIET**

***Observations in human subjects***

Diet seems to strongly influence gut microbial composition since the first stages of life[41]. De Filippo *et al*[42] compared fecal microbiota of European children (EU), mostly fed with a “modern western diet”, to gut microbiota of children coming from a rural African village of Burkina Faso (BF), mostly fed with a “high-fiber diet”. BF children showed a significant enrichment in *Bacteroidetes* and depletion in *Firmicutes*, associated to increased abundance of bacteria from the genus *Prevotella* and *Xylanibacter*, compared to EU children. On the other hand, *Enterobacteriaceae* (*Shigella* and *Escherichia*) were significantly underrepresented in BF compared to EU children. These differences reflect the adaptation of gut microbiota to host’s diet, with consequent enrichment of bacterial species hydrolyzing complex polysaccharides in BF group. The results of this adaptation are the maximization of energy extraction from dietary fibers, but also an enrichment of microbial diversity and the potential protection from inflammation and non-infectious colonic disease, observed in rural communities[42].

On the other hand, high-fat/low-fiber Western diet promotes the overgrowth of gram-negative pathogens, with consequent increased intestinal translocation of bacterial LPS[18]. LPS interaction with specific receptor of host’s immune-system (TLR-4/CD-14) culminates in an inflammatory cascade[43] that precedes the development of insulin resistance, obesity and diabetes[18].

Sequencing studies of fecal metagenomes of individuals coming from different countries lead to the identification of three robust clusters, defined “enterotypes”. The three main clusters are dominated by the genera *Bacteroides*, *Prevotella* and *Ruminococcus* (enterotype 1, 2 and 3 respectively). These clusters are indicative of the existence of limited numbers of well-balanced host-microbial symbiotic states that are not influenced by the geographical origin, but seem to be shaped by the diet[44].

Regular red meat consumption, as well as the high-fat/low fiber Western diet, is associated to a predominance of *Bacteroides* -rich gut ecosystem, with associated increased expression of genes involved in protein degradation. On the other hand, *Prevotella* species dominate in vegetarians with preferential expression of genes involved in starch break-down[41,45].

The gut microbiome seems to rapidly respond to specific changes of diet. Indeed, in a study in which “animal-based diet” and “plant-based diet” were assigned to two groups of healthy volunteers, rapid changes of gut microbial composition were observed in both groups[46]. In particular, the animal-based diet increased the abundance of bile-tolerant and amino-acids metabolizing microorganisms (*Alistipes*, *Bilophila* and *Bacteroides*), while it decreased the levels of *Firmicutes* that metabolize dietary plant polysaccharides (*Roseburia, Eubacterium rectale* and *Ruminococcus bromii*), thus reflecting the functional and metabolic changes induced by dietary compounds[46]. However, although these changes appeared within the first 24 h, the overall enterotype identity remains stable[47].

In conclusion, diet contributes to shape gut microbial composition, creating a stable cluster of microorganisms defined “enterotype”. Diet modification seems to induce rapid changes of gut microbial composition, although enterotype identity is not altered. However, further studies are needed to establish the effect of long term dietary changes on gut microbial composition and function.

***Lessons from animal models***

High-fat Western diet contributes to the development of obesity, to weight gain and to the increase of white adipose tissue through the intermediation of gut microbiota. A confirmation comes from experimental studies showing that high-fat diet (HFD) promotes weight gain only in conventional mice but not in germ-free mice[48].

Moreover HFD promotes the same changes in gut microbiota composition found in obese subjects, influencing the *Bacteroidetes/Firmicutes* ratio[49]. The colonization of GF-mice with gut microbiota coming from high-fat fed conventional mice is associated to significant weight gain.

De-Wit *et al*[50] found that saturated fatty acids promote weight gain, increased adiposity and the development of fatty liver by modifying gut microbial composition and enhancing lipogenesis.

Moreover, high-fat diet promote specific changes of gut microbial composition, such as a reduction of *Bacteroidetes* and an increase of *Firmicutes* and *Proteobacteria*, in both obese and lean phenotypes [51], suggesting its role in shaping intestinal flora, independently from genetically-determined host’s phenotype[51]. Furthermore, the experimental study by Fleissner and colleagues[52], reported that high-fat diet promotes weight gain, also in absence of gut microbiota. In fact, GF-mice, fed with high-fat chow, gained more body weight and body fat than their conventional counterpart[52].

Therefore, these observations demonstrate that a diet rich in lipids, in particular saturated fatty acids, promotes weight gain and increases visceral adiposity, shaping gut microbiota composition and influencing, both directly and indirectly through the intermediation of intestinal flora, energy absorption and harvest[53].

Other studies have also underlined the role of dietary lipids in promoting low-grade gut inflammation and increased intestinal permeability, as previously described also in GF mice[48]. Indeed, diet rich in lipids is associated to a significant decrease of *Bifidobacteria,* known to produce butyrate, which exerts anti-inflammatory effects and promote gut barrier integrity[54]. Moreover, it is associated to an increase of sulfate-reducing/endotoxin-producing bacteria belonging to the *Desulfovibrionaceae* family, leading to an increased gut inflammation and impaired barrier function[55]. HFD contributes also to the development of increased intestinal permeability as demonstrated by the reduced expression of genes encoding for components of tight junctions[56]. Furthermore, the extent of increased gut permeability is correlated to specific microbial changes, such as a reduction of *Lactobacillus* and an increase of *Oscillobacter*[56].

In conclusion, experimental evidences from animal models demonstrate that HFD promotes weight gain by altering gut microbial composition and by increasing intestinal permeability.

**GUT MICROBIOTA AND DIABETES**

***Experimental studies on animal models***

LPS-induced metabolic endotoxemia is the first step for the development of insulin resistance and diabetes[18]. Indeed, mice fed with high-fat diet have shown increased proportion of LPS-containing microbiota in the gut as well as circulating LPS. Experimental LPS infusion lead to fasted hyperglycemia and hyperinsulinemia. Moreover, CD14/TLR-4 mutant mice, resistant to LPS, were also resistant to high-fat diet-induced metabolic diseases, because, in this animal models, the subsequent expression of inflammatory cascade in liver and fat was significantly reduced [18,57]. CD14 mutant mice showed insulin hypersensitivity even during normal diet, suggesting the potential role of CD14 to set host’s insulin sensitivity in physiological conditions[18].

The modulation of gut microbiota, through the administration of a broad spectrum antibiotic therapy, ameliorated glucose tolerance in *ob/ob* and diet-induced obese and insulin-resistant mice, influencing inflammatory, and metabolic status of the host, independently from food intake[58].

Similarly, Cani *et al*[59] found that antibiotic treatment reduced metabolic endotoxemia and the cecal content of LPS in both high-fat-fed and *ob/ob* mice, with consequent reduction of systemic inflammation and improvement of insulin sensitivity. Similar results were observed in CD14 mutant *ob/ob* mice, independently from antibiotic treatment.

On the other hand, a recent study[60] defined the protective role of the bacterium *Akkermansia (A.) muciniphila* against the development of metabolic diseases.

*A. municiphila,* a member of the *Verrucomicrobia* phylum, is a mucus-degradating bacteria, located in the mucus layer, representing 1-4% of the bacterial population in the colon[61]. The abundance of this mucin-degrading bacterium,is inversely correlated to body weight in rodents and humans[60], and is negatively associated to type 1[62] and type 2[63] diabetes. The normalization of *A. muciniphila* abundance through prebiotic administration is correlated with an improved metabolic profile, reduced fat-mass, metabolic endotoxemia, adipose tissue inflammation and insulin resistance. Moreover, it seems that *A. muciniphila* administration led to increased intestinal levels of endocannabinoids that control inflammation, the gut barrier integrity, and gut peptide secretion[60]. However, the exploitation of all these effects requires viable bacteria, because treatment with heat-killed cells did not improve the metabolic profile[60].

In the presence of bacteria producing butyrate or conjugated linolenic acid, such as *Bifidobacteria* or *Lactobacillus*, an improvement of glucose tolerance in association with a decrease of endotoxemia, of circulating pro-inflammatory cytokines and of intestinal permeability, were observed[59,64].

In conclusion, gut microbiota promotes the development of insulin resistance and diabetes by inducing metabolic endotoxemia. Bacteria with potential anti-inflammatory properties, such as *A. municiphila, Bifidobacteria* and *Lactobacilli*, exert a protective role by enhancing gut barrier integrity and by preventing bacterial translocation.

***Human clinical studies***

As demonstrated in animals, high energy intake increases levels of circulating LPS also in humans[65]. Circulating LPS stimulates the TLR-2 mediated inflammatory response and increases the secretion of pro-inflammatory cytokines by the adipose tissue[32]. LPS levels are signficantly increased in diabetic subjects, compared to controls, and seem to decrease with the administration of antidiabetic therapy (rosiglitazone)[66].

A longitudinal study[67] found that increased levels of blood circulating bacteria are present before the development of diabetes. Moreover, pyrosequencing analyses conduced on subjects in the early phases of reduced glucose tolerance, identified a core blood microbiota, mostly (85-90%) composed by *Proteobacteria* phylum, which could represent a potential biomarker for predicting the development of diabetes[67].

Specific changes in gut microbiota composition have been observed in diabetic subjects: an increase of *Bacteroides* and *Prevotella* was associated to a proportional decrease of *Firmicutes* and *Clostridia*[68]. Furthermore, a decrease of anti-inflammatory bacteria, such as *Bifidobacteria* was also observed[69].

However, Zhang *et al*[70] found that specific changes of gut microbiota composition could be identified in each progressive stage leading to the development of diabetes. The relative abundances of butyrate-producing bacteria (*Akkermansia muciniphila* and *Faecalibacterium prausnitzii*) seems to decrease along with decreasing glucose tolerance, in association with a decrease of *Verrucomicrobiae*. On the other hand, *Betaproteobacteria* levels show an opposite trend.

Recently, Qin *et al*[63] have developed a novel gut microbiota analytical platform to identify disease-associated metagenomic markers. Comparing gut microbial metagenome of diabetic to healthy control subjects, the Authors found that in diabetic subjects only a moderate degree of gut microbial dysbiosis was present, characterized by a selective increase in several opportunistic pathogens and a reduction in bacteria producing beneficial metabolites, such as butyrate [63]. Indeed, it’s well known that butyrate may exert a protective role, enhancing the expression of tight junctions genes, promoting gut barrier function and reducing bacterial traslocation[71].

The beneficial effect of butyrate is confirmed by a study from de Vrieze *et al*[72], in which diabetic subjects received a fecal microbiota transplant from lean donors. After the transplant diabetic subjects showed a significant increase of intestinal butyrate-producing bacteria, which was correlated to an improvement of insulin sensitivity[72].

Similarly, Karlsson *et al*[73] developed a mathematical model, deriving from metagenome analysis of fecal samples’ from 145 European women with different degrees of glucose tolerance, to accurately predict the development of diabetes. Appling this model to a Chinese cohort, the Authors identified different metagenomic predictors for diabetes between European and Chinese people. Thus, they concluded that metagenomic predictive tools for diabetes should be specific for the age and geographical location of the studied population [73].

In conclusion, human studies confirmed the pathogenic role of metabolic endotoxemia for the development of insulin resistance and diabetes. The progressive development of glucose intolerance and diabetes proceeds along with a corresponding decrease of anti-inflammatory and butyrate-producing bacteria, as well as an increase of pathogens. Indeed, the experimental enrichment of butyrate-producing bacteria is associated to an improvement of insulin sensitivity.

**GUT MICROBIOTA AND NAFLD**

***Experimental studies on animal models***

As previously explained, gut microbiota strongly influences energy absorption and storage, in particular by modulating monosaccharides absorption and hepatic de novo lipogenesis through complex pathways which influence expression of genes involved in these specific metabolic reactions[9]. In fact, GF mice receiving gut microbial colonization from conventional mice show a significant increase in triglycerides synthesis and fatty storage in hepatocytes[9].

Although gut microbiota could modulate *per se* lipid metabolic pathways in hepatocytes, specific changes in microbial composition are able to influence the development of fatty liver.

Indeed, although high-fat diet experimentally induced weight gain in conventional mice, not all of them developed reduced glucose tolerance, hyperinsulinemia and overt fatty liver[74]. A pyrosequencing study revealed that mice developing insulin resistance and fatty liver showed an increased number of *Lachnospiraceae* and *Barnesiella*, associated with a decrease of *Lactobacilli.* These alterations were not observed in mice resistant to diet induced metabolic syndrome[74].

Moreover, gut microbiota could contribute to the development of fatty liver through the ethanol production[75]. In fact, in genetically obese mice breath ethanol tested levels were significantly higher than in lean mice and antibiotic treatment could reduce by 50% the cumulative ethanol production[75].

Other proposed mechanisms through which gut microbiota could influence the susceptibility to develop NAFLD are the alteration of the choline[76] and the bile acids[77] metabolisms.

More recently, the role of fructose-rich diet has been explored[78]: the experimental administration of a 30% fructose solution, for 8 wk, to a group of mice, is associated to the development of hepatic steatosis and a significant increase of hepatic transaminases. The onset of fructose induced-NAFLD is associated to the development of small bowel bacterial overgrowth, increased intestinal permeability, increased circulating endotoxin and the subsequent activation of Kupffer cells mediated hepatic inflammation[78].

Gut microbiota also exerts a role in the progression from fatty liver to non-alcoholic steatohepatitis (NASH) and the development of hepatic fibrosis. It has been observed that experimentally induced endotoxemia activates hepatic inflammatory response through the recruitment of Kupffer cells by TLR-4 mediated signaling[79]. Indeed, in TLR-4 deficient mice, as well as after the experimental destruction of Kupffer cells, inflammatory response and liver damage are significantly reduced[79].

Furthermore, recent studies[80,81] have underlined the role of cytoplasmic multiprotein complexes, called inflammosomes, in the development of inflammatory liver injury. These inflammosomes are expressed in most liver cells, such as Kupffer cells, liver sinusoidal endothelial cells, periportal myofibroblasts and hepatic stellate cells.. The activation of cytosolic inflammosomes, induced by the interaction with LPS or with other microbial antigens coming from bacteria circulating in the portal system, leads to the expression of the pro-inflammatory cascade[80,81] and modulates hepatic fibrotic tissue deposition[82].

Although inflammosomes play a critical role in the pathogenesis of liver disease, inflammosome-deficient mice show a more severe hepatic injury and a faster progression to NASH, probably because these cytosolic complexes may contribute to modulate gut microbial composition, and their dysfunction leads to gut dysbiosis[83].

In conclusion, gut microbiota affects the susceptibility to develop fatty liver and NASH. Bacterial ethanol production, alterations of choline and bile acids metabolism, the stimulation of hepatocytes’ lipogenesis and the development of an increased intestinal permeability leading to metabolic endotoxemia are the main mechanisms involved. The complex interaction between microbial antigens and the cytosolic inflammosomes affects the activation of inflammatory cascade and the development of hepatic fibrosis.

***Human clinical studies***

Similar mechanisms observed in animals have been proposed to explain the putative role of gut microbiota on the pathogenesis of NAFLD in humans.

In particular, an higher prevalence of small bowel bacterial overgrowth and an increased intestinal permeability have been observed in obese subjects affected by NAFLD, and these variables seem to be correlated with the severity of hepatic steatosis[84].

Moreover, specific changes in gut microbial composition have been observed in patients affected by NASH, such as a lower percentage of *Bacteroidetes* and higher fecal *Clostridium coccoides* concentrations. However, after adjusting for body mass index (BMI) and dietary intake, only the difference of *Bacteroidetes* fecal concentrations resulted significant. Thus, an inverse association between the presence of NASH and the percentage *Bacteroidetes* in the stools, independent from BMI and diet, was observed[85].

A significant increase of circulating levels of ethanol, promoted by intestinal overgrowth of ethanol-producing bacteria, such as *Enterobacteriaceae* and *Escherichia coli*, have been found also in patients affected by NASH[86].

Alteration of choline metabolism have been proposed as causative mechanism also in human subjects. In fact it’s well known that hepatic steatosis, promoted by parenteral nutrition, is partly due to choline deficiency, and its supplementation could reverse hepatic fat accumulation[87]. More recently the experimental administration of choline deficient diet was associated to variations of the intestinal concentrations of *Gammaproteobacteria* and *Erysipelotrich*i, that were directly associated to changes in liver fat amount[88].

The development of NASH is associated, also in humans, to increased systemic inflammation, promoted by TLR-4 mediated interaction with circulating PAMPs, with consequent release of pro-inflammatory cytokines[89].

In conclusion, the development of fatty liver is promoted by small bowel bacterial overgrowth and increased intestinal permeability. Bacterial ethanol production and choline deficiency have been confirmed as pathogenic mechanisms also in human subjects. Moreover, the development of NASH is affected by the complex interaction between circulating bacterial antigens and host’s immune system.

**THERAPEUTIC STRATEGIES**

***Diet induced weight loss and bariatric surgery***

Weight loss promoted by calories restricted diet and increased physical activity is associated to significant changes in the composition of gut microflora.

Sotos *et al*[90] found that nutritional intervention strategy based on an energy restricted diet associated to a physical activity program for 3 mo, on a group of obese adolescent, was associated to a significant reduction of sulphate-reducing bacteria and *Enterobacteriaceae*, which was more pronounced in subjects in which interventions were successful. Moreover, in subjects who didn’t reach significant weight loss, the proportion of beneficial bacteria belonging to *Roseburia–Eubacterium* populations remained low[90]. Furthermore, diet-induced weight loss has also been associated to a reduction of *C. histolyticum*, *C. lituseburense* and *E. rectale-C. coccoides* and an increase of the *Bacteroides-Prevotella* group[91].

As previously reported, subjects with a low bacterial gene richness are characterized by more marked overall adiposity, insulin resistance and dyslipidaemia and a more pronounced inflammatory phenotype when compared to high bacterial gene richness individuals[33]. A recent study of Cotillard *et al*[92] reported that dietary intervention improves low gene richness and clinical phenotypes in obese subjects, but the treatment strategies seem to be less efficient for inflammation variables in individuals with lower gene richness. Thus, in these latter subjects, dietary interventions could be less effective.

Some studies conducted on subjects submitted to surgical Roux-en-Y gastric by-pass (RYGB) reported a profound change of gut microbiota composition, related to the surgically reverted anatomy of alimentary tube. These changes might contribute to the successful weight loss obtained in these patients.

Zhang *et al*[93] found that the reduction of gastric acid and the modification of the total length of small bowel contribute to the growth of facultative anaerobes, with a significant increase of *Gammaproteobacteria*. On the other hand, *Firmicutes* and in particular methanogens bacteria, which seem to contribute to the increased energy extraction from fermentation of polysaccharides in obese subjects, are strongly decreased after RYGB[93].

The increase of *Bacteroides-Prevotella* group was also observed after weight loss promoted by RYGB, in association to an increase of *Faecalibacterium prausnitzii* species, directly linked to the reduction in low-grade inflammation[94].

The direct transit of carbohydrates to the small intestine, without the prior exposure to gastric acids, promotes the growth of *Proteobacteria* and *Enterobacteria* fermenting complex carbohydrates[95]. The increased production of metabolites deriving from oligosaccharides fermentation is well known to contribute to increased GLP-1 and peptide YY production, which contribute to reduce appetite and to improve beta-pancreatic cell function and insulin secretion[96].

After RYGB it has been also observed an increase of intestinal gamma-amino-butyric acid production by gut microbes, which also stimulates the release of GLP-1 and peptide YY[95].

Lips *et al*[97] also reported that RYGB improves gut hormone release, such as GLP-1 and peptide YY, and glucose tolerance in diabetic subjects. However, it is not sufficient alone to maintain glucose metabolism balance, since calories restriction is the major determinant of short-term benefit in glucose tolerance.

RYGB does not induce only beneficial effects. Indeed, it seems to influence the increase of pathogens bacteria, such as *Escherchia coli,* and the decrease of beneficial bacteria, such as *Lactobacilli* and *Bifidobacteria*[94]. Moreover, the reduced availability of energy extractable from glucose promotes increased energy extraction from tricarboxylic acid cycle intermediates and from protein catabolism, thus, facilitating the development of renal tubular acidosis[95].

In conclusion, diet induced weight loss is associated to specific changes in gut microbial composition, in terms of increased beneficial anti-inflammatory bacteria and reduced pathogens. A subgroup of patients with low microbial gene richness has shown a more aggressive clinical phenotype and a less responsiveness to therapeutic strategies.

Bariatric surgery promotes evident changes in intestinal bacterial composition. These changes could reinforce the beneficial effects of the surgical intervention on host’s appetite and insulin sensitivity. However, potential negative effects, such as the decrease of beneficial bacteria and the risk of developing renal tubular acidosis, need to be considered.

***Probiotics***

Probiotics are defined by the Food and Agricultural Organization and the World Health Organization as “live microorganisms which when administered in adequate amounts, confer a beneficial health effect on the host”[98].

Several studies have demonstrated that probiotic strains, in particular those of the *Lactobacillus* and *Bifidobacterium* genera, exert multiple beneficial effects in subjects affected by metabolic syndrome. Indeed, they seem to promote weight loss and the reduction of visceral adiposity, to improve glucose tolerance, and to modulate intestinal low grade inflammation.

The experimental studies[98-104] demonstrating the beneficial effects observed in HFD-induced metabolic syndrome, after the administration of probiotics containing *Bifidobacterium* strains, are reported in Table 1.

Cani *et al*[105] and Amar *et al*[21] have demonstrated the putative mechanisms through which *Bifidobacterium* strains could contribute to counteract detrimental effects of metabolic syndrome. The administration of probiotics containing *Bifidobacterium* is associated to an improvement of gut epithelial barrier, promoted by increased expression of tight-junction proteins[21,105]. Consequently, a significant reduction of bacterial translocation, intestinal inflammation and metabolic endotoxemia have been observed{Cani, 2007, Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia;Amar, 2011, Intestinal mucosal adherence and translocation of commensal bacteria at the early onset of type 2 diabetes: molecular mechanisms and probiotic treatment}[21].

Other studies[106-118] have demonstrated the beneficial effects exerted by probiotics containing *Lactobacillus* strains on animals and human subjects, showed in Table 2 and 3, respectively.

These studies underline that *Lactobacillus* strains, especially those producing conjugated linoleic acid[106-108], contribute to body weight loss, reduction of adipocyte size and adipose tissue mass, as well as to improve glucose tolerance, modulating the expression of leptin and fatty acid synthetase.

Other studies reported the positive effects of *Lactobacillus* probiotics in modulating serum lipid profile through the stimulation of fatty acids oxidation[109-111,115], or by inhibiting lipoprotein lipase activity through Angiopoietin like-4, a microbial regulated protein[114].

Nerstedt *et al*[115] also reported the improvement of gut immune functionality, promoted by *Lactobacillus* strains.

The administration of probiotics combining *Bifidobacterium* and *Lactobacillus* strains, such as VSL#3, significantly improve glucose tolerance and reduce food intake, increasing the production of SCFAs and of butyrate that stimulate the intestinal production of GLP-1[119].

Moreover, the administration of probiotics containing *Lactobacillus* strains alters gut microbial composition, promoting the expansion of the host’s own *Bifidobacteria* population, improving the metabolic functions and reducing the pro-inflammatory activity[120].

Recently, the role of probiotics as therapeutic strategy for the treatment of hepatic steatosis and NAFLD is emerging[121]. The putative mechanism involved are the improvement of gut microbial homeostasis, gut barrier function and integrity, the modulation of endotoxemia and of pro-inflammatory response[121], as well as the improvement of hepatic response against oxidative damage[110].

However, although encouraging results emerge from meta-analysis evaluating the role of probiotics for the treatment of NAFLD[122] and the results of most studies seem to be promising, they have to be considered with caution. Indeed, the available evidences suggesting the employ of probiotics for the treatment of obesity are still weak[123] and, therefore, the therapeutic use of probiotics for the treatment of metabolic disorders has not yet been recommended[124].

***Prebiotics***

Prebiotics are defined as non-digestible polysaccharides that promote “the selective stimulation of growth and/or activity(ies) of one or a limited number of microbial genus(era)/species in the gut microbiota that confer(s) health benefit to the host”[125].

The most studied prebiotics are the inulin and various types of fructo-oligosaccharides, which enhance the growth of beneficial bacteria such as *Bifidobacteria* or *Lactobacilli*.

Table 4 illustrates studies[105,126-131] conducted on animal models, employing several types of prebiotics, such as oligofructose, arabinoxylan and inulin and their related effects on the metabolic syndrome.

Prebiotics contribute to modify gut microbial composition, enhancing the growth of *Bifidobacteria*[105,130,131], *Bacteroides*[129-131], *Prevotella* and *Roseburia*[130] and promoting the relative decrease of *Firmicutes*[129,131].

Moreover, they contribute to reduce body weight, body fat and adipocyte size by modulating food intake and appetite, by promoting the production of GLP-1, peptide YY and the decrease of ghrelin, and, at the same time, by decreasing fatty acid storage[126,127,130,131].

Furthermore, the reduction of intestinal low grade inflammation promoted by the improvement of gut barrier integrity[128,130] and the decrease of pro-inflammatory[105] cytokines release, lead to an improvement of glucose tolerance and insulin sensitivity.

Similar effects have been observed in studies conducted on human subjects[132-136] as reported in Table 5.

A recent meta-analysis, exploring the beneficial effects of prebiotics on subjects with metabolic syndrome, reported a statistically significant reduction of post prandial glucose and insulin levels[137]. On the other hand, data regarding effects on body weight, total energy intake, satiety, GLP-1 and peptide YY production and inflammatory pattern seem to be controversial[137].

**CONCLUSION**

Available clinical and experimental evidence suggests that gut microbiota is a potential pathogenetic factor for the development of metabolic syndrome. The overall expression of its detrimental effects seems to be influenced by complex interactions involving diet, lifestyle, environmental factors, such as antibiotic therapies, genetic predisposition, as well as a complex cross-talk between intestinal microbes and the host’s immune system.

Administration of probiotics and prebiotics has been widely used in order to manipulate gut microbiota. However, although several studies reported encouraging results, solid clinical evidence recommending their therapeutic use for metabolic diseases has not emerged, and knowledge about the long term efficacy of this treatment is still lacking. Therefore, additional studies and randomized controlled trials using probiotics and prebiotics, are needed to further understand their clinical impact on gut microbiota manipulation.

**REFERENCES**

1 **Kaur J**. A comprehensive review on metabolic syndrome. *Cardiol Res Pract* 2014; **2014**: 943162 [PMID: 24711954 DOI: 10.1155/2014/943162]

2 **International Diabetes Federation**. The IDF consensus worldwide definition of the metabolic syndrome. Available from: http://www.idf.org/webdata/docs/MetSyndrome\_FINAL.pdf

3 **Cani PD**, Delzenne NM. Gut microflora as a target for energy and metabolic homeostasis. *Curr Opin Clin Nutr Metab Care* 2007; **10**: 729-734 [PMID: 18089955 DOI: 10.1097/MCO.0b013e3282efdebb]

4 **Fukuda S**, Ohno H. Gut microbiome and metabolic diseases. *Semin Immunopathol* 2014; **36**: 103-114 [PMID: 24196453 DOI: 10.1007/s00281-013-0399-z]

5 **Hooper LV**, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. *Science* 2012; **336**: 1268-1273 [PMID: 22674334 DOI: 10.1126/science.1223490]

6 **Jia W**, Li H, Zhao L, Nicholson JK. Gut microbiota: a potential new territory for drug targeting. *Nat Rev Drug Discov* 2008; **7**: 123-129 [PMID: 18239669 DOI: 10.1038/nrd2505]

7 **Zoetendal EG**, Vaughan EE, de Vos WM. A microbial world within us. *Mol Microbiol* 2006; **59**: 1639-1650 [PMID: 16553872 DOI: 10.1111/j.1365-2958.2006.05056.x]

8 **Turnbaugh PJ**, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. *Nature* 2007; **449**: 804-810 [PMID: 17943116 DOI: 10.1038/nature06244]

9 **Bäckhed F**, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF, Gordon JI. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci U S A* 2004; **101**: 15718-15723 [PMID: 15505215 DOI: 10.1073/pnas.0407076101]

10 **Mandard S**, Zandbergen F, van Straten E, Wahli W, Kuipers F, Müller M, Kersten S. The fasting-induced adipose factor/angiopoietin-like protein 4 is physically associated with lipoproteins and governs plasma lipid levels and adiposity. *J Biol Chem* 2006; **281**: 934-944 [PMID: 16272564 DOI: 10.1074/jbc.M506519200]

11 **Bäckhed F**, Manchester JK, Semenkovich CF, Gordon JI. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proc Natl Acad Sci U S A* 2007; **104**: 979-984 [PMID: 17210919 DOI: 10.1073/pnas.0605374104]

12 **Turnbaugh PJ**, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 2006; **444**: 1027-1031 [PMID: 17183312 DOI: 10.1038/nature05414]

13 **Samuel BS**, Shaito A, Motoike T, Rey FE, Backhed F, Manchester JK, Hammer RE, Williams SC, Crowley J, Yanagisawa M, Gordon JI. Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. *Proc Natl Acad Sci U S A* 2008; **105**: 16767-16772 [PMID: 18931303 DOI: 10.1073/pnas.0808567105]

14 **Tolhurst G**, Heffron H, Lam YS, Parker HE, Habib AM, Diakogiannaki E, Cameron J, Grosse J, Reimann F, Gribble FM. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. *Diabetes* 2012; **61**: 364-371 [PMID: 22190648 DOI: 10.2337/db11-1019]

15 **Hooper LV**, Wong MH, Thelin A, Hansson L, Falk PG, Gordon JI. Molecular analysis of commensal host-microbial relationships in the intestine. *Science* 2001; **291**: 881-884 [PMID: 11157169 DOI: 10.1126/science.291.5505.881]

16 **Ley RE**, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. *Proc Natl Acad Sci U S A* 2005; **102**: 11070-11075 [PMID: 16033867 DOI: 10.1073/pnas.0504978102]

17 **Bajzer M**, Seeley RJ. Physiology: obesity and gut flora. *Nature* 2006; **444**: 1009-1010 [PMID: 17183300 DOI: 10.1038/4441009a]

18 **Cani PD**, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, Waget A, Delmée E, Cousin B, Sulpice T, Chamontin B, Ferrières J, Tanti JF, Gibson GR, Casteilla L, Delzenne NM, Alessi MC, Burcelin R. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* 2007; **56**: 1761-1772 [PMID: 17456850 DOI: 10.2337/db06-1491]

19 **de La Serre CB**, Ellis CL, Lee J, Hartman AL, Rutledge JC, Raybould HE. Propensity to high-fat diet-induced obesity in rats is associated with changes in the gut microbiota and gut inflammation. *Am J Physiol Gastrointest Liver Physiol* 2010; **299**: G440-G448 [PMID: 20508158 DOI: 10.1152/ajpgi.00098.2010]

20 **Fei N**, Zhao L. An opportunistic pathogen isolated from the gut of an obese human causes obesity in germfree mice. *ISME J* 2013; **7**: 880-884 [PMID: 23235292 DOI: 10.1038/ismej.2012.153]

21 **Amar J**, Chabo C, Waget A, Klopp P, Vachoux C, Bermúdez-Humarán LG, Smirnova N, Bergé M, Sulpice T, Lahtinen S, Ouwehand A, Langella P, Rautonen N, Sansonetti PJ, Burcelin R. Intestinal mucosal adherence and translocation of commensal bacteria at the early onset of type 2 diabetes: molecular mechanisms and probiotic treatment. *EMBO Mol Med* 2011; **3**: 559-572 [PMID: 21735552 DOI: 10.1002/emmm.201100159]

22 **Cerf-Bensussan N**, Gaboriau-Routhiau V. The immune system and the gut microbiota: friends or foes? *Nat Rev Immunol* 2010; **10**: 735-744 [PMID: 20865020 DOI: 10.1038/nri2850]

23 **Vijay-Kumar M**, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, Srinivasan S, Sitaraman SV, Knight R, Ley RE, Gewirtz AT. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science* 2010; **328**: 228-231 [PMID: 20203013 DOI: 10.1126/science.1179721]

24 **Muccioli GG**, Naslain D, Bäckhed F, Reigstad CS, Lambert DM, Delzenne NM, Cani PD. The endocannabinoid system links gut microbiota to adipogenesis. *Mol Syst Biol* 2010; **6**: 392 [PMID: 20664638 DOI: 10.1038/msb.2010.46]

25 **Sekirov I**, Russell SL, Antunes LC, Finlay BB. Gut microbiota in health and disease. *Physiol Rev* 2010; **90**: 859-904 [PMID: 20664075 DOI: 10.1152/physrev.00045.2009]

26 **Lee YK**, Mazmanian SK. Has the microbiota played a critical role in the evolution of the adaptive immune system? *Science* 2010; **330**: 1768-1773 [PMID: 21205662 DOI: 10.1126/science.1195568]

27 **Ley RE**, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature* 2006; **444**: 1022-1023 [PMID: 17183309 DOI: 10.1038/4441022a]

28 **Armougom F**, Henry M, Vialettes B, Raccah D, Raoult D. Monitoring bacterial community of human gut microbiota reveals an increase in Lactobacillus in obese patients and Methanogens in anorexic patients. *PLoS One* 2009; **4**: e7125 [PMID: 19774074 DOI: 10.1371/journal.pone.0007125]

29 **Santacruz A**, Collado MC, García-Valdés L, Segura MT, Martín-Lagos JA, Anjos T, Martí-Romero M, Lopez RM, Florido J, Campoy C, Sanz Y. Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. *Br J Nutr* 2010; **104**: 83-92 [PMID: 20205964 DOI: 10.1017/S0007114510000176]

30 **Duncan SH**, Lobley GE, Holtrop G, Ince J, Johnstone AM, Louis P, Flint HJ. Human colonic microbiota associated with diet, obesity and weight loss. *Int J Obes (Lond)* 2008; **32**: 1720-1724 [PMID: 18779823 DOI: 10.1038/ijo.2008.155]

31 **Schwiertz A**, Taras D, Schäfer K, Beijer S, Bos NA, Donus C, Hardt PD. Microbiota and SCFA in lean and overweight healthy subjects. *Obesity (Silver Spring)* 2010; **18**: 190-195 [PMID: 19498350 DOI: 10.1038/oby.2009.167]

32 **Turnbaugh PJ**, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, Sogin ML, Jones WJ, Roe BA, Affourtit JP, Egholm M, Henrissat B, Heath AC, Knight R, Gordon JI. A core gut microbiome in obese and lean twins. *Nature* 2009; **457**: 480-484 [PMID: 19043404 DOI: 10.1038/nature07540]

33 **Le Chatelier E**, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, Almeida M, Arumugam M, Batto JM, Kennedy S, Leonard P, Li J, Burgdorf K, Grarup N, Jørgensen T, Brandslund I, Nielsen HB, Juncker AS, Bertalan M, Levenez F, Pons N, Rasmussen S, Sunagawa S, Tap J, Tims S, Zoetendal EG, Brunak S, Clément K, Doré J, Kleerebezem M, Kristiansen K, Renault P, Sicheritz-Ponten T, de Vos WM, Zucker JD, Raes J, Hansen T, Bork P, Wang J, Ehrlich SD, Pedersen O. Richness of human gut microbiome correlates with metabolic markers. *Nature* 2013; **500**: 541-546 [PMID: 23985870 DOI: 10.1038/nature12506]

34 **Kalliomäki M**, Collado MC, Salminen S, Isolauri E. Early differences in fecal microbiota composition in children may predict overweight. *Am J Clin Nutr* 2008; **87**: 534-538 [PMID: 18326589]

35 **Karlsson CL**, Onnerfält J, Xu J, Molin G, Ahrné S, Thorngren-Jerneck K. The microbiota of the gut in preschool children with normal and excessive body weight. *Obesity (Silver Spring)* 2012; **20**: 2257-2261 [PMID: 22546742 DOI: 10.1038/oby.2012.110]

36 **Santacruz A**, Marcos A, Wärnberg J, Martí A, Martin-Matillas M, Campoy C, Moreno LA, Veiga O, Redondo-Figuero C, Garagorri JM, Azcona C, Delgado M, García-Fuentes M, Collado MC, Sanz Y. Interplay between weight loss and gut microbiota composition in overweight adolescents. *Obesity (Silver Spring)* 2009; **17**: 1906-1915 [PMID: 19390523 DOI: 10.1038/oby.2009.112]

37 **Penders J**, Thijs C, Vink C, Stelma FF, Snijders B, Kummeling I, van den Brandt PA, Stobberingh EE. Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics* 2006; **118**: 511-521 [PMID: 16882802 DOI: 10.1542/peds.2005-2824]

38 **Hällström M**, Eerola E, Vuento R, Janas M, Tammela O. Effects of mode of delivery and necrotising enterocolitis on the intestinal microflora in preterm infants. *Eur J Clin Microbiol Infect Dis* 2004; **23**: 463-470 [PMID: 15168141 DOI: 10.1007/s10096-004-1146-0]

39 **Penders J**, Vink C, Driessen C, London N, Thijs C, Stobberingh EE. Quantification of Bifidobacterium spp., Escherichia coli and Clostridium difficile in faecal samples of breast-fed and formula-fed infants by real-time PCR. *FEMS Microbiol Lett* 2005; **243**: 141-147 [PMID: 15668012 DOI: 10.1016/j.femsle.2004.11.052]

40 **Dethlefsen L**, Huse S, Sogin ML, Relman DA. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. *PLoS Biol* 2008; **6**: e280 [PMID: 19018661 DOI: 10.1371/journal.pbio.0060280]

41 **Kovatcheva-Datchary P**, Arora T. Nutrition, the gut microbiome and the metabolic syndrome. *Best Pract Res Clin Gastroenterol* 2013; **27**: 59-72 [PMID: 23768553 DOI: 10.1016/j.bpg.2013.03.017]

42 **De Filippo C**, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, Collini S, Pieraccini G, Lionetti P. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proc Natl Acad Sci U S A* 2010; **107**: 14691-14696 [PMID: 20679230 DOI: 10.1073/pnas.1005963107]

43 **Wright SD**, Ramos RA, Tobias PS, Ulevitch RJ, Mathison JC. CD14, a receptor for complexes of lipopolysaccharide (LPS) and LPS binding protein. *Science* 1990; **249**: 1431-1433 [PMID: 1698311]

44 **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, 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]

45 **Brown K**, DeCoffe D, Molcan E, Gibson DL. Diet-induced dysbiosis of the intestinal microbiota and the effects on immunity and disease. *Nutrients* 2012; **4**: 1095-1119 [PMID: 23016134 DOI: 10.3390/nu4081095]

46 **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]

47 **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]

48 **Ding S**, Chi MM, Scull BP, Rigby R, Schwerbrock NM, Magness S, Jobin C, Lund PK. High-fat diet: bacteria interactions promote intestinal inflammation which precedes and correlates with obesity and insulin resistance in mouse. *PLoS One* 2010; **5**: e12191 [PMID: 20808947 DOI: 10.1371/journal.pone.0012191]

49 **Turnbaugh PJ**, Bäckhed F, Fulton L, Gordon JI. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. *Cell Host Microbe* 2008; **3**: 213-223 [PMID: 18407065 DOI: 10.1016/j.chom.2008.02.015]

50 **de Wit N**, Derrien M, Bosch-Vermeulen H, Oosterink E, Keshtkar S, Duval C, de Vogel-van den Bosch J, Kleerebezem M, Müller M, van der Meer R. Saturated fat stimulates obesity and hepatic steatosis and affects gut microbiota composition by an enhanced overflow of dietary fat to the distal intestine. *Am J Physiol Gastrointest Liver Physiol* 2012; **303**: G589-G599 [PMID: 22700822 DOI: 10.1152/ajpgi.00488.2011]

51 **Hildebrandt MA**, Hoffmann C, Sherrill-Mix SA, Keilbaugh SA, Hamady M, Chen YY, Knight R, Ahima RS, Bushman F, Wu GD. High-fat diet determines the composition of the murine gut microbiome independently of obesity. *Gastroenterology* 2009; **137**: 1716-24.e1-2 [PMID: 19706296 DOI: 10.1053/j.gastro.2009.08.042]

52 **Fleissner CK**, Huebel N, Abd El-Bary MM, Loh G, Klaus S, Blaut M. Absence of intestinal microbiota does not protect mice from diet-induced obesity. *Br J Nutr* 2010; **104**: 919-929 [PMID: 20441670 DOI: 10.1017/S0007114510001303]

53 **Shen W**, Gaskins HR, McIntosh MK. Influence of dietary fat on intestinal microbes, inflammation, barrier function and metabolic outcomes. *J Nutr Biochem* 2014; **25**: 270-280 [PMID: 24355793 DOI: 10.1016/j.jnutbio.2013.09.009]

54 **Brinkworth GD**, Noakes M, Clifton PM, Bird AR. Comparative effects of very low-carbohydrate, high-fat and high-carbohydrate, low-fat weight-loss diets on bowel habit and faecal short-chain fatty acids and bacterial populations. *Br J Nutr* 2009; **101**: 1493-1502 [PMID: 19224658 DOI: 10.1017/S0007114508094658]

55 **Zhang C**, Zhang M, Wang S, Han R, Cao Y, Hua W, Mao Y, Zhang X, Pang X, Wei C, Zhao G, Chen Y, Zhao L. Interactions between gut microbiota, host genetics and diet relevant to development of metabolic syndromes in mice. *ISME J* 2010; **4**: 232-241 [PMID: 19865183 DOI: 10.1038/ismej.2009.112]

56 **Lam YY**, Ha CW, Campbell CR, Mitchell AJ, Dinudom A, Oscarsson J, Cook DI, Hunt NH, Caterson ID, Holmes AJ, Storlien LH. Increased gut permeability and microbiota change associate with mesenteric fat inflammation and metabolic dysfunction in diet-induced obese mice. *PLoS One* 2012; **7**: e34233 [PMID: 22457829 DOI: 10.1371/journal.pone.0034233]

57 **Shi H**, Kokoeva MV, Inouye K, Tzameli I, Yin H, Flier JS. TLR4 links innate immunity and fatty acid-induced insulin resistance. *J Clin Invest* 2006; **116**: 3015-3025 [PMID: 17053832 DOI: 10.1172/JCI28898]

58 **Membrez M**, Blancher F, Jaquet M, Bibiloni R, Cani PD, Burcelin RG, Corthesy I, Macé K, Chou CJ. Gut microbiota modulation with norfloxacin and ampicillin enhances glucose tolerance in mice. *FASEB J* 2008; **22**: 2416-2426 [PMID: 18326786 DOI: 10.1096/fj.07-102723]

59 **Cani PD**, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, Burcelin R. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* 2008; **57**: 1470-1481 [PMID: 18305141 DOI: 10.2337/db07-1403]

60 **Everard A**, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, Guiot Y, Derrien M, Muccioli GG, Delzenne NM, de Vos WM, Cani PD. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proc Natl Acad Sci U S A* 2013; **110**: 9066-9071 [PMID: 23671105 DOI: 10.1073/pnas.1219451110]

61 **Belzer C**, de Vos WM. Microbes inside--from diversity to function: the case of Akkermansia. *ISME J* 2012; **6**: 1449-1458 [PMID: 22437156 DOI: 10.1038/ismej.2012.6]

62 **Hansen CH**, Krych L, Nielsen DS, Vogensen FK, Hansen LH, Sørensen SJ, Buschard K, Hansen AK. Early life treatment with vancomycin propagates Akkermansia muciniphila and reduces diabetes incidence in the NOD mouse. *Diabetologia* 2012; **55**: 2285-2294 [PMID: 22572803 DOI: 10.1007/s00125-012-2564-7]

63 **Qin J**, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, Zhang W, Guan Y, Shen D, Peng Y, Zhang D, Jie Z, Wu W, Qin Y, Xue W, Li J, Han L, Lu D, Wu P, Dai Y, Sun X, Li Z, Tang A, Zhong S, Li X, Chen W, Xu R, Wang M, Feng Q, Gong M, Yu J, Zhang Y, Zhang M, Hansen T, Sanchez G, Raes J, Falony G, Okuda S, Almeida M, LeChatelier E, Renault P, Pons N, Batto JM, Zhang Z, Chen H, Yang R, Zheng W, Li S, Yang H, Wang J, Ehrlich SD, Nielsen R, Pedersen O, Kristiansen K, Wang J. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* 2012; **490**: 55-60 [PMID: 23023125 DOI: 10.1038/nature11450]

64 **Wall R**, Ross RP, Shanahan F, O'Mahony L, O'Mahony C, Coakley M, Hart O, Lawlor P, Quigley EM, Kiely B, Fitzgerald GF, Stanton C. Metabolic activity of the enteric microbiota influences the fatty acid composition of murine and porcine liver and adipose tissues. *Am J Clin Nutr* 2009; **89**: 1393-1401 [PMID: 19357220 DOI: 10.3945/ajcn.2008.27023]

65 **Amar J**, Burcelin R, Ruidavets JB, Cani PD, Fauvel J, Alessi MC, Chamontin B, Ferriéres J. Energy intake is associated with endotoxemia in apparently healthy men. *Am J Clin Nutr* 2008; **87**: 1219-1223 [PMID: 18469242]

66 **Creely SJ**, McTernan PG, Kusminski CM, Fisher fM, Da Silva NF, Khanolkar M, Evans M, Harte AL, Kumar S. Lipopolysaccharide activates an innate immune system response in human adipose tissue in obesity and type 2 diabetes. *Am J Physiol Endocrinol Metab* 2007; **292**: E740-E747 [PMID: 17090751 DOI: 10.1152/ajpendo.00302.2006]

67 **Amar J**, Serino M, Lange C, Chabo C, Iacovoni J, Mondot S, Lepage P, Klopp C, Mariette J, Bouchez O, Perez L, Courtney M, Marre M, Klopp P, Lantieri O, Doré J, Charles M, Balkau B, Burcelin R. Involvement of tissue bacteria in the onset of diabetes in humans: evidence for a concept. *Diabetologia* 2011; **54**: 3055-3061 [PMID: 21976140 DOI: 10.1007/s00125-011-2329-8]

68 **Larsen N**, Vogensen FK, van den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, Al-Soud WA, Sørensen SJ, Hansen LH, Jakobsen M. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS One* 2010; **5**: e9085 [PMID: 20140211 DOI: 10.1371/journal.pone.0009085]

69 **Wu X**, Ma C, Han L, Nawaz M, Gao F, Zhang X, Yu P, Zhao C, Li L, Zhou A, Wang J, Moore JE, Millar BC, Xu J. Molecular characterisation of the faecal microbiota in patients with type II diabetes. *Curr Microbiol* 2010; **61**: 69-78 [PMID: 20087741 DOI: 10.1007/s00284-010-9582-9]

70 **Zhang X**, Shen D, Fang Z, Jie Z, Qiu X, Zhang C, Chen Y, Ji L. Human gut microbiota changes reveal the progression of glucose intolerance. *PLoS One* 2013; **8**: e71108 [PMID: 24013136 DOI: 10.1371/journal.pone.0071108]

71 **Lewis K**, Lutgendorff F, Phan V, Söderholm JD, Sherman PM, McKay DM. Enhanced translocation of bacteria across metabolically stressed epithelia is reduced by butyrate. *Inflamm Bowel Dis* 2010; **16**: 1138-1148 [PMID: 20024905 DOI: 10.1002/ibd.21177]

72 **Vrieze A**, Van Nood E, Holleman F, Salojärvi J, Kootte RS, Bartelsman JF, Dallinga-Thie GM, Ackermans MT, Serlie MJ, Oozeer R, Derrien M, Druesne A, Van Hylckama Vlieg JE, Bloks VW, Groen AK, Heilig HG, Zoetendal EG, Stroes ES, de Vos WM, Hoekstra JB, Nieuwdorp M. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology* 2012; **143**: 913-6.e7 [PMID: 22728514 DOI: 10.1053/j.gastro.2012.06.031]

73 **Karlsson FH**, Tremaroli V, Nookaew I, Bergström G, Behre CJ, Fagerberg B, Nielsen J, Bäckhed F. Gut metagenome in European women with normal, impaired and diabetic glucose control. *Nature* 2013; **498**: 99-103 [PMID: 23719380 DOI: 10.1038/nature12198]

74 **Le Roy T**, Llopis M, Lepage P, Bruneau A, Rabot S, Bevilacqua C, Martin P, Philippe C, Walker F, Bado A, Perlemuter G, Cassard-Doulcier AM, Gérard P. Intestinal microbiota determines development of non-alcoholic fatty liver disease in mice. *Gut* 2013; **62**: 1787-1794 [PMID: 23197411 DOI: 10.1136/gutjnl-2012-303816]

75 **Cope K**, Risby T, Diehl AM. Increased gastrointestinal ethanol production in obese mice: implications for fatty liver disease pathogenesis. *Gastroenterology* 2000; **119**: 1340-1347 [PMID: 11054393]

76 **Dumas ME**, Barton RH, Toye A, Cloarec O, Blancher C, Rothwell A, Fearnside J, Tatoud R, Blanc V, Lindon JC, Mitchell SC, Holmes E, McCarthy MI, Scott J, Gauguier D, Nicholson JK. Metabolic profiling reveals a contribution of gut microbiota to fatty liver phenotype in insulin-resistant mice. *Proc Natl Acad Sci U S A* 2006; **103**: 12511-12516 [PMID: 16895997 DOI: 10.1073/pnas.0601056103]

77 **Swann JR**, Want EJ, Geier FM, Spagou K, Wilson ID, Sidaway JE, Nicholson JK, Holmes E. Systemic gut microbial modulation of bile acid metabolism in host tissue compartments. *Proc Natl Acad Sci U S A* 2011; **108** Suppl 1: 4523-4530 [PMID: 20837534 DOI: 10.1073/pnas.1006734107]

78 **Spruss A**, Kanuri G, Wagnerberger S, Haub S, Bischoff SC, Bergheim I. Toll-like receptor 4 is involved in the development of fructose-induced hepatic steatosis in mice. *Hepatology* 2009; **50**: 1094-1104 [PMID: 19637282 DOI: 10.1002/hep.23122]

79 **Rivera CA**, Adegboyega P, van Rooijen N, Tagalicud A, Allman M, Wallace M. Toll-like receptor-4 signaling and Kupffer cells play pivotal roles in the pathogenesis of non-alcoholic steatohepatitis. *J Hepatol* 2007; **47**: 571-579 [PMID: 17644211 DOI: 10.1016/j.jhep.2007.04.019]

80 **Boaru SG**, Borkham-Kamphorst E, Tihaa L, Haas U, Weiskirchen R. Expression analysis of inflammasomes in experimental models of inflammatory and fibrotic liver disease. *J Inflamm (Lond)* 2012; **9**: 49 [PMID: 23192004 DOI: 10.1186/1476-9255-9-49]

81 **Csak T**, Ganz M, Pespisa J, Kodys K, Dolganiuc A, Szabo G. Fatty acid and endotoxin activate inflammasomes in mouse hepatocytes that release danger signals to stimulate immune cells. *Hepatology* 2011; **54**: 133-144 [PMID: 21488066 DOI: 10.1002/hep.24341]

82 **Seki E**, De Minicis S, Osterreicher CH, Kluwe J, Osawa Y, Brenner DA, Schwabe RF. TLR4 enhances TGF-beta signaling and hepatic fibrosis. *Nat Med* 2007; **13**: 1324-1332 [PMID: 17952090 DOI: 10.1038/nm1663]

83 **Henao-Mejia J**, Elinav E, Jin C, Hao L, Mehal WZ, Strowig T, Thaiss CA, Kau AL, Eisenbarth SC, Jurczak MJ, Camporez JP, Shulman GI, Gordon JI, Hoffman HM, Flavell RA. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. *Nature* 2012; **482**: 179-185 [PMID: 22297845 DOI: 10.1038/nature10809]

84 **Miele L**, Valenza V, La Torre G, Montalto M, Cammarota G, Ricci R, Mascianà R, Forgione A, Gabrieli ML, Perotti G, Vecchio FM, Rapaccini G, Gasbarrini G, Day CP, Grieco A. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. *Hepatology* 2009; **49**: 1877-1887 [PMID: 19291785 DOI: 10.1002/hep.22848]

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 **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]

87 **Buchman AL**, Dubin MD, Moukarzel AA, Jenden DJ, Roch M, Rice KM, Gornbein J, Ament ME. Choline deficiency: a cause of hepatic steatosis during parenteral nutrition that can be reversed with intravenous choline supplementation. *Hepatology* 1995; **22**: 1399-1403 [PMID: 7590654]

88 **Spencer MD**, Hamp TJ, Reid RW, Fischer LM, Zeisel SH, Fodor AA. Association between composition of the human gastrointestinal microbiome and development of fatty liver with choline deficiency. *Gastroenterology* 2011; **140**: 976-986 [PMID: 21129376 DOI: 10.1053/j.gastro.2010.11.049]

89 **Shanab AA**, Scully P, Crosbie O, Buckley M, O'Mahony L, Shanahan F, Gazareen S, Murphy E, Quigley EM. Small intestinal bacterial overgrowth in nonalcoholic steatohepatitis: association with toll-like receptor 4 expression and plasma levels of interleukin 8. *Dig Dis Sci* 2011; **56**: 1524-1534 [PMID: 21046243 DOI: 10.1007/s10620-010-1447-3]

90 **Sotos M**, Nadal I, Marti A, Martínez A, Martin-Matillas M, Campoy C, Puertollano MA, Wärnberg J, Marcos A, Sanz Y. Gut microbes and obesity in adolescents. *P Nutr Soc* 2008; **67**: E20

91 **Nadal I**, Santacruz A, Marcos A, Warnberg J, Garagorri JM, Moreno LA, Martin-Matillas M, Campoy C, Martí A, Moleres A, Delgado M, Veiga OL, García-Fuentes M, Redondo CG, Sanz Y. Shifts in clostridia, bacteroides and immunoglobulin-coating fecal bacteria associated with weight loss in obese adolescents. *Int J Obes (Lond)* 2009; **33**: 758-767 [PMID: 19050675 DOI: 10.1038/ijo.2008.260]

92 **Cotillard A**, Kennedy SP, Kong LC, Prifti E, Pons N, Le Chatelier E, Almeida M, Quinquis B, Levenez F, Galleron N, Gougis S, Rizkalla S, Batto JM, Renault P, Doré J, Zucker JD, Clément K, Ehrlich SD. Dietary intervention impact on gut microbial gene richness. *Nature* 2013; **500**: 585-588 [PMID: 23985875 DOI: 10.1038/nature12480]

93 **Zhang H**, DiBaise JK, Zuccolo A, Kudrna D, Braidotti M, Yu Y, Parameswaran P, Crowell MD, Wing R, Rittmann BE, Krajmalnik-Brown R. Human gut microbiota in obesity and after gastric bypass. *Proc Natl Acad Sci U S A* 2009; **106**: 2365-2370 [PMID: 19164560 DOI: 10.1073/pnas.0812600106]

94 **Furet JP**, Kong LC, Tap J, Poitou C, Basdevant A, Bouillot JL, Mariat D, Corthier G, Doré J, Henegar C, Rizkalla S, Clément K. Differential adaptation of human gut microbiota to bariatric surgery-induced weight loss: links with metabolic and low-grade inflammation markers. *Diabetes* 2010; **59**: 3049-3057 [PMID: 20876719 DOI: 10.2337/db10-0253]

95 **Li JV**, Ashrafian H, Bueter M, Kinross J, Sands C, le Roux CW, Bloom SR, Darzi A, Athanasiou T, Marchesi JR, Nicholson JK, Holmes E. Metabolic surgery profoundly influences gut microbial-host metabolic cross-talk. *Gut* 2011; **60**: 1214-1223 [PMID: 21572120 DOI: 10.1136/gut.2010.234708]

96 **Cani PD**, Delzenne NM. The role of the gut microbiota in energy metabolism and metabolic disease. *Curr Pharm Des* 2009; **15**: 1546-1558 [PMID: 19442172]

97 **Lips MA**, de Groot GH, van Klinken JB, Aarts E, Berends FJ, Janssen IM, Van Ramshorst B, Van Wagensveld BA, Swank DJ, Van Dielen F, Willems van Dijk K, Pijl H. Calorie restriction is a major determinant of the short-term metabolic effects of gastric bypass surgery in obese type 2 diabetic patients. *Clin Endocrinol (Oxf)* 2014; **80**: 834-842 [PMID: 23711328 DOI: 10.1111/cen.12254]

98 **FAO/WHO**. Health and Nutritional Properties of Probiotics in Food including Powder Milk with Live Lactic Acid Bacteria Report. 2001

99 **Kondo S**, Xiao JZ, Satoh T, Odamaki T, Takahashi S, Sugahara H, Yaeshima T, Iwatsuki K, Kamei A, Abe K. Antiobesity effects of Bifidobacterium breve strain B-3 supplementation in a mouse model with high-fat diet-induced obesity. *Biosci Biotechnol Biochem* 2010; **74**: 1656-1661 [PMID: 20699581]

100 **Cano PG**, Santacruz A, Trejo FM, Sanz Y. Bifidobacterium CECT 7765 improves metabolic and immunological alterations associated with obesity in high-fat diet-fed mice. *Obesity (Silver Spring)* 2013; **21**: 2310-2321 [PMID: 23418126 DOI: 10.1002/oby.20330]

101 **Chen JJ**, Wang R, Li XF, Wang RL. Bifidobacterium longum supplementation improved high-fat-fed-induced metabolic syndrome and promoted intestinal Reg I gene expression. *Exp Biol Med (Maywood)* 2011; **236**: 823-831 [PMID: 21685239 DOI: 10.1258/ebm.2011.010399]

102 **Chen J**, Wang R, Li XF, Wang RL. Bifidobacterium adolescentis supplementation ameliorates visceral fat accumulation and insulin sensitivity in an experimental model of the metabolic syndrome. *Br J Nutr* 2012; **107**: 1429-1434 [PMID: 21914236 DOI: 10.1017/S0007114511004491]

103 **An HM**, Park SY, Lee do K, Kim JR, Cha MK, Lee SW, Lim HT, Kim KJ, Ha NJ. Antiobesity and lipid-lowering effects of Bifidobacterium spp. in high fat diet-induced obese rats. *Lipids Health Dis* 2011; **10**: 116 [PMID: 21745411 DOI: 10.1186/1476-511X-10-116]

104 **Yin YN**, Yu QF, Fu N, Liu XW, Lu FG. Effects of four Bifidobacteria on obesity in high-fat diet induced rats. *World J Gastroenterol* 2010; **16**: 3394-3401 [PMID: 20632441]

105 **Cani PD**, Neyrinck AM, Fava F, Knauf C, Burcelin RG, Tuohy KM, Gibson GR, Delzenne NM. Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. *Diabetologia* 2007; **50**: 2374-2383 [PMID: 17823788 DOI: 10.1007/s00125-007-0791-0]

106 **Lee HY**, Park JH, Seok SH, Baek MW, Kim DJ, Lee KE, Paek KS, Lee Y, Park JH. Human originated bacteria, Lactobacillus rhamnosus PL60, produce conjugated linoleic acid and show anti-obesity effects in diet-induced obese mice. *Biochim Biophys Acta* 2006; **1761**: 736-744 [PMID: 16807088 DOI: 10.1016/j.bbalip.2006.05.007]

107 **Lee K**, Paek K, Lee HY, Park JH, Lee Y. Antiobesity effect of trans-10,cis-12-conjugated linoleic acid-producing Lactobacillus plantarum PL62 on diet-induced obese mice. *J Appl Microbiol* 2007; **103**: 1140-1146 [PMID: 17897219 DOI: 10.1111/j.1365-2672.2007.03336.x]

108 **Sato M**, Uzu K, Yoshida T, Hamad EM, Kawakami H, Matsuyama H, Abd El-Gawad IA, Imaizumi K. Effects of milk fermented by Lactobacillus gasseri SBT2055 on adipocyte size in rats. *Br J Nutr* 2008; **99**: 1013-1017 [PMID: 17977471 DOI: 10.1017/S0007114507839006]

109 **Tomaro-Duchesneau C**, Saha S, Malhotra M, Jones ML, Labbé A, Rodes L, Kahouli I, Prakash S. Effect of orally administered L. fermentum NCIMB 5221 on markers of metabolic syndrome: an in vivo analysis using ZDF rats. *Appl Microbiol Biotechnol* 2014; **98**: 115-126 [PMID: 24121931 DOI: 10.1007/s00253-013-5252-8]

110 **Wang LX**, Liu K, Gao DW, Hao JK. Protective effects of two Lactobacillus plantarum strains in hyperlipidemic mice. *World J Gastroenterol* 2013; **19**: 3150-3156 [PMID: 23716997 DOI: 10.3748/wjg.v19.i20.3150]

111 **Kim SW**, Park KY, Kim B, Kim E, Hyun CK. Lactobacillus rhamnosus GG improves insulin sensitivity and reduces adiposity in high-fat diet-fed mice through enhancement of adiponectin production. *Biochem Biophys Res Commun* 2013; **431**: 258-263 [PMID: 23313485 DOI: 10.1016/j.bbrc.2012.12.121]

112 **Fåk F**, Bäckhed F. Lactobacillus reuteri prevents diet-induced obesity, but not atherosclerosis, in a strain dependent fashion in Apoe-/- mice. *PLoS One* 2012; **7**: e46837 [PMID: 23056479 DOI: 10.1371/journal.pone.0046837]

113 **Takemura N**, Okubo T, Sonoyama K. Lactobacillus plantarum strain No. 14 reduces adipocyte size in mice fed high-fat diet. *Exp Biol Med (Maywood)* 2010; **235**: 849-856 [PMID: 20558839 DOI: 10.1258/ebm.2010.009377]

114 **Aronsson L**, Huang Y, Parini P, Korach-André M, Håkansson J, Gustafsson JÅ, Pettersson S, Arulampalam V, Rafter J. Decreased fat storage by Lactobacillus paracasei is associated with increased levels of angiopoietin-like 4 protein (ANGPTL4). *PLoS One* 2010; **5**: [PMID: 20927337 DOI: 10.1371/journal.pone.0013087]

115 **Nerstedt A**, Nilsson EC, Ohlson K, Håkansson J, Thomas Svensson L, Löwenadler B, Svensson UK, Mahlapuu M. Administration of Lactobacillus evokes coordinated changes in the intestinal expression profile of genes regulating energy homeostasis and immune phenotype in mice. *Br J Nutr* 2007; **97**: 1117-1127 [PMID: 17433125 DOI: 10.1017/S0007114507682907]

116 **Kadooka Y**, Sato M, Imaizumi K, Ogawa A, Ikuyama K, Akai Y, Okano M, Kagoshima M, Tsuchida T. Regulation of abdominal adiposity by probiotics (Lactobacillus gasseri SBT2055) in adults with obese tendencies in a randomized controlled trial. *Eur J Clin Nutr* 2010; **64**: 636-643 [PMID: 20216555 DOI: 10.1038/ejcn.2010.19]

117 **Kadooka Y**, Sato M, Ogawa A, Miyoshi M, Uenishi H, Ogawa H, Ikuyama K, Kagoshima M, Tsuchida T. Effect of Lactobacillus gasseri SBT2055 in fermented milk on abdominal adiposity in adults in a randomised controlled trial. *Br J Nutr* 2013; **110**: 1696-1703 [PMID: 23614897 DOI: 10.1017/S0007114513001037]

118 **Barreto FM**, Colado Simão AN, Morimoto HK, Batisti Lozovoy MA, Dichi I, Helena da Silva Miglioranza L. Beneficial effects of Lactobacillus plantarum on glycemia and homocysteine levels in postmenopausal women with metabolic syndrome. *Nutrition* 2013; In press [PMID: 24613434 DOI: 10.1016/j.nut.2013.12.004]

119 **Yadav H**, Lee JH, Lloyd J, Walter P, Rane SG. Beneficial metabolic effects of a probiotic via butyrate-induced GLP-1 hormone secretion. *J Biol Chem* 2013; **288**: 25088-25097 [PMID: 23836895 DOI: 10.1074/jbc.M113.452516]

120 **Park DY**, Ahn YT, Park SH, Huh CS, Yoo SR, Yu R, Sung MK, McGregor RA, Choi MS. Supplementation of Lactobacillus curvatus HY7601 and Lactobacillus plantarum KY1032 in diet-induced obese mice is associated with gut microbial changes and reduction in obesity. *PLoS One* 2013; **8**: e59470 [PMID: 23555678 DOI: 10.1371/journal.pone.0059470]

121 **Iacono A**, Raso GM, Canani RB, Calignano A, Meli R. Probiotics as an emerging therapeutic strategy to treat NAFLD: focus on molecular and biochemical mechanisms. *J Nutr Biochem* 2011; **22**: 699-711 [PMID: 21292470 DOI: 10.1016/j.jnutbio.2010.10.002]

122 **Ma YY**, Li L, Yu CH, Shen Z, Chen LH, Li YM. Effects of probiotics on nonalcoholic fatty liver disease: a meta-analysis. *World J Gastroenterol* 2013; **19**: 6911-6918 [PMID: 24187469 DOI: 10.3748/wjg.v19.i40.6911]

123 **Million M**, Angelakis E, Paul M, Armougom F, Leibovici L, Raoult D. Comparative meta-analysis of the effect of Lactobacillus species on weight gain in humans and animals. *Microb Pathog* 2012; **53**: 100-108 [PMID: 22634320 DOI: 10.1016/j.micpath.2012.05.007]

124 **Floch MH**, Walker WA, Madsen K, Sanders ME, Macfarlane GT, Flint HJ, Dieleman LA, Ringel Y, Guandalini S, Kelly CP, Brandt LJ. Recommendations for probiotic use-2011 update. *J Clin Gastroenterol* 2011; **45** Suppl: S168-S171 [PMID: 21992958 DOI: 10.1097/MCG.0b013e318230928b]

125 **Roberfroid M**, Gibson GR, Hoyles L, McCartney AL, Rastall R, Rowland I, Wolvers D, Watzl B, Szajewska H, Stahl B, Guarner F, Respondek F, Whelan K, Coxam V, Davicco MJ, Léotoing L, Wittrant Y, Delzenne NM, Cani PD, Neyrinck AM, Meheust A. Prebiotic effects: metabolic and health benefits. *Br J Nutr* 2010; **104** Suppl 2: S1-63 [PMID: 20920376 DOI: 10.1017/S0007114510003363]

126 **Cani PD**, Neyrinck AM, Maton N, Delzenne NM. Oligofructose promotes satiety in rats fed a high-fat diet: involvement of glucagon-like Peptide-1. *Obes Res* 2005; **13**: 1000-1007 [PMID: 15976142 DOI: 10.1038/oby.2005.117]

127 **Cani PD**, Daubioul CA, Reusens B, Remacle C, Catillon G, Delzenne NM. Involvement of endogenous glucagon-like peptide-1(7-36) amide on glycaemia-lowering effect of oligofructose in streptozotocin-treated rats. *J Endocrinol* 2005; **185**: 457-465 [PMID: 15930172 DOI: 10.1677/joe.1.06100]

128 **Cani PD**, Possemiers S, Van de Wiele T, Guiot Y, Everard A, Rottier O, Geurts L, Naslain D, Neyrinck A, Lambert DM, Muccioli GG, Delzenne NM. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut* 2009; **58**: 1091-1103 [PMID: 19240062 DOI: 10.1136/gut.2008.165886]

129 **Everard A**, Lazarevic V, Derrien M, Girard M, Muccioli GG, Neyrinck AM, Possemiers S, Van Holle A, François P, de Vos WM, Delzenne NM, Schrenzel J, Cani PD. Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice. *Diabetes* 2011; **60**: 2775-2786 [PMID: 21933985 DOI: 10.2337/db11-0227]

130 **Neyrinck AM**, Possemiers S, Druart C, Van de Wiele T, De Backer F, Cani PD, Larondelle Y, Delzenne NM. Prebiotic effects of wheat arabinoxylan related to the increase in bifidobacteria, Roseburia and Bacteroides/Prevotella in diet-induced obese mice. *PLoS One* 2011; **6**: e20944 [PMID: 21695273 DOI: 10.1371/journal.pone.0020944]

131 **Parnell JA**, Reimer RA. Prebiotic fibres dose-dependently increase satiety hormones and alter Bacteroidetes and Firmicutes in lean and obese JCR: LA-cp rats. *Br J Nutr* 2012; **107**: 601-613 [PMID: 21767445 DOI: 10.1017/S0007114511003163]

132 **Cani PD**, Joly E, Horsmans Y, Delzenne NM. Oligofructose promotes satiety in healthy human: a pilot study. *Eur J Clin Nutr* 2006; **60**: 567-572 [PMID: 16340949 DOI: 10.1038/sj.ejcn.1602350]

133 **Davis LM**, Martínez I, Walter J, Goin C, Hutkins RW. Barcoded pyrosequencing reveals that consumption of galactooligosaccharides results in a highly specific bifidogenic response in humans. *PLoS One* 2011; **6**: e25200 [PMID: 21966454 DOI: 10.1371/journal.pone.0025200]

134 **Dewulf EM**, Cani PD, Claus SP, Fuentes S, Puylaert PG, Neyrinck AM, Bindels LB, de Vos WM, Gibson GR, Thissen JP, Delzenne NM. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. *Gut* 2013; **62**: 1112-1121 [PMID: 23135760 DOI: 10.1136/gutjnl-2012-303304]

135 **Genta S**, Cabrera W, Habib N, Pons J, Carillo IM, Grau A, Sánchez S. Yacon syrup: beneficial effects on obesity and insulin resistance in humans. *Clin Nutr* 2009; **28**: 182-187 [PMID: 19254816 DOI: 10.1016/j.clnu.2009.01.013]

136 **Parnell JA**, Reimer RA. Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. *Am J Clin Nutr* 2009; **89**: 1751-1759 [PMID: 19386741 DOI: 10.3945/ajcn.2009.27465]

137 **Kellow NJ**, Coughlan MT, Reid CM. Metabolic benefits of dietary prebiotics in human subjects: a systematic review of randomised controlled trials. *Br J Nutr* 2014; **111**: 1147-1161 [PMID: 24230488 DOI: 10.1017/S0007114513003607]

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**Table 1 Studies conducted on animal models showing effects of probiotics containing *Bifidobacterium* strains on metabolic disorders**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Studied animals** | **Probiotic** | **Dose** | **Duration of treatment (wk)** | **Effects** | **Ref** |
| C57BL/6J mice | *Bifidobaterium breve B-3* | 109 CFU | 8 | ↓body weight, epididimal fat, serum cholesterol, glucose, insulin and HOMA index  ↑ expression of FIAF, adiponectin | [99] |
| C57BL-6 mice | *Bifidobacterium pseudocatenulatum* CECT 7765 |  | 7 wk | ↓serum cholesterol, triglycerides, glucose, insulin resistance, leptin, IL-6, monocyte chemotactic protein-1, liver steatosis, adipose tissue  ↑glucose tolerance  Improvement of immune system functionality | [100] |
| HFD-fed rats | *Bifidobacterium longum* |  |  | Improvement of HFD induced metabolic disorders trough ↓ endotoxin levels and intestinal inflammation, ↑expression of Reg I genes | [101] |
| HFD-rats, standard diets fed rats | *Bifidobacterium adolescentis* |  | 12 | ↓visceral fat, liver steatosis  ↑insulin sensitivity | [102] |
| Sprague-Dawley rats | *B. pseudocatenulatum* SPM 1204, *B. longum* SPM 1205, and *B. longum* SPM 1207 | 108-109 CFU | 7 | ↓body and fat weights, serum cholesterol, triglycerides, glucose, leptin, AST, ALT and lipase levels | [103] |
| Sprague-Dawley rats | *Bifidobacteria* L66-5, L75-4, M13-4 and FS31-12, originated from normal human intestines | 108 CFU | 6 | B. M13-4 strain ↑ body weight  B. L66-5 strain ↓ body weight  All strains ↓serum and liver triglycerides, serum and liver cholesterol. | [104] |

CFU: Colony-forming units; IL-6: Interleukin-6; HFD: High-fat diet; Reg I genes: Intestinal regenerating family genes; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

**Table 2 Studies conducted on animal models showing effects of probiotics containing *Lactobacillus* strains on metabolic disorders**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Studied subjects** | **Probiotic** | **Duration of treatment** | **Effects** | **Ref** |
| C57BL/6J mice | *Lactobacillus rhamnosus* PL60 | 8 wk | ↓body weight gain, white adipose tissue, hepatic steatosis | [106] |
| C57BL/6J mice | *Lactobacillus plantarum* PL62 | 8 wk | ↓body weight, visceral adipose tissue, serum glucose levels | [107] |
| Sprague-Dawley rats | *Lactobacillus gasseri* SBT2055 | 4 wk | ↓adipocyte size, leptin levels  No significant changes in serum glucose and lipids levels, and liver lipids levels | [108] |
| Zucker diabetic fatty rats | *Lactobacillus fermentum* NCIMB 5221 | 8 wk | ↓fasting insulin levels, insulin resistance, serum triglycerides and LDL cholesterol levels, atherosclerosis.  ↑ HDL cholesterol levels | [109] |
| Male Kunming mice | *L. plantarum* CAI6, *L. plantarum* SC4 | 28 d | ↓ serum total and LDL cholesterol levels, LDL/HDL cholesterol ratio, triglycerides levels, hepatic steatosis  ↑serum HDL cholesterol, hepatic anti-oxidant Nrf-2 mediated response | [110] |
| C57BL/6J mice | *Lactobacillus rhamnosus* GG | 13 wk | ↓liver and mesenteric adipose tissue, weight gain  ↑glucose tolerance, gluconeogenesis, fatty acids oxidation | [111] |
| Apoe-/- mice | *Lactobacillus reuteri* ATCC PTA 4659 (ATCC), DSM 17938 (DSM), L6798 | 12 wk | ↓body weight gain, insulin levels, hepatic steatosis  ↑fatty acids oxidation | [112] |
| C57BL/6 mice | *Lactobacillus plantarum* strain No. 14 | 11 wk | ↓adipocyte size, white adipose tissue, serum leptin and total cholesterol levels | [113] |
| C57B/6J mice | *Lactobacillus paracasei* ssp paracasei F19 | 10 d | ↓body weight  ↑triglyceride load of the lipoprotein VLDL, angiopoietin-like 4 protein that ↓ fatty storage | [114] |
| GF and NMF mice | *Lactobacillus paracasei* ssp. paracasei F19or *Lactobacillus acidophilus* NCFB 1748 | 10 d | ↑adispin, adiponectin, fatty acids oxidation  Improvement of efficacy of intestinal immunological barrier  ↓resistine like β | [115] |

LDL: Low-density lipoprotein; HDL: High-density lipoprotein; VLDL: Very low-density lipoprotein.

**Table 3 Studies conducted on humans showing effects of probiotics on metabolic disorders**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Studied subjects** | **Probiotics** | **Duration of treatment** | **Effects** | **Ref** |
| Overweight humans | *Lactobacillus gasseri* SBT2055 | 12 wk | ↓body weight, visceral and subcutaneous fat area, BMI, waist and hip circumference  ↑serum adiponectin | [116] |
| Subjects with increased abdominal adiposity | *Lactobacillus gasseri* SBT2055 | 12 wk | ↓body weight, visceral fat area, BMI, waist and hip circumference, body fat mass | [117] |
| Women affected by postmenopausal metabolic syndrome | *Lactobacillus plantarum* | 90 d | ↓serum glucose and homocysteine levels | [118] |

BMI: Body mass index.

**Table 4 Studies conducted on animal models showing effects of prebiotics on metabolic disorders**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Studied subjects** | **Prebiotic** | **Duration of treatment** | **Effects** | **Ref** |
| Wistar rats | OFS | 50 d | ↓body weight, food intake, fat mass, serum triglycerides, ghrelin  ↑GLP-1 | [126] |
| Wistar rats | OFS | 6 wk | ↓food intake, serum glucose and insulin  ↑GLP-1, glucose tolerance | [127] |
| HFD fed mice | OFS | 13 wk | ↑*Bifidobacterium*, glucose tolerance  ↓pro-inflammatory cytokines, endotoxemia | [105] |
| C57B/6J mice | OFS | 4 wk | ↓LPS, hepatic inflammatory and oxidative stress markers, intestinal permeability  ↑GLP-2 | [128] |
| C57B/6J mice | OFS | 8 wk | ↓*Firmicutes/Bacteroides* ratio, fat mass, oxidative stress, low grade inflammation  ↑glucose tolerance, GLP-1 and leptin sensitivity | [129] |
| C57B/6J mice | AX | 4 wk | ↑*Bacteroides, Prevotella, Roseburia, Bifidobacterium* spp.  Improvement of gut barrier function,  ↓adipocyte size, fatty acids storage, body weight, serum cholesterol, insulin resistance, low grade inflammation | [130] |
| Lean and obese JCR:LA.cp rats | Inulin-OFS | 10 wk | ↓*Firmicutes*, food intake  ↑*Bacteroides, Bifidobacterium*, satiety hormones | [131] |

OFS: Oligofructose; GLP-1: GLucagon-like peptide-1; LPS: Lipopolysaccharides; GLP-2: Glucagon-like peptide-2; AX: Arabinoxylose.

**Table 5** **Studies conducted on humans showing effects of prebiotics on metabolic disorders**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Studied subject** | **Prebiotic** | **Duration of treatment** | **Effects** | **Ref** |
| Healthy men and women | OFS | 2 wk | ↓food and energy intake, hunger  ↑satiety | [132] |
| Healthy humans | GOS | 12 wk | Significant ↑ *Bifidobacterium* | [133] |
| Obese women | Inulin-type fructans | 3 mo | ↑*Bifidobaterium* and *Faecalibacterium prausnitzii*  ↓ circulating LPS, *Bacteroides*, *Propionibacterium* | [134] |
| Obese-dyslipidemic women | Yacon syrup (containing OFS) | 120 d | ↓body weight, BMI, waist circumference, serum LDL cholesterol levels | [135] |
| Overweight and obese adults | OFS | 12 wk | ↓body weight, ghrelin, calories intake, serum glucose, insulin  ↑peptide YY | [136] |

OFS: Oligofructose; GOS; Galactooligosaccharides; LPS: Lipopolysaccharides; BMI: Body mass index; LDL: Low-density lipoprotein.

1 Kaur J. A Comprehensive Review on Metabolic Syndrome. *Cardiol Res Pract* 2014; **2014**: 943162 [PMID: 24711954 PMCID: PMC3966331 DOI: 10.1155/2014/943162]

2 International Diabetes Federation: The IDF consensus worldwide definition of the metabolic syndrome.

3 Cani PD, Delzenne NM. Gut microflora as a target for energy and metabolic homeostasis. *Curr Opin Clin Nutr Metab Care* 2007; **10**(6): 729-734 [PMID: 18089955 DOI: 10.1097/MCO.0b013e3282efdebb]

4 Fukuda S, Ohno H. Gut microbiome and metabolic diseases. *Semin Immunopathol* 2014; **36**(1): 103-114 [PMID: 24196453 DOI: 10.1007/s00281-013-0399-z]

5 Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. *Science* 2012; **336**(6086): 1268-1273 [PMID: 22674334 DOI: 10.1126/science.1223490]

6 Jia W, Li H, Zhao L, Nicholson JK. Gut microbiota: a potential new territory for drug targeting. *Nat Rev Drug Discov* 2008; **7**(2): 123-129 [PMID: 18239669 DOI: 10.1038/nrd2505]

7 Zoetendal EG, Vaughan EE, de Vos WM. A microbial world within us. *Mol Microbiol* 2006; **59**(6): 1639-1650 [PMID: 16553872 DOI: 10.1111/j.1365-2958.2006.05056.x]

8 Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. *Nature* 2007; **449**(7164): 804-810 [PMID: 17943116 PMCID: PMC3709439 DOI: 10.1038/nature06244]

9 Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF, Gordon JI. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci U S A* 2004; **101**(44): 15718-15723 [PMID: 15505215 PMCID: PMC524219 DOI: 10.1073/pnas.0407076101]

10 Bäckhed F, Manchester JK, Semenkovich CF, Gordon JI. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proc Natl Acad Sci U S A* 2007; **104**(3): 979-984 [PMID: 17210919 PMCID: PMC1764762 DOI: 10.1073/pnas.0605374104]

11 Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 2006; **444**(7122): 1027-1031 [PMID: 17183312 DOI: 10.1038/nature05414]

12 Samuel BS, Shaito A, Motoike T, Rey FE, Backhed F, Manchester JK, Hammer RE, Williams SC, Crowley J, Yanagisawa M, Gordon JI. Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. *Proc Natl Acad Sci U S A* 2008; **105**(43): 16767-16772 [PMID: 18931303 PMCID: PMC2569967 DOI: 10.1073/pnas.0808567105]

13 Tolhurst G, Heffron H, Lam YS, Parker HE, Habib AM, Diakogiannaki E, Cameron J, Grosse J, Reimann F, Gribble FM. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. *Diabetes* 2012; **61**(2): 364-371 [PMID: 22190648 PMCID: PMC3266401 DOI: 10.2337/db11-1019]

14 Hooper LV, Wong MH, Thelin A, Hansson L, Falk PG, Gordon JI. Molecular analysis of commensal host-microbial relationships in the intestine. *Science* 2001; **291**(5505): 881-884 [PMID: 11157169 DOI: 10.1126/science.291.5505.881]

15 Rabot S, Membrez M, Bruneau A, Gérard P, Harach T, Moser M, Raymond F, Mansourian R, Chou CJ. Germ-free C57BL/6J mice are resistant to high-fat-diet-induced insulin resistance and have altered cholesterol metabolism. *FASEB J* 2010; **24**(12): 4948-4959 [PMID: 20724524 DOI: 10.1096/fj.10-164921]

16 Mandard S, Zandbergen F, van Straten E, Wahli W, Kuipers F, Müller M, Kersten S. The fasting-induced adipose factor/angiopoietin-like protein 4 is physically associated with lipoproteins and governs plasma lipid levels and adiposity. *J Biol Chem* 2006; **281**(2): 934-944 [PMID: 16272564 DOI: 10.1074/jbc.M506519200]

17 Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. *Proc Natl Acad Sci U S A* 2005; **102**(31): 11070-11075 [PMID: 16033867 PMCID: PMC1176910 DOI: 10.1073/pnas.0504978102]

18 Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, Waget A, Delmée E, Cousin B, Sulpice T, Chamontin B, Ferrières J, Tanti JF, Gibson GR, Casteilla L, Delzenne NM, Alessi MC, Burcelin R. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* 2007; **56**(7): 1761-1772 [PMID: 17456850 DOI: 10.2337/db06-1491]

19 Amar J, Chabo C, Waget A, Klopp P, Vachoux C, Bermúdez-Humarán LG, Smirnova N, Bergé M, Sulpice T, Lahtinen S, Ouwehand A, Langella P, Rautonen N, Sansonetti PJ, Burcelin R. Intestinal mucosal adherence and translocation of commensal bacteria at the early onset of type 2 diabetes: molecular mechanisms and probiotic treatment. *EMBO Mol Med* 2011; **3**(9): 559-572 [PMID: 21735552 PMCID: PMC3265717 DOI: 10.1002/emmm.201100159]

20 de La Serre CB, Ellis CL, Lee J, Hartman AL, Rutledge JC, Raybould HE. Propensity to high-fat diet-induced obesity in rats is associated with changes in the gut microbiota and gut inflammation. *Am J Physiol Gastrointest Liver Physiol* 2010; **299**(2): G440-448 [PMID: 20508158 PMCID: PMC2928532 DOI: 10.1152/ajpgi.00098.2010]

21 Cerf-Bensussan N, Gaboriau-Routhiau V. The immune system and the gut microbiota: friends or foes? *Nat Rev Immunol* 2010; **10**(10): 735-744 [PMID: 20865020 DOI: 10.1038/nri2850]

22 Vijay-Kumar M, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, Srinivasan S, Sitaraman SV, Knight R, Ley RE, Gewirtz AT. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science* 2010; **328**(5975): 228-231 [PMID: 20203013 DOI: 10.1126/science.1179721]

23 Muccioli GG, Naslain D, Bäckhed F, Reigstad CS, Lambert DM, Delzenne NM, Cani PD. The endocannabinoid system links gut microbiota to adipogenesis. *Mol Syst Biol* 2010; **6**: 392 [PMID: 20664638 PMCID: PMC2925525 DOI: 10.1038/msb.2010.46]

24 Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature* 2006; **444**(7122): 1022-1023 [PMID: 17183309 DOI: 10.1038/4441022a]

25 Armougom F, Henry M, Vialettes B, Raccah D, Raoult D. Monitoring bacterial community of human gut microbiota reveals an increase in Lactobacillus in obese patients and Methanogens in anorexic patients. *PLoS One* 2009; **4**(9): e7125 [PMID: 19774074 PMCID: PMC2742902 DOI: 10.1371/journal.pone.0007125]

26 Santacruz A, Collado MC, García-Valdés L, Segura MT, Martín-Lagos JA, Anjos T, Martí-Romero M, Lopez RM, Florido J, Campoy C, Sanz Y. Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. *Br J Nutr* 2010; **104**(1): 83-92 [PMID: 20205964 DOI: 10.1017/S0007114510000176]

27 Duncan SH, Lobley GE, Holtrop G, Ince J, Johnstone AM, Louis P, Flint HJ. Human colonic microbiota associated with diet, obesity and weight loss. *Int J Obes (Lond)* 2008; **32**(11): 1720-1724 [PMID: 18779823 DOI: 10.1038/ijo.2008.155]

28 Schwiertz A, Taras D, Schäfer K, Beijer S, Bos NA, Donus C, Hardt PD. Microbiota and SCFA in lean and overweight healthy subjects. *Obesity (Silver Spring)* 2010; **18**(1): 190-195 [PMID: 19498350 DOI: 10.1038/oby.2009.167]

29 Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, Sogin ML, Jones WJ, Roe BA, Affourtit JP, Egholm M, Henrissat B, Heath AC, Knight R, Gordon JI. A core gut microbiome in obese and lean twins. *Nature* 2009; **457**(7228): 480-484 [PMID: 19043404 PMCID: PMC2677729 DOI: 10.1038/nature07540]

30 Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, Almeida M, Arumugam M, Batto JM, Kennedy S, Leonard P, Li J, Burgdorf K, Grarup N, Jørgensen T, Brandslund I, Nielsen HB, Juncker AS, Bertalan M, Levenez F, Pons N, Rasmussen S, Sunagawa S, Tap J, Tims S, Zoetendal EG, Brunak S, Clément K, Doré J, Kleerebezem M, Kristiansen K, Renault P, Sicheritz-Ponten T, de Vos WM, Zucker JD, Raes J, Hansen T, Bork P, Wang J, Ehrlich SD, Pedersen O, consortium M. Richness of human gut microbiome correlates with metabolic markers. *Nature* 2013; **500**(7464): 541-546 [PMID: 23985870 DOI: 10.1038/nature12506]

31 Kalliomäki M, Collado MC, Salminen S, Isolauri E. Early differences in fecal microbiota composition in children may predict overweight. *Am J Clin Nutr* 2008; **87**(3): 534-538 [PMID: 18326589]

32 Karlsson CL, Onnerfält J, Xu J, Molin G, Ahrné S, Thorngren-Jerneck K. The microbiota of the gut in preschool children with normal and excessive body weight. *Obesity (Silver Spring)* 2012; **20**(11): 2257-2261 [PMID: 22546742 DOI: 10.1038/oby.2012.110]

33 Kovatcheva-Datchary P, Arora T. Nutrition, the gut microbiome and the metabolic syndrome. *Best Pract Res Clin Gastroenterol* 2013; **27**(1): 59-72 [PMID: 23768553 DOI: 10.1016/j.bpg.2013.03.017]

34 De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, Collini S, Pieraccini G, Lionetti P. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proc Natl Acad Sci U S A* 2010; **107**(33): 14691-14696 [PMID: 20679230 PMCID: PMC2930426 DOI: 10.1073/pnas.1005963107]

35 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, 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, Consortium M. Enterotypes of the human gut microbiome. *Nature* 2011; **473**(7346): 174-180 [PMID: 21508958 PMCID: PMC3728647 DOI: 10.1038/nature09944]

36 Brown K, DeCoffe D, Molcan E, Gibson DL. Diet-induced dysbiosis of the intestinal microbiota and the effects on immunity and disease. *Nutrients* 2012; **4**(8): 1095-1119 [PMID: 23016134 PMCID: PMC3448089 DOI: 10.3390/nu4081095]

37 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**(7484): 559-563 [PMID: 24336217 PMCID: PMC3957428 DOI: 10.1038/nature12820]

38 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**(6052): 105-108 [PMID: 21885731 PMCID: PMC3368382 DOI: 10.1126/science.1208344]

39 Ding S, Chi MM, Scull BP, Rigby R, Schwerbrock NM, Magness S, Jobin C, Lund PK. High-fat diet: bacteria interactions promote intestinal inflammation which precedes and correlates with obesity and insulin resistance in mouse. *PLoS One* 2010; **5**(8): e12191 [PMID: 20808947 PMCID: PMC2922379 DOI: 10.1371/journal.pone.0012191]

40 Turnbaugh PJ, Bäckhed F, Fulton L, Gordon JI. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. *Cell Host Microbe* 2008; **3**(4): 213-223 [PMID: 18407065 PMCID: PMC3687783 DOI: 10.1016/j.chom.2008.02.015]

41 de Wit N, Derrien M, Bosch-Vermeulen H, Oosterink E, Keshtkar S, Duval C, de Vogel-van den Bosch J, Kleerebezem M, Müller M, van der Meer R. Saturated fat stimulates obesity and hepatic steatosis and affects gut microbiota composition by an enhanced overflow of dietary fat to the distal intestine. *Am J Physiol Gastrointest Liver Physiol* 2012; **303**(5): G589-599 [PMID: 22700822 DOI: 10.1152/ajpgi.00488.2011]

42 Shen W, Gaskins HR, McIntosh MK. Influence of dietary fat on intestinal microbes, inflammation, barrier function and metabolic outcomes. *J Nutr Biochem* 2014; **25**(3): 270-280 [PMID: 24355793 DOI: 10.1016/j.jnutbio.2013.09.009]

43 Brinkworth GD, Noakes M, Clifton PM, Bird AR. Comparative effects of very low-carbohydrate, high-fat and high-carbohydrate, low-fat weight-loss diets on bowel habit and faecal short-chain fatty acids and bacterial populations. *Br J Nutr* 2009; **101**(10): 1493-1502 [PMID: 19224658 DOI: 10.1017/S0007114508094658]

44 Zhang C, Zhang M, Wang S, Han R, Cao Y, Hua W, Mao Y, Zhang X, Pang X, Wei C, Zhao G, Chen Y, Zhao L. Interactions between gut microbiota, host genetics and diet relevant to development of metabolic syndromes in mice. *ISME J* 2010; **4**(2): 232-241 [PMID: 19865183 DOI: 10.1038/ismej.2009.112]

45 Lam YY, Ha CW, Campbell CR, Mitchell AJ, Dinudom A, Oscarsson J, Cook DI, Hunt NH, Caterson ID, Holmes AJ, Storlien LH. Increased gut permeability and microbiota change associate with mesenteric fat inflammation and metabolic dysfunction in diet-induced obese mice. *PLoS One* 2012; **7**(3): e34233 [PMID: 22457829 PMCID: PMC3311621 DOI: 10.1371/journal.pone.0034233]

46 Membrez M, Blancher F, Jaquet M, Bibiloni R, Cani PD, Burcelin RG, Corthesy I, Macé K, Chou CJ. Gut microbiota modulation with norfloxacin and ampicillin enhances glucose tolerance in mice. *FASEB J* 2008; **22**(7): 2416-2426 [PMID: 18326786 DOI: 10.1096/fj.07-102723]

47 Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, Guiot Y, Derrien M, Muccioli GG, Delzenne NM, de Vos WM, Cani PD. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proc Natl Acad Sci U S A* 2013; **110**(22): 9066-9071 [PMID: 23671105 PMCID: PMC3670398 DOI: 10.1073/pnas.1219451110]

48 Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, Burcelin R. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* 2008; **57**(6): 1470-1481 [PMID: 18305141 DOI: 10.2337/db07-1403]

49 Wall R, Ross RP, Shanahan F, O'Mahony L, O'Mahony C, Coakley M, Hart O, Lawlor P, Quigley EM, Kiely B, Fitzgerald GF, Stanton C. Metabolic activity of the enteric microbiota influences the fatty acid composition of murine and porcine liver and adipose tissues. *Am J Clin Nutr* 2009; **89**(5): 1393-1401 [PMID: 19357220 DOI: 10.3945/ajcn.2008.27023]

50 Amar J, Burcelin R, Ruidavets JB, Cani PD, Fauvel J, Alessi MC, Chamontin B, Ferriéres J. Energy intake is associated with endotoxemia in apparently healthy men. *Am J Clin Nutr* 2008; **87**(5): 1219-1223 [PMID: 18469242]

51 Creely SJ, McTernan PG, Kusminski CM, Fisher f, Da Silva NF, Khanolkar M, Evans M, Harte AL, Kumar S. Lipopolysaccharide activates an innate immune system response in human adipose tissue in obesity and type 2 diabetes. *Am J Physiol Endocrinol Metab* 2007; **292**(3): E740-747 [PMID: 17090751 DOI: 10.1152/ajpendo.00302.2006]

52 Amar J, Serino M, Lange C, Chabo C, Iacovoni J, Mondot S, Lepage P, Klopp C, Mariette J, Bouchez O, Perez L, Courtney M, Marre M, Klopp P, Lantieri O, Doré J, Charles M, Balkau B, Burcelin R, Group DESIRS. Involvement of tissue bacteria in the onset of diabetes in humans: evidence for a concept. *Diabetologia* 2011; **54**(12): 3055-3061 [PMID: 21976140 DOI: 10.1007/s00125-011-2329-8]

53 Larsen N, Vogensen FK, van den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, Al-Soud WA, Sørensen SJ, Hansen LH, Jakobsen M. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS One* 2010; **5**(2): e9085 [PMID: 20140211 PMCID: PMC2816710 DOI: 10.1371/journal.pone.0009085]

54 Wu X, Ma C, Han L, Nawaz M, Gao F, Zhang X, Yu P, Zhao C, Li L, Zhou A, Wang J, Moore JE, Millar BC, Xu J. Molecular characterisation of the faecal microbiota in patients with type II diabetes. *Curr Microbiol* 2010; **61**(1): 69-78 [PMID: 20087741 DOI: 10.1007/s00284-010-9582-9]

55 Zhang X, Shen D, Fang Z, Jie Z, Qiu X, Zhang C, Chen Y, Ji L. Human gut microbiota changes reveal the progression of glucose intolerance. *PLoS One* 2013; **8**(8): e71108 [PMID: 24013136 PMCID: PMC3754967 DOI: 10.1371/journal.pone.0071108]

56 Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, Zhang W, Guan Y, Shen D, Peng Y, Zhang D, Jie Z, Wu W, Qin Y, Xue W, Li J, Han L, Lu D, Wu P, Dai Y, Sun X, Li Z, Tang A, Zhong S, Li X, Chen W, Xu R, Wang M, Feng Q, Gong M, Yu J, Zhang Y, Zhang M, Hansen T, Sanchez G, Raes J, Falony G, Okuda S, Almeida M, LeChatelier E, Renault P, Pons N, Batto JM, Zhang Z, Chen H, Yang R, Zheng W, Yang H, Wang J, Ehrlich SD, Nielsen R, Pedersen O, Kristiansen K. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* 2012; **490**(7418): 55-60 [PMID: 23023125 DOI: 10.1038/nature11450]

57 Lewis K, Lutgendorff F, Phan V, Söderholm JD, Sherman PM, McKay DM. Enhanced translocation of bacteria across metabolically stressed epithelia is reduced by butyrate. *Inflamm Bowel Dis* 2010; **16**(7): 1138-1148 [PMID: 20024905 DOI: 10.1002/ibd.21177]

58 Vrieze A, Van Nood E, Holleman F, Salojärvi J, Kootte RS, Bartelsman JF, Dallinga-Thie GM, Ackermans MT, Serlie MJ, Oozeer R, Derrien M, Druesne A, Van Hylckama Vlieg JE, Bloks VW, Groen AK, Heilig HG, Zoetendal EG, Stroes ES, de Vos WM, Hoekstra JB, Nieuwdorp M. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology* 2012; **143**(4): 913-916.e917 [PMID: 22728514 DOI: 10.1053/j.gastro.2012.06.031]

59 Le Roy T, Llopis M, Lepage P, Bruneau A, Rabot S, Bevilacqua C, Martin P, Philippe C, Walker F, Bado A, Perlemuter G, Cassard-Doulcier AM, Gérard P. Intestinal microbiota determines development of non-alcoholic fatty liver disease in mice. *Gut* 2013; **62**(12): 1787-1794 [PMID: 23197411 DOI: 10.1136/gutjnl-2012-303816]

60 Cope K, Risby T, Diehl AM. Increased gastrointestinal ethanol production in obese mice: implications for fatty liver disease pathogenesis. *Gastroenterology* 2000; **119**(5): 1340-1347 [PMID: 11054393]

61 Dumas ME, Barton RH, Toye A, Cloarec O, Blancher C, Rothwell A, Fearnside J, Tatoud R, Blanc V, Lindon JC, Mitchell SC, Holmes E, McCarthy MI, Scott J, Gauguier D, Nicholson JK. Metabolic profiling reveals a contribution of gut microbiota to fatty liver phenotype in insulin-resistant mice. *Proc Natl Acad Sci U S A* 2006; **103**(33): 12511-12516 [PMID: 16895997 PMCID: PMC1567909 DOI: 10.1073/pnas.0601056103]

62 Swann JR, Want EJ, Geier FM, Spagou K, Wilson ID, Sidaway JE, Nicholson JK, Holmes E. Systemic gut microbial modulation of bile acid metabolism in host tissue compartments. *Proc Natl Acad Sci U S A* 2011; **108 Suppl 1**: 4523-4530 [PMID: 20837534 PMCID: PMC3063584 DOI: 10.1073/pnas.1006734107]

63 Rivera CA, Adegboyega P, van Rooijen N, Tagalicud A, Allman M, Wallace M. Toll-like receptor-4 signaling and Kupffer cells play pivotal roles in the pathogenesis of non-alcoholic steatohepatitis. *J Hepatol* 2007; **47**(4): 571-579 [PMID: 17644211 PMCID: PMC2094119 DOI: 10.1016/j.jhep.2007.04.019]

64 Boaru SG, Borkham-Kamphorst E, Tihaa L, Haas U, Weiskirchen R. Expression analysis of inflammasomes in experimental models of inflammatory and fibrotic liver disease. *J Inflamm (Lond)* 2012; **9**(1): 49 [PMID: 23192004 PMCID: PMC3599703 DOI: 10.1186/1476-9255-9-49]

65 Csak T, Ganz M, Pespisa J, Kodys K, Dolganiuc A, Szabo G. Fatty acid and endotoxin activate inflammasomes in mouse hepatocytes that release danger signals to stimulate immune cells. *Hepatology* 2011; **54**(1): 133-144 [PMID: 21488066 DOI: 10.1002/hep.24341]

66 Seki E, De Minicis S, Osterreicher CH, Kluwe J, Osawa Y, Brenner DA, Schwabe RF. TLR4 enhances TGF-beta signaling and hepatic fibrosis. *Nat Med* 2007; **13**(11): 1324-1332 [PMID: 17952090 DOI: 10.1038/nm1663]

67 Henao-Mejia J, Elinav E, Jin C, Hao L, Mehal WZ, Strowig T, Thaiss CA, Kau AL, Eisenbarth SC, Jurczak MJ, Camporez JP, Shulman GI, Gordon JI, Hoffman HM, Flavell RA. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. *Nature* 2012; **482**(7384): 179-185 [PMID: 22297845 PMCID: PMC3276682 DOI: 10.1038/nature10809]

68 Miele L, Valenza V, La Torre G, Montalto M, Cammarota G, Ricci R, Mascianà R, Forgione A, Gabrieli ML, Perotti G, Vecchio FM, Rapaccini G, Gasbarrini G, Day CP, Grieco A. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. *Hepatology* 2009; **49**(6): 1877-1887 [PMID: 19291785 DOI: 10.1002/hep.22848]

69 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**(1): 120-127 [PMID: 23401313 DOI: 10.1002/hep.26319]

70 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**(2): 601-609 [PMID: 23055155 DOI: 10.1002/hep.26093]

71 Buchman AL, Dubin MD, Moukarzel AA, Jenden DJ, Roch M, Rice KM, Gornbein J, Ament ME. Choline deficiency: a cause of hepatic steatosis during parenteral nutrition that can be reversed with intravenous choline supplementation. *Hepatology* 1995; **22**(5): 1399-1403 [PMID: 7590654]

72 Spencer MD, Hamp TJ, Reid RW, Fischer LM, Zeisel SH, Fodor AA. Association between composition of the human gastrointestinal microbiome and development of fatty liver with choline deficiency. *Gastroenterology* 2011; **140**(3): 976-986 [PMID: 21129376 PMCID: PMC3049827 DOI: 10.1053/j.gastro.2010.11.049]

73 Shanab AA, Scully P, Crosbie O, Buckley M, O'Mahony L, Shanahan F, Gazareen S, Murphy E, Quigley EM. Small intestinal bacterial overgrowth in nonalcoholic steatohepatitis: association with toll-like receptor 4 expression and plasma levels of interleukin 8. *Dig Dis Sci* 2011; **56**(5): 1524-1534 [PMID: 21046243 DOI: 10.1007/s10620-010-1447-3]

74 Sotos M, Nadal I, Marti A, Martínez A, Martin-Matillas M, Campoy C, Puertollano MA, Wärnberg J, Marcos A, Sanz Y. Gut microbes and obesity in adolescents. *Proceedings of the Nutrition Society* 2008; **67**(OCE)

75 Nadal I, Santacruz A, Marcos A, Warnberg J, Garagorri JM, Garagorri M, Moreno LA, Martin-Matillas M, Campoy C, Martí A, Moleres A, Delgado M, Veiga OL, García-Fuentes M, Redondo CG, Sanz Y. Shifts in clostridia, bacteroides and immunoglobulin-coating fecal bacteria associated with weight loss in obese adolescents. *Int J Obes (Lond)* 2009; **33**(7): 758-767 [PMID: 19050675 DOI: 10.1038/ijo.2008.260]

76 Cotillard A, Kennedy SP, Kong LC, Prifti E, Pons N, Le Chatelier E, Almeida M, Quinquis B, Levenez F, Galleron N, Gougis S, Rizkalla S, Batto JM, Renault P, Doré J, Zucker JD, Clément K, Ehrlich SD, consortium AM. Dietary intervention impact on gut microbial gene richness. *Nature* 2013; **500**(7464): 585-588 [PMID: 23985875 DOI: 10.1038/nature12480]

77 Zhang H, DiBaise JK, Zuccolo A, Kudrna D, Braidotti M, Yu Y, Parameswaran P, Crowell MD, Wing R, Rittmann BE, Krajmalnik-Brown R. Human gut microbiota in obesity and after gastric bypass. *Proc Natl Acad Sci U S A* 2009; **106**(7): 2365-2370 [PMID: 19164560 PMCID: PMC2629490 DOI: 10.1073/pnas.0812600106]

78 Furet JP, Kong LC, Tap J, Poitou C, Basdevant A, Bouillot JL, Mariat D, Corthier G, Doré J, Henegar C, Rizkalla S, Clément K. Differential adaptation of human gut microbiota to bariatric surgery-induced weight loss: links with metabolic and low-grade inflammation markers. *Diabetes* 2010; **59**(12): 3049-3057 [PMID: 20876719 PMCID: PMC2992765 DOI: 10.2337/db10-0253]

79 Li JV, Ashrafian H, Bueter M, Kinross J, Sands C, le Roux CW, Bloom SR, Darzi A, Athanasiou T, Marchesi JR, Nicholson JK, Holmes E. Metabolic surgery profoundly influences gut microbial-host metabolic cross-talk. *Gut* 2011; **60**(9): 1214-1223 [PMID: 21572120 PMCID: PMC3677150 DOI: 10.1136/gut.2010.234708]

80 Cani PD, Delzenne NM. The role of the gut microbiota in energy metabolism and metabolic disease. *Curr Pharm Des* 2009; **15**(13): 1546-1558 [PMID: 19442172]

81 Lips MA, de Groot GH, van Klinken JB, Aarts E, Berends FJ, Janssen IM, Van Ramshorst B, Van Wagensveld BA, Swank DJ, Van Dielen F, Willems van Dijk K, Pijl H. Calorie Restriction is a Major Determinant of the Short-Term Metabolic Effects of Gastric Bypass Surgery in Obese Type 2 Diabetic Patients. *Clin Endocrinol (Oxf)* 2013 [PMID: 23711328 DOI: 10.1111/cen.12254]

82 FAO/WHO. Health and Nutritional Properties of Probiotics in

Food including Powder Milk with Live Lactic

Acid Bacteria

Report. 2001

83 Kondo S, Xiao JZ, Satoh T, Odamaki T, Takahashi S, Sugahara H, Yaeshima T, Iwatsuki K, Kamei A, Abe K. Antiobesity effects of Bifidobacterium breve strain B-3 supplementation in a mouse model with high-fat diet-induced obesity. *Biosci Biotechnol Biochem* 2010; **74**(8): 1656-1661 [PMID: 20699581]

84 Cano PG, Santacruz A, Trejo FM, Sanz Y. Bifidobacterium CECT 7765 improves metabolic and immunological alterations associated with obesity in high-fat diet-fed mice. *Obesity (Silver Spring)* 2013; **21**(11): 2310-2321 [PMID: 23418126 DOI: 10.1002/oby.20330]

85 Chen JJ, Wang R, Li XF, Wang RL. Bifidobacterium longum supplementation improved high-fat-fed-induced metabolic syndrome and promoted intestinal Reg I gene expression. *Exp Biol Med (Maywood)* 2011; **236**(7): 823-831 [PMID: 21685239 DOI: 10.1258/ebm.2011.010399]

86 Chen J, Wang R, Li XF, Wang RL. Bifidobacterium adolescentis supplementation ameliorates visceral fat accumulation and insulin sensitivity in an experimental model of the metabolic syndrome. *Br J Nutr* 2012; **107**(10): 1429-1434 [PMID: 21914236 DOI: 10.1017/S0007114511004491]

87 An HM, Park SY, Lee dK, Kim JR, Cha MK, Lee SW, Lim HT, Kim KJ, Ha NJ. Antiobesity and lipid-lowering effects of Bifidobacterium spp. in high fat diet-induced obese rats. *Lipids Health Dis* 2011; **10**: 116 [PMID: 21745411 PMCID: PMC3146849 DOI: 10.1186/1476-511X-10-116]

88 Yin YN, Yu QF, Fu N, Liu XW, Lu FG. Effects of four Bifidobacteria on obesity in high-fat diet induced rats. *World J Gastroenterol* 2010; **16**(27): 3394-3401 [PMID: 20632441 PMCID: PMC2904885]

89 Cani PD, Neyrinck AM, Fava F, Knauf C, Burcelin RG, Tuohy KM, Gibson GR, Delzenne NM. Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. *Diabetologia* 2007; **50**(11): 2374-2383 [PMID: 17823788 DOI: 10.1007/s00125-007-0791-0]

90 Lee HY, Park JH, Seok SH, Baek MW, Kim DJ, Lee KE, Paek KS, Lee Y. Human originated bacteria, Lactobacillus rhamnosus PL60, produce conjugated linoleic acid and show anti-obesity effects in diet-induced obese mice. *Biochim Biophys Acta* 2006; **1761**(7): 736-744 [PMID: 16807088 DOI: 10.1016/j.bbalip.2006.05.007]

91 Lee K, Paek K, Lee HY, Park JH, Lee Y. Antiobesity effect of trans-10,cis-12-conjugated linoleic acid-producing Lactobacillus plantarum PL62 on diet-induced obese mice. *J Appl Microbiol* 2007; **103**(4): 1140-1146 [PMID: 17897219 DOI: 10.1111/j.1365-2672.2007.03336.x]

92 Sato M, Uzu K, Yoshida T, Hamad EM, Kawakami H, Matsuyama H, Abd El-Gawad IA, Imaizumi K. Effects of milk fermented by Lactobacillus gasseri SBT2055 on adipocyte size in rats. *Br J Nutr* 2008; **99**(5): 1013-1017 [PMID: 17977471 DOI: 10.1017/S0007114507839006]

93 Tomaro-Duchesneau C, Saha S, Malhotra M, Jones ML, Labbé A, Rodes L, Kahouli I, Prakash S. Effect of orally administered L. fermentum NCIMB 5221 on markers of metabolic syndrome: an in vivo analysis using ZDF rats. *Appl Microbiol Biotechnol* 2014; **98**(1): 115-126 [PMID: 24121931 DOI: 10.1007/s00253-013-5252-8]

94 Wang LX, Liu K, Gao DW, Hao JK. Protective effects of two Lactobacillus plantarum strains in hyperlipidemic mice. *World J Gastroenterol* 2013; **19**(20): 3150-3156 [PMID: 23716997 PMCID: PMC3662957 DOI: 10.3748/wjg.v19.i20.3150]

95 Kim SW, Park KY, Kim B, Kim E, Hyun CK. Lactobacillus rhamnosus GG improves insulin sensitivity and reduces adiposity in high-fat diet-fed mice through enhancement of adiponectin production. *Biochem Biophys Res Commun* 2013; **431**(2): 258-263 [PMID: 23313485 DOI: 10.1016/j.bbrc.2012.12.121]

96 Fåk F, Bäckhed F. Lactobacillus reuteri prevents diet-induced obesity, but not atherosclerosis, in a strain dependent fashion in Apoe-/- mice. *PLoS One* 2012; **7**(10): e46837 [PMID: 23056479 PMCID: PMC3467285 DOI: 10.1371/journal.pone.0046837]

97 Takemura N, Okubo T, Sonoyama K. Lactobacillus plantarum strain No. 14 reduces adipocyte size in mice fed high-fat diet. *Exp Biol Med (Maywood)* 2010; **235**(7): 849-856 [PMID: 20558839 DOI: 10.1258/ebm.2010.009377]

98 Aronsson L, Huang Y, Parini P, Korach-André M, Håkansson J, Gustafsson J, Pettersson S, Arulampalam V, Rafter J. Decreased fat storage by Lactobacillus paracasei is associated with increased levels of angiopoietin-like 4 protein (ANGPTL4). *PLoS One* 2010; **5**(9) [PMID: 20927337 PMCID: PMC2948012 DOI: 10.1371/journal.pone.0013087]

99 Nerstedt A, Nilsson EC, Ohlson K, Håkansson J, Thomas Svensson L, Löwenadler B, Svensson UK, Mahlapuu M. Administration of Lactobacillus evokes coordinated changes in the intestinal expression profile of genes regulating energy homeostasis and immune phenotype in mice. *Br J Nutr* 2007; **97**(6): 1117-1127 [PMID: 17433125 DOI: 10.1017/S0007114507682907]

100 Kadooka Y, Sato M, Imaizumi K, Ogawa A, Ikuyama K, Akai Y, Okano M, Kagoshima M, Tsuchida T. Regulation of abdominal adiposity by probiotics (Lactobacillus gasseri SBT2055) in adults with obese tendencies in a randomized controlled trial. *Eur J Clin Nutr* 2010; **64**(6): 636-643 [PMID: 20216555 DOI: 10.1038/ejcn.2010.19]

101 Kadooka Y, Sato M, Ogawa A, Miyoshi M, Uenishi H, Ogawa H, Ikuyama K, Kagoshima M, Tsuchida T. Effect of Lactobacillus gasseri SBT2055 in fermented milk on abdominal adiposity in adults in a randomised controlled trial. *Br J Nutr* 2013; **110**(9): 1696-1703 [PMID: 23614897 DOI: 10.1017/S0007114513001037]

102 Barreto FM, Colado Simão AN, Morimoto HK, Batisti Lozovoy MA, Dichi I, Helena da Silva Miglioranza L. Beneficial effects of Lactobacillus plantarum on glycemia and homocysteine levels in postmenopausal women with metabolic syndrome. *Nutrition* 2013 [PMID: 24613434 DOI: 10.1016/j.nut.2013.12.004]

103 Yadav H, Lee JH, Lloyd J, Walter P, Rane SG. Beneficial metabolic effects of a probiotic via butyrate-induced GLP-1 hormone secretion. *J Biol Chem* 2013; **288**(35): 25088-25097 [PMID: 23836895 PMCID: PMC3757173 DOI: 10.1074/jbc.M113.452516]

104 Park DY, Ahn YT, Park SH, Huh CS, Yoo SR, Yu R, Sung MK, McGregor RA, Choi MS. Supplementation of Lactobacillus curvatus HY7601 and Lactobacillus plantarum KY1032 in diet-induced obese mice is associated with gut microbial changes and reduction in obesity. *PLoS One* 2013; **8**(3): e59470 [PMID: 23555678 PMCID: PMC3605452 DOI: 10.1371/journal.pone.0059470]

105 Iacono A, Raso GM, Canani RB, Calignano A, Meli R. Probiotics as an emerging therapeutic strategy to treat NAFLD: focus on molecular and biochemical mechanisms. *J Nutr Biochem* 2011; **22**(8): 699-711 [PMID: 21292470 DOI: 10.1016/j.jnutbio.2010.10.002]

106 Ma YY, Li L, Yu CH, Shen Z, Chen LH, Li YM. Effects of probiotics on nonalcoholic fatty liver disease: a meta-analysis. *World J Gastroenterol* 2013; **19**(40): 6911-6918 [PMID: 24187469 PMCID: PMC3812493 DOI: 10.3748/wjg.v19.i40.6911]

107 Million M, Angelakis E, Paul M, Armougom F, Leibovici L, Raoult D. Comparative meta-analysis of the effect of Lactobacillus species on weight gain in humans and animals. *Microb Pathog* 2012; **53**(2): 100-108 [PMID: 22634320 DOI: 10.1016/j.micpath.2012.05.007]

108 Floch MH, Walker WA, Madsen K, Sanders ME, Macfarlane GT, Flint HJ, Dieleman LA, Ringel Y, Guandalini S, Kelly CP, Brandt LJ. Recommendations for probiotic use-2011 update. *J Clin Gastroenterol* 2011; **45 Suppl**: S168-171 [PMID: 21992958 DOI: 10.1097/MCG.0b013e318230928b]

109 Roberfroid M, Gibson GR, Hoyles L, McCartney AL, Rastall R, Rowland I, Wolvers D, Watzl B, Szajewska H, Stahl B, Guarner F, Respondek F, Whelan K, Coxam V, Davicco MJ, Léotoing L, Wittrant Y, Delzenne NM, Cani PD, Neyrinck AM, Meheust A. Prebiotic effects: metabolic and health benefits. *Br J Nutr* 2010; **104 Suppl 2**: S1-63 [PMID: 20920376 DOI: 10.1017/S0007114510003363]

110 Cani PD, Neyrinck AM, Maton N, Delzenne NM. Oligofructose promotes satiety in rats fed a high-fat diet: involvement of glucagon-like Peptide-1. *Obes Res* 2005; **13**(6): 1000-1007 [PMID: 15976142 DOI: 10.1038/oby.2005.117]

111 Cani PD, Daubioul CA, Reusens B, Remacle C, Catillon G, Delzenne NM. Involvement of endogenous glucagon-like peptide-1(7-36) amide on glycaemia-lowering effect of oligofructose in streptozotocin-treated rats. *J Endocrinol* 2005; **185**(3): 457-465 [PMID: 15930172 DOI: 10.1677/joe.1.06100]

112 Cani PD, Possemiers S, Van de Wiele T, Guiot Y, Everard A, Rottier O, Geurts L, Naslain D, Neyrinck A, Lambert DM, Muccioli GG, Delzenne NM. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut* 2009; **58**(8): 1091-1103 [PMID: 19240062 PMCID: PMC2702831 DOI: 10.1136/gut.2008.165886]

113 Everard A, Lazarevic V, Derrien M, Girard M, Muccioli GG, Muccioli GM, Neyrinck AM, Possemiers S, Van Holle A, François P, de Vos WM, Delzenne NM, Schrenzel J, Cani PD. Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice. *Diabetes* 2011; **60**(11): 2775-2786 [PMID: 21933985 PMCID: PMC3198091 DOI: 10.2337/db11-0227]

114 Neyrinck AM, Possemiers S, Druart C, Van de Wiele T, De Backer F, Cani PD, Larondelle Y, Delzenne NM. Prebiotic effects of wheat arabinoxylan related to the increase in bifidobacteria, Roseburia and Bacteroides/Prevotella in diet-induced obese mice. *PLoS One* 2011; **6**(6): e20944 [PMID: 21695273 PMCID: PMC3111466 DOI: 10.1371/journal.pone.0020944]

115 Parnell JA, Reimer RA. Prebiotic fibres dose-dependently increase satiety hormones and alter Bacteroidetes and Firmicutes in lean and obese JCR:LA-cp rats. *Br J Nutr* 2012; **107**(4): 601-613 [PMID: 21767445 PMCID: PMC3827017 DOI: 10.1017/S0007114511003163]

116 Cani PD, Joly E, Horsmans Y, Delzenne NM. Oligofructose promotes satiety in healthy human: a pilot study. *Eur J Clin Nutr* 2006; **60**(5): 567-572 [PMID: 16340949 DOI: 10.1038/sj.ejcn.1602350]

117 Davis LM, Martínez I, Walter J, Goin C, Hutkins RW. Barcoded pyrosequencing reveals that consumption of galactooligosaccharides results in a highly specific bifidogenic response in humans. *PLoS One* 2011; **6**(9): e25200 [PMID: 21966454 PMCID: PMC3180383 DOI: 10.1371/journal.pone.0025200]

118 Dewulf EM, Cani PD, Claus SP, Fuentes S, Puylaert PG, Neyrinck AM, Bindels LB, de Vos WM, Gibson GR, Thissen JP, Delzenne NM. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. *Gut* 2013; **62**(8): 1112-1121 [PMID: 23135760 PMCID: PMC3711491 DOI: 10.1136/gutjnl-2012-303304]

119 Genta S, Cabrera W, Habib N, Pons J, Carillo IM, Grau A, Sánchez S. Yacon syrup: beneficial effects on obesity and insulin resistance in humans. *Clin Nutr* 2009; **28**(2): 182-187 [PMID: 19254816 DOI: 10.1016/j.clnu.2009.01.013]

120 Parnell JA, Reimer RA. Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. *Am J Clin Nutr* 2009; **89**(6): 1751-1759 [PMID: 19386741 PMCID: PMC3827013 DOI: 10.3945/ajcn.2009.27465]

121 Kellow NJ, Coughlan MT, Reid CM. Metabolic benefits of dietary prebiotics in human subjects: a systematic review of randomised controlled trials. *Br J Nutr* 2014; **111**(7): 1147-1161 [PMID: 24230488 DOI: 10.1017/S0007114513003607]

1 Kaur J. A Comprehensive Review on Metabolic Syndrome. *Cardiol Res Pract* 2014; **2014**: 943162 [PMID: 24711954 PMCID: PMC3966331 DOI: 10.1155/2014/943162]

2 International Diabetes Federation: The IDF consensus worldwide definition of the metabolic syndrome.

3 Cani PD, Delzenne NM. Gut microflora as a target for energy and metabolic homeostasis. *Curr Opin Clin Nutr Metab Care* 2007; **10**(6): 729-734 [PMID: 18089955 DOI: 10.1097/MCO.0b013e3282efdebb]

4 Fukuda S, Ohno H. Gut microbiome and metabolic diseases. *Semin Immunopathol* 2014; **36**(1): 103-114 [PMID: 24196453 DOI: 10.1007/s00281-013-0399-z]

5 Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. *Science* 2012; **336**(6086): 1268-1273 [PMID: 22674334 DOI: 10.1126/science.1223490]

6 Jia W, Li H, Zhao L, Nicholson JK. Gut microbiota: a potential new territory for drug targeting. *Nat Rev Drug Discov* 2008; **7**(2): 123-129 [PMID: 18239669 DOI: 10.1038/nrd2505]

7 Zoetendal EG, Vaughan EE, de Vos WM. A microbial world within us. *Mol Microbiol* 2006; **59**(6): 1639-1650 [PMID: 16553872 DOI: 10.1111/j.1365-2958.2006.05056.x]

8 Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. *Nature* 2007; **449**(7164): 804-810 [PMID: 17943116 PMCID: PMC3709439 DOI: 10.1038/nature06244]

9 Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF, Gordon JI. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci U S A* 2004; **101**(44): 15718-15723 [PMID: 15505215 PMCID: PMC524219 DOI: 10.1073/pnas.0407076101]

10 Bäckhed F, Manchester JK, Semenkovich CF, Gordon JI. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proc Natl Acad Sci U S A* 2007; **104**(3): 979-984 [PMID: 17210919 PMCID: PMC1764762 DOI: 10.1073/pnas.0605374104]

11 Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 2006; **444**(7122): 1027-1031 [PMID: 17183312 DOI: 10.1038/nature05414]

12 Samuel BS, Shaito A, Motoike T, Rey FE, Backhed F, Manchester JK, Hammer RE, Williams SC, Crowley J, Yanagisawa M, Gordon JI. Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. *Proc Natl Acad Sci U S A* 2008; **105**(43): 16767-16772 [PMID: 18931303 PMCID: PMC2569967 DOI: 10.1073/pnas.0808567105]

13 Tolhurst G, Heffron H, Lam YS, Parker HE, Habib AM, Diakogiannaki E, Cameron J, Grosse J, Reimann F, Gribble FM. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. *Diabetes* 2012; **61**(2): 364-371 [PMID: 22190648 PMCID: PMC3266401 DOI: 10.2337/db11-1019]

14 Hooper LV, Wong MH, Thelin A, Hansson L, Falk PG, Gordon JI. Molecular analysis of commensal host-microbial relationships in the intestine. *Science* 2001; **291**(5505): 881-884 [PMID: 11157169 DOI: 10.1126/science.291.5505.881]

15 Rabot S, Membrez M, Bruneau A, Gérard P, Harach T, Moser M, Raymond F, Mansourian R, Chou CJ. Germ-free C57BL/6J mice are resistant to high-fat-diet-induced insulin resistance and have altered cholesterol metabolism. *FASEB J* 2010; **24**(12): 4948-4959 [PMID: 20724524 DOI: 10.1096/fj.10-164921]

16 Mandard S, Zandbergen F, van Straten E, Wahli W, Kuipers F, Müller M, Kersten S. The fasting-induced adipose factor/angiopoietin-like protein 4 is physically associated with lipoproteins and governs plasma lipid levels and adiposity. *J Biol Chem* 2006; **281**(2): 934-944 [PMID: 16272564 DOI: 10.1074/jbc.M506519200]

17 Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. *Proc Natl Acad Sci U S A* 2005; **102**(31): 11070-11075 [PMID: 16033867 PMCID: PMC1176910 DOI: 10.1073/pnas.0504978102]

18 Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, Waget A, Delmée E, Cousin B, Sulpice T, Chamontin B, Ferrières J, Tanti JF, Gibson GR, Casteilla L, Delzenne NM, Alessi MC, Burcelin R. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* 2007; **56**(7): 1761-1772 [PMID: 17456850 DOI: 10.2337/db06-1491]

19 Amar J, Chabo C, Waget A, Klopp P, Vachoux C, Bermúdez-Humarán LG, Smirnova N, Bergé M, Sulpice T, Lahtinen S, Ouwehand A, Langella P, Rautonen N, Sansonetti PJ, Burcelin R. Intestinal mucosal adherence and translocation of commensal bacteria at the early onset of type 2 diabetes: molecular mechanisms and probiotic treatment. *EMBO Mol Med* 2011; **3**(9): 559-572 [PMID: 21735552 PMCID: PMC3265717 DOI: 10.1002/emmm.201100159]

20 de La Serre CB, Ellis CL, Lee J, Hartman AL, Rutledge JC, Raybould HE. Propensity to high-fat diet-induced obesity in rats is associated with changes in the gut microbiota and gut inflammation. *Am J Physiol Gastrointest Liver Physiol* 2010; **299**(2): G440-448 [PMID: 20508158 PMCID: PMC2928532 DOI: 10.1152/ajpgi.00098.2010]

21 Cerf-Bensussan N, Gaboriau-Routhiau V. The immune system and the gut microbiota: friends or foes? *Nat Rev Immunol* 2010; **10**(10): 735-744 [PMID: 20865020 DOI: 10.1038/nri2850]

22 Vijay-Kumar M, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, Srinivasan S, Sitaraman SV, Knight R, Ley RE, Gewirtz AT. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science* 2010; **328**(5975): 228-231 [PMID: 20203013 DOI: 10.1126/science.1179721]

23 Muccioli GG, Naslain D, Bäckhed F, Reigstad CS, Lambert DM, Delzenne NM, Cani PD. The endocannabinoid system links gut microbiota to adipogenesis. *Mol Syst Biol* 2010; **6**: 392 [PMID: 20664638 PMCID: PMC2925525 DOI: 10.1038/msb.2010.46]

24 Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature* 2006; **444**(7122): 1022-1023 [PMID: 17183309 DOI: 10.1038/4441022a]

25 Armougom F, Henry M, Vialettes B, Raccah D, Raoult D. Monitoring bacterial community of human gut microbiota reveals an increase in Lactobacillus in obese patients and Methanogens in anorexic patients. *PLoS One* 2009; **4**(9): e7125 [PMID: 19774074 PMCID: PMC2742902 DOI: 10.1371/journal.pone.0007125]

26 Santacruz A, Collado MC, García-Valdés L, Segura MT, Martín-Lagos JA, Anjos T, Martí-Romero M, Lopez RM, Florido J, Campoy C, Sanz Y. Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. *Br J Nutr* 2010; **104**(1): 83-92 [PMID: 20205964 DOI: 10.1017/S0007114510000176]

27 Duncan SH, Lobley GE, Holtrop G, Ince J, Johnstone AM, Louis P, Flint HJ. Human colonic microbiota associated with diet, obesity and weight loss. *Int J Obes (Lond)* 2008; **32**(11): 1720-1724 [PMID: 18779823 DOI: 10.1038/ijo.2008.155]

28 Schwiertz A, Taras D, Schäfer K, Beijer S, Bos NA, Donus C, Hardt PD. Microbiota and SCFA in lean and overweight healthy subjects. *Obesity (Silver Spring)* 2010; **18**(1): 190-195 [PMID: 19498350 DOI: 10.1038/oby.2009.167]

29 Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, Sogin ML, Jones WJ, Roe BA, Affourtit JP, Egholm M, Henrissat B, Heath AC, Knight R, Gordon JI. A core gut microbiome in obese and lean twins. *Nature* 2009; **457**(7228): 480-484 [PMID: 19043404 PMCID: PMC2677729 DOI: 10.1038/nature07540]

30 Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, Almeida M, Arumugam M, Batto JM, Kennedy S, Leonard P, Li J, Burgdorf K, Grarup N, Jørgensen T, Brandslund I, Nielsen HB, Juncker AS, Bertalan M, Levenez F, Pons N, Rasmussen S, Sunagawa S, Tap J, Tims S, Zoetendal EG, Brunak S, Clément K, Doré J, Kleerebezem M, Kristiansen K, Renault P, Sicheritz-Ponten T, de Vos WM, Zucker JD, Raes J, Hansen T, Bork P, Wang J, Ehrlich SD, Pedersen O, consortium M. Richness of human gut microbiome correlates with metabolic markers. *Nature* 2013; **500**(7464): 541-546 [PMID: 23985870 DOI: 10.1038/nature12506]

31 Kalliomäki M, Collado MC, Salminen S, Isolauri E. Early differences in fecal microbiota composition in children may predict overweight. *Am J Clin Nutr* 2008; **87**(3): 534-538 [PMID: 18326589]

32 Karlsson CL, Onnerfält J, Xu J, Molin G, Ahrné S, Thorngren-Jerneck K. The microbiota of the gut in preschool children with normal and excessive body weight. *Obesity (Silver Spring)* 2012; **20**(11): 2257-2261 [PMID: 22546742 DOI: 10.1038/oby.2012.110]

33 Kovatcheva-Datchary P, Arora T. Nutrition, the gut microbiome and the metabolic syndrome. *Best Pract Res Clin Gastroenterol* 2013; **27**(1): 59-72 [PMID: 23768553 DOI: 10.1016/j.bpg.2013.03.017]

34 De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, Collini S, Pieraccini G, Lionetti P. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proc Natl Acad Sci U S A* 2010; **107**(33): 14691-14696 [PMID: 20679230 PMCID: PMC2930426 DOI: 10.1073/pnas.1005963107]

35 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, 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, Consortium M. Enterotypes of the human gut microbiome. *Nature* 2011; **473**(7346): 174-180 [PMID: 21508958 PMCID: PMC3728647 DOI: 10.1038/nature09944]

36 Brown K, DeCoffe D, Molcan E, Gibson DL. Diet-induced dysbiosis of the intestinal microbiota and the effects on immunity and disease. *Nutrients* 2012; **4**(8): 1095-1119 [PMID: 23016134 PMCID: PMC3448089 DOI: 10.3390/nu4081095]

37 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**(7484): 559-563 [PMID: 24336217 PMCID: PMC3957428 DOI: 10.1038/nature12820]

38 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**(6052): 105-108 [PMID: 21885731 PMCID: PMC3368382 DOI: 10.1126/science.1208344]

39 Ding S, Chi MM, Scull BP, Rigby R, Schwerbrock NM, Magness S, Jobin C, Lund PK. High-fat diet: bacteria interactions promote intestinal inflammation which precedes and correlates with obesity and insulin resistance in mouse. *PLoS One* 2010; **5**(8): e12191 [PMID: 20808947 PMCID: PMC2922379 DOI: 10.1371/journal.pone.0012191]

40 Turnbaugh PJ, Bäckhed F, Fulton L, Gordon JI. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. *Cell Host Microbe* 2008; **3**(4): 213-223 [PMID: 18407065 PMCID: PMC3687783 DOI: 10.1016/j.chom.2008.02.015]

41 de Wit N, Derrien M, Bosch-Vermeulen H, Oosterink E, Keshtkar S, Duval C, de Vogel-van den Bosch J, Kleerebezem M, Müller M, van der Meer R. Saturated fat stimulates obesity and hepatic steatosis and affects gut microbiota composition by an enhanced overflow of dietary fat to the distal intestine. *Am J Physiol Gastrointest Liver Physiol* 2012; **303**(5): G589-599 [PMID: 22700822 DOI: 10.1152/ajpgi.00488.2011]

42 Shen W, Gaskins HR, McIntosh MK. Influence of dietary fat on intestinal microbes, inflammation, barrier function and metabolic outcomes. *J Nutr Biochem* 2014; **25**(3): 270-280 [PMID: 24355793 DOI: 10.1016/j.jnutbio.2013.09.009]

43 Brinkworth GD, Noakes M, Clifton PM, Bird AR. Comparative effects of very low-carbohydrate, high-fat and high-carbohydrate, low-fat weight-loss diets on bowel habit and faecal short-chain fatty acids and bacterial populations. *Br J Nutr* 2009; **101**(10): 1493-1502 [PMID: 19224658 DOI: 10.1017/S0007114508094658]

44 Zhang C, Zhang M, Wang S, Han R, Cao Y, Hua W, Mao Y, Zhang X, Pang X, Wei C, Zhao G, Chen Y, Zhao L. Interactions between gut microbiota, host genetics and diet relevant to development of metabolic syndromes in mice. *ISME J* 2010; **4**(2): 232-241 [PMID: 19865183 DOI: 10.1038/ismej.2009.112]

45 Lam YY, Ha CW, Campbell CR, Mitchell AJ, Dinudom A, Oscarsson J, Cook DI, Hunt NH, Caterson ID, Holmes AJ, Storlien LH. Increased gut permeability and microbiota change associate with mesenteric fat inflammation and metabolic dysfunction in diet-induced obese mice. *PLoS One* 2012; **7**(3): e34233 [PMID: 22457829 PMCID: PMC3311621 DOI: 10.1371/journal.pone.0034233]

46 Membrez M, Blancher F, Jaquet M, Bibiloni R, Cani PD, Burcelin RG, Corthesy I, Macé K, Chou CJ. Gut microbiota modulation with norfloxacin and ampicillin enhances glucose tolerance in mice. *FASEB J* 2008; **22**(7): 2416-2426 [PMID: 18326786 DOI: 10.1096/fj.07-102723]

47 Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, Guiot Y, Derrien M, Muccioli GG, Delzenne NM, de Vos WM, Cani PD. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proc Natl Acad Sci U S A* 2013; **110**(22): 9066-9071 [PMID: 23671105 PMCID: PMC3670398 DOI: 10.1073/pnas.1219451110]

48 Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, Burcelin R. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* 2008; **57**(6): 1470-1481 [PMID: 18305141 DOI: 10.2337/db07-1403]

49 Wall R, Ross RP, Shanahan F, O'Mahony L, O'Mahony C, Coakley M, Hart O, Lawlor P, Quigley EM, Kiely B, Fitzgerald GF, Stanton C. Metabolic activity of the enteric microbiota influences the fatty acid composition of murine and porcine liver and adipose tissues. *Am J Clin Nutr* 2009; **89**(5): 1393-1401 [PMID: 19357220 DOI: 10.3945/ajcn.2008.27023]

50 Amar J, Burcelin R, Ruidavets JB, Cani PD, Fauvel J, Alessi MC, Chamontin B, Ferriéres J. Energy intake is associated with endotoxemia in apparently healthy men. *Am J Clin Nutr* 2008; **87**(5): 1219-1223 [PMID: 18469242]

51 Creely SJ, McTernan PG, Kusminski CM, Fisher f, Da Silva NF, Khanolkar M, Evans M, Harte AL, Kumar S. Lipopolysaccharide activates an innate immune system response in human adipose tissue in obesity and type 2 diabetes. *Am J Physiol Endocrinol Metab* 2007; **292**(3): E740-747 [PMID: 17090751 DOI: 10.1152/ajpendo.00302.2006]

52 Amar J, Serino M, Lange C, Chabo C, Iacovoni J, Mondot S, Lepage P, Klopp C, Mariette J, Bouchez O, Perez L, Courtney M, Marre M, Klopp P, Lantieri O, Doré J, Charles M, Balkau B, Burcelin R, Group DESIRS. Involvement of tissue bacteria in the onset of diabetes in humans: evidence for a concept. *Diabetologia* 2011; **54**(12): 3055-3061 [PMID: 21976140 DOI: 10.1007/s00125-011-2329-8]

53 Larsen N, Vogensen FK, van den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, Al-Soud WA, Sørensen SJ, Hansen LH, Jakobsen M. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS One* 2010; **5**(2): e9085 [PMID: 20140211 PMCID: PMC2816710 DOI: 10.1371/journal.pone.0009085]

54 Wu X, Ma C, Han L, Nawaz M, Gao F, Zhang X, Yu P, Zhao C, Li L, Zhou A, Wang J, Moore JE, Millar BC, Xu J. Molecular characterisation of the faecal microbiota in patients with type II diabetes. *Curr Microbiol* 2010; **61**(1): 69-78 [PMID: 20087741 DOI: 10.1007/s00284-010-9582-9]

55 Zhang X, Shen D, Fang Z, Jie Z, Qiu X, Zhang C, Chen Y, Ji L. Human gut microbiota changes reveal the progression of glucose intolerance. *PLoS One* 2013; **8**(8): e71108 [PMID: 24013136 PMCID: PMC3754967 DOI: 10.1371/journal.pone.0071108]

56 Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, Zhang W, Guan Y, Shen D, Peng Y, Zhang D, Jie Z, Wu W, Qin Y, Xue W, Li J, Han L, Lu D, Wu P, Dai Y, Sun X, Li Z, Tang A, Zhong S, Li X, Chen W, Xu R, Wang M, Feng Q, Gong M, Yu J, Zhang Y, Zhang M, Hansen T, Sanchez G, Raes J, Falony G, Okuda S, Almeida M, LeChatelier E, Renault P, Pons N, Batto JM, Zhang Z, Chen H, Yang R, Zheng W, Yang H, Wang J, Ehrlich SD, Nielsen R, Pedersen O, Kristiansen K. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* 2012; **490**(7418): 55-60 [PMID: 23023125 DOI: 10.1038/nature11450]

57 Lewis K, Lutgendorff F, Phan V, Söderholm JD, Sherman PM, McKay DM. Enhanced translocation of bacteria across metabolically stressed epithelia is reduced by butyrate. *Inflamm Bowel Dis* 2010; **16**(7): 1138-1148 [PMID: 20024905 DOI: 10.1002/ibd.21177]

58 Vrieze A, Van Nood E, Holleman F, Salojärvi J, Kootte RS, Bartelsman JF, Dallinga-Thie GM, Ackermans MT, Serlie MJ, Oozeer R, Derrien M, Druesne A, Van Hylckama Vlieg JE, Bloks VW, Groen AK, Heilig HG, Zoetendal EG, Stroes ES, de Vos WM, Hoekstra JB, Nieuwdorp M. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology* 2012; **143**(4): 913-916.e917 [PMID: 22728514 DOI: 10.1053/j.gastro.2012.06.031]

59 Le Roy T, Llopis M, Lepage P, Bruneau A, Rabot S, Bevilacqua C, Martin P, Philippe C, Walker F, Bado A, Perlemuter G, Cassard-Doulcier AM, Gérard P. Intestinal microbiota determines development of non-alcoholic fatty liver disease in mice. *Gut* 2013; **62**(12): 1787-1794 [PMID: 23197411 DOI: 10.1136/gutjnl-2012-303816]

60 Cope K, Risby T, Diehl AM. Increased gastrointestinal ethanol production in obese mice: implications for fatty liver disease pathogenesis. *Gastroenterology* 2000; **119**(5): 1340-1347 [PMID: 11054393]

61 Dumas ME, Barton RH, Toye A, Cloarec O, Blancher C, Rothwell A, Fearnside J, Tatoud R, Blanc V, Lindon JC, Mitchell SC, Holmes E, McCarthy MI, Scott J, Gauguier D, Nicholson JK. Metabolic profiling reveals a contribution of gut microbiota to fatty liver phenotype in insulin-resistant mice. *Proc Natl Acad Sci U S A* 2006; **103**(33): 12511-12516 [PMID: 16895997 PMCID: PMC1567909 DOI: 10.1073/pnas.0601056103]

62 Swann JR, Want EJ, Geier FM, Spagou K, Wilson ID, Sidaway JE, Nicholson JK, Holmes E. Systemic gut microbial modulation of bile acid metabolism in host tissue compartments. *Proc Natl Acad Sci U S A* 2011; **108 Suppl 1**: 4523-4530 [PMID: 20837534 PMCID: PMC3063584 DOI: 10.1073/pnas.1006734107]

63 Rivera CA, Adegboyega P, van Rooijen N, Tagalicud A, Allman M, Wallace M. Toll-like receptor-4 signaling and Kupffer cells play pivotal roles in the pathogenesis of non-alcoholic steatohepatitis. *J Hepatol* 2007; **47**(4): 571-579 [PMID: 17644211 PMCID: PMC2094119 DOI: 10.1016/j.jhep.2007.04.019]

64 Boaru SG, Borkham-Kamphorst E, Tihaa L, Haas U, Weiskirchen R. Expression analysis of inflammasomes in experimental models of inflammatory and fibrotic liver disease. *J Inflamm (Lond)* 2012; **9**(1): 49 [PMID: 23192004 PMCID: PMC3599703 DOI: 10.1186/1476-9255-9-49]

65 Csak T, Ganz M, Pespisa J, Kodys K, Dolganiuc A, Szabo G. Fatty acid and endotoxin activate inflammasomes in mouse hepatocytes that release danger signals to stimulate immune cells. *Hepatology* 2011; **54**(1): 133-144 [PMID: 21488066 DOI: 10.1002/hep.24341]

66 Seki E, De Minicis S, Osterreicher CH, Kluwe J, Osawa Y, Brenner DA, Schwabe RF. TLR4 enhances TGF-beta signaling and hepatic fibrosis. *Nat Med* 2007; **13**(11): 1324-1332 [PMID: 17952090 DOI: 10.1038/nm1663]

67 Henao-Mejia J, Elinav E, Jin C, Hao L, Mehal WZ, Strowig T, Thaiss CA, Kau AL, Eisenbarth SC, Jurczak MJ, Camporez JP, Shulman GI, Gordon JI, Hoffman HM, Flavell RA. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. *Nature* 2012; **482**(7384): 179-185 [PMID: 22297845 PMCID: PMC3276682 DOI: 10.1038/nature10809]

68 Miele L, Valenza V, La Torre G, Montalto M, Cammarota G, Ricci R, Mascianà R, Forgione A, Gabrieli ML, Perotti G, Vecchio FM, Rapaccini G, Gasbarrini G, Day CP, Grieco A. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. *Hepatology* 2009; **49**(6): 1877-1887 [PMID: 19291785 DOI: 10.1002/hep.22848]

69 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**(1): 120-127 [PMID: 23401313 DOI: 10.1002/hep.26319]

70 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**(2): 601-609 [PMID: 23055155 DOI: 10.1002/hep.26093]

71 Buchman AL, Dubin MD, Moukarzel AA, Jenden DJ, Roch M, Rice KM, Gornbein J, Ament ME. Choline deficiency: a cause of hepatic steatosis during parenteral nutrition that can be reversed with intravenous choline supplementation. *Hepatology* 1995; **22**(5): 1399-1403 [PMID: 7590654]

72 Spencer MD, Hamp TJ, Reid RW, Fischer LM, Zeisel SH, Fodor AA. Association between composition of the human gastrointestinal microbiome and development of fatty liver with choline deficiency. *Gastroenterology* 2011; **140**(3): 976-986 [PMID: 21129376 PMCID: PMC3049827 DOI: 10.1053/j.gastro.2010.11.049]

73 Shanab AA, Scully P, Crosbie O, Buckley M, O'Mahony L, Shanahan F, Gazareen S, Murphy E, Quigley EM. Small intestinal bacterial overgrowth in nonalcoholic steatohepatitis: association with toll-like receptor 4 expression and plasma levels of interleukin 8. *Dig Dis Sci* 2011; **56**(5): 1524-1534 [PMID: 21046243 DOI: 10.1007/s10620-010-1447-3]

74 Sotos M, Nadal I, Marti A, Martínez A, Martin-Matillas M, Campoy C, Puertollano MA, Wärnberg J, Marcos A, Sanz Y. Gut microbes and obesity in adolescents. *Proceedings of the Nutrition Society* 2008; **67**(OCE)

75 Nadal I, Santacruz A, Marcos A, Warnberg J, Garagorri JM, Garagorri M, Moreno LA, Martin-Matillas M, Campoy C, Martí A, Moleres A, Delgado M, Veiga OL, García-Fuentes M, Redondo CG, Sanz Y. Shifts in clostridia, bacteroides and immunoglobulin-coating fecal bacteria associated with weight loss in obese adolescents. *Int J Obes (Lond)* 2009; **33**(7): 758-767 [PMID: 19050675 DOI: 10.1038/ijo.2008.260]

76 Cotillard A, Kennedy SP, Kong LC, Prifti E, Pons N, Le Chatelier E, Almeida M, Quinquis B, Levenez F, Galleron N, Gougis S, Rizkalla S, Batto JM, Renault P, Doré J, Zucker JD, Clément K, Ehrlich SD, consortium AM. Dietary intervention impact on gut microbial gene richness. *Nature* 2013; **500**(7464): 585-588 [PMID: 23985875 DOI: 10.1038/nature12480]

77 Zhang H, DiBaise JK, Zuccolo A, Kudrna D, Braidotti M, Yu Y, Parameswaran P, Crowell MD, Wing R, Rittmann BE, Krajmalnik-Brown R. Human gut microbiota in obesity and after gastric bypass. *Proc Natl Acad Sci U S A* 2009; **106**(7): 2365-2370 [PMID: 19164560 PMCID: PMC2629490 DOI: 10.1073/pnas.0812600106]

78 Furet JP, Kong LC, Tap J, Poitou C, Basdevant A, Bouillot JL, Mariat D, Corthier G, Doré J, Henegar C, Rizkalla S, Clément K. Differential adaptation of human gut microbiota to bariatric surgery-induced weight loss: links with metabolic and low-grade inflammation markers. *Diabetes* 2010; **59**(12): 3049-3057 [PMID: 20876719 PMCID: PMC2992765 DOI: 10.2337/db10-0253]

79 Li JV, Ashrafian H, Bueter M, Kinross J, Sands C, le Roux CW, Bloom SR, Darzi A, Athanasiou T, Marchesi JR, Nicholson JK, Holmes E. Metabolic surgery profoundly influences gut microbial-host metabolic cross-talk. *Gut* 2011; **60**(9): 1214-1223 [PMID: 21572120 PMCID: PMC3677150 DOI: 10.1136/gut.2010.234708]

80 Cani PD, Delzenne NM. The role of the gut microbiota in energy metabolism and metabolic disease. *Curr Pharm Des* 2009; **15**(13): 1546-1558 [PMID: 19442172]

81 Lips MA, de Groot GH, van Klinken JB, Aarts E, Berends FJ, Janssen IM, Van Ramshorst B, Van Wagensveld BA, Swank DJ, Van Dielen F, Willems van Dijk K, Pijl H. Calorie Restriction is a Major Determinant of the Short-Term Metabolic Effects of Gastric Bypass Surgery in Obese Type 2 Diabetic Patients. *Clin Endocrinol (Oxf)* 2013 [PMID: 23711328 DOI: 10.1111/cen.12254]

82 FAO/WHO. Health and Nutritional Properties of Probiotics in

Food including Powder Milk with Live Lactic

Acid Bacteria

Report. 2001

83 Kondo S, Xiao JZ, Satoh T, Odamaki T, Takahashi S, Sugahara H, Yaeshima T, Iwatsuki K, Kamei A, Abe K. Antiobesity effects of Bifidobacterium breve strain B-3 supplementation in a mouse model with high-fat diet-induced obesity. *Biosci Biotechnol Biochem* 2010; **74**(8): 1656-1661 [PMID: 20699581]

84 Cano PG, Santacruz A, Trejo FM, Sanz Y. Bifidobacterium CECT 7765 improves metabolic and immunological alterations associated with obesity in high-fat diet-fed mice. *Obesity (Silver Spring)* 2013; **21**(11): 2310-2321 [PMID: 23418126 DOI: 10.1002/oby.20330]

85 Chen JJ, Wang R, Li XF, Wang RL. Bifidobacterium longum supplementation improved high-fat-fed-induced metabolic syndrome and promoted intestinal Reg I gene expression. *Exp Biol Med (Maywood)* 2011; **236**(7): 823-831 [PMID: 21685239 DOI: 10.1258/ebm.2011.010399]

86 Chen J, Wang R, Li XF, Wang RL. Bifidobacterium adolescentis supplementation ameliorates visceral fat accumulation and insulin sensitivity in an experimental model of the metabolic syndrome. *Br J Nutr* 2012; **107**(10): 1429-1434 [PMID: 21914236 DOI: 10.1017/S0007114511004491]

87 An HM, Park SY, Lee dK, Kim JR, Cha MK, Lee SW, Lim HT, Kim KJ, Ha NJ. Antiobesity and lipid-lowering effects of Bifidobacterium spp. in high fat diet-induced obese rats. *Lipids Health Dis* 2011; **10**: 116 [PMID: 21745411 PMCID: PMC3146849 DOI: 10.1186/1476-511X-10-116]

88 Yin YN, Yu QF, Fu N, Liu XW, Lu FG. Effects of four Bifidobacteria on obesity in high-fat diet induced rats. *World J Gastroenterol* 2010; **16**(27): 3394-3401 [PMID: 20632441 PMCID: PMC2904885]

89 Cani PD, Neyrinck AM, Fava F, Knauf C, Burcelin RG, Tuohy KM, Gibson GR, Delzenne NM. Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. *Diabetologia* 2007; **50**(11): 2374-2383 [PMID: 17823788 DOI: 10.1007/s00125-007-0791-0]

90 Lee HY, Park JH, Seok SH, Baek MW, Kim DJ, Lee KE, Paek KS, Lee Y. Human originated bacteria, Lactobacillus rhamnosus PL60, produce conjugated linoleic acid and show anti-obesity effects in diet-induced obese mice. *Biochim Biophys Acta* 2006; **1761**(7): 736-744 [PMID: 16807088 DOI: 10.1016/j.bbalip.2006.05.007]

91 Lee K, Paek K, Lee HY, Park JH, Lee Y. Antiobesity effect of trans-10,cis-12-conjugated linoleic acid-producing Lactobacillus plantarum PL62 on diet-induced obese mice. *J Appl Microbiol* 2007; **103**(4): 1140-1146 [PMID: 17897219 DOI: 10.1111/j.1365-2672.2007.03336.x]

92 Sato M, Uzu K, Yoshida T, Hamad EM, Kawakami H, Matsuyama H, Abd El-Gawad IA, Imaizumi K. Effects of milk fermented by Lactobacillus gasseri SBT2055 on adipocyte size in rats. *Br J Nutr* 2008; **99**(5): 1013-1017 [PMID: 17977471 DOI: 10.1017/S0007114507839006]

93 Tomaro-Duchesneau C, Saha S, Malhotra M, Jones ML, Labbé A, Rodes L, Kahouli I, Prakash S. Effect of orally administered L. fermentum NCIMB 5221 on markers of metabolic syndrome: an in vivo analysis using ZDF rats. *Appl Microbiol Biotechnol* 2014; **98**(1): 115-126 [PMID: 24121931 DOI: 10.1007/s00253-013-5252-8]

94 Wang LX, Liu K, Gao DW, Hao JK. Protective effects of two Lactobacillus plantarum strains in hyperlipidemic mice. *World J Gastroenterol* 2013; **19**(20): 3150-3156 [PMID: 23716997 PMCID: PMC3662957 DOI: 10.3748/wjg.v19.i20.3150]

95 Kim SW, Park KY, Kim B, Kim E, Hyun CK. Lactobacillus rhamnosus GG improves insulin sensitivity and reduces adiposity in high-fat diet-fed mice through enhancement of adiponectin production. *Biochem Biophys Res Commun* 2013; **431**(2): 258-263 [PMID: 23313485 DOI: 10.1016/j.bbrc.2012.12.121]

96 Fåk F, Bäckhed F. Lactobacillus reuteri prevents diet-induced obesity, but not atherosclerosis, in a strain dependent fashion in Apoe-/- mice. *PLoS One* 2012; **7**(10): e46837 [PMID: 23056479 PMCID: PMC3467285 DOI: 10.1371/journal.pone.0046837]

97 Takemura N, Okubo T, Sonoyama K. Lactobacillus plantarum strain No. 14 reduces adipocyte size in mice fed high-fat diet. *Exp Biol Med (Maywood)* 2010; **235**(7): 849-856 [PMID: 20558839 DOI: 10.1258/ebm.2010.009377]

98 Aronsson L, Huang Y, Parini P, Korach-André M, Håkansson J, Gustafsson J, Pettersson S, Arulampalam V, Rafter J. Decreased fat storage by Lactobacillus paracasei is associated with increased levels of angiopoietin-like 4 protein (ANGPTL4). *PLoS One* 2010; **5**(9) [PMID: 20927337 PMCID: PMC2948012 DOI: 10.1371/journal.pone.0013087]

99 Nerstedt A, Nilsson EC, Ohlson K, Håkansson J, Thomas Svensson L, Löwenadler B, Svensson UK, Mahlapuu M. Administration of Lactobacillus evokes coordinated changes in the intestinal expression profile of genes regulating energy homeostasis and immune phenotype in mice. *Br J Nutr* 2007; **97**(6): 1117-1127 [PMID: 17433125 DOI: 10.1017/S0007114507682907]

100 Kadooka Y, Sato M, Imaizumi K, Ogawa A, Ikuyama K, Akai Y, Okano M, Kagoshima M, Tsuchida T. Regulation of abdominal adiposity by probiotics (Lactobacillus gasseri SBT2055) in adults with obese tendencies in a randomized controlled trial. *Eur J Clin Nutr* 2010; **64**(6): 636-643 [PMID: 20216555 DOI: 10.1038/ejcn.2010.19]

101 Kadooka Y, Sato M, Ogawa A, Miyoshi M, Uenishi H, Ogawa H, Ikuyama K, Kagoshima M, Tsuchida T. Effect of Lactobacillus gasseri SBT2055 in fermented milk on abdominal adiposity in adults in a randomised controlled trial. *Br J Nutr* 2013; **110**(9): 1696-1703 [PMID: 23614897 DOI: 10.1017/S0007114513001037]

102 Barreto FM, Colado Simão AN, Morimoto HK, Batisti Lozovoy MA, Dichi I, Helena da Silva Miglioranza L. Beneficial effects of Lactobacillus plantarum on glycemia and homocysteine levels in postmenopausal women with metabolic syndrome. *Nutrition* 2013 [PMID: 24613434 DOI: 10.1016/j.nut.2013.12.004]

103 Yadav H, Lee JH, Lloyd J, Walter P, Rane SG. Beneficial metabolic effects of a probiotic via butyrate-induced GLP-1 hormone secretion. *J Biol Chem* 2013; **288**(35): 25088-25097 [PMID: 23836895 PMCID: PMC3757173 DOI: 10.1074/jbc.M113.452516]

104 Park DY, Ahn YT, Park SH, Huh CS, Yoo SR, Yu R, Sung MK, McGregor RA, Choi MS. Supplementation of Lactobacillus curvatus HY7601 and Lactobacillus plantarum KY1032 in diet-induced obese mice is associated with gut microbial changes and reduction in obesity. *PLoS One* 2013; **8**(3): e59470 [PMID: 23555678 PMCID: PMC3605452 DOI: 10.1371/journal.pone.0059470]

105 Iacono A, Raso GM, Canani RB, Calignano A, Meli R. Probiotics as an emerging therapeutic strategy to treat NAFLD: focus on molecular and biochemical mechanisms. *J Nutr Biochem* 2011; **22**(8): 699-711 [PMID: 21292470 DOI: 10.1016/j.jnutbio.2010.10.002]

106 Ma YY, Li L, Yu CH, Shen Z, Chen LH, Li YM. Effects of probiotics on nonalcoholic fatty liver disease: a meta-analysis. *World J Gastroenterol* 2013; **19**(40): 6911-6918 [PMID: 24187469 PMCID: PMC3812493 DOI: 10.3748/wjg.v19.i40.6911]

107 Million M, Angelakis E, Paul M, Armougom F, Leibovici L, Raoult D. Comparative meta-analysis of the effect of Lactobacillus species on weight gain in humans and animals. *Microb Pathog* 2012; **53**(2): 100-108 [PMID: 22634320 DOI: 10.1016/j.micpath.2012.05.007]

108 Floch MH, Walker WA, Madsen K, Sanders ME, Macfarlane GT, Flint HJ, Dieleman LA, Ringel Y, Guandalini S, Kelly CP, Brandt LJ. Recommendations for probiotic use-2011 update. *J Clin Gastroenterol* 2011; **45 Suppl**: S168-171 [PMID: 21992958 DOI: 10.1097/MCG.0b013e318230928b]

109 Roberfroid M, Gibson GR, Hoyles L, McCartney AL, Rastall R, Rowland I, Wolvers D, Watzl B, Szajewska H, Stahl B, Guarner F, Respondek F, Whelan K, Coxam V, Davicco MJ, Léotoing L, Wittrant Y, Delzenne NM, Cani PD, Neyrinck AM, Meheust A. Prebiotic effects: metabolic and health benefits. *Br J Nutr* 2010; **104 Suppl 2**: S1-63 [PMID: 20920376 DOI: 10.1017/S0007114510003363]

110 Cani PD, Neyrinck AM, Maton N, Delzenne NM. Oligofructose promotes satiety in rats fed a high-fat diet: involvement of glucagon-like Peptide-1. *Obes Res* 2005; **13**(6): 1000-1007 [PMID: 15976142 DOI: 10.1038/oby.2005.117]

111 Cani PD, Daubioul CA, Reusens B, Remacle C, Catillon G, Delzenne NM. Involvement of endogenous glucagon-like peptide-1(7-36) amide on glycaemia-lowering effect of oligofructose in streptozotocin-treated rats. *J Endocrinol* 2005; **185**(3): 457-465 [PMID: 15930172 DOI: 10.1677/joe.1.06100]

112 Cani PD, Possemiers S, Van de Wiele T, Guiot Y, Everard A, Rottier O, Geurts L, Naslain D, Neyrinck A, Lambert DM, Muccioli GG, Delzenne NM. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut* 2009; **58**(8): 1091-1103 [PMID: 19240062 PMCID: PMC2702831 DOI: 10.1136/gut.2008.165886]

113 Everard A, Lazarevic V, Derrien M, Girard M, Muccioli GG, Muccioli GM, Neyrinck AM, Possemiers S, Van Holle A, François P, de Vos WM, Delzenne NM, Schrenzel J, Cani PD. Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice. *Diabetes* 2011; **60**(11): 2775-2786 [PMID: 21933985 PMCID: PMC3198091 DOI: 10.2337/db11-0227]

114 Neyrinck AM, Possemiers S, Druart C, Van de Wiele T, De Backer F, Cani PD, Larondelle Y, Delzenne NM. Prebiotic effects of wheat arabinoxylan related to the increase in bifidobacteria, Roseburia and Bacteroides/Prevotella in diet-induced obese mice. *PLoS One* 2011; **6**(6): e20944 [PMID: 21695273 PMCID: PMC3111466 DOI: 10.1371/journal.pone.0020944]

115 Parnell JA, Reimer RA. Prebiotic fibres dose-dependently increase satiety hormones and alter Bacteroidetes and Firmicutes in lean and obese JCR:LA-cp rats. *Br J Nutr* 2012; **107**(4): 601-613 [PMID: 21767445 PMCID: PMC3827017 DOI: 10.1017/S0007114511003163]

116 Cani PD, Joly E, Horsmans Y, Delzenne NM. Oligofructose promotes satiety in healthy human: a pilot study. *Eur J Clin Nutr* 2006; **60**(5): 567-572 [PMID: 16340949 DOI: 10.1038/sj.ejcn.1602350]

117 Davis LM, Martínez I, Walter J, Goin C, Hutkins RW. Barcoded pyrosequencing reveals that consumption of galactooligosaccharides results in a highly specific bifidogenic response in humans. *PLoS One* 2011; **6**(9): e25200 [PMID: 21966454 PMCID: PMC3180383 DOI: 10.1371/journal.pone.0025200]

118 Dewulf EM, Cani PD, Claus SP, Fuentes S, Puylaert PG, Neyrinck AM, Bindels LB, de Vos WM, Gibson GR, Thissen JP, Delzenne NM. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. *Gut* 2013; **62**(8): 1112-1121 [PMID: 23135760 PMCID: PMC3711491 DOI: 10.1136/gutjnl-2012-303304]

119 Genta S, Cabrera W, Habib N, Pons J, Carillo IM, Grau A, Sánchez S. Yacon syrup: beneficial effects on obesity and insulin resistance in humans. *Clin Nutr* 2009; **28**(2): 182-187 [PMID: 19254816 DOI: 10.1016/j.clnu.2009.01.013]

120 Parnell JA, Reimer RA. Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. *Am J Clin Nutr* 2009; **89**(6): 1751-1759 [PMID: 19386741 PMCID: PMC3827013 DOI: 10.3945/ajcn.2009.27465]

121 Kellow NJ, Coughlan MT, Reid CM. Metabolic benefits of dietary prebiotics in human subjects: a systematic review of randomised controlled trials. *Br J Nutr* 2014; **111**(7): 1147-1161 [PMID: 24230488 DOI: 10.1017/S0007114513003607]