The Journal of Nutrition
Supplement: Fourth Global Summit on the Health Effects of Yogurt. Yogurt and Type 2 Diabetes: Translating Evidence into Practice

Factors Influencing the Gut Microbiota, Inflammation, and Type 2 Diabetes

Li Wen[1] and Andrew Duffy[2]

[1]Section of Endocrinology and [2]Department of Surgery, Yale University School of Medicine, New Haven, CT

Abstract

The gut microbiota is a complex community of bacteria residing in the intestine. Animal models have demonstrated that several factors contribute to and can significantly alter the composition of the gut microbiota, including genetics; the mode of delivery at birth; the method of infant feeding; the use of medications, especially antibiotics; and the diet. There may exist a gut microbiota signature that promotes intestinal inflammation and subsequent systemic low-grade inflammation, which in turn promotes the development of type 2 diabetes. There are preliminary studies that suggest that the consumption of probiotic bacteria such as those found in yogurt and other fermented milk products can beneficially alter the composition of the gut microbiome, which in turn changes the host metabolism. Obesity, insulin resistance, fatty liver disease, and low-grade peripheral inflammation are more prevalent in patients with low α diversity in the gut microbiome than they are in patients with high α diversity. Fermented milk products, such as yogurt, deliver a large number of lactic acid bacteria to the gastrointestinal tract. They may modify the intestinal environment, including inhibiting lipopolysaccharide production and increasing the tight junctions of gut epithelia cells. *J Nutr* 2017;147(Suppl):1468S–75S.

Keywords: microbiota, diet, yogurt, type 2 diabetes, inflammation, environment

Introduction

The gut microbiota is a complex community of bacteria residing in the intestine. The bacterial load in the stomach is significantly lower, and the load increases exponentially through the digestive system from the stomach to the duodenum, the jejunum, and the ileum, and ultimately to the colon, which contains between 10^9 and 10^{13} bacteria (1). Both animal and human studies have demonstrated that diet can influence the composition and function of the gut microbiome. Other factors, including genetics; the mode of delivery at birth; the method of infant feeding; and the use of medications, especially antibiotics, also contribute to the composition and function of the gut microbiome. Diet plays an important role in obesity, in addition to other factors (2–6). Yogurt, a fermented dairy product containing a variety of probiotic bacteria, is found to be associated with a reduction in inflammation markers and weight loss (7, 8). Studies found that regular yogurt consumption is involved in energy balance and/or energy homeostasis, which in turn controls body weight and reduces the risk of the development of type 2 diabetes (T2D) (9). It is well known that diet, including yogurt consumption, has a direct impact on the gut bacteria; therefore, it is possible that the effect of yogurt on energy balance and body weight control in some studies is mediated by the alteration of the gut microbiota. Despite the fact that there are certain enterotypes in the composition of the human gut microbiome, there is tremendous variability between individuals, and some of these differences are associated with chronic conditions. Dysbiosis is a state in which the homeostasis of the gut microbiome is disrupted, often leading to health problems. One of the causes of dysbiosis is diet, and studies have shown that diet may change the gut microbiota and contribute to obesity and diabetes (10, 11). Over 80% of patients with T2D in the Western world are overweight. Obesity and T2D are characterized by an altered gut microbiota, inflammation, and gut barrier disruption (12–14). Diabetes is a complex disorder that is influenced

Published in a supplement to *The Journal of Nutrition*. The Fourth Global Summit on the Health Effects of Yogurt is part of the international partnership ''Yogurt in Nutrition, Initiative for a Balanced Diet'' (YINI). This initiative is a collaborative project between Danone Institute International, the ASN, and the International Osteoporosis Foundation, which aims to advance scientific knowledge on the health effects of yogurt and broadly disseminate the findings (http://yogurtinnutrition.com). The Supplement Coordinators for the supplement publication are Jordi Salas-Salvadó and Ana Pires. Supplement Coordinator disclosures: Jordi Salas-Salvadó is a member of the Executive Committee of Danone Institute–Spain, and travel expenses and an honorarium were received from the Danone Institute for delivering a lecture at the Fourth International Yogurt Summit at the Experimental Biology meeting in April 2016. Ana Pires is the General Representative of the Danone Institute International. The article contents are the responsibility of the authors and do not necessarily represent the official views of institutions or sponsors involved. Publication costs for this supplement were defrayed in part by the payment of page charges. This publication must therefore be hereby marked "advertisement" in accordance with 18 USC section 1734 solely to indicate this fact. The opinions expressed in this publication are those of the authors and are not attributable to the sponsors or the publisher, Editor, or Editorial Board of *The Journal of Nutrition*.
This work was funded by research grants from the American Diabetes Association (14-13 BS-222) and NIH (DK100500).
Author disclosures: LW and AD, no conflicts of interest.
Address correspondence to LW (e-mail: li.wen@yale.edu).

Manuscript received August 24, 2016. Initial review completed October 12, 2016. Revision accepted January 11, 2017.
First published online June 14, 2017; doi: https://doi.org/10.3945/jn.116.240754.

by a combination of genetic and environmental factors. However, there may exist a gut microbiota signature that promotes intestinal inflammation and subsequent systemic low-grade inflammation, which in turn promotes the development of T2D.

Composition of the Gut Microbiome

A few main phyla of bacteria exist in the gut: Actinobacteria, Bacteroidetes, Firmicutes, Proteobacteria, and Verrucomicrobia. The genes of bacteria in the gut are 150 times larger than that in the human genome, and the mass of bacteria in the body can reach 1.5 kg, or ~2% of the weight of an average 75-kg person. Studies in germ-free animals have shown that shifts in the composition of the gut microbiome may play an important role in disease development, specifically obesity and diabetes (15–17). There is evidence demonstrating that the composition of the gut microbiota also influences metabolism and can affect energy balance (18), gut permeability (19), and inflammation (20), all of which are associated with obesity and associated disorders, including T2D (14). Gastric bypass surgery, characterized by ~70% weight loss and an improvement in glucose metabolism, has been recommended by the American Diabetes Association as an effective treatment for obesity and T2D. The rationale of this surgical procedure was originally to cause a restriction in food intake and calorie malabsorption. Studies support the notion that gastric bypass leads to a substantial shift in the gut microbiota, which may contribute to weight loss. Samples from the duodena of bypass patients show a marked difference in the gut microbiota between patients with diabetes and those without, specifically, fewer bacterial strains exist among obese individuals with T2D (21). The change in physiology after bariatric surgery may also promote a different composition in the gut microbiota, but the microbiota alone may not be the primary driver of weight loss after bypass surgery.

The Gut Microbiota, Inflammation, and Diabetes

Accumulating evidence in animal models and in humans shows that obesity and T2D are associated with dysbiosis of the gut microbiota. Given that >80% of patients with T2D are overweight in the West, and that obesity and T2D are characterized by an altered gut microbiota, inflammation, and gut barrier disruption, it is conceivable that the microbiota may play a role in the development of these conditions (14, 22).

The immune system is "educated" and matured by commensal bacteria, especially bacteria in the gut. Germ-free mice have abnormal immune systems, including the absence or underdevelopment of lymph nodes systemically and specifically in gut-associated lymphoid tissues. Homeostasis of the gut microbiota is therefore important in modulation of the host immunity and control of inflammation (23). An altered gut microbiota influenced by different factors (see "Factors that Influence Gut Bacterial Composition" below) can directly affect immune cells in the gut and indirectly affect immune cells via microbial products (24, 25) including LPS (18, 20, 26, 27), metabolites, and SCFAs (28–30), all of which can affect adipogenesis and/or insulin resistance (31). LPS is believed to cause low-grade inflammation mediated by the induction of inflammatory cytokines by immune cells and adipocytes, and acetate or butyrate can modulate immune cell function. Acetate, butyrate, and propionate are end products of the microbial fermentation of macronutrients. These SCFAs can strongly modulate gene expression of human monocytes and reduce proinflammatory cytokine and chemokine production by monocytes (32, 33). They can also promote regulatory T cell generation, thereby suppressing the function of inflammatory T cells (34). Butyrate is able to block IFNγ-inducible protein 10 (IP-10) release in human colonic subepithelial myofibroblasts (35). Thus, these immune regulatory SCFAs act not only on immune cells systemically but also on intestinal tissue cells locally.

With advanced sequencing technology, including metagenome-wide association studies, scientists have discovered significant correlations between specific intestinal bacteria, metabolic pathways, and T2D (36). Among 345 Chinese individuals, butyrate-producing *Roseburia intestinalis* and *Faecalibacterium prausnitzii* concentrations were found to be lower in subjects with T2D, whereas those of *Lactobacillus gasseri* and *Streptococcus mutans,* Proteobacteria, and certain Clostridiales were higher (36). Butyrate-producing bacteria are able to exert substantial beneficial immunometabolic effects (22), as discussed earlier. In addition, T2D is associated with increased bacterial expression of the genes involved in oxidative stress, creating a proinflammatory signature in the intestinal microbiome (36). A study cohort in European women showed that women with high glycated hemoglobin concentrations were characterized by an increase in Lactobacillales, mainly *Streptococcus* species, and a decrease in species belonging to *Bacteroids*, *Eubacterium*, and *Clostridium* (37). Although the metagenomic markers of microbiota in Chinese and European cohorts are different, it is clear that the gut microbiota closely correlates to T2D. Therefore, it has been suggested that gut microbial markers might be useful for classifying T2D. Studies also showed that the presence of *Akkermansia muciniphila* in the gut, which constitutes 3–5% of the gut microbiota (22) inversely correlates with body weight in rodents and humans, although the precise physiologic roles are not fully understood (14). It is also currently unclear where inflammatory processes are initiated, but a significantly altered microbiota in the gastrointestinal tract could be one of the early events in the process (22).

A study of nonobese and obese Danish individuals showed that obesity, insulin resistance, fatty liver, and low-grade inflammation (increased C-reactive protein and leptin concentrations and decreased serum adiponectin concentrations) were more prevalent in patients with low α diversity in the gut microbiome than they were in patients with high α diversity (38).

All of these studies suggest a correlation between the composition of the gut microbiome and disease. However, there are several shortcomings in human studies. The populations studied were heterogeneous in nature, they were not sex matched, and there were no data on diabetes medication that the subjects might have been taking. It is clear that more investigations are needed to better understand the mechanisms of how gut bacteria affect T2D.

Factors that Influence Gut Bacterial Composition

There are several intrinsic and extrinsic factors that can influence the composition of the gut bacteria and ultimately affect health.

Method of delivery at birth. According to the CDC, as of 2014, 32.2% of all deliveries in the United States are performed by cesarean section (39). The composition of the gut bacterial community is different in infants delivered by cesarean section from that of infants born by vaginal delivery (40, 41). Infants born by vaginal delivery are exposed to the mother's bacteria at

birth, which influences the infant's gut bacteria and stimulates white blood cells and other components of the immune system (42). Studies have suggested that infants born by cesarean section are at greater risk of developing obesity and/or diabetes than those born vaginally (43–47). In a recent cross-sectional study of 8900 preschool children, the authors found that the odds of overweight were 1.35 and of obesity were 1.25 in children delivered by cesarean section (48). A similar study in a small cohort also showed that the prevalence rates of overweight and obesity were 15.6% and 12.9%, respectively, in 672 preschool children who were born by cesarean section (46). However, opposite findings are also reported (49, 50). Although more studies appear to support the association, many factors can influence the outcomes of these studies, including study population, sex of the offspring, and body weight of the mother.

Infant feeding. Infant feeding is another important factor for establishing the bacterial community in the gut, because the mother's milk is not sterile (51). Human breast milk has been recognized as a source of commensal and potential probiotic bacteria that influence the development of infant gut bacteria (52). Human breast milk contains >700 species of bacteria (53). Although human milk bacterial communities are generally complex and vary individually, the median bacterial load is $\sim 10^6$ bacterial cells/mL through time (54). Thus, it has been estimated that a lactating infant consuming 800 mL breast milk/d could ingest up to 8×10^8 bacterial cells daily, which is ~100 times higher than previous estimates, and the composition changes over the course of lactation. It appears that *Streptococci* and *Staphylococci* are predominant bacterial genera in human milk (51); both of these are also predominant in the skin microbiota. Therefore, human milk may also contain some skin bacteria. However, *Weissella*, *Leuconostoc*, *Staphylococcus*, *Streptococcus*, and *Lactococcus* are predominant in colostrum samples of infants, whereas in milk taken at 1 and 6 mo, *Veillonella*, *Leptotrichia*, and *Prevotella* increased significantly (52). Evidence suggests that the transfer of microbiota from mothers to their infants affect infant growth and development (55, 56). Milk from obese mothers has been found to contain different, less-diverse bacteria than milk from normal-weight mothers. Milk from obese mothers also showed more proinflammatory properties (56). In addition, breast milk from mothers who underwent cesarean section contained bacteria that was different from milk samples from mothers who had vaginal deliveries (53). The bacteria present in breast milk, as well as those on the mother's skin, are among the first microbes to enter the infant's body, and they could play an important role in health (53). Breast milk is also a rich source of IgA antibodies against different pathogens (57–59). However, some infant formulas containing probiotics have been shown to beneficially affect the infant immune systems and the gut microbiota.

Genetics. The number of specific bacteria found in the gut microbiota is influenced in part by the genetic makeup of the host in ways that affect host metabolism and ultimately can affect health (15). Family members have been found to have more similar microbiota communities than unrelated individuals, and the gut microbiota is more similar in monozygotic than in dizygotic twins (15). However, there are currently no genome-wide studies that have characterized specific genes and pathways that determine the composition of the gut microbiome (60), although certain genes in the immune system are associated with inflammatory bowel disease (61, 62).

Infections. Although the gut microbiota affects viral and bacterial infections, the reverse is also true (63–68). One study investigated the effect of an enteropathogenic infection with *Citrobacter rodentium* on the microbiota of mice and found that certain bacterial groups in the gut are altered in response to *C. rodentium* infection, including a reduction in the relative abundance of *Lactobacillus* (69). A human study of *Clostridium difficile* patients and asymptomatic carriers with the use of 16S ribosomal RNA gene pyrosequencing found that both had reduced microbial richness and diversity compared with healthy subjects (70). *C. difficile* infection is a typical result of severe dysbiosis in the gut microbiota (71, 72). Interestingly, transplantation of the gut microbiome from healthy donors to infected patients increased microbial richness and diversity, and it is currently applied clinically (73–76). These studies demonstrated that the characterization and diversity of the gut microbiota are altered with bacterial infections. While using a mouse model of hepatitis B virus infection, Chou et al. (63) showed that the clearance of hepatitis B virus infection requires the establishment of the gut microbiota. It is evident that the shift in the host gut microbiota affects both pathogenesis and clearance of bacterial and viral infections.

Medications. Increasing evidence suggests that many nonantibiotic drugs have an impact on the gut microbiota (77–79), including the drugs used to treat T2D (80). Likewise, the gut microbiota also affects the efficacy of drugs (81, 82). Antibiotics are commonly prescribed drugs that have saved millions of lives from infections; antibiotics also have a profound effect on the normal gut microbiota. The effect is rapid and sometimes persistent. Broad-spectrum antibiotics reduce bacterial diversity while increasing the abundance of some bacteria that can be used by opportunistic pathogens and decreasing the number of beneficial bacteria (83). The use of broad-spectrum antibiotics, such as clindamycin, in infants and young children has been found to have the longest-lasting effects on the composition of the gut microbiota (84–86). Early antibiotic exposure in neonates can lead to microbial dysbiosis, which may be a predisposing factor to inflammatory bowel disease (87). There also appears to be an interaction between antibiotic administration and diet. Studies in both mice and humans have found that the use of antibiotics early in life could promote obesity later in life, mediated by the alteration of the gut microbiota (88–90). However, there are limitations in those studies. The retrospective nature, the diversity of diet, and the heterogeneous (or not heterogeneous) population are the inevitable limitations in human studies. Most mouse studies on obesity induced by a high-fat diet with or without antibiotic treatment used only male mice because they gain more weight than female mice, whereas there is no obvious sex bias in human obesity. A recent study showed that antibiotics altered the host's gut microbiota without changing the metabolism of the hosts (91, 92). Other studies demonstrated that antibiotics reduce body weight and increase insulin sensitivity (93, 94). Berberine, the main component of a Chinese herb extract used to treat bacterial diarrhea, also has an antidiabetic effect by modulating the gut microbiota and lowering glucose and insulin resistance (95, 96). Thus, it is not clear whether antibiotics are to be blamed for the sharp rise in obesity, especially childhood obesity. It is clear, however, that the use of antibiotics has a profound effect on the alteration in the gut microbiota.

Metformin is routinely used to help with control of hyperglycemia in T2D. The drug increases the insulin sensitivity of body cells, especially fat cells, muscle cells, and hepatocytes.

Metformin also prevents the overproduction of glucose by hepatocytes. Furthermore, metformin delays glucose absorption during digestion after a meal. Interestingly, recent studies have found that the administration of metformin alters the composition of the microbiota (97–99). In a study in which obesity was induced in mice by feeding a high-fat diet, the authors found that metformin led to a greater abundance of the mucin-degrading bacterium *Akkermansia* in the obese mice than in their obese counterparts not given metformin (98). A recent human study confirmed the effect of metformin on the gut microbiota (80). It is possible that an altered gut microbiota may be the cause of the drug's common side effect in the digestive system, and the altered gut microbiota is also likely to influence the drug's antidiabetic efficacy.

Diet. The role that food-ingested bacteria play in the gut microbiome had been underestimated in the past, possibly because of methodologic limitations that have been overcome in recent years (100). Numerous studies, both in research mice and in humans, have shown that high-calorie diets contribute to obesity and T2D (101–105). However, increasing evidence suggests that the link between diet and obesity lies in the gut microbiota (106–112). Understanding that diet is an important contributing factor to the composition of the gut microbiome makes it the most logical target to manipulate. Interventional studies show that dietary changes result in substantial and rapid changes in the make-up of the gut microbiome (10, 113). Studies in mice have demonstrated that a high-fat diet (60% fat) decreases the number of bacterial species (α diversity) in the gut microbiome, and the composition of the gut microbiome between mice given a high-fat diet (unpurified) and those given a regular unpurified diet is very different (β diversity). One study in mice found that the abundance of *A. muciniphila* decreased in obese mice and those with type 2 diabetes and that prebiotic feeding of *A. muciniphila* normalized its abundance and improved metabolic profiles (14). Treatment with *A. muciniphila* also reduced fat mass, inflammation, and insulin resistance induced by a high-fat diet (14). A fiber-rich diet has been shown to be beneficial to health because it modulates the gut microbiome (114).

Studies in humans by 16S ribosomal RNA sequencing have characterized the human gut microbiota into different enterotypes distinguished by the types of bacteria present (115). Enterotypes were strongly associated with long-term diets, particularly those with protein and animal fat. Wu et al. (10) showed that protein and animal fat were associated with *Bacteroides,* whereas carbohydrates were associated with *Prevotella*. In that study, the authors also investigated controlled feeding in 10 subjects and found that the microbiome composition changed within 24 h of initiating a high-fat and low-fiber or low-fat and high-fiber diet, and remained stable during the 10-d study (10). The results suggest that diet is particularly strongly associated with enterotype partitioning. The issue then becomes whether the effects of a Western-type diet on gut microbiota composition is associated with a higher or lower incidence of disease and whether long-term dietary interventions can create stable alterations in the bacterial enterotype.

In another diet and enterotype study that involved 6 male and 4 female volunteers between the ages of 21 and 33 y with a BMI (in kg/m^2) ranging from 19 to 32, the study subjects consumed either a plant-based diet rich in grains, legumes, fruits, and vegetables, or an animal-based diet composed of meat, eggs, and cheese. Each diet was consumed ad libitum for 5 consecutive days, and the subects' fecal samples were cultured or directly analyzed by 16S ribosomal RNA gene sequencing (113). The authors showed that microbiota changes in the animal-based diet, which was high in fat, were hypothetically linked to altered fecal bile acid profiles and the growth of microorganisms capable of triggering inflammatory bowel disease (113). The results showed that a high-fat diet can alter gut bacteria and lead to dysbiosis and ultimately disease.

Yogurt and the gut microbiome. A body of evidence suggests that the gut microbiota plays an important role in obesity and chronic inflammatory disorders. Obesity and/or T2D have been considered to be chronic inflammatory disorders. As discussed earlier, the Western diet is an important contributor to obesity and T2D. Different from consumption of a high-fat diet, yogurt consumption is believed to be beneficial to health, and the mechanism of that is possibly mediated by altering the host gut microbiota in addition to other nutritional factors. Elie Metchnikoff theorized over a century ago that health could be improved by manipulating the intestinal microbiome with bacteria found in yogurt (116). Few studies had been conducted to examine the effect of yogurt consumption and the composition of the gut microbiota for decades. However, with advanced technology, especially high-throughput sequencing technology and adequate bioinformatical computation, there has been a sharp rise in the number of studies in the last 8 y or so, including clinical trials, that have investigated the effect of yogurt consumption on the change in the gut microbiota and its benefits on health (117–120). Many fermented foods, and yogurt in particular, contain up to 10^9 CFU live bacteria/g yogurt (100). Yogurt is fermented with a combination of *Lactobacillus delbrueckii* subspecies *bulgaricus* and *Streptococcus salivarius* subspecies *thermophiles*. Other bacteria, mainly *Lactobacilli* or *Bifidobacteria,* are often added to yogurt as well. In a phase-I clinical trial, Merenstein et al. (117) showed that the consumption of yogurt containing *Bifidobacterium lactis* activated an array of immune genes in the immune cells from the peripheral blood of study subjects. It is interesting that both anti-inflammatory and inflammatory genes were activated, including genes that regulate interferons and T cell differentiation. It is also interesting that there were no major changes in the composition of the gut microbiota in the subjects in the 10-d trial period (117). However, the consumption of yogurt that contained *Lactobacilli* (6×10^7 – 2.4×10^8/g yogurt) in a Japanese study showed a significant effect on alteration in the gut microbiota (120). Fermented milk products, such as yogurt, deliver a large number of lactic acid bacteria to the gastrointestinal tract. Lactic acid bacteria may modify the intestinal environment by increasing tight junctions in the gut epithelium (121) and by decreasing potentially harmful enzymes produced by the resident bacteria (122). Olivares et al. (123) reported that dietary deprivation of fermented foods caused a fall in innate immune response, including decreased phagocytosis by leukocytes and decreased immune response against infections, whereas lactic acid bacteria can reverse the impaired immune response. Childhood obesity has been a critical public health issue for at least the past 20 y. Marette and Picard-Deland (124) recently reviewed yogurt consumption and its impact on childhood obesity and cardiometabolic disease risk based on the outcome of different clinical trials. The authors concluded that yogurt not only provided important nutrients, but was also beneficial to the regulation of body weight and cardiovascular health in the children and adolescents studied. The beneficial effect was in part contributed by the change in the gut microbiota. Studies have shown that patients with obesity and/or T2D have elevated

endotoxin, such as LPS, in the circulation, which in turn activates immune cells and promotes inflammation. The increase in LPS is likely due to the change in the gut microbiota in obesity. Odamaki et al. (119) studied 420 healthy subjects and found that the consumption of yogurt containing *Bifidobacterium longum* BB536 significantly decreases enterotoxigenic *Bacteroides fragilis* in the gut microbiota. Although this study was not designed for investigating obesity and inflammation, the results support the notion that the consumption of certain types of yogurt suppresses endotoxin-producing gut bacteria, which may ameliorate endotoxinemia and inflammation. The consumption of yogurt containing *Bifidobacterium animalis* subspecies *lactis* BB-12 also led to a reduction in inflammatory cytokines and the suppression of Toll-like receptor 2 (TLR2) expression in immune cells (125). However, not all yogurt consumption has beneficial effects. Some yogurts have no effect on the gut microbiota and/or weight (126). Moreover, long-term yogurt consumption in immune-deficient patients can cause fatal *Lactobacillus rhamnosus* septicemia (127). Although yogurt consumption, in most cases, has beneficial effects on the health of hosts, we need to be careful in applying this popular biotherapy in different clinical settings.

Conclusion

Jean Anthelme Brillat-Savarin, a French lawyer and politician from the 18th century, is credited with saying, "Tell me what you eat, and I will tell you what you are" (128). Today, this statement has been contracted to, "You are what you eat." The statement is particularly applicable to the gut microbiome. Numerous studies suggest that a high-fat diet can lead to gut microbiota dysbiosis, which contributes to increased gut permeability and metabolic endotoxemia. This in turn contributes to low-grade inflammation and insulin resistance and, ultimately, obesity, diabetes, and other metabolic disorders. Although not conclusive, research strongly suggests that the consumption of probiotic bacteria such as those found in yogurt and other fermented milk products can beneficially alter the composition of the gut microbiome. The unanswered question is whether a gut signature exists that promotes intestinal inflammation, low-grade systemic inflammation, and T2D, and what the most effective methods would be, including dietary changes, to alter the gut microbiome to one that is conducive to disease prevention.

Acknowledgments

We thank Densie Webber for her editorial assistance and Susan Wong for critical reading and comments on the manuscript. The authors' responsibilities were as follows—LW: conceived of the study and wrote the manuscript; and AD: participated in the study and edited the manuscript. Both authors read and approved the final manuscript.

References

1. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. Plos Biol 2016;14:e1002533.
2. Turnbaugh PJ, Backhed 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;3:213–23.
3. Respondek F, Gerard P, Bossis M, Boschat L, Bruneau A, Rabot S, Wagner A, Martin JC. Short-chain fructo-oligosaccharides modulate intestinal microbiota and metabolic parameters of humanized gnotobiotic diet induced obesity mice. PLoS One 2013;8:e71026.
4. Rothe M, Blaut M. Evolution of the gut microbiota and the influence of diet. Benef Microbes 2013;4:31–7.
5. Zhang C, Yin A, Li H, Wang R, Wu G, Shen J, Zhang M, Wang L, Hou Y, Ouyang H, et al. Dietary modulation of gut microbiota contributes to alleviation of both genetic and simple obesity in children. EBioMedicine 2015;2:968–84.
6. Compare D, Rocco A, Sanduzzi Zamparelli M, Nardone G. The gut bacteria-driven obesity development. Dig Dis 2016;34:221–9.
7. Kong LC, Holmes BA, Cotillard A, Habi-Rachedi F, Brazeilles R, Gougis S, Gausseres N, Cani PD, Fellahi S, Bastard JP, et al. Dietary patterns differently associate with inflammation and gut microbiota in overweight and obese subjects. PLoS One 2014;9:e109434.
8. Santiago S, Sayon-Orea C, Babio N, Ruiz-Canela M, Marti A, Corella D, Estruch R, Fito M, Aros F, Ros E, et al. Yogurt consumption and abdominal obesity reversion in the PREDIMED study. Nutr Metab Cardiovasc Dis 2016;26:468–75.
9. Panahi S, Tremblay A. The potential role of yogurt in weight management and prevention of type 2 diabetes. J Am Coll Nutr 2016;35:717–31.
10. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, Bewtra M, Knights D, Walters WA, Knight R, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science 2011;334:105–8.
11. Muegge BD, Kuczynski J, Knights D, Clemente JC, Gonzalez A, Fontana L, Henrissat B, Knight R, Gordon JI. Diet drives convergence in gut microbiome functions across mammalian phylogeny and within humans. Science 2011;332:970–4.
12. Gómez-Ambrosi J, Silva C, Galofré JC, Escalada J, Santos S, Gil MJ, Valenti V, Rotellar F, Ramiíez B, Salvador J, et al. Body adiposity and type 2 diabetes: increased risk with a high body fat percentage even having a normal BMI. Obesity (Silver Spring) 2011;19:1439–44.
13. Wander PL, Boyko EJ, Leonetti DL, McNeely MJ, Kahn SE, Fujimoto WY. Change in visceral adiposity independently predicts a greater risk of developing type 2 diabetes over 10 years in Japanese Americans. Diabetes Care 2013;36:289–93.
14. Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, Guiot Y, Derrien M, Muccioli GG, Delzenne NM, et al. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. Proc Natl Acad Sci USA 2013;110:9066–71.
15. Goodrich JK, Waters JL, Poole AC, Sutter JL, Koren O, Blekhman R, Beaumont M, Van Treuren W, Knight R, Bell JT, et al. Human genetics shape the gut microbiome. Cell 2014;159:789–99.
16. 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;444:1027–31.
17. Koren O, Goodrich JK, Cullender TC, Spor A, Laitinen K, Backhed HK, Gonzalez A, Werner JJ, Angenent LT, Knight R, et al. Host remodeling of the gut microbiome and metabolic changes during pregnancy. Cell 2012;150:470–80.
18. Cani PD, Osto M, Geurts L, Everard A. Involvement of gut microbiota in the development of low-grade inflammation and type 2 diabetes associated with obesity. Gut Microbes 2012;3:279–88.
19. Cani PD, Possemiers S, Van de Wiele T, Guiot Y, Everard A, Rottier O, Geurts L, Naslain D, Neyrinck A, Lambert DM, et al. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. Gut 2009;58:1091–103.
20. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 2007;56:1761–72.
21. Liou AP, Paziuk M, Luevano JM Jr., Machineni S, Turnbaugh PJ, Kaplan LM. Conserved shifts in the gut microbiota due to gastric bypass reduce host weight and adiposity. Sci Transl Med 2013;5:178ra41.
22. Tilg H, Moschen AR. Microbiota and diabetes: an evolving relationship. Gut 2014;63:1513–21.
23. Saita D, Ferrarese R, Foglieni C, Esposito A, Canu T, Perani L, Ceresola ER, Visconti L, Burioni R, Clementi M, et al. Adaptive immunity against gut microbiota enhances apoE-mediated immune regulation and reduces atherosclerosis and western-diet-related inflammation. Sci Rep 2016;6:29353.
24. Burcelin R. Gut microbiota and immune crosstalk in metabolic disease. Mol Metab 2016;5:771–81.
25. Pomié C, Blasco-Baque V, Klopp P, Nicolas S, Waget A, Loubieres P, Azalbert V, Puel A, Lopez F, Dray C, et al. Triggering the adaptive immune system with commensal gut bacteria protects against insulin resistance and dysglycemia. Mol Metab 2016;5:392–403.

26. Clemente-Postigo M, Queipo-Ortuno MI, Murri M, Boto-Ordonez M, Perez-Martinez P, Andres-Lacueva C, Cardona F, Tinahones FJ. Endotoxin increase after fat overload is related to postprandial hypertriglyceridemia in morbidly obese patients. J Lipid Res 2012;53:973–8.
27. Hersoug LG, Moller P, Loft S. Gut microbiota-derived lipopolysaccharide uptake and trafficking to adipose tissue: implications for inflammation and obesity. Obes Rev 2016;17:297–312.
28. Meijer K, de Vos P, Priebe MG. Butyrate and other short-chain fatty acids as modulators of immunity: what relevance for health? Curr Opin Clin Nutr Metab Care 2010;13:715–21.
29. Remely M, Aumueller E, Merold C, Dworzak S, Hippe B, Zanner J, Pointner A, Brath H, Haslberger AG. Effects of short chain fatty acid producing bacteria on epigenetic regulation of FFAR3 in type 2 diabetes and obesity. Gene 2014;537:85–92.
30. Alvarez-Curto E, Milligan G. Metabolism meets immunity: the role of free fatty acid receptors in the immune system. Biochem Pharmacol 2016;114:3–13.
31. Scheithauer TP, Dallinga-Thie GM, de Vos WM, Nieuwdorp M, van Raalte DH. Causality of small and large intestinal microbiota in weight regulation and insulin resistance. Mol Metab 2016;5:759–70.
32. Nastasi C, Candela M, Bonefeld CM, Geisler C, Hansen M, Krejsgaard T, Biagi E, Andersen MH, Brigidi P, Odum N, et al. The effect of short-chain fatty acids on human monocyte-derived dendritic cells. Sci Rep 2015;5:16148.
33. Usami M, Kishimoto K, Ohata A, Miyoshi M, Aoyama M, Fueda Y, Kotani J. Butyrate and trichostatin A attenuate nuclear factor kappaB activation and tumor necrosis factor alpha secretion and increase prostaglandin E2 secretion in human peripheral blood mononuclear cells. Nutr Res 2008;28:321–8.
34. Arpaia N, Campbell C, Fan X, Dikiy S, van der Veeken J, deRoos P, Liu H, Cross JR, Pfeffer K, Coffer PJ, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature 2013;504:451–5.
35. Inatomi O, Andoh A, Kitamura K, Yasui H, Zhang Z, Fujiyama Y. Butyrate blocks interferon-gamma-inducible protein-10 release in human intestinal subepithelial myofibroblasts. J Gastroenterol 2005;40:483–9.
36. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, Zhang W, Guan Y, Shen D, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature 2012;490:55–60.
37. Karlsson FH, Tremaroli V, Nookaew I, Bergstrom G, Behre CJ, Fagerberg B, Nielsen J, Backhed F. Gut metagenome in European women with normal, impaired and diabetic glucose control. Nature 2013;498:99–103.
38. Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, Almeida M, Arumugam M, Batto JM, Kennedy S, et al. Richness of human gut microbiome correlates with metabolic markers. Nature 2013;500:541–6.
39. CDC. [cited 2017 May 17]. Available from: www.cdc.gov/nchs/fastats/delivery.htm.
40. Dominguez-Bello MG, De Jesus-Laboy KM, Shen N, Cox LM, Amir A, Gonzalez A, Bokulich NA, Song SJ, Hoashi M, Rivera-Vinas JI, et al. Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. Nat Med 2016;22:250–3.
41. Tamburini S, Shen N, Wu HC, Clemente JC. The microbiome in early life: implications for health outcomes. Nat Med 2016;22:713–22.
42. Kulas T, Bursac D, Zegarac Z, Planinic-Rados G, Hrgovic Z. New views on cesarean section, its possible complications and long-term consequences for children's health. Med Arch 2013;67:460–3.
43. Huh SY, Rifas-Shiman SL, Zera CA, Edwards JW, Oken E, Weiss ST, Gillman MW. Delivery by caesarean section and risk of obesity in preschool age children: a prospective cohort study. Arch Dis Child 2012;97:610–6.
44. Blustein J, Attina T, Liu M, Ryan AM, Cox LM, Blaser MJ, Trasande L. Association of caesarean delivery with child adiposity from age 6 weeks to 15 years. Int J Obes (Lond) 2013;37:900–6.
45. Li H, Ye R, Pei L, Ren A, Zheng X, Liu J. Caesarean delivery, caesarean delivery on maternal request and childhood overweight: a Chinese birth cohort study of 181 380 children. Pediatr Obes 2014;9:10–6.
46. Portela DS, Vieira TO, Matos SM, de Oliveira NF, Vieira GO. Maternal obesity, environmental factors, cesarean delivery and breastfeeding as determinants of overweight and obesity in children: results from a cohort. BMC Pregnancy Childbirth 2015;15:94.
47. Kuhle S, Tong OS, Woolcott CG. Association between caesarean section and childhood obesity: a systematic review and meta-analysis. Obes Rev 2015;16:295–303.
48. Rutayisire E, Wu X, Huang K, Tao S, Chen Y, Tao F. Cesarean section may increase the risk of both overweight and obesity in preschool children. BMC Pregnancy Childbirth 2016;16:338.
49. Flemming K, Woolcott CG, Allen AC, Veugelers PJ, Kuhle S. The association between caesarean section and childhood obesity revisited: a cohort study. Arch Dis Child 2013;98:526–32.
50. Pei Z, Heinrich J, Fuertes E, Flexeder C, Hoffmann B, Lehmann I, Schaaf B, von Berg A, Koletzko S; Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus Air Pollution and Genetics (LISAplus) Study Group. Cesarean delivery and risk of childhood obesity. J Pediatr 2014;164:1068–73.e2.
51. Fitzstevens JL, Smith KC, Hagadorn JI, Caimano MJ, Matson AP, Brownell EA. Systematic review of the human milk microbiota. Nutr Clin Pract 2016 Sep 27 (Epub ahead of print; DOI: 10.1177/0884533616670150).
52. Boix-Amorós A, Collado MC, Mira A. Relationship between milk microbiota, bacterial load, macronutrients, and human cells during lactation. Front Microbiol 2016;7:492.
53. Cabrera-Rubio R, Collado MC, Laitinen K, Salminen S, Isolauri E, Mira A. The human milk microbiome changes over lactation and is shaped by maternal weight and mode of delivery. Am J Clin Nutr 2012;96:544–51.
54. Obermajer T, Pogacic T. Commentary: relationship between milk microbiota, bacterial load, macronutrients, and human cells during lactation. Front Microbiol 2016;7:1281.
55. Panagos P, Matthan N, Sen S. Effects of maternal obesity on breastmilk composition and infant growth. FASEB J 2014;28(1 Suppl 247.7).
56. Panagos PG, Vishwanathan R, Penfield-Cyr A, Matthan NR, Shivappa N, Wirth MD, Hebert JR, Sen S. Breastmilk from obese mothers has pro-inflammatory properties and decreased neuroprotective factors. J Perinatol 2016;36:284–90.
57. Hanson LA, Ahlstedt S, Carlsson B, Fallstrom SP, Kaijser B, Lindblad BS, Akerlund AS, Eden CS. New knowledge in human milk immunoglobulin. Acta Paediatr Scand 1978;67:577–82.
58. Hanson LA, Soderstrom T. Human milk: defense against infection. Prog Clin Biol Res 1981;61:147–59.
59. Hanson LA, Ahlstedt S, Andersson B, Cruz JR, Dahlgren U, Fallstrom SP, Porras O, Svanborg Eden C, Soderstrom T, Wettergren B. The immune response of the mammary gland and its significance for the neonate. Ann Allergy 1984;53:576–82.
60. Blekhman R, Goodrich JK, Huang K, Sun Q, Bukowski R, Bell JT, Spector TD, Keinan A, Ley RE, Gevers D, et al. Host genetic variation impacts microbiome composition across human body sites. Genome Biol 2015;16:191.
61. Thompson-Chagoyán OC, Maldonado J, Gil A. Aetiology of inflammatory bowel disease (IBD): role of intestinal microbiota and gut-associated lymphoid tissue immune response. Clin Nutr 2005;24:339–52.
62. Rehman A, Sina C, Gavrilova O, Hasler R, Ott S, Baines JF, Schreiber S, Rosenstiel P. Nod2 is essential for temporal development of intestinal microbial communities. Gut 2011;60:1354–62.
63. Chou HH, Chien WH, Wu LL, Cheng CH, Chung CH, Horng JH, Ni YH, Tseng HT, Wu D, Lu X, et al. Age-related immune clearance of hepatitis B virus infection requires the establishment of gut microbiota. Proc Natl Acad Sci USA 2015;112:2175–80.
64. Singh P, Teal TK, Marsh TL, Tiedje JM, Mosci R, Jernigan K, Zell A, Newton DW, Salimnia H, Lephart P, et al. Intestinal microbial communities associated with acute enteric infections and disease recovery. Microbiome 2015;3:45.
65. Qin N, Zheng B, Yao J, Guo L, Zuo J, Wu L, Zhou J, Liu L, Guo J, Ni S, et al. Influence of H7N9 virus infection and associated treatment on human gut microbiota. Sci Rep 2015;5:14771.
66. Zaiss MM, Rapin A, Lebon L, Dubey LK, Mosconi I, Sarter K, Piersigilli A, Menin L, Walker AW, Rougemont J, et al. The intestinal microbiota contributes to the ability of helminths to modulate allergic inflammation. Immunity 2015;43:998–1010.
67. Yang L, Poles MA, Fisch GS, Ma Y, Nossa C, Phelan JA, Pei Z. HIV-induced immunosuppression is associated with colonization of the proximal gut by environmental bacteria. AIDS 2016;30:19–29.

68. Zilberman-Schapira G, Zmora N, Itav S, Bashiardes S, Elinav H, Elinav E. The gut microbiome in human immunodeficiency virus infection. BMC Med 2016;14:83.
69. Hoffmann C, Hill DA, Minkah N, Kirn T, Troy A, Artis D, Bushman F. Community-wide response of the gut microbiota to enteropathogenic Citrobacter rodentium infection revealed by deep sequencing. Infect Immun 2009;77:4668–78.
70. Zhang L, Dong D, Jiang C, Li Z, Wang X, Peng Y. Insight into alteration of gut microbiota in Clostridium difficile infection and asymptomatic C. difficile colonization. Anaerobe 2015;34:1–7.
71. Seekatz AM, Young VB. Clostridium difficile and the microbiota. J Clin Invest 2014;124:4182–9.
72. Blanchi J, Goret J, Megraud F. Clostridium difficile infection: a model for disruption of the gut microbiota equilibrium. Dig Dis 2016;34:217–20.
73. Youngster I, Russell GH, Pindar C, Ziv-Baran T, Sauk J, Hohmann EL. Oral, capsulized, frozen fecal microbiota transplantation for relapsing Clostridium difficile infection. JAMA 2014;312:1772–8.
74. Kelly CR, Ihunnah C, Fischer M, Khoruts A, Surawicz C, Afzali A, Aroniadis O, Barto A, Borody T, Giovanelli A, et al. Fecal microbiota transplant for treatment of Clostridium difficile infection in immunocompromised patients. Am J Gastroenterol 2014;109:1065–71.
75. Youngster I, Sauk J, Pindar C, Wilson RG, Kaplan JL, Smith MB, Alm EJ, Gevers D, Russell GH, Hohmann EL. Fecal microbiota transplant for relapsing Clostridium difficile infection using a frozen inoculum from unrelated donors: a randomized, open-label, controlled pilot study. Clin Infect Dis 2014;58:1515–22.
76. Bashan A, Gibson TE, Friedman J, Carey VJ, Weiss ST, Hohmann EL, Liu YY. Universality of human microbial dynamics. Nature 2016;534:259–62.
77. Xu X, Zhang X. Effects of cyclophosphamide on immune system and gut microbiota in mice. Microbiol Res 2015;171:97–106.
78. Imhann F, Bonder MJ, Vich Vila A, Fu J, Mujagic Z, Vork L, Tigchelaar EF, Jankipersadsing SA, Cenit MC, Harmsen HJ, et al. Proton pump inhibitors affect the gut microbiome. Gut 2016;65:740–8.
79. Devkota S. MICROBIOME. Prescription drugs obscure microbiome analyses. Science 2016;351:452–3.
80. Forslund K, Hildebrand F, Nielsen T, Falony G, Le Chatelier E, Sunagawa S, Prifti E, Vieira-Silva S, Gudmundsdottir V, Krogh Pedersen H, et al. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. Nature 2015;528:262–6.
81. Kang MJ, Kim HG, Kim JS, Oh DG, Um YJ, Seo CS, Han JW, Cho HJ, Kim GH, Jeong TC, et al. The effect of gut microbiota on drug metabolism. Expert Opin Drug Metab Toxicol 2013;9:1295–308.
82. Yoo DH, Kim IS, Van Le TK, Jung IH, Yoo HH, Kim DH. Gut microbiota-mediated drug interactions between lovastatin and antibiotics. Drug Metab Dispos 2014;42:1508–13.
83. Modi SR, Collins JJ, Relman DA. Antibiotics and the gut microbiota. J Clin Invest 2014;124:4212–8.
84. Cho I, Yamanishi S, Cox L, Methé BA, Zavadil J, Li K, Gao Z, Mahana D, Raju K, Teitler I, et al. Antibiotics in early life alter the murine colonic microbiome and adiposity. Nature 2012;488:621–6.
85. Gough EK, Moodie EE, Prendergast AJ, Johnson SM, Humphrey JH, Stoltzfus RJ, Walker AS, Trehan I, Gibb DM, Goto R, et al. The impact of antibiotics on growth in children in low and middle income countries: systematic review and meta-analysis of randomised controlled trials. BMJ 2014;348:g2267.
86. Kozyrskyj AL, Ernst P, Becker AB. Increased risk of childhood asthma from antibiotic use in early life. Chest 2007;131:1753–9.
87. Shaw SY, Blanchard JF, Bernstein CN. Association between the use of antibiotics in the first year of life and pediatric inflammatory bowel disease. Am J Gastroenterol 2010;105:2687–92.
88. Trasande L, Blustein J, Liu M, Corwin E, Cox LM, Blaser MJ. Infant antibiotic exposures and early-life body mass. Int J Obes (Lond) 2013;37:16–23.
89. Cox LM, Yamanishi S, Sohn J, Alekseyenko AV, Leung JM, Cho I, Kim SG, Li H, Gao Z, Mahana D, et al. Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. Cell 2014;158:705–21.
90. Mahana D, Trent CM, Kurtz ZD, Bokulich NA, Battaglia T, Chung J, Muller CL, Li H, Bonneau RA, Blaser MJ. Antibiotic perturbation of the murine gut microbiome enhances the adiposity, insulin resistance, and liver disease associated with high-fat diet. Genome Med 2016;8:48.
91. Fujisaka S, Ussar S, Clish C, Devkota S, Dreyfuss JM, Sakaguchi M, Soto M, Konishi M, Softic S, Altindis E, et al. Antibiotic effects on gut microbiota and metabolism are host dependent. J Clin Invest 2016;126:4430–43.
92. Reijnders D, Goossens GH, Hermes GD, Neis EP, van der Beek CM, Most J, Holst JJ, Lenaerts K, Kootte RS, Nieuwdorp M, et al. Effects of gut microbiota manipulation by antibiotics on host metabolism in obese humans: a randomized double-blind placebo-controlled trial. Cell Metab 2016;24:63–74.
93. Membrez M, Blancher F, Jaquet M, Bibiloni R, Cani PD, Burcelin RG, Corthesy I, Mace K, Chou CJ. Gut microbiota modulation with norfloxacin and ampicillin enhances glucose tolerance in mice. FASEB J 2008;22:2416–26.
94. Chou CJ, Membrez M, Blancher F. Gut decontamination with norfloxacin and ampicillin enhances insulin sensitivity in mice. Nestle Nutr Workshop Ser Pediatr Program 2008;62:127–37, discussion 37–40.
95. Han J, Lin H, Huang W. Modulating gut microbiota as an antidiabetic mechanism of berberine. Med Sci Monit 2011;17:RA164–7.
96. Chang W, Chen L, Hatch GM. Berberine as a therapy for type 2 diabetes and its complications: from mechanism of action to clinical studies. Biochem Cell Biol 2015;93:479–86.
97. Lee H, Ko G. Effect of metformin on metabolic improvement and gut microbiota. Appl Environ Microbiol 2014;80:5935–43.
98. Shin NR, Lee JC, Lee HY, Kim MS, Whon TW, Lee MS, Bae JW. An increase in the Akkermansia spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. Gut 2014;63:727–35.
99. Forslund K, Hildebrand F, Nielsen T, Falony G, Le Chatelier E, Sunagawa S, Prifti E, Vieira-Silva S, Gudmundsdottir V, Pedersen HK, et al. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. Nature 2015;528:262–6.
100. Veiga P, Pons N, Agrawal A, Oozeer R, Guyonnet D, Brazeilles R, Faurie JM, van Hylckama Vlieg JE, Houghton LA, Whorwell PJ, et al. Changes of the human gut microbiome induced by a fermented milk product. Sci Rep 2014;4:6328.
101. Field AE, Willett WC, Lissner L, Colditz GA. Dietary fat and weight gain among women in the Nurses' Health Study. Obesity (Silver Spring) 2007;15:967–76.
102. Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, Golan R, Fraser D, Bolotin A, Vardi H, et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med 2008;359:229–41.
103. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, McManus K, Champagne CM, Bishop LM, Laranjo N, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009;360:859–73.
104. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med 2011;364:2392–404.
105. Winzell MS, Ahren B. The high-fat diet-fed mouse: a model for studying mechanisms and treatment of impaired glucose tolerance and type 2 diabetes. Diabetes 2004;53 Suppl 3:S215–9.
106. Musso G, Gambino R, Cassader M. Obesity, diabetes, and gut microbiota: the hygiene hypothesis expanded? Diabetes Care 2010;33:2277–84.
107. DiBaise KK, Frank DN, Mathur R. Impact of the gut microbiota on the development of obesity: current concepts. Am J Gastroenterol Suppl 2012;1:22–27.
108. 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;57:1470–81.
109. 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 USA 2010;107:14691–6.
110. Scott KP, Gratz SW, Sheridan PO, Flint HJ, Duncan SH. The influence of diet on the gut microbiota. Pharmacol Res 2013;69:52–60.
111. Graf D, Di Cagno R, Fak F, Flint HJ, Nyman M, Saarela M, Watzl B. Contribution of diet to the composition of the human gut microbiota. Microb Ecol Health Dis 2015;26:26164.
112. Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, Sonnenburg JL. Diet-induced extinctions in the gut microbiota compound over generations. Nature 2016;529:212–5.

113. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature 2014;505:559–63.
114. Koh A, De Vadder F, Kovatcheva-Datchary P, Backhed F. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell 2016;165:1332–45.
115. Arumugam M, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, Fernandes GR, Tap J, Bruls T, Batto JM, et al. Enterotypes of the human gut microbiome. Nature 2011;473:174–80.
116. Mackowiak PA. Recycling metchnikoff: probiotics, the intestinal microbiome and the quest for long life. Front Public Health 2013;1:52.
117. Merenstein DJ, Tan TP, Molokin A, Smith KH, Roberts RF, Shara NM, Mete M, Sanders ME, Solano-Aguilar G. Safety of Bifidobacterium animalis subsp. lactis (B. lactis) strain BB-12-supplemented yogurt in healthy adults on antibiotics: a phase I safety study. Gut Microbes 2015;6:66–77.
118. Granata M, Brandi G, Borsari A, Gasbarri R, Gioia DD. Synbiotic yogurt consumption by healthy adults and the elderly: the fate of bifidobacteria and LGG probiotic strain. Int J Food Sci Nutr 2013;64:162–8.
119. Odamaki T, Sugahara H, Yonezawa S, Yaeshima T, Iwatsuki K, Tanabe S, Tominaga T, Togashi H, Benno Y, Xiao JZ. Effect of the oral intake of yogurt containing Bifidobacterium longum BB536 on the cell numbers of enterotoxigenic Bacteroides fragilis in microbiota. Anaerobe 2012;18:14–8.
120. Uyeno Y, Sekiguchi Y, Kamagata Y. Impact of consumption of probiotic lactobacilli-containing yogurt on microbial composition in human feces. Int J Food Microbiol 2008;122:16–22.
121. Lim SM, Jeong JJ, Woo KH, Han MJ, Kim DH. Lactobacillus sakei OK67 ameliorates high-fat diet-induced blood glucose intolerance and obesity in mice by inhibiting gut microbiota lipopolysaccharide production and inducing colon tight junction protein expression. Nutr Res 2016;36:337–48.
122. Alvaro E, Andrieux C, Rochet V, Rigottier-Gois L, Lepercq P, Sutren M, Galan P, Duval Y, Juste C, Dore J. Composition and metabolism of the intestinal microbiota in consumers and non-consumers of yogurt. Br J Nutr 2007;97:126–33.
123. Olivares M, Paz Diaz-Ropero M, Gomez N, Sierra S, Lara-Villoslada F, Martin R, Miguel Rodriguez J, Xaus J. Dietary deprivation of fermented foods causes a fall in innate immune response. Lactic acid bacteria can counteract the immunological effect of this deprivation. J Dairy Res 2006;73:492–8.
124. Marette A, Picard-Deland E. Yogurt consumption and impact on health: focus on children and cardiometabolic risk. Am J Clin Nutr 2014; 99(5 Suppl):1243S–7S.
125. Meng H, Ba Z, Lee Y, Peng J, Lin J, Fleming JA, Furumoto EJ, Roberts RF, Kris-Etherton PM, Rogers CJ. Consumption of Bifidobacterium animalis subsp. lactis BB-12 in yogurt reduced expression of TLR-2 on peripheral blood-derived monocytes and pro-inflammatory cytokine secretion in young adults. Eur J Nutr 2015 Nov 30 (Epub ahead of print; DOI: 10.1007/s00394-015-1109-5).
126. Sayón-Orea C, Bes-Rastrollo M, Marti A, Pimenta AM, Martin-Calvo N, Martinez-Gonzalez MA. Association between yogurt consumption and the risk of metabolic syndrome over 6 years in the SUN study. BMC Public Health 2015;15:170.
127. MacGregor G, Smith AJ, Thakker B, Kinsella J. Yoghurt biotherapy: contraindicated in immunosuppressed patients? Postgrad Med J 2002;78:366–7.
128. Brillat-Savarin JA. La physiologie du gout. [The physiology of taste.] 1848. Bibiotheque Nationale de France [French National Library.] [cited 2017 May 17]. Available from: http://gallica.bnf.fr/ark:/12148/bpt6k1063697. (in French).