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The Role of Supplemental Complex Dietary Carbohydrates and Gut Microbiota in Promoting Cardiometabolic and Immunological Health in Obesity: Lessons from Healthy Non-Obese Individuals

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Dietary supplementation with complex carbohydrates is known to alter the composition of gut microbiota, and optimal implementation of the use of these so called “prebiotics” could be of great potential in prevention and possibly treatment of obesity and associated cardiometabolic and inflammatory diseases *via* changes in the gut microbiota. An alternative to this “microbiocentric view” is the idea that health-promoting effects of certain complex carbohydrates reside in the host, and could secondarily affect the diversity and abundance of gut microbiota. To circumvent this potential interpretational problem, we aimed at providing an overview about whether and how dietary supplementation of different complex carbohydrates changes the gut microbiome in healthy non-obese individuals. We then reviewed whether the reported changes in gut bacterial members found to be established by complex carbohydrates would benefit or harm the cardiometabolic and immunological health of the host taking into account the alterations in the microbiome composition and abundance known to be associated with obesity and its associated disorders. By combining these research areas, we aimed to give a better insight into the potential of (foods containing) complex carbohydrates in the treatment and prevention of above-mentioned diseases. We conclude that supplemental complex carbohydrates that increase Bifidobacteria and Lactobacilli, without increasing the deleterious *Bacteroides*, are most likely promoting cardiometabolic and immunological health in obese subjects. Because certain complex carbohydrates also affect the host’s immunity directly, it is likely that host–microbiome interactions in determination of health and disease characteristics are indeed bidirectional. Overall, this review article shows that whereas it is relatively clear in which direction supplemental fermentable carbohydrates can alter the gut microbiome, the relevance of these changes regarding health remains controversial. Future research should take into account the different causes of obesity and its adverse health conditions, which in turn have drastic effects on the microbiome balance.

Keywords: gut microbiota, prebiotics, obesity, cardiometabolic, inflammation, metabolic syndrome

INTRODUCTION

It is now well recognized that the bacteria living in our gut play an important role in the development and maintenance of the innate and adaptive immune system (1, 2) as well as the fermentation of low-, or non-digestible dietary carbohydrates (3–5). While the human intestinal microbiome is dominated by the phyla Bacteroidetes and Firmicutes (representing more than 90% of the total bacterial population) and with Proteobacteria, Verrucomicrobia, Actinobacteria, Fusobacteria, and Cyanobacteria generally being present in minor proportions (6), the exact composition can vary widely between individuals. Contributing factors to this variation are (1) the host's genetic make-up (7), (2) early-life environmental conditions under which the host was born and nourished (i.e., cesarean section versus vaginal delivery, breast milk versus infant formula feeding, perinatal stress) (8–11), (3) the type and intensity of antibiotic treatment the host has undergone (12), and (4) the microbial composition that appears to change slowly with age (13–15). Whereas the acquired microbial abundance and diversity was initially thought to be relatively stable and withstand sudden perturbations (16, 17), it was found more recently that changes in the diet can affect microbial composition *after* its initial establishment (18–20). For diet-driven alterations of gut microbial composition particularly the type and proportion of complex indigestible carbohydrates that reach the colon turn out to be of great importance (18, 19, 21–24). The digestibility of dietary carbohydrates depends, among others, on structural properties of the carbohydrate, such as the degree of polymerization (DP) and branching. In general, carbohydrates with a low DP can rapidly be absorbed or digested in the small intestine. The larger oligosaccharides and polysaccharides have a variety of branching and polymerizations, which render them more difficult for host enzymes in the small intestine to be hydrolyzed (25). Carbohydrates with higher DP's will, therefore, enter the large bowel, where they will be fermented by bacteria, which are highest in abundance in this part of the gastrointestinal tract (3, 4). Another factor for digestibility of polysaccharides is of course whether or not the digestive enzymes for specific cleavages are present in the digestive tract of an animal. For example, humans do not have the enzymes required to cleave the relevant linkages in, e.g., cellulose and beta-glucan, which render them indigestible and therefore reach the bowel where they can be fermented.

Besides playing a role in fermentation and immune functioning, the diversity and abundance of gut microbiota also plays a role in regulation of body weight and energy balance (26–28). This notion started with the discovery of Turnbaugh and colleagues in 2006 showing that transplantation of gut microbiota of genetically obese *ob/ob* mice into the gut of germ-free mice resulted in greater weight gain of the receiving animals than animals that received the microbiota of their lean counterparts (29). Comparable studies have since then been done, all adding to the conclusion that obesity risk, as well as related cardiometabolic and inflammatory derangements may rely, at least in part, on gut microbiota (30–34). Because of the apparent fact that the relative abundance and diversity of gut

microbiota is related to the host's health and/or disease status (20, 35), the possibility to affect the composition of intestinal microbiota by complex indigestible carbohydrates—so-called “prebiotics”—and subsequently improve the health of the host (36) has gained a lot of interest over the past few years.

Several randomized-controlled studies have been conducted over the years to elucidate the effects of supplementation of indigestible carbohydrates on several health indices in (1) healthy volunteers (37, 38), (2) subjects diagnosed with metabolic syndrome (MetS), type-2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and/or inflammatory bowel disease (IBD), and (3) subjects at risk of having these diseases because of the fact that they are overweight or obese (39–43). It is difficult to evaluate the role of the microbiome in the reported health effect of supplemental carbohydrates. It was for example recently shown that a polymer of fructose molecules (i.e., β 2 \rightarrow 1-fructan) has a direct modulatory effects on immunity, which in turn affects the colonizing microbiota. Of note, the effects of the tested carbohydrates were dependent on the chain length of the β 2 \rightarrow 1-fructans type polymer (44). These results suggest that health-promoting effects of certain complex carbohydrates are actually residing in the host, and could secondarily affect the diversity and abundance of gut microbiota, thereby providing an alternative to the current “microbiocentric” view on health and disease. For this reason, we aimed at providing an overview, based on human trials, about whether and how dietary supplementation of different (potentially prebiotic) carbohydrates changes the gut microbiome in healthy individuals. We then reviewed whether the reported changes in gut bacterial members found to be established by prebiotic carbohydrates would benefit or harm the host's health taking into account the alterations in the microbiome composition and abundance known to be associated with obesity, CVD, T2DM, and/or IBD. By combining these research areas, we aimed to give a better insight into the potential of (foods containing) prebiotic carbohydrates in the treatment and prevention of above-mentioned diseases.

HOW CAN PREBIOTICS AFFECT THE HOST HEALTH THROUGH GUT MICROBIOTA

Before discussing the studies investigating the health effects of supplemental carbohydrate on the microbiome, we first discuss a few potential mechanisms how these health effects can be substantiated. Microbial fermentation can convert the carbohydrate residues in, among others, short-chain fatty acids (SCFAs). These SCFAs comprise acetate, propionate, and butyrate (5) and can account for up to 10% of the energy absorbed from the diet, benefiting the microbiota as well as the host. The SCFAs acetate and propionate are mainly produced by Bacteroidetes, and butyrate is the primary product of the Firmicutes bacteria (45, 46). Besides the delivery of extra fuels from fermentation of complex carbohydrates that escape digestion, the host also benefits from these microbial fuels in other ways. For example, through their effects on gastric motility and intestinal transit

stimulation, SCFAs stimulate serotonin release as reported in an *in vitro* colonic mucosal system (47). Locally butyrate functions as an important energy source for colonocytes, and this interaction contributes to a reduction in the risk of colorectal cancer (4, 48). Butyrate also affects fuel fluxes and energy balance by stimulating leptin and glucagon-like peptide 1 amide (49). Butyrate has even been reported to elicit antidepressant effects in the mouse (50) and to stimulate social behavior and facilitating long-term memory consolidation and neuroprotection/regeneration (51, 52). Importantly, SCFAs appear to also reduce the risk of CVD, IBD, T2DM, and diet-induced obesity (4). The processes underlying the aforementioned effects of SCFAs are subject to intense investigation, and several interesting leads have been elucidated.

Besides fermenting poorly or indigestible carbohydrates, resulting in among others increased levels of SCFAs, the gut microbiota can also modulate the uptake and deposition of dietary lipids by affecting the activity of the lipoprotein lipase in adipose tissues, an enzyme that promotes fatty acid uptake into adipocytes (33), and by affecting the synthesis of colipases, which are involved in the hydrolysis of dietary lipids (53). Endocrine (cortisol, gut hormones), immune (cytokines), and neural (vagus and enteric nervous system) routes have been suggested to play a role in the communication between gut microbiota (e.g., *via* the metabolites it produces upon digestion of prebiotics) and peripheral organs and the brain (54–57). Although underlying mechanisms are far from understood, it is likely that the communication between the central nervous system and gut microbiota functions bidirectionally (54, 57–59).

ASSESSING EFFECTS OF PREBIOTICS IN HEALTHY SUBJECTS AND RELEVANCE FOR THOSE WITH CARDIOMETABOLIC/INFLAMMATORY DISEASES AND OBESITY

Food ingredients with prebiotic properties are often oligosaccharides and polysaccharides (Table 1) (25, 60–63), such as

inulins, pectins, and β -glucan compounds. Most prebiotics are already included in the diet as they are naturally present in several types of food [e.g., legumes, wheat, rye, and onions (64, 65)], and are, therefore, considered to be part of a diet that contributes to the maintenance of sustainable health (66–68). Of note, although usually ignored in research reports, the (excessive) use of prebiotics could eventually lead to undesirable effects like excessive flatus, borborygmi, abdominal pain, and diarrhea (69, 70). To assess the effect of dietary supplemental (potentially prebiotic) carbohydrates on gut microbiota composition, a literature search was performed in PubMed and Google Scholar, as shown in Table 2. The initial literature search was performed in January 2016 and was revised in January 2017. The search term always included “gut microbiota OR microbiota,” which was then combined with the terms “composition,” “prebiotic,” and “polysaccharides” or oligosaccharides. Search results were then screened for clinical trials in healthy humans, which eventually narrowed down the results to 20 clinical studies. All studies included daily supplementation of (potentially prebiotic) carbohydrates for a minimum of 2 weeks and for a maximum of 10 weeks. We first subdivided these trails on the basis of the type of supplemental carbohydrates that were used in the different trials, and we then assessed the direction of change in the different bacterial phyla and/or genera. All studies used freshly voided fecal samples, and subsequently, a variety of methodologies were used to determine microbiota composition, including Florescent *in situ* hybridization (FISH), quantitative (q)PCR, 16S ribosomal RNA sequencing, and whole-genome shotgun sequencing.

Traditionally, the composition of the microbiota was analyzed by using culturing techniques, which select for specific bacterial populations based on their metabolic requirements. These techniques, however, are clearly only applicable to the culturable fraction of the members (i.e., which is only true for about 20–50%) and has limited resolution (6, 71, 72). Culture-independent techniques that are frequently used nowadays include 16S ribosomal RNA-based techniques such as qPCR and illumina (deep) sequencing. Last, whole-genome shotgun

TABLE 1 | Overview of the major dietary carbohydrates.

Class (DP)	Subgroup	Principal components	Physiology	Possible source
Sugars (1–2)	Monosaccharides	Glucose, fructose, galactose	Absorbed	Fruits
	Disaccharides	Sucrose, maltose, trehalose Lactose	Absorbed Absorbed/fermented	Sugar cane/beets Dairy
	Polyols (sugar alcohols)	Sorbitol, mannitol, lactitol, xylitol, erythritol, isomalt, maltitol	Absorbed/fermented	Synthetic
Oligosaccharides (3–9) (short-chain carbohydrates)	Malto-oligosaccharides (α -glucans)	Maltodextrins	Digested/fermented	Glucose syrups
	Non- α -glucan oligosaccharides	Raffinose, stachyose Fructo-oligosaccharides, galacto-oligosaccharides Polydextrose Inulin	Fermented	Beans, peas, soya Enzymatic synthesis Synthetic Wheat, onion, banana
	Polysaccharides (≥ 10)	Starch (α -glucans) Non-starch polysaccharides	Digested/fermented Fermented	Potatoes Cell wall plant cells (fruits/vegetables)

DP, degree of polymerization or number of monomeric (single sugar) units.

Table based on Cummings and Stephan (25), Cummings et al. (62), and Roberfroid (63).

TABLE 2 | Overview of search terms and the number of hits in PubMed.

Search term	Total	Clinical trials
((gut microbiota) OR microbiota) AND carbohydrate	2,465	187
((gut microbiota) OR microbiota) AND prebiotic	1,077	106
((gut microbiota) OR microbiota) AND composition AND prebiotic	391	43
((gut microbiota) OR microbiota) AND composition AND prebiotic AND polysaccharides	232	36
((gut microbiota) OR microbiota) AND composition AND prebiotic AND oligosaccharides	106	18
((gut microbiota) OR microbiota) AND composition AND prebiotic AND polysaccharides AND human	190	35
((gut microbiota) OR microbiota) AND composition AND prebiotic AND oligosaccharides AND human	79	18

Search terms were combined to find studies assessing the effect of potentially prebiotic carbohydrates on gut microbiota composition. Studies referred to in review articles published on the topic were also included in some cases. Only studies supplementing the diet of healthy individuals were included. Second, the microbiota genera that were found to be altered upon carbohydrate supplementation were then further investigated in a second literature search in which the name of the genera was combined with the search terms "correlation," "health," "obesity," "diabetes," "inflammation," "cardio(-) metabolic disease," and "cardio(-)vascular disease." Again, studies referred to in review articles published on the topic were also included in some cases. Here, animal studies were included, in addition to human studies, because they can often be instrumental in explaining the health effects of the genera in the (sometimes scarce) human studies.

sequencing does not only sequence a marker gene such as the 16S ribosomal RNA but also examines the whole-genome in which it provides more detailed information about the functional and metabolic potential of the community (71, 72). An overview of the trials that were found by using the (combined) search terms (Table 2) is presented in Table 3 (24, 64, 73–91). We subsequently characterized the effects of the different supplemental carbohydrates per phylum, and for each of them discussed the feasibility of treating subjects diagnosed with obesity, cardiometabolic, and/or inflammatory diseases with any of these prebiotics.

BACTEROIDES

Most studies demonstrated an increase in *Bacteroides* abundance by a variety of supplemental disaccharides, oligosaccharides, and polysaccharides, with doses ranging between 2.2 and 45.6 g per day, and duration between 2 and 10 weeks of treatment (73, 75, 76). Supplemental carbohydrates that reduced *Bacteroides* were a very long-chain inulin given in a dose of 10 g/day over the course of 3 weeks (84) and soluble corn fiber given in a dose of 20 g/day over 4 weeks (89). Some studies, however, showed results that may be explained by other means than the supplemental carbohydrate per se. For example, the study by Walton et al. (76) used a relatively low dose of arabinoxylan-oligosaccharides in bread with potential effects on *Bacteroides*, suggesting that its supplementation has a high feasibility for long-term human application. However, in that study, the increase in *Bacteroides* was also observed in the control group, presumably due to the higher total amount of (complex) carbohydrates present in the diet due to the control bread (76). Therefore, it is unknown whether

arabinoxylan-oligosaccharides specifically are able to increase *Bacteroides* at this dose. The *Bacteroides*-increasing effect of 5.5 g per day by the mixture of galacto-oligosaccharides in the study by Vulevic et al. (75) was, therefore, more convincing.

If most prebiotics increase *Bacteroides* abundance (with the exception of very long-chain inulin), it is of interest to know whether this direction would be either beneficial or detrimental for subjects with obesity and cardiometabolic and/or inflammatory diseases. Studies investigating the association between *Bacteroides* and obesity and cardiometabolic health are abundant but highly contradicting (5, 92). Several studies have reported changes at the phylum level in relation to obesity, with a low abundance of Bacteroidetes relative to the proportion of Firmicutes in obese individuals (93, 94), as well as in genetically obese (ob/ob) mice (29, 95). For instance, a study by Armougom et al. (96) in 20 normal weight and 20 obese French individuals confirmed the decrease in Bacteroidetes abundance in obese individuals, accompanied by an increase of the genus *Lactobacillus*, belonging to the phylum Firmicutes. Studies by Turnbaugh et al. (97) and Furet et al. (98) only detected a reduced representation of Bacteroidetes, like *Bacteroides* and *Prevotella*, without changes in Firmicutes abundance in obese individuals. However, contradicting results were found in a study by Schwartz et al. (99), where in overweight and obese subjects the ratio of Firmicutes to Bacteroidetes was increased in favor of the Bacteroidetes. Other findings even suggest that the proportions of Bacteroidetes and Firmicutes do not have a major relation with human obesity at all (100). At the genus level, a study investigating gut microbiota in pregnant women revealed a positive correlation between BMI before pregnancy and the abundance of *Bacteroides*. The high abundance of *Bacteroides* was also associated with excessive weight gain during pregnancy (101). Due to the higher number of studies reporting a decrease in Bacteroidetes in obesity, combined with the fact that some of these studies used 16S rRNA sequencing, which is more accurate than qPCR and FISH used in the contradicting studies, it is more likely that obesity is associated with a decrease in Bacteroidetes. However, at this point a causal role of Bacteroidetes or of the genus *Bacteroides* in obesity has not been convincingly proven.

One possible explanation for the above-mentioned indecisive link between *Bacteroides* and obesity is that it is not obesity *per se*, but the presence of adverse health conditions that are part of MetS that are closely associated with the abundance of *Bacteroides*. As mentioned before, MetS is often seen in obese individuals and is a risk factor for the development of cardiometabolic/inflammatory diseases (102). In a study by Haro et al. (22) on 239 volunteers of which 138 met the criteria for MetS, the relative abundance of *Bacteroides* indeed turned out to be higher in the MetS subjects than in subjects without MetS. The study did not report a relation between *Bacteroides* abundance and BMI or magnitude of obesity. Only a negative relation between waist circumference and the relative abundance of *Bacteroides thetaiotaomicron* was observed ($R = 0.162$, $P = 0.022$). It must be noted that the non-MetS group in this trial did not include healthy individuals, but individuals with a history of coronary heart disease that were involved in another clinical trial at the time (23). Furthermore,

TABLE 3 | Overview of the studies in which the diet of healthy subjects was supplemented with prebiotic carbohydrates.

Carbohydrate group	Supplement	Treatment	Affected microbiota	-/+	N ^a	Analysis	Reference
Disaccharide	Maltitol	45.6 g/day—2 weeks	<i>Bifidobacterium</i> <i>Bacteroides</i> Lactobacilli Eubacteria <i>Atopobium</i>	+ + + +	40	Florescent <i>in situ</i> hybridization (FISH)	Beards et al. (73)
Oligosaccharide	Fermented soybean milk (containing raffinose/stachyose)	11.7 g raffinose + 53.5 g stachyose/day—2 weeks	<i>Bifidobacterium</i> Lactobacilli Clostridia	+ + -	10	Plate count technique	Inoguchi et al. (74)
	Xylo-oligosaccharide	1.4 g/2.8 g/day—8 weeks	<i>Bifidobacterium</i>	+	32	bTE-FAP/16S rRNA gene sequencing	Finegold et al. (64)
	Xylo-oligosaccharide	2.8 g/day—8 weeks	<i>Bacteroides fragilis</i>	+	32	bTE-FAP/16S rRNA gene sequencing	Finegold et al. (64)
	Stachyose-enriched α-galacto-oligosaccharides	5 g/day—2 weeks	Bifidobacteria Lactobacilli <i>Clostridium perfringens</i>	+ + -	50	Plate count technique	Li et al. (91)
	Galacto-oligosaccharide mixture: B-GOS	5.5 g/day—10 weeks	<i>Bacteroides</i> <i>Bifidobacterium</i>	+ +	45	FISH	Vulevic et al. (75)
	Arabinoxylan-oligosaccharides	2.2 g/day—3 weeks	Lactobacilli <i>Bacteroides</i>	+ +	44	FISH	Walton et al. (76)
	Arabinoxylan-oligosaccharides	10 g/day—3 weeks	<i>Bifidobacterium</i>	+	20	qRT-PCR	Cloetens et al. (77)
	Galacto-oligosaccharides	8 g/day—3 weeks	<i>Bifidobacterium</i>	+	39	qPCR	Walton et al. (78)
	Xylooligosaccharide	5 g/day—4 weeks	<i>Bifidobacterium</i>	+	60	qPCR	Lecerf et al. (79)
	Xylo-oligosaccharide	2 g/day—8 weeks	<i>Catenibacterium</i> <i>Blautia</i> <i>Eubacterium</i> <i>Subdoligranulum</i> <i>Collinsella</i> <i>Streptococcus</i>	- - - - - -	7	qPCR	Yang et al. (90)
Polysaccharide	Short-chain fructo-oligosaccharides + <i>Sideritis euboica</i> extract	5 g/day—30 days	<i>Bifidobacterium</i>	+	52	Plate count technique	Mitsou et al. (80)
	Resistant maltodextrin	50 g/day—24 days	<i>Bifidobacterium</i>	+	14	16S rRNA approach (DGGE-based profiling, qPCR, FISH, 454-titanium tech.-based 16S rRNA sequencing)	Baer et al. (81)
	Resistant starch type 2	33 g/day—3 weeks	<i>Eubacterium rectale</i> <i>Ruminococcus bromii</i>	+ +	13	Selective culture, PCR-DGGE, qRT-PCR	Martínez et al. (82)
Resistant starch type 4	33 g/day—3 weeks	Actinobacteria (<i>Bifidobacterium</i>) Bacteroidetes (<i>Parabacteroides</i>) Firmicutes (Ruminococcaceae)	+ + -	13	Selective culture, PCR-DGGE, qRT-PCR	Martínez et al. (82)	
Resistant starch + maltitol blend	45.6 g/day—2 weeks	<i>Bifidobacterium</i> <i>Bacteroides</i> Lactobacilli Eubacteria	+ + + +	40	FISH	Beards et al. (73)	
Agave inulin	5.0/7.5 g/day—3 weeks	Actinobacteria <i>Bifidobacterium</i> <i>Desulfovibrio</i>	+ + -	29	16S Illumina sequencing	Holscher et al. (83)	
Very long-chain inulin	10 g/day—3 weeks	<i>Bifidobacterium</i> Lactobacilli-enterococci <i>Atopobium</i> <i>Bacteroides-Prevotella</i>	+ + + -	32	FISH	Costabile et al. (84)	

(Continued)

TABLE 3 | Continued

Carbohydrate group	Supplement	Treatment	Affected microbiota	-/+	N ^a	Analysis	Reference
	Inulin	10 g/day—16 days	<i>Bifidobacterium adolescentis</i> <i>Faecalibacterium prausnitzii</i>	+ +	12	qRT-PCR	Ramirez-Farias et al. (85)
	Inulin/partially hydrolyzed guar gum	15 g/day—3 weeks	<i>Clostridium</i> sp.	-	60	RT-PCR + gas chromatography	Linetzky Waitzberg et al. (86)
	Soluble corn fiber	6 g/day—2 weeks	<i>Bifidobacterium</i>	+	24	FISH	Costabile et al. (24)
	Soluble corn fiber	12 g/day—2 weeks	<i>C. histolyticum</i> / <i>C. perfringens</i>	-	24	FISH	Costabile et al. (24)
	Soluble corn fiber	21 g/day—3 weeks	<i>Firmicutes</i> Bacteroidetes	- +	21	Whole-genome shotgun 454 pyrosequencing FLX-titanium	Holscher et al. (87)
	Soluble corn fiber	10 g/day—4 weeks	<i>Parabacteroides</i>	+	27	16S Illumina sequencing	Whisner et al. (89)
	Soluble corn fiber	20 g/day—4 weeks	<i>Bacteroides</i> <i>Parabacteroides</i> <i>Lachnospira</i>	- + -	27	16S Illumina sequencing	Whisner et al. (89)
	Soluble corn fiber	21 g/day—3 weeks	<i>Bifidobacterium</i> Actinobacteria Proteobacteria	+ - +	20	454 pyrosequencing FLX-titanium	Hooda et al. (88)

The studies investigated the subsequent changes in gut microbiota composition.

^aTotal number of volunteers, divided over study groups.

a higher abundance of *Bacteroides* has been reported to be associated with impaired glucose tolerance in T2DM patients as well (103). Finally, *Bacteroides* abundance was higher in individuals with several disease characteristics (but not necessarily marked as MetS) rendering them more at risk to develop pre-diabetes, T2DM, and CVD (104). While there are also studies showing no clear link between *Bacteroides* abundance and cardiometabolic diseases (105, 106), the available data on MetS and *Bacteroides* abundance are exciting enough to emphasize on research investigating causal mechanisms between the two. It may for instance be speculated that obese individuals are more prone to develop MetS due to an already existing high abundance in *Bacteroides*, or alternatively, it could be that MetS in the host causes changes in *Bacteroides* abundance bidirectionally.

A pathological feature that is commonly observed in a wide range of chronic conditions such as MetS, non-alcoholic fatty liver disease, CVD, and T2DM is a persistent low-grade inflammatory state, characterized by increased levels of inflammatory cytokines (107–110). It is possible that the gut microbial imbalance and the permeability of the intestinal barrier contribute to this low-grade systemic inflammation, which may then be related to the onset and progression of cardiometabolic derangements (111). However, it could also be the other way around, being that the state of inflammation is the cause of the microbial dysbiosis. Interestingly, also higher abundances of *Bacteroides* species were found in patients with IBD compared to healthy individuals (112, 113), suggesting that a disturbance of the gut microbial balance in favor of *Bacteroides* is linked to inflammation of the GI tract. IBD is relatively frequently associated with MetS (114, 115), which adds to the possibility that *Bacteroides* abundance and disturbances in the inflammatory system are linked. The direction of this relation is currently unclear.

CLOSTRIDIUM

Clostridium levels were reported to decrease by the supplementation of 65.2 g of raffinose/stachyose for 2 weeks (74), by 15 g of a mixture of inulin and partially hydrolyzed guar gum during a 3-week supplemental intervention study (86), or by supplementation with 5 g of α -galacto-oligosaccharides for 2 weeks (91). Of the previous studies, the latter has a highest feasibility due to the lower dose. Furthermore, it must be noted that the study supplementing with a mixture of inulin and partially hydrolyzed guar gum investigated the matter in constipated women, leading to an increased transit time wherefore the effect could be different in individuals without constipation.

The decrease of *Clostridium* abundance has been linked to decreased severity of T2DM and obesity (101, 105, 116). For example, in the studies by Karlsson et al. (105) and Larsen et al. (116), lower levels of the genus *Clostridium* and the class Clostridia, respectively, were found in T2DM patients compared to healthy controls. In addition, an inverse relation between *Clostridium* genus abundance and high-sensitivity C-reactive protein (hs-CRP), an inflammatory marker associated with the risk of CVD (26), has been observed (117). This suggests a potentially beneficial link between abundance of the *Clostridium* genus and metabolic health. Moreover, the expansion of Clostridia species belonging to *Clostridium* cluster IV and XIVa after the conventionalization of germ-free mice coincided with increasing concentrations of SCFAs, such as acetate, propionate, and butyrate (118), of which the beneficial effects have been discussed before. These latter studies all describe beneficial effects of the presence of specific *Clostridium* species. However, studies reporting higher T2DM and CVD risk with lowered *Clostridium* levels are available as well (119, 120). Due to the controversy, it remains unclear whether the decrease in *Clostridium* that could possibly

be established by the consumption of supplemental dietary carbohydrates is beneficial for health.

One explanation for this contradiction could be the accuracy of the detection methods employed to assess the composition of microbiota. The majority of these studies reveal difference on phylum or genus level, which fails to differentiate between commensal and opportunistic Clostridia. Indeed, studies assessing health effects of *Clostridium* that focus on the species level reported high levels of opportunistic pathogens like *Clostridium hathewayi* and *Clostridium ramosum* to be linked to T2DM (106), whereas high weight loss was associated with a decrease in *Clostridium coccoides* and *histolyticum* (121, 122). In addition, *Clostridium difficile* is well known for its infectious properties, as it is an important cause of diarrhea in hospitalized patients (123). Finally, the presence of *Clostridium septicum* is suspected to play a role in colorectal carcinogenesis (124).

Altogether, there is no clear answer to the question how changes in *Clostridium* affect health, mainly because at the species level changes in abundance are known to have a great variety of effects. Moreover, the *Clostridium* genus includes species with a rather widespread evolutionary distribution, based on which this genus is not considered a phylogenetically coherent taxon (125). This high diversity in species within this genus makes it hard and possibly unreliable to identify health effects of the genus as a whole.

LACTOBACILLUS

Merely increases in Lactobacilli abundance were reported by supplementation with disaccharides, oligosaccharides, and polysaccharides (73, 74, 76, 84, 91). In cases where changes in Bacteroidetes and *Lactobacillus* counts were found in the same study, their abundance increased, except for the study by Costabile et al. (84), where *Lactobacillus enterococci* abundance increased, whereas the *Bacteroides* and *Prevotella* counts decreased by supplementation of very long-chain inulin supplementation. In general, an increase in *Lactobacillus* abundance by supplemental dietary carbohydrates may be of potential interest since levels have been inversely associated with obesity (119, 122, 126). For example, the prevalence of the species *Lactobacillus plantarum* was higher in a group of lean versus obese individuals (76 versus 27%, $p = 0.005$) (119). Weight loss in overweight adolescents due to a calorie-restricted diet and increased physical activity has been reported to be associated with an increase in Lactobacilli abundance (122). In addition, a study in obese rats showed that *Lactobacillus* abundance was increased upon controlled exercise training (i.e., which is often associated with weight loss) (126). Contradicting results have been mentioned too. Armougom et al. (96) observed significantly higher *Lactobacillus* species concentrations in adult obese subjects compared to lean ones. The same was recently reported for obese children (127). With qPCR as technique used in these studies, as well as in two out of three studies reporting an inverse relation between *Lactobacillus* and obesity, it is unlikely that the contradicting results are caused by differences in microbiota assessment.

A study by Karlsson et al. (105) in European women with normal, impaired, and diabetic glucose control revealed a positive

association between *Lactobacillus* abundance and blood glucose levels by making use of metagenome-wide Illumina sequencing. Similar results were found in two qPCR studies in Japanese and Danish adults with T2DM, when compared to healthy individuals (116, 120). In addition, higher *Lactobacillus* abundance was found in participants diagnosed with MetS (23). These findings support the study by Armougom et al. (96) suggesting a positive association of high abundance of Lactobacilli with obesity and its implications.

There is nevertheless a plethora of studies showing that probiotic treatment (with or without supplemental dietary carbohydrates) with Lactobacilli strains could potentially be useful to combat obesity and cardiometabolic derangements. For instance, yogurt containing Lactobacilli led to decreased fasting plasma glucose and improved antioxidant status (and thus may have the potential to treat and/or prevent T2DM), which matches the previous studies in support of the benefits of increased *Lactobacillus* (128). Second, a study by Sanchez et al. in which capsules containing *Lactobacillus rhamnosus* and a mixture of inulin and oligofructose were ingested twice a day for a period of 24 weeks by obese women was able to cause better sustained weight maintenance after a period of weight loss than controls (129). Because of the fact that supplemental dietary carbohydrates often lead to an increase in *Lactobacillus* as well as in *Bacteroides* abundance, the latter effect may potentially abolish the positive effect of *Lactobacillus*.

BIFIDOBACTERIUM

Abundance of *Bifidobacterium* increased upon supplementation with disaccharides, oligosaccharides, and polysaccharides (64, 73–75, 77–85, 88, 91). Supplementation with xylo-oligosaccharide seemed to have the highest feasibility, since only 1.4 g per day was found to be sufficient to increase *Bifidobacterium* abundance, with a treatment duration of 8 weeks (64). Xylo-oligosaccharide is naturally present in vegetables, fruits, milk, and honey, and can also be produced industrially (64).

The effects of the *Bifidobacterium* abundance on the host's health have been well established. A study by Teixeira et al. (119) investigated whether the abundance of specific microbes was associated with anthropometric, body composition, and biochemical measurements. The study was performed in 20 lean and 20 obese Brazilian women in their late twenties or early thirties. *Bifidobacterium* genus counts were found to be significantly higher in lean women. In addition, Bifidobacteria abundance appeared to be inversely associated with insulin homeostasis model assessment (HOMA) index. The low abundance of Bifidobacteria in overweight adults and children, as well as in women gaining relatively much weight during pregnancy, has been reported in other studies as well (20, 101, 122, 130, 131). The inverse relation between Bifidobacteria abundance and diabetes was also found in a cohort study of 50 Chinese T2D patients compared to 30 healthy Chinese individuals (132). Comparable findings were reported in mice (133).

Plasma levels of bacterial lipopolysaccharide (LPS), a cell wall constituent of gram-negative bacteria with potent inflammatory actions (108), are inversely related to *Bifidobacterium*

abundance in the colon. Because chronic treatment with LPS in rodents is able to induce obesity and insulin resistance (134), there may be a course of events that link LPS, *Bifidobacterium* abundance, obesity, and inflammation (134, 135). The underlying mechanism may lie in the fact that Bifidobacteria is known to be involved in the maintenance of the mucosal barrier (136, 137). Two possible scenarios may explain the link between *Bifidobacterium* loss and obesity and inflammation could be explained. Loss of *Bifidobacterium* may lead to higher transit of LPS and other bacterial fragments across the gut into systemic circulation, resulting in a state of high plasma LPS. This state is referred to as metabolic endotoxemia and is frequently observed in obesity (20, 134). The second scenario is that this mechanism might be preceded by inflammation, which would enable certain members of the microbiota to survive the environment, while others would not. These surviving members will mainly be pathobionts, resulting in a microbial dysbiosis leading to a washout of beneficial members like Bifidobacteria (138). A breach in the epithelial layer as a result of inflammation could subsequently lead to the transfer of LPS across the epithelial layer into the blood circulation, resulting in endotoxemia. Also other pathways exist that may not require LPS, which have been reviewed by others (139, 140).

Aside from the relation between *Bifidobacterium* counts and the prevalence of obesity, MetS, and T2DM, the potential of Bifidobacteria in the treatment of T2DM came to light more recently. A study by Tonucci et al. (141) in 50 Brazilian volunteers with T2DM (BMI <35 kg/m², aged 35–60 years) revealed that treatment with fermented milk containing *Bifidobacterium lactis* and *Lactobacillus acidophilus* was able to improve glycemic control and decrease inflammatory markers. Similar findings have been reported by other studies in humans as well (128, 142). In contrast to these findings, however, two studies in Estonia revealed a relation between higher *Bifidobacterium* abundance and higher blood glucose levels and occurrence of obesity in elderly and preschool children, respectively (143, 144). Bacteriological evaluation of the fecal samples in these studies, however, was based on manual counting of bacterial colony forming units on different agar plates, a method that is prone to errors (71, 145). Therefore, these contradicting conclusions are not highly reliable.

Overall, the effects of complex dietary supplemental carbohydrates to increase abundance of *Bifidobacterium* are useful since there is consensus that abundance of *Bifidobacterium* is lower in subjects who are obese and have cardiometabolic and/or inflammatory diseases.

ATOPOBIUM

The *Atopobium* genus was reported to be increased by disaccharides and polysaccharides, with a treatment of 10–45.6 g a day for 2–3 weeks (73, 84). Very long-chain inulin was able to establish the increase within three weeks at a dose of 10 g a day, which seems a feasible dose (84). *Atopobium* is a genus belonging to the class Actinobacteria, the class to which Bifidobacteria belongs to as well. How *Atopobium* is related to health is only reported in a limited number of studies, but all report favorable

effects of higher *Atopobium* abundance. The genus is relatively unknown and only four studies were found investigating the relation of *Atopobium* to health. The first study by Sato et al. (120) reported lower counts of the *Atopobium* cluster in 50 Japanese T2DM patients, compared to 50 healthy individuals. This increase in *Atopobium* abundance could potentially play a role in the prevalence of T2DM. In addition, the study found a negative correlation of *Atopobium* abundance with levels of the inflammation marker hs-CRP and BMI, and a positive correlation with HDL cholesterol. These correlation all support the beneficial effects of increased *Atopobium* counts on cardiometabolic health. A second study by Maccaferri et al. (146) investigated changes in the gut microbiota composition upon treatment with Rifaximin, a drug which is suggested to be able to induce clinical remission of active Crohn's disease, which belongs to the cluster of IBDs. The study in an *in vitro* human colonic model system revealed that *Atopobium* levels were increased upon treatment, suggesting that increasing *Atopobium* could be part of the underlying mechanisms of the Rifaximin-induced reduction of inflammation of the bowel. Finally, Khachatryan et al. (147) analyzed the composition of the gut microbiota in patients with familial Mediterranean fever (FMF), an auto-inflammatory disease characterized by recurrent self-resolving attacks of fever and polyserositis, followed by periods of remission without clinical signs. In that study, a trend was observed in which *Atopobium* was less abundant in the gut microbiota of FMF patients compared to healthy controls, where abundance was lowest in attack and slightly higher during remission (42.2 counts per gram of fecal specimen for healthy individuals, 28.9 in remission, and 16.9 in attack, where this last value was significantly lower compared to the counts in healthy controls).

In conclusion, not many studies investigating the link between *Atopobium* abundance and cardiometabolic health are available, but the available ones discussed here do point in the direction of a beneficial effect of *Atopobium* abundance.

DESULFOVIBRIO

Desulfovibrio abundance was reported to be decreased by 5.0 g of agave inulin intake per day for 21 days (83). Similar findings were reported in obese subjects supplemented with a mixture of galacto-oligosaccharides (148). In a Chinese cohort, this genus, that includes sulfate-reducing bacteria, has been reported to be increased in T2DM patients (106). In addition, a study in mice that were fed a diet supplemented with glycomacropptide, a 64-amino acid glycoposphopeptide, showed that this diet reduced *Desulfovibrio* bacteria. This reduction was associated with decreased plasma concentrations of the inflammation markers interferon-gamma, tumor necrosis factor-alpha, Interleukin-1beta, and Interleukin-2. These changes could contribute to the management of obesity, IBD, and phenylketonuria (i.e., a disease due to impaired metabolism of the amino acid phenylalanine) (149). This finding perhaps shares some grounds with the increased presence of *Desulfovibrio* species in patients suffering from ulcerative colitis, a type of IBD (150).

The aforementioned studies are all in favor of the hypothesis that lowered *Desulfovibrio* abundance can benefit health. However, the one study by Karlsson et al. (151) contradicts this because they reported lowered levels of *Desulfovibrio* in overweight and obese children in the age of 4–5 years, compared to children with a normal BMI. This contradiction might be age-related as the other studies investigating the *Desulfovibrio* abundance in humans all involved older participants.

THE CHOICE OF SUPPLEMENTAL FERMENTABLE CARBOHYDRATES

Based on the data discussed above, it appears that dietary carbohydrate supplementation in healthy individuals seems to be associated with increases in the abundance of *Bacteroides*, *Lactobacillus*, *Bifidobacterium*, and *Atopobium*, whereas lower levels of abundance were generally observed in *Clostridium* and *Desulfovibrio*. With respect to the health effects of *Bacteroides*, there are discrepancies between obesity on the one hand and the cardiometabolic/inflammatory derangements that are often associated with it on the other hand. Thus, while both lower levels and higher levels of *Bacteroides* are reported to be found in obese individuals, higher levels seem to be associated primarily with the occurrence of MetS, T2DM, and IBD, all derangements known to involve increased activity of the inflammatory system (107–109). For this reason, it seems counterproductive to treat obese individuals, particularly those with MetS, and/or related inflammatory diseases with dietary supplemental carbohydrates that would augment *Bacteroides* abundance. Dietary supplemental carbohydrates that do not increase the abundance of *Bacteroides*, but *Bifidobacteria* and potentially also *Lactobacillus* (although it is not yet clear about the latter whether it contributes to or protects against the onset of obesity, but see discussion on this subject below) instead, appear more helpful. Inulin, for example, may fulfill the above-mentioned criteria, as it increases *Bifidobacteria* abundance, and in some cases reduces *Bacteroides* abundance. Several papers show positive effects of inulin supplementation to reduce the severity of cardiometabolic and inflammatory derangements in obese and diabetic patients (42, 152). Also several animal studies point in this direction. For example, Rault-Nania et al. (153) showed that long-chain inulin supplementation in the diet of Wistar rats was able to reduce hypertriglyceridemia, hypertension, and heart peroxidation (i.e., increases in these are all signs of impaired cardiometabolic health) as a result of feeding a high fructose diet. Furthermore, mice exposed to a high-fat diet for 8 weeks with supplemental inulin (10%) or β -glucan (10%) had lower body weight gain relative to controls, with a lower energy intake observed in β -glucan supplemented mice than in inulin supplemented mice. In addition, the latter group showed reduced body fat content, but the former presented stronger hypothalamic neuronal effects. Fecal/cecal *Bifidobacterium* and *Lactobacillus* abundance was increased in both supplemental groups (154). The effect of inulin supplementation on cardiometabolic health was also assessed in gnotobiotic mice colonized with simplified human microbiota and challenged with a high-fat diet. Although the degree of obesity induction in these mice was comparable

to control mice subjected to a high-fat diet, the inulin supplemented mice had increased bacterial diversity (including those of *Bifidobacterium* counts), significantly elevated concentrations of total SCFA in cecum and portal vein plasma, signs of reduced lipogenesis, and an increased ratio of plasma and liver omega-3 versus omega-6 fatty acids (155). A very recent paper by Salazar et al. (156) indeed showed that inulin-type fructan supplementation of 16g/day over a 3-month period in 30 obese women (i.e., with maltodextrin as control treatment) caused significant fecal increases in several *Bifidobacterium* species, with *Bifidobacterium longum* being negatively correlated with serum LPS endotoxin levels. In addition, fasting insulinemia and HOMA index were significantly lower in the supplemented group than in the placebo group after the treatment period, albeit that SCFA, acetate and propionate concentrations also declined.

An important point that deserves more attention is the dose of the dietary carbohydrate supplementation needed to establish the alterations in gut microbiota, since some of the reported studies used doses of which long-term tolerability is questionable. For example, a dose-response study by Bruhwylter et al. (157) showed that a dose of 20 g of inulin per day resulted in gastrointestinal complaints like flatulence. However, the cutoff of tolerability will likely differ per prebiotic and individual. Also the method of application may be of importance as it has been reported that soluble corn fiber is well tolerated up to 65 g/day, but only when consumed in multiple doses (158). Related to this point is the fact that none of the studies reporting on gut microbiota changes by supplemental carbohydrates assessed the regular dietary micro-/macronutrient and fiber composition of the participants. Since it is clear that the composition of the diet can affect the composition of the gut microbiota, this is a possible factor underlying the reported variability in responses and sometimes contradicting results between studies.

CONCLUSION AND GAPS IN UNDERSTANDING

Whereas it is relatively clear in which direction supplemental fermentable carbohydrates can alter the gut microbiome, the relevance of these changes regarding health remains controversial. As already mentioned above, a clear exception is the genus *Bifidobacterium*, of which the benefits of an increased abundance have been well established. Increases in *Lactobacillus* by dietary supplemental carbohydrates could potentially be health promoting as well (i.e., given the plethora of studies showing that probiotics that increase *Lactobacilli* generally can counter obesity and cardiometabolic diseases) but these effects may be counteracted by the stimulatory effects on *Bacteroides* abundance that often associates the effects on *Lactobacillus*. The controversy regarding *Bacteroides* and its role in obesity is also related to the discussion regarding the ratio between the phyla Bacteroidetes and Firmicutes, which has been reported to be related to obesity numerous times. However, the studies do not agree upon which of the phyla is the higher abundant phylum in obese individuals. The answer is still indefinite, indicating that it concerns a very complex matter of which not all the details are known yet.

Various health effects are reported at the species level, but the diversity of species within a genus makes that it is difficult to draw conclusions at the genus level. Therefore, there is a need for more comprehensive and species-specific characterization of the human microbiome. Studying the meta-transcriptome may be the most informative when linked also to either a species level picture of the microbiome or the genetic profile of the population as a whole. The difficulty here of course is that we know the function of so few of the genes (i.e., not only what they mean for functioning of the specific bacteria but also for the host) but this knowledge is expected to grow quickly.

The majority of studies performed on obesity and microbiota ignore the fact that different causes of obesity should be taken into account. In short, maintenance of body weight is the result of a sustained match between energy intake and energy expenditure, and increased intake of energy-dense foods and/or a decreased physical activity can logically underlie weight gain (94). Resistance to the adipocyte hormone leptin has been mentioned to be the result of the above-mentioned mismatch (159), or even the cause (140), which both could also explain the associated co-morbidities (160). Differences in energy-harvesting efficiency of microbiota (as a result of variation in its composition and abundance) can also play a role in the energy balance or imbalance herein, and the latter may contribute significantly to weight gain as well (2, 9, 94, 161, 162). As with recording of the habitual diet, also none of the studies reported in this review have assessed the energy budgets of the participants, which thus obstructs further insight into the contribution of energy absorption versus expenditure in the resultant body fat. Designing a study in which a large cohort of obese individuals with and without MetS (or related non-communicable diseases) is further divided into subgroups based on their energy budget, with one group having a more positive energy budget than the other, and subsequently investigate whether gut microbiota abundance and diversity between these subgroups differs at baseline would be of high relevance. Subsequent supplementation with dietary carbohydrates aiming to relief obesity and/or cardiometabolic/inflammatory diseases should then include investigation of the entire energy balance equation in these individuals.

Weight gain in the form of increasing adiposity stores (i.e., which is a key risk factor to attract cardiometabolic and inflammatory health problems) is probably the result of selective or evolutionary pressures that have shaped our paleolithic (or even earlier) ancestors to deal with food shortages. This theory was first hypothesized by Neel to explain the current epidemic of diabetes (163), and was later expanded toward the epidemic of obesity [see Ref. (164) as an example]. The above-mentioned evolutionary pressure probably also co-shaped the gut microbiome (165, 166). To this end, it is of interest to consider the possibility that the gut microbiota affects the hosts' (and therefore its own) energy balance to increase the chances of survival in times of famine by offering ample nutrients from otherwise indigestible food ingredients, but also—via the microbiota-gut-brain axis—to affect the host's eating behavior, hunger/satiety, and even reward and mood aspects of food, to stimulate food searching, craving, etc. (167). In our current western-industrialized society, where industrialized and processed foods are highly abundant, but contain relatively

little amounts of fibers, this may underlie a conflict between host and microbiota leading to increased craving as well (167). Recent findings in line with this hypothesis are reported by Perry et al. (168). This study in rats revealed that exposure to a calorically dense high-fat diet resulted in increased ghrelin secretion and glucose-stimulated insulin secretion, which may promote hyperphagia and increased energy storage as fat. The reported changes were found to be the result of an altered gut microbiota, acting through the parasympathetic nervous system. For this reason, a primal or ancestral diet, which contains in itself many of the complex carbohydrates with prebiotic properties as discussed in this review, should be promoted more rigorously in order to prevent obesity and cardiometabolic/inflammatory diseases [e.g., by restoring leptin sensitivity (140)]. These sorts of mechanisms are of interest from an “evolutionary medicine” point of view, and should certainly be taken into account to fully understand the role of the microbiome in health and disease.

FUTURE DIRECTIONS

Although there is consensus that supplemental dietary carbohydrates have the tendency to increase the abundance of *Bifidobacterium*, *Bacteroides*, *Lactobacilli*, and *Atopobium* and to decrease the abundance of *Clostridium* and *Desulfovibrio* in the human gut, it remains unclear whether specific types of fermentable carbohydrates target specific bacterial groups, or whether a change in abundance of one group would influence the rest of the community through cross feeding. That being said, the definition of prebiotics as it is currently used—“non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already resident in the colon, in the attempt to improve host health” (36)—might need revision. The stimulation of beneficial bacterial species might in fact be mediated by or coincided with a decrease or increase in abundance of a species with undetermined health effects. Therefore, a suggested alternative definition of prebiotics would be “non-digestible food ingredients that affect the host by selectively stimulating or inhibiting the growth and/or activity of one or a limited number of bacterial species already resident in the colon, with the net effect of the microbial change being beneficial for the host's health.” It might not be reliable to generalize the effects of prebiotics since this will likely depend on the host genotype, current health status, and susceptibility to disease (169). How then alterations in gut microbiota exactly influence the host's health remains largely undetermined, but several mechanisms may contribute as already explained in the previous parts of this review and elsewhere (140, 170).

The gut microbiota carry out a wide range of biotransformation reactions during metabolism of the diet, including those that are not present in the mammalian host (171). This provides an important way to further investigate the effect of changes in the gut microbiota, established by prebiotics, on the host's health, i.e., by means of investigating the microbiota-dependent metabolites. Trimethylamine, for example, is the product of microbiota-dependent choline (essential dietary nutrient) metabolism (172). A potential link between the intestinal microbiota, dietary choline, and CVD risk has been suggested,

where increased metabolites of the dietary lipid phosphatidylcholine have been observed in the serum of patients with CVD pathogenesis (19, 173, 174). This makes that these metabolites are potential measures to assess health effects of changes in microbial genera discussed in this review, but applicability and reliability of this measure must be elucidated first. This research area of mass spectrometry identified signatures is quickly expanding and candidate metabolite factors are increasingly identified with notable bioactivities (175). With the current knowledge, however, it remains hard to determine whether alterations in gut microbiota and/or their metabolites are cause or consequence of cardiometabolic/inflammatory diseases. Thus, while it has been confirmed that obesity, MetS, T2DM, and CVD are usually associated with chronic inflammation (176) and convincing evidence links the gut microbiome to inflammation (177–179), future research should focus on whether, how and to what extent mechanisms of inflammation and beyond are indeed bidirectional between the host and the microbiome. This requires system biological approaches and “big-data” analysis combined with in depth analysis of the effect of targeted perturbations in microbiota as well as in the host.

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- Refined studies on the effects of reconstitution of microbiota in gnotobiotic mouse systems may be important for unraveling some of these interactions. Human intestinal organoids (i.e., near physiological 3D models of the human gut grown from human stem cells) appear to have great potential for studying these interactions as well (180) and eventually may take this to a “personalized” therapeutic level (181), from the perspective of both the host and the microbiome.

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All authors were involved in designing and planning this paper. PV wrote the first drafts that were corrected and added by SA and GD. GD edited the final versions. All authors take public responsibility for the content of the article regarding data interpretation. They do not have any conflict of interest.

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