Interactions of dietary fat with the gut microbiota: evaluation of mechanisms and metabolic consequences

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Abstract

The current scientific literature proposes that both the amount and type of dietary fat modulate homeostasis of the gut microbiota; disturbances in homeostasis may have metabolic consequences with potentially serious clinical manifestations. The evidence for interactions between dietary fat and gut microbiota has been mostly derived from animal studies, but there is now also evidence emerging from human studies. We will review the current literature on how dietary fat influences the gut microbiota, particularly focusing on the type of fat. Mechanisms detailing how this crosstalk may impact on host metabolism and health will also be discussed. Some studies have reported somewhat controversial findings and therefore we will evaluate critically which possible aspects should be considered when interpreting current and planning further studies to explore the diet-microbiota crosstalk and its metabolic and clinical implications for the host.

Key words: Gut microbiota, Dietary fat, Health, Diet

Abbreviations: ↑ increase; ↓ decrease; Ahr, aryl hydrocarbon receptor; CLA, conjugated linoleic acid; COX-2, cyclooxygenase-2 enzyme; CVD, cardiovascular disease; DGGE, denaturing gradient gel electrophoresis; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid ; FFAR, free fatty acid receptors; FIAF, Fasting Induced Adipocyte Factor; GLP-1, glucagon-like peptide-1; GM: gut microbiota; H2S, hydrogen sulphide; I3A, indole-3-aldehyde; IAP, intestinal alkaline phosphatase; IC50, inhibitory concentration; LC, long chain; LPS, lipopolysaccharide; MAMPs, micro-organism-associated molecular patterns; MUFA, monounsaturated fatty acids; NGS, next-generation sequencing; PPARG2, Peroxisome proliferator activated receptor gamma 2; PRR, pattern recognition receptors; PUFA, polyunsaturated fatty acids; qPCR, quantitative polymerase chain reaction; SCFA, short chain fatty acids; SFA, saturated fatty acids; TLR, toll-like receptor; T-RFLP, terminal-

restriction fragment length polymorphism; TMA, trimethylamine; TMAO, Trimethylamine N-oxide

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Introduction

It is well known that diet is an important factor contributing to many various metabolic disorders, one example being consumption of saturated fatty acids (SFA) that elevate the serum cholesterol concentration, a risk factor for cardiovascular diseases (CVD) (Berry et al. 2012; Hooper et al. 2015). Several recent meta-analyses have emphasized the beneficial properties of dietary modification, e.g. the diverse effects of macronutrients on glucose-insulin homeostasis, particularly the benefits of polyunsaturated fatty acids (PUFA) in improving glycaemia and insulin resistance (Imamura et al. 2016), or reductions in the level of low-grade inflammation by adoption of plant-based diets (Eichelmann et al. 2016). Modification of the macronutrient intake may be also utilized in weight reduction diets (Tobias et al. 2015). The potential of diet to prevent disease outcomes was demonstrated in individuals at high cardiovascular risk as the incidence of major cardiovascular events was reduced when the participants consumed extra-virgin olive oil or nuts as a part of a Mediterranean diet (Estruch et al. 2018).

Indeed, diet may be directly involved in metabolic disorders and disease conditions, but it is also possible that some of the metabolic effects of the diet are mediated through the gut microbiota (GM), the microbe population living in the gastrointestinal tract (Daliri et al.

2017). The GM exerts many beneficial effects with regard to human physiology and nutritional status; these include the capacity to produce vitamins and to convert undigestible fibre into a form available for human metabolism (Rowland et al. 2018). In general, microbial metabolites may exert both local and systemic influences on the host's health. These metabolites, such as short chain fatty acids (SCFAs) and vitamins, may interact with the intestinal epithelium, altering its function; if these compounds are absorbed into the circulation, they can evoke systemic effects on the host's metabolism and health. It is evident that the GM can interact with the host through different mechanisms and furthermore, that these may be modified through differing dietary compositions (Figure 1).

Excellent examples of how diet influences the GM have emerged from studies in populations consuming distinctive diets such as vegetarian or plant-based diets compared to an animal-based diet (David et al. 2014), or an African diet compared to a European diet (De Filippo et al. 2010; De Filippo et al. 2017). Furthermore, different dietary patterns, i.e. diets that are characterized by consumption of particular foods, for example adherence to a Mediterranean diet have been linked with a modulation of the GM (De Filippis et al. 2016; Mitsou et al. 2017). Generally a healthier diet pattern, defined as a higher adherence to dietary recommendations, has been associated with higher microbial richness (Kong et al. 2014; Röytiö et al. 2017). These different dietary patterns reflect the extensive variation in the consumption of foods, for example foodstuffs that are rich in fibre and carbohydrates that mainly originate from plants, or foods rich in fat and protein, derived from animal sources.

According to a recent systematic review, the best characterized association between diet and GM is related to dietary fibre intake and polyphenols (Shortt et al. 2018). Changes in GM composition due to high fibre consumption have been observed to lead to a predominance of *Prevotella* over *Bacteroides*, and an increase in the production of SCFA, whilst diets low in fibre but high in fat and sugar, have been linked with an increase in Proteobacteria (Simpson

and Campbell 2015). Protein breakdown and fermentation by GM lead to the subsequent production of ammonia, amines, phenols and branched chain fatty acids (Shortt et al. 2018).

In terms of consumption, dietary fat is the second most important macronutrient after carbohydrates, with protein following in third place, but the impacts of different types of fat on GM composition and function have been incompletely characterised. Nonetheless, because of the putative health effects of both dietary fat and GM, there is increasing research interest in this area, and also evidence that some of the health effects of dietary fat may be mediated by the GM. In particular, different types of dietary fats may exert different effects on the GM and subsequently on its metabolic functions, as will be reviewed in this article. The majority (95%) of dietary fat is present as triacylglycerols which contain three fatty acids bound to a glycerol backbone. Diet contains also other fats which are present in small amounts, mainly phospholipids and sterols, such as cholesterol. Dairy products also contain SCFAs (fatty acid chain length less than six carbons). The fatty acids have differing chain lengths and different degrees of saturation; the main classes are SFA, monounsaturated (MUFA) and PUFA. Long-chain (LC) PUFAs are also divided to n-3 and n-6 fatty acids according to location of the carbon double bond with respect to the methyl group on the carbon chain. Some of these LC-PUFAs are very interesting e.g. n-3 LC-PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA); it is believed that these compounds may contribute to human health through several pathways, including the modulation of inflammation (Lin et al. 2016).

Although the absorption of dietary fat is almost completely conducted within the small intestine, in cases when high quantities have been consumed, some fat will reach the colon, where most of the GM reside. Although fewer in number, small intestinal microbiota may be important inducer of dietary signals, as demonstrated in mice (Martinez-Guryn et al. 2018).

The aim of this review is to examine diet-GM interactions, focusing on dietary fat. We will critically appraise the current literature and elucidate not only how different dietary fats can influence GM composition and function but also speculate on the subsequent metabolic consequences. We will also point to the current gaps and methodological challenges in research to help in designing future studies. We will focus on studies conducted in humans and mice, but also some studies done in rats and hamsters are presented.

The amount and type of dietary fat in relation to the gut microbiota of mice and rats

Amount of fat

The initial evidence that there was a relationship between dietary fat intake and GM composition originated from animal studies. The same four predominant phyla detected in humans are found in mice with Bacteroidetes and Firmicutes representing the dominating phyla, followed by Proteobacteria and Actinobacteria (Ley et al. 2005). Nonetheless, discrepancies start to appear at the lower taxonomic levels, as 85% of bacterial genera in the mouse gut are not found in the human gut (Ley et al. 2005). Several studies in wild type and obese mice models have revealed that high fat diets, varying from just over 30% up to about 70% of energy (E%) from fat, influence the animals' GM composition. Supplemental table 1 describes the typical finding at the phylum level of bacteria after high fat consumption i.e. there is an increase in the relative abundance of Firmicutes and a reduction in the abundance of Bacteroidetes (see references in the table) and consequently, an increase in the Firmicutes to Bacteroidetes ratio (Shang et al. 2017; L. Xiao et al. 2017; K. A. Kim et al. 2012). With regard to the lower taxonomic levels, the results are variable (see supplemental table 1 for

129 details). Consumption of a high fat diet has also evoked a decrease in GM diversity and
130 richness (Zhang et al. 2012), although also opposite results have been reported (Shang et al.
131 2017). When investigating the global GM composition, a clear separation of GM clusters has
132 been detected between the animals fed a high fat diet and those consuming control chow
133 (Ravussin et al. 2012; Parks et al. 2013; Lecomte et al. 2015).

134 All in all, one clear and common finding in the GM after animals are fed a high fat diet is that
135 there is an increase in the ratio of Firmicutes to Bacteroidetes i.e. a high fat intake increase
136 the abundance of Firmicutes. The alterations at the lower taxonomic levels due to high fat
137 consumption have been more variable and less consistent. There are several possible reasons
138 for the different findings such as the composition of the high fat diet, in fact, there does not
139 seem to be any common factor which would account for the different results.

140 **Type of fat**

141 In addition to high fat diets, mice have been used to explore the impact of different types of
142 fat on the GM. A typical finding is that mice fed with a high SFA diet, have a reduced
143 microbial diversity (Caesar et al. 2015) and richness (Devkota et al. 2012), and decreased
144 abundance of Bacteroidetes and increased abundance of Firmicutes as compared to control
145 animals eating low fat diet (Devkota et al. 2012; De Wit et al. 2012) (Table 1) reminiscent of
146 the response seen in mice consuming a high fat diet (supplemental table 1). In contrast, an
147 intake of unsaturated fatty acids, such as PUFA-rich diets including fish oil or safflower oil
148 has exerted an opposite effect as compared to SFA-rich diets, including increased GM
149 diversity (Patterson et al. 2014), and a decreased Firmicutes to Bacteroidetes ratio (Gibson et
150 al. 2015).

151 A more critical inspection of the animal studies investigating the types of dietary fats,
152 revealed one study in which mice made obese by consuming a high fat diet (60.3 E%)

exhibited a restoration of their GM after treatment with a n-3 LC-PUFA diet (EPA and DHA, 3000 mg/kg per day) (Mujico et al. 2013). In mice, consumption of fish oil in fat (45 E%) , a food stuff rich in 3-n LC-PUFA, increased the numbers of Actinobacteria, lactic acid bacteria such as Lactobacillus, Verrucomicrobiota, Alphaproteobacteria and Deltaproteobacteria in caecal samples as compared to animals fed with lard (Caesar et al. 2015).

Interestingly, n-3 and n-6 LC-PUFA may exert distinct effects on GM, as shown in several studies. For example, compared to n-3 LC-PUFA, a decrease in anti-inflammatory *Bifidobacterium* (Lam et al. 2015), and an increase in *Clostridium* i.e. bacteria which may induce inflammation have been reported (Ghosh et al. 2013). In aged wild type (C57BL/6) mice, switching from an n-6 LC-PUFA rich diet to an n-3 LC-PUFA rich diet (fish oil) for 2 months, resulted in decreased abundances of lipopolysaccharide (LPS) producing and/or pro-inflammatory bacteria and increased abundances of LPS-suppressing and/or anti-inflammatory bacteria including micro-organism associated with intestinal inflammation (Devkota et al. 2012) i.e Proteobacteria and its members *Enterobacteriaceae*, *Escherchia coli*, gamma- and delta-Proteobacteria (Kaliannan et al. 2015).

There are also a few studies that have evaluated the impact of PUFA rich diets on early life GM; for example, Gibson and co-workers (2015) fed female rats high amounts of n-3 LC-PUFA as fish oil and n-6 LC-PUFA as safflower oil during gestation and lactation; it was found that their offspring exhibited a lower Firmicutes to Bacteroidetes ratio. When evaluating the changes in individual bacteria, surprisingly the offspring of rat dams fed with a diet rich in n-3 LC-PUFA (fish oil 18 E%) had elevated numbers of opportunistic pathogens in their faeces, such as *Bilophila wadsworthia*, *Enterococcus faecium* and *Bacteroides fragilis* (Gibson et al. 2015). The authors speculated that an excessive intake of fish oil in utero could disturb the capability of the immune system to cope with the increased pathobionts i.e. pathological microorganisms which, under normal circumstances, live in

symbiosis with the host, whereas an optimal level of fish oil encouraged the growth of beneficial bacteria. In a recent study, the offspring's GM were more affected by the fatty acid profile of their dams during lactation than during gestation (Robertson et al. 2018). Interestingly, an early life stress i.e. early separation of rat pups from their mothers influenced GM, an effect which was claimed to be reversed by provision of an n-3 LC-PUFA rich diet (Pusceddu et al. 2015).

In terms of SFA, the study of Caesar and co-workers (2015) found that lard-fed (45 E%) mice, compared to fish oil- fed mice, had a decreased phylogenetic diversity and there was a reduced abundance of *Akkermansia*, i.e bacteria generally considered as beneficial, and increased abundances of *Turicibacteria* and *Bilofila wadsworthia*, species which have been previously linked with colitis (Rowan et al. 2009). Li et al. (2017) reported that *Verrucomicrobia*, *Tenericutes* and *Akkermansia* were more abundant in the faeces of middle aged rats fed a lard diet compared to those consuming a fish oil or a soybean oil diet.

High fat diets are usually rich in cholesterol which may be a sign of the effects of dietary cholesterol on the GM. Bo et al. (2017) reported that wild type rats consuming a high cholesterol diet had a decreased Firmicutes to Bacteroidetes ratio as well as increases in non-beneficial bacteria including *Prevotella*, compared to wild type rats eating normal chow diet as well as when they were compared to ApoE-/- Sprague Dawley rats consuming either the high cholesterol or normal chow diet. In contrast, Dimova and co-workers (2017) stated that dietary cholesterol did not have any effect on GM in mice. Unlike dietary cholesterol, plant sterols have beneficial effects on lipid metabolism, since they lower the circulating LDL cholesterol concentration. A study in which hamsters were fed with 5% plant sterols esterified with stearic acid or beef tallow revealed that plant sterols could reduce faecal numbers of *Coriobacteriaceae* and *Erysipelotrichaceae* which were associated with cholesterol metabolism (Martinez et al 2013).

The impacts of dietary SCFA on GM have not been studied extensively. In one rat study, oral administration of SCFA was shown to reshape the GM (Needell et al. 2017), suggesting that the GM may also be modified by dietary SCFAs. Another fat type, namely conjugated linoleic acid (CLA), has been of interest to researchers since it may have beneficial health effects, such as weight loss. Marques and co-workers (2015) reported that feeding with trans-10, cis-12 CLA reduced fecal Firmicutes and increased Bacteroidetes in mice compared to non-supplemented controls (Marques et al. 2015). Den Hartigh and others (2018) found that there were increases in butyrate-producing bacteria including *Butyrivibrio* and *Roseburia* and other bacteria such as *Lactobacillus,* Actinobacteria and *Ileibacterium valens* in faeces in the trans-10, cis-12 CLA treated mice as compared to the other groups which did not receive CLA.

Overall, regarding the type of dietary fat, n-3 LC-PUFA seems to increase the intestinal abundance of those bacteria considered to be beneficial while the impact of SFA-rich diets on GM resembles that of a high fat diet and has been linked with a higher abundance of pathogenic bacteria. However, the discrepancies between the studies should not be overlooked, and thus more trials are needed to clarify how the GM responds to different types of dietary fats, particularly to those fat types present in lower quantities such as SCFAs and cholesterol. Finally, very little is known about the role of MUFA, oral SCFA, cholesterol and CLA on the GM.

The amount and type of dietary fat in relation to human gut microbiota

Amount of dietary fat

There are rather few human intervention studies that have investigated the impact on the GM of a high fat diet (Supplemental table 2) or the type of dietary fat (Table 2). This may be due to the challengers in conducting these studies, i.e. in order to maintain an isocaloric intake, the change in the quantity of fat intake must take place at the expense of other nutrients, such as carbohydrates. In one dietary intervention study conducted in overweight and obese men and women, a 8-week consumption of a high fat (61 E%) diet resulted in a decrease in the abundance of *Bifidobacteria*, whereas a lower fat (30 E%) intake induced an increase in total anaerobes enumerated by conventional bacterial plating (Brinkworth et al. 2009). It is noteworthy that participants in both study arms consumed the same amount of energy, nonetheless in the diet with the higher fat content, the protein content was 35% and that of carbohydrate only 4 E%, while in the diet with the lower fat content, the protein content was 24% with carbohydrate accounting for 46 E% (Brinkworth et al. 2009). Thus, one cannot conclude that the observed result arose simply from the change in the dietary fat content. There was a similar finding regarding gut *Bifidobacteria*, in a study conducted in subjects at risk of developing the metabolic syndrome: 24 weeks' intake of diet with a lower fat (28 E%) and higher carbohydrate (55 E%) content was related to an increased abundance of *Bifidobacteria*, whilst a higher fat intake (38 E%) and a lower carbohydrate (45 E%) intake was related to reduced numbers of total bacteria (Fava et al. 2013). In another study the individuals consuming an animal-based higher fat diet had an increased abundance of bile acid tolerant bacteria *Alistipes*, *Bilophila* and *Bacteroides*, simultaneously with a decrease in Firmicutes (David et al. 2014). The dietary contributor to these results is difficult to evaluate since in addition to the differences in the amount of fat consumed, the source of fat also differed, i.e. the animal-based diet presumably contained higher amounts of SFA.

Some studies have investigated the relationship of dietary fat intake on the composition of the GM whilst consuming a habitual diet, i.e. the regularly consumed diet from which the intakes

of energy yielding nutrients have been calculated using computerized programmes. At a global level, the long-term habitual intake of a diet rich in fat has been associated with Bacteroidetes and Actinobacteria (Wu et al. 2011). Other studies investigating the impact on the GM of the fat present in habitual diets have detected correlations between the intake of animal fat and *Catenibacterium* (Shin et al. 2016), the abundance of this species has been claimed to increase in insulin-resistant obese subjects (Moreno-Indias et al. 2016) as wells as inverse correlation between the intake of fat and a commensal *Clostridium* IV cluster and positive correlation with *Clostridium difficile* containing a *Clostridium* XI cluster as (Yamaguchi et al. 2016). In a study conducted in pregnant overweight women, those individuals consuming the recommended dietary intake of fat had a lower proportion of *Bacteroides* and a higher GM richness (Röytiö et al. 2017). A higher microbiota richness also correlated inversely with the fat intake (Röytiö et al. 2017).

Type of fat

Although thus far scarce, the human trials evaluating the effect of type of dietary fat on GM have adopted both intervention and observation approaches, ranging in duration from weeks to years (Table 2). In the intervention studies, typically the impact of different oils including PUFA rich corn, flax, or MUFA-rich canola, olive, safflower or fish oils, or fish such as sardines or salmon have been compared to a control diet, which is a habitual diet or a standardized diet without the specific fatty acids incorporated within the intervention diet. At present, there are only a few human studies in which fatty acids have been used as supplements (e.g. capsules). Furthermore, there have been trials examining also different dietary patterns, such as a Mediterranean diet in which the fat source is usually olive oil, which is MUFA-rich or a Western diet pattern with its high SFA content. Certainly, the impact of PUFA on the GM composition has been more widely studied than that of other fatty acids and fats such as cholesterol.

PUFA

As in the animal studies, dietary n-3 and n-6 LC-PUFA also seem to exert distinct effects on the GM in humans. For example, observational studies have demonstrated e.g. higher numbers of bacteria within the *Lactobacillus* group in association with the intake of n-3 LC-PUFAs whereas dietary n-6 LC-PUFAs were negatively associated with the faecal *Bifidobacteria* (Simoes et al. 2013) and an association has been noted between serum PUFA and GM diversity (Menni et al. 2017). In our own study with pregnant overweight and obese women, we found that the type of fat exhibited a distinct relationship with the GM richness; the intakes of SFA, MUFA, PUFA and n-6 LC-PUFA, but not that of n-3 LC-PUFA, correlated inversely with the richness of the GM (Röytiö et al. 2017).

The studies investigating the effect of consumption of fish and fish oil, which are rich in n-3 LC-PUFA, on microbiota have detected decreases in the Firmicutes to Bacteroidetes ratio and increased abundance of *Bacteroides- Prevotella* in patients with type 2 diabetes who consumed a sardine-rich diet for 6 weeks compared to the control group (Balfego et al. 2016) and a lower heterogeneous *Atopobium* cluster in babies whose mothers consumed 150 g of oily fish salmon from 38 weeks of gestation until delivery (Urwin et al. 2014). However, the result was seen only in formula-fed infants and not in breast-fed infants (Urwin et al. 2014). Similarly, differences in GM clustering were seen in 10-month-old-infants, when they received fish oil as well as cow's milk. Fatty acid status or diet per se, e.g. breast-feeding, may modulate influence the impact of the intervention as demonstrated in another study. Fish oil supplementation compared to sunflower oil supplementation increased GM diversity and contributed to the changes occurring in the bacterial groups (Bacteroidetes) in 18-month-old-children, but this effect was only present in those children who had stopped breast-feeding before they were 9 months old (Andersen et al. 2011).

In a recent study, PUFA as a mixture of fish oil and safflower oil, was administered to premature infants with enterostomies for nine weeks and the impact was compared to infants receiving standard treatment (Younge et al. 2017). Several bacterial community modules were found to differ between the study groups. In the same study, based on the microbial gene function analysis, a number of pathways, mainly those related to lipid metabolism, but also those involved in the metabolism of butyrate and specific amino acids, were found to differ between the intervention groups (Younge et al. 2017).

Only two studies exploring the impacts on the GM due to dietary fatty acid supplementation have been conducted in healthy adults (Pu et al. 2016; Watson et al. 2017) although there is also one trial in adult patients with ulcerative colitis (Prossomariti et al. 2017) (Table 2b). In one study conducted in healthy adults, the consumption of a high dose of EPA and DHA as soft gel capsules failed to exert any impact of the composition of the GM (Watson et al. 2017) but in another trial, an increase was observed in the genus *Isobaculum* and there was also a correlation between provision of DHA rich diet and *Lachospiraceae* (Pu et al. 2016). In a study conducted in patients with ulcerative colitis who were stable and in clinical remission, EPA administration at a dose of 2 g/day as fatty acids for 90 days increased the relative faecal abundance of the family *Porphyrominadaceae* while decreasing that of the family *Ruminococcaceae* (Prossomariti et al. 2017). In addition, the mucosal microbiota was has been examined; EPA consumption reduced the abundance of *Bacteroidaceae* and bacteria belonging to the genus *Bacteroides*.

SFA

Similar to the results from the experimental studies, also in the human studies, a high SFA intake has been related to an increase in Firmicutes and Proteobacteria, an example being a

study conducted in 60 women who were assessed at four days after delivery (Mandal et al. 2016). In another study in pregnant women, there was a negative association between SFA intake and *Barnsiellaceae* (Röytiö et al. 2017). Fava and co-workers (2013), revealed that a high SFA intake increased the numbers of *Faecalibacterium prausnitzii* in 88 adults at risk of developing the metabolic syndrome.

MUFA

The MUFA intake, similarly as the SFA intake, has been related to an increased abundance of Firmicutes and Proteobacteria in women at four days postpartum (Mandal et al. 2016). In another trial, the study subjects were grouped according to their adherence to the Mediterranean diet, typically a high MUFA diet. Subjects with high adherence to the Mediterranean diet had lower *Escherichia coli* counts and increased *Bifidobacteria* to *E. coli* ratio and the abundance of *Candida albicans* as compared to low adherence subjects (Mitsou et al. 2017). Consumption of a Mediterranean diet has also resulted in a decreased abundance of Prevotella and an increase in butyrate-producing bacteria as well as bacteria belonging to the family *Bifidobacteriaceae* (Haro, Montes-Borrego et al. 2016) and this diet has also been linked with *Parabacteroidetes distasonis* (Haro, Garcia-Carpintero et al. 2016).

Other fat types

There is very little data on the impact of different fats other than fatty acids on the composition of the GM. In one study, the impact of phytosterols on GM was evaluated in a randomized placebo-controlled crossover trial with 13 adult subjects who consumed plant stanol esters (3g/day) or control margarine for 3 weeks followed by 4-week washout period and another 3-week intervention period. The consumption of plant stanol esters for 3 weeks

did not affect the GM composition. (Baumgartner et al. 2017) Similarly, little data exist on SCFAs. In one human study, butyrate (sodium butyrate) was consumed by lean or obese men for one month and the composition of the GM determined: *Lachnospiraceae* and *Bacteroides* were identified in lean men and *Coriobacteriaceae* and *Clostridiales cluster* XIVa in their obese counterparts due to butyrate consumption (Bouter et al. 2018). Other human studies using oral SCFAs have focused mainly on subjects and not one the GM e.g. the effect of SCFAs on energy expenditure and lipid metabolism (Chambers et al. 2018) or on disease development such as inflammatory bowel disease (Di Sabatino et al. 2005) but both lack any evaluation of the GM. With regard to CLA, one study revealed that drinking milk containing trans-10, cis-12 CLA decreased fecal *Lactobacilli* and *Bifidobacteria* in humans (Farnworth et al. 2007).

Combination of fatty acids and probiotics

Thus far only one small scale human study (n=15 in each study group) combining n-3 LC-PUFA and probiotics has been conducted; this was a 6 weeks' trial in overweight adults, investigating the effect of combining n-3 LC-PUFAs (capsules containing 180 mg EPA and 120 mg DHA) with probiotic (VSL#3) supplements. Although the primary aim of the study was to evaluate the metabolic effects of the intervention, bacterial colony counting was also carried out. The administration of the probiotic mixture modified the GM, but no impact was seen due to the consumption of n-3 LC-PUFA (Rajkumar et al. 2014). Instead, the combination of the two supplements resulted in a further increase in the abundance of *Bacteroides* accompanied by a decrease in those of Coliforms and *E. coli*. Although this is an interesting approach allowing the investigation of combinations of two active dietary ingredients, it appears that there is no simple relationship between dietary fats and GM and thus far the human studies have failed to provide compelling evidence for the potential added

benefit of supplementation of diet with different fats or fatty acids in combination of probiotics, at least with regard to the GM.

In summary, an SFA diet seems to associate with bacteria linked with dysbiosis, such as Proteobacteria (Shin, Whon, and Bae 2015), while a PUFA intake, particularly that of n-3 LC-PUFA, has been associated with a decreased Firmicutes to Bacteroidetes ratio and an increased diversity which are considered to be beneficial for the host. However, our current knowledge is limited and there is inconsistent knowledge on how different types of fat alter the composition of the GM and further studies will be needed before one can draw more firm conclusions.

The mechanisms of dietary fat - intestinal microbiota crosstalk

There is convincing evidence that dietary fat and fatty acid composition can modulate the GM, both in humans and mice (Tables 1 and 2, Supplemental tables 1 and 2). This crosstalk may be one contributor to the GM dysbiosis in several metabolic disturbances detected in both mice and humans such as obesity. Several mechanisms (Figure 1 and 2) may be postulated to explain how the crosstalk between dietary fat and GM can influence the health of the host; dietary fat may modulate the GM composition and thus influence the metabolites produced by bacteria; on the other hand, GM may modulate dietary fat and fits absorption. In addition, dietary fat may modulate the properties of the GM, such as bacterial adherence and inflammatory potential. Most of the evidence describing the cross-talk between dietary fat and GM has emerged from experiments conducted in animal or *in vitro* studies.

Modulation of GM composition by dietary fat

Dietary fat may modulate the abundance of bacteria with either anti-inflammatory properties, like *Bifidobacteria* or pro-inflammatory effects, such as lipopolysaccharide, LPS,-containing

bacteria. These changes in the GM can be reflected in an altered metabolite profile produced by the GM, which can then have consequences. These can be mediated either locally, for example by modifying the toxicity of the intestinal environment which subsequently impacts on the health of the intestinal epithelium (Lee et al. 2017), or systematically, e.g. through the presence of low grade inflammation. There are several mechanism through which dietary fatty acids can modulate the GM composition, as discussed below.

Regulation of Intestinal alkaline phosphatase activity

Intestinal alkaline phosphatase (IAP) is an enzyme that plays an important role in GM homeostasis; it regulates intestinal membrane pH, detoxifies LPS and promotes mucosal tolerance towards resident bacteria (Bilski et al. 2017). Dietary n-3 LC-PUFA may modulate IAP and subsequently induce alterations in the composition of the GM, as suggested in a study performed in transgenic fat-1 mice capable of producing n-3 LC-PUFA from n-6 LC-PUFA (Kaliannan et al. 2015). In that study, the expression of IAP was elevated after n-6 LC-PUFA feeding in the transgenic mice in comparison to their wild type counterparts. This suggests that elevated tissue levels of n-3 LC-PUFAs are able to modulate the activity of IAP, with this being reflected in the differences detected in the composition of the GM between the wild type and fat-1 mice (Kaliannan et al. 2015). Thus, the changes observed in the composition of the GM after the consumption of the 3-n LC-PUFA diet may be at least partly explained by an interaction between n-3 LC- PUFA, IAP and the GM.

Antimicrobial properties of dietary fatty acids

Some fatty acids exert their effects on the GM through their antimicrobial properties, as shown in several *in vitro* studies: EPA in the ethyl ester form, inhibited the growth of the anaerobe symbiont, *Bacteroides thetaiotaomicron* (Thompson and Spiller 1995), and linoleic acid and CLA inhibited the growth of five *Lactobacillus* strains in a dose-dependent manner

(Jenkins and Courtney 2003). In another study, linoleic acid, γ-linolenic acid, α-linolenic acid, arachidonic acid and DHA at high concentrations inhibited the growth of *Lactobacillus rhamnosus* GG, *Lactobacillus casei Shirota* and *Lactobacillus bulgaricus* (Kankaanpää et al. 2001). These findings with the commensal bacteria and probiotics indicate that dietary ingredients may directly influence the properties of those bacteria. There is also some evidence that medium-chain fatty acids are capable of GM modulation; *in vitro*, the relative abundance of *Lactobacillus* and *Bifidobacterium* increased in the presence of medium-chain fatty acids (Nejrup et al. 2015). This suggests that during early life when the GM is becoming established, medium-chain fatty acids, which are products of lipid hydrolysis, and also abundant in breast milk, may influence the composition of the developing GM (Nejrup et al. 2015).

Antimicrobial properties of bile acids

One putative mechanism linking fat intake to GM is related to the secretion of bile acids (Yokota et al. 2012). One physiological consequence of fat consumption is the secretion of bile. In addition to their role in solubilizing fat in the gastrointestinal tract, bile acids also possess antimicrobial properties (Yokota et al. 2012). In animal studies, feeding of bile acids has resulted in dramatic alterations in the GM. In a mouse study, a diet rich in taurocholic acid increased the abundance of *Bilophila wadsworthia*, a H_2S producing bacterium (Devkota et al. 2012). The introduction of cholic acid into the diet of rats led to an increase in Firmicutes at the expense of Bacteroidetes (Islam et al. 2011). Further investigations into the *in vitro* tolerance of Firmicutes and Bacteroidetes to deoxycholic acid, the secondary bile acid form of cholic acid produced by bacteria, showed that Firmicutes displayed a higher median inhibitory concentration (IC_{50}) as compared to Bacteroidetes (Islam et al. 2011). The cholic acid induced changes resembled those induced by high fat feeding suggesting that bile acids may mediate the changes in the composition of the GM induced by a high fat diet. This was

442 further demonstrated in a recent study in mice, in which a typical diet that had been
443 supplemented with bile acids resulted in a GM composition similar to that induced by feeding
444 a high fat diet (Zheng et al. 2017).

445 The bile acid tolerant bacteria have been shown to participate in the metabolism of the bile
446 acids i.e. bile acid deconjugation. In mice, the provision of high fat diet increased the
447 proportion of *Lactobacillus* strains (H. Zeng et al. 2013). These strains are among the bacteria
448 that produce bile salt hydrolase, an enzyme capable of deconjugating bile acids. Some other
449 bacteria have been associated with bile acid metabolism e.g. *Clostridum* and *Eubacterium*,
450 both of which are capable of producing deoxycholic acids (Wahlström et al. 2016). Thus, it is
451 clear that one mechanism whereby dietary fat intake can influence the GM is mediated
452 through the bile acids. Furthermore, there appears to be a crosstalk in this phenomenon i.e.
453 the bile acids regulate the composition of the GM, while the GM participates in the regulation
454 of bile acid metabolism via deconjugation and dehydroxylation.

455

456 **Modulation of GM properties by dietary fat**

457 The GM can utilize multiple mechanisms through which it can interact with the host. Dietary
458 fat may modulate these bacterial properties, such as altering bacterial adherence to the host
459 epithelium or changing the characteristics of bacterial metabolites. In addition, dietary fat and
460 GM may participate in the regulation of the intestinal epithelium integrity and thus influence
461 the permeability of gut components to allow them to gain access to the circulation, as
462 discussed below.

463 *Bacterial adherence*

464 The adhesion and colonization of the bacteria to the intestinal surface is an essential
465 component of the microbiota-host interaction, both for pathogenic bacteria and their
466 beneficial probiotic counterparts. The majority of the bacteria are able to use the exogenous
467 fatty acids provided by the host's diet, and to incorporate these fatty acids into bacterial
468 membrane phospholipids, where the ratio of saturated to unsaturated fatty acids controls the
469 fluidity of the bacterial membrane (Yao and Rock 2015). The ability of probiotics to adhere
470 to the intestinal surface is influenced by PUFA (Kankaanpää et al. 2001). Most bacteria are
471 able to incorporate exogenous PUFA into their lipids, as detected in an *in vitro* study in
472 which free PUFAs introduced into the growth medium were identified within *Lactobacilli*
473 (Kankaanpää et al. 2004). However, the alterations in the bacterial lipid profile did not
474 change the hydrophilic or hydrophobic characteristics of the bacteria, thus it was not expected
475 that this would influence the adhesion properties of *Lactobacilli* (Kankaanpää et al. 2004).
476 On the contrary, in a recent study, microcapsulation of *Lactobacillus casei* with n-3 LC-
477 PUFA rich tuna oil (using a whey protein isolate-gum Arabic complex coacervative)
478 increased both the survival and bacterial surface hydrophobicity compared to *L.casei*
479 microcapsulation only (Eratte et al. 2017). This experiment indicated that n-3 LC-PUFAs
480 may be able to improve the adherence of *L.casei* to the intestinal wall, although other
481 mechanisms explaining the possible beneficial influence of PUFA on probiotics may also
482 exist.

483

484

485 *Intestinal epithelium and LPS permeability*

486 A high fat intake in animal studies has been shown to induce alterations in the intestinal
487 epithelium, with a subsequent increase in intestinal permeability (Cani et al. 2008; de La

Serre et al. 2010; K. A. Kim et al. 2012). The type of dietary fat may have distinct properties, as EPA has been shown to enhance the heat stress-impaired intestinal epithelial barrier in Caco-2 cells, while DHA was less effective and arachidonic acid, an n-6 LC-PUFA, exerted no effect at all (G. Xiao et al. 2013). In another study, addition of EPA to Caco-2 cells improved membrane permeability as measured by fluorescein sulfonic acid permeability (Usami et al. 2001). Furthermore, DHA has been shown to have complex actions on intestinal epithelial integrity i.e. an increase in the integrity was observed in Caco-2 cells using a short cell growth protocol without cell stress (Mokkala et al. 2016) but a reduction in the integrity has also been detected by other investigators in unstressed Caco-2 cells (Roig-Pérez et al. 2004; Aspenström-Fagerlund et al. 2007).

One way that the GM can influence the host's health is via its ability to increase intestinal permeability; this property is evident in the transfer of LPS from gut to the circulation (Cândido et al., 2018). A high fat diet has been demonstrated to increase both the abundance of LPS-containing bacteria (Cani, Neyrinck et al. 2007) as well as the caecal content of LPS (Cani et al. 2008). LPS may be able to gain access to the blood circulation, especially after the intake of a high fat diet.

Modulation of microbial metabolites

A diverse and rich GM produces and also modulates a huge number of metabolites that have been linked not only to health benefits but also to disease. Diet may contribute to the production of metabolites by the GM. Some substrates, such as fibre, are utilized for the bacterial production of SCFA (acetate, propionate and butyrate); diet may modulate the composition of the GM by enhancing the growth of bacteria and modulating their subsequent capabilities to produce metabolites (Scott et al. 2013; Postler and Ghosh 2017). SCFAs are the end products of fibre fermentation by the GM but dietary fat may indirectly influence the

512 production of these fats by altering the abundance of SCFA fermenting bacteria. For example
513 in animal studies, provision of a high fat diet was shown to decrease the levels of
514 *A.muciniphila*, a propionate producing bacterial species (Everard et al. 2013) whereas
515 treatment with n-3 LC PUFA increased the abundance of this species (Caesar et al. 2015;
516 Kaliannan et al. 2015). There was an increase in the proportion of *F.prausnitzii*, a butyrate
517 producing bacterium after feeding mice a high fat diet (W. Liu et al. 2016); in humans, a
518 similar phenomenon was observed after a high intake of SFA (Fava et al. 2013), and
519 furthermore an increase in the abundance of this bacterium was detected in a trial where
520 subjects consumed a Mediterranean diet rich in PUFA (Haro et al. 2016). It has also been
521 demonstrated that consumption of a high fat diet reduced the formation of SCFAs in rats,
522 with the concentration being gradually increased over a longer period of feeding (Jakobsdottir
523 et al. 2013). In humans at an increased risk of developing the metabolic syndrome, the
524 consumption for 4 weeks of a diet with high levels of SFA (38 E% fat, 18 E% SFA)
525 increased the fecal SCFA concentration (Fava et al. 2013).

526 Another link between diet and the GM is related to the neurotransmitter serotonin, which is
527 synthetized in the gastrointestinal tract and exerts both local and systemic effects, for
528 example, regulating endocrine function. Serotonin is produced from tryptophan, which is an
529 essential amino acid and thus needs to be acquired from either the diet or from microbial
530 sources (Sharon et al. 2014). It was shown in a recent study conducted in mice that there were
531 reduced levels of two tryptophan metabolites, indole-3-aldehyde (I3A) and tryptamine, which
532 are both aryl hydrocarbon receptor (Ahr) ligands, after the animals were fed a high fat diet
533 (Krishnan et al. 2018). Thus, the dietary fat intake may act indirectly through the GM to
534 influence the production of tryptophan metabolites, which consequently would have
535 metabolic consequences such as attenuating fatty acid- and LPS-stimulated production of
536 pro-inflammatory cytokines in macrophages (Krishnan et al. 2018). The evidence is scarce in

this respect; thus the role of dietary fat in the synthesis of bacterial metabolites, such as in the production of serotonin needs to be clarified. It is noteworthy that this relationship may be intertwined with other components that are invariably present with dietary fats such as the retinoids, which also have been linked with effects on host immunity. Nonetheless, it may be hypothesized that dietary fat, by modulating the abundance of bacteria which produce these metabolites, also indirectly influences the synthesis of other gut origin metabolites.

Endocannabinoids

The GM has been demonstrated to be able to modulate the endocannabinoid system, which in addition to its significance in neural signaling, is proposed to have an important role in energy metabolism, gut physiology and inflammation (Cani, Plovier et al. 2016). The GM may modulate the levels of endocannabinoids in gut and adipose tissue, for example by regulating the numbers of endocannabinoid receptors or by altering the activities of the enzymes involved in endocannabinoid synthesis as reviewed by Cani and co-workers in 2016. In mice, the addition of *A.muciniphila* to a high fat diet increased intestinal levels of endocannabinoids, such as 2-arachidonoylglycerol, improved gut-barrier function and decreased the severity of metabolic endotoxemia (Everard et al. 2013). In humans, increased circulating levels of endocannabinoids have been detected in overweight and obese subjects (Côté et al. 2007 and Banni et al. 2011). As 2-arachidonoylglycerol is derived from arachidonic acid, any increase in the n-3 to n-6 LC-PUFA ratio may subsequently decrease the synthesis of N-arachidonoylethanolamine and 2-arachidonoylglycerol, as observed in a study conducted in mice fed with a DHA supplemented diet (J. Kim et al. 2016) as well as in obese humans after supplementation with n-3 LC-PUFA rich krill oil (Banni et al. 2011). As 2-arachidonoylglycerol has been associated with both anti-inflammatory and pro-inflammatory effects (Turcotte et al. 2015), further studies are clearly needed to clarify the role of endocannabinoids and their interactions with the GM and host health.

GM influence on dietary fatty acids

It is evident that dietary fat modulates GM, but on the other hand, dietary fatty acids may be modified by the GM, as demonstrated in a study where a novel, steatohepatitis-inducing diet containing 72 E% fat with a high content of cholesterol was fed to mice (Yamada et al. 2017). Subsequently, changes were detected in the GM composition, and also in luminal SFA and n-6 LC-PUFA metabolic pathways (Yamada et al. 2017). Furthermore, in an *in vitro* study, *L. acidophilus* was shown to be able to convert linoleic acid into 13-hydroxy-cis-9-octadecenoic acid (Hirata et al. 2015) indicating that there can be GM-mediated alterations in the gut lipid profile. These findings will need to be clarified in further experiments as the potential of the GM to modulate fatty acids may be important when one considers the well-known impacts of dietary fats on several metabolic disorders. A good example of this is the absorption of SFAs which are known to increase the risk of cardiovascular diseases (Berry et al. 2012; Hooper et al. 2015). The GM are also capable of biohydrogenating fatty acids, such as linoleic acid, as shown in a recent *in vitro* study (De Weirdt et al. 2017). The biohydrogenation of linoleic acid leads to the formation of a compound with less anti-microbial activity, vaccenic acid, which is also a precursor of CLA (De Weirdt et al. 2017).

GM influence on lipid metabolism

In addition to modifying fatty acids, the GM may also participate in host lipid metabolism outside the gastrointestinal tract. In mice, it seems that conventionally raised and germ-free mice display different serum lipid profiles with lower triglyceride levels being found in the conventionally raised mice (Velagapudi et al. 2011). This may result from the property of the GM to regulate energy storage of fat by suppressing the expression of Fasting Induced Adipocyte Factor (FIAF). Since FIAF inhibits lipoprotein lipase, the reduction in the activity of FIAF increases both lipoprotein lipase activity and triglyceride deposition in adipocytes

(Bäckhed et al. 2004). In humans, a negative correlation was found in a metagenomics study between the level of metagenomic gene clusters of the order Clostridiales and serum levels of triglycerides and there was a positive correlation with that of HDL (Karlsson et al. 2013). Furthermore, the GM richness has been related to the host serum lipid profile, i.e. a lower richness being associated with dyslipidemia. The authors suggested that the GM in subjects with a low GM richness had increased levels of FIAF, which resulted in the increased release of triglycerides and free fatty acids (Le Chatelier et al. 2013). Our own study, which applied a metabolomics approach, found a relationship between GM and serum lipids, e.g. there was an inverse correlation between genus *Lachnospira* and different lipoprotein particles and triglycerides, while that of *Blautia* correlated positively with different lipoprotein particles (Röytiö et al. 2017). Based on these findings, it is evident that the GM participates in host lipid metabolism. In a systematic analysis of 893 humans, it was estimated that the GM explained 6% of the variation in serum triglycerides and 4% in HDL and furthermore, a total of 28 bacterial taxa was associated with blood lipids (Fu et al. 2015). The GM may also participate in fat absorption, as evidenced in a recent study, where high fat diet induced jejunal microbiota in germ free mice exhibited increased absorption of lipids, even when the mice were fed a low fat diet (Martinez-Guryn et al. 2018). Furthermore, the GM, specifically Firmicutes, promoted fatty acid uptake and lipid drop formation in zebrafish enterocytes (Semova et al. 2012). In mice fed with a high fat diet, elevated faecal lipid levels were reported in conventionally raised mice as compared to germ free mice (Rabot et al. 2010), indicating that the GM participates in fat absorption. There is still a paucity of evidence detailing which of the GM's properties participates in host lipid metabolism, the mechanism may involve GM metabolites, such as bile acids and SCFAs, both of which are capable of regulating lipid metabolism.

Interestingly, small intestinal microbiota may be potentially an important regulator of host lipid absorption (Martinez-Guryn et al. 2018). This notion was based on an experiment in germ free mice conventionalized with high fat or low fat diet induced jejunal microbiota. In this model, gavaged radioisotope labelled lipids (triolein and cholesterol) were measured in plasma as markers of lipid absorption. Those mice, which were conventionalized with high fat diet induced microbiota, had an increased plasma level of radiolabeled lipids compared to mice conventionalized with low fat diet induced microbiota. The increase in plasma radiolabeled lipids was observed regardless of the amount of fat in chow, i.e. even when the conventionalized mice were fed with low fat diet. This suggest that small intestinal bacteria participate in lipid absorption of the host, the anticipated mechanism being upregulation of the genes involved in lipid absorption (Martinez-Guryn et al. 2018). In human, a recent study in healthy adults demonstrated (using luminal fluid samples) firstly, a high interindividual variability in the proximal gastrointestinal tract microbiota (Seekatz et al. 2019), Firmicutes being the dominant phylum across the multiple proximal gastrointestinal sites, while a higher abundance of Bacteroidetes species (*Prevotella*) was found in the stomach and duodenum. Secondly, the lower microbial diversity was detected in the small intestinal compared to stool microbiota (Seekatz et al. 2019), that is generally considered to reflect lower gastrointestinal tract microbiota. The lower diversity and lower abundance of bacteria within small intestine may originate from its environment, knowingly influenced by host factors including low pH, bile acids and antimicrobial peptides (Martinez-Guryn et al. 2018). To this end, it appears that small intestinal microbiota may participate in host lipid metabolism, but confirmatory research is needed.

The consequences of dietary fat - gut microbiota crosstalk

The influence of dietary fat on human health is well established. As discussed, there are several possible ways in which dietary fat and GM may interact. This crosstalk may at least partly explain the observed health effects of dietary fat and GM, for example the influence of SCFAs on glucose homeostasis and the ability of LPS to evoke low grade inflammation.

GM metabolites

It is well-known that the SCFAs produced by GM are involved in energy metabolism. SCFA production is one means to provide energy to the host, in other words, it contributes to the energy harvest. This may be both beneficial in cases when additional energy is needed such as in conditions when the diet is rich in fibre but low in fat or energy, but harmful in cases when obesity is the outcome. The association between SCFAs and body weight is not fully understood, beneficial effects on obesity have emerged from work done in mice, when supplementation with acetate, propionate, butyrate or their mixture inhibited the body weight gain induced by feeding a high fat diet (W. Liu et al. 2016). It seems likely that SCFAs exert a beneficial influence on energy metabolism. However, opposite outcomes have also been detected as higher levels of SCFAs were detected in fecal samples from overweight and obese individuals as compared to their lean counterparts (Schwiertz et al. 2010; Fernandes et al. 2014). In addition to providing an energy source, SCFAs have displayed anti-inflammatory and immune-signaling properties as reviewed by Puddu et al. (2014). SCFAs are signaling molecules acting through many receptors, such as the free fatty acid receptors 2 (FFAR2) and 3 (FFAR3) (Le Poul et al. 2003). The targets for SCFA induced signals are glucose homeostasis and inflammation. Glucagon-like peptide -1 (GLP-1) is a well-known mediator involved in glucose homeostasis; this hormone is expressed in intestine and has a

crucial role in controlling the plasma glucose concentration. Rectal administration of SCFAs was shown to increase the secretion of GLP-1 (Freeland and Wolever 2010), evidence for a close link between SCFAs and GLP-1. The ability of SCFAs to act as anti-inflammatory agents may be due to their inhibitory actions on the toll-like receptor (TLR) 4 as well as on the production of cytokines (Puddu et al. 2014). Another example is bile acids since the GM participates and even regulates bile acid metabolism. This is of importance as bile acids are participants in several metabolic pathways in many body locations including gut, liver and other peripheral organs. For example, bile acids participate in the regulation of glucose and lipid metabolism as well as being involved in inflammatory processes through the Farnesoid X receptor and the G protein-coupled bile acid receptor 5 (Wahlström et al. 2016). Another example described above is the finding that a diet with a high fat content may decrease the production of tryptophan, the amino acid precursor of the neurotransmitter, serotonin. If there is a reduction in the levels of this key neurotransmitter in the gut, this may subsequently influence the function of the nervous system.

Low grade inflammation

GM dysbiosis has been related to low-grade inflammation as evidenced by the increased levels of circulating inflammatory markers (Le Chatelier et al. 2013). Similarly diet, mainly the intake of SFAs, has been associated with increased inflammation, whilst consumption of n-3 LC-PUFA may dampen an established inflammatory condition (Calder et al. 2011). Taking these two aspects together, one could argue that low-grade inflammation may arise from the cross-talk between dietary fats and the GM with one possible mediating factor being LPS. Elevated concentrations of circulating LPS, i.e. metabolic endotoxemia (Cani et al. 2008) may induce low-grade inflammation in adipose tissue (K. A. Kim et al. 2012). Alternatively, LPS may act systemically, as it has been shown to impair glucose metabolism by interfering with insulin signaling (Robbins et al. 2014). High LPS concentrations have

been detected in metabolic disorders such as obesity and diabetes in both mice and humans (Creely et al. 2007; Pussinen et al. 2011; Jayashree et al. 2014; Cani and Everard 2016). Alterations in both glucose metabolism and intestinal permeability have been outcomes in several studies conducted in experimental animals investigating the relationships between an intake of a diet with a high fat, the GM composition and the host's health (K. A. Kim et al. 2012; Martinez-Medina et al. 2014; Hamilton et al. 2015). In humans, similar associations have been observed between increased intestinal permeability and metabolic disorders, such as in the metabolic syndrome (Leber et al. 2012), obesity and alterations in glucose metabolism in obese women (Teixeira et al. 2012) and in patients with liver malfunctions (Benjamin et al. 2013; Damms-Machado et al. 2017). It is not well established if the mechanism underpinning these clinical conditions is a metabolic endotoxemia secondary to the increased intestinal permeability and then on to subsequent inflammation. Furthermore, it is far from clear whether it is the amount and/or the type of dietary fats which is important in humans in this phenomenon. It is noteworthy that in addition to modulating the LPS content in intestine and impacting on intestinal epithelial integrity, a high fat diet also influences the transport of LPS. It is known that LPS is also transported in chylomicrons; the LPS concentration is increased after fat consumption, providing another mechanism to explain how dietary fat may be involved in the cross-talk between diet, the GM and the host's health. Furthermore, in addition to LPS, there are several other bacterial components, like flagellins, peptidoglycan (Rooks and Garrett 2016) and phosphatidylglycerols (Dugail, Kayser, and Lhomme 2017) that might gain access to the circulation and evoke metabolic effects.

The mechanism underpinning the GM induced inflammation may involve an interaction between pattern recognition receptors (PRR), including TLRs and micro-organism-associated molecular patterns (MAMPs). PRR recognize MAMPs, such as LPS, flagellin and peptidoglycan, which trigger a PRR-mediated immune response (Rooks and Garrett 2016).

For example, TLR4 recognizes bacterial LPS and activates an immune response. Interestingly, fatty acids are also ligands for TLR4. Thus, SFA may also directly induce inflammation through TLR4 activation, as was shown in a study performed in mice. In contrast to the mice fed fish oil, those animals receiving SFA in the diet showed signs of increased TLR activation together with inflammation in white adipose tissue as well as reduced insulin sensitivity (Caesar et al. 2015). In addition, DHA has been shown to inhibit LPS or SFA induced activation of TRL4 (Hwang, Kim, and Lee 2016). Another link may be mediated through the soluble CD14, a PRR that not only binds LPS (Goldblum et al. 1994), but also phospholipids (Yu, Hailman, and Wright 1997). The amount of soluble CD14 has been found to correlate with the concentrations of LC-PUFAs, particularly with the level of arachidonic acid, with this being measured from breast milk (Laitinen et al. 2006). It may be speculated that soluble CD14 is an immune regulatory link in the pathway leading from dietary composition to infant health as its concentrations were lower in breast milk fed infants without atopic eczema as compared to those suffering from this skin disorder (Laitinen et al. 2006).

Resolvins and protectins are lipid derivatives of EPA and DHA; it has been proposed that one anti-inflammatory action of n-3 LC- PUFA may be related to the resolution of inflammation (Serhan, Chiang, and Van Dyke 2008). The GM may participate in this process by promoting the formation of the E-series resolvins from dietary EPA. The mechanism by which EPA is converted to resolvins involves cytochrome P450 enzymes, which are found both in mammals and microbiota (Serhan et al. 2000). DHA is a substrate for the D-series resolvins and protectins (Serhan, Chiang, and Van Dyke 2008). The role of resolvins and protectins as both anti-inflammatory and inflammation-resolving factors has been evaluated in many animal disease models (Serhan, Chiang, and Van Dyke 2008). In a recent study, resolvin D1 was found to reduce the extent of inflammation in colon and to normalize the barrier integrity

733 in mice fed with a high fat-high SFA diet (Lam et al. 2015). PUFA may also alter the
734 immunomodulatory effects of the GM, as shown in a study where EPA supplementation
735 increased the levels of transforming growth factor β1 mRNA and protein expression induced
736 by commensal *Lactobacillus gasseri* in colonic cell lines (Bentley-Hewitt et al. 2014).
737 Interestingly, two well-known pathogens, *Eschericia coli* and *Staphylococcus aureus*, did not
738 evoke this kind of effect. Liver malfunction is another inflammatory condition which has
739 been proposed to be influenced by the GM. In a recent study, the Ahr ligand I3A was shown
740 to attenuate inflammatory responses in hepatocytes exposed to lipid loading, suggesting that
741 the metabolites produced by the GM may beneficially modulate liver inflammation (Krishnan
742 et al. 2018).

743

744

745 **6. Critical appraisal and gaps in research**

746 It is challenging to gather scientific evidence demonstrating the cross-talk between dietary fat
747 and GM due to a range of factors related to the study design, the populations being studied
748 and the complexity of both diet and GM composition. There are thus several possible reasons
749 which could account for the apparent discrepancies encountered in the outcomes of the
750 published studies. Similarly, there are many factors that can influence the translation of the
751 results from animal or experimental studies to the situation in humans.

752 **Methods of analysing gut microbiota**

753 The methodological aspects that are considered to influence the reliability of the GM
754 analyses include variations in faecal sample collections such as whether the sample is fecal,
755 caecal or mucosal, storage conditions prior to freezing or analysis and the choice of methods

applied for analyzing the GM composition or function including the techniques utilized for faecal DNA extraction. The initial studies investigating the impact of diet on GM utilized approaches requiring bacterial cultivation, e.g. colony counting or reporting alterations either in selected or specific bacterial groups. The most common detection techniques have been fluorescent in situ hybridization (FISH), denaturing gradient gel electrophoresis (DGGE), qPCR and selected plating. Recently, high-throughput methods, such as 16S rRNA gene or metagenomic sequencing have allowed the generation of much more detailed information about the GM profile, including also the possibility to make predictions of the function of the GM. There are other omics, i.e. metatranscriptomics, that may be used to analyze gene expression (Heintz-Buschart and Wilmes 2017), metaproteomics that gathers information on functional proteins (Lee et al. 2017) and metabolomics that provides data about the metabolites (Vernocchi, Del Chierico, and Putignani 2016) produced by the bacteria; the application of these sophisticated techniques will be needed if we are to clarify the functionality of the GM. Many of these methods, such as DNA extraction, will require standardization if we intend to make comparisons between studies (Costea et al. 2017). Furthermore, it is noteworthy that the term "healthy microbiota" is not an established condition, instead the GM is complex with extensive inter-individual variation. These gaps, together with the lack of standard methods in the published studies, have complicated the interpretation of the results across many studies, as also observed in this review.

Dietary intake

Diet in human studies

When interpreting the dietary impact on GM in human trials, the study setting needs to be considered, i.e. whether the investigators have examined the impact of a habitual diet or

780 utilized either a short or long-term intervention period using either foods or food
781 supplements. Another concept is related to the energy intake from the diet. Some studies have
782 not formulated the diets in such a way that they would be isocaloric and further, there may
783 have been differences in the sources of energy and fat. In other words, the energy yield and
784 the amount of other lipid molecules within the fat may vary and influence the composition of
785 the GM. This was demonstrated in a recent study in which germ-free mice, but not their
786 specific pathogen -free counterparts, were resistant to a high fat diet rich in cholesterol,
787 suggesting that it was cholesterol, rather than the high fat intake, which had influenced the
788 GM (Kübeck et al. 2016). In addition, it is noteworthy that if one alters the amount of dietary
789 fat, then the contents of carbohydrates and protein will have to change simultaneously, if the
790 diet is to be kept isocaloric. Diet also consists of multiple other nutrients, such as vitamins,
791 which may also influence the composition of the GM (Berrington et al. 2013; Biesalski
792 2016).

793 The complexity inherent in the diet complicates the evaluation of the effect of single changes
794 within the human diet on the GM and these kinds of studies should take into account the
795 variation in the diet. For instance, it has been reported that consumption of virgin olive oil
796 containing added phenolic compounds and thyme increased the faecal content of
797 *Bifidobacterium* in contrast to virgin olive oil with only naturally occurring phenolic
798 compounds, suggesting that it is the constitute of the oil such as the phenolic compounds, that
799 exert an independent role in modifying the GM (Martin-Pelaez et al. 2017).

800 One challenge lies in the measurement of dietary intakes in free-living humans. Although
801 there are various validated dietary assessment methods including food diaries and
802 questionnaires, their accuracy may be criticized e.g. due to over- or under-reporting; this
803 problem has been emphasized particularly in overweight individuals (Lioret et al. 2011). In

addition, the accuracy of some nutrient calculation databases may not achieve the necessary levels.

The extensive interindividual variation in the GM may challenge the success of short-term intervention trials, since the high variation between different subjects tends to overwhelm any possible alterations due to the change in the diet or the intake of some supplement (Wu et al. 2011; Kelder et al. 2014; Watson et al. 2017). However, a study in monozygotic twins confirmed the impact of diet on the GM; co-twins who consumed the same amount of energy, had a more similar pattern of *Bacteroides spp*. as compared to co-twins who consumed different amounts of energy (Simoes et al. 2013). Furthermore, the co-twins with the same SFA intake had a similar *Bacteroides* profile, but in contrast, a similar consumption of fiber resulted in a very low *bifidobacterial* profile similarity (Simoes et al. 2013). Differences in the findings between the intervention studies with food supplements may arise from the formulation of the supplement, for example, the chemical form of PUFAs may differ. In addition, the food matrix used for administration of the intervention product may have an impact on the properties of investigated product. This is another factor that needs to be taken into account during study planning, but interestingly with respect to the LC-PUFAs, it was recently demonstrated that it was irrelevant whether n-3 LC-PUFA oil was supplemented as soft-gel capsules or drinks since the formulation did not influence the intervention outcome on the GM (Watson et al. 2017). Nonetheless, it is noteworthy that the effects of probiotics tend to be strain specific and therefore the trials using different probiotics should not be grouped. In addition, the interaction between dietary fat and probiotics has been rarely considered, but a recent study implied that beneficial metabolic effects may take place (Rajkumar et al. 2014). Our research group is conducting an on-going clinical trial in 439 pregnant women which aims to study the impact of probiotics and LC-PUFA (fish oil) separately or in combination as compared to placebo on both maternal and child health. This

trial will include mechanistic studies examining whether the supplements can modify both the inflammatory response and the GM (ClinicalTrials.gov, NCT01922791). The initial report from the study could detect no influence of the probiotics, the fish oil or their combination on serum zonulin levels, which was used as a marker of intestinal permeability (Mokkala et al. 2018). This was surprising considering that the published literature has indicated that both probiotics and n-3 LC-PUFAs are able to enhance intestinal epithelial integrity (McNaught et al. 2005; Q. Li et al. 2008; J. Zeng et al. 2008; Sharma et al. 2011; Leber et al. 2012; Horvath et al. 2016; Mokkala, Laitinen, and Röytiö 2016). In addition, our evaluation of the baseline data from 100 women in the same study, revealed a relationship between the dietary intake and the GM (Röytiö et al. 2017). Nevertheless, it is possible that although zonulin has been found to correlate with more traditional measures of intestinal permeability, this protein may not be an optimal marker of intestinal permeability; in addition to being produced in the intestine, zonulin may also be synthesized in other tissues (Wang et al. 2000). Moreover, a recent study revealed that instead of specifically recognizing serum zonulin, the widely used zonulin commercial kit detects multiple proteins, some of which may be possibly structurally and functionally related to zonulin (Scheffler et al. 2018).

In conclusion, although there are several issues that complicate the interpretation of how diet impacts on GM composition, it is possible to overcome at least some of the confounding factors in well-controlled randomized trials.

Diet in animal studies

As diet is a complex mixture of nutrients, some diet-related issues are better resolved in animal studies than can be addressed in human studies. Most animal studies utilize standard chow, instead of a refined low fat chow, as the control. Standard chow contains fibre from

various sources and thus has a heterogeneous fibre composition. As fibre is a major component influencing the composition of the GM, wide variations in the fibre content may induce extensive variation in the GM, a factor which has not been always taken into account in these studies. For example, when the effects of a refined high fat diet, a refined low fat diet and standard chow diet were investigated, large changes in GM composition were observed with both refined diets in comparison to standard chow (Dalby et al. 2017). The authors concluded that the use of standard chow as a control could overestimate the changes detected in studies that investigated the impact of a high fat diet on GM. Similarly to the situation in human trials, although isocaloric diets are used in many experiments, the impact of an increasing/decreasing fat content in the feed may require an increase or decrease in other dietary components, such as fibre and/or protein and these will exert their own independent impacts on GM. Further problems arise from vitamins and other minerals in the feeds, since these tend to be rich in fibre sources. When evaluating the impact of various fatty acid forms including PUFA and MUFA, the exact composition of fatty acids is not always determined; these may influence the outcome and thus exert an impact on the interpretation of the study's results. In animal experiments, the content of fat in the high fat feed (up to 70 E%) or in PUFA enriched feed (Gibson et al. 2015; Yu et al. 2014; Martinez, Leone and Chang et al. 2017) is far higher than any normal fat consumption in humans, i.e. it is a physiologically abnormal situation, and evidently not extrapolatable to any human situation.

Host characteristics

The environment is one factor that influences the GM, e.g. mice are housed under laboratory conditions, lacking any contact with pathogens. In humans, family members are known to share more similarities in their GM profiles as compared to unrelated individuals (Turnbaugh,

877 Hamady et al. 2009). Host gut phenotype, e.g. nutritional status, animal strain, the use of
878 antibiotics, intestinal disease and inflammation may also influence the GM composition and
879 its localization, thus obscuring any dietary impact on GM.

880

881 ***Nutritional status***

882 In humans, the dietary intake influences the nutritional status; for example, this can be
883 manifested in either overweight or obesity, conditions which in turn, have been associated
884 with alterations in GM. However, it has been debated whether the detected alterations are a
885 cause or a consequence of their body weight. On one hand, the difference in the composition
886 of the GM in overweight and obese individuals as compared to normal weight subjects may
887 originate from their increased energy intake e.g. their consumption of energy-rich nutrients
888 including fat. On the other hand, the GM may contribute to host metabolism via the
889 metabolites produced by the micro-organisms, such as SCFAs or via their energy harvesting
890 properties. In addition to body weight, nutritional status at baseline may contribute to the
891 findings. For example, the n-3 LC- PUFA status at baseline may vary, as was suggested in a
892 study in infants receiving infant formula (containing n-3 LC-PUFA) as compared to babies
893 being fed cow's milk (Nielsen et al. 2007). Indeed, distinct GM clusters due to fish oil
894 consumption were detected only in the group consuming the cow's milk (Nielsen et al. 2007),
895 probably due to their lower n-3 LC-PUFA status at the start of the intervention. Another
896 study conducted in infants revealed that the GM response to fish oil and sunflower oil was
897 dependent on the breast-feeding status (Andersen et al. 2011). Fish oil, but not sunflower oil,
898 induced alterations in the GM in those infants who stopped receiving breast milk before the
899 study as compared to those who continued to be breast-fed (Andersen et al. 2011). In another
900 study, pregnant women consumed 150 g of an oily fish (salmon) from 20 weeks of gestation

until delivery and when the infants' GM was measured, the abundance of the *Atopobium* cluster was found to be decreased in the formula-fed, but not in the breast-fed infants (Urwin et al. 2014). These findings suggest that breast milk either has nutrients or components, such as prebiotics, with GM modulating effects, or that the baseline n-3 LC-PUFA status was lower in the infants who responded to fish oil since they were not being breast-fed (Andersen et al. 2011).

The most widely used model to study GM composition has utilized C57BL/6 mice fed with a high fat diet to induce obesity. Other models have involved mice which have been genetically modified to be obesity-prone. The studies have revealed the major impact of the diet on the GM, i.e. GM has been shown to change regardless of the obesity status, either induced by dietary means or genetic obesity (Hildebrandt et al. 2009; de La Serre et al. 2010; Murphy et al. 2010; Zhang et al. 2010; Ravussin et al. 2012; L. Xiao et al. 2017). This suggests that a high fat diet influences GM regardless of the phenotype.

Host genetics and gender

Host genetics may exert a strong influence on shaping the GM or in the plasticity of the GM in response to dietary composition, as shown in a study performed in mice (Benson et al. 2010; Parks et al. 2013). Nonetheless, in another mouse study, the diet was shown to shape the GM despite the presence of widely divergent genotypes (Carmody et al. 2015). In human twins, there have been observations of either a lack of any genetic effect on GM (Turnbaugh, Hamady et al. 2009) or some influence of genotype on the abundance of specific members of the GM (Goodrich et al. 2014). In healthy children (9-18 months of age), polymorphism in peroxisome proliferator activated receptor gamma 2 (PPARG2) and cyclooxygenase-2 enzyme 2 (COX-2) was associated with the fish oil induced reduction in *Lactobacillus*

paracasei-stimulated immunological capacity *ex vivo* (Harsløf et al. 2015). These findings suggest that genetics may be involved in modulating the diet-GM cross-talk and the host response to GM properties. Interestingly, recent studies in mice have revealed gender-based differences in the diversity and structure of the GM regardless of the diet as well as in the responses to a high fat diet or supplemental feeding (Bridgewater et al 2017, Org et al 2016, Sheng et al 2017). This correlation between diet and sex was also evident in human studies (Bolnick et al 2014). Animal studies suggest that the sex hormones such as testosterone and oestrogen are the main factors explaining the gender-related differences in the GM (Benedek et al 2017, Baker et al 2017).

Other factors: Antibiotics, alcohol

Medication, mainly antibiotics, exerts a detrimental and long lasting influence on the GM. The influence of antibiotics on GM and their consequences on long term health have been widely studied both in children and adults (Francino 2015). In general, treatment with antibiotics has been shown to decrease the GM diversity and the proportion of specific bacteria, and furthermore, the effects depend on which antibiotic has been administered (Lange et al. 2016). It noteworthy that it may take a long time before there is a recovery in the GM profile after exposure to the antibiotic; possibly the original state is never achieved, suggesting that also the health consequences of antibiotic use may be long lasting (Francino 2015). However, a study conducted in mice demonstrated that the adverse metabolic effects mediated by the GM after antibiotic exposure in early life could be prevented by PUFA administration (Kaliannan et al. 2016). In addition, there are interesting findings made by Chen and co-workers (2016) and Li and co-workers (2011) i.e that PUFA could prevent the adverse effects of alcohol use or of an intestinal transplant on the GM as well as on the

permeability and integrity of the intestine. Thus in human studies, it is important to record the medical history also before the initiation of the study, but unfortunately, as the effects of antibiotics use may be long-term (Jernberg et al. 2010), this is a clear confounding factor which could well influence the results. One option for consideration in future studies that should perhaps become a standard procedure, might be to access prescription registers to allow a more detailed record of the subject's use of antibiotics.

7. Summary and future perspectives

It may be concluded from the published experimental and clinical studies that there is a crosstalk between dietary fat and the GM. This is reflected in changes in the GM diversity, alterations in the composition of particular bacteria and their metabolic functions. Ultimately, there is evidence that this cross-talk exerts metabolic consequences such as a regulation of low-grade systemic inflammation. The key findings are that high intakes of dietary fat and SFA generally exert adverse effects on the GM, primarily increasing the Firmicutes to Bacteroidetes ratio and reducing the abundance of *bifidobacteria*, which potentially could contribute to many health related conditions such as obesity and type 2 diabetes. Instead, most studies examing unsaturated fats, have concentrated on n-3 LC-PUFAs. These compounds seem to exert opposite effects to those encountered with a high fat and high SFA diet, e.g. they may promote GM homeostasis and have beneficial health effects. Nevertheless, the mechanisms explaining how dietary fat could influence the GM and its metabolic consequences are thus far poorly understood. The complexity of both diet and GM are clearly key factors that hinder the implementation of trials and complicate the interpretation of the results. Furthermore, dietary fibre has been the focus of studies addressing the impact of dietary composition on GM. We conclude that there is potential for dietary modification

973 through adjusting both the amount and type of dietary fat, particularly by lowering the intake
974 of SFA and increasing the intake of unsaturated fatty acids. This is in line with the current
975 dietary reference guidelines for promoting the health of the general population.

976 Even though there are multiple factors that modulate the GM and various host dependent
977 responses, it is however essential that we strive to have a detailed understanding of this cross-
978 talk as it could provide a means of lowering the risk of diseases at both the level of the
979 individual and the general population. This challenge may be addressed by collecting and
980 analyzing longitudinal data from well-planned randomized clinical trials, with the data also
981 including dietary intakes. Modern technology also provides a means to investigate an
982 individual's characteristics such as host epigenetics; GM may be an important mediator of the
983 diet-epigenome-health interactions (Gerhauser 2018; Vähämiko et al. 2018), but further
984 studies will be needed to determine causal effects. Furthermore, tailored medicine may serve
985 as one future goal for preventive care, as has been suggested for the treatment of cancer
986 (Rajpoot et al. 2018). In this approach, targeted treatment is tailored to subpopulations that
987 differ in their susceptibility to some particular disease. With regard to the GM, this approach
988 will be challenging - first, it will require a linkage between the composition of the GM and
989 some disease, not only in epidemiological terms but also causally, and second, novel methods
990 will be needed to modify the GM composition so that it can benefit the target patients
991 (Petrosino 2018). As evidenced in this review, this will be extremely challenging as the GM
992 is highly variable between subjects and vulnerable to dietary intake. Nonetheless, the dietary
993 solutions may include the use of synergistic interactions, e.g. combining n-3 LC-PUFAs EPA
994 and DHA with probiotics. This approach could be utilized to generate health benefits as
995 active dietary ingredients have been shown to exhibit immunomodulatory benefits, one of the
996 key underlying factors in the lifestyle related diseases. It is clear that more research will be
997 needed to verify the benefits of the combination. It is noteworthy that since it is the entire

dietary pattern, rather than single nutrients that may have a modifying role in human health, these types of public health approaches may be feasible when designing a general risk reduction protocol for non-communicable diseases. In general, the dietary approaches used to modulate the GM can be considered as safe, as dietary induced changes in GM do not appear to be permanent, as seen in the study of David and co-workers (2014), in which the composition of the GM changed in one day, but reverted to the original composition two days after termination of an animal-based diet.

To conclude, recent investigations into the cross-talk between GM and human health have opened new approaches for diet-based interventions. Targeting human health by modulating the GM through the diet represents a visionary approach. However, there is a need to characterize in greater detail both the extent and the mechanisms through which these interactions occur. One challenge will involve compliance in individuals to the suggested dietary modifications and subsequently in the identification of effective means to induce the desired dietary alterations. One solution might arise from the exploitation of food supplements combined with dietary counselling. Another approach might involve the application of E-health technologies that support of lifestyle changes through electronic apps e.g. apps based on gamification i.e. the use of gaming techniques in non-game contexts. In an ideal world we will find more and more products on supermarket shelves claiming to contain active dietary ingredients with specific functions and efficacies. It is clear that consumers will need guidance if they are to make sense of the many health claims swirling around in the printed and social media; these claims should be verified by the appropriate authorities.

Conflict of Interest

The authors disclose no conflicts of interests.

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Tables

Figures

Figure 2. Multiple possible mechanisms whereby different dietary fatty acids may induce alterations in GM composition and gut function. 1. N-3-LC-PUFAs regulate IAP which modifies GM composition and intestinal membrane pH and also detoxifies LPS. 2. Some n-3 and n-6-LC-PUFAs manifest antimicrobial properties. 3 Both n-3-LC-PUFAs and SFAs increase the abundance of SCFA producing bacteria. 4. PUFAs induce alterations in intestinal permeability with both increasing and reducing the intestinal epithelial barrier integrity. 5. PUFAs incorporate into bacterial membranes and thus modify bacterial adherence to intestinal epithelium. 6. EPA and DHA are substrates for resolvins and thereby participate in resolution of inflammation. 7. DHA inhibits LPS or SFA induced TLR4 activation. 8. EPA increases the synthesis of TGF-β1. 9. Alterations in n-3 to n-6 LC-PUFA ratio may influence the synthesis of endocannabinoids and thus modulate the endocannabinoid system with further anti-/pro-inflammatory effects. 10. The influence of MUFA on GM is mostly unknown. FA: fatty acids; GM: gut microbiota; IAP: intestinal alkaline phosphatase; LPS, lipopolysaccharide; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SCFA, short chain fatty acids; SFA, saturated fatty acids; TGF β: transforming growth factor β1; TLR, toll-like receptor.