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Review

Dietary fat, the gut microbiota, and metabolic health – A systematic review conducted within the MyNewGut project

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SUMMARY

Background and aims: Studies indicate that dietary fat quantity and quality influence the gut microbiota composition which may as a consequence impact metabolic health. This systematic review aims to summarize the results of available studies in humans on dietary fat intake (quantity and quality), the intestinal microbiota composition and related cardiometabolic health outcomes.
Methods: We performed a systematic review (CRD42018088685) following PRISMA guidelines and searched for literature in Medline, EMBASE, and Cochrane databases.
Results: From 796 records, 765 records were excluded based on title or abstract. After screening of 31 full-text articles six randomized controlled trials (RCT) and nine cross-sectional observational studies were included. Our results of interventional trials do not suggest strong effects of different amounts and types of dietary fat on the intestinal microbiota composition or on metabolic health outcomes while observational studies indicate associations with the microbiota and health outcomes. High intake of fat and saturated fatty acids (SFA) may negatively affect microbiota richness and diversity and diets high in monounsaturated fatty acids (MUFA) may decrease total bacterial numbers whereas dietary polyunsaturated fatty acids (PUFA) had no effect on richness and diversity.
Conclusions: High fat and high SFA diets can exert unfavorable effects on the gut microbiota and are associated with an unhealthy metabolic state. Also high MUFA diets may negatively affect gut microbiota whereas PUFA do not seem to negatively affect the gut microbiota or metabolic health outcomes. However, data are not consistent and most RCT and observational studies showed risks of bias.

Abbreviations: ACE, abundance-based coverage estimation; ALA, α-linolenic acid; BF%, body fat percentage; BMI, body mass index; BP, blood pressure; CG, control group; CHD, coronary heart disease; CHO, carbohydrates; CI, confidence interval; CV, cardiovascular; d, day; DGGE, Denaturing Gradient Gel Electrophoresis; DHA, docosahexaenoic acid; EPA, eicosapentanoic acid; *EreC*, *Eubacterium rectale-Clostridium coccoides*; E%, energy percentage; FBG, fasting blood glucose; F/B, Firmicutes to Bacteroides; FISH, fluorescence in-situ hybridization; GI, glycemic index; HDL, high-density lipoprotein cholesterol; HOMA, Homeostasis model of insulin resistance; IG, intervention group; IQ, interquartile range; KO, Knockout; LA, linoleic acid; LDL, low-density lipoprotein cholesterol; LFHCC diet, low-fat, high-complex carbohydrate diet; LN, lean; LOM, logarithmic orders of magnitude; Med diet, Mediterranean diet; MetS, Metabolic Syndrome; MUFA, monounsaturated fatty acids; NEFA, non-esterified fatty acids; NOS, Newcastle-Ottawa Scale; n3 PUFA, omega-3 polyunsaturated fatty acid; n6 PUFA, omega-6 polyunsaturated fatty acid; NW, normal weight; OB, obese; OTU, operational taxonomic unit; OW, overweight; PCoA, Principal coordinate analysis; PICO, Population-Intervention-Comparison-Outcome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; PCR, polymerase chain reaction; PUFA, polyunsaturated fatty acids; qPCR, quantitative polymerase chain reaction; RCT, randomized controlled trial; resp., respectively; SCFA, short-chain fatty acids; SE, standard error; SEM, standard error of the mean; SFA, saturated fatty acid; TC, total cholesterol; TG, triglycerides; T2D, Type 2 diabetes; USFA, unsaturated fatty acids; UW, underweight; VLDL, very low density lipoprotein; VO2max, maximum oxygen uptake; WC, waist circumference; y, year.

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1. Introduction and rationale

In recent years, the gut microbiota has emerged as a significant factor for the regulation of energy balance and has been shown to be associated with obesity and metabolic diseases. The gut microbiota plays an important role in polysaccharide fermentation and the production of short-chain fatty acids (SCFA) which can be metabolized or used for the *de novo* synthesis of glucose, lipids or bile acids [1,2]. Additionally the gut microbiota is involved in the maintenance of barrier function of the intestinal epithelium preventing the translocation of lipopolysaccharides and related endotoxemia which can lead to inflammation and increased risk of insulin resistance [3,4]. Studies indicated that impaired gut microbiota-host interactions at infancy, e.g. by antibiotic use could increase the risk of metabolic diseases in later life [5].

1.1. Dietary intervention and metabolic health outcome

Dietary sources of energy and nutrients play a significant role in the development of obesity and metabolic diseases and also modulate the gut microbiota. Theoretically, dietary-induce microbiota changes could also be partly responsible for the metabolic phenotype of the person. Indeed, the obese microbiome has previously been reported to have an increased capacity to harvest energy from the diet when transferred from humans to germ-free mice [6]. In observational studies in humans, *Bacteroides* spp., *Bilophila wadsworthia* and *Alistipes* have been associated with a long-term diet high in animal protein and saturated fats, whereas *Prevotella, Roseburia, Eubacterium rectale* and *Facalibacterium prausnitzii* have been associated with plant-based diets high in carbohydrates and simple sugars [1,7,8]. Animal studies indicate that high fat diets are associated with changes in the gut microbiota leading to inflammation and increased risk of insulin resistance. In particular, high-fat diets rich in long-chain saturated fatty acids (SFA) have been found to modulate the gut microbiota resulting in dysbiosis, inflammation and consequently an increased risk of obesity and metabolic syndrome (MetS) [9,10]. In contrast, beneficial effects were observed for high tissue levels of n3 polyunsaturated fatty acids (PUFA) which reduced body weight gain and the severity of insulin resistance, fatty liver and dyslipidemia resulting from early-life exposure to antibiotics in a mouse model [11] but effects on microbiota are less well documented. Selective enrichment of specific microorganisms has also been found to promote metabolic health in a number of dietary intervention studies in humans [12,13].

1.2. The gut microbiome and metabolic biomarkers in at-risk populations

An altered gut microbiome has been reported in individuals with type 2 diabetes, independent of body mass index (BMI) [14,15]. When compared to individuals with normal glucose tolerance, an increased abundance of *Lactobacillus* spp. and a decreased abundance of *Clostridium* spp. were shown in individuals with type 2 diabetes [14]. Furthermore, a mathematical model based on shotgun metagenomic profiles identified an increase in *Clostridium clostridioforme* and a decrease in *Roseburia* 272 metagenomic clusters in type 2 diabetes from two cohorts [14,16]. Depletion of *Akkermansia muciniphila* has also been described as a microbial biomarker for type 2 diabetes prior to the onset of disease in a metagenomics study in monozygotic Korean twins [15]. Reduced butyrate and a decreased abundance of butyrate-producing genera, such as *Roseburia, Faecalibacterium* and *Clostridium,* have been found to be associated with obesity and impaired glucose tolerance [17,18]. Interestingly, an increase in propionate-producing genera, such as *Bacteroides* and *Prevotella*, were found in overweight and obese human individuals [19], suggesting a potential inverse relationship between butyrate and propionate with regard to metabolic health although also beneficial effects of propionate on metabolic health have been reported [17,20].

Thus this systematic literature review intends to investigate effects of dietary fat quantity and quality including different types of fatty acids on the gut microbiota and metabolic health outcomes in humans. It was performed within MyNewGut (http://www.mynewgut.eu/), a FP7 EU project which aimed to disentangle the role played by the gut microbiota (via interactions with lifestyle factors, e.g. diet, eating habits, stress, etc.), in the regulation of pathways leading to the development of obesity and the associated metabolic and behavioral disorders. This review is part of a series of position papers of the MyNewGut project aiming at informing future recommendations for dietary guidelines based on project results and the latest advantages in the field regarding insights gained in the role of the gut microbiome.

2. Methods

2.1. Search strategy and in-/exclusion criteria

We performed a systematic literature review following Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [21]. Our review protocol was registered on PROSPERO under the Registration Number CRD42018088685.

To identify studies we searched for literature in Medline via PubMed, EMBASE via the Elsevier platform, and the Cochrane databases via Wiley from their inception. All searches were performed on January 17, 2018 using a combination of subject and free-text terms with no date limit or language restriction. The search strategy was developed for Medline and adapted to yield results in other databases. Details on the Medline search strategy are provided in Supplementary Table 1.

Eligibility criteria included dietary fat or fatty acids as exposure of interest, the composition of the intestinal microbiota, and metabolic health markers such as MetS score, overweight/obesity, increased waist circumference, insulin resistance, hypertension, dyslipidemia or cardiovascular diseases as outcomes. After extraction of the references, the following four criteria were considered for further evaluation of an abstract: a) an experimental or observational comparative study in humans, b) diets varying in composition or quantity of fat or fatty acid intake including biomarkers for the intake, e.g. serum level of PUFA, c) association with or effects on the gut microbiota composition, d) a metabolic health outcome in terms of the MetS, any of its components or cardiovascular diseases. Study exclusions were no study in humans, a review and/or meta-analysis, insufficient information on the quantity and/or quality of dietary fat or fatty acids or on the gut microbiota composition or on the metabolic outcome. Guidelines, editorials, case-reports, dissertations or unpublished studies as well as conference abstracts and conference proceedings were not considered.

Titles, abstracts and full-texts of articles were screened independently by two reviewers (MW, JA) for eligibility. Disagreement was resolved by discussion and by a third senior reviewer (KG), when needed.

2.2. Data extraction

The following data were extracted from each included study: first author's last name, publication year, country, information on study design, number and characteristics of participants, dietary fat/fatty acid intake and/or biomarkers, intestinal microbiota

composition, weight status, metabolic health outcomes, and follow-up time. Data extraction was performed independently by pairs of reviewers (MW, JA). A third reviewer (KG) resolved disagreement if needed.

2.3. Assessment of risk of bias

Quality assessment of risk of bias of randomized controlled trials (RCT) was conducted using the Cochrane risk of bias tool [22] through which selection, performance, detection, attrition and reporting bias of each study were judged as high, low or unclear risk. The assessment of observational studies was performed using the Newcastle-Ottawa Scale (NOS) [23] that evaluates 9 items grouped in 3 domains: selection of participants (maximum score 4 stars), comparability of groups (maximum score 2 stars) and ascertainment of the outcomes of interest (maximum score 4 stars). Total score ranged from 0 to 9 and higher score indicated better methodological quality. Two reviewers (MRP, CW) independently assessed the risk of bias of individual studies and any differences in quality assessment results were resolved through consensus.

2.4. Data synthesis and analysis

As study designs and outcome assessments varied, results are presented in a narrative way. Studies are presented based on the PICO criteria (Population, Intervention [or Exposure], Comparison [if applicable], Outcome).

3. Results

Figure 1 shows the flow diagram of the screened and selected studies.

Fifteen studies were included in this systematic review. Table 1 summarizes the characteristics and results of the interventional studies and Table 2 of the observational studies included. Six of the studies evaluated dietary interventions [24–29], five reviewed dietary records [30–35], one investigated serum metabolites of fatty acids [36] and three applied a food frequency questionnaire [35,37,38]. All of the included studies were published between 2013 and 2017. Distinct study designs were found, with six RCT [24–29], seven cross-sectional studies [30–32,34,35,37,38], and two longitudinal cohort studies which analyzed cross-sectional data [33,36]. Geographically, nine of the studies were performed in Europe [24–27,30,36], three in North America [28,31,37] and three in Asia [29,35,38]. Considering the patient selection, ten studies had no gender limit, three included only women [30,32,34] and two included only men [27,36]. Total sample sizes ranged from 20 [27] to 88 [26] in interventional and from nine [37] to 531 [36] in observational studies. The mean age of participants in the included studies varied between 8.1 and 63.3 years. The length of the interventions varied from three weeks to one year, with a follow-up time of up to six months. With one exception [28], in all interventional studies, a baseline assessment of the gut microbiota was obtained, and microbial compositional changes were reported.

3.1. Risk of bias assessment

3.1.1. Quality assessment of randomized controlled interventional studies based on the Cochrane tool

In total, six RCT were evaluated based on the Cochrane risk of bias tool (Table 3). All six studies were considered of 'low-risk' with regard to 'random sequence generation'. The sequence generation was described as being computer generated in each of the studies, with the exception of Rajkumar et al., 2014 [29] where an identification number was assigned to each participant by a scientist blind to the treatments corresponding with each code. Four of the six studies were considered 'low-risk' with regard to 'allocation concealment' as the assignment of codes was reported as blinded.

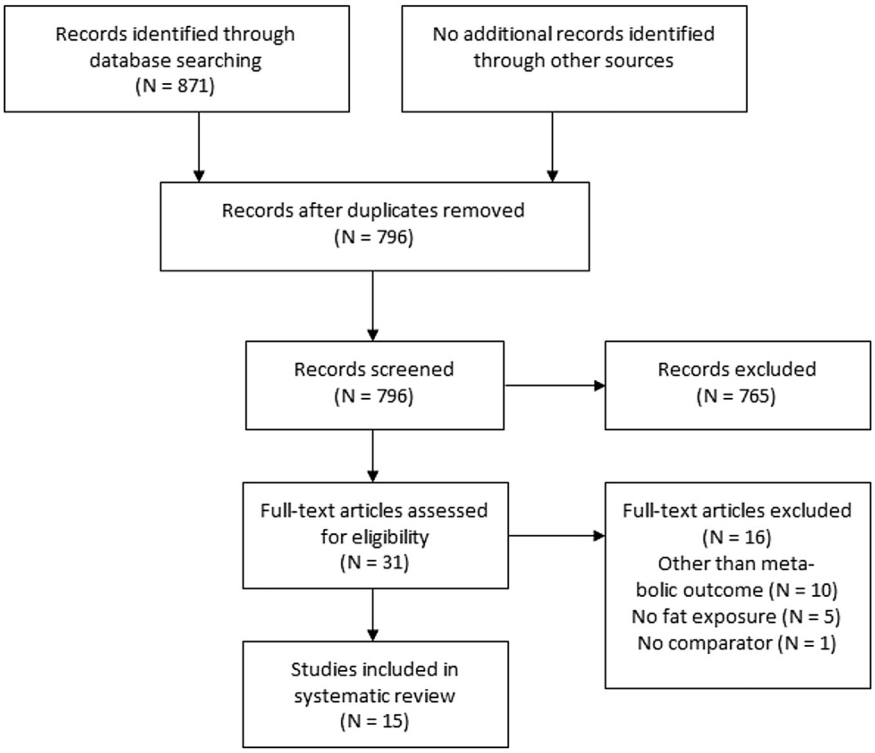

Fig. 1. Flow chart of the selection process.

In two studies [26,27], risk was considered 'unclear' as the allocation of codes was not reported. The blinding of participants was considered 'low-risk' in two of the six studies as blinding of participants and study coordinators was performed for each study [25,28]. Four of the remaining studies were considered 'high-risk' as either the participants or study group were not reported to be blinded. The blinding of outcomes was considered 'low-risk' in five of the six studies, with the exception of one study [26] which was considered 'unclear' as the analysis performed in the study was not clearly reported as blinded. With regard to 'incomplete outcomes', two of the six studies were considered 'low-risk' as the number of missing data points was minimal and would not be considered as a source of bias in these studies. One study [28] was considered 'high-risk' as a number of participants did not provide a sample at every time point throughout the study, and three of the remaining studies were considered 'unclear' as missing data points and/or the final number of participants was not stated. Overall, all six studies were considered 'low-risk' with regard to 'selective reporting' as all outcome assessments provided in the methods were stated in the results section, and two of the six studies were considered 'high-risk' with regard to other forms of bias due to gender (all participants were men) [27] and the obese state of the participants [28].

3.1.2. Quality assessment of case–control studies based on Newcastle-Ottawa Scale

In total, nine cross-sectional studies were analyzed according to the NOS (Table 4). Two studies received a score of 2 in the 'selection' category because of their study design. Three studies received a score of 3 in the 'selection' category as they successfully completed the criteria required for an adequate case-study definition with the selection of suitable control groups. Four studies received the maximum of 4 stars in the 'selection' category as they completed all of the necessary requirements for the selection and definition of a high quality case–control study. In the 'comparability' category six studies received a score of 2 (maximum score) due to the number of variable confounding factors which were included and adjusted for in the analysis, such as BMI, age and dietary intake among others. Four of the studies received a score of 1 in this 'comparability' category as only one confounding factor was controlled for throughout the study. In the 'exposure' category six studies received a score of 2 (maximum score is 4) as the methods used to attain the results for each study did not appear to create potential bias in either the case or control groups; however these six studies did not clearly describe the non-response rate in each group and therefore were not awarded an additional star. Two studies received a score of 1 in the 'exposure' category as the ascertainment of results was only adequate in either the case or control group. Fernandes et al., 2014 received a total score of 3 in the 'exposure' category as only one participant was reported to drop-out of the study. Overall, three studies received a total score of 8, three studies received a total score of 7, one study received a total score of 6 and two studies received a total score of 5 in the NOS quality assessment scale. Studies which received higher scores of 7 or 8 indicate better methodological quality.

3.2. High versus low fat diets in relation to the intestinal microbiota and metabolic outcomes

3.2.1. Interventional studies

High fat interventional diets reduced total bacteria compared to baseline, whereas this reduction was not seen in low fat/high carbohydrate diets in adults at increased risk of MetS. Instead, the latter increased *Bifidobacterium* spp. and *Bacteroides* spp. At the end of the interventions with three high-fat and two low-fat diets, no differences in cardiometabolic risk factors were observed [26]. Accordingly, no differences between either a high-fat Mediterranean (high in MUFA) or a low-fat diet were observed in main metabolic variables of glucose/insulin metabolism and lipoprotein profile after one year of intervention. The Mediterranean diet resulted in a decrease of the genus *Prevotella* and increased the genera *Roseburia and Oscillospira* and the species *Parabacteroides distasonis* compared to baseline [27].

3.2.2. Observational studies

In overweight and obese pregnant women with different dietary patterns the intake of total fat was negatively associated with gut microbiota diversity and richness [32]. In a cross-sectional study with postmenopausal obese women, a healthy lipoprotein profile showed a positive association with the species *Faecalibacterium prausnitzii* A2-165, *Bacteroides pectinophilus* and *Akkermansia muciniphila* which were negatively correlated with fat intake. *Clostridium bolteae* was positively correlated with fat intake and showed a positive correlation with markers of insulin resistance [30]. In Philipine children, the families *Bacteroidaceae* and *Ruminococcaceae* were higher in urban living children with low fat intake compared to rural living children with very low fat intake who had higher abundance of the family *Prevotellaceae*. Fat intake was positively correlated with the *Firmicutes*-to-*Bacteroidetes* (*F/B*) ratio, *Firmicutes*, an *Oscillibacter* species, various *Bacteroides/Parabacteroides* species, genus *Bacteroides* and the order *Clostridiales* (*Firmicutes*) and was negatively correlated with the genera *Bacteroidetes* and *Prevotella* (family *Prevotellaceae*) and *Succinivibrio* (phylum *Proteobacteria*) [38]. Contrary correlations with fat intake were seen for *Clostridium* cluster XI which correlated positively and *Clostridium* cluster IV (*Clostridium leptum*) which correlated negatively in 59 patients with type 2 diabetes. The latter was also negatively correlated with fecal acetate which was shown to be beneficial for glucose tolerance [35]. In premenopausal women, *Eubacterium. rectale-Clostridium coccoides (EreC)* was positively correlated with fat intake and showed a positive correlation with body fat percentage. In a multivariable regression analysis *EreC* contributed the most to body fat percentage, HDL and TG [34].

3.3. High versus low SFA diets in relation to the intestinal microbiota and metabolic outcomes

3.3.1. Interventional studies

In a crossover RCT in healthy men who received for 21 days either a diet enriched with whole-fat milk (40 E% of fat) which contains mainly SFA or an isoenergetic standard diet with 35 E% of fat no effects on the fecal microbiota, on the blood lipoprotein profile or on insulin and glucose concentrations were observed [25]. A high total fat/high SFA diet (18 E% of SFA, 38 E% of total fat) increased *Faecalibacterium prausnitzii* compared to baseline. The comparison of five diets including the high SFA diet, two isoenergetic low SFA diets (10 E%) with the same amount of total fat and two low fat/high carbohydrate diets did not result in differences in BMI, waist circumference, body fat percentage, blood pressure and insulin sensitivity parameters between the diets at the end of the intervention [26].

3.3.2. Observational studies

In overweight and obese pregnant women, SFA consumption was negatively associated with all gut microbiota diversity and richness indexes [32]. In adult men, higher abundance of the genus *Blautia* which was positively associated with SFA serum metabolites was detected in persons with high BMI. Higher abundance of the phylum *Tenericutes* which was negatively associated with SFA metabolites correlated with lower triglyceride levels [36]. In a study with monozygotic twin pairs, co-twins with the same SFA

Table 1
Characteristics and results of the randomized controlled interventional studies included in the systematic review.

Study	Population		Study design and intervention		Results/effects on outcomes	
Reference	N	Characteristics	Description	Fat intake	Microbiota	Metabolic health
Balfegó et al., 2016 [24]	N = 35 (32 finished) F: 54.3% IG: N = 19 CG: N = 16	T2D patients Mean (SE) Age: 60.6 (1.4) y BMI: IG 30.5 (1.0) kg/m^2 CG 28.8 (0.8) kg/m^2	Randomized controlled nutritional pilot trial Country: Spain 2-week lead-in period, then 6 months dietary intervention; 1 visit/month by the dietician IG: standard diet for T2D enriched with 100 g of sardines (instead of usual protein foods) on 5 d/week CG: standard T2D diet	Daily intake, mean (SE), IG/CG: Fat (g): 88.3 (4.8)/79.2 (4.5) (Baseline) 84.4 (8.1)/83.7 (5.8) (6 months) PUFA (E%): 5.8 (0.4)/7.1 (0.5) (Baseline) 6.2 (0.4)/6.3 (0.4) (6 months) IG from sardines, g: n3 PUFA: 3.5 (0.2) EPA+DHA: 3.0 (0.2)	No differences in the abundance of the bacterial groups analyzed comparing IG and CG at 6 months Changes after 6 months compared to baseline: IG: ↓ *Firmicutes* ↑ *Escherichia coli* ↑ *Bacteroides-Prevotella* CG: ↓ *Firmicutes* ↑ *Escherichia coli* Trend of ↓ *Firmicutes*/*Bacteroidetes* ratio	Both groups: ↓ Fasting insulin and HOMA (compared to baseline) but mean change from baseline to 6 months was not different between IG and CG - IG patients exhibited greater decrease from baseline: IG: −6.1 ± 1.8 mU/l insulin, −2.3 ± 0.7 HOMA CG: −3.4 ± 1.5 mU/l insulin, −1.1 ± 0.7 HOMA CG: ↓ HbA1c (−0.3 ± 0.1%) IG: non-significant ↓HbA1c (−0.2 ± 0.1%)
Blædel et al., 2016 [25]	N = 21 (18 finished) F: 0	Healthy men, aged 23–45 y Mean (SE) Age: 32.9 (0.85) y BMI: 29.3 (0.5) kg/m^2	Randomized, controlled, crossover study Country: Denmark 21 d intervention periods, separated by a wash-out period 3 arms: Isoenergetic standard diet with either - whole-fat milk (IG) - water (CG) - inulin powder (not considered here)	IG/CG (E%): CHO: 45/55 Fat: 40/35 Protein: 15/15	The overall fecal microbiota composition did not change significantly in response to milk (IG) compared with CG.	- No change in blood lipid profile, insulin or glucose concentration in IG compared to CG - No effect of diets on resting energy expenditure and lipid oxidation.
Fava et al., 2013 [26]	N = 88 F: 51.1%	Adults at increased risk for MetS Mean (SD) Age: 54.0 (9.5) y BMI: 28.8 (4.9) kg/m^2 HDL: 1.6 (0.4) mmol/l	Randomized, controlled, single blind, parallel design Country: United Kingdom 4-week run-in reference diet (CG, baseline: after run-in), then 24 weeks of one of the diets (matched for age, BMI, HDL) CG: reference diet IG1: HM/HGI: high MUFA/high GI IG2: HM/LGI: high MUFA/low GI IG3: HC/HGI: high CHO/high GI IG4: HC/LGI: high CHO/low GI	High fat diets: IG1/IG2/CG (E%): Total fat: 38/38/38 SFA: 10/10/18 MUFA: 20/20/12 PUFA: 6/6/6 CHO: 45/45/45 GI: 64/53/64 High CHO diets: IG3/IG4 (E%): Total fat: 28/28 SFA: 10/10 MUFA: 11/11 PUFA: 6/6 CHO: 55/55 GI: 64/51	↓ Total bacteria after intervention in the 3 diets with highest fat content (CG, IG1, IG2) compared to baseline ↓ Total bacterial numbers after both high MUFA-diets (IG1, IG2) compared with IG3 and with baseline ↑ *Faecalibacterium prausnitzii* after intervention with CG compared to baseline and IG4 ↑ *Bifidobacterium* spp. population levels in IG3 compared to CG ↑ *Bifidobacterium* spp. population levels in IG3 and IG4 diets compared to baseline ↑ *Bacteroides* spp. in IG3 compared to baseline, but not compared to the other diets	- No significant changes in BMI, WC, BF% or BP between the diets at the end of intervention - No effect of the dietary interventions on insulin sensitivity parameters ↓ in NEFA concentration after intervention with IG4 compared to CG and to IG3 After treatment compared to baseline: ↓ in WC in IG2 ↓ in TC and LDL in all intervention groups ↓ in BF% in IG3 ↓ in HDL after IG3 ↓ FBG after IG3 and IG4 ↓ Plasma insulin after IG3 ↑ NEFA after IG3 ↓ NEFA after IG4 ↑ *Bacteroides* spp. numbers after IG3 diet was associated with decreases in body weight, BMI and WC (r = −0.64, r = −0.64 and r = − 0.45, resp.)
Haro et al., 2016 [27]	N = 20 F: 0	Obese CHD patients Mean (SE) Age: 63.3 (2.0) y BMI: 32.2 (0.5) kg/m^2	Interventional study Country: Spain Participants received either a low-fat, high-complex CHO diet (LFHCC) or a Mediterranean diet (Med diet) for 1 year	LFHCC diet/Med diet (E%): Fat: 28/35 MUFA: 12/22 PUFA: 8/6 SFA: 8/7	LFHCC diet compared to baseline: ↑ *Prevotella* ↓ *Roseburia* ↑ *Faecalibacterium prausnitzii* - No change in *Oscillospira* Med diet compared to baseline: ↓ *Prevotella* ↑ *Roseburia* ↑ *Oscillospira* ↑ *Parabacteroides distasonis*	- After 1 y: no differences in main metabolic variables (glucose, HbA1c, insulin sensitivity index, TG, TC, HDL, LDL) between groups ↑ Insulin sensitivity index for both the LFHCC and Med diets, when measured from an OGTT performed at baseline and after 1 year of dietary intervention
Pu et al., 2014 [28]	N = 25 (Finished	Adults with at least one	Randomized, controlled, double-blind, crossover	Oil treatments (all diets were low in SFA):	Comparisons between groups (no information on	- BMI had no significant impact on richness

Table 1 (*continued*)

Study	Population		Study design and intervention		Results/effects on outcomes	
Reference	N	Characteristics	Description	Fat intake	Microbiota	Metabolic health
	per diet with stool sample: N = 9–17) F: 76% 1 stool sample after interventions	cardiovascular risk factor Mean (SD) Age: 53.6 (11.7) y BMI: 29.6 (4.59) kg/m^2	clinical trial Country: Canada • 7-day rotation iso-caloric menu (3 meals, 2 snacks, 3000 kcal/d: CHO: 50E% Protein: 15E% Fat: 35E% • 60 g/d dietary oils equally distributed to 2 beverage shakes at breakfast and supper • Five oil treatments. Each treatment phase lasted 30 days, separated with 4 weeks washout periods	High MUFA, E%: IG1: canola oil [Canola; 63% MUFA, 20% LA, 10% ALA] IG2: DHA enriched canola-oil [CanolaDHA; 64% MUFA, 13% LA, 6% DHA] IG3: high OA canola oil (CanolaOleic; 72% MUFA, 15% LA, 2% ALA) High PUFA, E% IG4 a blend of corn oil/ safflower oil (CornSaff; 18% MUFA, 69% LA) - high n6 PUFA IG5: a blend of flax oil/ safflower oil (FlaxSaff; 18% MUFA, 38% LA, 32% ALA) – high n3 PUFA	baseline microbiota) and correlations: - Oil treatments had no significant impact on richness (Chao1, ACE) and α-diversity (Shannon, Simpson) - β-diversity did not change among treatments - Phylum distribution did not fluctuate across treatments or among MUFA vs PUFA groups - Average ratio of *Bacteroidetes*-to-*Firmicutes* was 0.15 across diets and did not differ among interventions - Genera *Parabacteroides, Prevotella, Turicibacter*, and family *Enterobacteriaceae* were positively correlated to MUFA-rich diets, while genus *Isobaculum* was correlated to PUFA-rich diets ($R^2 = 0.43$, $Q^2 = 0.07$) - CanolaDHA correlated to family *Lachnospiraceae* and phylum *Firmicutes* whereas CanolaOleic was associated with genera *Faecalibacterium* and *Coprobacillus* ($R^2 = 0.78$, $Q^2 = 0.45$) - CornSaff (but not FlaxSaff) had an impact on genera *Eggerthella, Slackia, Soehngenia, Anaerostipes, Robinsoniella, Phascolarctobacterium* ($R^2 = 0.67$, $Q^2 = 0.22$) In OW participants: - The genera *Streptococcus, Tepidimicrobium, Robinsoniella*, and *Turicibacter* were correlated to MUFA-rich and *Coriobacterium* and *Mogibacterium* to PUFA-rich diets ($R^2 = 0.69$, $Q^2 = 0.26$) - Comparing CanolaDHA and CanolaOleic, the genera *Adlercreutzia, Coriobacterium, Alistipes*, and *Robinsoniella* were correlated with CanolaDHA and *Lactobacillus* with CanolaOleic ($R^2 = 0.90$, $Q^2 = 0.60$) - Comparing PUFA-rich diets, CornSaff was associated with the genus *Adlercreutzia* and FlaxSaff with the genera *Collinsella, Barnesiella, Streptococcus, Roseburia, Coprobacillus*, and the	(Chao1, ACE) and α-diversity (Shannon, Simpson) - Rarefaction curves showed higher richness and diversity in OW/OB compared to NW participants - Similarity/differences in microbiota among treatments and BMI (β-diversity) were compared using PCoA and PERMANOVA analyses of Bray–Curtis distances: Difference in OW vs OB ↑ Proportion of *Firmicutes* in OB compared to the combined NW/OW group - At the genus level, PLS-DA analysis confirmed a significant difference in the composition of bacteria among three BMI groups ($R^2 = 0.60$, $Q^2 = 0.32$) - TG was negatively correlated with phylum *Aquificae* ($r = -0.27$) but positively with *Cyanobacteria* ($r = 0.24$) - LDL was positively correlated with phylum *Proteobacteria* ($r = 0.28$) - HDL was positively correlated with *Verrucomicrobia* ($r = 0.21$) - In CanolaDHA treatment, TC levels positively correlated with *Firmicutes* ($r = 0.55$) - In CornSaff treatment, TC levels were correlated with *Bacteroidetes* ($r = 0.64$) and *Bacteroidetes*-to-*Firmicutes* ratio ($r = -0.65$)

(*continued on next page*)

Table 1 (*continued*)

Study	Population		Study design and intervention		Results/effects on outcomes	
Reference	N	Characteristics	Description	Fat intake	Microbiota	Metabolic health
					family Peptostreptococcaceae ($R^2 = 0.98$, $Q^2 = 0.74$) In OB participants: - The genera *Parabacteroides, Prevotella, Flexithrix, and Fusibacter*; the family *Enterobacteriaceae*, and phylum *Firmicutes* were correlated to MUFA-rich diets, but no specific taxa was associated with PUFA-rich diets ($R^2 = 0.66$, $Q^2 = -0.20$) - Comparing CanolaDHA and CanolaOleic, only the genus *Parasutterella* correlated with CanolaDHA ($R^2 = 0.91$, $Q^2 = 0.29$) - Comparing the PUFA-rich diets, the genera *Collinsella, Hydrogenobaculum*, and *Parabacteroides* were impacted by the CornSaff, while the genus *Clostridium* was correlated to the FlaxSaff diet ($R^2 = 0.98$, $Q^2 = 0.63$)	
Rajkumar et al., 2014 [29]	N = 60 F: 50%	OW, healthy adults aged 40–60 y Mean (range) Age: 49 (40–60) y BMI: 28.8 (27–30) kg/m^2	Randomized, placebo-controlled trial Country: India Fecal samples were obtained at baseline and after 45 days (6 weeks of intervention)	Participants received either (1) placebo (CG) (2) VSL#3 capsules (not considered here) (3) n3 PUFA capsules providing 180 mg EPA and 120 mg DHA per day (IG) (4) n3 PUFA capsule + VSL#3 (not considered here) Intervention effects are only considered for n3 PUFA (IG) compared to CG	n3 group: No effect on gut microbiota	At baseline: - Participants with vs without lipid abnormalities had lower total *Lactobacilli, Bifidobacteria*, and *Streptococcus* and higher *Escherichia coli* and *Bacteroides* - Similar trend for persons with vs without insulin resistance CG (compared to baseline): ↑ FBG rose slightly n3 group (compared to baseline): ↓ insulin levels and FBG ↓ TC, TG, LDL, VLDL ↑ HDL, atherogenic index

↓ reduced ↑ increased.

intake had very similar *Bacteroides* spp. profiles whereas low similarity was observed in twin pairs with distinct SFA intake [33].

3.4. High MUFA diets in relation to the intestinal microbiota and metabolic outcomes

3.4.1. Interventional studies

Two high fat/high MUFA diets decreased total bacterial numbers compared to a low fat/high carbohydrate diet and compared to baseline. While waist circumference decreased in the high MUFA group with low glycemic index compared to baseline, no significant changes in BMI, waist circumference, body fat percentage, blood pressure or insulin sensitivity between the different MUFA- and/or PUFA-rich diets were detected at the end of the intervention [26]. In a cross-over RCT with identical total fat intake but different MUFA-rich oil treatments, high MUFA diets showed no effect on richness/diversity indexes, the phylum distribution or *Bacteroidetes*-to-*Firmicutes* ratio. MUFA-rich diets were positively correlated to the genera *Parabacteroides*, *Prevotella* and *Turicibacter*, and the family *Enterobacteriaceae*. The BMI had no significant association with richness (Chao1, ACE) and α-diversity (Shannon, Simpson) although rarefaction curves showed higher richness and diversity in overweight/obese compared to normal weight participants. Additionally, similarity and differences in microbiota among BMI (β-diversity) showed differences in normal weight versus obese participants. Also a higher proportion of the phylum *Firmicutes* was reported in obese compared to the combined normal weight/overweight group. Triglyceride levels were negatively correlated with the phylum *Aquificae* and positively with *Cyanobacteria* while LDL was positively correlated with *Proteobacteria* and HDL with *Verrucomicrobia* [28]. Compared to baseline, a MUFA-rich Mediterranean diet decreased the genus *Prevotella* and increased the genera *Roseburia* and *Oscillospira*, and the species *Parabacteroides. distasonis* while a low-fat diet with a high proportion of complex carbohydrates (LFHCC)

Table 2
Characteristics and results of the observational studies included in the systematic review.

Study	Population		Study design and exposure		Results/Associations with outcomes	
Reference	N	Characteristics	Description	Fat intake	Microbiota	Metabolic health
Brahe et al., 2015 [30]	N = 53 F: 100%	Postmenopausal obese women (BMI 30–45 kg/m^2) Mean (SD) Age: 60 (6) y BMI: 34.5 (3.8) kg/m^2	Cross-sectional study Country: Denmark Baseline assessment of a study sample recruited for a dietary intervention study 3-d weighed dietary intake Fecal sample	Dietary intake/d, mean (SD): Total energy, kJ: 7572 (1797) E%: Fat: 35.3 (6.3) CHO: 40.8 (6.8) Protein: 18.9 (3.6) Fiber, g: 21.3 (6.0)	*Faecalibacterium prausnitzii* A2-165 and *Bacteroides pectinophilus* which were associated with a healthy metabolic profile were negatively correlated with E% of fat intake (r = −0.47 and r = −0.32, resp.). *Akkermansia muciniphila* which was associated with a healthy lipid profile was negatively associated with E% of fat intake (r = −0.28). *Clostridium bolteae* which was associated with an unhealthy metabolic profile was positively associated with E% of fat intake (r = 0.35).	Negative correlation between metabolic markers of insulin resistance and the bacterial species *Bacteroides faecis, Intestinibacter bartlettii, Bifidobacterium longum, Faecalibacterium prausnitzii* A2-165, *Dorea longicatena*. The negative correlation between *Faecalibacterium prausnitzii* A2-165 and markers of insulin resistance disappeared after adjustment for fat intake. Positive correlation between metabolic markers of insulin resistance and the bacterial species *Ruminococcus torques, Clostridium bolteae, Eubacterium ramulus, Bilophila wadsworthia* Association between a healthy serum lipid profile and the following bacterial species: *Odoribacter splanchnicus, Bacteroides pectinophilus, Bacteroides cellulosilyticus, Bacteroides nordii, Roseburia inulini-vorans, Akkermansia muciniphila, Faecalibacterium prausnitzii* A2-165, and *Bifidobacterium longum* Association between an unhealthy serum lipid profile and the bacterial species *Catenibacterium mitsuokai, and Holdemanella biformis*
Fernandes et al., 2014 [31]	N = 94 LN N = 52 F: 57.7% OW/OB N = 42 F: 50%	NW, OW and OB adults Mean (SEM) LN (BMI ≤25 kg/m^2): Age 32.0 (1.8) y BMI: 21.8 (0.3) kg/m^2 Asian: 44% Caucasian: 50% Black: 2% Hispanic: 4% OW/OB (BMI >25 kg/m^2): Age: 37.9 (2.0) BMI: 30.3 (0.7) kg/m^2 Asian: 31% Caucasian: 55% Black: 12% Hispanic: 2%	Cross-sectional study Case-control study: Comparison of LN vs OW/OB group Country: Canada 3-d diet record Fecal sample	Dietary intake/d, mean (SEM), LN / OW/OB: Energy, kcal: 2035 (80) / 2063 (101) E%: Fat: 34 (1) / 36 (1) CHO: 47.3 (1.2) / 45.0 (1.4) Protein: 17 (1) / 18 (1) g/1000 kcal: SFA: 11.6 (0.5) / 12.6 (0.7) MUFA: 11.3 (0.6) / 12.0 (0.7) PUFA, 5.2 (0.3) / 6.0 (0.5) Total fiber 11 (1) / 10 (1) Alcohol 1.4 (0.6) / 1.7 (0.5) TC: 129 (9) / 139 (9) Trans FA, g/d: 0.76 (0.12) / 0.76 (0.15)	Combined groups: - Intake of PUFA was negatively correlated with *Bacteroidetes* (r = −0.21), all bacteria (r = −0.22) and *Firmicutes* (r = −0.25)	- *F/B* ratio was not different between the groups - LN (compared with OW/OB): ↑ *Escherichia coli* - BMI was inversely related to the number of *Bacteroidetes* (r = −0.21) and *Escherichia* coli (r = −0.34) - No association between the BMI and the log *Firmicutes*-to-*Bacteroides/Prevotella* ratio - No differences in the proportion of participants between groups who were *Archaea* positive
Mayorga Reyes et al., 2016 [37]	N = 9 F: 66.7% N = 3 in	Young adults Mean (SD) Age: 27.1 (6.27) LN:	Cross-sectional study Country: Mexico Semi-quantitative FFQ Phyla and bacterial	Average dietary intake/d of LN/OW/OB: Energy, kcal: 2688/2520/1667	- No correlation between food intake and abundance of *Firmicutes* and	- No differences in the abundance of the phylum *Bacteriodetes* among groups

(*continued on next page*)

Table 2 (*continued*)

Study	Population		Study design and exposure		Results/Associations with outcomes	
Reference	N	Characteristics	Description	Fat intake	Microbiota	Metabolic health
	each group, LN, OW, OB	BMI: 19.8 (0.94) kg/m^2 WC: 67.7 (1.53) cm OW: BMI: 27.2 (0.51) kg/m^2 WC: 87.8 (8.22) cm OB: BMI: 41.3 (5.25) kg/m^2 WC: 114.3 (2.31) cm OW and OB persons had a slightly higher intake of SFA than recommended	species from fecal samples	Fiber, g: 30.6/22.9/18.7 Range (E%): Fat: 36-40 CHO: 46.2–52.8 Protein: 11.2–14.8 SFA: 9-11 USFA: 8-9 No difference in the intake of SFA and USFA among the groups	*Bacteroidetes* phyla or between food intake and *Bacteroides thetaiotaomicron, Faecalibacterium prausnitzii, Clostridium leptum* or *Prevotella* - Abundance of *Bifidobacterium longum* was positively correlated with an intake of foods that contained USFA - Intake of fiber was correlated to the abundance of the *Bacteroidetes* phylum	- Abundance of *Firmicutes* in LN and OW groups was two logarithmic order of magnitude (LOM) greater than in OB - *Prevotella* and *Bacteroides thetaiotaomicron* were not different among groups - LN and OW participants had one LOM more of *Faecalibacterium prausnitzii* than OB participants - LN and OW had four LOM greater *Clostridium leptum* abundance than did the OB group - Abundance of *Bifidobacterium longum* in LN was two LOM more than in OW and five LOM more than in OB participants.
Nakayama et al., 2017 [38]	N = 43 Ormoc N = 19 F: 36.8% Baybay N = 24 F: 41.7%	7–9 year old children Mean (SD) Ormoc city (urban): Age: 8.11 (0.66) y BMI: 18.8 (4.5) kg/m^2 Baybay city (rural): Age: 8.21 (0.51) y BMI: 14.8 (1.4) kg/m^2	Cross-sectional study Country: Philippines (Leyte island) FFQ for dietary assessment Fecal sample 85 and 95th percentiles were used for the classification into OW and OB groups, resp. Participants below 15th percentile were classified as underweight.	Dietary intake/d, mean (SD) Ormoc city (urban): E%: Fat: 26.8 (5.2) CHO: 60.4 (6.0) Protein: 12.9 (2.3) g/d: SFA: 29.2 (10.7), MUFA: 22.0 (8.1), PUFA 8.94 (4.24), Trans FA, mg/d: 0.34 (0.22) Baybay city (rural): E%: Fat: 17.9 (4.7) CHO: 71.6 (6.0) Protein: 11.2 (2.2) g/d: SFA: 15.9 (5.9), MUFA: 13.5 (5.7), PUFA: 4.69 (1.63), Trans FA, mg/d: 4.72 (18.84)	Ormoc city (compared to Baybay city): ↑ *Bacteroidaceae* ↑ *Ruminococcaceae* Baybay city (compared to Ormoc city): ↑ *Prevotellaceae* - No differences in *Bifidobacteriaceae*and *Lachnospiraceae* between cities Positive correlation of fat intake with: - *Firmicutes-to-Bacteroidetes (F/B)* ratio - *Firmicutes* - an *Oscillibacter* sp. - a series of *Bacteroides/Parabacteroides* spp. - genus *Bacteroides* - Order *Clostridiales* Negative correlation of fat intake with: - *Bacteroidetes* - family *Prevotellaceae*/genus *Prevotella* - genus *Succinivibrio*	- All OW/OB children were living in Ormoc, suggesting a link between OW/OB and modern high-fat dietary habits - Higher fat intake in the OW/OB group than in the NW/UW group - *F/B* ratio was higher and relative abundance of *Prevotella* was lower in the OW/OB than in the NW/UW group (observed power determined retrospectively was not statistically high enough to warrant significance) - The correlation between altered gut microbiota and high BMI suggests that a high-fat diet associated obesity is present among Filipino children on Leyte island
Org et al., 2017 [36]	N = 531 F: 0%	45-70 year-old men Mean (SD) Age: 61.97 (5.45) y BMI: 27.92 (3.60) kg/m^2	Cross-sectional analysis Data based on a follow-up study of the population-based study cohort (subcohort of the METSIM cohort) Country: Finland Fecal samples	No information on dietary fat intake Serum metabolites of fatty acids	- Several associations with various fatty acids, accounting altogether for 41% of all taxonomy level (19 out of 46) and 33.8% of all OTU level (51 out of 151) associations The most significant associations were observed with the abundance of members of the genus *Blautia* and phylum *Tenericutes*: - Abundance of *Blautia* was positively associated with SFA	- Fasting glucose levels were strongly associated with unclassified *Coriobacteriaceae* and several OTUs from *Blautia* were positively associated with pyruvate and glycerol - Higher abundances of genus *Methanobrevibacter (Archaea)*, *Tenericutes*, *Peptococcaceae* and *Christensenellaceae* correlated with lower TG levels

Table 2 (*continued*)

Study	Population		Study design and exposure		Results/Associations with outcomes	
Reference	N	Characteristics	Description	Fat intake	Microbiota	Metabolic health
					and MUFA and negatively associated with degree of unsaturation and PUFA, including n3, DHA, n6, and LA - Negative associations of SFA with phylum *Tenericutes* - Negative associations of MUFA with *Peptococcaceae* - Positive associations of PUFA with *Tenericutes* and *Peptococcaceae* (for the latter also with LA, n6 PUFA) - Positive association of n3 PUFA incl. DHA with *Bacteroidales*	- No differences in either bacterial richness or in the *F/B* ratio between participants with different body weights and predisposition to T2D In persons with high BMI: ↑ the family *Tissierellacea* and the genus *Blautia* ↓ *Archaea (Methanobrevibacter)* ↑genus *Anaerostipes* In pre-diabetic persons: ↓ lower abundances of an OTU from the families *Ruminococcaceae* and *Christencenellacea* and the genus *Methanobrevibacter* - ↑ abundance of the order *Bacteroidales* in obese subjects was associated with lower HOMA and the higher abundance of the genus *Collinsella* with higher levels of glycerol and phenylalanine - Opposite effect in LN subjects
Röytiö et al., 2017 [32]	N = 100 (88 with complete data) F: 100%	OW/OB women at early pregnancy (≤17 week of gestation) Mean (SD) Age: 30.1 (4.7) y Pre-pregnancy BMI: 30.2 (4.6) kg/m^2 The three groups did not differ in BMI	Cross-sectional analysis within an ongoing mother–infant dietary intervention trial Country: Finland A 10-h fasting blood sample was drawn from the participants. Fecal samples from mothers were collected. 3-d food diaries recorded within the week before the study visit	Group 1: low-fiber/moderate-fat group (N = 57) - fiber intake (<25 g/d)/total fat intake (25–40 E%) Group 2: high-fiber/moderate fat group (N = 18) - fiber (≥25 g/d)/total fat intake (25–40 E %) but higher energy intake than the other groups. Group 3: low-fiber/high-fat group (N = 13) - fat intake (≥40E%). SFA consumption above reference (>10 E%). Consumption of SFA, MUFA and PUFA, in addition to total fat, was higher than in the other groups; consumption of fiber and total CHO lower than recommended.	- Intakes of total fat and different fat types (except for n3 PUFA) were negatively associated with one (PUFA, n6 PUFA) or more indicators of gut microbiota diversity and richness (α-diversity, measured as Chao1, observed OTU, phylogenetic diversity, Shannon index) - SFA were negatively associated with all diversity and richness indexes, whereas n3 PUFA showed no correlation - Negative correlations between the intake of fat (E%) and SFA (E%) and relative abundance in the family *Barnesiellaceae* Comparison of the 3 groups, Mean (SD): Higher in the high-fiber/moderate-fat group compared with the low-fiber/high-fat group: α-diversity (Chao1 index) 406.2 (44.4) vs 341.0 (SD 57.9), phylogenetic diversity (PD) 39.0 (4.5) vs 31.3 (6.7) and observed number of OTU 355.8 (38.7) vs 293.8 (59.0). The low fiber/moderate-fat group did not differ from the other groups (Chao 1	- Contradictory findings were found at the genus level within the family *Lachnospiraceae*: *Lachnospira* was negatively and *Blautia* positively correlated with concentrations of various sized VLDL particles and TG in VLDL - The genus *Lachnospira* was negatively associated with serum TG - The genus *Blautia* was positively associated with VLDL diameter, but negatively with the diameters of LDL and HDL. - No correlations were detected between gut microbiota richness indexes and serum lipidomics variables. - No differences were detected in markers of low-grade inflammation, serum lipidomic variables or zonulin concentration among the three diet groups.

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Table 2 (*continued*)

Study	Population		Study design and exposure		Results/Associations with outcomes	
Reference	N	Characteristics	Description	Fat intake	Microbiota	Metabolic health
					index 380.0 (57.3), PD 35.8 (5.9), observed number of OTU 333.0 (55.2).	
Simoes et al., 2013 [33]	N = 40 F: 55% NW: N = 11 OW: N= 18 OB: N = 11	Monozygotic twin pairs Mean (SD) NW: Age: 26 (3) y BMI: 22.9 (2.2) kg/m^2 OW: Age: 29 (3) y BMI: 26.5 (1.2) kg/m^2 OB: Age: 28 (4) y BMI: 32.4 (2.1) kg/m^2	Cross-sectional analysis of data from a population-based longitudinal survey Country: Finland Participants were divided into 3 BMI (kg/m^2) groups: NW (19 ≤ BM < 25), OW (25 ≤ BMI<30), OB (BMI ≥ 30) 3-d food diary, supervised by a specialist	NW/OW/OB, mean (SD): Energy, MJ: 8.0 (1.7)/8.4 (2.2)/9.8 (2.0) g/d: Fat: 77 (29)/75 (26)/85 (22) SFA: 30 (12)/28 (9.9)/32 (8.6) MUFA: 23 (8.9)/19 (6.9)/23 (6.9) PUFA: 10 (4.0)/10 (5.1)/13 (5.2) n3 PUFA: 1.8 (0.7)/1.5 (0.7)/1.6 (0.6) n6 PUFA: 7.9 (3.2)/8.6 (4.5)/11 (4.4) CHO: 200 (50)/219 (58)/255 (51) Protein: 85 (29)/86 (31)/81 (31) Total fiber: 21 (14)/16 (6.1)/17 (5.5)	High energy intake compared to lower intake: ↓ *Bacteroides* spp. ↑ *Bifidobacteria* Greater MUFA compared to lower consumption: ↓ *Bifidobacteria* - Increased ingestion of n3 PUFA had a significant association with higher numbers of bacteria within the *Lactobacillus* group - Greater n6 PUFA consumption was negatively correlated with the numbers of *Bifidobacteria* - Co-twins with the same SFA intake had very similar *Bacteroides* spp. profiles (80–100% similarity) whereas the twin pairs with distinct SFA intake had low similarity (0–25%). The group of co-twins who consumed similar amounts of fiber had very low *Bifidobacterial* similarity (0–25%).	- The numbers of bacteria within the different bacterial groups, as measured by qPCR, did not differ between BMI groups. - The diversity of the studied bacterial groups, defined as the number of the bands obtained by different group-specific PCR DGGE did not differ between BMI groups. - No relation was found between the intrapair DGGE profile similarities and the co-twin concordance for BMI, intrapair difference in BMI, or body fat.
Yamaguchi et al., 2016 [35]	N = 59 F: 57.6% NW: N = 42 OW: N = 13 OB: N = 4	T2D patients Median (IQ) Age: 65 (58.5–69.0) y BMI: 23.0 (20.4–25.6) kg/m^2	Cross-sectional study Country: Japan Fasting blood and fecal samples Data-based short FFQ	Dietary intake/d, mean (SD): Energy: 1692 (380) kcal E%: Fat: 23.2 (5.3) CHO: 57.5 (5.2) Protein: 13.2 (2.2)	- *Clostridium* cluster IV: negatively correlated with fat intake (r = −0.261); positively correlated with CHO (r = 0.266) - *Clostridium* cluster XI: positively correlated with both fat (r = 0.301) and protein intake (r = 0.363)	- *Bifidobacterium* spp., order *Lactobacillales* and *Bacteroides* spp. were negatively correlated with fasting blood glucose (r = −0.264) - *Clostridium* subcluster XIVa: positively correlated with TC (r = 0.385) - *Clostridium* cluster IV was negatively correlated with fecal acetate which was shown to be beneficial for glucose tolerance - Propionate and acetate were negatively correlated to insulin and HOMA. Butyrate was positively correlated to HDL. Total SCFA were negatively correlated with insulin and HOMA.
Yang et al., 2017 [34]	N = 71 F: 100% Low fitness:N = 24 Moderate fitness: N = 23 High fitness: N = 24	Premenopausal women aged 19–49 y Mean (95% CI) Low fitness: Age: 40.4 (36.9–44.0) y BMI: 31.7 (30.2–33.1) kg/m^2 BF%: 40.6 38.1–43.0) Moderate fitness: Age: 39.7 (35.5–43.8) y	Cross-sectional study Country: Finland Food diary records 3 groups according to cardiorespiratory fitness (tertiles of VO_{2max}): (1) high fitness (high) (2) moderate fitness = control	Daily mean intake of low/moderate/high fitness group (E%, unless otherwise stated): Fat: 32.8/34.1/35.2 CHO: 47.1/45.6/44.7 Protein: 18.4/18.0/18.0 Alcohol (E%): 1.73/2.38/0.63 Fiber, g/d: 20.4/24.1/21.0	High fitness (low BMI) compared to low fitness group (high BMI): ↑ proportions of *Bacteroides* ↓ *EreC*, phylum *Firmicutes* No differences between groups for *Bifidobacterium,*	- *EreC* was positively correlated with BF% (r = 0.382) and TG (r = 0.390) and negatively with HDL (r = 0.26) After adjustment for BF%, correlations disappeared. - Multivariable regression analysis

Table 2 (*continued*)

Study	Population		Study design and exposure		Results/Associations with outcomes	
Reference	N	Characteristics	Description	Fat intake	Microbiota	Metabolic health
		BMI: 27.9 (26.7–29.1) kg/m^2 BF%: 35.5 (33.2–37.8) High fitness: Age: 30.6 (25.6–35.6) y BMI: 24.6 (23.0–26.2) kg/m^2 BF%: 28.0 (25.0–31.0)	(moderate) (3) low fitness (low)		*Enterobacteria, Faecalibacterium prausnitzii* - *EreC* was positively correlated with fat intake (r = 0.258) - *EreC* was inversely correlated with CHO intake (r = −0.252)	showed that *EreC* contributed the most to VO_{2max}, BF%, Leptin, HDL,TG - VO_{2max} was negatively correlated with BF% (r = 0.755), TG (r = −0.274) and leptin (r = −0.574)

↓ lower ↑ higher.

showed opposite effects in the genera *Prevotella* and *Roseburia*, no effect on *Oscillospira*, and an increase of the species *Faecalibacterium prausnitzii*. While insulin sensitivity was increased after one year on both diets compared to baseline, no differences in the main metabolic outcomes of glucose/insulin status and lipoprotein profile were observed between the groups [27].

3.4.2. Observational studies

In adult men, abundance of the genus *Blautia* which was shown to be positively associated with MUFA serum metabolites was increased in persons with high BMI. Higher abundance of the phylum *Tenericutes* which was negatively associated with MUFA metabolites correlated with lower triglyceride levels. MUFA were also negatively associated with the family *Peptococcaceae* [36]. In a study with monozygotic twin pairs, higher compared to lower MUFA consumption was correlated to lower number of the genus *Bifidobacterium*. The numbers of bacteria within the different bacterial groups as measured by qPCR and diversity of studied bacterial groups did not differ between BMI groups [33].

3.5. High PUFA diets in relation to the intestinal microbiota and metabolic outcomes

3.5.1. Interventional studies

Three RCT investigated the effects of n3 PUFA enriched diets on the gut microbiota and found no effects on the intestinal microbiota compared to control groups [24,28,29]. However, only one of the interventions had a longer duration of six months [24], whereas the other two interventions lasted for only 30 days [28] or six weeks [29]. Ingestion of a docosahexaenoic acid (DHA)-enriched high MUFA diet and a high n3 (α-linolenic acid, ALA) or n6 (linoleic, LA) PUFA diet had no impact on bacterial richness, diversity or phylum distribution. Compared to a high MUFA diet with low n3 PUFA a DHA-enriched high MUFA diet correlated to the family *Lachnospiraceae* and the phylum *Firmicutes*. Total cholesterol levels were positively associated with *Firmicutes* in the group with the DHA-enriched high MUFA diet. In the n6 LA enriched diet total cholesterol levels were positively correlated with the phylum *Bacteroidetes* and negatively with the *Bacteroidetes*-to-*Firmicutes* ratio [28].

3.5.2. Observational studies

In accordance with the results of the interventional studies, Röytiö et al. (2017) also reported no correlation between any diversity or richness index and n3 PUFA intake in pregnant women [32]. In adults, an inverse association between PUFA intake and *Bacteroidetes*, all bacteria and *Firmicutes* was shown. The BMI was inversely related to the number of *Bacteroidetes* [31]. Org et al. (2017) [36] investigated serum metabolites of fatty acids in 45–70 year-old men and found that the abundance of the genus *Blautia* was negatively associated with PUFA including n6 and n3 PUFA and was increased in participants with higher BMI. In contrast positive associations with PUFA were observed with the genus *Bacteroidales*, the phylum *Tenericutes* and the family *Peptococcaceae*. Higher abundances of the latter two correlated with lower triglyceride levels [36]. In monozygotic twin pairs high n3 PUFA ingestion was associated with higher numbers of bacteria within the *Lactobacillus* group whereas higher intake of n6 PUFA was negatively associated with the abundance of the genus *Bifidobacterium* [33]. In contrast, in a study with nine participants the abundance of the species *Bifidobacterium longum* was positively correlated with the intake of unsaturated fatty acids and was higher in lean than in overweight and obese participants [37].

4. Discussion

To our knowledge, this is the first systematic review that compiles and provides effects/associations of dietary fat quantity and quality on/with the gut microbiota composition and cardiometabolic health in humans. Based on 15 included studies, our results of interventional trials do not suggest strong effects of dietary fat quantity or quality on the gut microbiota or on metabolic health outcomes while observational studies indicate associations with the gut microbiota and health outcomes. It has to be noted that half of the interventional studies had a relatively short duration of three to six weeks [25,28,29], which may be one reason why they showed no strong effects of fat type on either the gut microbiota or on metabolic health. Figure 2 gives an overview of the main results of intervention and observational studies included in this systematic review. As evidence provided by observational studies is less strong than that

Table 3
Risk of bias assessment of the randomized controlled trials (RCT) based on Cochrane risk of bias tool. Risk of bias of each item was judged as low (+), high (−) or unclear (?).

Reference	Random sequence generation	Allocation concealment	Blinding of participants/personnel	Blinding of outcome assessment	Incomplete outcome	Selective reporting	Other bias
Balfego et al., 2016 [24]	+	+	−	+	?	+	+
Blaedel el al. 2016 [25]	+	+	+	+	+	+	+
Fava et al., 2013 [26]	+	?	−	?	?	+	+
Haro et al., 2016 [27]	+	?	−	+	+	+	−
Pu et al., 2014 [28]	+	+	+	+	−	+	−
Rajkumar et al., 2014 [29]	+	+	−	+	?	+	+

Table 4
Quality assessment for the selected studies based on Newcastle-Ottawa Quality Assessment Scale for case–control studies. Total score ranges from 0 to 9. Higher scores indicated better methodological quality.

Reference	Selection				Comparability	Exposure			Total
	Case definition	Representativeness of the cases	Selection of controls	Definition of controls	Study controls for …	Ascertaiment of the exposure	Same method of ascertaiment for cases and controls	Non-response rate	
Brahe et al., 2015 [30]	*	*	*		**	*	*		**7**
Fernandes et al., 2014 [31]	*	*	*		*	*	*	*	**7**
Mayorga Reyes et al., 2016 [37]	*	*	*		*	*	*		**6**
Nakayama et al., 2017 [38]	*	*	*	*	*	*	*		**7**
Simoes et al., 2013 [33]	*	*	*	*	**	*	*		**8**
Org et al., 2017 [36]	*	*	*	*	**	*	*		**8**
Röytiö et al., 2017[a] [32]		*	*		**		*		**5**
Yamaguchi et al., 2016[a] [35]	*	*			**	*			**5**
Yang et al., 2017 [34]	*	*	*	*	**	*	*		**8**

[a] Analysis of associations between diet and the gut microbiota composition and clinical markers only, no case–control design.

from intervention studies the following discussion section will primarily focus on the latter studies.

It should be noted that the value of the results of microbiota analysis is limited due to the use of qPCR and FISH methods in most of the studies published, which do not allow a complete taxonomic assessment of the hundreds of species inhabiting the intestine. Consequently, comprehensive analyses by Next Generation Sequencing methods are required to better reflect the impact of fat quantity and quality on gut microbiota at the community structure level. Additionally, a recent study conducted in three different populations that investigated the temporal stability of specific microbiome features, based on 16S ribsomal RNA (rRNA) gene profiles and including two biological samples from each subject separated by approximately six months, revealed a large variability and low temporal stability of major phyla and alpha-diversity metrics. This makes it very difficult to draw reliable conclusions from cross-sectional studies as well as to identify robust associations between the microbiota changes with health outcomes in intervention studies unless several samples are analyzed longitudinally [39].

4.1. High fat, high SFA and high MUFA diets

High fat (Western) diets have been shown to be associated with lower richness and diversity of the intestinal microbiota in animals and humans [40–42] whereas high intake of vegetables and fruit

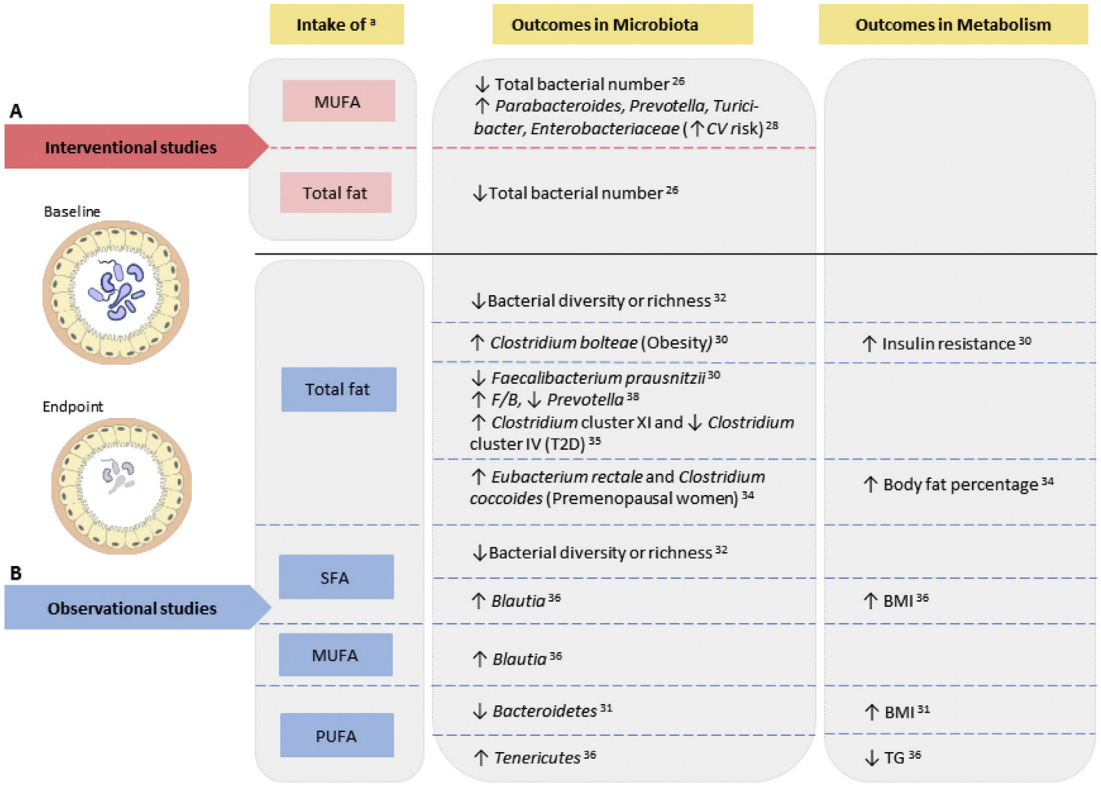

Fig. 2. Main associations between dietary fat and intestinal microbiota and between intestinal microbiota and metabolic health markers. Both, interventional (A) and observational studies (B) show associations between total fat intake, mainly SFA, and reduction of bacterial abundance, diversity and richness in the gut. (A) Dietary fat interventions do not suggest strong effects on gut microbiota. (B) High intake of total fat or SFA is positively correlated with the abundance of *Clostridium bolteae* and *Blautia* respectively, both species associated with unhealthy metabolic outcomes (insulin resistance and increased BMI). PUFA-enriched diet is associated with increased abundance of *Tenericutes* which is associated with lower levels of TG in plasma. [a] In the study by Org et al., 2017 [36], serum levels instead of dietary intake were measured.

(rich in fiber) is associated with high richness and diversity [43,44]. This is in line with the observed reduction of total bacteria after dietary interventions with high compared to low fat content in adults with increased MetS risk [26]. Also in pregnant women total fat and SFA intake were negatively associated with the gut microbiota richness and diversity [32]. While previous studies showed that lower microbiome richness is associated with obesity, higher fat mass, insulin resistance and dyslipidemia compared to higher richness [45,46], no significant differences of metabolic markers after high versus low fat interventional diets were observed in a randomized study although total bacteria decreased after the high fat interventions [26]. Accordingly, in adults with at least one cardiovascular risk factor the BMI had no significant impact on richness and α-diversity although rarefaction curves showed higher microbiota richness and diversity in overweight/obese compared to normal weight participants. Additionally, similarity and differences in microbiota among BMI (β-diversity) showed differences in normal weight versus obese participants [28].

In contrast to SFA, results on the effects of MUFA-rich diets are less consistent. In mice, MUFA do not seem to affect microbiota richness and diversity [47] and may even increase bacterial density [48]. Also in adults with increased cardiovascular disease risk, microbiome richness and diversity were not affected by high MUFA intake after an interventional period of 30 days [28]. However, in adults with an increased risk of MetS, high MUFA diets decreased total bacteria cells after 24 weeks of intervention compared to a high carbohydrate diet and compared to baseline. As this decrease was not accompanied by a decrease in any of the fluorescence in-situ hybridization (FISH)-enumerated bacteria, unrecognized bacterial populations must have been reduced which may suggest that the high MUFA diets negatively affected richness and diversity of the gut micriobiota [26]. Also in a cross-sectional study, a high MUFA intake was negatively associated with microbiota diversity and richness [32].

A higher relative abundance of *Firmicutes* and a lower abundance of *Bacteroidetes* after the ingestion of high-fat diets was previously reported in mice [41,49,50] and was confirmed in a study with children indicating that fat intake is positively correlated with *Firmicutes* and the *F/B* ratio but negatively with *Bacteroidetes* [38]. A higher proportion of *Firmicutes* was also reported in obese compared to the combined normal weight/overweight group in adults with at least one cardiovascular disease risk factor [28]. Results of the included intervention and observational studies in general confirm previous findings suggesting that a decrease of *Bacteroidetes* and an increase of *Firmicutes* are correlated with obesity in humans [51] and animals [6,47,52]. Nevertheless, a recent meta-analysis pooling data of 10 studies conducted by 16S rRNA gene sequencing did not confirm such association [53]. Animal studies indicate that changes in the gut microbiota composition are directly caused by fat intake rather than the degree of obesity because contrary to a high fat/SFA diet, a high fat/MUFA diet was not associated with changes in the gut microbiota but resulted in a higher degree of obesity than an energy-matched low-fat/SFA diet. However, differences in the gut microbiota composition were only found on the high fat/SFA diet and, thus, seem to result from the overflow of dietary fat but not from the obese phenotype [47]. Another study reported consistent and strong changes in the gut microbiota composition upon switching to a high fat diet for both wild-type and RELMβ (expression depends upon the presence of the gut microbiome) Knockout (KO) mice indicating that the high fat diet itself but not the obese state caused the alterations of the microbiota [50].

In contrary to the reported results with high fat diets, high MUFA diets ingested for 30 days showed no effect on the *Bacteroidetes*-to-*Firmicutes* ratio in an RCT with different oil treatments but identical energy% of total fat [28] which confirms previous results in mice [47].

Intervention studies also showed changes in single bacterial genus or species by high or low fat diets although there was no consistent trend. Supplementary Table 2 provides a short summary description of the affected bacteria [44,67].

High abundance of the genus *Prevotella* is typical for a high carbohydrate and fiber rich diet [8,43,54]. Accordingly, a high-fat Mediterranean diet resulted in a decrease of the genus *Prevotella* compared to a low-fat/high complex carbohydrate diet and compared to baseline in obese coronary heart disease patients but did not result in differences in metabolic endpoints [27]. In an RCT with identical total fat intake of 35 energy%, MUFA-rich diets were correlated with the genus *Prevotella* and the composition of bacteria differed between different weight status groups [28]. This was also the case in a study with pregnant women which reported a higher relative abundance of the genus *Prevotella* and of the family *Prevotellaceae* in obese than in overweight women [55].

Higher abundance of the species *Faecalibacterium prausnitzii* was observed in association with high-fiber diets and with beneficial effects on intestinal barrier function [56], on the fat-free mass as seen in young male children [57] and on health [58]. In contrast, according to results of included studies, a diet high in total fat (and SFA) negatively affects *Faecalibacterium prausnitzii* [26,30] whereas a low-fat/high complex carbohydrate diet increased *Faecalibacterium prausnitzii* compared to a high fat Mediterranean diet but both improved insulin sensitivity [27] which may have resulted from higher vegetable and fiber intake typical for these diets. Despite an increase of *Faecalibacterium prausnitzii* in a high fat/high SFA group, an RCT did not detect changes in adiposity or cardiometabolic risk factors [26] whereas an observational study reported positive associations of *Faecalibacterium prausnitzii* with a healthy lipoprotein profile [30].

Pu et al. showed a positive correlation between MUFA-rich diets and populations of *Enterobacteriaceae* which is the only family in the order *Enterobacteriales* [28]. In contrast, in mice fed a high-fat diet supplemented with a MUFA-rich (oleic acid) compound decreased the order *Enterobacteriales* and *Clostridium* cluster XIVa which had been increased by the high-fat diet and increased *Bifidobacterium* spp. which had been decreased by the high-fat diet [48].

4.2. High PUFA diets

In contrast to high fat and high SFA diets, evidence from three included RCT suggests that n3 PUFA-enriched diets have no effect on the gut microbiota compared to control diets [24,28,29] although two of the interventions lasted for only 30 [28] and 45 [29] days, respectively. The above null effects of dietary PUFA were also evidenced in the cross-over intervention study performed in the frame of the MyNewGut project where no impact on gut microbiota, anthropometry, metabolism, and physiology was observed after administration of fish oil capsules containing 3.6 g/d n3 PUFA (DHA and eicosapentanoic acid, EPA). In contrast, a recently published cross-over intervention with 4 g/d n3 PUFA for 8 weeks did not find changes in α or β diversity, or phyla composition but showed an increased abundance of beneficial bacteria such as *Bifidobacterium*, *Roseburia* and *Lactobacillus* [59]. Thus, a high dose and long-duration intake of n3 PUFA may be necessary to induce positive effects on the microbiome composition. The beneficial effects on metabolic outcomes observed by n3 PUFA-rich diets in the two included studies above [24,29] which confirm previous studies with n3 PUFA supplementation [60,61] seem to be independent of the gut microbiota.

Also in mice microbial diversity was not affected by diets high in PUFA [47]. Accordingly, diets including n3 PUFA-enriched (DHA)

high MUFA oil and high n3 (ALA) or n6 (LA) PUFA oil treatments for 30 days did not result in changes in bacterial richness, diversity or phylum distribution [28].

A DHA-enriched high MUFA oil treatment for 30 days correlated to *Firmicutes* which were positively associated with total cholesterol levels [28]. This type of diet also correlated to *Lachnospiraceae* [28] which has been reported to be increased by high fat diets in animal studies [41,62]. Compared to diets rich in SFA, diets rich in n3 or n6 PUFA resulted in lower decreases in *Bacteroidetes* in mice [63].

4.3. Limitations

The *reduction* of one of the major components of diet usually influences the ingestion of other macronutrients. In this regard, an increase of dietary fat intake is mostly paralleled by lower carbohydrate and fiber consumption. Therefore, it is hardly possible to attribute observed changes only to fat or specific fatty acids if there is no comparison group with identical intake of the other nutrients. This increases the risk of bias in observational studies and in the RCT comparing a Mediterranean and a low-fat diet [27]. Also, the energy intake can vary because of different fat intake and can influence the results. Some papers indicated that the energy content of the diet is as important as or even more important than the composition of the diet in driving gut microbiota changes [30–33]. Thus, associations between dietary fat/fatty acid intake and the intestinal microbiota as well as between the microbiota and metabolic health outcomes reported from observational studies may have been influenced by other dietary factors and energy intake as well. Also, other lifestyle factors (e.g. physical activity) influence an individuals' microbiota and (metabolic) health and may have affected the results of the included studies [64]. Another limitation, particularly of observational studies is that – with the exception of the study on biomarkers [36] – fat and fatty acid intake was estimated based on participant's self-reported dietary intake. Further, most studies included only small sample sizes of highly selected participants.

4.4. Conclusions and recommendations

Based on the included intervention and observational studies, this systematic review indicates that a high fat diet and a high fat diet rich in SFA may exert unfavorable effects on the gut microbiota characterized by lower richness and diversity and is generally associated with an unhealthy metabolic state. Results on diets rich in MUFA are less consistent. MUFA may have no effect on gut microbiota richness and diversity or may negatively affect total bacterial numbers and gut microbiota richness and diversity. In contrast, diets rich in n3 or n6 PUFA do not seem to negatively affect the gut microbiota or metabolic health outcomes. Thus, high fat intake and in particular high SFA intake should be reduced in favor of higher PUFA intake. Considering the conflicting results and a potential negative effect of MUFA on the gut microbiome, the dietary recommendation to reduce SFA and to replace them with (plant-sources of) MUFA and PUFA [65,66] may need additional research. However, data are not consistent and the overall evidence was weak due to risk of bias and small, not representative samples. Additional ongoing data analyses within the MyNewGut project will help to elucidate the role of the diet in altering the gut microbiota and associations with metabolic health outcomes. In particular, high quality longitudinal and intervention studies comparing effects of SFA, MUFA and specific n3 and n6 PUFA are missing.

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Conflict of interest

None

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Appendix A. Supplementary data

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