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Effects of Dietary Interventions on Gut Microbiome in Overweight or Obese Adults: A Systematic Review of Randomized Controlled Trials

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ABSTRACT

Background: It has been shown that gut microbiota dysbiosis may induce intestinal permeability, and systemic inflammation, leading to metabolic dysregulation. Furthermore, it has been implicated in the etiology of obesity. Dietary intake is known to affect the gut microbiota. These RCTs suggested that different dietary interventions may exhibit different effects on the composition of gut microbiota in overweight or obese individuals.

Objectives: This systematic review aimed to determine the effect of dietary intervention on the gut microbiota profiles in overweight or obese adults. The primary outcome of this systematic review is alpha-beta diversity and its changes at the species level.

Materials and Methods: This systematic review followed the PRISMA guidelines and was registered in the PROSPERO database with registration number CRD42022298891. A systematic search was conducted through the databases PubMed, MEDLINE, CINAHL, and Scopus literature using the terms: "gut microbiota","microbiome","overweight","obesity", "insulin sensitivity","insulin resistance","blood glucose","randomized controlled trial". After screening abstracts and full texts, 18 articles were extracted by two authors.

Results: Among the 18 RCT studies, dietary intervention gave an impact on gut microbiota alpha diversity changes in four studies. However, 7 studies showed no significant changes or differences compared to the placebo group. Beta diversity analysis was reported in 7 among 11 studies that performed alpha diversity analysis. Significant changes were found in food nutrients group (fiber supplementation) studies conducted over 8-12 weeks period. Seven more studies did not report any analysis of variance in either alpha or beta diversity. Changes in the composition of gut microbiota could be observed in dietary pattern interventions and resulting in improved metabolic status, except in the fried meat group diet. Interventions with food groups, food nutrients, and probiotics did not change the composition of gut microbiota.

Conclusion: The effects of dietary interventions on alpha-beta diversity are inconsistent, but rather showed more consistent effects on the changes in microbiota composition, especially in dietary pattern interventions.

Keywords: dietary interventions; gut microbiota; obesity; insulin resistance; randomized controlled trial

BACKGROUND

The prevalence of obesity worldwide has sharply increased according to the World Health Organization in 2016 [1], indicating that 39% of adult population are overweight and more than 13% of them are obese [1]. Obesity is characterized by increase in body-fat mass [2] and low-grade inflammation[3] which may determine chronic diseases such as type 2 diabetes mellitus, stroke, coronary heart disease, several types of cancer, and recently, increasing in mortality caused by COVID-19 infection [4,5].

Obesity is caused by a long-term energy surplus, can be influenced by genetic, neurobiology, and environmental factors [6,7]. Recently, the gut microbiota has been implicated in the etiology of

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obesity [8]. The gut microbiota contains genes that encode thousands of microbial enzymes and metabolites [9] that interact with human as the host to play a role in the immune system and metabolic regulation [10]. Furthermore, the gut microbiota has been shown to regulate glucose homeostasis and lipid metabolism. In addition to that, the gut microbiota metabolites such as short-chain fatty acid are also known to regulate satiety by stimulating the production of hormone peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) via the gut-brain axis [11–14].

Dietary intake is known to affect the gut microbiota [15]. Cumulative evidence has shown that western diet rich in saturated fat and low in fibre decreases the composition of gut microbiota towards dysbiosis. It has been shown that gut microbiota dysbiosis may induce intestinal permeability, fat colonization, and systemic inflammation, leading to metabolic dysregulation [16]. An intervention study with 40% of the total energy consisted of high-fat diet (HFD) showed changes in the composition of gut microbiota in which associated with an increase in Alistipes, a decrease in Faecalibactreium and concentration of short-chain fatty acids (SCFA), as well as an increase in arachidonic acid, lipopolysaccharide biosynthesis and inflammatory cytokines (CRP) [17].

On the other hand, the dietary pattern of Mediterranean diet, which is rich in vegetables, fruit, nuts, whole grains, fish, and olive oil, showed a decrease in the phylum Firmicutes and was followed by the level of *Ruminococcus gnavus* species which has potential for pro-inflammatory conditions [18]. Supported by an acute intervention study of the Mediterranean diet for four days, it showed changes in the abundance of fibre-fermenting bacteria, such as *Lachnospiraceae* and *Butyricicoccus*, which increased significantly and decreased after being given a high-fat diet [19]. Another study of probiotic strain *A. muciniphilla* supplementation was able to increase insulin sensitivity index by 30% compared to placebo [20]. Moreover, an intervention using inulin and resistant starch within 24 hours showed an increasing trend of SCFA production [21].

These randomized controlled trials (RCT) suggested that different dietary interventions may exhibit differences effect in the composition of gut microbiota in overweight or obese individuals. Therefore, we conducted this systematic review to determine the effect of dietary intervention on the gut microbiota profiles in overweight or obese adults. The primary outcome of this systematic review is alpha-beta diversity and its changes at species level.

MATERIALS AND METHODS

This systematic review was carried out by published protocols and refers to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guideline 2020[22]. This systematic review protocol has been registered in the Prospective Register of Systematic Reviews, PROSPERO (reg.no. CRD42022298891).

Data Source and Collection

A comprehensive literature search was conducted through PubMed, MEDLINE (Medical Literature Analysis and Retrieval System Online), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and Scopus. The main keywords used were as follows: gut microbiota, microbiome, overweight, obesity, insulin sensitivity, insulin resistance, blood glucose, randomized controlled trial. These keywords were combined with Boolean operators (e.g. OR, AND, NOT), and all fields or MeSH (Medical Subject Heading) terms.

The interest of primary outcome was the change in gut microbiota profile seen from alpha diversity, beta diversity, and richness or abundance on specific species levels. The association of specific species with fasting insulin and fasting glucose could also be reported as a secondary outcome.

Study Selection

Eligibility criteria included studies that met the PICOS (Patients/participants, Intervention, Comparison/control group, Outcome, and Study design) in which the study population consisted of 1) individuals with overweight and/or obesity (with or without insulin resistance, metabolic syndrome; 2) adults only (more than 18 years old); 3) the minimum duration of the intervention is 1 month (4 weeks); 4) diet intervention is performed daily; 5) the reported outcome is gut microbiota profile included alpha-diversity, beta diversity and richness/abundance of species level, fasting insulin, fasting glucose; and 6) the experiment is in RCT. Exclusion criteria were consisted of individual with type 1 diabetes, type 2 diabetes, gestational diabetes, NASH, NAFLD, infectious diseases (e.g. HIV, TB, COVID-19), cancer disease, gastrointestinal disease, end-stage renal disease, neurological disease, and studies performed in adolescents or children.

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During the collection process, duplicate studies were manually identified and removed. The articles were then analyzed using two-steps procedure. Initially, the retrieved titles and abstracts were independently analyzed by two authors. Next, the full text of all included articles were subjected to other analysis, then the eligible articles based on the inclusion and exclusion criteria were identified. Disagreements were resolved by consensus-based discussion or by another author's opinion.

Data Extraction and Quality

Assessment

Two authors (TAST and AP) independently extracted data from each study using an extract table template (Ms. Excel). Data extracted included: first author, year of publication, study design, place of study, participants' characteristics (*n*, age, BMI), dietary intervention (whole diet or specific diet), duration of interventions, and outcome measures (change of alpha -beta diversity is derived from any tools such as Shannon or Simpsons Index, Chao-1, UniFrac distance, specific species level of richness or abundance, and associated of specific species with fasting insulin and fasting glucose). Each RCT was assessed for its quality using the National Heart, Lung, and Blood Institute (NHLBI) tool for intervention studies. Four of these items represented fatal flaws if answered "No/Not reported/ Can't determine": (i) randomization (#1), (ii) dropout rate <20% (#7), (iii) valid/reliable outcome measure (#11), (iv) intent-to-treat analysis (#14). Study quality was determined based on the number of fatal flaws: good quality (0 fatal flaws), fair quality (1 fatal flaws), or poor quality (≥ 2 fatal flaws).

Data Synthesis

The findings from the included studies would be presented as a narrative synthesis and illustrated in a table, including the following information; authors, year, subject characteristics, type of intervention, duration, primary outcome, and secondary outcome. Subgroups analysis would be conducted for different types of dietary interventions and based on durations.

RESULTS

Study Selection

The literature search identified 130 studies that have been reported in PubMed (63); Medline (10); CHINAHL (19); Scopus (38), and after excluding the duplicates and non-eligible titles and abstracts, 29 original articles were included. The identification and study selection detail are presented in the PRISMA flow chart (Figure 1).

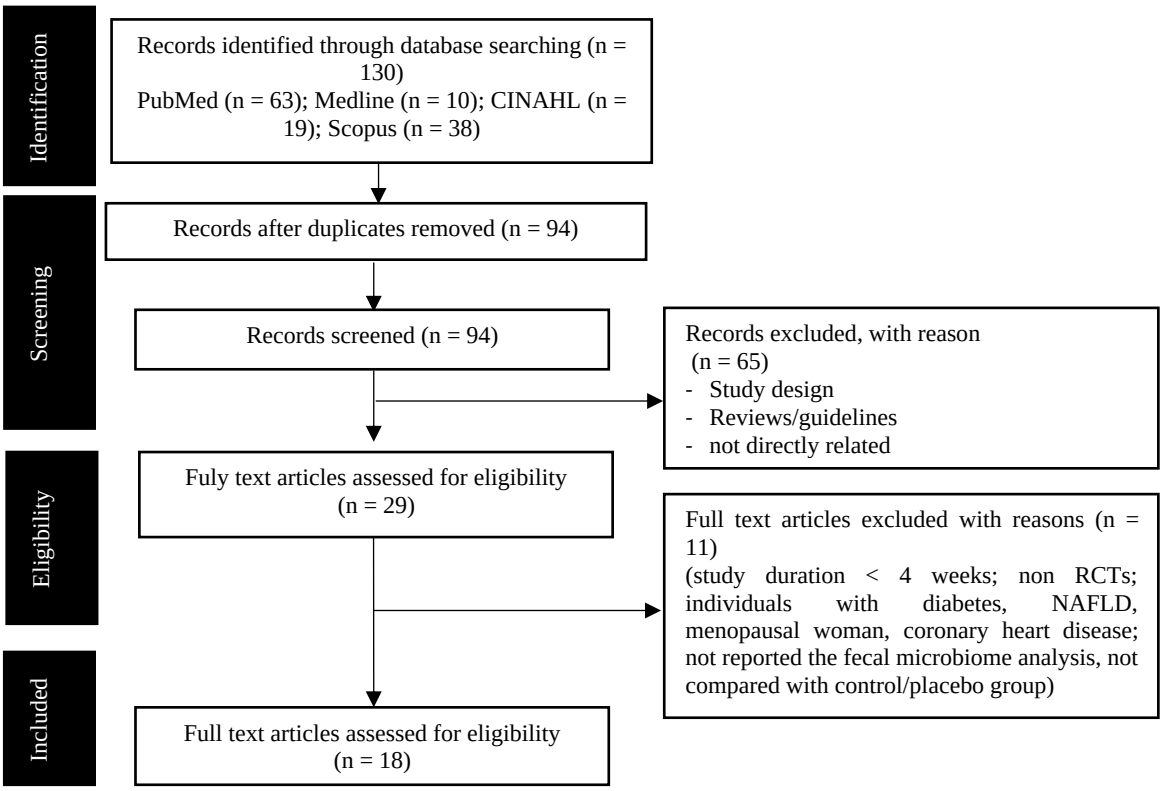

Figure 1. Flowchart Diagram for Study Selection of Systematic Review (based on PRISMA Guideline)

After a review of the full text some studies were excluded: 2 non-RCT studies, 6 ineligible studies according to the inclusion criteria, 1 study without fecal microbiota analysis, 1 study with less than 4 weeks duration, and 1 study without comparison to the control or placebo group. Finally, 18 studies were selected for review.

Study Characteristics

Characteristics of these studies are shown in Table 1, in relation to this review, study design, study location, participants, sample size, age, body composition (e.g. body mass index/BMI), health status, dietary intervention, and duration were also included. In total, 18 RCTs were selected [23,24, 25–32,33–40,] with publication year was between 2013-2021. There were 9 studies enrolled healthy overweight or obese participants, meanwhile the remaining studies were conducted on overweight or obese individual with insulin resistance, metabolic syndrome. Among the 18 RCT studies, 1 was single-blinded, 11 were double-blinded, 3 were open-labelled, and 3 had no report on the study design.

Any dietary interventions in the studies were classified into many sub-categories [41] such as dietary patterns (e.g., Mediterranean diet, high fat diet, vegan diet, multifunctional diet), food groups (e.g., kimchi, the red wine polyphenol, pea fiber, and whole grain), food nutrients (inulin, arabinoxylan oligosaccharides, genistein supplementation) and probiotic supplementation which was compared to the control or placebo group. The duration the intervention vary from a minimum of 4 weeks to 1 year.

Dietary Interventions and Gut Microbiota Diversity (α and -diversity)

Table 2 shows an alpha-beta diversity analysis. Alpha diversity was only measured in 11 [23,24,40,25,27,28,32,35,37–39] out of 18 reviewed studies. The measurement of alpha diversity used the Shannon index, Simpson index, and Chao1. Dietary intervention gave impact in in gut microbiota diversity changes in four studies [37–40]. However, 7 studies [23–25,27,28,32,35] showed no significant changes or differences compared to the control/placebo group. Dietary intervention with a period of more than four weeks showed changes in alpha diversity, both enrichment and decreased diversity. One of them, Vitale et al., 8 weeks intervention of Mediterranean diet showed a significant increase in gut microbiota diversity compared to the Western diet [37]. Similar intervention in obese adults with metabolic syndrome within one year of period by Muralidharan et al. showed no change in alpha diversity compared to baseline[28].

Beta diversity analysis reported in 7 [23–25,27,28,39,42] among 11 studies [23–25,27,28,32,37–40] which performed alpha diversity analysis. Significant changes were found in food nutrients group (fiber supplementation) studies conducted over 8-12 weeks period. Seven more studies [26,29–31,33,34,36] did not report any analysis of variance in either alpha or beta diversity.

Changes in the diversity of the gut microbiota were not only from food intake and food composition, but also from dietary patterns and the environment (such as lighting settings) affecting circadian rhythms which influence the composition of microbiota[43]. It is interesting to consider it during the intervention which was not found in this review.

Dietary Interventions, Bacterial Taxa, and Metabolic Marker Changes

The abundance of bacterial taxa is reported in this study review; 15 studies were analyzed up to species level and 3 studies[25,40,44] were analyzed up to genus levels. Details of the results are reported in Figure 2.

<table>
<tr><th colspan="2">DIETARY PATTERNS*</th><th colspan="2">FOOD GROUPS*</th><th colspan="2">FOOD NUTRIENT*</th><th>PROBIOTIC</th></tr>
<tr><td>Vegan</td><td>↔ Firmicutes/Bacteroidetes

Species:
↑ Faecalibacterium prausnitzii</td><td>All Groups (Fermented and Non Fermented Kimchi)</td><td>↓ Firmicutes/Bacteroidetes</td><td>IPE</td><td>↓ Firmicutes (B. obeum, E. ruminantium)
↑ Bacteroidetes spp (B. uniformis, B. xylanisolvens)</td><td rowspan="4">Changes based on the probiotic given.</td></tr>
<tr><td>Mediteranian Diet</td><td>↑ Bacteroidetes/Firmicutes

Species:
↑ Faecalibacterium prausnitzii
↑ A. muciniphilla</td><td>Redwine</td><td>Species:
↑ Faecalibacterium prausnitzii</td><td>AXOS</td><td>Species:
↑ Faecalibacterium prausnitzii</td></tr>
<tr><td rowspan="2">Fried Meat (High Fat Diet)</td><td rowspan="2">↓ Firmicutes/Bacteroidetes

↑ Dialister, Dorea, and Veilloella as a pathogenic bacterium</td><td colspan="2">Refined vs. Whole Grains</td><td rowspan="2">Genistein Group</td><td rowspan="2">↓Firmicutes/Bacteroidetes

Species:
↑ A. muciniphilla</td></tr>
<tr><td>Whole Grains</td><td>Species:
↑ Faecalibacterium prausnitzii</td></tr>
</table>

Figure 2. Primary Outcome for Gut Microbiome Taxa Following Dietary Interventions

*Grouping of dietary interventions are reffered on the reference (Toi PL, Anothasintawee T, Chaikledkaew U, Briones JR, Reutrakul S, Thakkinstian A. Preventive Role of Diet Interventions and Dietary Factors in Type 2 Diabetes Mellitus: An Umbrella Review. *Nutrients*, 2020;12(9):2722. Published 2020 Sep 6, doi:10.3390/nu12092722

Dietary Pattern Interventions

Mediterranean Diet

There were 3 clinical trials that used Mediterranean diet for the intervention. The main characteristics of this diet is high in fiber, indicated by consumption patterns rich in fruits, vegetables, whole grain foods, and low in saturated fat (e.g. olive oil). A study by Muralidharan et al. reported that subjects with metabolic syndrome experienced a decrease in body weight and an increase in the ration of Bacteroidetes/Firmicutes after one year of intervention with the combination of Mediterraniean diets, calorie restriction, and physical activity, compared to the control group[28]. This study is in line with the study by Remely et al. revealing that there was an increase in the abundance of Bacteroidetes after a weight loss in obese individuals [45]. In taxa composition, there were differences in abundance between the two intervention and control groups. Reduction was observed in the genus of Firmicutes, *Butyricicoccus, Eubacterium halii,* and *Ruminiclostridium 5*, meanwhile in the intervention group, the genus of Coprobacter was seen increased, as well as the species of *Ruminococcaceae NK4A214* and *Lachnospiraceae NK4A*136 from the family of Lachnospiraceae [28].

In other intervention studies using Mediterranean diet, Tagliamonte et al. and Vitale et al. found that the healthy-obese group under treatment for eight weeks showed consistent results in the increasing amount of *Akkermansia muciniphilla* [26,37], which are markers for healthy gut bacteria from the phylum of Verrucomicrobia [46].

Three interventions with Mediterranean diets demonstrated favorable metabolic changes to lower glucose and insulin levels [26,28,37]. There was also an increase in postprandial plasma butyric acid after intervention [37], considering that butyric acid provides health benefits in several studies [47]. On the other side, a study by Muralidharan et al. did not report SCFA metabolome analysis. It only included an analysis on related producer bacteria (*Lachnospira* and *Lachnospiraceae NK4A136*) which number was increased in both intervention and control groups [28].

Multifunctional Diet (MFD)

Marungruang et al. mentioned that a multifunctional dietary intervention (MFD) diet enriched with natural antioxidant food and omega-3 supplementation also showed a significant increase in the ratio of Prevotella/Bacteroides, including the species of *Prevotella copri*. Metabolic improvement which marked by lowered diastolic blood pressure, total cholesterol, LDL-cholesterol, and triglycerides. Following those improvements, weight loss was observed after eight weeks compared to the baseline. However, there was no statistical report of taxa abundance correlated between them [23].

Vegan Diet

In study by Kahleova et al., the intervention group was given low fat-vegan diet and vitamin B12 supplementation. Participants were requested to consistently eat a diet rich in vegetables, grains, legumes, and fruit, while avoiding animal products and added oils. The results showed a non-significant increase in the abundance of Bacteroidetes. However, reduction in body weight and improved insulin sensitivity were observed, although it had negative correlation with *Bacteroidetes fragilis* species. SCFA-producing bacteria, the species *Faecalibacterium prautnizii* (butyrate producer) showed increasing in abundance in the low-fat vegan diet group. Although there was a decrease in *Bacteroidetes fragilis* in both intervention groups, but in the vegan diet group was slightly higher compared to the control group [35].

Low Fiber Diet / High Fat Diet

A study by Gao Jian et al., using fried meat as the diet[40], showed contradictive results to those in Mediterranean diet. This finding strengthened the evidence of gut microbiota changes following the high fiber diet especially in individuals consuming Mediterranean diet [26,28,37]. An increase in the abundance of *Dialister* and *Veilloella* from the Firmicutes group occurred in the fried meat group. Deep-frying was used as cooking method to fry the meat during 4 weeks and resulted in a drop of SCFA producing bacteria (*Lachnospiraceae* and *Flavonifractor*). This proved that the result of fried meat intervention was identical to the high-fat diet, in which a significant decrease of butyric acid, valeric acid, and an increase in lipopolysaccharide were observed. Insulin levels was also amplified by an increase in muscle insulin resistance index (MIRI) and several inflammatory cytokines.TNF-α, IL-10, and IL-1β) [40].

Fava et al. reported that total bacteria was decreased after subjects were given high-fat diet. Interestingly, reduction in fat intake accompanied by increasing in carbohydrate intake (thigh carbohydrate

(HC)/high glycemic index (HGI) group) exhibited an increase in *Bacteroides* and *Bifidobacterium spp* that independently increase energy regulation homeostasis. Lowered fasting blood glucose and plasma insulin levels were also observed in the groups taking high carbohydrate (HC)/low glycemic index (LGI) and HC/HGI. Regarding the fecal SCFA, the HS group showed a significant increase in butyric and propionic acids. Fecal SCFA and plasma SCFA levels may provide different interpretations of host metabolism which should be investigated further.

Food Groups

Whole Grain vs Refined Grain

Roager et al. investigated two dietary intervention studies, in which each duration was 8 weeks. The subjects were given either whole-grain diet or refined-grain diet. A total of 60 adults at risk of developing metabolic syndrome participated in these randomized controlled cross-over design studies. It was found that the whole-grain dietary intervention did not significantly impact the changes of bacterial species composition and diversity in the gut microbiota (even after FDR correction for multiple tests was performed). However, among several species, *Faecalibacterium prautsnitzii* and *Prevotella copri* responded with an increase in abundance after being given whole-grain diet, while decreased immediately after consumption of refined-grain diet. Decreasing in body weight, fat-free mass, and inflammatory biomarkers (IL-6) after adjusting for weight loss was observed[32].

Kimchi

Kimchi is a traditional food from South Korean. It is a fermented food with main ingredients are Chinese cabbage, garlic, red pepper, green onion, and ginger. Han et al. compared the difference of giving fresh kimchi vs fermented kimchi to overweight/obese individuals during 8 weeks. The result showed that the group receiving fermented kimchi had greater proportion of bacterial strains than those receiving fresh kimchi. Some changes observed towards the ratio of bacteria after fermented kimchi administration were as follow: 1) the number of Firmicutes and Bacteroidetes were dropped; 2) *Bacteroides* and Prevotella were escalated; and 3) Blautia was decreased. On the other side, in the group consuming fresh kimchi, there was a slight reduction in fasting glucose and insulin levels in comparison to the baseline. This result was not found in the group consuming fermented kimchi[33].

Red wine

A cross-over RCT study with red wine polyphenol supplementation in individuals with metabolic syndrome by Moreno et al. reported that there was an increase in *Bifidobacterium bifidum* species after 30 days of red wine supplementation. At baseline, microbiota analysis showed low abundance of several species such as *Bifidobacterium, Eggerthella lenta, Prevotella, Blautia coccoides–Eubacterium rectale group, Lactobacillus, Faecalibacterium prausnitzii and Roseburia.* A consistent increase in *Faecalibacterium prausnitzii* from the phylum Firmicutes in both intervention and control groups, although there was no significant difference between the two groups. This might happen because red wine polyphenols have prebiotic capacity that presents positive effect towards fasting blood glucose levels, LPS concentrations, and CRP levels in Mets individuals.[36].

Food nutrients

Fiber

The composition, diversity, and abundance of gut microbiota are largely influenced by fiber consumption. Fiber provides a number of metabolic substrates that are used for fermentation reactions carried out by the gut microbiota [48]. In this review, there are three studies with fiber supplementation that consistently show increasing in the Firmicutes phylum [24,30,38].

An intervention study by Chambers et al. that supplemented the subjects with 20 g/day of inulin-propinate ester (IPE), resulted in a rise of Firmicutes phylum, with species bacteria from *B. obeum, E. ruminantium,* meanwhile in the inulin group the subject experienced an increase in *B. obeum, B. luti, B. faecis, R. faecis, Oscillibacter spp*. Similarly, supplementation of IPE or inulin only significantly improved insulin sensitivity (HOMA index, Matsuda index) when compared to cellulose administration [38].

A crossover-RCT study about supplementation of arabinoxylan (AXOS) and PUFA on central obese individuals with metabolic syndrome by Kjolbaek at al., resulted in a drop of Bacteroidetes phylum abundance and a rise in the abundance of Actinobacteria and Bifidobacteria phylum. It also showed an abundance increasing of butyrate-producing species from Firmicutes phylum and Clostridales order such as *Eubacterium rectale, Faecalibacterium prausnitzii, Blautia wexlerae, Dorea longicatena, Eubacterium hallii, Blautia luti, Ruminococcus obeum, Fusicatenibacter saccharivorans*. Unfortunately, there was no washout period between supplementation of AXOS and PUFA. On the other hand, both AXOS and PUFA

supplementation did not result in the changes of metabolic parameters. [24]. Meanwhile, there was no change observed in the composition of gut microbiota after PUFA supplementation.

Supplementation of 15 g/d yellow pea fiber for 12 weeks in a study conducted by Lambert et al. showed a non-significant increase in total bacteria. However, there was a trend of increasing gut microbiota abundance, which was followed by an increase in the abundance of *Clostridium leptum, Clostridium cluster I,* and *Roseburia spp* when compared to the placebo group. This supplementation has a slightly significant metabolic effect to improve body fat profile and glucose tolerance [30].

Genistein

Genistein is an isoflavone compound found in foods, especially soybeans. Genistein is able to modulate the composition of the gut microbiota and reduce metabolic endotoxemia (LPS) and is able to increase insulin sensitivity as indicated by the HOMA index or Matsuda index. A study by Guevara et al. showed a decrease in the Firmicutes/Bacteroidetes ratio, an increase in the Verrucomicrobia phylum, and abundance increasing A. municiphilla, Ruminococcos bromii, and B. uniformis after 50 mg/day of genistein supplementation for 2 months in comparison to the placebo group[39].

Probiotic Supplementation

There are 4 studies of probiotic supplementation in this review; all of them reported changes in the composition of gut microbiota and metabolic markers after supplementation[25,27,29,34] although there was no change in total composition of bacteria.[27]. The metabolic markers observed were reduced insulin levels [25], fasting blood glucose [29], improved insulin sensitivity [34], and improvement of cell-mediated incretin function occurred in *L.reuteri* probiotic supplementation..

A study by Teronio et al. using Lactobacillus spp supplementation with dosage of 9log10 cfu/capsule and omega-3 in individuals with metabolic syndrome resulted in increasing of *Verrucomicrobia* phylum with specific genus is Akkermansia. Significant differences in changes of the metabolic markers between both groups (prebiotic and omega-3) were also observed. A trend of reduced insulin levels, inflammatory cytokines (IL-6), and soluble vascular cell adhesion molecule 1 (sVCAM) which were closely associated with cardiovascular disease risk was also seen [25].

Similar results in a study by Depomnier et al. showed an inclined number of *A. muciniphila* after administration of living *A. muciniphila* or pasteurized *A. muciniphila* [34]. Pasteurized *A. muciniphila* markedly and significantly improved insulin sensitivity index by about 30% as compared to the placebo group.

A double blind RCT probiotic supplementation by Rajkumar et al. (group 1: placebo, group 2: VSL3, group 3 = omega 3, group 4 =VSL3 and omega 3 capsules) showed a significant increase in total bacteria aerobes, *Lactobacillus, Bifidobacteria* and *Streptococcus* in groups 2 and 4. Interestingly, the total bacteria Bacteroides, Coliforms, and *Escherichia coli* was changed in group 4. It was only group 3 that showed no changes [29]

Quality of Included Studies

Table 3. Quality Assessment of Studies

Author	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	Quality
Fava et al. 2013	Y	Y	NR	N	CD	N	N	Y	Y	Y	Y	Y	N	N	Poor
Rajkumar et al. 2014	Y	NR	N	Y	Y	Y	Y	Y	CD	Y	Y	Y	Y	Y	Fair
Han et al. 2015	Y	NR	NR	NR	NR	Y	Y	Y	Y	Y	Y	Y	N	N	Fair
Simon et al. 2015	Y	N	N	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Fair
Moreno et al. 2016	Y	NR	NR	NR	NR	N	Y	Y	Y	Y	Y	NR	NR	Y	Fair
Lambert et al. 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	N	Fair
Marungruang et al. 2017	Y	Y	Y	NR	NR	Y	Y	Y	NR	NA	Y	Y	Y	N	Fair
Roager et al. 2017	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Poor
Chambers et al. 2019	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Good
Depomnier et al. 2019	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Fair
Kjolbaek et al. 2019	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Poor
Guevara et al. 2020	Y	CD	N	Y	Y	Y	Y	Y	NR	Y	Y	NR	Y	Y	Fair
Teronio et al. 2019	Y	N	NR	NR	NR	Y	Y	Y	Y	Y	Y	Y	N	Y	Fair

Author	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	Quality
Kahleova et al. 2020	Y	Y	N	N	Y	Y	N	N	Y	Y	Y	Y	N	N	Poor
Vitale et al. 2020	Y	Y	Y	Y	NR	Y	Y	Y	Y	Y	Y	Y	N	Y	Good
Gao Jian et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Good
Muralidharan et al. 2021	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	N	Poor
Tagliamonte et al. 2021	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Fair

Of the 18 included studies in this review (Table 3), the methodogical qualities of three studies were stated to be good, ten were classified as fair, and five were placed as poor. Related the prominent flaws, four studies did not use randomized controlled design; two studies presented droupout rates above 20%, and eight studies did not perform intention to treat analysis.

DISCUSSION

In general, it is difficult to draw conclusions about the effect of dietary intervention in this regard. Metabolic health status, type of dietary intervention, duration of intervention, study design, and sample size may lead to different outcomes among studies. Although there are differences in study results, most of the studies showed association between taxa-specific changes after dietary intervention was given and the metabolic health parameters such as glucose metabolism, fat, insulin sensitivity, inflammation, and some SCFA metabolites due to changes in taxa composition.

Dietary intervention is an important external factor because it influenced the composition and abundance of the gut microbiota. The nutrients contained in the foods are used for survival of the microbes in the digestive tract [49]. Beneficial bacteria is associated with high-fiber intake in either dietary pattern intervention (Mediterranian diet, MFD diet, vegan diet), food groups (kimchi), or food nutrients (inulin, axos supplementation). Similar effects were confirmed by the systematic review by Wagenaar et al [50].

There is an increase in the genus of Lachnospiraceae NK4A136 from the family of Lachnospiraceae [28], species of *Faecalibacterium prautsnitzii* [24,32,35], *Eubacterium rectale*, *Eubacterium halii* [24], and *Roseburia spp* [30]. Several types of these bacteria are believed to be part of the butyrate-producing taxa [51]. A rising number of *Akkermansia muciniphilla* also occurred after the administration of Mediterranean diet[26,37] and fiber supplementation (AXOS)[24]. *Akkermansia muciniphila* has an important role to maintain intestinal barrier function as a feature of healthy gut profile [46,52]. The number of *Prevotella copri* was inclined after being given whole-grain diet but immediately dropped when the diet was replaced with refined-grains[32].

High-fat and low-fiber consumption pattern such as in typical Western diet can reduce total bacteria, as well as the abundance of the Lachnospiraceae and Flavonifractor families (SCFA-producing bacteria)[33,40], meanwhile the amount of pathogenic bacteria which is closely related to obesity was increased [40,53]. In another study conducted by Mocanu et al., low-fiber diet did not change the composition and diversity of bacteria, but on the other side, changes after fecal microbial transplantation (FMT) was found [54].

High-fiber intake in a whole-diet intervention showed improvements in metabolic parameters such as improved insulin sensitivity [26,28,35,37], diastolic blood pressure, total cholesterol, LDL and triglycerides [23], an inflammatory cytokine (IL-6), reduced glucose levels[32], and an increase in postprandial butyric acid after Mediterranean diet intervention [37].

Some supplements such as IPE and inulin improved insulin sensitivity compared to cellulose administration. On the other hand, AXOS supplementation did not show significant changes in blood pressure, glucose metabolism, and lipids[24]. Similarly, fibre supplementation from yellow pea resulted in a slight improvement on body fat and glucose tolerance [30].

Phytochemicals (polyphenols) are able to provide two effects on the gut microbiota; 1) inhibiting the growth of certain taxa, and 2) increasing the growth of bacteria because they can be metabolized into substrates for the host[55]. Regarding these properties, red wine-polyphenols administration can increase the abundance of *Faecalibacterium prausnitzii* and affect the metabolic health by decreasing fasting blood glucose levels, LPS concentrations and CRP levels[36]. Another type of phytochemicals is genistein, which in some studies were shown a rising number of *Akkermansia muciniphilla* after genistein supplementation and significantly improved the insulin sensitivity by 30% compared to the control group[39].

Faecalibacterium prautsnitzii is butyrate-producing microbiota that consistently presents in high-fiber intake (Mediterranean, Vegan, and AXOS) and in red wine-polyphenol interventions. Dietary fibre is a carbohydrate polymer that cannot be metabolised by amylase[56] and cannot be absorbed in small intestine[57].

Dietary fibre can only be processed by certain species of gut microbiota through an anaerobic fermentation process, with the main product being SCFA (butyrate, propionate, acetate) [48]. Short-chain fatty acid is a metabolite products that play a role in energy regulation processes, immune system, and cell proliferation[58]. Butyrate is present in a greater proportion in the intestinal lumen[58].

Gram-positive butyrate-producing bacteria plays important role in gut health, by carrying out the fermentation process in the colon. The process takes place by obtaining ATP through substrate-level phosphorylation during the breakdown of oxidative-substrate[48]. Then, combination of two molecules of acetyl-CoA to form acetoacetyl-CoA, accompanied by a gradual reduction to butyryl-CoA for the next step in the formation of butyrate [51]. Intestinal mucosa requires butyrate as its main energy and plays a role in the regulation of gene expression, inflammation, differentiation, and apoptosis in host cells. Butyrate is able to reduce the negative effects of lipopolysaccharides and simultaneously increase the regulation of intestinal barrier function by stimulating the production of mucin, as well as activation of G-protein receptors (GPR41 and GPR43) in the large intestine, stimulation of the production of hormone peptide YY (PYY) and glucagon-like peptide. -1 (GLP-1) which affects glucose homeostasis.[11].

High-fat and low-fibre diets cause gut bacteria to use mucin glycans for self-metabolism by inducing the expression of enzyme genes that result in decreased the mucin [57], leading to a risk of leaky gut barrier which is characterised by increased permeation of luminal contents into the mucosa and submucosa layer around immune cells. This condition has potential to cause translocation of lipopolysaccharide compounds (LPS) into the blood circulation[59] which leads to metabolic dysregulation [16]

In the fried-meat intervention group, a drop in butyric and valeric acid, a rise in lipopolysaccharide and insulin levels were occurred due to amplification by an increase in muscle insulin resistance index (MIRI) and several inflammatory cytokines (TNF-α, IL-10, and IL-1β).[40]. In addition, the study reported by Fava et al in the high showed a significant increase in fecal butyrate and propionate. In this perspective, the increase in fecal SCFA in obese individuals is interesting to understand in regard to the intestinal absorption function and/or activity modulation of the composition of gut microbiota present[44]. Moreover, it is probably the choice of plasma SCFA measurement as in the study of Vitale et al can be considered to assess the exact amount of SCFA levels [37].

Probiotic supplementation also provides significant changes in the composition and abundance of gut microbiota, excluding symbiotic supplementation[60] and only omega-3 supplementation without any combination with probiotics[29]. An increase in *Akkermansia muciniphilla* appeared after supplementation with the probiotic Lactobacillus, in the form of living or pasteurized *A. Muciniphilla* [46,52]. Reduced insulin levels[25] and fasting blood glucose[29], improvement in insulin sensitivity[34] and cell-mediated incretin function occurred with probiotic supplementation of *L. reuteri*,[27].

The plausible mechanism that might explain the improvement in metabolic health is the ability of probiotics to repair the intestinal epithelial barrier and reduce intestinal permeability due to previous dietary consumption patterns, leading to inflammation suppression and translocation of endotoxins into the blood vessels[61,62]. Positive correlation in regards to improved insulin sensitivity was reported in relation to bacterial species of A. Muciniphilla [34], *Bacteroides fragilis* [35], *Bacteroides stercoris, Bacteroides caccae, Phascolarctobacterium faecium* [54], *Intestimonas butryriciproducens, Desulfovibrio piger, Coprobacter fastidious s*[24], one OTU (unpublished species name) classified as *Prevotella* genus [44], and also *Lactobacillus reuteriI*. Meanwhile, negative correlation was found in the types of bacteria *Dialister succinatiphilus*, Turcibacter sanguinis, Alloprevotella [24]. In addition, *Faecalibacterium prausnitzii* [28], Eubacterium eligens [37] has negative correlation with blood glucose levels

Akkermansia muciniphilla is one of species that appears consistently for a minimum of eight weeks duration [25,26,37,39] (more details in Table 3). Nine dietary intervention studies were administered to healthy overweight/obese individuals. Seven studies (78%) demonstrated significant improvements in metabolic health, occurring at a minimum duration of four weeks of intervention [23,26,30,35,37,38,40]. Two studies in the obese group with insulin resistance showed improvement in metabolic status beginning at week 6 [29,39]. One study in pre-diabetic individuals did not report any change in metabolic markers [63].

Inconsistent changes were also still visible at long duration of 10-12 weeks [24,25,34,36,54], but starting at 28 weeks up to one year of the duration, it showed significant change results [28,33]. These results possibly indicated that individuals with metabolic syndrome require a long-term diet to achieve significant change. Several other studies suggest the possibility that there is no significant effect of diet on gut microbiota and metabolic health, depending on interpersonal variability in enterotype composition, even if the individuals have been subjected to appropriate extreme diets [64]. Therefore, further mechanisms need to be investigated.

In this review, differences in the diversity and composition of gut microbiota taxa may be influenced by factors such as metabolic health status, duration of intervention and types in the dietary intervention itself. In general, a high-fibre diet and dietary interventions rich in polyphenols (there is prebiotic capacity) have a positive effect on the diversity and composition of beneficial microbes that are beneficial in improving metabolic function. It could be partly associated with increased levels of SCFA through the process of bacterial fermentation[44]. Furthermore, the effectiveness of probiotic administration depends on the specific strain used on the initial composition of the individual gut microbiota. Finally, the limited included studies in this review might also be a major limitation of this systematic review; thus, further investigation in a large well-controlled study is needed to confirm these findings

CONCLUSIONS

In conclusion**,** the effects of dietary interventions on alpha-beta diversity are inconsistent but showed more consistent effects on microbiota composition changes. Meanwhile, interventions with food groups, food nutrients, and probiotic did not change gut microbiota composition. Changes in gut microbiota composition could be observed after modifying the diets, resulting in improved metabolic status. However, this does not include the group receiving dietary interventions with fried meat. Future studies on the effects of cooking methods on the gut microbiota and metabolic health status are interesting to investigate further.

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Table 1. Characteristic of Studies

Author	Design	Location	N (subject)		n, GM was analyzed	age (years)	BMI (kg/m^2)	Health Status	Intervention	Duration
			pre	post						
Dietary pattern										
Fava et al. 2013	SB-RCT	UK	130	88 (HS group = 11, HM/HGI group = 17, HM/LGI gorup = 22, HC/HGI group = 21, HC/LGI group = 17)	88 (HS group = 11, HM/HGI group = 17, HM/LGI gorup = 22, HC/HGI group = 21, HC/LGI group = 17)	54±9,5	28,8±4,9	obese with metabolic syndrome	Following a high saturated fat diet (HS) - high glycemic index (GI) diet (total fat 38%E fat, SFA 18%E, MUFA 12%E, PUFA 6%E, CHO 45%E, GI 64%), after which participants were randomly assigned to one of four experimental diets (HM/HGI: total fat 38%E, SFA 10%E, MUFA 20%E, PUFA 6%E, CHO 45%E, GI 64%; HM/LGI: total fat 38%E, SFA 10%E, MUFA 20%E, PUFA 6%E, CHO 45%E, GI 53%; HC/HGI: total fat 28%E, SFA 10%E, MUFA 11%E, PUFA 6%E, CHO 55%E, GI 64%; HC/LGI: total fat 28%E, SFA 10%E, MUFA 11%E, PUFA 6%E, CHO 55%E, GI 51%)	28 weeks (4 weeks run out HS diet, 24 weeks one of four diet intervention HM/HGI; HM/LGI; HC/HGI; HC/LGI)
Marungruang et al. 2017	RCT	Sweden	52 (multifunctional diet = 25, control diet = 27)	47 (multifunctional diet = 23, control diet = 24)	47 (multifunctional diet = 23, control diet = 24)	50-73	25-33	obese	MFD group were given foods rich in natural antioxidants, omega-3 fatty acids, high-(prebiotic) fiber, low glycemic, blood cholesterol-normalizing ingredients. MFD provided 2 g stanol/d for women and 2,7 g/d for males. Total dietary fiber content was 62 g/day vs control. Both diets were designed in agreement with the Nordic Nutrition Recommendations and supplied 2500–2600 Kcal/day for men and 2000–2100 Kcal/day for women, combining foods from plant and animal origins.	8 weeks

Author	Design	Location	N (subject)		n, GM was analyzed	age (years)	BMI (kg/m^2)	Health Status	Intervention	Duration
			pre	post						
Kahleova et al. 2020	opened label-RCT	Columbia	168 (vegan group =84; control group = 84)	115 (vegan group =65; control group = 50)	115 (vegan group =65; control group = 50)	>18	28-40	healthy overweight adult	low fat vegan diet vs control. Vitamin B12 was supplemented for vegan group (500µg/day)	16 weeks
Vitale et al. 2020	DB-RCT Parallel Group	Italy	Mediterannian diet = 16; Control Diet (western diet) = 13	Mediterranian diet = 16; Control Diet (western diet) = 13	Mediteranian diet = 16; Control Diet (western diet) = 13	Mediteranian diet = 41.6 ± 12.3; control diet = 45.9 ± 13.0	Mediteranian Diet = 28,9,1±2,3 ; Control Diet = 29,3±3,5)	ow/obese	The control diet was instructed to keep their habitual diet unvaried during the intervention and did not consume extra virgin olive oil Mediterranean Diet was designed to have fruit and vegetable 500gr/day, nuts 30gr/day, refined cereal products replaced with wholegrain products 200gr/day, meat and derived meat products, fish 300gr/day, legumes 200gr/day, extra virgin olive oil	8 weeks
Gao Jian et al. 2021	DB-RCT	China	117 (control group = 58; fried meat group = 59)	117 (control group = 58; fried meat group = 59)	117 (control group = 58; fried meat group = 59)	Control group = 21,73; fried meat group = 21,13	Control group = 26,39; fried meat group = 26,06	healthy overweight adult	Fried meat was provided four times per week in the experimental the group with cooking methods, which was frying at 150 C for <3 min; and boiling, steaming, or dressing with sauce at 100 C in the control group.	4 weeks

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Author	Design	Location	N (subject)		n, GM was analyzed	age (years)	BMI (kg/m^2)	Health Status	Intervention	Duration
			pre	post						
Muralidharan et al. 2021	DB-RCT	Spain	400 (intervention group = 200; control group = 200)	400 (intervention group = 200; control group = 200)	262 (intervention group = 183; control group = 179)	intervention group = 64.3 ± 5.1; control group = 65.1 ± 4.9	intervention group = 33.4; control group = 32.9	ow/ob with metabolic syndrome	intervention group = individualized behavioral support, restricted caloric Mediteranian Diet, and physical activity promotion; control group = information on maintaining ad libitum unrestricted caloric Mediteranian Diet with no advice on weight loss strategies	1 year
Tagliamonte et al. 2021	DB-RCT	Italy	82 (Mediterranian Diet = 43, Control Diet =39)	82 (Mediteranian Diet = 43, Control Diet =39)	82 (Mediteranian Diet = 43, Control Diet =39)	Mediterranian Diet = 43±1,4 ; Control Diet = 43±1,9)	Mediteranian Diet = 31,1±0,5 ; Control Diet = 31,2±2,0)	ow/obese	group 1 = Isocaloric Tailored Mediteranian Diet; group 2 = control	8 weeks
Food groups										
Han et al. 2015	RCT	Korea	fresh kimchi group = 12; fermented kimchi group = 11	fresh kimchi group = 12; fermented kimchi group = 11	fresh kimchi group = 10; fermented kimchi group = 10	30 - 60	fresh kimchi group = 28 ± 2.31; fermented kimchi group = 27.8 ± 2.20	ow/obese	consuming 180 g of fresh or fermented kimchi per day (60 g/pkg × 3 meals)	8 weeks

Author	Design	Location	N (subject)		n, GM was analyzed	age (years)	BMI (kg/m^2)	Health Status	Intervention	Duration
			pre	post						
Moreno et al. 2016	RCT-cross over	Spain	MetS group = 10, control group = 10	MetS group = 10, control group = 10	MetS group = 10, control group = 10	48±2	MetS vs control group: 35,24±4,21 vs 27,52±2,10 (washout period); 34,49±4,17 vs 27,34±2,31 (red wine period); 34,53±4,23 vs 27,27±2,19 (de-alcoholized red wine period)	metabolic syndrome	Divided into three periods; the first period was the washout period (participants did not consume any red wine), the second period was drunk only red wine (272 ml/d), the third period was drunk de-alcoholized red wine (272 ml/d)	10 weeks (two weeks/15 days of washout period, followed by two intervention periods of 30 days each)
Lambert et al. 2017	DB-RCT	Canada	53 (pea fiber group = 29; placebo group = 24)	44 (pea fiber group = 22, placebo group = 22)	pea fiber group = 22, placebo group = 22	44±15	33,4±1,3 (PG); 32,8±1,3 (Pea fiber group)	obesity	The pea fiber group received 15g/d pea fiber supplementation with the dose was increased incrementally during the first 3 weeks of the study (week 1 ¼ 5 g/d; week 2 ¼ 10 g/d; week 3 ¼ 15 g/d. Pea fiber is packaged in wafers containing 5 g/serving of yellow pea fiber vs placebo group received an isocaloric dose of control wafers with no pea fiber	12 weeks
Roager et al. 2017	DB-RCT crossover	Denmark	60	60	50 (men = 18; women = 32)	20-65	25-35	ow/ob at risk of developing metabolic syndrome	group 1 = whole-grain ≥ 75 gr/day; group 2 = < 10gr/day of refined grain	8 weeks for each group, with washout period 6 weeks

Author	Design	Location	N (subject)		n, GM was analyzed	age (years)	BMI (kg/m^2)	Health Status	Intervention	Duration
			pre	post						
Food nutrients										
Chambers et al. 2019	DB-RCT-cross over	UK	14	12	12	18-65	29,8±0,9	ow/obese	20 g/day of inulin , 20 g/day inulin-propionate ester / IPE (14,6 g/day of inulin and 5,4 g/day of esterified propionate vs 20 g/day of cellulose (placebo - negative control)	42 days each in random order. The washout period for the next intervention was carried out for 28 days
Kjolbaek et al. 2019	Opened label RCT-cross over	Denmark	30	27	27 (completed all study interventions, AXOS, and PUFA intervention)	18 - 60	25-40	central obese and one criterion of metabolic syndrome	phase 1 (AXOS intervention) consumed a powder supplement of 15 g of wheat bran extract with 4 biscuits/cracker per day; phase 2 (PUFA intervention) consumed fish oil supplement (capsules), containing 3,6 g/d g of N-3 PUFA	12 weeks (two diet periods of 4 weeks each separated by a 4-week washout period)
Guevara et al. 2020	DB-RCT	Mexico	45 (PG = 23; GTG = 22)	45 (PG = 23; GTG = 22)	45 (PG = 23; GTG = 22)	20-60	PG = 34.5 ± 0.98; GTG = 34.6 ± 0.86	obese with insulin resistance	The subjects were randomly selected to form part of the placebo group (PG) or the genistein-treated group (GTG) with genistein capsules (50mg/day)	8 weeks
Probiotic										

Author	Design	Location	N (subject)		n, GM was analyzed	age (years)	BMI (kg/m^2)	Health Status	Intervention	Duration
			pre	post						
Rajkumar et al. 2014	DB-RCT	India	placebo (n = 15), VSL#3 probiotic capsules (n = 15), omega-3 fatty acid capsules (n = 15), or omega-3 capsule + VSL#3 probiotic capsule (n = 15)	placebo (n = 15), VSL#3 probiotic capsules (n = 15), omega-3 fatty acid capsules (n = 15), or omega-3 capsule + VSL#3 probiotic capsule (n = 15)	placebo (n = 15), VSL#3 probiotic capsules (n = 15), omega-3 fatty acid capsules (n = 15), or omega-3 capsule + VSL#3 probiotic capsule (n = 15)	40-60	± 28,79 (range 27-30)	obese, dyslipidemia and insulin resistance	Group 1 = nothing; group 2 = 1 capsule probiotic of VSL#3 everyday; group 3 = 1 capsule of omega 3 everyday; group 4 = 1 capsule of omega 3 and VSL#3 probiotic everyday	6 weeks
Simon et al. 2015	DB-RCT	Jerman	21	21	21 (men = 10, women = 11)	lean group = 49 ± 7; obese = 51 ± 7	lean group = 19-25, obese group = 30-45	obese	placebo group = receive Nutraceutix capsule placebo; intervention group = Nutraceutix capsule contain 10^10 cells of L. reuteri	8 weeks
Depomnier et al. 2019	DB-RCT	Belgium	40	32 (n placebo = 11; n pasteurized = 12; n alive = 9)	32	18-70	placebo = 37,63±5,82; pasteurized = 39,81±4,77; alive = 36,82±3,68	ow/obese with insulin resistance and metabolic syndrome	Alive *A. muciniphila* (live 10^{10} bacteria per day); pasteurized *A. muciniphila* (pasteurized 10^{10} bacteria per day); Placebo	12 weeks
Teronio et al. 2019	DB RCT-crossover	Spanyol	53 (group 1 = 28, group 2 = 25)	53 (group 1 = 28, group 2 = 25)	53 (group 1 = 28, group 2 = 25)	18-65	> 30	obese with metabolic syndrome	placebo group = maltodextrin; intervention group = probiotic *Lactobacillus spp* 9 log10 cfu/capsule, 1 capsule/day, with wash out periode (6 weeks)	12 weeks

IPE: inulin propionate ester, MD: Mediteranian Diet, CD: Control Diet, MFD: Multi Functional Diet, HS: high saturated fat diet, HC: High Carbo, HGI: High glycemic index, HF: high fiber, AXOS: arabinoxylan oligosaccharides, ow/ob = overweight/obese

Table 2. Primary Outcome for Gut Microbiome Following Dietary Interventions (Alpha-Beta Diversity)

Author	Health Status	Dietary pattern	Food Groups	Food Nutrient	Probiotic	Dietary pattern	Food Groups	Food Nutrient	Probiotic
		Alpha Diversity				Beta Diversity			
Fava et al. 2013	Obese Mets	-				-			
Rajkumar et al. 2014	Ob, dislipid, IR				-				-
Han et al. 2015	Ow/ob		-				-		
Simon et al. 2015	Ob				Not changed				Not changed
Moreno et al. 2016	Mets		-				-		
Lambert et al. 2017	Obesity		-				-		
Marungruang et al. 2017	Obese	Not changed				Not changed			
Roager et al. 2017	Ow/ob Mets risk		Not changed				-		
Chambers et al. 2019	Ow/ob			Changed				-	
Depomnier et al. 2019	Ob, IR. Mets				-				-
Kjolbaek et al. 2019	Healthy ow			Not changed				Changed	
Guevara et al. 2020	Ob IR			Changed				Changed	
Teronio et al. 2019	Mets				Not changed				Not changed
Kahleova et al. 2020	Healthy ow	Not changed				-			
Vitale et al. 2020	Ow/ob	Changed				-			
Gao Jian et al. 2021	Healthy ow	Changed				Changed			
Muralidharan et al. 2021	Mets	Not changed				Not changed			
Tagliamonte et al. 2021	Ow/ob	-				-			

Ow/ob: overweight/obese, Mets: metabolic syndrome, IR: insulin resistance

REFERENCES

1. Vaamonde JG, Álvarez-Món MA. Obesity and overweight. Med. 2020;13(14):767–76.
2. Goossens GH. The Metabolic Phenotype in Obesity: Fat Mass, Body Fat Distribution, and Adipose Tissue Function. Obes Facts. 2017;10(3):207–15.
3. Castro AM, Macedo-de la Concha LE, Pantoja-Meléndez CA. Low-grade inflammation and its relation to obesity and chronic degenerative diseases. Rev Médica del Hosp Gen México. 2017;80(2):101–5.
4. Mitchell NS, Catenacci VA, Wyatt HR, Hill JO. Obesity: Overview of an epidemic. Psychiatr Clin North Am. 2011;34(4):717–32.
5. Hill MA, Sowers JR, Mantzoros CS. Commentary: COVID-19 and obesity pandemics converge into a syndemic requiring urgent and multidisciplinary action. Metabolism [Internet]. 2021;114:154408. Available from: https://doi.org/10.1016/j.metabol.2020.154408
6. Chooi YC, Ding C, Magkos F. The epidemiology of obesity. Metabolism. 2019;92:6–10.
7. Biddle SJH, Bengoechea García E, Pedisic Z, Bennie J, Vergeer I, Wiesner G. Screen Time, Other Sedentary Behaviours, and Obesity Risk in Adults: A Review of Reviews. Curr Obes Rep. 2017;6(2):134–47.
8. Pigeyre M, Yazdi FT, Kaur Y, Meyre D. Recent progress in genetics, epigenetics and metagenomics unveils the pathophysiology of human obesity. Clin Sci. 2016;130(12):943–86.
9. Ruan W, Engevik MA, Spinler JK, Versalovic J. Healthy Human Gastrointestinal Microbiome: Composition and Function After a Decade of Exploration. Dig Dis Sci. 2020;65(3):695–705.
10. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. Nat Rev Microbiol. 2021;19(1):55–71.
11. Blaak EE, Canfora EE, Theis S, Frost G, Groen AK, Mithieux G, et al. Short chain fatty acids in human gut and metabolic health. Benef Microbes. 2020;11(5):411–55.
12. Kallus SJ, Brandt LJ. The intestinal microbiota and obesity. J Clin Gastroenterol. 2012;46(1):16–24.
13. Corfe BM, Harden CJ, Bull M, Garaiova I. The multifactorial interplay of diet, the microbiome and appetite control: Current knowledge and future challenges. Proc Nutr Soc. 2015;74(3):235–44.
14. Bauer P V., Hamr SC, Duca FA. Regulation of energy balance by a gut-brain axis and involvement of the gut microbiota. Cell Mol Life Sci. 2016;73(4):737–55.
15. Thursby E, Juge N. Introduction to the human gut microbiota. Biochem J. 2017;474(11):1823–36.
16. Cândido TLN, Bressan J, Alfenas R de CG. Dysbiosis and metabolic endotoxemia induced by high-fat diet. Nutr Hosp. 2018;35(6):1432–40.
17. Wan Y, Wang F, Yuan J, Li J, Jiang D, Zhang J, et al. Effects of dietary fat on gut microbiota and faecal metabolites, and their relationship with cardiometabolic risk factors: a 6-month randomised controlled-feeding trial. Gut. 2019;68(8):1417–29.
18. Meslier V, Laiola M, Roager HM, De Filippis F, Roume H, Quinquis B, et al. Mediterranean diet intervention in overweight and obese subjects lowers plasma cholesterol and causes changes in the gut microbiome and metabolome independently of energy intake. Gut. 2020;69(7):1258–68.
19. Zhu C, Sawrey-Kubicek L, Beals E, Rhodes CH, Houts HE, Sacchi R, et al. Human gut microbiome composition and tryptophan metabolites were changed differently by fast food and Mediterranean diet in 4 days: a pilot study. Nutr Res. 2020;77:62–72.
20. Depommier C, Everard A, Druart C, Plovier H, Van Hul M, Vieira-Silva S, et al. Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: a proof-of-concept exploratory study. Nat Med. 2019 Jul;25(7):1096–103.
21. Rahat-Rozenbloom S, Fernandes J, Cheng J, Gloor GB, Wolever TMS. The acute effects of inulin and resistant starch on postprandial serum short-chain fatty acids and second-meal glycemic response in lean and overweight humans. Eur J Clin Nutr. 2017;71(2):227–33.
22. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;372.
23. Marungruang N, Tovar J, Björck I, Hållenius FF. Improvement in cardiometabolic risk markers following a multifunctional diet is associated with gut microbial taxa in healthy overweight and obese subjects. Eur J Nutr [Internet]. 2018;57(8):2927–36. Available from: http://dx.doi.org/10.1007/s00394-017-1563-3
24. Kjølbæk L, Benítez-Páez A, Gómez del Pulgar EM, Brahe LK, Liebisch G, Matysik S, et al. Arabinoxylan oligosaccharides and polyunsaturated fatty acid effects on gut microbiota and metabolic markers in overweight individuals with signs of metabolic syndrome: A randomized cross-over trial. Clin Nutr. 2020;39(1):67–79.

25. Tenorio-Jiménez C, Martínez-Ramírez MJ, Del Castillo-Codes I, Arraiza-Irigoyen C, Tercero-Lozano M, Camacho J, et al. Lactobacillus reuteri V3401 Reduces Inflammatory Biomarkers and Modifies the Gastrointestinal Microbiome in Adults with Metabolic Syndrome: The PROSIR Study. Nutrients. 2019 Jul;11(8).
26. Tagliamonte S, Laiola M, Ferracane R, Vitale M, Gallo MA, Meslier V, et al. Mediterranean diet consumption affects the endocannabinoid system in overweight and obese subjects: possible links with gut microbiome, insulin resistance and inflammation. Eur J Nutr. 2021 Oct;60(7):3703–16.
27. Simon M-C, Strassburger K, Nowotny B, Kolb H, Nowotny P, Burkart V, et al. Intake of Lactobacillus reuteri improves incretin and insulin secretion in glucose-tolerant humans: a proof of concept. Diabetes Care. 2015 Oct;38(10):1827–34.
28. Muralidharan J, Moreno-Indias I, Bulló M, Lopez JV, Corella D, Castañer O, et al. Effect on gut microbiota of a 1-y lifestyle intervention with Mediterranean diet compared with energy-reduced Mediterranean diet and physical activity promotion: PREDIMED-Plus Study. Am J Clin Nutr. 2021 Sep;114(3):1148–58.
29. Rajkumar H, Mahmood N, Kumar M, Varikuti SR, Challa HR, Myakala SP. Effect of probiotic (VSL#3) and omega-3 on lipid profile, insulin sensitivity, inflammatory markers, and gut colonization in overweight adults: a randomized, controlled trial. Mediators Inflamm. 2014;2014:348959.
30. Lambert JE, Parnell JA, Tunnicliffe JM, Han J, Sturzenegger T, Reimer RA. Consuming yellow pea fiber reduces voluntary energy intake and body fat in overweight/obese adults in a 12-week randomized controlled trial. Clin Nutr. 2017 Feb;36(1):126–33.
31. Han K, Bose S, Wang J-H, Kim B-S, Kim MJ, Kim E-J, et al. Contrasting effects of fresh and fermented kimchi consumption on gut microbiota composition and gene expression related to metabolic syndrome in obese Korean women. Mol Nutr Food Res. 2015;59(5):1004–8.
32. Roager HM, Vogt JK, Kristensen M, Hansen LBS, Ibrügger S, Maerkedahl RB, et al. Whole grain-rich diet reduces body weight and systemic low-grade inflammation without inducing major changes of the gut microbiome: A randomised cross-over trial. Gut. 2019;68(1):83–93.
33. Fava F, Gitau R, Griffin BA, Gibson GR, Tuohy KM, Lovegrove JA. The type and quantity of dietary fat and carbohydrate alter faecal microbiome and short-chain fatty acid excretion in a metabolic syndrome "at-risk" population. Int J Obes [Internet]. 2013;37(2):216–23. Available from: http://dx.doi.org/10.1038/ijo.2012.33
34. Depommier C, Everard A, Druart C, Plovier H, Van Hul M, Vieira-Silva S, et al. Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: a proof-of-concept exploratory study. Nat Med. 2019;25(7):1096–103.
35. Kahleova H, Rembert E, Alwarith J, Yonas WN, Tura A, Holubkov R, et al. nutrients E ff ects of a Low-Fat Vegan Diet on Gut Microbiota in. Nutrients [Internet]. 2020;121(6):1–16. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7598634/pdf/nutrients-12-02917.pdf
36. Moreno-Indias I, Sánchez-Alcoholado L, Pérez-Martínez P, Andrés-Lacueva C, Cardona F, Tinahones F, et al. Red wine polyphenols modulate fecal microbiota and reduce markers of the metabolic syndrome in obese patients. Food Funct. 2016;7(4):1775–87.
37. Vitale M, Giacco R, Laiola M, Della Pepa G, Luongo D, Mangione A, et al. Acute and chronic improvement in postprandial glucose metabolism by a diet resembling the traditional Mediterranean dietary pattern: Can SCFAs play a role? Clin Nutr [Internet]. 2021;40(2):428–37. Available from: https://doi.org/10.1016/j.clnu.2020.05.025
38. Chambers ES, Byrne CS, Morrison DJ, Murphy KG, Preston T, Tedford C, et al. Dietary supplementation with inulin-propionate ester or inulin improves insulin sensitivity in adults with overweight and obesity with distinct effects on the gut microbiota, plasma metabolome and systemic inflammatory responses: a randomised cross-over . Gut. 2019 Aug;68(8):1430–8.
39. Guevara-Cruz M, Godinez-Salas ET, Sanchez-Tapia M, Torres-Villalobos G, Pichardo-Ontiveros E, Guizar-Heredia R, et al. Genistein stimulates insulin sensitivity through gut microbiota reshaping and skeletal muscle AMPK activation in obese subjects. BMJ open diabetes Res care. 2020 Mar;8(1).
40. Gao J, Guo X, Wei W, Li R, Hu K, Liu X, et al. The Association of Fried Meat Consumption With the Gut Microbiota and Fecal Metabolites and Its Impact on Glucose Homoeostasis, Intestinal Endotoxin Levels, and Systemic Inflammation: A Randomized Controlled-Feeding Trial. Diabetes Care. 2021 Sep;44(9):1970–9.
41. Toi PL, Anothaisintawee T, Chaikledkaew U, Briones JR, Reutrakul S, Thakkinstian A. Preventive role of diet interventions and dietary factors in type 2 diabetes mellitus: An umbrella review. Nutrients.

2020;12(9):1–17.
42. Gao J, Guo X, Wei W, Li R, Hu K, Liu X, et al. The association of fried meat consumption with the gut microbiota and fecal metabolites and its impact on glucose homoeostasis, intestinal endotoxin levels, and systemic inflammation: A randomized controlled-feeding trial. Diabetes Care. 2021;44(9):1970–9.
43. Dabke K, Hendrick G, Devkota S. The gut microbiome and metabolic syndrome. J Clin Invest. 2019;129(10):4050–7.
44. Karl JP, Fu X, Wang X, Zhao Y, Shen J, Zhang C, et al. Fecal menaquinone profiles of overweight adults are associated with gut microbiota composition during a gut microbiota-targeted dietary intervention. Am J Clin Nutr [Internet]. 2015 Jul;102(1):84–93. Available from: https://search.ebscohost.com/login.aspx?direct=true&AuthType=ip,shib&db=ccm&AN=109811791&site=ehost-live&scope=site&custid=ns003811
45. Remely M, Tesar I, Hippe B, Gnauer S, Rust P, Haslberger AG. Gut microbiota composition correlates with changes in body fat content due to weight loss. Benef Microbes. 2015;6(4):431–9.
46. Geerlings SY, Kostopoulos I, de Vos WM, Belzer C. Akkermansia muciniphila in the human gastrointestinal tract: When, where, and how? Microorganisms. 2018;6(3):1–26.
47. Sanna1 S, , Natalie R. van Zuydam2 3, , Anubha Mahajan2 3, Kurilshikov1 A, Arnau Vich Vila1, 4, Urmo Võsa1, Zlatan Mujagic5, Ad A. M. Masclee5 DMAEJ, Marije Oosting6, Leo A.B. Joosten6, Mihai G. Netea6, Lude Franke1 A, et al. Causal relationships between gut microbiome, short-chain fatty acids and metabolic diseases. Nat Genet. 2019;51(4):600–5.
48. Cronin P, Joyce SA, O'toole PW, O'connor EM. Dietary fibre modulates the gut microbiota. Nutrients. 2021;13(5):1–22.
49. Gentile CL, Weir TL. The gut microbiota at the intersection of diet and human health. Science (80-). 2018;362(6416):776–80.
50. Wagenaar CA, van de Put M, Bisschops M, Walrabenstein W, de Jonge CS, Herrema H, et al. The effect of dietary interventions on chronic inflammatory diseases in relation to the microbiome: A systematic review. Nutrients. 2021;13(9).
51. Louis P, Flint HJ. Formation of propionate and butyrate by the human colonic microbiota. Environ Microbiol. 2017;19(1):29–41.
52. Macchione IG, Lopetuso LR, Ianiro G, Napol M, Gibiino G, Rizzatt G, et al. Akkermansia muciniphila: Key player in metabolic and gastrointestinal disorders. Eur Rev Med Pharmacol Sci. 2019;23(18):8075–83.
53. Allin KH, Tremaroli V, Caesar R, Jensen BAH, Damgaard MTF, Bahl MI, et al. Aberrant intestinal microbiota in individuals with prediabetes. Diabetologia. 2018;61(4):810–20.
54. Mocanu V, Zhang Z, Deehan EC, Kao DH, Hotte N, Karmali S, et al. Fecal microbial transplantation and fiber supplementation in patients with severe obesity and metabolic syndrome: a randomized double-blind, placebo-controlled phase 2 trial. Nat Med. 2021 Jul;27(7):1272–9.
55. Leeming ER, Johnson AJ, Spector TD, Roy CIL. Effect of diet on the gut microbiota: Rethinking intervention duration. Nutrients. 2019;11(12):1–28.
56. Beam A, Clinger E, Hao L. Effect of diet and dietary components on the composition of the gut microbiota. Nutrients. 2021;13(8):1–15.
57. Makki K, Deehan EC, Walter J, Bäckhed F. The Impact of Dietary Fiber on Gut Microbiota in Host Health and Disease. Cell Host Microbe. 2018;23(6):705–15.
58. Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From dietary fiber to host physiology: Short-chain fatty acids as key bacterial metabolites. Cell. 2016;165(6):1332–45.
59. Rohr MW, Narasimhulu CA, Rudeski-Rohr TA, Parthasarathy S. Negative Effects of a High-Fat Diet on Intestinal Permeability: A Review. Adv Nutr. 2020;11(1):77–91.
60. Kassaian N, Aminorroaya A, Feizi A, Jafari P, Amini M. The effects of probiotic and synbiotic supplementation on metabolic syndrome indices in adults at risk of type 2 diabetes: study protocol for a randomized controlled trial. Trials. 2017 Mar;18(1):148.
61. Li YT, Xu H, Ye JZ, Wu WR, Shi D, Fang DQ, et al. Efficacy of Lactobacillus rhamnosus GG in treatment of acute pediatric diarrhea: A systematic review with meta-analysis. World J Gastroenterol. 2019;25(33):4999–5016.
62. Y. Derwa1, 2,* | D. J. Gracie1, 2,* | P. J. Hamlin1 | A. C. Ford1 2, 1Leeds. Systematic review with meta-analysis the efficacy of probiotics in inflammatory.pdf. Wlley. 2017;46:389–400.
63. Kassaian N, Feizi A, Rostami S, Aminorroaya A, Yaran M, Amini M. The effects of 6 mo of supplementation with probiotics and synbiotics on gut microbiota in the adults with prediabetes: A

176 double blind randomized clinical trial. Nutrition. 2020;79–80.
177 64. Knight R. Dietary effects on human gut microbiome diversity. Br J Nutr. 2015;113:S1–5.
178
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