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REVIEW

Targeting microbiota in dietary obesity management: a systematic review on randomized control trials in adults

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ABSTRACT

Obesity is an alarming public health problem. Tailored nutritional therapy is advisable since emerging evidence on complex cross-talks among multifactorial agents. In this picture, the gut microbiota is highly individualized and intricately dependent on dietary patterns, with implications for obesity management. Most of the papers on the topic are observational and often conflicting. This review aimed to systematically organize the body of evidence on microbiota deriving from dietary trials in adult obesity giving the most certain phylogenetic, and metabolomic signatures in relation to both the host metabolism and phenotype changes published until now. We retrieved 18 randomized control trials on 1385 subjects with obesity who underwent several dietary interventions, including standard diet and healthy dietary regimens. Some phyla and species were more related to diets rich in fibers and others to healthy diets. Weight loss, metabolism improvements, inflammatory markers decrease were specifically related to different microorganisms or functions. The *Prevotella/Bacteroides* ratio was one of the most reported predictors. People with the burden of obesity comorbidities had the most significant taxonomic changes in parallel with a general improvement. These data emphasize the possibility of using symbiotic approaches involving tailored diets, microbiota characteristics, and maybe drugs to treat obesity and metabolic disorders. We encourage Authors to search for specific phylogenetic associations beyond a too generally reported Firmicutes/Bacteroides ratio.

KEYWORDS

Obesity; diet; fibers; microbiota; short chain fatty acids; human

Introduction

Obesity is an alarming public health problem, rapidly growing both in developed and developing countries, enough to be considered as an epidemic: in the US, more than two-thirds of the adults are classified as overweight, more than one-third are classified as obese, with a prevalence that is expected to increase further in the closer future (Ng et al. 2014). Personal, social, and economic costs of obesity comorbidities (i.e., cardiovascular diseases, cancer, diabetes, and other chronic conditions) represent a considerable issue (Tremmel et al. 2017); thus, the identification of consistently effective and, possibly, as more personalized as possible weight-reduction therapies are desirable.

The Mediterranean diet (MD) is recognized as one of the healthiest dietary regimens since it results in a reduced incidence of insulin resistance, hypertension, cardiovascular diseases (CVD), type 2 diabetes mellitus (T2DM), and metabolic syndrome (Estruch et al. 2018). The traditional MD is characterized by the consumption of a high intake of extra-virgin olive oil, fruits, cereals, nuts, legumes, and vegetables; moderate to low intake of fish and seafood, eggs, white meat, and dairy products; low intake of red and processed meats, and sweets. The MD exerts its beneficial effects through the synergistic mechanisms of several bioactive food components, which include unsaturated fatty acids, phytosterols, polyphenols, complex carbohydrates, fibers, vegetable protein, and non-sodium minerals. The PREDIMED multi-center randomized trial on 7,447 participants with high CVD risks receiving an energy-unrestricted MD supplemented with extra-virgin olive oil or nuts demonstrated decreased incidences of cardiovascular events compared to control diet (Salas-Salvadò et al., 2008; Babio et al. 2014; Estruch et al. 2018).

Other dietary patterns demonstrated to have a role in decreasing weight and cardiovascular risks are low-carbohydrate (low-carb) and low-fat diets. The basic principle of the low-carb diet is to restrict the total daily calories from carbohydrate intake to less than 45% of daily calories. Similarly, a low-fat

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diet is characterized by the reduction of total calories coming from fat to less than 20% of daily calories, with the acquisition of the remaining ones through the consumption of vegetables, fruits, and lean protein sources (Pace and Crowe 2016). According to a recent meta-analysis of randomized clinical trials (Mansoor et al. 2016), participants on low-carb diets experienced a greater reduction in body weight compared with participants on low-fat diets, but, at the same time, a greater increase in HDL-cholesterol and LDL-cholesterol, demonstrating an opposite change in two important cardiovascular risk factors. Moreover, the Primary care-led weight management for remission of T2DM (DiRECT) trial demonstrated that 825–853 kcal/day formula diet for 3–5 months (59% carbohydrate, 13% fat, 26% protein, 2% fiber) resulted in diabetes remission in almost half of participants (Lean et al. 2018).

Thus, the importance of tailored obesity nutritional therapy is clear. To date, different dietary interventions can lead to weight loss, although a substantial variability in diet success outcomes is visible (Johnston et al. 2014).

The emergence of the gut microbiota as a key regulator of health and disease has further complicated this issue. Since a mutualistic relation exists between diet and gut microbiota, dietary factors are among the most potent modulators of microbiota composition and function. Intestinal microbial communities in turn influence the absorption, metabolism, and storage of ingested nutrients, with potentially profound effects on the host physiology. Gut microbiota is highly individualized and intricately dependent on the quantity and quality of nutrients extracted from our diets, with direct implications for obesity (Ley et al. 2006; Turnbaugh et al. 2006; David et al. 2014). Microbial metabolites and proteins are known to communicate with the host influencing appetite control (Cani and Knauf 2016). Data collected over the past decade have identified the gut microbiota as an important factor defining inter-individual variation in disease risk and dietary response. In spite of this, the current knowledge of the role of diet on microbiome-mediated health outcomes in humans mainly relies on observational studies in which confounding factors affect the conclusions (Grosso et al. 2017). Intervention studies to address the causal effects of diet on microbiome functions are still scarce or have been performed in animal models. Despite their cost and complexity, randomized controlled trials (RCTs) are the gold standard for evidence-based medicine and are an appropriate tool for identifying a causal relationship of a specific nutrient or diet on a health outcome in humans (Blumberg et al. 2010).

The aim of our systematic review (SR) is to explore the effects of MD diet, low-carb, and low-fat diet, and other standardized dietary habits on metabolic outcomes in subjects with overweight and obesity in relation to changes in the gut microbiota composition or function.

Methods

Literature search

We conducted a systematic review of randomized controlled trials (RCTs) on the effects of dietary habits in humans. To achieve this goal, the study protocol was organized according to PRISMA-P guidelines (Shamseer et al. 2015), and the resulting report was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al. 2015).

PICO methodology (Population: obese and overweight adult subjects; Intervention: MD diets or low-carb diet or low-fat diet, or other standardized healthy dietary habits; Comparison: other dietary patterns; Outcomes: metabolic parameters and gut microbiota composition or function) to develop a search strategy based on medical subject headings (MeSH) and keywords were used.

The Cochrane Central Register of Controlled Trials, PubMed, and EMBASE databases (until December 2020) were systematically used. The reference lists of identified studies and key review articles, including previously published reviews, were also searched for all randomized clinical trials assessing the effects of MD, low-carb diet, or low-fat diet on metabolic outcomes together with gut microbiota composition. No country restrictions were imposed.

The search terms used included "diet" and "microbiota" and "metabolic" and "human" and "adult". The search strategy used both keywords and MeSH terms. No further limitations were made so the search terms would be as sensitive as possible. The research was restricted to RTCs only. In addition, we checked the references of eligible articles for further papers that were not captured by our search strategy, and we corresponded with authors when the relevant information was missing in the paper. Only articles in English were considered. The review has been registered on PROSPERO (CRD42022301419).

Outcome measures

The primary outcome measures were as follows:

1. body weight, body weight excess (e.g., overweight, obesity), body mass index (BMI), metabolic syndrome (MetS), arterial hypertension, lipid profile, glucose levels, insulin resistance
2. gut microbiota composition (16S rDNA, metagenomics, metaproteomics, shotgun metagenomics), gut microbiota function (short-chain fatty acids, lactic acid, end-metabolic products, metabolomics).

Included studies had to report at least results on gut microbiota composition.

Inclusion and exclusion criteria

For inclusion, studies were required to (i) include overweight or obese adult subjects; (ii) be published in peer-reviewed journals in the English language; (iii) be a randomized interventional study.

We excluded studies on subjects affected by diabetes mellitus.

Identification of relevant studies

Potentially relevant papers were selected by reading the titles and abstracts. If abstracts were not available or did not

provide enough results the entire article was retrieved and screened to determine whether it met the inclusion criteria.

Data extraction and synthesis

A form was generated to register whether individual studies met eligibility criteria and to collect data regarding the study design and methodological quality. Four authors (MC, SP, AC, and EA) independently reviewed the titles and the abstracts to identify studies to be included in the review. Any disagreement was discussed with the other three reviewers (FP, MM, EB). Finally, the full texts of articles that passed the screening and eligibility steps were retrieved and read by the same reviewers and all the other authors.

Any difference in opinion about the studies was resolved by discussion between all the investigators. The following data were extracted: author, date of publication, study design, characteristics of the participants, type of diet intervention, assessment methodology and reliability and validity of dietary measures, length of follow-up, methods of evaluation of gut microbiota, clinical outcomes, and changes in gut microbiota composition or function. This information is summarized in Table 1.

Quality assessment

The methodological quality of the included studies was assessed according to the Cochrane's revised risk of bias tool RoB 2 (Sterne et al. 2019). Two authors independently evaluated the following domains for risk of bias: (1) randomization process; (2) deviations from intended interventions; (3) missing outcome data; (4) measurement of the outcome; (5) selection of the reported result. For each domain, there are three categories for risk of bias judgements: low risk, high risk, and some concerns (Sterne et al. 2019). The study was classified as having a low risk of bias if all domains were judged as at low risk of bias and as having a high risk of bias if it was at high risk of bias in any one domain or if it had some concerns in multiple domains. Otherwise, the study was considered as having some concerns (Sterne et al. 2019). Consequently, for visualizing risk-of-bias assessments for the selected studies, two figures were generated using the web app robvis (McGuinness and Higgins 2021). Disagreements were resolved by discussion with a third reviewer.

Results

Cumulatively, our search identified a total of 727 potentially eligible studies. After duplicates removal, there were 355 residual records. Of these, 319 were excluded as judged irrelevant according to titles. The remaining 36 records were screened by reading abstracts and 7 further were excluded because including diabetic patients (n = 3) or normal-weight subjects (n = 4) in the study population. Thus, 29 articles were retrieved and underwent full-text assessment. Among these, 7 were excluded for reasons related to the randomization process (n = 2) or to the intervention dietary pattern (n = 2), or because of being post-hoc analysis of RCTs conducted irrespective of the randomized dietary intervention (n = 3). The selection process is summarized in Figure 1.

Study characteristics

The 22 articles included in SR were publications of results from 18 RCTs. All RCTs had been deposited in the ClinicalTrial.gov registry except 2 which had been set up before clinical trial registration was required by law regardless of intervention type (Russell et al. 2011; Walker et al. 2011; Salonen et al. 2014).

Articles included collectively encompassed 1385 subjects who completed the studies, 48.7% of whom were women (N = 675). These numbers may be overestimated as some studies were conducted in a subset of subjects recruited in a larger parental trial and may have included the same participants while 2 studies certainly involved the same population (Salonen et al. 2014; Walker et al. 2011). However, since the outcome differs in different papers, we decided to consider data from all reports.

At baseline, subjects' age ranged from a mean of 27.6 ± 5.9 years to a mean of 63.72 ± 1.70 years. The maximum BMI was 39.37 ± 1. Kg/m^2 and 338 patients (24.3%) were affected by metabolic syndrome. Subjects came from 9 countries (Spain, Denmark, USA, Italy, United Kingdom, Finland, France, Netherlands, Canada). Characteristics of included studies are detailed in Table 1.

Risk of bias within studies

The risk of bias assessment for the selected studies is presented in Figures 2 and 3. Most studies (68.2%) (Russell et al. 2011; Walker et al. 2011; Christensen et al. 2013; Fava et al. 2013; Lappi et al. 2013; Salonen et al. 2014; Haro et al. 2016a, 2016b, 2017; Vuholm et al. 2017; Bendtsen et al., 2018; Kopf et al. 2018; Fragiadakis et al. 2020; Grembi et al. 2020; Johnstone et al. 2020) were judged to have some concerns in at least one domain, especially in bias arising from the randomization process (45.5%) (Russell et al. 2011; Walker et al. 2011; Christensen et al. 2013; Fava et al. 2013; Salonen et al. 2014; Haro et al. 2016b, 2017; Vuholm et al. 2017; Kopf et al. 2018; Johnstone et al. 2020) and in the selection of the reported result (54.5%) (Russell et al. 2011; Walker et al. 2011; Christensen et al. 2013; Fava et al. 2013; Lappi et al. 2013; Salonen et al. 2014; Haro et al. 2016a, 2016b, 2017; Bendtsen et al. 2018; Fragiadakis et al. 2020; Grembi et al. 2020), mainly due to lack of information regarding allocation concealment or unavailable protocol study, respectively. Only 2 RCTs (9%) (Haro et al. 2016b; Lappi et al. 2013) were classified as having a high risk of bias: one probably didn't conceal allocation adequately (Lappi et al. 2013), while the other provided no information about the extent of missing outcome data (Haro et al. 2016b). All trials (Russell et al. 2011; Walker et al. 2011; Christensen et al. 2013; Fava et al. 2013; Lappi et al. 2013; Salonen et al. 2014; Vitaglione et al. 2015; Haro et al. 2016a, 2016b, 2017; Beaumont et al. 2017; Vuholm et al. 2017; Bendtsen et al. 2018; Hjorth et al. 2018; Kopf et al. 2018; Schutte et al. 2018; Mayengbam et al. 2019; Roager et al. 2019; Fragiadakis et al. 2020; Grembi

Table 1. Characteristics of included studies.

Author, journal, year	Study/Country	Study length	Study subjects	Diet before intervention	Intervention	Adherence to diet evaluation
Beaumont et al. 2017	ClinicalTrial.gov number NCT02351297 France	2 weeks run-in diet + 3 weeks intervention period	N = 42 overweight subjects 38 subjects completed the study – MD group (aged 31 ± 2 years, BMI 27.10 ± 0.41 kg/m^2, 9F, 4 M) – CAS group (aged 28 ± 1 years, BMI 28.27 ± 0.41 kg/m^2, 9F, 3 M) SOY group (aged 31 ± 2 years, BMI 27.32 ± 0.42 kg/m^2, 7F, 6 M)	Not specified	• Run-in diet (normal protein diet) • Intervention: ° SOY group ° CAS group MD group	3d food diary after the run -in and the intervention period
Bendtsen et al., 2018	ClinicalTrial.gov number NCT01199835 MEPEB study Denmark	24 weeks	N = 80 (11 M/69F) – 40 HD (aged 42 ± 1 years, BMI 31.5 ± 0.4 kg/m^2, F 35,88%) – 40 LD (aged 45 ± 2 years, BMI 30.8 ± 0.4 kg/m^2, F 34,85 %) 52 subjects completed all the 24 weeks of dietary intervention period (HD: M/F, 2/20; LD: M/F, 5/25)		– Hypocaloric high dairy diet (HD) – Hypocaloric low dairy diet (LD) 7 individual dietary counseling visit and 1 group session scheduled at week 0, 2, 4, 8, 12, 16, 20, and 24	7-day dietary records at 12 and 24 weeks
Christensen et al. 2013	ClinicalTrial.gov number NCT00869531 Denmark	2 weeks run in + 12 weeks intervention	N = 79 postmenopausal women (aged 45-70 years, BMI 27–37 kg/m^2) 72 subjects completed the study	Not specified	– whole-grain wheat (WW) refined wheat (RF)	
Fava et al. 2013	ISRCTN registry ISRCTN29111298 RISCK trial United Kingdom	4-weeks run-in reference diet + 24 weeks of treatment	N = 130 subjects with a minimum of two features of MetS 88 subjects completed the study (45 F, aged 59.1 ± 9.0 years, BMI 29.4 ± 5.5 kg/m^2; 43 M, aged 52.7 ± 9.8 years, BMI 28.2 ± 4.0 kg/m^2)	Not specified	– Control diet: high saturated fat diet- high glycemic index (GI) diet (HS/HGI) – high monounsaturated fat (MUFA)/high GI (HM/HGI) – high MUFA/low GI (HM/LGI) – high carbohydrate (CHO)/high GI (HC/HGI) – high CHO/ low GI (HC/LGI)products specifically chosen or formulated to provide the required fat/carbohydrate intake and composition in each of the intervention diets.	
Fragiadakis et al. 2020	ClinicalTrial.gov number NCT01826591 DIETFITS study USA	52 weeks of treatment	N = 609 generally healthy, nondiabetic participants [BMI (kg/m^2): 28–40] 49 subjects included in the study on microbiota – Low carb (aged 42.6 ± 5.8 years, BMI 32.8 ± 3.9 kg/m^2, 20F, 5 M) – Low fat (aged 39.2 ± 5.5 years, BMI 33.7 ± 3.5 kg/m^2, 19F, 5 M)	Not specified	1 year healthy low-carb vs healthy low-fat diet: "limbo" phase: 20 g/d carb or fat (8w) "titrate" phase: carb or fat increase (5 to 15 g/d) to reach the amount for a lifelong eating pattern 22 evening session with health educators Maximization of vegetable and whole-food intake and minimization or elimination of added sugars and refined grains Diet-tracking tools Support group created by the participants to share successful strategies	
Grembi et al. 2020	ClinicaTrial.gov number NCT01826591 DIETFITS study USA	12 months 52 weeks	Discovery cohort N = 66 (39F, 27 M) – Low carb (N = 32, aged 43.1 ± 6 years, BMI 33.4 ± 3.7 kg/m^2, 22F, 10 M) – Low fat (N = 34, aged 40.5 ± 6.9 years, BMI 33.2 ± 3.3 kg/m^2, 17F, 17 M) Validation cohort N = 56 (44F, 12 M) – Low carb (N = 31, aged 42.5 ± 6 years, BMI 32.8 ± 3.5 kg/m^2, 25F, 6 M) Low fat (N = 25, aged 39.6 ± 6 years, BMI 33.2 ± 3.5 kg/m^2,19F, 6 M)	Not specified (US population: western)	– Low carb diet – low fat diet	3 unannounced 24-hour dietary recalls at T0, 3, 6, 12 months of dietary intervention Dietary adherence: % kcal consumed from non-restricted food dietary change: the difference in percentage of total daily kcals consumed from restricted foods between baseline and during the dietary intervention (average 12 months) In-person instructional sessions related to nutrition, behavior, emotions, and physical activity

Haro et al. 2016a	ClinicalTrial.gov number NCT00924937 CORDIOPREV study Spain	1 year 52 weeks	N = 20 obese men with coronary heart disease (M, aged f 63.3 ± 2.0 years, BMI 32.2 ± 0.5 kg/m^2)	Not specified	– Mediterranean diet – low-fat high-complex carbohydrate diet (LFHCC) Olive oil and food pack provided by researchers	– Mediterranean diet: 14-item questionnaire Low-fat diet: 9-point score
Haro et al. 2016b	ClinicalTrial.gov number NCT00924937 CORDIOPREV study Spain	2 years 104 weeks	N = 239 subjects with coronary heart disease:138 MetS patients (aged 60.16 ± 0.74 years, 111 M, 27 F) – 101 subjects without MetS (aged 61.41 ± 0.94 years, 87 M, 14 F)	Not specified	– Mediterranean diet – low-fat high-complex carbohydrate diet Olive oil and food pack provided by researchers	• Mediterranean diet: 14-item questionnaire • Low-fat diet: 9-point score
Haro et al. 2017	ClinicalTrial.gov number NCT00924937 CORDIOPREV study Spain	2 years 104 weeks	N = 106 men with coronary heart disease: – 33 obese patients with MetS (5 criteria for metabolic syndrome) (aged 59.03 ± 1.83 years, BMI 32.42 ± 0.76 kg/m^2) (MetS–OB) – 32 obese patients without Mets (2 or less criteria for metabolic syndrome) (aged 63.72 ± 1.70 years, BMI 32.88 ± 0.56 kg/m^2) (non-MetS–OB) 41 non-obese subjects (aged 61.73 ± 1.39 years, BMI 27.05 ± 0.27 kg/m^2) (non-MetS–non-OB).	Not specified	– Mediterranean diet – low-fat high-complex carbohydrate diet (LF) – Dietary counseling	• Mediterranean diet: 14-item questionnaireLow-fat diet: 9-point score
Hjorth et al. 2018	ClinicalTrial.gov number NCT01195610 Denmark	26 weeks treatment + 12 months follow up (52 weeks) with NND	N = 181 Fecal analysis of 62 subjects: – High P/B group (N = 28, aged 41.9 (30.4; 56.7) years, BMI 31.0 ± 4.7 2.8 kg/m^2, %F/M 64.3/35.7) Low P/B group (N = 34, aged 47.5 (33; 55.6) years, BMI 29.0 ± 4.4 kg/m^2, %F/M 69.2/30.8)	Average Danish Diet (ADD)	– New Nordic Diet (NND) – Average Danish Diet (ADD) Follow up (1 year) with NND without food provision Food and beverage provided from a study shop	
Johnstone et al. 2020	ClinicalTrial.gov number NCT01724411 within-subject crossover design United Kingdom	49 days	N = 24 19 subjects completed the study (BMI 32.8 ± 4.07 kg/m^2, 8 F, 11 M)	UK diet	– days 1–4, habitual diet consumed ad libitum (4 d) – days 5–7, maintenance diet (M; 3 d) – days 8–28, high-protein WL diet (WL; 21 d); days 29–38 and 39–48, randomly assigned WM diets (10 d), RS (RSWM) or control (C-WM).	breakfast test meal on 4 occasions, at the end of each dietary phase, corresponding to the morning of day 8, 29, 39, and 49.
Kopf et al. 2018	ClinicalTrial.gov number NCT02602496 USA	6 weeks	N = 52 49 subjects completed the study: – 14 controls (aged 27.6 ± 5.9 years, BMI 30.1 ± 5.2 kg/m^2, 7 F, 7 M) – 17 WG (aged 39.2 ± 13.5 years, BMI 33.7 ± 6.3 kg/m^2, 11 F, 6 M) 18 FV (aged 29.4 ± 12.8 years, BMI 30.3 ± 6.0 kg/m^2, 12 F, 6 M)	Western diet	Whole grains intervention (WG) vs fruits and vegetables intervention (FV) vs control diet	Weekly visits: food diary and gastrointestinal symptom questionnaire
Lappi et al. 2013	ClinicalTrial.gov number NCT00573781 Sysdimet study Finland	12 weeks of treatment	N = 106 subjects with MetS 51 studied for effects of diet on the microbiota composition and clinical variables (aged 60 ± 6 years, BMI 31 ± 4 kg/m^2, 26 F, 25 M)	Finnic diet (rich in WG)	– rye bread (RB) dietrefined white wheat bread (WWB) diet	Daily questionnaires 4-d food records at baseline and after 11 weeks
Mayengbam et al. 2019	ClinicalTrial.gov number NCT01719900 Canada	12 weeks	N = 53 (aged 18-70 years, BMI 25–38 kg/m^2, 43 F, 10 M)	Not specified	– 24 Control group (CO) – 29 Pea fiber group (PF)	
Meslier et al. 2020	ClinicalTrial.gov number NCT03071718 Italy	8 weeks	N = 82 (aged 43 ± 12 years, BMI 31.1 ± 4.5 kg/m^2, 43 F, 39 M)	Western	– Isocaloric Mediterranean diet (MedD) – Control diet (CoD: habitual diet, western)	11-unit dietary score MD index Self-recorded 7-day food diaries and physical activity questionnaires every 2 weeks

(*Continued*)

Table 1. (Continued)

Author, journal, year	Study/Country	Study length	Study subjects	Diet before intervention	Intervention	Adherence to diet evaluation
Roager et al. 2019	ClinicalTrials.gov, NCT01731366 Denmark	8 weeks	N = 60 (BMI of 25–35 kg/m2 and/or increased WC (M ≥ 94 cm and F ≥ 80 cm)) with at least one of the following criteria: -non-diabetic dysglycaemia (fasting plasma glucose 6.1–6.9 mmol/L) -dyslipidaemia (HDL ≤1.03 mmol/L for M and ≤1.29 mmol/L for F) -hypertension (systolic BP >130mmHg or medical treatment of hypertension). 50 subjects completed the two dietary intervention period (aged 48.6 ± 11.1 years, BMI 28.9 ± 3.6 kg/m^2, 32 F, 18 M)	Not specified	• Two 8-weeks dietary intervention, separated by a washout period of at least 6 weeks, comprising: – whole grain diet – refined grain diet	– study diary – fasting concentrations of plasma alkylresorcinols – 4-day precoded dietary registration (National Food Institute at the Technical University of Denmark)
Russell et al. 2011	Not registered United Kingdom	2-5 days run-in + 9 weeks intervention (28d HPLC + 28d HPMC)	N = 17 obese males (aged 56.38 ± 12.1 years, BMI 36.15 ± 5.68 kg/m^2)	Not specified	– Weight maintenance diet (M diet) – high-protein and low-carbohydrate diet (HPLC) – high-protein and moderate-carbohydrate diet (HPMC)	daily intakes were recorded by weighing the food components provided and that remained after each meal
Salonen et al. 2014	Not registered United Kingdom	1-week run-in diet + 9 weeks of intervention	N = 14 males with MetS (aged 54 ± 4 years, BMI 39.37 ± 1.49 kg/m^2) (SEM)	Not specified	1-week M diet + 3 weeks RS or NPSs diet + 3 weeks NPSs or RS diet + 3 weeks weight loss diet	
Schutte et al. 2018	ClinicalTrial.gov number NCT02385149 Netherlands	4-weeks run-in + 12 weeks intervention	N = 50: – 25 RW (aged 61 [51 – 70] years, BMI 27.6 ± 2.6 kg/m^2, 9F, 16M) – 25 WGW (aged 61 [47 – 69] years, BMI 28.0 ± 2.1 kg/m^2, 10F, 15M)	Netherland diet (quite high in WGW products)	– Whole-grain wheat (WGW) diet – refined wheat (RW) diet	Diary to report all deviations from the protocol, a weekly recall of empty product packages as well as by measuring total plasma alkylresorcinols
Vitaglione et al. 2015	ClinicalTrial.gov number NCT01293175 Italy	8 weeks	N = 80 68 subjects completed the study 32 controls (aged 37 ± 2 years, BMI 29.5 ± 0.4 kg/m^2, 20 F, 12 M) 36 WG (aged 40 ± 2 years, BMI 30.0 ± 0.5 kg/m^2, 25 F, 11 M)	limited fruit and vegetable intake	Whole grains intervention (WG) vs control diet	self-recorded 4-d (3 working days and 1 weekend day) food diaries every 2 weeks weighing the uneaten foods every 4 weeks phone call interviews by expert dietitian International Physical Activity Questionnaire
Vuholm et al. 2017	ClinicalTrial.gov number NCT02358122 Denmark	6 weeks	N = 75 70 subjects completed the study – 24 WGR (aged 53.0 ± 8.9 years, BMI 28.0 ± 1.9 kg/m^2, 13 F, 11 M) – 24 WGW (aged 48.2 ± 9.9 years, BMI 27.7 ± 1.9 kg/m^2, 14 F, 10 M) 22 RW (aged 51.8 ± 9.0 years, BMI 27.8 ± 2.0 kg/m^2, 11 F, 11 M)	Danish diet	– whole-grain rye (WGR) – whole-grain wheat (WGW)refined wheat (RW)	study diary with the amount and type of study products eaten daily concentration of plasma alkylresorcinols
Walker et al. 2011	Not registered United Kingdom	1-week run-in diet + 9 weeks of intervention	N = 14 males with MetS (aged 54 ± 4 years, BMI 39.37 ± 1.49 kg/m^2) (SEM)	Not specified	1-week M diet + 3 weeks RS or NPSs diet + 3 weeks NPSs or RS diet + 3 weeks weight loss diet	

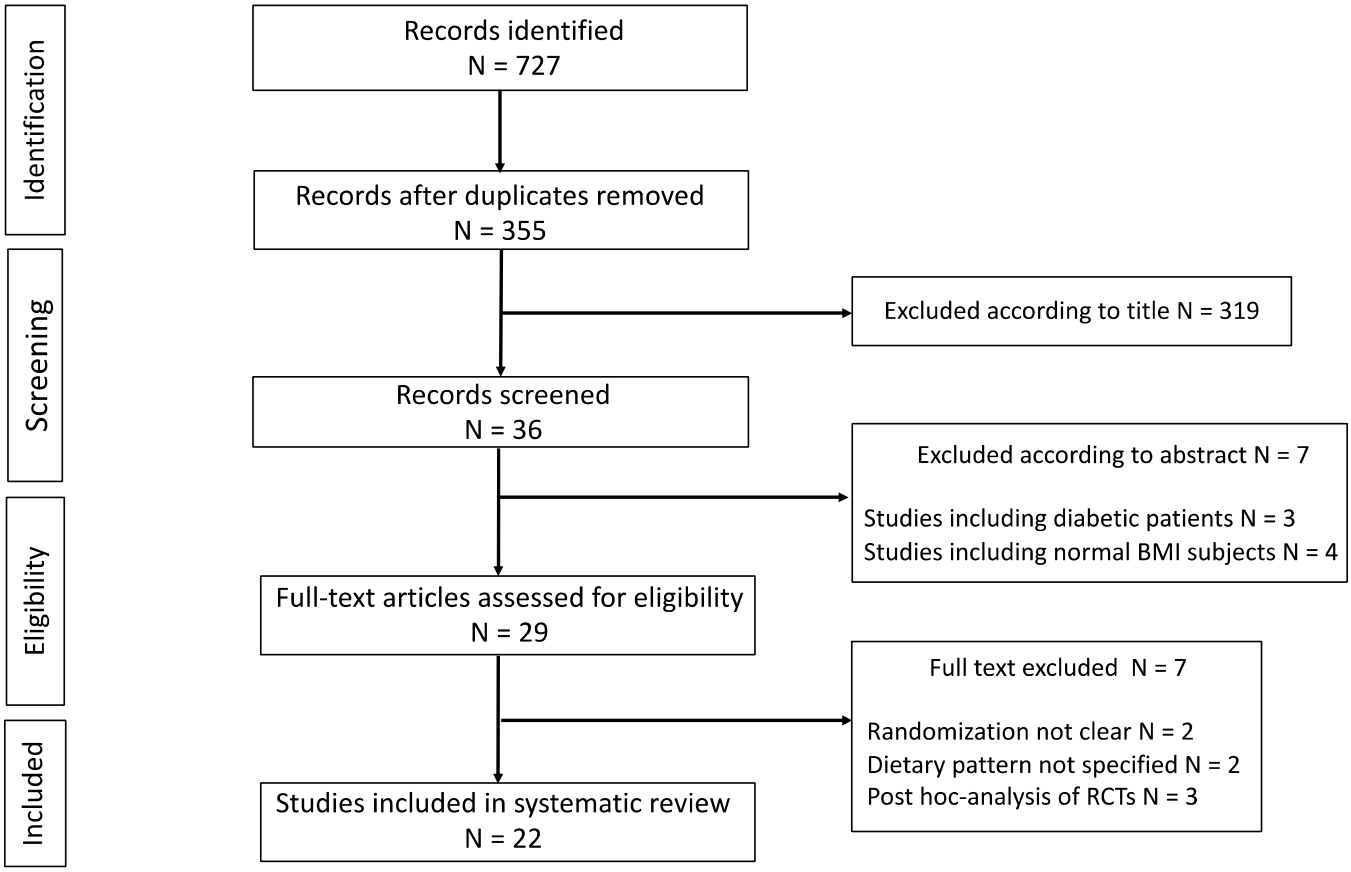

Figure 1. Flow diagram for study retrieval and selection.

et al. 2020; Johnstone et al. 2020; Meslier et al. 2020) were considered at low risk both for bias due to deviations from intended interventions and bias in the measurement of the outcome.

Clinical results

Intervention diets are detailed in Table 2. In particular, 3 studies evaluated the effects of the MD and low-fat diet (N = 365) (Haro et al. 2016a, 2016b, 2017), 1 of MD only (N = 82) (Meslier et al. 2020), 1 of low dairy versus high dairy diet (N = 52) (Bendtsen et al., 2018), 1 of New Nordic Diet (N = 62) (Hjorth et al. 2018), 2 of low-carb or low-fat diet (N = 171) (Fragiadakis et al. 2020; Grembi et al. 2020); the other studies considered different standardized healthy dietary patterns (N = 653). The control diets were specified in 8 studies only (average Danish diet, western diet, limited fruit and vegetable intake, Finnic diet, Netherland diet, UK diet) (N = 451) (Lappi et al. 2013; Vitaglione et al., 2015; Vuholm et al., 2017; Hjorth et al. 2018; Kopf et al. 2018; Schutte et al. 2018; Johnstone et al. 2020; Meslier et al. 2020).

No intervention on physical activity was considered. One study estimated physical activity by International Physical Activity Questionnaire (Vitaglione et al., 2015).

Most studies recorded data about adherence to diet by food frequency questionnaires (Lappi et al. 2013; Haro et al. 2016a, 2016b, 2017; Kopf et al. 2018), some on a recall-based methodology (Vitaglione et al., 2015; Grembi et al. 2020) or by food diaries (Fava et al. 2013; Vitaglione et al., 2015; Beaumont et al. 2017; Vuholm et al. 2017; Bendtsen et al., 2018; Kopf et al. 2018; Schutte et al. 2018; Meslier et al. 2020). Three studies evaluated the fasting concentrations of plasma alkylresorcinols, phenolic lipids, used as biomarkers for people who eat wholegrains wheat and rye rather than refined cereals (Vuholm et al. 2017; Schutte et al. 2018; Roager et al. 2019).

Most, but not all studies, evaluated clinical changes related to anthropometric or metabolic parameters during the intervention diet (Christensen et al. 2013 Fava et al. 2013; Lappi et al. 2013; Salonen et al. 2014; Vitaglione et al., 2015; Haro et al. 2016a, 2017; Beaumont et al. 2017; Bendtsen et al., 2018; Vuholm et al. 2017; Hjorth et al. 2018; Kopf et al. 2018; Schutte et al. 2018; Fragiadakis et al. 2020; Grembi et al. 2020; Johnstone et al. 2020; Meslier et al. 2020). Two studies considered the results according to the *Prevotella/Bacteroides* (P/B) ratio (Hjorth et al. 2018; Grembi et al. 2020). One study evaluated the P/B ratio as a prognostic marker for successful body fat loss on two diets differing greatly in dietary fiber and whole-grain content (New Nordic Diet and Average Danish Diet). For this purpose, fecal samples were collected at baseline and the relative abundance of *Prevotella* spp. and *Bacteroides* spp. was determined. This resulted in a clear bimodal separation of subjects based on the log *Prevotella* spp. to *Bacteroides* spp. ratio, allowing designation of low P/B (<0.01) or high P/B (>0.01) ratio subjects (Hjorth et al. 2018). Similarly, another study investigating the correlation between pre-diet P/B ratio and weight loss success on low-carb or low-fat diet classified

Figure 2. Traffic light plot presenting the risk of bias within the RCTs included in the systematic review.

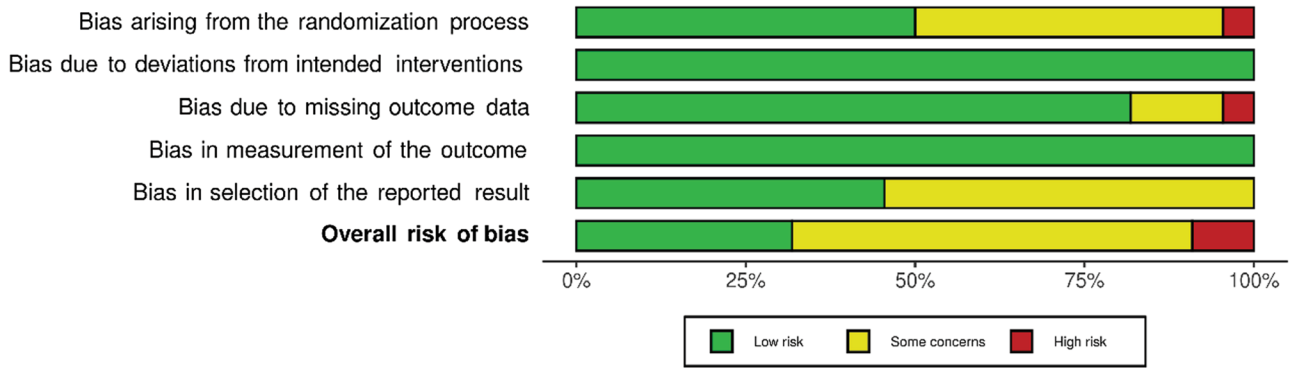

Figure 3. Summary plot presenting the risk of bias within the RCTs included in the systematic review.

subjects as having high or low P/B ratio, although using a lower P/B ratio cutoff value (0.003) due to the lower prevalence and quantity of *Prevotella* spp. in fecal samples (Grembi et al. 2020).

Standard diet regimens

MD and low-fat diet reduced triglycerides levels in male obese subjects affected by metabolic syndrome (Haro et al. 2017). Moreover, the two dietary patterns were associated with an improvement in insulin sensitivity index measured from OGTT (Haro et al. 2016a).

An isocaloric MD (Meslier et al. 2020) reduced total plasma cholesterol and HDL-cholesterol if compared to the Western diet. A low-carb diet and low-fat diet showed similar effects on reduction in BMI, body fat, waist circumference, blood pressure, insulin, glucose levels, and resting energy expenditure. A low-carb diet compared to a low-fat diet caused an increase in LDL and HDL levels and a reduction in triglycerides and in respiratory exchange ratio (Fragiadakis et al. 2020).

Hypocaloric (daily 500-kcal of energy deficit compared with the estimated energy requirement of each subject) high-dairy and low-dairy diets were associated with a reduction in body weight, fat mass, hip, and waist circumference but a low-dairy diet resulted in greater loss of hip circumference (Bendtsen et al., 2018).

Other or healthy dietary regimens

Dietary interventions promoting a high intake of whole grains, fruits, and vegetables showed no difference in BMI, while whole grains diet reduced TNFα, or IL6 and C-reactive protein (Vitaglione et al., 2015; Kopf et al. 2018; Roager et al. 2019) compared to western diet (Kopf et al. 2018) or selected refined wheat products (Vitaglione et al., 2015), and fruits and vegetable diet reduced IL-6 compared to western diet (Kopf et al. 2018).

A whole-grain diet, compared to a refined grain diet, reduced body weight, fat-free mass and showed a tendency in reduction of fat mass ($p = 0.057$), reduced sagittal abdomen diameter, and a similar tendency was observed for waist circumference (Roager et al. 2019). Moreover, whole-grain wheat diet compared to refined wheat diet was associated with a reduction in liver steatosis measured with proton magnetic resonance spectroscopy (1H-MRS) was used to quantify lipid content in the liver (3-Tesla whole-body MRI scanner) (Schutte et al. 2018).

Rye bread diet, compared to refined white wheat bread, in subjects with metabolic syndrome had similar effects on body weight, markers of glucose metabolism, and inflammation but a decrease in high sensitivity C-reactive protein concentration was recorded (Lappi et al. 2013).

High MUFA/low glycemic index (GI) diet (HM/HG: total fat 38%, saturated fat 10%, MUFA 20%, PUFA 6%, CHO 45%, GI 53%), high carbohydrate/high GI diet (HC/HG: total fat 28%, SFA 10%, MUFA 11%, PUFA 6%, CHO 55%, GI 51%) and high carbohydrate/low GI diet (total fat 28%, saturated fat 10%, MUFA 11%, PUFA 6%, CHO 55%, GI 51%) reduced plasma total and LDL cholesterol compared to the starting high saturated fat diet- high GI diet (HS/HG: total fat 38%, high saturated fat 18%, MUFA 12%, PUFA 6%, CHO 45%, GI 64%). HDL cholesterol was slightly decreased after a high carbohydrate/high GI diet compared to a high saturated fat/HG diet. The concentration of NEFA increased after intervention with high carbohydrate/high GI compared to high saturated fat/high GI diet, while it decreased after intervention with high carbohydrate/low GI diet. Fasting plasma glucose concentrations were significantly lower after intervention with both high carbohydrate diets and high carbohydrate/high GI also decreased plasma insulin concentrations compared to baseline with high saturated fat diet- high GI diet (Fava et al. 2013).

Table 2. Diets compositions of the included studies.

Study	Study diets	Diet composition 1	Diet composition 2	Diet composition 3	Diet composition 4	Diet composition 5
Beaumont et al. 2017	• run-in diet • SOY group • CAS group • MD group	Run-in diet: individualized normal-protein diet with 15%, 50%, and 35% of energy provided by proteins, carbohydrates, and lipids, respectively.	SOY group: substitution of 15% of energy intake from starchy food with isolated soy protein	CAS group: substitution of 15% of energy intake from starchy food with isolated milk protein enriched in micellar casein	MD group: substitution of 15% of energy intake from starchy food with maltodextrin	
Bendtsen et al. 2018	• Low dairy product diet (LD) • High dairy product diet (HD)	LD diet: daily 500-kcal (2100 kJ) energy deficit vs EER: 30 energy percentage (E%) fat, 52 E% carbohydrate and 18 E% protein. ≤ 600 mg calcium/day	HD diet: daily 500-kcal (2100 kJ) energy deficit vs EER: 30 energy percentage (E%) fat, 52 E% carbohydrate and 18 E% protein. ≈1500 mg calcium/day (1200 mg from dairy products)			
Christensen et al. 2013	• run-in diet • whole-grain wheat (WW) • refined wheat (RF)	Run-in diet: consumption of RW-containing food	WW: deficit of ~1250 kJ/d. Bread, pasta and biscuits providing 105 g of whole grain daily (2 MJ/day)	RW: deficit of ~1250 kJ/d. Bread, pasta and biscuits providing 105 g of refined wheat daily (2 MJ/day)		
Fava et al. 2013	• Control diet: high saturated fat diet- high glycemic index (GI) diet (HS/HGI) • high monounsaturated fat (MUFA)/high GI (HM/HGI) • high MUFA/low GI (HM/LGI) • high carbohydrate (CHO)/high GI (HC/HGI) • high CHO/ low GI (HC/LGI)	HS/HGI: total fat 38%E, high saturated fat (SFA) 18%E, high monounsaturated fat (MUFA) 12%E, polyunsaturated fatty acid (PUFA) 6%E, CHO 45%E, GI 64%	HM/HGI: total fat 38%E, SFA 10%E, MUFA 20%E, PUFA 6%E, carbohydrate (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%
Fragiadakis et al. 2020	• healthy low carb diet • healthy low fat diet	HLC diet: ↓cereals, grains, rice, starchy vegetables, and legumes	HLF diet: ↓edible oils, fatty meats, whole-fat dairy, and nuts			
Grembi et al. 2020	Low carb or low fat diet with no specific caloric, fat or carbohydrates restriction. Phase I (8 weeks): Limbo (go as low as you can go): Reduction fat or carbohydrate (20 g/day); participants were instructed to progressively cut back on fat or carbohydrate intake until they had achieved a daily intake of no more than 20 grams of fat or carbohydrate per day, depending on their group assignment. Phase II (Titration): increase fat or carbohydrate consumption by increments of 5-15 g/daily with no set endpoint goal for a specific level of fat or carbohydrate (increase level of fat or carbohydrate affected both their satisfaction with their daily intake and their weight loss progress). If satisfaction and weight loss progress were acceptable, they had the option of maintaining that level of fat or carb intake for another week or adding an incremental 5-15 grams/day. Both diet groups were instructed to (1) maximize vegetable intake; (2) minimize intake of added sugars, refined flours, and *trans* fats; and (3) focus on whole foods that were minimally processed, nutrient dense, and prepared at home whenever possible.	Low-carb with no specific caloric restriction but promoting high dietary quality (i.e. high-quality oils and fats, avocados, hard cheeses, nut butters, and nuts & seeds).	Low-fat with no specific caloric restriction but promoting high dietary quality (whole-grain foods, i.e. rather than whole wheat flour products, steel cut oats, farro, barley, quinoa, brown rice, and wild rice, wide range of legumes and beans, fresh fruit, low-fat dairy products, and lean meats).			
Haro et al. 2016a	• Mediterranean diet • Low-fat high-carbohydrate diet	Mediterranean diet: 35% fat (22% monounsaturated; 6% polyunsaturated and 7% saturated)	Low-fat high-carbohydrate diet 28% fat (12% monounsaturated; 8% polyunsaturated and 8% saturated)			
Haro et al. 2016b	• Mediterranean diet • Low-fat high-carbohydrate diet	Mediterranean diet: 35% fat (22% monounsaturated, 6% polyunsaturated, and 7% saturated)	Low-fat high-carbohydrate diet: 28% fat (12% monounsaturated, 8% polyunsaturated, and 8% saturated)			

Haro et al. 2017	• Mediterranean diet • Low-fat high-carbohydrate diet	Mediterranean diet minimum 35% of calories as fat (22% MUFA fat, 6% PUFA fat and <10% saturated fat), 15% proteins and a maximum of 50% carbohydrates. Cholesterol content adjusted to < 300 mg/day	Low-fat diet: <30% total fat (<10% saturated fat, 12–14% MUFA fat and 6–8% PUFA fat), 15% protein and a minimum of 55% carbohydrates. Cholesterol content adjusted to < 300 mg/day		
Hjorth et al. 2018	• Intervention: New Nordic Diet (NDD) • Control: Average Danish Diet (ADD)	NDD: very high in dietary fiber, whole grain, fruit and vegetables; dietary fiber 43.3 g/MJ, protein 18.1%, fat 30.4%, carbohydrates 46.6%	ADD: dietary fiber 28.6 g/MJ, protein 16.4%, fat 33.8%, carbohydrates 45.3%		
Johnstone et al. 2020	• Maintenance diet (M diet) • high-protein weight loss diet (WL diet) • control weight maintenance diet (C-WM diet) • resistant-starch weight maintenance diet (RS-WM)	M diet: 15% protein, 30% fat, and 55% carbohydrate fed to 1.5 × measured rest metabolic rate (RMR)	WL diet: fed as 100% RMR as a 7-d rotation menu, as 3 meals/d, each 30% protein, 30% fat, and 40% carbohydrate	C-WM diet: 1.2 × RMR with 20% protein, 30% fat, and 50% carbohydrate. Digestible starch was incorporated as control	RS-WM diet: 1.2 × RMR with 20% protein, 30% fat, and 50% carbohydrate. daily amount of 22 g for females and 26 g for males of resistant starch type 3 was provided
Kopf et al. 2018	• Control diet • Fruits and vegetables intervention • Whole grains intervention • The serving sizes supplied to each group were set according to the Nutrition Labeling and Education Act (NLEA) standards	Control diet: 3 servings/day of refined grain	Fruits and vegetables intervention: 3 servings/day of fruits and vegetable	Whole grain intervention: 3 servings/day of whole grains	
Lappi et al. 2013	• rye bread (RB) diet • refined white wheat bread (WWB) diet	RB diet: rye breads with a high-fiber content (7–15%). The breads are a selection of commercial WG rye breads (50% share of all the breads), endosperm rye bread (40% share), and a whole-meal wheat bread (10% share). They consumed whole-meal pasta [3.5 dL/wk (measured as uncooked)] and were given high-fiber oat biscuits for voluntary intake	WWB diet: refined wheat breads with a low fiber content (4%). The test breads were a selection of commercial refined wheat breads and the intake of rye products was restricted to 1–2 portions/d.		
Mayengbam et al. 2019	• control (CO) • pea fiber (PF)	CO group: isocaloric amount of control wafer with no fiber. The wafers provided the participants with 204 kcal/d derived from 55.2% carbohydrate, 5.2% protein and 39.6% fat in the control wafers and 53.1% carbohydrate, 5.2% protein and 41.7% fat in the fiber wafers (expressed as a percent of total energy content). Wafers consumed 30 min before 3 main meals	PF group: wafers containing 5 g per serving of yellow pea fiber thrice per day. The wafers provided the participants with 204 kcal/d derived from 55.2% carbohydrate, 5.2% protein and 39.6% fat in the control wafers and 53.1% carbohydrate, 5.2% protein and 41.7% fat in the fiber wafers (expressed as a percent of total energy content). Wafers consumed 30 min before 3 main meals		

(*Continued*)

Table 2. (Continued)

Study	Study diets	Diet composition 1	Diet composition 2	Diet composition 3	Diet composition 4	Diet composition 5
Meslier et al. 2020	• Intervention: Isocaloric Mediterranean diet (MedD) • Control diet (CoD): habitual western diet	Isocaloric Mediterranean diet (MedD): inclusion of fruit and vegetables and nuts (at least 5 portions, ~500 g/day) and nuts (30 g/day) as well as calorie-adjusted replacement of refined cereal products with wholegrain products (at least 2 portions, ~200 g/day between wholegrain pasta, bread and breakfast cereal); replacement of meat, eggs and dairy products with fish and legumes (at least 2 portions, ~300 g/week of fish and 3 portions, ~300 g/week of legumes); replacement of butter/margarine with extra-virgin olive oil.	Control diet (CoD): habitual western diet			
Roager et al. 2019	• whole grain diet • refined grain diet	Whole grain diet: intact, ground, cracked or flaked caryopses, where the starchy endosperm, germ and bran are present in the same relative proportions as in the intact caryopsis according to the definition proposed by the HEALTHGRAIN consortium in 2013				
Russell et al. 2011	• weight maintenance diet • high-protein and low-carbohydrate diet (HPLC) • high-protein and moderate-carbohydrate diet (HPMC)	weight maintenance diet: 13% protein, 50% carbohydrates, and 37% fat as calories. 2 fixed meal	HPLC: 29% protein, 5% carbohydrate, and 66% fat as calories	HPMC: 28% protein, 35% carbohydrate, and 37% fat		
Salonen et al. 2014	• Run-in maintenance diet • Resistant starch diet (RS) • non-starch polysaccharides diet (NSPs) • Weight loss diet	Run-in maintenance diet: protein/carbohydrate/fat % as 13:52:35 of metabolizable energy and 27.7 g per day NSP	Resistant starch diet (RS): high in type 3 resistant starch	non-starch polysaccharides diet (NSPs): high in non-starch polysaccharides	Weight loss diet: high protein and medium carbohydrate levels	
Schutte et al. 2018	• Run-in diet • Whole-grain wheat (WGW) diet • refined wheat (RW) diet	Run-in diet: RW products. Absence of any whole-grain food products including products from other grain sources.	WGW diet: 98 g/d WGW products. 4 slices of bread (in total 100 g) and 1 serving of ready-to-eat-cereals of 33.4 g in total, adding up to a total of 98 g of WGW flour per day. Small buns, currant buns, and currant bread were provided on the weekends instead of the slices of bread	RW diet: 98 g/d RW products. 4 slices of bread (in total 100 g) and 1 serving of ready-to-eat-cereals of 33.4 g in total, adding up to a total of 98 g of RW flour per day. Small buns, currant buns, and currant bread were provided on the weekends instead of the slices of bread		
Vitaglione et al. 2015	• Control diet • Whole grains intervention	Control diet: 60 g refined wheat products/day	Whole grain intervention: 70 g whole grains wheat/day			

Vuholm et al. 2017	• whole-grain rye (WGR) • whole-grain wheat (WGW) • refined wheat (RW)	WGR: one choice of breakfast cereal, pasta, kernels, crisp bread and two choices of bread. Bread produced by university of Copenhagen while other study products are commercially available. Products consumed *ad libitum*	WGW: one choice of breakfast cereal, pasta, kernels, crisp bread and two choices of bread. Bread produced by university of Copenhagen while other study products are commercially available. Products consumed *ad libitum*	RW: one choice of breakfast cereal, pasta, kernels, crisp bread and two choices of bread. Study products are commercially available and consumed *ad libitum*	
Walker et al. 2011	• Run-in maintenance diet • Resistant starch diet (RS) • non-starch polysaccharides diet (NSPs) • Weight loss diet	Run-in maintenance diet: protein/carbohydrate/fat % as 13:52:35 of metabolizable energy and 27.7 g per day NSP	Resistant starch diet (RS): high in type 3 resistant starch	non-starch polysaccharides diet (NSPs): high in non-starch polysaccharides	Weight loss diet: high protein and medium carbohydrate levels

Microbiome results

Microbiota changes in ecology and function are detailed in Table 3 and in Figure 4. Twenty studies sequenced 16S rDNA and the last two studies used the FISH technique (Russell et al. 2011; Fava et al. 2013). Among studies using 16S rDNA, two of them also performed a shotgun metagenomic sequencing analysis (Roager et al. 2019; Meslier et al. 2020), and the other two a quantitative real-time PCR (Walker et al. 2011; Christensen et al. 2013). Thirteen studies evaluated fecal and/or blood metabolic end-products of microbiota (Russell et al. 2011; Haro et al. 2016a; Fava et al. 2013; Salonen et al. 2014; Vitaglione et al., 2015; Beaumont et al. 2017; Vuholm et al. 2017; Bendtsen et al. 2018; Kopf et al. 2018; Mayengbam et al. 2019; Roager et al. 2019; Meslier et al. 2020; Johnstone et al. 2020).

Microbiota composition

Standard diet regimens. The four studies which analyzed MD reported several species or genera that increased or decreased after the dietary intervention (Haro et al. 2016a, 2016b, 2017; Meslier et al. 2020). Increases in *Faecalibacterium prausnitzii*, *Parabacteroides distasonis*, and *Roseburia, Prevotella*, *Rumninococcus,* and *Eubacterium rectale* were the most frequently reported changes in comparison to a low-fat high-carbohydrate diet. Changes after the MD were influenced by the metabolic phenotype being more pronounced in subjects more compromised at baseline or showing a greater improvement in insulin resistance during the intervention.

Furthermore, studies with low-fat high-carbohydrate diets or low dairy products generally observed decreases in some species or genera, including some reported above as *Faecalibacterium prausnitzii*, *Parabacteroides distasonis*, and *Roseburia,* (Haro et al. 2016a, 2016b, 2017; Bendtsen et al., 2018; Fragiadakis et al. 2020; Grembi et al. 2020). Firmicutes/Bacteroidetes ratio, *Streptococcus* and *Clostridium* genera decreased, and *Prevotella* and generally Bacteroidetes increased, as microbiome plasticity. Changes were again more prevalent in subjects with a worse metabolic phenotype at baseline. A high saturated fat diet with a high glycemic index reported an increase in *F. prausnitzii*, meanwhile, high MUFA diets (with low or high glycemic index) reported a decrease in total bacteria with respect to diets with high carbohydrate with a high glycemic index or high saturated fat diet- high glycemic index (Fava et al. 2013). Some changes were indistinguishable after one year, suggesting resilience and an "obesity memory" (Fragiadakis et al. 2020).

Not standard or healthy dietary regimens. Most of the other dietary regimens described interventions with fibers, resistant starch, whole wheat, vegetables, and fruits with respect to conventional weight-loss diets or diets rich in foods with refined carbohydrates. The diet compositions, mainly regarding the glycemic index, fats, and type of fibers influenced the microbiome composition with more numerous genera and species described. Increases in *Bacteroidetes*, *Ruminococcus* bromii, *F. prausnitzii*, *Roseburia*, *Prevotella*, *Eubacterium rectale*, and *Oscillobacter* were the most frequently reported changes in comparison to control diets. Furthermore, decreases in *Bacteroides*, in particular *thetaiotaomicron*, *Fecalibacterium*, *Blautia*, *Alistipes*, and *Bifidobacterium* were also reported (Walker et al. 2011; Christensen et al. 2013; Lappi et al. 2013; Salonen et al. 2014; Vitaglione et al., 2015; Vuholm et al. 2017; Kopf et al. 2018; Schutte et al. 2018; Mayengbam et al. 2019; Roager et al. 2019; Johnstone et al. 2020). Fewer modifications than dietary models described above were described with high-protein diets that reported decreases in *Roseburia*, *Eubacterium rectale,* and Bacteroidetes (Russell et al. 2011; Beaumont et al. 2017).

Microbiota metabolic end-products

Standard diet regimens. The MD did not modify stool SCFAs in any study (Fava et al. 2013; Haro et al. 2016a, 2016b, 2017; Meslier et al. 2020), except for a control diet rich in high-saturated fats in which SCFAs increased (Fava et al. 2013). Diversely, a reduction in stool content of BCFAs (valerate, isovalerate, isobutyrate, and 2- methyl butyrate) and biliary acids (deoxycholic and lithocholic acid) and an increase in urinary urolithin glucuronides were reported, in relation with changes in the intake of some foods (decrease in meat and increase in nuts consumption) (Meslier et al. 2020). Serum metabolites expressed a shift of energy production from beta-oxidation to glycolysis in the previous models (Meslier et al. 2020) or also amino acid, and sphingolipid metabolism if a low-fat high carbohydrate diet is included (Haro et al. 2016a). The latter metabolites were mainly related with 3 bacterial genera and 2 bacterial species (*Roseburia; Prevotella; Oscillospira; Faecalibacterium prausnitzii; Bacteroides uniformis*) (Haro et al. 2016a).

Not standard or healthy dietary regimens. Fecal SCFA decreased in some (Salonen et al. 2014; Vuholm et al. 2017; Mayengbam et al. 2019) but not all the studies (Kopf et al. 2018; Roager et al. 2019; Johnstone et al. 2020) on the role of whole grain/resistant starch/fibers in comparison to other dietary models. Pea-derived fibers decreased fecal primary, secondary, and total bile acids (Mayengbam et al. 2019). Consumption of whole-grain was associated with high levels of fecal ferulic acid and serum dihydro-ferulic acid (DHFA) that were mostly related to an increase in Bacteroidetes abundance in one study (Vitaglione et al., 2015), and several urinary biomarkers of whole-grain intake, including phenolic metabolites (Roager et al. 2019). Although the microbial variations were negligible, diets rich in protein demonstrated a shift in bacterial metabolism toward amino acid degradation

Table 3. Results of the included studies.

Author, journal, year	Outcomes	Method	Results on microbiota	Microbiota-mediated metabolic changes	Clinical results
Beaumont et al. 2017	effects of the quantity and source of dietary proteins on the gut microbiota composition and metabolic activity and the consequences on the large intestinal mucosa	V3 - V4 region of 16S rRNA gene sequencing analysis Mucosal transcriptome GAS chromatography and HPLC analysis	↔ α and β diversity between dietary treatments	Fecal metabolome: ↑fecal concentrations branched-chain AAs in CAS group vs SOY and MD groups ↓ relative concentration of butyrate in CAS and SOY groups vs MD group ↑ fecal pH in CAS group ↑isoleucine-derived bacterial metabolite 2-methylbutyrate in CAS and SOY groups vs MD group ↑relative concentration of several AA-derived bacterial metabolites (valerate, phenylacetate, and tyramine) in SOY group ↑acetoin in SOY group Urinary metabolome: ↑ relative concentrations of AA-derived bacterial metabolites isobutyrate, microbiota-host cometabolites indoxyl sulfate and phenylacetylglutamine, and phenylacetylglutamine in SOY and CAS groups vs MD group ↑ 3-hydroxyisovalerate, 3-hydroxybutyrate, and the cometabolite p-cresyl sulfate in CAS group ↑acetoin and isoflavone in SOY group	↑Blood and urinary urea in SOY and CAS groups ↓systolic blood pressure in SOY group
Bendtsen et al., 2018	increase BW loss, FM loss, and/or fecal fat excretion over 24 weeks of HD or LD. effects of dairy intake on fecal calcium and energy excretion, resting energy expenditure (REE), blood pressure, and lipid metabolism HD and LD effects on gut microbiota composition	V3 + V4 region of 16S rRNA gene sequencing analysis	↔ α diversity ↓*Veillonella* genus in LD POS correlation between relative abundance of *Papillibacter* (family *Ruminococcaceae*) and the total FM loss, independent of diet group	↔ fecal fat excretion in LD vs HD diet ↔ fecal energy excretion in LD vs HD diet	24 weeks ↓ body weight, ↓fat mass, ↓hip and waist circumference in LD and HD diet. ↑ hip circumference loss in LD vs HD diet ↔ SBP, DBP, total-, LDL-, and HDL-cholesterol, TAG, glucose, insulin, NEFA, and hsCRP The between-group change in RQ differed over 24 weeks HD diet:↑Fecal and total calcium excretion ↓ respiratory quotient (RQ) LD diet:↓ Fecal and total calcium excretion ↓ resting energy expenditure

(*Continued*)

Table 3. (Continued)

Author, journal, year	Outcomes	Method	Results on microbiota	Microbiota-mediated metabolic changes	Clinical results
Christensen et al. 2013	changes in gut bacterial composition caused by the energy-restricted diet enriched with WW or RW	quantitative real time PCR targeting regions within the 16S rRNA genes	↔ microbiota composition ↑*Bifidobacterium* in WW ↓*Bacteroides* in RW ↓ *Firmicutes* from baseline in all subjects		↔ effects of fecal water on trans-epithelial resistance POS correlation in run-in samples (RW diet): – Fecal pH of the original sample and *Bacteroidetes* – relative abundance of *Bifidobacterium* with fat mass percentage and trunk fat percentage – NEG correlation in run-in samples (RW diet):relative abundance of the phylum *Bacteroidetes* and fat mass percentage and trunk fat percentage – systolic and diastolic blood pressure with the relative abundance of *Firmicutes* – *Firmicutes* with IL-6
Fava et al. 2013	effects of the type and quantity of dietary fat and carbohydrate on gut microbiota and colonic fermentation in human subjects 'at risk' or suffering from the MetS. Impact of any gut microbial changes on metabolic and cardiovascular disease biomarkers	FISH	↓ total bacteria in HM/HGI and HM/LGI vs HC/HGI and baseline ↔ total bacteria in HC/HGI and HC/LGI ↑*Bifidobacterium spp.* in HC/HGI and HC/LGI vs baseline or control HS (only for HC/HGI) ↑ *Bacteroides spp.* in HC/HGI vs baseline, associated with ↓ in body weight, BMI, waist circumference ↑*Faecalibacterium prasnutzii* in control HS vs baseline	↔ SCFA comparing 5 diets ↑ fecal acetate, propionate, and n-butyrate in HS vs baseline	↔ anthropometric, blood pressure, biochemical parameters (TG, TC, LDL, HDL, glucose, insulin, leptin, PAI-1, ICAM-1, CRP), and insulin sensitivity from IVGTT between the 5 diets ↓ % body fat in HC/HGI vs baseline ↑waist circumference in HM/LGI vs baseline ↓NEFA in HC/LGI vs control HS and HC/HGI ↓Plasma total and LDL cholesterol in all diets vs baseline ↓HDL cholesterol in HC/HGI vs baseline ↓ Fasting plasma glucose with both HC diets vs baseline ↓ plasma insulin concentration with HC/HGI ↑ Soluble ICAM-1 with HM/HGI vs baseline

Fragiadakis et al. 2020	effect of a healthy low-fat (HLF) diet vs a healthy low-carbohydrate (HLC) diet on weight change at 12 months	V4 region of 16S rRNA gene sequencing analysis	After 3 m: HLC diet: ↑*Proteobacteria*, *Bacteroidetes*, and *Firmicutes* phyla (*Bilophila* and *Desulfovibrio* genera - *Desulfovibrionaceae* family) HLF diet: ↓ *Actinobacteria* and the *Firmicutes* phyla (*Dorea* and *Blautia* genera - L*achnospiraceae* family) *Bacteroidetes* ↑ both in low carb and low fat diet *Oscillospira* and *Lachnospira* were NEG associated with weight *Firmicutes* were POS associated with weight ↔ α diversity		↓ BMI, % body fat, waist circumference, blood pressure, insulin, and glucose in both diets ↑ LDL in HLC ↑ HDL and ↓ TG > in HLC vs HLF diet ↓Respiratory exchange ratio in HLC vs HLF diet ↓ Resting energy expenditure in both diets
Grembi et al. 2020	Explore whether attributes of gut microbiota predispose individuals to successful 12-month weight loss. Identifying pre-diet features of the gut microbiota that can predict adherence and/or success on a specific diet for personalization of dietary intervention strategies to maximize weight loss	V4 region of 16S rRNA gene sequencing analysis	Pre-diet microbiota composition did not cluster by 12-month weight loss success category, age, gender, pre-diet weight, body mass index or dietary adherence ↑pre-diet microbiota plasticity in very successful (VS) vs unsuccessful (US) subjects on low-fat diet ↑microbiota plasticity between T0 and 10 weeks in VS in both diets Pre-diet plasticity ↔ independently from baseline fiber, fat, protein or carbohydrate consumption. Daily pre-diet plasticity was POS correlated with plasticity over 10 weeks for subjects on the low-fat diet		↑ 12-month weight loss for high P/B *vs* low P/B subjects on low-carb diet in discovery but not validation cohort
Haro et al. 2016a	changes in microbiota of obese people with CHD after long term consumption of healthy diets relationship between specific bacteria and the metabolomics profile found in feces and plasma	16S rRNA gene sequencing analysis	LF diet: • ↑ *Prevotella* bacterial genus • ↓*Roseburia, Faecalibacterium prausnitzii* • ↔ *Oscillospira* bacterial genera Med diet: • ↓ *Prevotella* bacterial genus • ↑*Roseburia* and *Oscillospira* bacterial genera, *Parabacteroides distasonis*	Changes in: *Roseburia*: • POS correlation with changes in N-Acetylaspartate in feces and XHWESASXXR in plasma • NEG correlation with changes in Arginylproline in feces *Prevotella*: • POS correlation with changes in Glutamate, Arginylproline, and 3,7-Dimethylurate in feces *Oscillospira*: • NEG correlation with changes in Glutamate and Pantothenate in feces • POS correlation with changes in cis-Vaccenate (18:1n7) in feces and Valylglutamine in plasma *Faecalibacterium prausnitzii*: • POS correlation with changes in Leucylvaline in feces *Bacteroides uniformis:* • POS correlation with changes in Glycocholenate sulfate in plasma ↔ SCFA and secondary bile acids	1 year MED or LF diet: ↑insulin sensitivity index (OGTT) ↔ Glucose, HbA1c, TG, TC HDL, LDL

(*Continued*)

Table 3. (Continued)

Author, journal, year	Outcomes	Method	Results on microbiota	Microbiota-mediated metabolic changes	Clinical results
Haro et al. 2016b	differences in the bacterial community structure in MetS and nonMets patients effect of the long-term consumption of two healthy diets in restoring the gut microbiota composition.	16S rRNA gene sequencing analysis	T0 – ↑*Bacteroides, Eubacterium*, and *Lactobacillus* genera in MetS vs non-MetS – ↓*Bacteroides fragilis* group, *Parabacteroides distasonis, Bacteroides thetaiotaomicron, Faecalibacterium prausnitzii, Fusobacterium nucleatum, Bifidobacterium longum, Bifidobacterium adolescentis, Ruminococcus flavefaciens* subgroup, and *Eubacterium rectal* MetS vs non-MetS Met diet: – ↑ *P. distasonis, B. thetaiotaomicron, F. prausnitzii, B. adolescentis,* and *B. longum* in the MetS – ↑ *E. rectale* in the non-MetS Low fat diet: – ↓ *P. distasonis* in the non-MetS group ↔ *P. distasonis* in MetS patient group		
Haro et al. 2017	restoration of gut microbiome dysbiosis in obese patients depending on the degree of metabolic dysfunction	16S rRNA gene sequencing analysis	T0: – ↔ bacterial diversity or microbiota composition MetS-B vs NonMetS-OB vs NonMetS-NonOB – ↓*Actinobacteria* and *Bacteroidetes phyla* in MetS-OB vs NonMetS-NonOB – ↑*Firmicutes/Bacteroidetes* ratio MetS-OB vs NonMetS-NonOB – ↓ *Bacteroides, Prevotella, Roseburia, Faecalibacterium*, and *Ruminococcus* MetS-OB vs NonMetS-NonOB – ↑ *Streptococcus* and *Clostridium* genera MetS-OB vs NonMetS-NonOB – ↓ *P.distasonis* and *F.prausnitzii* MetS-OB vs NonMetS-NonOB 2 years: – ↔ bacterial diversity or microbiota composition MetS-B vs NonMetS-OB vs NonMetS-NonOB – ↑ *Bacteroides, Prevotella* and *Faecalibacterium* genera in MetS-OB with MED or LF vs T0 – ↓ *Firmicutes/ Bacteroidetes* ratio, *Streptococcus and Clostridium* genera after LF in MetS-OB – ↑ *Roseburia* and *Ruminococcus* genera and *P. distasonis* and *F. prausnitzii* bacterial species after MED diet in MetS-OB – ↔ microbiota in NonMetS-NonOB and NonMetS-OB vs T0		↓ TG levels in MetS-OB after MED or LF diet ↔ TG levels NonMetS-Ob and NonMetS-NonOB groups

Hjorth et al. 2018	pre-treatment Prevotella-to-Bacteroides (P/B) ratio as a prognostic marker for successful body fat loss on two diets differing greatly in dietary fiber and whole-grain content.	16S rRNA gene sequencing analysis			26 weeks follow-up: – High P/B ratio: ↑3.15 kg body fat loss, ↑3.49 kg BW loss, and ↓4.75 cm WC in NND vs ADD – Low P/B ratio: ↔ body fat, BW, and WC between NND and ADD Difference in responsiveness to diets between the P/B groups high-low): – 2.27 kg body fat – 3.95 cm waist circumference 1 year follow up: 3.99 kg difference in responsiveness to NDD between P/B groups (↓1.23 Kg in high P/B; ↑ 2.76 Kg in low P/B) ↔ weight in high P/B ratio subjects ↑2.76 kg in low P/B subjects
Johnstone et al. 2020	investigate the effect of nondigestible fibers on weight maintenance after weight loss. Assess the impact of the fibers on potential mechanisms via the gut microbiota and plasma gut hormone profiles in healthy but obese and overweight volunteers in free-living conditions.	16S rRNA gene sequencing analysis SCFA content of fecal samples was determined by capillary GC following conversion to t-butyldimethylsilyl derivatives	Microbial composition (alla data): *Firmicutes* (72.5% ± 10.7%), Bacteroidetes (17% ± 9.1%), and Actinobacteria (6.7% ± 8.1%) Principal bacterial genera (all data): *Faecalibacterium* (12.3% ± 6%), *Ruminococcus* (8.9% ± 6.3%), *Bacteroides* (8.4% ± 5.6%), *Blautia* (7.9% ± 4.4%), *Bifidobacterium* (6.7% ± 8.2%), and *Roseburia* (5.5 ± 4.3%) Addition of RS: modification of *Roseburia*, *Ruminococcus*, and *Faecalibacterium*. ↑ *Ruminococcus* and *Roseburia* after RS-WM vs C-WM diet. ↑ *Ruminococcus* (especially *Ruminococcus bromii*) after RS-WM diet vs WL diet ↑ *Eubacterium rectale Roseburia faecis* after RS-WM diet vs C-WM diet ↓ *Blautia* in RS-WM vs WL diet ↑*Faecalibacterium prausnitzii* in RS-WM POS association between the genus *Anerostipes* and blood glucose	↔ acetate, propionate, or butyrate in fecal samples ↑ iso-valerate and iso-butyrate after WL or C-WM vs M or RS-WM ↔ N-nitroso compounds in fecal water	Mean weight loss: 3.64 kg ± 1.93 ↔ loss of lean and fat mass ↓ systolic (6%) and diastolic (5%) blood pressure after WL ↓ 2.57 cm in waist circumference and 2.35 cm in hip circumference in WL ↓ −3.57 cm during C-WM and RS-WM ↔ motivation to eat ↓ 3.8% fasting glucose after WL ↓ by 0.5% after RS-WM vs after C-WM ↓ total cholesterol, LDL, and fasting triglycerides after WL ↓ Triglycerides after C-WM and RS-WM vs M diet. ↓Nonesterified fatty acids after C-WM and RS-WM vs WL diet period ↔ 180-min plasma glucose profile after test meal ↓ insulin after WL diet vs M diet period. This effect was maintenance after RS-WM while ↑ in C-WM ↔ inflammatory biomarkers

(*Continued*)

Table 3. (Continued)

Author, journal, year	Outcomes	Method	Results on microbiota	Microbiota-mediated metabolic changes	Clinical results
Kopf et al. 2018	impact of increasing intake of WG or FV against the background of a typical Western diet on inflammatory makers and gut microbiota composition in individuals affected by overweight or obesity	V4+V5 region of 16S rRNA gene sequencing analysis	↑ α-diversity in FV ↔ β-Diversity Change in dominant bacteria from baseline to the end of the study (mean): – *Bacteroides*: ↓ in C and FV; ↑ in WG – *Ruminococcus* (Ruminococcaceae): ↑ in C; ↓ in FV and WG – *Ruminococcus* (Lachnospiraceae): ↑ in C, FV and WG – *Bifidobacterium*: ↓ in C and WG, and FV – *Fecalibacterium*: ↓ in C, FV and WG	↔ fecal SCFAs	↔ BMI, hs-CRP ↓LPB in WG and FV (individuals with higher Firmicutes and lower Bacteroidetes at baseline showed a greater decrease in LBP during the study) ↓ TNFα in WG ↓IL6 in FV
Lappi et al. 2013	effects of refined low-fiber wheat bread and WG and high-fiber rye bread intake on the intestinal microbiota composition subjects with metabolic syndrome	HITChip on V1 and V6 regions of 16S rRNA	↔ microbiota composition between RB and WWB except for ↑ *Bryantella formatexigens* in WWB WWB vs baseline: – ↑ *Clostridium cluster* IV (Clostridium leptum et rel., Clostridium cellulosi et rel., and Anaerotruncus colihominis et rel.), and XI (Anaerovoranx odorimutans et rel.) and *Actinobacteria* (Collinsella and Atopobium spp.) – ↓ Bacteroidetes phylum (Bacteroides plebeius et rel, B. vulgatus et rel. and Prevotella tannerae et rel.) – Largest mean ↓ in B. vulgatus et rel. (19%) which also ↓ in ~50% RB participants Dietary variables associated with Bacteroides cluster variation (>10%): – % energy intake from PUFA and 18:2n6 (~30% variation) – % energy from 18:3n3 – WG and refined breads Dietary variables associated with butyrate producers variation (40-50%): – WG and refined white breads – total fiber and grain fiber Correlations between individual bacterial group and single nutrient/food intakes (all data): – *B. vulgatus et rel., B. ovatus et rel., P. tannerae et rel., and P. oralis et rel.* POS correlated with the intake of 18:2n6, other fat-derived compounds, and margarine – *F. prausnitzii et rel.* NEG correlated with the intake of refined white breads – *R. intestinalis et rel.* POS correlated with the intake of total fiber, grain fiber, and WG breads, while NEG correlated with that of refined white breads – *E. ventriosum* POS correlated with energy intake from alcohol		↔ body weight, markers of glucose metabolism and inflammation ↓ in the high sensitivity C-reactive protein concentration within the RB group

Mayengbam et al. 2019	investigate the potential gut related mechanisms by which pea-derived mixed fiber improves body weight, fat mass, glucose tolerance and appetite regulation	16S rRNA gene sequencing analysis	PF group: ↓ *Actinomycetaceae* ↑ *Barnesiellaceae* ↓ *Actinomyces, Holdermania* and *Oscillospira* ↑ *Lachnospira* CO group: ↑*Prevotellaceae*, *Porphyromonadaceae*, *Rikenellaceae* and S24-7 ↑*Anaerostipes, Collinsella, Paludibacter* and *Prevotella*, ↓ *Lachnospira* and *Paraprevotella* ↓α diversity in CO e PF group (Chao1 metric) NEG correlation (all data): – body weight and Lachnospira abundance – Anaerostipes and 2-hydroxybutyrate, 3-hydroxybutyrate and proline levels – Actinomyces and Collinsella with propionate and butyrate – Oscillospira and BAs such as DCA and isoLCA. POS correlation (all data): – *Lachnospira* abundance with acetate level. – *Prevotella* with branched SCFAs (isovalerate and isobutyrate) – *Paraprevotella* abundance and Propionate, total SCFA, acetoacetate concentrations *Holdermania* and glucose-AUC	PF group after 12w: ↑acetate ↓isovalerate ↓fecal primary bile acid (BAs) cholic acid and chenodeoxycholic acid, and secondary BAs deoxycholic acid and total Bas CO group after 12w: ↔ BAs	
Meslier et al. 2020	• Primary outcomesPlasma lipids • fecal levels SCFAs • Secondary outcomes: • changes in gut microbiota • changes in markers of metabolic disease (blood pressure, fasting blood glucose, hs-CRP, urinary and plasma TMAO, plasma gastrointestinal peptides and urinary polyphenols)	16S rRNA gene sequencing analysis shotgun metagenomics Metagenomic species pangenome (MSP)	↑ differentially abundant Metagenomic species pangenome (MSP) between MedD and ConD: ↓*Ruthenibacterium lactatiformans, Flavonifractor plautii*, *Parabacteroides merdae*, *Ruminococcus torques* and *Ruminococcus gnavus*, *Streptococcus thermophilus* in MedD vs ConD ↑ *Faecalibacterium prausnitzii*, *Roseburia* and *Lachnospiraceae* taxa in MedD vs ConD ↑ baseline levels of several Bacteroides species and ↓ Prevotella sp. and P. copri levels in subjects showing HOMA reduction at 4 weeks on MedD	18% variation in the metabolic potential captured by gut metabolic modules after 4 weeks of treatment. Enrichment in amino acid, carbohydrate, triglyceride and glycoprotein degradation, and conversion of acetyl-CoA and glutamate degradation to crotonyl-CoA in MedD group. 6% variation after 8 weeks. Enrichment in glutamate degradation to crotonyl-CoA maintained in the MedD group. Metabolites changes: – ↑ urinary urolithin glucuronides (↑Eggerthellaceae family) in MedD vs ConD – ↓ fecal BAs in MedD during intervention *vs* baseline – ↓ fecal deoxycholic and lithocholic acid after 4 and 8 weeks in MedD – ↔ SCFAs acetate, butyrate, propionate – ↓ BCFAs valerate, isovalerate, isobutyrate and 2- methylbutyrate in MedD over intervention	↓total plasma cholesterol and (HDL)-cholesterol after 4 weeks in MedD vs ConD (proportional to MD adherence rate) ↔ blood glucose, HOMA, serum hs- CRP, plasma insulin, TMAO, glucagon, ghrelin, GIP, GLP-1, leptin, C- peptide, resistin, visfatin and PAI-1

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Table 3. (Continued)

Author, journal, year	Outcomes	Method	Results on microbiota	Microbiota-mediated metabolic changes	Clinical results
Roager et al. 2019	Primary outcomes: effects of replacing refined grains with whole grains in improving insulin sensitivity and alterations on gut microbiome Secondary outcomes: biomarkers of metabolic health and gut functionality	16S rRNA gene sequencing analysis Shotgun metagenomic sequencing	– ↔ Microbial gene diversity and richness – ↔ abundance of individual bacterial species – four distinct strains of *Faecalibacterium prausnitzii* and one *Prevotella copri* ↑ after whole grain and ↓ after refined grain consumption – *Bacteroides thetaiotaomicron* ↓ after whole grain and ↑ after refined grain consumption – several strains of *Clostridiales* and *F. prausnitzii* were POS associated with whole grain and fiber intake, – *B. thetaiotaomicron* was NEG associated with whole grain and fiber intake – *Erysipelatoclostridium ramosum* was POS associated with IL-6 – ↔ fasting nor postprandial breath hydrogen excretion between the intervention periods	↔ fasting plasma SCFA concentrations ↑ plasma concentrations of butyrate after the whole grain intervention ↑ five urinary metabolites (DHPPA-glucuronide, 2-aminophenol-sulfate, pyrocatechol-glucuronide, pyrocatechol-sulfate, 3-methyladipic acid) during whole grain period. NEG association between: – urinary concentrations of DHPPA-glucuronide and serum concentrations of both IL-6 and CRP – urinary concentrations of pyrocatechol-glucuronide and 2-aminophenol-sulfate with CRP – urinary concentrations of 3-methyladipic acid, and body weight ↑lactose/L-arabinose transport system substrate-binding protein (KO K10188) and a glycosyl-1-phosphate transferase (KO K15915) with whole grain diet – ↔ carbohydrate active enzymes – ↔ acetate CoA-transferase genes	– ↔ HOMA-IR, HbA1c, fasting serum C-peptide, fasting glucose and insulin, lipid metabolism (fasting serum concentrations of TG, HDL, LDL and total cholesterol and FFA), AST, ALT, fasting plasma concentrations of leptin, GLP-1 and GLP-2 and systolic/diastolic BP – ↓body weight, fat-free mass and tendency for ↓in fat mass ($p = 0.057$) in whole grain – ↓sagittal abdomen diameter and a similar tendency was observed for WC in whole grain↓body weight and energy intake both significantly associated with ↓plasma leptin in whole grain – ↓CRP, IL-6, IL1 in whole grain – ↔ TNF alpha

Russell et al. 2011	monitor the effect of a high-protein and reduced-carbohydrate weight-loss diets on a wide range of fecal metabolites	FISH analysis	↑ total number of bacteria in M diet vs HPLC and HPMC ↓*Roseburia/Eubacterium rectale* group as proportion of total bacteria in HPLC ↔ *Lachnospiraceae* and *Faecalibacterium prausnitzii*. ↓*Bacteroides* spp in HPLC vs M diet	↓ total SCFA in HPLC ↓butyrate in HPLC vs M diet ↑isovalerate and isobutyrate in HPLC and HPMC vs M diet ↑pH of fecal water in HPLC vs HPMC and M diet ↑N-nitroso compounds in HPLC and HPMC vs M diet ↓ ferulic acid and its metabolites in HPLC vs M diet ↓ gentisic acid (2,5-dihydroxybenzoic acid), 3,5-dihydroxybenzoic acid, and a 4-hydroxy3-methoxy-, 3,4-dihydroxy-substituted phenylacetic acid in HPLC diet ↓ phenylpropionic acid concentrations in HPLC diet ↑ PAA concentrations in HPLC and HPMC vs M diet ↓Indole and ↑ indole-3-pyruvic acid in HPMC diet POS association: – fecal NOCs, BCFAs, valerate, lactate, and phenyl acetic acid concentration with high protein diets – phenolic metabolites, including FA derivatives, as well as various bacterial groups plus acetate, butyrate, and propionate with M diet	
Salonen et al. 2014	Effects of the changes in the major type of non-digestible carbohydrates in the diets on dominant bacterial phylotypes.	HITChip microarray on V1 and V6 hypervariable regions of the 16S rRNA	↓ β diversity in M and RS diet ↓ α diversity in RS diet RS diet: ↑ *Oscillospira guillermondii, R. bromii. Sporobacter termitis, Clostridium leptum,* *C. cellulosi* (Clostridium cluster IV). ↓*Alistipes spp.* (Bacteroidetes), Lachnospiraceae (Clostridium cluster XIVa: in particular, ↑*E. rectale* and the uncultured bacterium D522 and ↓ related uncultured phylotypes and *R. inulinivorans* L1-83) ↑*Lachnospiraceae* in NSP diet vs M and SP diet NSP diet: ↑*Eggerthella, Collinsella* and *Corynebacterium* (Actinobacteria), ↑bacteria related to Bacteroides vulgatus and Prevotella oralis. ↓ *C. leptum, C. cellulosi, Oscillospira spp.* and *Sprorobacter spp.* (Ruminococcaceae) ↓*Bifidobacteria, Bacilli* and *Proteobacteria;* ↑ *Lactococci, Sutterella wadsworthia* in WL diet	↓ SCFA acetate, propionate, butyrate, and succinate and ↑minor fermentation acids in RS and WL vs NSP and M diet POS correlation between 16s rRNA signal and concentrations of both total and major SCFA in the three maintenance diets (RS, NSP, M) NEG correlation between SCFA and cluster IV *Ruminococcus* group SCFA in the three maintenance diets (RS, NSP, M) ↑branched chain SCFA in RS and WL; NEG correlated with 16s rRNA signal in the three maintenance diets (RS, NSP, M)	WL diet ↑ SCFA and insulin sensitivity POS correlation between fecal *Bifidobacteria* and insulin

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Table 3. (Continued)

Author, journal, year	Outcomes	Method	Results on microbiota	Microbiota-mediated metabolic changes	Clinical results
Schutte et al. 2018	investigate the potential benefits of WGW consumption compared with RW consumption on liver health and associated parameters.	V4 region of 16S rRNA gene sequencing analysis	↓α diversity in RW ↔ α diversity in WGW ↔ *Lachnospiraceae* and *Ruminococcaceae* between RW and WGW		↔ total cholesterol, HDL cholesterol, TGs, NEFAs, glucose, insulin, and HOMA-IR ↔ abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) mass ↑49% in intrahepatic triglyceride in RW ↑ %subjects with steatosis in RW ↓%subjects with steatosis in WGW ↔ fasting plasma ALT, AST, GGT, and postprandial NEFA ↓serum amyloid A and CRP in WGW ↑TG levels 4 h postprandially in WGW after intervention vs baseline ↔ adipocyte size, expression of the genes LPL, ANGPTL4, CD36, CD68, TGFB1, MMP9, and LOX
Vitaglione et al. 2015	assess circulating concentration, excretion, and the physiologic role of WG wheat polyphenols in subjects with suboptimal dietary and lifestyle behaviors	V4 region of 16S rRNA gene sequencing analysis	↑*Prevotella* (1.8% to 3.5%) in WG ↓ *Dialister* (from 2.5% to 0.6%), *Bifidobacterium* (from 6.6% to 5.3%), *Blautia* (from 9.7% to 6.7%), and *Collinsella* (from 1.8% to 0.9%) in WG ↑ *Bacteroides* from 9.9% to 14.7% and Lactobacillus from 0.03% to 0.12% correlate with ↓ TNFα in WG after 8 weeks	↔ single and total phenolic acids in biological samples from WG and control subjects at T0 WG intervention: – 4.2- and 5-fold increase in serum DHFA after 4 and 8 weeks – 1.3- and 0.8-fold increase in fecal FA after 4 and 8 weeks – 0.8 fold increase in FA urinary excretion after 8 weeks – FA serum concentrations at 4 and 8 week POS correlated with serum DHFA – Urinary FA POS correlated with fecal and urinary DHFA – in those ↑ urinary FA, a ↑ fecal FA after 8-wk – urinary FA and DHFA NEG correlated with PAI-1 – ↓ relative abundance at T0 of *Bifidobacteriales* (Actinobacteria) of 5.0% and *Bacteroidetes* of 9.6% associated with ↑ FA in the gut and urinary excretion, respectively after treatment, fecal FA POS associated with *Bacteroidetes* (↑ from 9.6% to 14.5%) and Firmicutes (↑from 75.3% to 79.7%), whereas NEG associated with *Clostridium* (↓from 3.1% to 1.6%)	↔ anthropometric data, body composition, plasma lipids, and glycemia ↓ TNFα in WG after 8 weeks ↑ IL10 in WG after 4 weeks

Vuholm et al. 2017	evaluate whether consumption of whole grains compared to refined grains for 6 wk improved gut health	V3-V4 region of 16S rRNA gene sequencing analysis	↔ UniFrac distance matrices ↔ bacterial diversity ↔ genera relative abundance ↑ unassigned genus of *Ruminococcaceae* in WGR vs RW in women	↔ fecal pH, total SCFAs, propionate among diets RW group: ↓ fecal concentration of butyrate, total SCFA, and propionate	GI symptoms: – ↑ flatulence in WGW and WGR vs RW – ↓bloating in WGW and WGR vs RW – ↓fatigue in WGW and WGR vs RW ↑stool frequency, ↓ stool consistency in WGR group at weeks 2 and 4 vs RW ↔ intestinal permeability ↔ breath hydrogen
Walker et al. 2011	Effects of the changes in the major type of non-digestible carbohydrates in the diets on dominant bacterial phylotypes.	V2 – V5 region of 16S rRNA gene sequencing analysis Quantitative real time PCR denaturing gradient gel electrophoresis of V3 region of 16S	↔ proportion of Bacteroidetes, Firmicutes, Actinobacteria or Proteobacteria ↑ *E. rectale* and *Ruminococcus bromii* in RS diet ↓ *Collinsella aerofaciens* in WL diet ↑ Ruminococcaceae (*R. bromii, R. flavefaciens* and *R. albus*) in RS diet vs NPSs diet ↑*Oscillibacter valericigenes* in RS and WL vs M and NPS diets ↔ *F. prausnitzii* *Roseburia* and *E. rectale* ↑ RS diet and ↓WL diet ↔ Methanogenic archaea		

HbA_{1c}: glycated hemoglobin A_{1c}, TG: triglycerides, TC: total cholesterol, HDL: High density lipoprotein, LDL: low density lipoprotein, LD: Low dairy product diet, HD: High dairy product diet, SBP: systolic blood pressure, DBP: diastolic blood pressure, hsCRP: high sensitivity C-reactive peptide, NEFA: plasma nonesterified fatty acids TMAO: trimethylamine N- oxide, LBP: lipopolysaccharide binding protein, SCFAs: short chain fatty acids, DHFA: dihydroferulic acid, FA: ferulic acid, GGT: γ-glutamyl transferase, DCA: deoxycholic acid, LCA: lithocholic acid, NOCs: N-nitroso compounds, BCFAs: branched-chain fatty acids.

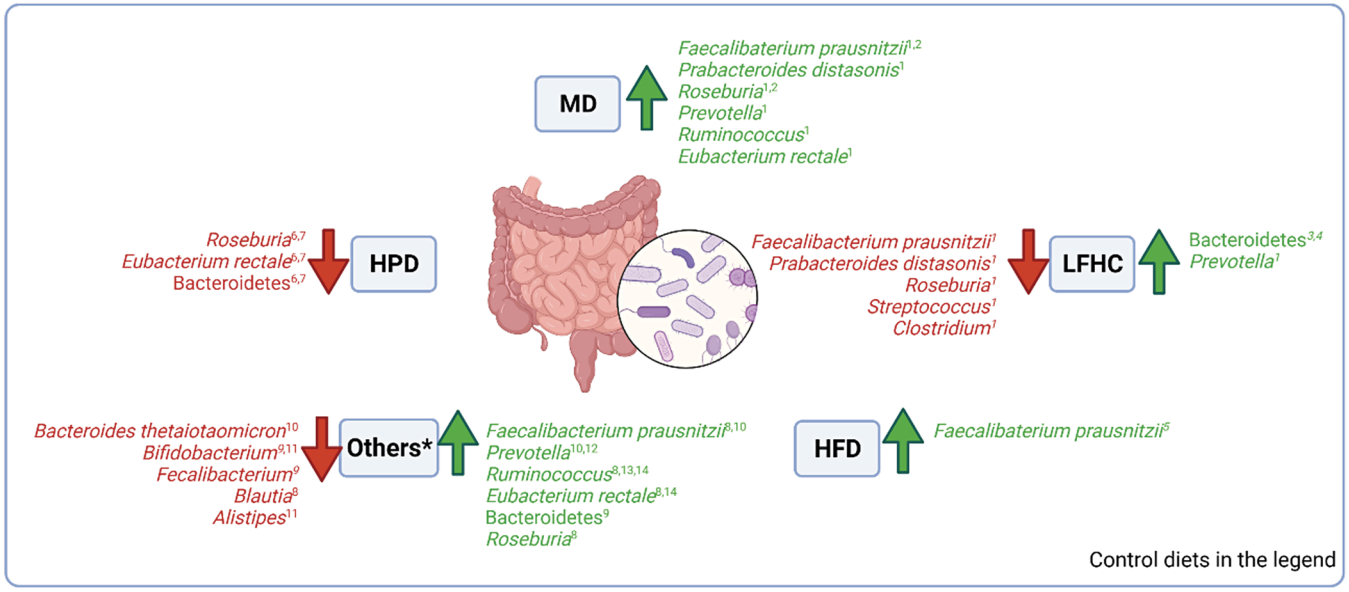

Figure 4. Microbiota main changes in individuals with obesity following classical or healthy dietary regimens in comparison to several control diets. MD: Mediterranean Diet, compared to low-fat high carbohydrate diet in [1]Haro et al. (2016a, 2016b, 2017) and to a habitual western diet in [2]Meslier et al. (2020). LFHC: Low-fat high-carbohydrate diet shows changes in comparison to MD ([1]Haro et al. 2016a, 2016b, 2017; *P. diastonis* only in the non-MetS group; *Streptococcus* and *Clostridium* in MetS-OB) and in microbiome plasticity ([3]Fragiadakis et al. 2020; [4]Grembi et al. 2020). HFD: High fat diet; *F. prausnitzii* increased in high saturated fat diet with a high glycemic index as opposed to baseline ([5]Fava et al. 2013). HPD: high protein diet presents variations in *Roseburia/Eubacterium rectale* as proportion of total bacteria and decreased of Bacteroidetes versus MD ([6]Russell et al. 2011; [7]Beaumont et al. 2017). *Others: dietary interventions with resistant-starch weight maintenance diet (RS-WM) versus control weight maintenance diet (C-WM diet) ([8]Johnstone et al. 2020); whole grain (WG) and fruits and vegetables (FV) interventions versus baseline ([9]Kopf et al. 2018). WG diet was also studied against refined grain (RG) consumption ([10]Roager et al. 2019; [12]Vitaglione et al. 2015), with correlation in women ([13]Vuholm et al. 2017); resistant starch (RS) diet, non-starch polysaccharides (NSPs) diet and weight loss (WL) diet versus Run-in maintenance diet (protein/carbohydrate/fat % as 13:52:35 of metabolizable energy) ([11]Salonen et al. 2014, [14] Walker et al. 2011). Created with BioRender.com.

with different metabolite profiles according to the protein source (Russell et al. 2011; Beaumont et al. 2017). The butyrate concentration in stools was directly related to the content of carbohydrates (Russell et al. 2011).

Microbiota relation with host metabolism

A decrease in *Prevotella copri* was associated with an improvement in insulin resistance in subjects on the MD (Meslier et al. 2020) and a decrease in *Holdemania* with amelioration in glucose levels during an oral glucose tolerance test on a pea fiber diet (Mayengbam et al. 2019). Furthermore, the highest reduction in fecal biliary acids was related to a reduced relative abundance of *Bilophila wadsworthia* (Meslier et al. 2020). Taxonomic changes after MD reported in the previous paragraphs were more pronounced in subjects more metabolically compromised at baseline (Haro et al. 2016b, 2017). Weight was negatively associated with genera *Lachnospira* and *Oscillospira*, whereas *Faecalibacterium*, *Clostridiales*, and *Clostridium* were positively associated with it (Fava et al. 2013; Mayengbam et al. 2019). Furthermore, *Bacteroides* spp., and mainly *Prevotella* abundance, were associated with a decrease in body weight, BMI, waist circumference, fat mass percentage, and trunk fat percentage in several dietary models including a diet rich in fiber and whole grain or with high carbohydrate/high glycemic index (Christensen et al. 2013; Fava et al. 2013).

Healthy diet regimens resulted in improvements in inflammatory biomarkers related to some taxa. Individuals with higher Firmicutes and lower Bacteroidetes showed a greater decrease in lipopolysaccharides binding protein during the study (Kopf et al. 2018). Reduced TNF-α was associated with an increased abundance of *Bacteroides* and *Lactobacillus* (Vitaglione et al. 2015), meanwhile *Erysipelatoclostridium ramosum* positively with IL-6 (Roager et al. 2019).

Studies stratifying analysis according to prevotella/bacteroides ratio

High P/B ratio (> 0.01) subjects after 26-week of New Nordic Diet (very high in dietary fiber, whole grain, fruit and vegetables; dietary fiber 43.3 g/MJ, protein 18.1%, fat 30.4%, carbohydrates 46.6%) compared to Average Danish Diet (dietary fiber 28.6 g/MJ, protein 16.4%, fat 33.8%, carbohydrates 45.3%), showed a 3.15 kg and a 3.49 kg larger body fat and body weight loss respectively, and a 4.75 cm reduction in waist circumference, whereas no difference in such parameters was observed between NND and ADD among individuals with low P/B ratio (<0.01). A 2.27 kg body fat difference in responsiveness to the diets was found between the P/B groups, which came from a difference in response to NND. Similar differences in responsiveness to the diets were found for waist circumference (3.95 cm) and were borderline significant for body weight (2.33 kg) (Hjorth et al. 2018). During the 1-year follow-up period, subjects with the high P/B ratio changing from ADD to being recommended NND maintained their weight (−1.23 kg; NS), whereas subjects with the low P/B ratio changing from ADD

to being recommended NND regained 2.76 kg (Hjorth et al. 2018).

Considering high P/B (>0.003) and low P/B (<0.003) ratio subjects on a low carb-diet compared to a low-fat diet (reduction of daily intake of carbohydrate or fat to 20 g/day, followed by slow increments of 5-15 g/day, according to individuals' satisfaction with their daily intake and weight loss progress, with the ultimate objective of finding the lowest level of carbohydrate or fat they could achieve and conceivably maintain), high P/B ratio subjects on the low-carb diet had more weight loss than those with low P/B ratio, although this finding was not confirmed in a validation cohort. No association was found between weight loss and P/B ratio for subjects on the low-fat diet (Grembi et al. 2020).

Discussion

Recent literature strongly suggests that dietary approaches in obesity should be tailored to patients, and microbiota composition and function could be markers to select the best regimen. However, microbiota findings are still quite confusing. For the first time, we have tried to systematically review the dietary interventions with standard or healthy dietary patterns in controlled trials in adult obesity with a focus also on the microbiota.

First, standard diet regimens, including low-carbohydrate, low-fat, or MD resulted in decreasing weight and BMI, whereas other healthy regimens related to the promotion of whole grain, fruits, and vegetables could be related or not to a weight decrease (Johnstone et al. 2020; Fava et al. 2013; Lappi et al. 2013; Bendtsen et al. 2018; Hjorth et al. 2018; Kopf et al. 2018, Roager et al. 2019; Fragiadakis et al. 2020; Grembi et al. 2020). However, the latter interventions were clearly followed by a better phenotype, by decreasing inflammation, and improving glucose metabolism, lipid profile, and metabolic syndrome (Fava et al. 2013; Lappi et al. 2013; Vitaglione et al., 2015; Kopf et al. 2018; Schutte et al. 2018; Roager et al. 2019) similarly to the standard regimens (Haro et al. 2016a, 2017; Bendtsen et al. 2018; Meslier et al. 2020; Fragiadakis et al. 2020).

Second, the diet regimens clearly modified the microbiota signature in a dependent fashion mainly related to the macronutrient composition. Percentage in carbohydrates, fats, and fibers seem to be the master regulators of the microbiome composition, richness, and function, at least in a relatively short-term period, whereas increasing protein influenced relatively few species and genera. *Bacteroides*, and *Prevotella* sp, belonging from Bacteroidetes phylum, were among the species most frequently changed in their relative abundance, mainly when the dietary regimens were rich in fibers, as in the Mediterranean and Nordic diet, or because fruits, vegetables, and whole cereals were promoted (Russell et al. 2011; Christensen et al. 2013; Fava et al. 2013; Lappi et al. 2013; Vitaglione et al. 2015; Haro et al. 2016a, 2016b, 2017; Kopf et al. 2018; Mayengbam et al. 2019; Roager et al. 2019; Fragiadakis et al. 2020; Meslier et al. 2020). These results indicated a metabolic shift that included important changes in carbohydrate metabolism. Subjects with a higher abundance of *Bacteroides* appeared to have lower fiber- degrading potential than the *Prevotella* abundant subjects (Christensen et al. 2013; Vuholm et al. 2017; Hjorth et al. 2018). In line with this, in cross-sectional studies vegans and vegetarians had an abundance of Prevotellaceae, Ovo-Lacto vegetarians were characterized by the presence of *Prevotella micans*, *Bacteroides vulgatus,* and *Faecalibacterium prausnitzii*, and they presented the highest abundance of microbial carbohydrate- and protein-hydrolyzing enzymes (Ferrocino et al. 2015; De Angelis et al. 2020). The distinction in *Prevotella* abundance might help explain metabolic differences in response to a fiber-rich, whole-grain diet among people with metabolic diseases, and should be one of the first microbiota signatures to exploit large clinical trials on tailored nutrition. Furthermore, they are in line with the involvement of the Firmicutes/Bacteroidetes ratio in the obesity phenotype, likely related to usual diet composition, among the pathophysiological mechanisms (Ley et al. 2006; Cani 2019). However, by the analyzing data deriving from of all the papers we summarized, it appears clear that this ratio is too general to be considered a hallmark of obesity. Host's characteristics and dietary interventions have a strong influence, frequently ignored in observational studies on obesity, and signatures of obesity are not consistent when the data are analyzed with consistent methods (Walters, Xu, and Knight 2014; Sze and Schloss 2016; Magne et al. 2020; Manor et al. 2020). Herein, most of the studies are burdened by confounding factors masked by the genetic traits for niche competitiveness between Firmicutes and Bacteroidetes sp. as determined by advanced phylogenetic assessments though shotgun sequencing (Bradley, Nayfach, and Pollard 2018).

In agreement with these considerations, moving from generalized categories, to species and genus levels, *Parabacteroides distasonis*, *Roseburia* sp., *Rumninococcus* sp., and *Eubacterium rectale* showed also a relative increased abundance after the MD or diets rich in fibers (Walker et al. 2011; Russell et al. 2011; Salonen et al. 2014; Haro et al. 2016a, 2016b, 2017; Vuholm et al. 2017; Kopf et al. 2018; Meslier et al. 2020; Johnstone et al. 2020). Similarly to *Prevotella*, *Roseburia*, *Rumnicoccus*, and *Eubacterium rectale*, belonging of the phylum Firmicutes, and *Parabacteroides distasonis*, belonging from *Bacteroides*, are known to ferment complex polysaccharides entering the colon to butyrate or succinate and acetate as a terminal product (Hillman et al. 2020; Ezeji et al. 2021; Steimle et al. 2021), and have demonstrated decreased in low-carb diets dependently by the carbohydrate total amount in cross-sectional studies (Duncan et al. 2007; Russell et al. 2011). Furthermore, *Roseburia* was strongly associated with a high Alternate Healthy Eating Index and Mediterranean Diet Score and a high intake of fruits, vegetables, legumes, and whole grains in the Cooperative Health Research in the Region of Augsburg (KORA) FF4 study (Breuninger et al. 2021). All these species seem to be a master signature of healthy diets, although their abundance could be modulated by the preexistent microbiota as well as mechanisms of resilience to return to an obesity microbiota phenotype (Xu and Knight 2015; Fragiadakis et al. 2020).

Interestingly, *Faecalibacterium prausnitzii* increased both after diets rich in fibers, including the MD (Lappi et al. 2013; Ferrocino et al. 2015; Haro et al. 2017; Roager et al. 2019; De Angelis et al. 2020; Meslier et al. 2020; Johnstone et al. 2020), and diets high in fats (Fava et al. 2013). *F. prausnitzii*, belonging to the Ruminococcaceae family (Clostridium cluster, Firmicutes), is one of the most abundant commensal bacteria, and was found to be a characteristic species also in subjects who followed a vegetarian diet (Ferrocino et al. 2015; De Angelis et al. 2020), in line with our results on fibers, and has recently been shown having the probiotic ability to produce vitamin B12 and hydrolyze lactulose and galacto-oligosaccharides increasing the content of fructose into the gut to support colonic epithelium growth (Cecchini et al. 2013; Fagundes et al. 2021). It has also been recognized as one of the most abundant butyrate producers in human feces (Cecchini et al. 2013). Since no more data than those in the papers we reviewed explain a role or modulation in relation to the dietary fat content, cross-feeding interactions with other species could be hypothesized (Kim 2020).

Although most of the reviews discussed the role of changes in SCFA production to drive some bacterial metabolic effects, we failed to observe a significant change in their quantity or balance in studies on the MD despite the fibers (Fava et al. 2013; Haro et al. 2016a, 2016b, 2017; Meslier et al. 2020). These findings suggest that the modulation of gut microbiota composition we discussed before may have a neutral effect. Phylogenetic changes may be functionally compensated for main metabolic end-products because other primary sources as amino acids could be used for SCFA production. On the other hand, SCFA decreased more often after dietary models were rich in fibers (Salonen et al. 2014; Vuholm et al. 2017; Mayengbam et al. 2019). Since fibers are known to increase SCFA production (Cummings and Macfarlane 1991), these findings in certain studies could result from a threshold effect of fiber intake or specific fiber subgroups that could differently modulate higher fermentation in the proximal colon, reduced fermentation in the distal one, or changes in the transit rate time (Govers et al. 1999). Unfortunately, the papers did not contain enough details to be conclusive on this point.

Two out of three studies evaluating bile acids reported a decrease in the content of both primary and secondary forms in stools after diet or foods rich in fibers (Haro et al. 2016b; Mayengbam et al. 2019; Meslier et al. 2020). Bile acids are synthesized from cholesterol and excreted through the stools. These findings in patients with obesity are in line with the demonstration that mixed fibers diluted bile acids by increasing fecal mass and transit time (Woodbury and Kern Jr, Woodbury and Kern 1971), and contrasting data could result from the content of insoluble fibers in the patients' diet. The decrease in bile acids could be also related to a reduction in meat consumption when fibers were increased (Draper et al. 2018).

In general, the concordant decreased concentrations of BCFAs and the better metabolism of some phenolic compounds (Russell et al. 2011; Vitaglione et al., 2015; Desai et al. 2016; Beaumont et al. 2017; Mayengbam et al. 2019; Roager et al. 2019; Johnstone et al. 2020; Meslier et al. 2020; Benítez-Páez et al. 2021) suggested that both the MD and the healthy regimens could improve the inflammatory state of subjects with obesity and that some effects of diets are driven by microbiota functions.

Interestingly, microbiota composition at baseline or after interventions was associated with clinical and metabolic characteristics of the host.

Weight and weight decrease (BMI, waist circumference, trunk fat depending on the studies) was strongly associated with *Prevotella* abundance, mainly in the context of a high fiber diet (Fava et al. 2013; Christensen et al. 2013; Desai et al. 2016; Hjorth et al. 2018, 2020; Grembi et al. 2020; Benítez-Páez et al. 2021). Hjorth and coworkers proposed that *Prevotella*, in particular *Prevotella copri* – dominant in high-P/B subjects - has a greater potential to ferment dietary fiber than the low P/B subjects instead who had high abundances of *Bacteroides* spp. Moreover, an inverse association of the *Prevotella* genus with android fat post-weight-loss in older individuals, and an increased abundance of *P. copri* in high-responders was observed. Furthermore, subjects with a high P/B ratio lost more weight also in a low-carb diet regimen and regained less weight in the follow-up than those with a low P/B abundance (Hjorth et al. 2018, 2020). These results clearly indicated a post-weight-loss metabolic shift that included important changes in carbohydrate metabolism. In agreement with these findings, as stated before, other authors reported that subjects associated with a higher percentage of *Bacteroides* appeared to have lower fiber-degrading potential than the higher abundant *Prevotella* subjects (Vieira-Silva et al. 2019). This distinction might help to explain weight and metabolic differences in response to a fiber-rich, whole-grain diet.

The mechanisms through which *Prevotella* sp. could act on weight balance are still a matter of debate. *Prevotella* abundant patients may produce higher levels of SCFAs, propionate and succinate metabolism, that contribute to greater weight loss (Hjorth et al. 2020). Propionate is formed almost completely through the succinate pathway, characteristic of Bacteroidetes, including *Prevotella* (Reichardt et al. 2014; Precup and Vodnar 2019) and has been shown to be metabolized mainly in the liver. Its implication in reducing serum cholesterol and decreasing hepatic lipogenesis, acting on anti-inflammatory pathways, and preventing weight gain in overweight adult humans has been hypothesized based on consistent data in rodents (Chambers, Morrison, and Frost 2015). Furthermore, the potential role of propionate in enhancing satiety (Arora and Sharma 2011) is of increasing interest. Enhancing propionate production in the colon through dietary intervention with non-digestible carbohydrates is an attractive approach for increasing satiety and maintaining health and weight; however, in-depth knowledge of propionate producers within the gut microbiota is required for the development of tailored dietary strategies (Reichardt et al. 2014). Furthermore, very recently, a short intervention trial giving arabinoxylan-oligosaccharides to subjects with overweight has demonstrated that in individuals with low

P/B ratio the prevalence of Bacteroides cellulosilyticus was the main predictor of body weight gain during the fiber rich diet and had an impact on host metabolism, mainly cholesterol levels, without changes in SCFAs (Christensen et al. 2020). Indeed, information beyond genus level could help in explaining mechanisms.

Weight was also negatively associated with genera *Lachnospira* and *Oscillospira*, whereas *Faecalibacterium*, *Clostridiales*, and *Clostridium* were positively associated with it in our results (Fava et al. 2013; Mayengbam et al. 2019). Although the studies we selected focused on these bacterial species, other components of the microbiota resulted to be associated with bodyweight loss in observational studies.

Dhakal and coworkers recently observed that high-responder subjects to losing weight with retail programs had a different abundance of *Bacteroides eggerthii*, *Akkermansia muciniphila*, *Turicibacter* sp., and *Christensenella* sp. (Dhakal, McCormack, and Dey 2020). Moreover, other species such as *Lactobacillus* and *Bifidobacterium* are currently used as probiotics and consumed for health promotion, including weight loss, although the evidence is still anecdotic or conflicting (Guazzelli Marques et al. 2020; Vallianou et al. 2020; Solito et al. 2021). All these findings suggest that microbiota composition is related to weight, but specific dietary interventions seem to modulate more frequently some phyla and, more importantly, species in obesity. Further studies are needed in populations with different microbiota signatures as well as studies with shotgun sequencing techniques to provide further insights and obtain consensus signals supporting a coherent and noteworthy association between diet, gut microbiota and health (Walters, Xu, and Knight 2014; Sze and Schloss 2016; Bradley, Nayfach, and Pollard 2018; Magne et al. 2020; Manor et al. 2020).

In contrast with data on weight, an improvement in insulin resistance in subjects on the MD was related to a decrease in *Prevotella copri* (Meslier et al. 2020) in line with other authors that reported a detrimental role of it on glucose metabolism and insulin resistance (Pedersen et al. 2016). On the other hand, a Swedish, high-fiber, barley-kernel intervention was found to improve glucose metabolisms among subjects with high *Prevotella* abundances, and *P. copri* was highly abundant in the metagenome of responders, probably because it promotes glycogen storage into the liver (Kovatcheva-Datchary et al. 2015), and similar findings have been reported recently in the PREDICT-1 study (Asnicar et al. 2021). These differences could be linked to the nature of the studies (randomized vs observational), the selected cohorts, and the diet-driven selection on *P. copri* machinery. It has been shown that *P. copri* strains related to an omnivorous diet have a high prevalence of genes involved in the branched-chain amino acid synthesis, a risk factor for glucose intolerance, and type 2 diabetes mellitus (Tett et al. 2021; Beaumont and Blachier 2020). This hypothesis is in line with the better metabolism of some phenolic compounds after a MD discussed before (Russell et al. 2011; Vitaglione et al., 2015; Beaumont et al. 2017; Mayengbam et al. 2019; Roager et al. 2019; Johnstone et al. 2020; Meslier et al. 2020). To help in clarifying all these results, a recent study has shown that *P. copri* is not a monotypic species but encompasses four distinct clades (A, B, C, and D) with functional diversity in carbohydrate metabolism (Fehlner-Peach et al. 2019; Tett et al. 2019). Since western diet demises its abundance, *P. copri* seems to confer a host metabolic benefit under a fiber-rich diet, but not if fats are abundant (Pedersen et al. 2016; Fehlner-Peach et al. 2019; Tett et al. 2019). These data shed light on the pivotal role also of the source and subtype of macronutrient substrates and considering them in studies will contribute to pitch microbiota-diseases signatures (Fehlner-Peach et al. 2019; Tett et al. 2019), as also discussed before regarding *B. cellulosilyticus* (Christensen et al. 2020). On the other hand, the apparently discrepant results about *Prevotella* abundance on weight and *P. copri* on the glucose metabolism stress again the interpretative bias caused by different methodologies and the lack of correspondence with health of too generalist microbial categories.

A decrease in *Holdemania* was associated with amelioration in glucose levels during an oral glucose tolerance test on pea fiber diet (Mayengbam et al. 2019), in agreement with another report (Lippert et al. 2017). *Holdemania*, a Firmicutes belonging to the family *Erysipelotrichaceae*, is capable of fermenting sugars such as fructose, glucose, and sucrose but not complex carbohydrates including polyols or starch (Willems et al. 1997). It also contributes to the breakdown of the mucin layer (Raimondi et al. 2021). We can hypothesize that a diet rich in fibers favors species with metabolism for complex carbohydrates with a parallel drop of relative abundance of others as *Holdemania* that could contribute to the absorption and metabolism of sugars and leaky gut. Furthermore, generally healthy dietary patterns were associated with a reduction of inflammatory markers. These findings are all concordant with other research indicating that the modification of the microbiota in various diseases, in these cases diet-driven, can blunt inflammation and improve the metabolic profile, with a signature related to the disease and the intervention (Barber et al. 2021).

Last, subjects with the worse metabolic profile at the starting of the trials were those who presented the most significant taxonomic changes and parallel metabolic improvement (Haro et al. 2016b, 2017). This means that subjects with the worse phenotype are those characterized by a more pronounced reduction in the abundance of genera with saccharolytic activity, which likely leads to the production of energy from amino acids and, therefore, branch chain amino acids that impair glucose metabolism as discussed before. These results strengthen the importance of strongly promoting chances in lifestyle habits in subjects with obesity and related diseases.

Some limits exist regarding our data since populations and dietary intervention are heterogeneous, but the risk of bias was generally low. Most of the currently published papers are observational and often conflicting. Controlled clinical interventions are spare, but this review aimed to organize the body of evidence on microbiota deriving from dietary trials in adult obesity giving the most certain signatures that should lead to further studies.

In conclusion, our findings support the importance of tailored dietary approaches to improve host metabolism as well as microbiota composition and function in obesity. Some phyla and species are more strictly related to diets rich in fibers and others to healthy diets. Changes in weight and metabolism are related to different microorganisms or functions and should be approached with in-depth further trials. The Firmicutes/Bacteroidetes ratio, so cited in many observational studies on obesity, is frequently a wrong or misleading conception to provide any association with health status, due to lack of the evaluation of masked factors, first of all diet and niche competitiveness. We encourage researchers to use more specific metrics, focusing on genus and species levels, and ever consider diet. Deeply identifying associations among host lifestyle factors, health, and microbiota signatures at genus and species levels can enable to design the roadmap of personalized interventions and clinical trials. These data emphasize the possibility of using a symbiotic approach involving both tailored diet, microbiota changes, and maybe drugs to treat obesity and metabolic disorders.

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