doi: 10.1111/obr.12541

Etiology and Pathophysiology

Weight-loss interventions and gut microbiota changes in overweight and obese patients: a systematic review

F. B. Seganfredo,[1] C. A. Blume,[2] M. Moehlecke,[2] A. Giongo,[3] D. S. Casagrande,[4] J. V. N. Spolidoro,[5] A. V. Padoin,[1,4,5] B. D. Schaan[6] and C. C. Mottin[1,4,5]

[1]Medicine and Health Sciences Post-Graduate Program, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brazil, [2]Post-Graduate Program in Medical Sciences: Endocrinology, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, [3]Instituto do Petróleo e dos Recursos Naturais, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brazil, [4]Centro de Obesidade e Síndrome Metabólica, Hospital São Lucas da PUCRS, Porto Alegre, Brazil, [5]Faculty of Medicine, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brazil, and [6]Faculty of Medicine and Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Received 11 December 2016; revised 14 February 2017; accepted 27 February 2017

Address for correspondence: FB Seganfredo, Medicine and Health Sciences Post-Graduate Program, Pontifícia Universidade Católica do Rio Grande do Sul, Av. Ipiranga, 6690 – Prédio 60 – Partenon – Porto Alegre, RS 90610-000, Brazil.
E-mail: fbseganfredo@gmail.com

Summary

Imbalances in the gut microbiota, the bacteria that inhabit the intestines, are central to the pathogenesis of obesity. This systematic review assesses the association between the gut microbiota and weight loss in overweight/obese adults and its potential manipulation as a target for treating obesity. This review identified 43 studies using the keywords 'overweight' or 'obesity' and 'microbiota' and related terms; among these studies, 17 used dietary interventions, 11 used bariatric surgery and 15 used microbiota manipulation. The studies differed in their methodologies as well as their intervention lengths. Restrictive diets decreased the microbiota abundance, correlated with nutrient deficiency rather than weight loss and generally reduced the butyrate producers Firmicutes, *Lactobacillus sp*. and *Bifidobacterium sp*. The impact of surgical intervention depended on the given technique and showed a similar effect on butyrate producers, in addition to increasing the presence of the Proteobacteria phylum, which is related to changes in the intestinal absorptive surface, pH and digestion time. Probiotics differed in strain and duration with diverse effects on the microbiota, and they tended to reduce body fat. Prebiotics had a bifidogenic effect and increased butyrate producers, likely due to cross-feeding interactions, contributing to the gut barrier and improving metabolic outcomes. All of the interventions under consideration had impacts on the gut microbiota, although they did not always correlate with weight loss. These results show that restrictive diets and bariatric surgery reduce microbial abundance and promote changes in microbial composition that could have long-term detrimental effects on the colon. In contrast, prebiotics might restore a healthy microbiome and reduce body fat.

Keywords: Bariatric surgery, microbiota, obesity, weight loss.

Abbreviations: BF, body fat; BIB, bilio-intestinal bypass; BMI, body mass index; BP, blood pressure; BW, body weight; CRC, colorectal cancer; DBP, diastolic blood pressure; DGGE, denaturing gradient gel electrophoresis; F/B ratio, Firmicutes to Bacteroidetes ratio; FBG, fasting blood glucose; FBI, fasting blood insulin; FISH, fluorescence *in situ* hybridization; GB, gastric banding; LSG, laparoscopic sleeve gastrectomy; NRCT, non-randomized clinical trial; qPCR, quantitative polymerase chain reaction; RCT, randomized clinical Trial; RoB, risk of bias [Cochrane Collaboration's tool]; RoBANS, risk of bias assessment tool for nonrandomized studies; RYGB, Roux-en-Y gastric bypass; SBP, systolic blood pressure; SCFA, short-chain fatty acids; SD, standard deviation; TC, total cholesterol; TG, triglycerides; T2DM, type 2 diabetes mellitus; VBG, vertical banded gastroplasty; WC, waist circumference.

Introduction

Overweight and obesity, which are defined as excessive body fat accumulation (1), constitute a global epidemic. According to the World Health Organization, more than 1.9 billion adults were overweight in 2014, and of these, more than 600 million were obese (1). The obesity epidemic is related to several health-threatening diseases, such as arterial hypertension, type 2 diabetes mellitus [T2DM], dyslipidaemia, coronary heart disease [CHD], stroke, asthma and arthritis, among others (2). Furthermore, this condition has important economic impacts, increasing medical costs for the treatment of related conditions and indirectly causing reduced productivity, disabilities and premature mortality (3).

Classically, obesity has been attributed to an excessive caloric intake along with a sedentary lifestyle (4). Other factors include genetic predisposition, increasing maternal age, sleep deprivation, endocrine disruptors, pharmaceutical iatrogenesis and epigenetics (5). More recently, the gut microbiota, which is made up of the collection of microorganisms that inhabits human intestines, has been implicated in the aetiology of obesity (6). These bacteria play an important role in physiological processes such as digestion and metabolism, and they are suggested to participate in obesity and metabolic disorder development because they are able to increase energy production from the diet, induce low-grade inflammation, regulate the fatty acid tissue composition and participate in appetite regulation through the gut–brain axis (7–10).

Many pre-clinical and clinical studies have related the gut microbiota to obesity. Animal data have shown that germ-free mice are resistant to obesity, and, upon the introduction of gut microbes, the animals are likely to increase their caloric uptake and develop fat deposition and insulin resistance (11,12). Furthermore, mice that were colonized with gut microbiota from obese mice harvested energy more efficiently and developed body fat more quickly (13). The sequencing of the gut microbiota using the 16S rRNA gene from the distal intestine in mice showed a distinct pattern between lean and obese animals with regards to the two major bacterial phyla, Firmicutes and Bacteroidetes. A proportional reduction in Bacteroidetes, along with an increase in Firmicutes, was observed in the obese population (14). Clinical studies also support the link between gut microbiota and obesity, and although the differences at the phylum level between lean and obese individuals are conflicting (15,16), other microbiota features have been suggested to interfere with weight responses to interventions (17,18). Thus, the association between microbiota and obesity exists, yet the causative versus consequential association and the magnitude of its contribution in humans, remains unclear.

Among the therapeutic options for addressing obesity, lifestyle modifications [diet, physical activity and behavioural therapy], pharmacological treatment and, for severe cases, surgical intervention are currently available. Lifestyle modifications alone promote a long-term weight loss of 5–10% of the original weight, although there is a tendency to regain 30–50% of the lost weight within the first year and the remaining weight during the second year (19). Pharmacological therapy can also promote modest weight loss, but the majority of drugs are limited due to side effects and a lack of compliance (20). Bariatric surgery is currently the most effective option for the long-term treatment of severe obesity, promoting significant weight loss and mortality reduction (19). Despite its relative effectiveness, a significant number of patients experience poor weight-loss outcomes, and long-term weight regain can reach up to 75% (21,22). Therefore, further approaches are needed to overcome those issues and help patients to reduce and maintain a healthy weight. In that respect, gut microbiota manipulation might represent a novel target, as such an approach has been associated with sustainable weight loss (23).

Although the interplay between the gut microbiota and weight modifications in overweight and obese populations is currently a topic of interest, the interaction between these factors remains unclear. This systematic review assesses the association between the gut microbiota, weight-loss treatments and metabolic outcomes in overweight and obese adults and its potential manipulation as a target to treat obesity.

Methods

Protocol and registration

The protocol for this systematic review was registered on PROSPERO [CRD42015030003] and is fully available on the NIHR HTA program website [http://www.crd.york.ac.uk/PROSPERO].

Eligibility criteria

Studies were selected on the basis of the following criteria: observational studies with weight-loss interventions [quasi-experiments] or clinical trials that evaluated the gut microbiota of overweight or obese adults [≥18 years old]. Overweight and obesity were defined by body mass index [BMI] and were dependent on patient ethnicity. Weight-loss interventions included dietary interventions, bariatric surgery and pre-, pro- or symbiotics use.

Information sources

The following electronic databases were assessed, covering studies that were published up until November 2016:

MEDLINE [as accessed by PubMed], EMBASE, Science Direct, the Cochrane Central Register of Controlled Trials and LILACS. No date or language restriction was used while conducting this search.

Search strategy

No systematic reviews addressing this research question were available in MEDLINE [via PubMed] or the Cochrane Database at the beginning of this study. During this search, the terms for 'obesity' and 'microbiota' were obtained. To amplify our search strategy, no terms referring to interventions or controls were used. In December of 2015 [and updated in November 2016], database searches were performed using the terms 'overweight' or 'obesity' and 'microbiota' or 'microbiome' and related terms to obtain the broadest possible results [see Table S1: Search Strategy]. Potentially eligible papers were searched by screening reference lists and grey literature.

Study selection

Duplicates were manually identified and excluded. The articles were then analysed using the following two-step procedure. First, titles and abstracts that were retrieved from our literature search were independently analysed by two reviewers on the basis of inclusion/exclusion criteria. Then, all of the included articles were subjected to another analysis of their full text, and the eligible articles were identified. Disagreements were resolved by consensus-based discussion or by a third reviewer's opinion. The agreement between the reviewers was assessed using Cohen's kappa coefficient (24).

Data extraction and quality assessment

Two reviewers independently extracted data from each study using an extract table template. The extracted data were as follows: identification of the study, population description, study design, intervention details and outcomes. The primary outcome was a gut microbiota assessment (for total bacterial abundance, richness, alpha and beta diversity, and bacterial taxonomic composition [phylum, genus and species]). Secondary outcomes included anthropometric and clinical outcomes. A third reviewer assessed all of the studies for the completeness of their data extraction.

To assess the internal quality of the studies, the Cochrane Collaboration's tool for assessing the risk of bias [RoB] was used for each randomized clinical trial [RCT] (25). The following areas were assessed: sequence generation, allocation concealment, the blinding of participants and personnel, the blinding of outcomes, incomplete outcome data, selective reporting and other bias. Each domain was graded as having a low, unclear or high RoB. For non-randomized studies [NRCTs], the Risk of Bias Assessment Tool for Nonrandomized Studies [RoBANS] was used (26). The RoBANS included an evaluation of the participant selection, confounding variables, measurements of exposures, blinding of outcomes, incomplete outcome data and selective reporting. The assessment of the RoB was made according to the RoBANS criteria, and each criterion was graded as having a low, unclear or high RoB.

Data synthesis and analysis

This review summarizes the available results from the literature about gut microbiota changes related to weight loss in obese and overweight populations. A narrative synthesis is presented.

Results

Literature search

Overall, we identified 7,311 records, and after excluding the duplicates and non-eligible titles, 43 original articles were included. A detailed flowchart showing the study selection process is presented in Fig. 1. The inter-rater agreement as calculated by Cohen's kappa coefficient was 0.9. We classified studies based on intervention type as follows: (i) dietary; (ii) surgical and (iii) microbiota interventions [pre-, pro-, symbiotics]. The results are presented according to this classification.

General characteristics of the studies

The primary characteristics of the 43 included studies are described in Tables 1, 2 and 3. Seventeen of the studies evaluated dietary interventions, 11 involved surgery and 15 addressed specific therapeutics relating to the gut microbiota. Twenty-five [59%] of the included studies were published in the last 3 years. Distinct study designs were found, with 17 RCTs [40%], 15 NRCTs [35%], 8 quasi-experiments [20%] and 2 [5%] observational studies with cross-sectional designs. Geographically, 27 [65%] of the studies were performed in Europe, 10 [23%] in Asia and 5 [12%] in North America. Considering the patient selection, 25 [60%] studies had no gender limit, 11 [26%] included only women and 6 [14%] included only men. The ages of the included patients varied between 19 and 73 years old. The intervention type and setup were highly diverse among the trials, and the lengths of the interventions varied from 7 to 52 weeks, with a follow-up of up to 2 years. In all of the studies, a baseline assessment of the gut microbiota was obtained, and microbial composition changes were reported as outcomes.

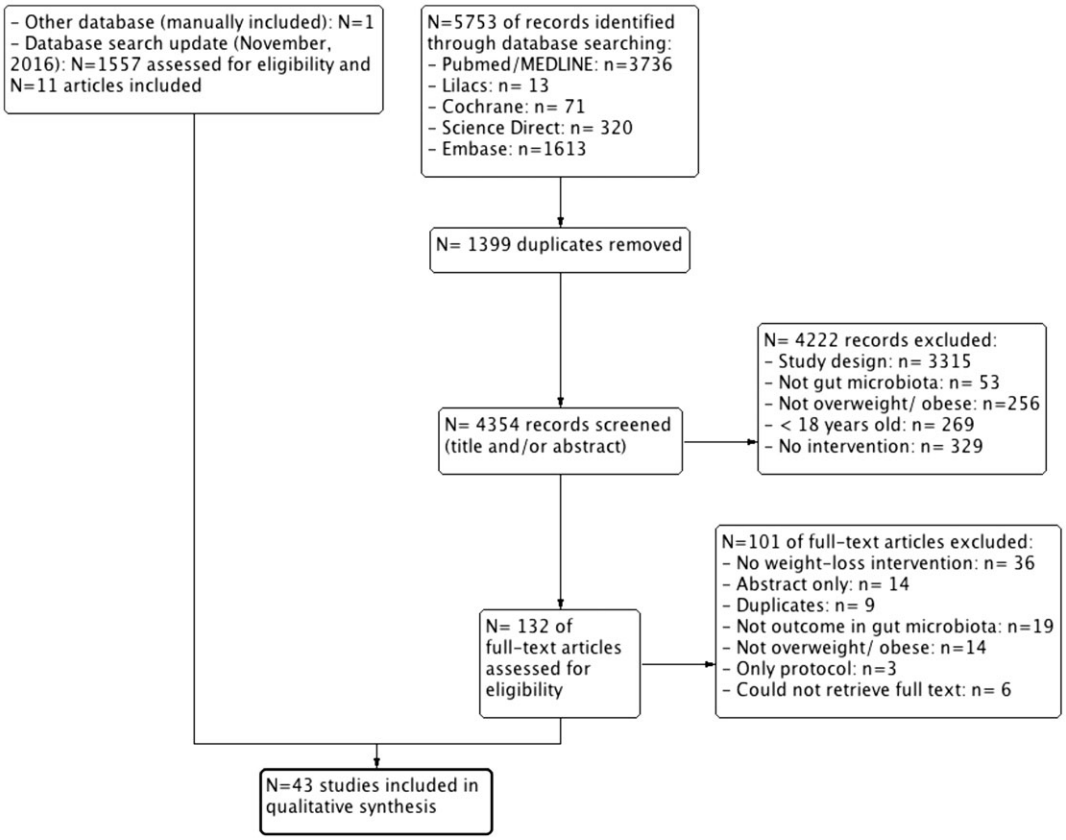

Figure 1 Study flow diagram for study selection.

Several molecular biology techniques were used to assess the gut microbiota, and some studies employed more than one approach. Five studies [11%] obtained a microbial community fingerprint using denaturing gradient gel electrophoresis [DGGE], 20 studies [46%] used at least one technique for targeted analysis (fluorescence *in situ* hybridization [FISH] using probes or group-specific real-time [quantitative] polymerase chain reaction [qPCR]), 13 studies [30%] performed metabarcoding 16S rRNA and 10 studies [23%] used metagenomics [shotgun sequencing]. Furthermore, one study used a computational analysis with the CASINO tool to predict microbial responses to dietary interventions, and others involved a HITChip analysis. In addition to assessing microbial richness and taxon profiles, some of the studies also reported microbiome measures of microbial metabolites and metabolic pathway expression that are beyond the scope of this review and therefore will not be discussed here. Further details on the molecular biology techniques used in the included studies are available in the supplementary material [See Table S2: Molecular Biology Techniques].

-Dietary interventions *(*Table 1 – *Extended version available [see Table S3])*:

This review included 17 studies on 11 different clinical trials that evaluated changes in gut microbiota following dietary interventions for weight loss. Of those trials, only five [45%] were RCTs (16,27–30). The number of patients included in each trial varied between 12 and 56 (average: 30, standard deviation [SD]: 16).

The composition of the gut microbiota was assessed through different techniques. Among the 11 included trials, 1 [9%] used only DNA targeted probes [FISH] (29), 3 [28%] used only metabarcoding 16S rRNA (16,28,31), 3 [28%] used only shotgun sequencing (27,32,33) and the 4 [36%] remaining trials combined techniques including the aforementioned ones, namely species-specific qPCR, DGGE and computational tools (18,30,34,35).

The first trial to evaluate the impact of a weight-loss intervention [low-fat vs. low-carbohydrate diets] on the gut microbiota was published in 2006, and the results showed no changes in bacterial abundance (16). However, marked interpersonal differences in the bacterial composition were described, in addition to percentage reductions in the frequency of the Firmicutes phylum along with increases in the Bacteroidetes phylum, which correlated with weight loss (16). Following this finding, several similar trials were performed.

Considering all of the included trials with dietary interventions, the total bacterial abundance was assessed in only six trials. Within those, five performed hypocaloric

Table 1 Characteristics of studies with dietary interventions

Study	Intervention		Population		Outcomes	
Identification	*Description*	*Follow-up*	*n*	*Description*	*Microbiota*	*Anthropometry*
Ley et al., 2006	Fat-restricted versus carbohydrate-restricted diet	52 weeks	14	Sex: 64% female BMI: 30.0–43.0	Marked interpersonal differences [70% unique to each person] with remarkably constancy. Both diets had no impact on bacterial abundance, ↓Firmicutes, ↑Bacteroidetes [correlated to percentage loss of body weight].	——
Duncan et al., 2007 φ	3 to 7-day weight maintenance, 8-week diets [4 weeks each]: high protein low carb, ketogenic [LC] or high protein moderate carb [MC]	9 weeks	20	Sex: 100% male BMI: 35.4 ± 0.9	Weight-loss diets: ↓Total bacterial count; No impact on *Bacteroides* or *Clostridium* cluster XIVa, IX or I, but ↓subgroup *Roseburia* spp. and *E. rectale* subgroup of cluster XIVa and *Bifidobacterium* along with ↓carbohydrate intake.	-LC diet: ↓5.8%BW, ↓13.3% BF -MC diet: ↓4.0%BW, ↓10.5% BF
Duncan et al., 2008 φ			23	Sex: 100% male BMI: 20.0–44.0	Weight-loss diets [LC and MC]: ↓Total bacterial count; Phylum: no impact on Bacteroidetes or Firmicutes abundance; however, ↓in Butyrate-producers within this phylum [*Roseburia spp.* + *E. rectale* group, belonging to *Clostridium*], especially with LC; ↓*Bifidobacterium*.	-LC diet: ↓5.8%BW, ↓13.3% BF -MC diet: ↓4.0%BW, ↓10.5% BF
Russel et al., 2011 φ			17	Sex: 100% male BMI: 36.1 ± 5.6	↓Total bacterial count and ↓butyrate-producers *Roseburia spp./E. rectale group* [*Lachnospiraceae*], although no difference in *F. prausnitzii* [second main butyrate producer].	-LC diet: ↓5.7% BW -MC diet: ↓3.5% BW
Walker et al., 2011η	1-week weight maintenance, 6-week diets [3 weeks each]: resistant starch [RS] or non-starch polysaccharides [NSPs], 3-week hypocaloric diet with high protein and moderate carb [WL]	10 weeks	14	Sex: 100% male BMI: 39.3 ± 1.4	Bacterial composition profiles were consistent over time within an individual for a given diet. -RS diet: ↑*Clostridium* Cluster IV [*Ruminococcaceae*], *E. rectale* and *Roseburia spp.* [Firmicutes]. -WL diet: ↓*E. rectale*, *Roseburia spp.* [Firmicutes] and *Collinsella aerofaciens* [Actinobacteria]. -No dietary impact on bacterial or archaeal phylum level composition or on *F. prausnitzii*, *Bifidobacterium*, *Bacteroides*.	——
Salonen et al., 2014 η					-RS diet: ↓Bacterial abundance and alpha-diversity, ↑*Clostridium* Cluster IV [*Ruminococcaceae*], ↓*Clostridium* Cluster XIVa. -NSP diet: ↑Actinobacteria, *Lachnospiraceae*, *Bacteroides vulgatus*, *Prevotella oralis* and ↓*Ruminococcaceae*. -WL diet: ↓microbial abundance, ↓*Bifidobacterium*, ↑*Lactobacillus*. -RS and WL diets: Overall, individual variation was more important than diet-responsive variation, which were higher in individuals with lower baseline microbial diversity.	—

(*Continues*)

Table 1 (Continued)

Study	Intervention		Population		Outcomes	
Identification	*Description*	*Follow-up*	*n*	*Description*	*Microbiota*	*Anthropometry*
Cotillard et al., 2013 δ	6-week hypocaloric, high protein, low carb, fibre enriched + 6-week weight maintenance -Subgroups based on bacterial diversity: low gene count [LGC] or high gene count [HGC]	12 weeks	49	Sex: 84% female BMI: 33.2 ± 0.5	- Baseline: LGC – 40%, HGC – 60%. Identification of 18 bacterial clusters, all more abundant in HGC individuals. -Post-intervention: ↑bacterial diversity in LGC individuals. Species: ↓*E. rectale* and *Bifidobacterium spp*. Majority of bacterial cluster suffered transient abundance changes during the intervention, but some changes that favour similarity of LGC to HGC were persistent.	↓5.8% BW, ↓5.4%WC, ↓3.5% BF*
Kong et al., 2013 δ	6-week hypocaloric, high protein, low carb, fibre enriched + 6-week weight maintenance -Subgroups based on weight trajectory: A, B lost more weight during energy restriction; A continued loosing, B remained stable at stabilization. C lost less weight and rapidly regained.		50	Sex: 84% female BMI: 27.0–38.0	-Baseline: *Lactobacillus*/*Leuconostoc*/*Pediococcus* group was most abundant in cluster C. No differences in *C. leptum*, *C. coccoides*, *Bacteroides*/*Prevotella*, *Bifidobacterium*, *E. coli* and *F. prausnitzii* were observed between groups.	Month 12 [t0–12]: -A: ↓10% BW, ↓9.2% WC, ↓2.8% BF* -B: ↓5% BW, ↓6.3% BC, ↓1.9% BF* -C: ↓1.5%BW, ↓1.6% WC, ↓0.95% BF*
Shoaie et al., 2015 δ	Computational simulation of same intervention/patients as Cotillard et al. (2013)		45	Sex: 83% female BMI: 33.2 ± 0.5	-Baseline: dominance of *E. coli*, *F. prausnitzii* and 4 species associated with *Clostridium*, *Bacteroides*, *Bifidobacteria* and *Lactobacillus*. -Post-intervention: HGC individuals: ↑*B. thetaiotaomicron* and ↓*L. reuteri* and *F. prausnitzii*. LGC individuals: ↓*L. reuteri*.	—
Dao et al., 2016 δ	6-week hypocaloric, high protein, low carb, fibre enriched + 6-week weight maintenance-Subgroups: high or low *A. muciniphila* [HAk, LAk]		49	Sex: 83% female BMI: 32.5 ± 1.0 [HAk], 33.0 ± 0.9 [LAk]	-Baseline: 70% of the species were more abundant in HAk. -Post-intervention: HAk group had ↓*A. muciniphila*.	-Baseline: HAk versus LAk: HAk had lower waist-to-hip ratio and adipocyte size; -Post-intervention: no impact on BW between the groups.
Simoes et al., 2014	Very-low-energy diet [VLED], high protein and low carb for 6 weeks, followed by weight-maintenance diet	52 weeks	16	Sex: 62% female BMI: 34.5 ± 2.6	↓Bacterial abundance, ↓*Bifidobacterium* and *Lactobacillus* and ↑*Bacteroides*. ↓*Roseburia*/*E. rectale* group and ↓*Bifidobacterium* and ↑*Ruminococcus*. Gut microbiota changes were correlated to dietary intake and not to weight changes. High intra-individual similarity at all points.	↓9.2% BW, ↓11.4% WC, ↓7.6% BF* [&]
Remely et al., 2015	Weight maintenance, low fat and animal products, rich in fruits and vegetables	16 weeks	33	Sex: NA BMI: 46.6 ± 11.1	↑ Bacterial abundance, ↓F/B ratio, ↑*Lactobacillus*, *Clostridium* Cluster IV [↑*F. prausnitzii*], *A. muciniphila* and Archaea; ↓*Clostridium* Cluster XIVa.	↓6% BW, ↓5.5% BF[&]

(*Continues*)

Table 1 (Continued)

Study	Intervention			Population	Outcomes	
Identification	*Description*	*Follow-up*	*n*	*Description*	*Microbiota*	*Anthropometry*
Remely et al., 2016	Weight reduction diet [DACH recommendation] – insulin-dependent T2D versus obese controls versus lean controls	16 weeks	56	Sex: 57% femaleBMI: 38.4 ± 5.1 [T2DM], 33.7 ± 4.2 [obese]	No differences in total bacteria between the groups or after intervention. F/B ratio was increased in T2D compared with controls, mainly due to Clostridiales and Lactobacilli. -T2D group: intervention caused ↑relative abundance of *F. prausnitzii* and *A. muciniphila.*	—
Louis et al., 2016	52-week multidisciplinary weight-loss program, including very-low-calorie diet [VLED] fibre-enriched [3 m], gradual substitution to normal food [8 weeks], followed by weight maintenance. -Subgroups: persistent success [PS: *n* = 9] or regain/no success [NS: *n* = 7].	104 weeks	16	Sex: 56% female BMI: 43.0 ± 7.0	- Baseline: Phylum: Bacteroidetes [68%] > Firmicutes [27%] > Proteobacteria [1.7%] > Actinobacteria [1.7%] > Verrucomicrobia [1.3%]. Genus: *Bacteroides* [55%] > *Alistipes* [8.0%] > *Faecalibacterium* [6.4%] > *Eubacterium* [5.4%]. High F/B ratio variability, without BMI correlation, although higher F/B ratio value in MetS patients. Predictors of success: *Alistipes*, *Pseudoflavonifractor*, *Gordonibacter* and *Symbiobacterium.* Alpha-diversity tended to be higher in patients with lower BMI at T0 but did not correlate to weight loss at T24. - Intervention: No impact on phylum level. VLED had impact on 56 genera, but only ↑*A. muciniphila* remained stable.	-Month 6 [t0–t6]: ↓20.9% BW, ↓18.4% WC -Month 24 [t0–t24]: ↓10% BW, ↓10.4% WC - PS versus NS: PS had higher relative weight loss during caloric restriction
Pataky et al., 2016	3-week hypocaloric, high-protein diet [starch free]	6 weeks	15	Sex: 26% female BMI: 34.6 ± 2.2	No significant impact in bacterial diversity. No impact on phylum composition; significant changes in lower-level taxa belonging to the Clostridiales [↓relative abundance of *Lachnospira*, ↑relative-abundance of *Blautia*, *Butyricicoccus*]; and changes in 10 OTUs [including ↓in several OTUs of *Bacteroides*]	↓3.5% BW, ↓8% BF[&]
Candela et al., 2016	3-week Ma-Pi diet [hypocaloric, fibre-enriched macrobiotic diet] versus control diet for T2DM versus normal weight controls	3 weeks	53	Sex: 50% female BMI: 34.3 ± 6.5 [Ma-Pi], 32.1 ± 6.3 [control]	-*T2DM comparison to normal weight controls:* ↓diversity, different UniFrac distances [PCoA], revealing segregation between the two groups [mainly due to ↑relative abundance of *Enterobacteriaceae*, *Collinsella* and *Streptococcus* and ↓relative abundance SCFA producers, such as *Bacteroides*, *Prevotella*, *Lachnospira*, *Roseburia* and *Faecalibacterium*] [0.4 times less]. -Ma-Pi versus control diet: Both diets tended to increase diversity [ns], both diets were effective in counteracting the ↓*Bacteroides*, *Dorea* and *Faecalibacterium* seen T2D patients and to ↑*Akkermancia* above healthy controls abundance. Ma-Pi diet induced ↑relative proportion of *Faecalibacterium*, *Bacteroides* and *Akkermansia* and ↓relative proportion of *Lachnospiraceae*: *Ruminococcus.*	-Ma-Pi: ↓6.3%BW, WC [ns] -Control diet: ↓3% BW; WC [ns]

(*Continues*)

Table 1 (Continued)

Study	Intervention		Population		Outcomes	
Identification	*Description*	*Follow-up*	*n*	*Description*	*Microbiota*	*Anthropometry*
Haro et al., 2016	Mediterranean diet [M] versus low-fat, high-complex-carb diet [LFHC]	52 weeks	20	Sex: 100% male BMI: 32.2 ± 0.5	Proportions of main phylum were stable and similar in each subject. -M diet: *Relative abundances:* ↓*Prevotella*,↑*Roseburia* and *Oscillospira;* ↑relative abundance of *P. distasonis.* -LFHC diet: Relative abundances – ↑*Prevotella* and ↓*Roseburia*, ↑*F. prausnitzii.*	—

Equal symbols [**φ**, **δ**, **η**] identify common patients.
*BF analysis using dual energy X-ray absorptiometry [DEXA].
&BF analysis using bioelectrical impedance analysis [BIA].
Units: Age [in years] shown in range or mean ± standard deviation, BMI [kg/m^2] shown in range or mean values ± standard deviation and anthropometric parameters are shown in percentage changes.
BIA, bioelectrical impedance analysis; BF, body fat; BMI, body mass index; BW, body weight; CHD, coronary heart disease; DEXA, dual energy X-ray absorptiometry; F/B, Firmicutes/Bacteroidetes ratio; LC, low carbohydrate; MetS, metabolic syndrome; MC, moderate carbohydrate; MRI, magnetic resonance imaging; NA, not available; ns, not significant; NAFLD, non-alcoholic fatty liver disease; NSP diet, non-starch polysaccharides; RS diet, resistant starch diet; SCFA, short-chain fatty acids; T2CM, type 2 diabetes mellitus; WC, waist circumference; WL, weight loss.

interventions, which resulted in reduced total bacterial abundance in three trials [60%] (29,35,36) and no impact on bacterial abundance in the remaining two trials [40%] (16,31). The only trial that evaluated bacterial abundance after a non-hypocaloric but low-fat intervention showed an increase in bacterial abundance despite a comparable amount of weight loss (18).

Another evaluated criterion was intra-individual microbial richness [alpha diversity], as reported in four trials. Of those trials, 2 [50%] found increased richness after the dietary intervention (28,34), while the other 2 [50%] showed no impact (32,33).

Taxonomic analyses were performed in all of the included trials, although the reported results varied with respect to the use of targeted versus untargeted techniques to assess the composition profiles. The analysis of phylum composition was performed in eight trials, of which five observed no impact (15,27,30,32,33), two showed an increase in the relative abundance of Bacteroidetes along with a decrease in Firmicutes (16,18) and one trial reported the opposite effects in those phyla (31).

A species assessment was performed in 10 trials. Among those, six trials used similar interventions [hypocaloric, low carbohydrate and high protein], and all showed a reduction in *Roseburia spp.*, *Eubacterium rectale* and other species belonging to the *Clostridium Cluster XIVa* as well as a reduction in the *Bifidobacterium sp.* relative abundance (15,30–32,34,35). By contrast, the only trial using a non-hypocaloric but low-fat intervention found an increase in *Clostridium Cluster IV*, *Bifidobacterium sp.*, *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* (18). Changes in *Lactobacillus sp.*, *A. muciniphila* and *F. prausnitzii* were not consistent among the studies, although we observed an increasing trend in the relative abundances of those species (18,28,30,31,33).

Among the included trials, three showed the importance of the intrapersonal microbiota composition and its consistency, despite the implementation of dietary interventions (16,35,36). In addition, a high bacterial gene count and a higher abundance of *A. muciniphila* correlated with better metabolic parameters, while the *Lactobacillus/Leuconostoc/Pediococcus* group abundance was related to a poorer profile of metabolic markers and weight regain (17,34,37). Furthermore, another trial suggested that the individual gut microbiota composition was a predictor of successful weight loss after very-low-calorie interventions, with higher frequencies of *A. muciniphila* and *Dialister* along with the abundance of *Gordonibacter*, *Alistipes* and *Symbiobacterium* being correlated with successful weight-loss maintenance (33).

As expected, carbohydrate restriction generally improved the metabolic parameters, including a reduction in the fasting blood glucose [FBG] (28,29,32–35), insulin resistance index [HOMA-IR] (29,33,34), blood lipids

Table 2 Characteristics of studies involving surgical interventions

Study	Intervention		Population		Outcomes	
Identification	*Description*	*Follow-up*	*n*	*Description*	*Microbiota*	*Anthropometry*
Zhang et al., 2009	RYGB	Interval surgery evaluation >6 m	9 [3 each: eutrophic, obese, post-op]	Sex: 66% female BMI: 48.3 ± 7.7 [obese]	Post-op [compared with eutrophic or obese]: ↑Gammaproteobacteria and ↓*Clostridium* IV, ↑*Enterobacteriaceae* and *Fusobacteriaceae*.	—
Furet et al., 2010 δ	RYGB	24 weeks	43 [30 post-op and 13 lean]	Sex: 90% female BMI: 47.6 ± 1.5	Relative abundances: ↑*F. prausnitzii*, ↓*Lactobacillus* and *Bifidobacterium*; ↓F/B ratio.	↓22.2% BW, ↓13.7% BF*
Kong et al., 2013 δ			30	Sex: 100% female BMI: 47.6 ± 1.5	↑Microbial richness estimated by Chao [58 new genera]. ↓Firmicutes [*Blautia*, *Lactobacillus* and *Dorea*], ↑Bacteroidetes [*Bacteroides*, *Alistipes*] and Proteobacteria [*E. coli*].	↓20.5% BW
Patil et al., 2012	RT [LSG or GB]	Interval surgery-evaluation: ±7 m	20 [5 each: lean, eutrophic, obese, post-op]	Sex: 40% female BMI: 15.0–53.0	Post-op: No changes in microbial abundance and diversity, ↓*Bacteroides* and Archaea.	↓20.5% BW
Graessler et al., 2013	RYGB	12 weeks	6	Sex: 50% female BMI: 41.0–52.0	Phylum: ↑Proteobacteria, ↓Firmicutes and Bacteroidetes; ↓F/B ratio; Species: ↑*E. cancerogenous*, *Veilonella*, *V. dispar*, *Salmonella* and ↓*Treponema pallidum*, *Mycobacterium*, *F. prausnitzii*, *Lactobacillus*.	↓21.1% BW
Damms-Machado et al., 2015	RT [LSG]	24 weeks	10 [5 post-LSG versus 5 very-low-calorie diet]	Sex: 100% female BMI: 45.8 ± 0.9	Post-LSG: ↑Bacteroidetes, ↓Firmicutes [↓*Clostridium* Clusters IV and XIaV], *Faecalibacterium*, *Dorea*, *Coprococcus* and butyrate producers [*E. rectale*, *Ruminococcus* and *Lachnospiraceae*] and ↓F/B ratio	Post-LSG: ↓23.9% BW, ↓19% WC
Tremaroli et al., 2015	RYGB versus VBG	Interval surgery evaluation: 9.4 years	21 [7 post-RYBG, 7 post-VBG, 7 obese controls]	Sex: 100% female BMI: 42.1 ± 4.2 [pre-RYGB], 43 ± 5.1 [pre-VBG]	Significant differences in microbiota composition for RYGB versus OBS samples, but not for VBG versus OBS or RYGB versus VBG. ↑Gammaproteobacteria, ↓Firmicutes [*Clostridium difficile*, *C. hiranonis* and *Gemella sanguinis*] in RYGB versus OBS. ↑Proteobacteria [e.g. *Escherichia*, *Klebsiella* and *Pseudomonas*] in RYGB. No differences in microbiota profiles for RYGB and VBG patients.	Post-RYGB: ↓27% BW, ↓ 18.1% BF Post-VBG: ↓18.6% BW, ↓9.1% BF
Patrone et al., 2016	BIB	24 weeks	11	Sex: 81.8% female BMI: 47.4 ± 7.4	↓Alpha diversity; ↓*Lactococcus* and Clostridiales; ↑*Enterobacter* and *Lactobacillus*; ↓Faecal pH	↓16.5% BW
Palleja et al., 2016	RYGB	52 weeks	13	Sex: 61.5% female BMI: >35.0	Tendency to ↑richness, especially in the first 3 months; changes on beta diversity; ↑Proteobacteria and Fusobacteria; Changes in 19 species, including ↑*Escherichia coli*, *Klebsiella pneumoniae*, 10 species from *Streptococcus*, 4 from *Veillonella*, 2 from *Alistipes*, *Bifidobacterium dentium*, *Enterococcus faecalis*, *F. nucleatum* and *Akkermansia muciniphila*; besides ↓in *F. prausnitzii*	↓21.7% BW
Murphy et al., 2016	RYGB and LSG	52 weeks	14	Sex: 42% female BMI: 38.4 ± 5.2 [RYGB], 36.9 ± 5.1 [LSG]	Greater relative abundance of Actinobacteria at baseline and increase in *Roseburia* after surgery correlated with T2DM remission. -RYGB: ↑diversity, major impact on microbial composition including ↑Firmicutes and Actinobacteria and ↓Bacteroidetes. -LSG: no impact on diversity; ↑Bacteroidetes.	-RYGB: ↓27% BW -LSG: ↓20.5% BW

(*Continues*)

Table 2 (Continued)

Study	Intervention		Population		Outcomes	
Identification	*Description*	*Follow-up*	*n*	*Description*	*Microbiota*	*Anthropometry*
Federico et al., 2016	BIB	24 weeks	56 [28 normal weight controls, 28 obese]	Sex: 66% female BMI: >35.0	-Pre and post-BIB: DGGE band patterns were highly heterogeneous. Prevalent bands in obese corresponded to *Butyrivibrio*, *Roseburia*, *Dorea* and *Blautia/Ruminococcus*, and were reduced or absent after surgery. The band correspondent to *Lactobacillus* was increased in all patients after surgery.	-BIB: ↓18% BW

Equal symbols [δ] identify common patients.
*BF analysis using dual energy X-ray absorptiometry [DEXA].
Units: Age [in years] shown in range or mean ± standard deviation, BMI [kg/m^2] shown in range or mean values ± standard deviation and anthropometric parameters are shown in percentage changes.
BIB, bilio-intestinal bypass; BF, body fat; BMI, body mass index; BW, body weight; DM, diabetes mellitus; F/B ratio, Firmicutes to Bacteroidetes; GB, gastric banding; KEGG Orthologues – genetic pathways, Kos; LSG, low-sleeve gastrectomy; NA, not available; ns, not significant; RT, restrictive technique; RYGB, Roux-en-Y gastric bypass; SCFA, short-chain fatty acids; T2DM, type 2 diabetes mellitus; VBG, vertical banding gastroplasty; WC, waist circumference.

(28,29,32–35) and inflammatory markers (28,32–34). Several correlations between bacterial taxa and metabolic parameters were found as follows. *A. muciniphila* was negatively correlated with FBG and triglycerides (17) and with metabolic syndrome in general (33); *Bifidobacterium* correlated with plasma insulin (36) and *F. prausnitzii* was inversely correlated with inflammatory markers (32). Furthermore, using a computational tool, Shoaie et al. (37) correlated a lower bacterial gene count with the production of several amino acids and metabolic diseases, and these authors showed that dietary intervention might reduce those products and therefore improve insulin sensitivity, reducing the cardiometabolic risk. Considering these trials, we could not relate the amount of weight loss to specific changes in the gut microbial composition.

-Surgical interventions *(*Table 2 – *Extended version available [see Table S4])*:

Eleven papers reported the impact of surgical interventions for weight loss on the gut microbiota over 10 trials; eight of these were quasi-experimental studies (38–45), two were cross-sectional studies comparing the gut microbiota of post-bariatric patients and controls (46,47) and one was an RCT (48). The chosen surgical interventions varied; five studies involved Roux-en-Y gastric bypasses [RYGB] (38–40,43,46), two used bilio-intestinal bypasses [BIB] (42,45) and in two other studies, the technique was primarily restrictive (laparoscopic sleeve gastrectomy [LSG] or gastric banding [GB]) (41,47). The remaining two studies compared RYGB to LSG (44,48). The number of patients included in each study varied between 6 and 56 [average: 21, SD: 15].

The techniques used to assess the gut microbiota in the included studies were as follows: five studies [45%] used metagenomics [shotgun sequencing] (40,41,43,44,48), four studies [36%] used 16S rRNA gene metabarcoding [a group-specific qPCR was also performed in two of them] (39,42,46,47), one study [9%] used DGGE (45) and one study [9%] used only group-specific qPCR (38).

The differences between obese and normal-weight individuals were assessed in five studies. Federico et al. (45) observed differences in the microbial community fingerprints between normal-weight and obese individuals using DGGE. The remaining four trials involved taxonomic analysis. In 75% of cases, there was a higher level of the Bacteroidetes phylum [*Prevotella sp.*] (38,46,47), and 50% also reported a higher level of Archaea in obese patients (38,46,47). In contrast, Patrone et al. (42) found a reduced Bacteroidetes rate in obese patients relative to that in normal-weight patients, with a remarkably lower count for that phylum percentage. A reduced *A. muciniphila* abundance and a higher SCFA production were also reported in obese patients (46,47).

We included five studies using RYGB surgery (38–40,43,46), covering four different trials. One study reported an

Table 3 Characteristics of studies with microbiota interventions

Study	Intervention		Population		Outcomes	
Identification	*Description*	*Follow-up*	*n*	*Description*	*Microbiota*	*Anthropometry*
Christensen et al., 2013	Prebiotic: Hypocaloric diet + whole-grain wheat [RGW] + refined wheat [RW]	12 weeks	72	Sex: 100% female BMI: 27.0–37.0	WW promoted ↑*Bifidobacterium* and RW promoted ↓*Bacteroides*. No further impact on microbiota.	Both RW and WG showed ↓BW [ns]; The BF*↓ was greater in the WW group [−3%] than in the RW group [−2.1%]
Dewulf et al., 2013	Prebiotic: Supplementation with inulin-type fructans [ITF]	12 weeks	44	Sex: 100% female BMI: 36.1 ± 4.1 [ITF], 35.6 ± 4.3 [placebo]	ITF-induced changes in phylum [↑Firmicutes and Actinobacteria, ↓Bacteroidetes], genus levels [↑*Clostridium* cluster IV and XIV, *Bifidobacterium*, *Lactobacillus*] and ↑*F. prausnitzii*, ↓*B. intestinalis and B. vulgatus*.	No impact on BW or WC, ↓0.7% BF[&] [ns]
Sharafedtinov et al., 2013	Probiotic: Hypocaloric diet + *L. plantarum* cheese versus placebo cheese	3 weeks	40	Sex: 67% female BMI: 37.0 ± 4.3	Total bacterial: no impact on probiotic group, but ↓in controls. *Lactobacillus* count: no impact on probiotic group, but tended to ↓ in controls.	Probiotic group showed greater ↓ in BW [+1.1%], correlated with body water content. No impact on WC or BF.
Omar et al., 2013	Probiotic: 42-day interventions + 6-week washout (control, *L. fermentum* [LF], *L. amylovorus* [LA])	25 weeks	28	Sex: 64% female BMI: 31.6 ± 0.7	LA and LF: ↑*Lactobacillus* compared with control. No impact on *Bacteroides*, *Bifidobacterium*, *Clostridium* Cluster IV, *Roseburia* or *Enterobacter* compared with control. LA inhibited *Clostridium* Cluster IV.	No impact on BW or WC; greater ↓ in BF* both with LF [3%] and LA [4%] compared with control [1%].
Sanchez et al., 2014	Probiotic: 2-week washout + 12-week energy restriction + 12 week no energy restriction, both with *L. rhamnosus* [LPR] versus placebo	26 weeks	125	Sex: 61% female BMI: 33.8 ± 3.3 [LPR], 33.3 ± 3.2 [placebo]	In general, no impact on gut microbiota diversity or composition [phylum, class, order, family or genus]. A treatment versus sex interaction with ↓Lachnospiraceae [mainly *Roseburia*] in women treated with LPR.	Overall, no impact on WL/BF. Treatment versus sex interaction: 40% greater ↓in BW and 55% greater↓in BF* in LPR-treated women.
Song et al., 2014	Prebiotic: Supplementation with *Panax ginseng* extracts	8 weeks	10	Sex: 100% female BMI: 28.3 ± 2.0	↑Diversity in 5 and ↓in 3 patients. No impact on phylum distribution. Genus dominance changed from *Blautia*, *Bifidobacterium* and *Anaerostipes* to *Bifidobacterium*, *Blautia*, *Faecalibacterium* after intake. Effective weight-loss group had ↑richness and predominance of Firmicutes, Tenericutes and Bacteroidetes.	↓1.4% BM, ↓WC [ns], ↓1.5% BF[&]
Kim et al., 2014	Prebiotic: Supplementation with Ephedra extracts	8 weeks	7	Sex: 100% female BMI: 30.1 ± 3.3	Gut microbial changes in phylum/genus composition were dependent on unique basal microbiota composition. ↑Diversity in 4 and ↓in 3 patients.	↓2.6% BW, no impact on WC, ↓2.7% BF[&]
Lee et al., 2014	Symbiotic: Bofutsushosan [BTS] + probiotic versus BTS + placebo	8 weeks	50	Sex: 100% female BMI: 28.3 ± 1.3	Probiotic: ↑*Bifidobacterium* [*B. breve*, *B. lactis*] and ↑*Lactobacillus* [*L. rhamnosus*] compared with placebo. No impact on total bacterial abundance.	Both groups had changes in body compositions parameters, but no difference probiotic versus placebo.
Remely et al., 2015	Probiotic: 7-day fasting + laxatives, followed by 6-week probiotics [7 strains of *Bifidobacterium* sp. and *Lactobacillus* sp.]	7 weeks	13	Sex: NA BMI: 28.1 ± 3.5	No impact on bacterial abundance. ↑Bacterial diversity. Phylum: no impact on Bacteroidetes [*Bacteroides* or *Prevotella*] or Firmicutes or F/B ratio. Class: no impact on Clostridiales IV or XIVa. Species: ↑*F. prausnitzii* [main butyrate producer], ↑*Bifidobacteria sp.*, ↑*A. muciniphila*.	——
Han et al., 2015a	Prebiotic: Supplementation of *Rehmannia glutinosa*	8 weeks	12	Sex: 100% female BMI: 27.8 ± 3.9	Phylum: ↑Actinobacteria, ↓Firmicutes, ↓Bacteroidetes; Genus: dominance changed from *Blautia* to *Bifidobacterium* and ↓*Eubacterium*.	↓BW [ns], ↓2.6% WC, no impact on BF[&]
Song et al., 2015	Prebiotic: Supplementation with *Schisandra chinensis* fruit [SCF] versus placebo	12 weeks	28	Sex: 100% female BMI: 29.9 ± 4.2	SCF: No impact on phylum composition [SCF and placebo showed ↓Firmicutes and ↑Bacteroidetes]; but major impact on genus composition [↑*Akkermansia*, *Roseburia*, *Bacteroides*, *Prevotella*, *Bifidobacterium* and ↓*Ruminococcus*].	No impact on BW compared with placebo, but promoted greater↓in WC and BF[&]

(*Continues*)

Table 3 (Continued)

Study	Intervention		Population		Outcomes	
Identification	*Description*	*Follow-up*	*n*	*Description*	*Microbiota*	*Anthropometry*
Han et al., 2015b	Prebiotic: Supplementation with fresh kimchi versus fermented kimchi	8 weeks	23	Sex: 100% female BMI: 28 ± 2.3 [fresh], 27.8 ± 2.2 [fermented]	Both groups: ↓F/B ratio and ↑Proteobacteria and Actinobacteria. Fermented kimchi: ↑*Bacteroides*, *Prevotella* and *Bifidobacterium*, ↓*Blautia*	Fresh kimchi: no impact on BW, ↓2.4%WC and ↓4.8% BF. Fermented kimchi: no impact on BW, WC or BF
Karl et al., 2015	Prebiotic: 9 weeks hypocaloric diet with whole grains, herbal medicines and prebiotic [guargun, pectin, konjac flour] + 14 weeks maintenance	23 weeks	77	Sex: 63% female BMI: 32.3 ± 2.9	↓Alpha diversity. Inter-individual variability > intra-individual variation. Phylum: ↑*Actinobacter* and ↓*Proteobacter*, no impact on Firmicutes, Bacteroidetes or F/B ratio. Family: ↑*Bifidobacteriaceae* and ↓*Enterobacteriaceae* and *Desulfovibrionaceae*.	↓6.6% BW, WC and BF not available
Uphadyaya et al., 2016	Prebiotic: 12 weeks interventions (resistant starch type 4 [RST4] versus placebo) with 2-week wash-out periods	26 weeks	20	Sex: 60% female BMI: 32.8	-RST4 compared with placebo: No impact on bacterial diversity; modifications in 71 OTUs, including ↑*Ruminococcus*, *Blautia*, *Bacteroides*, *Oscillospira*, *Parabacteroides*. Overall, tended to ↑Bacteroidetes and reduce F/B ratio. -Pre and post-RST4: ↑*Clostridium* Cluster XIVa [but not Cluster IV]; ↑*Bifidobacterium* and *Parabacteroides*. No impact on *Ruminococcus*, *F. prausnitzii* and *Dorea*.	-Post-RST4: no impact on BW,↓2.2% WC,↓0.8% BF
Takahashi et al., 2016	Probiotic: 12-week supplementation with *Bifidobacterium animalis ssp*. [BA] versus placebo	12 weeks	160	Sex: 36.4% female BMI: 26.8 ± 1.5	BA group showed ↑total bifidobacteria counts and *B. lactis*. No impact on *B. bifidum*, *B. breve*, *B. longum*, *B. adolescentis*, *B. angulatum*, *B. catenulatum*, *B. dentium* and *B. infantis*.	No differences between BA and placebo on BMI changes

Symbols

*BF analysis using dual energy X-ray absorptiometry [DEXA].

&BF analysis using bioelectrical impedance analysis [BIA].

Units: Age [in years] shown in range or mean ± standard deviation, BMI [kg/m^2] shown in range or mean values ± standard deviation and anthropometric parameters are shown in percentage changes.

BA, *Bifidobacterium animalis* ssp.; BIA, bioelectrical impedance analysis; BTS, Bofutsushosan; BF, body fat; BMI, body mass index; BW, body weight; F/B ratio, Firmicutes to Bacteroidetes ratio; ITF, inulin-type fructans; LA, *Lactobacillus amylovorus*; LF, *Lactobacillus fermentum*; LPR, *Lactobacillus plantarum rhamnosus*; MetS, metabolic syndrome; NA, not available, ns, not significant; NSP diet, non-starch polysaccharides; RGW, refined grain wheat; SCF, Schisandra chinensis fruit; SCFA, short-chain fatty acids; WC, waist circumference; WGW, whole grain wheat.

increase in bacterial richness (43). Upon comparing the composition of gut microbiota pre- and post-RYGB procedure, a data analysis of those four trials showed no difference in the phylum level, although a decreasing Firmicutes trend and an increase in Proteobacteria were observed at the post-operative stage. Furthermore, all four trials showed an increase in *Escherichia coli* [phylum Proteobacteria], and 75% reported a decrease in *Lactobacillus sp*. [phylum Firmicutes] (38–40). Moreover, a decrease in the *Blautia*, *Dorea* [phylum Firmicutes] and *Bifidobacterium* [phylum Actinobacteria] genera was reported (39). The abundance of *F. prausnitzii*, a member of the *Clostridiaceae* family [phylum Firmicutes], showed inconsistent results. The Firmicutes to Bacteroidetes ratio was reduced in 75% of the included studies.

Laparoscopic sleeve gastrectomy, which is primarily a restrictive surgical technique, was assessed in two studies (41,47). Damms-Machado et al. (41) reported that LSG promoted more profound changes in the gut microbiota composition than a very-low-calorie diet, despite producing similar weight loss. These changes included a decrease in Firmicutes along with an increase in Bacteroidetes and were comparable to the RYGB result. Specifically, *Clostridium Clusters IV and XIV*, *Dorea*, *Faecalibacterium* and butyrate producers [*Eubacterium rectale*, *Ruminococcus* and genera from the *Lachnospiraceae* family] were decreased. The Firmicutes to Bacteroidetes ratio was again reduced. A cross-sectional study including post-LSG patients showed no impact on the bacterial diversity and decreased *Bacteroides* and Archaea (47).

One study using the BIB technique reported a reduction in the bacterial richness, and, along with the results from the RYGB technique, there was an increase in Proteobacteria [family *Enterobacteriaceae*]. As shown for restrictive techniques, the abundance of butyrate producers [order *Clostridiales*, including the *Faecalibacterium*, *Ruminococcus*, *Clostridium* and *Eubacterium* genera] was reduced (42). The impact of BIB was also evaluated by Federico et al. (45), who showed different microbial community fingerprints before and after surgery. Using DGGE, they showed that the abundant bands found for the obese population were absent after the intervention, along with an increase in the band that corresponded to *Lactobacillus sp*.

Two studies compared different surgical interventions for weight loss (44,48). While Tremaroli et al. (48) did not observe any differences between the microbial profiles after RYGB and vertical banded gastroplasty [VBG], Murphy et al. (44) observed an increase in the bacterial diversity and a decrease in the relative abundance of Bacteroidetes after RYGB but no impact on the diversity and an increased relative abundance of Bacteroidetes after LSG.

Considering the amount of weight loss, RYGB [five studies] exerted a major impact on weight reduction, showing 21–27% losses, while RT [three studies] resulted in body weight reductions of 20–24%, and BIB [two studies] led to body weight reductions of 16–18%.

Improvements in metabolic markers, including a reduction in FBG and blood lipids and a reduction in blood pressure [BP], were reported regardless of the chosen technique, although correlations with bacterial taxa were conflicting. Graessler et al. (40) found a positive correlation between *F. prausnitzii* and FBG, unlike Furet et al. (38). Another study also found a negative correlation between FBG and *Lactobacillus* (42). Inflammatory markers were positively correlated with *Propionibacterium* (44) and negatively correlated with *F. prausnitzii* (38).

-Microbiota interventions *(*Table 3 – *Extended version available [see Table S5])*:

Three types of microbiota-driven therapies for weight loss were identified among the included studies: probiotics, symbiotics and prebiotics. Probiotics are live microorganisms that can reach the intestines in an active state and promote positive health effects, while prebiotics are selectively fermented ingredients that allow specific changes in the composition and/or activity of gut microbiota, thereby conferring benefits. The synergistic combination of pre- and probiotics is known as symbiotics (49).

From the 15 studies that included direct interventions in the gut microbiota, five involved probiotics, one used symbiotics and nine included prebiotics. Considering the study design, six were single-group assessments (50–55) and nine were RCTs [seven with parallel assignments and two with a cross-over design] (23,56–63). The number of patients included in each trial varied between 7 and 160 [average: 47, SD: 44]. The length of the intervention varied between 3 and 26 weeks [average: 13 weeks, SD: 8].

The techniques used here to assess the gut microbiota in the included studies were as follows: seven studies [47%] involved 16S rRNA gene metabarcoding [one also included a qPCR analysis of specific taxa] (23,51,52,54,55,61,62), five studies [33%] used only qPCR (50,57–59,63) and three studies [20%] combined qPCR with HITChip analysis or DGGE (53,56,60).

The impact of six types of probiotics on weight loss was assessed in five studies (23,53,57,58,63). In four studies performed to test *5* [80%] different probiotic strains [*Lactobacillus rhamnosus*, *Lactobacillus fermentum*, *Lactobacillus amylovorus*, *Bifidobacterium animalis* or a mix of strains], there was no impact on body weight. Of those, the study using *L. rhamnosus* reported a pronounced treatment–sex interaction, with a reduction in the *Lachnospiraceae* family along with a body weight and fat percentage reduction after a probiotic intervention in women (23). Body fat was also decreased after *L. fermentum* and *L. amylovorus* intake (58). One study [25%] on *Lactobacillus plantarum* associated probiotic intake with weight loss (57). Probiotic intake was also correlated with changes in the relative abundance of

Clostridium Cluster IV, *Bifidobacterium* and *A. muciniphila*, with differences between trials. While *L. amylovorus* inhibited *Clostridium Cluster IV*, the mix of different strains did not exert any impact on the cluster. *Bifidobacterium* was increased after the intake of either the mix of strains or the intake of *B. animalis*, although this genus showed no changes in relative abundance after *L. fermentum* or *L. amylovorus* intake.

One study used a symbiotic intervention (a combination of seven probiotic strains and herbal medicine [Bofutsushosan]), resulting in increased *Bifidobacterium* and *Lactobacillus* abundance, but there was no impact on body weight (59).

The use of prebiotics was assessed in nine trials (50–52,54–56,60–62). The tested prebiotics varied and included the following: inulin-type fructans [ITF] (56), *Rehmannia glutinosa* (54), *Schisandra chinensis* fruit [SCF] (60), kimchi (61), whole grains (50), *Ephedra* (52), *Panax* (51), resistant starch type 4 [RST4] (62) or a combination [guar gum, pectin and konjac flour] (55). The impact of the interventions on the gut microbiota phylum composition varied, and 71% of the included studies showed an increase in the Actinobacteria phylum (50,54–56,59,61). Further changes included an increasing tendency for important bacterial groups such as *Clostridium Clusters IV* and *XIVa*, *Lactobacillus and F. prausnitzii* [phylum Firmicutes], *A. muciniphila* [phylum Verrucomicrobia] and *Bifidobacterium* [phylum Actinobacteria], with decreases in *Bacteroides* [phylum Bacteroidetes] and *Enterobacter* [phylum Proteobacteria]. Additionally, two trials showed that the impacts of the compounds as prebiotics were dependent on the individual gut microbiota composition, and the authors suggested that the different dietary patterns and preferred foods, digestive times [transit time and digestive secretions], and age, among other factors, could determine the baseline richness and taxonomic microbial composition of the gut microbiota and their changes following prebiotic intervention (51,52).

Over half of these studies [55%] reported no impact on body weight (50,54,56,60,62), while the remaining trials showed weight loss (51,52,55,61). In addition, 75% of studies reported body fat reductions (50–52,60–62).

In general, the manipulation of gut microbiota with the use of pro-, pre- or symbiotics had no impact on BP or metabolic markers such as FBG and blood lipids. However, some compounds tended to improve the blood lipid profile (54,55,57,60) and to reduce the levels of inflammatory markers (55,56). In addition, some correlations between bacterial taxa and metabolic markers were found. For instance, the FBG was positively correlated with *Roseburia* (52) and negatively correlated with *Blautia* (54), *Ruminococcus* (60), *Enterobacter* (52) and *Clostridium Cluster IV* (56). In addition, the total cholesterol was negatively correlated with *Parabacteroides* and *Oscillospira*, and the Low-density-lipoprotein [LDL] cholesterol was correlated with *Methanobrevibacter* and *Ruminococcus* (62).

Quality assessment

Among the included studies, 18 involved an evaluation of the RoB through an RoB [RCT] and 25 included RoBANs [NRCT] [See Table S6: Quality Assessment]. Using the RoB evaluation, 77% presented adequate sequence generation, 61% reported allocation concealment, 55% had the authors were blinded to individual data, 100% involved a blinded assessment of outcomes, 50% reported losses in the follow-up and exclusions, 88% reported suggested information and 77% were judged free of other sources of bias. Considering the RoBANs, 52% presented an adequate patient selection, 48% were judged to be free of confounding variables, 84% had adequate exposure measurements, 100% had blinded outcomes, 48% reported drop-outs and 56% reported the suggested information.

Discussion

The growing interest in gut microbiota studies in the obesity field is motivated by the possibility that gut microbiota manipulation may help in achieving sustained weight loss. Our review shows that any type of weight-loss intervention [dietary, surgical or direct manipulation of gut microbiota] impacts the gut microbiota composition, although this impact is not always correlated with the amount of weight loss. More importantly, it appears that the baseline composition of the gut microbiota influences responses to weight-loss interventions. This is the first systematic review to assess different approaches to obesity and their relations to the gut microbiota.

The gut microbial composition is unique to each person and is strongly influenced by environmental factors, such as genetics, the delivery route, infant feeding patterns, sanitary conditions and antibiotic usage (64). Marked changes in the microbiota composition occur in early infancy, after which point it becomes relatively stable (65). Long-term dietary patterns have a powerful influence on the gut microbiota composition (66), and they are associated with the three gut microbiota profile variants [clusters], which are known as 'enterotypes' (67). The enterotypes are divided according to the predominance of *Bacteroides* [which is associated with high-protein and animal fat diets], *Prevotella* [which is associated with carbohydrate-rich diets] *or Ruminococcus*, and these enterotypes might correlate with individual health status. However, lifestyle modifications, dietary changes and supplements rapidly and broadly impact microbiota dynamics, which might occur on a day-to-day timescale (68).

The first challenge in summarizing the results of this review was that several different molecular biology techniques [DGGE, FISH, qPCR, 16S rRNA metabarcoding and shotgun sequencing] have been used to assess the gut microbial composition, which results in distinct ways of presenting microbiota changes. These assessments include differences at the taxonomic level [phylum, genus and species] and other characterizations of microbiota, such as richness [alpha diversity] and inter-individual variation [beta diversity]. Even when the same data type [shotgun sequencing or 16S rRNA metabarcoding] is present, differences in clustering methodology, distance metrics, operational taxonomic units (OTU)-picking approaches and the sequencing depth or 16S rRNA region represent possible sources of differing results (69). In addition, the methodology for faecal specimen collection and storage lack uniformity among the studies included herein, which may alter the reported microbial composition (70). Considering those differences and the small number of patients tested using similar methods to assess the same class of organisms, this was the first obstacle to conducting a meta-analysis.

Another challenge was that several intervention types and lengths were used, and there was a wide range of study designs. Most of our included studies were not optimal for assessing the relation between interventions on the gut microbiota and weight, as only 18 [41%] were RCTs.

Furthermore, the assessed RoB for the included studies generally showed poor to moderate quality due to the potential sources of bias. These biases included the use of small samples [58% of the studies included fewer than 30 patients], broad criteria for patient inclusion [diverse BMIs, genders and ages], a lack of controls, a poor description of population characteristics and consideration of potential confounding issues.

Another possible confounder for microbiota composition results is the presence of comorbidities, which were not always described in the included studies. Historically, obesity was associated with an increased relative abundance of Firmicutes and decreased Bacteroidetes (16,18,38,54); however, this association was not supported in further studies (15,33,41,47). One of the possible explanations for those divergent results is the presence of comorbidities. Specifically, the presence of type 2 diabetes has been associated with an increased Firmicutes/Bacteroidetes ratio (31).

Despite the aforementioned issues, this review highlights the following observations. First, when considering dietary interventions, restrictive diets seem to promote a reduction in gut microbiota diversity, which is correlated with macronutrient deficiency rather than weight loss. For instance, carbohydrate restriction might lead to changes in the activity and abundance of several bacterial groups (29). Dietary fat intake impacts the gut microbial composition, intestinal permeability and metabolic endotoxaemia (71). In addition, high-protein diets also exert impacts on the gut microbiota by reducing microbial diversity and changing the taxon profiles (72). In addition to these phenomena, the dietary interventions in this review led to a reduction in certain bacterial groups, such as the abundance of the butyrate-producing Firmicutes [*Clostridium Clusters IV* and *XIVa*], *Lactobacillus sp*. and *Bifidobacterium sp*. These results indicate a reduction in complex carbohydrate intake and suggest that these bacteria function as prebiotics (73).

The included studies with dietary interventions for weight loss also indicate that the inter-individual differences in the microbiota composition at the baseline are important (30,36,74) and might be a useful tool for predicting weight-loss responses and the best individual therapies in the future (33). Further studies also show that the baseline microbiota composition can predict responsiveness to weight-loss diets, including metabolic improvement (75), besides influencing responses to prebiotic interventions (76,77). Microbial richness plays a role in individual responses to dietary interventions, and low microbial gene counts indicate a poor response to the intervention. However, weight-loss diets were able to increase the microbial gene richness in some studies, suggesting an advance from risk detection to risk alleviation (34). Furthermore, the higher relative abundance of *A. muciniphila*, a mucus-degrading bacterium, seems to play a role in the response to dietary interventions and weight trajectory success (17,33,35,36); this same bacterium has been associated with intestinal integrity, glucose homeostasis and cardiometabolic health (17). Another microbe with a promising role in maintaining health is *F. prausnitzii*, a butyrate producer that is related to the lean phenotype and is capable of improving gut barrier function (78). These observations highlight the possible benefit of personalized approaches to weight management that account for the baseline composition of individual microbiota.

Data collected from surgical interventions suggest that gut microbiota changes occur due to several factors, related to the technique used. Laparoscopic sleeve gastrectomy, a primary restrictive procedure, induces the smallest impact on the gut microbiota, which is related to bacterial adaptation to caloric restriction; this process leads to similar changes as those observed with dietary restriction and other surgical techniques (41). This reduction in the Firmicutes phylum and therefore the fermentation activity may result in reduced energy harvest and SCFA production, such as acetate and propionate, which are substrates for gluconeogenesis and lipogenesis (41). Roux-en-Y gastric bypass also induces a similar decrease in the presence of the Firmicutes phylum, yet it promotes wider microbial adaptation, possibly because the anatomic changes provoke the exposure of the remnant stomach to higher gastric acid

levels and reduce the absorptive intestinal surface (41). In addition, the ingestion transit time is accelerated, and the increased intestinal pH modifies the oxidoreduction potential in the gut, likely affecting aerobes and facultative aerobic microorganisms, such as Proteobacteria. The increase in Proteobacteria in the gut after RYGB might also be related to reduced bacterial translocation in the blood along with improved insulin resistance and systemic inflammation, as these species account for the majority of blood bacterial DNA (39). An increase in *E. coli* [phylum Proteobacteria] could contribute to energy harvest, as animal data show that *E. coli* might help the host to survive under starvation situations (39). Although those changes improve metabolic markers, there are concerns about the risk of colon inflammation and colorectal cancer [CRC], which are especially attributed to increases in *Enterobacter cancerogenus*, *Shigella boydii* and *Salmonella enterica* and to a reduction in butyrate-producing Firmicutes (40).

The included studies involving probiotic interventions were highly diverse in duration, strain and concentration. While *L. plantarum* promoted body weight reduction, *L. fermentum* and *L. amylovorus* had no impact on body weight but reduced the body fat content. Furthermore, *L. rhamnosus* generally had no impact on anthropometric markers, yet it was able to reduce body weight and body fat in women. Additional studies that did not fulfil the inclusion criteria for this systematic review also reported associations between certain strains and weight changes. In 2011, a systematic review on this topic reported the associations of *L. acidophilus*, *L. fermentum* and *L. ingluviei* with weight gain and *L. plantarum* and *L. gasseri* with weight loss (79). Later, there was criticism about those conclusions because the weight gain observed for some species was seen in children and could therefore represent their physiological development and growth rather than indicate an increased risk for obesity development in adulthood (80). More recently, further systematic reviews including clinical trials with probiotic interventions for weight loss were performed, with divergent results. While one group concluded that probiotics had limited effects in terms of reducing body weight, another concluded that their intake could reduce body weight, especially if multiple strains are used (81,82).

The intake of prebiotics, or compounds that resist digestion in the small intestine and reach the colon to be fermented by gut microbes, as primarily represented by carbohydrates, was also evaluated. An analysis of the studies included in this systematic review shows that not only oligosaccharides can act as prebiotics, but that other compounds are also able to promote changes in the composition and function of gut microbiota, including the increase of bifidobacteria. Along with this bifidogenic effect, prebiotic intake facilitates a cross-feeding interaction that results in an increase in butyrate producers and butyrate synthesis, which contributes to gut barrier function, immunomodulation and anti-inflammatory properties, as this fatty acid is the preferred source of energy for colonocytes (83). Accompanying this information, this review suggests a possible benefit of prebiotic intake, which is primarily due to fat mass reduction and improved metabolic outcomes such as reduced glucose tolerance and lipid metabolism. Furthermore, a published meta-analysis found a reduction in the total plasma cholesterol, triglycerides and fasting insulin after pre- and symbiotic intake in the overweight or obese population (84). However, the potential benefit of this approach is likely to be dependent on the individual gut microbiota composition and long-term dietary pattern, specifically fibre intake (85).

The observed results after the manipulation of the gut microbiota in the included studies suggest a possible causal effect of the microbiota composition on weight management and metabolism. In line with these observations in humans, animal studies have shown that transplanting the intestinal microbiota of mice that were discordant for obesity and comorbidities impacted the weight gain, insulin resistance and development of non-alcoholic fatty liver disease in recipient mice (86,87). Furthermore, a human study showed that an infusion of intestinal microbiota from lean donors to metabolic syndrome patients promoted changes in the gut microbial composition and improved insulin sensitivity (88). However, in light of current knowledge, a conclusion about the causal versus consequential effects of the gut microbial composition and the exact species involvement in weight management in humans is not yet possible.

Despite the great reduction in morbidity and mortality usually associated with weight loss in obese populations, changes in the gut taxonomic profiles and microbial products might be detrimental to the colon. Some types of diets that are commonly used for weight loss (e.g. high-protein low-fibre diets) can contribute to the production of dietary components and metabolites that contribute to intestinal inflammation, reactive oxygen species [ROS] production and genotoxicity, increasing the risk of CRC (89). Reductions in butyrate producers and increased Proteobacteria are common after dietary and surgical interventions for weight loss, and they are also associated with colon cancer (90). Microbiota-targeting therapy, such as the use of pre- or probiotics, has been suggested to combat CRC-associated dysbiosis (91).

In summary, the available results in humans suggest that any intervention type for weight-loss impacts the gut microbiota; however, the relationship between the gut microbial composition and weight management remains to be determined.

Limitations

This review provides a comprehensive update on this topic, although certain limitations should be acknowledged. The different protocols used to collect the faecal material along with the wide range of methodologies [targeted vs. untargeted] used to assess the gut microbiota resulted in different ways to present data about microbial abundance and composition [with different levels of assessment]. Furthermore, several study designs [RCTs, NRCTs, observational studies and quasi-experimental studies] were implemented, and these also represented a limiting factor in generalizations. In addition, the length of the intervention and observation periods and differences in the populations [age, gender, comorbidities and geographic location] might represent confounding factors. A meta-analysis of the results was not feasible or appropriate; therefore, generalizations should be made with caution.

Conclusions

This review systematically assessed studies of weight-loss interventions in obese and overweight patients. There were significant differences in the methodology, design, length of intervention and observation among the included studies, and their risks of bias were generally considered to be low to moderate. The gut microbial composition is unique to each person and is strongly influenced by several factors. This review shows that any type of intervention for weight loss [dietary, surgical or the use of pre-, pro- or symbiotics] impacts the gut microbiota composition, but this impact is not always correlated with the amount of weight loss. More importantly, it appears that the baseline composition of gut microbiota might influence individual responses to weight-loss interventions. Restrictive diets and bariatric surgery seem to reduce microbial abundance and promote changes in composition that might be detrimental to the colon in the long-term. The use of prebiotics might be able to restore a healthy gut microbiome in addition to reducing body fat. Further trials that include a larger number of patients are needed to draw conclusions about the role of specific bacterial taxa in human health and to evaluate the impact of specific probiotics on gut microbiota.

Declarations

All of the authors approved this manuscript before submission.

All of the data used to prepare this manuscript are available.

Acknowledgements

We thank Rita Mattiello for her support.

Conflict of interest statement

The authors have no potential conflicts of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or material disclosed in the manuscript. M.D. Seganfredo reports receiving personal fees [PhD Scholarship] from the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – CAPES while conducting this study.

Funding

This study was supported by a grant from the Brazilian Federal Agency for Support and Evaluation of Graduate Education [CAPES].

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article. http://dx.doi.org/10.1111/obr.12541

Table S1. Search strategy.
Table S2. Molecular biology techniques.
Table S3. Extended version of characteristics of studies with dietary interventions.
Table S4. Extended version of characteristics of studies with surgical interventions.
Table S5. Extended version of characteristics of studies with microbiota interventions.
Table S6. Risk of bias assessment.

References

1. Organisation WH. Obesity and overweight: World Health Organisation; 2016 [updated January, 2015. Fact sheet N°311: Available from: http://www.who.int/mediacentre/factsheets/fs311/en/.
2. Pi-Sunyer FX. The obesity epidemic: pathophysiology and consequences of obesity. *Obes Res* 2002; **10**: 97S–104S.
3. Hammond RA, Levine R. The economic impact of obesity in the United States. *Diabetes Metab Syndr Obes* 2010; **3**: 285–295.
4. Morgen CS, Sorensen TI. Obesity: global trends in the prevalence of overweight and obesity. *Nat Rev Endocrinol* 2014; **10**: 513–514.
5. McAllister EJ, Dhurandhar NV, Keith SW *et al.* Ten putative contributors to the obesity epidemic. *Crit Rev Food Sci Nutr* 2009; **49**: 868–913.
6. Baothman OA, Zamzami MA, Taher I, Abubaker J, Abu-Farha M. The role of gut microbiota in the development of obesity and diabetes. *Lipids Health Dis* 2016; **15**: 108.
7. Cani PD, Osto M, Geurts L, Everard A. Involvement of gut microbiota in the development of low-grade inflammation and type 2 diabetes associated with obesity. *Gut Microbes* 2012; **3**: 279–288.
8. Corfe BM, Harden CJ, Bull M, Garaiova I. The multifactorial interplay of diet, the microbiome and appetite control: current knowledge and future challenges. *Proc Nutr Soc* 2015; **74**: 235–244.

9. Bauer PV, Hamr SC, Duca FA. Regulation of energy balance by a gut–brain axis and involvement of the gut microbiota. *Cell Mol Life Sci* 2016; **73**: 737–755.
10. Kallus SJ, Brandt LJ. The intestinal microbiota and obesity. *J Clin Gastroenterol* 2012; **46**: 16–24.
11. Bäckhed F, Manchester JK, Semenkovich CF, Gordon JI. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proc Natl Acad Sci U S A* 2007; **104**: 979–984.
12. Bäckhed F, Ding H, Wang T *et al.* The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci U S A* 2004; **101**: 15718–15723.
13. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 2006; **444**: 1027–1031.
14. Ley RE, Backhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. *Proc Natl Acad Sci U S A* 2005; **102**: 11070–11075.
15. Duncan SH, Lobley GE, Holtrop G *et al.* Human colonic microbiota associated with diet, obesity and weight loss. *Int J Obes* 2008; **32**: 1720–1724.
16. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature* 2006; **444**: 1022–1023.
17. Dao MC, Everard A, Aron-Wisnewsky J *et al. Akkermansia muciniphila* and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology. *Gut* 2016; **65**: 426–436.
18. Remely M, Tesar I, Hippe B, Gnauer S, Rust P, Haslberger AG. Gut microbiota composition correlates with changes in body fat content due to weight loss. *Benefic Microbes* 2015; **6**: 431–439.
19. Westerveld D, Yang D. Through thick and thin: identifying barriers to bariatric surgery, weight loss maintenance, and tailoring obesity treatment for the future. *Surg Res Pract* 2016; **2016** :8616581.
20. Li Z, Maglione M, Tu W *et al.* Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med* 2005; **142**: 532–546.
21. Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003–2012. *JAMA Surg* 2014; **149**: 275–287.
22. Lauti M, Kularatna M, Hill AG, MacCormick AD. Weight regain following sleeve gastrectomy–a systematic review. *Obes Surg* 2016; **26**: 1326–1334.
23. Sanchez M, Darimont C, Drapeau V *et al.* Effect of *Lactobacillus rhamnosus* CGMCC1.3724 supplementation on weight loss and maintenance in obese men and women. *Br J Nutr* 2014; **111**: 1507–1519.
24. McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med (Zagreb)* 2012; **22**: 276–282.
25. Higgins JP, Altman DG, Gotzsche PC *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928.
26. Kim SY, Park JE, Lee YJ *et al.* Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. *J Clin Epidemiol* 2013; **66**: 408–414.
27. Haro C, Montes-Borrego M, Rangel-Zúñiga OA *et al.* Two healthy diets modulate gut microbial community improving insulin sensitivity in a human obese population. *J Clin Endocrinol Metab* 2016; **101**: 233–242.
28. Candela M, Biagi E, Soverini M *et al.* Modulation of gut microbiota dysbioses in type 2 diabetic patients by macrobiotic Ma-Pi 2 diet. *Br J Nutr* 2016; **116**: 80–93.
29. Duncan SH, Belenguer A, Holtrop G, Johnstone AM, Flint HJ, Lobley GE. Reduced dietary intake of carbohydrates by obese subjects results in decreased concentrations of butyrate and butyrate-producing bacteria in feces. *Appl Environ Microbiol* 2007; **73**: 1073–1078.
30. Walker AW, Ince J, Duncan SH *et al.* Dominant and diet-responsive groups of bacteria within the human colonic microbiota. *ISME J* 2011; **5**: 220–230.
31. Remely M, Hippe B, Zanner J, Aumueller E, Brath H, Haslberger AG. Gut microbiota of obese, type 2 diabetic individuals is enriched in *Faecalibacterium prausnitzii*, *Akkermansia muciniphila* and *Peptostreptococcus anaerobius* after weight loss. *Endocr Metab Immune Disord Drug Targets* 2016; **16**: 99–106.
32. Pataky Z, Genton L, Spahr L *et al.* Impact of hypocaloric hyperproteic diet on gut microbiota in overweight or obese patients with nonalcoholic fatty liver disease: a pilot study. *Dig Dis Sci* 2016; **61**: 2721–2731.
33. Louis S, Tappu RM, Damms-Machado A, Huson DH, Bischoff SC. Characterization of the gut microbial community of obese patients following a weight-loss intervention using whole metagenome shotgun sequencing. *PLoS One* 2016; **11**: e0149564.
34. Cotillard A, Kennedy SP, Kong LC *et al.* Dietary intervention impact on gut microbial gene richness. *Nature* 2013; **500**: 585–588.
35. Simoes CD, Maukonen J, Scott KP, Virtanen KA, Pietilainen KH, Saarela M. Impact of a very low-energy diet on the fecal microbiota of obese individuals. *Eur J Nutr* 2014; **53**: 1421–1429.
36. Salonen A, Lahti L, Salojarvi J *et al.* Impact of diet and individual variation on intestinal microbiota composition and fermentation products in obese men. *ISME J* 2014; **8**: 2218–2230.
37. Shoaie S, Ghaffari P, Kovatcheva-Datchary P *et al.* Quantifying diet-induced metabolic changes of the human gut microbiome. *Cell Metab* 2015; **22**: 320–331.
38. Furet JP, Kong LC, Tap J *et al.* Differential adaptation of human gut microbiota to bariatric surgery-induced weight loss: links with metabolic and low-grade inflammation markers. *Diabetes* 2010; **59**: 3049–3057.
39. Kong LC, Tap J, Aron-Wisnewsky J *et al.* Gut microbiota after gastric bypass in human obesity: increased richness and associations of bacterial genera with adipose tissue genes. *Am J Clin Nutr* 2013; **98**: 16–24.
40. Graessler J, Qin Y, Zhong H *et al.* Metagenomic sequencing of the human gut microbiome before and after bariatric surgery in obese patients with type 2 diabetes: correlation with inflammatory and metabolic parameters. *Pharmacogenomics J* 2013; **13**: 514–522.
41. Damms-Machado A, Mitra S, Schollenberger AE *et al.* Effects of surgical and dietary weight loss therapy for obesity on gut microbiota composition and nutrient absorption. *Biomed Res Int* 2015; **2015**: 806248.
42. Patrone V, Vajana E, Minuti A *et al.* Postoperative changes in fecal bacterial communities and fermentation products in obese patients undergoing bilio-intestinal bypass. *Front Microbiol* 2016; **7**: 200.
43. Palleja A, Kashani A, Allin KH *et al.* Roux-en-Y gastric bypass surgery of morbidly obese patients induces swift and persistent changes of the individual gut microbiota. *Genome Med* 2016; **8**: 67.
44. Murphy R, Tsai P, Jüllig M, Liu A, Plank L, Booth M. Differential changes in gut microbiota after gastric bypass and sleeve gastrectomy bariatric surgery vary according to diabetes remission. *Obes Surg* 2016.
45. Federico A, Dallio M, Tolone S *et al.* Gastrointestinal hormones, intestinal microbiota and metabolic homeostasis in obese patients: effect of bariatric surgery. *In Vivo* 2016; **30**: 321–330.
46. Zhang H, DiBaise JK, Zuccolo A *et al.* Human gut microbiota in obesity and after gastric bypass. *Proc Natl Acad Sci U S A* 2009; **106**: 2365–2370.

47. Patil DP, Dhotre DP, Chavan SG *et al.* Molecular analysis of gut microbiota in obesity among Indian individuals. *J Biosci* 2012; **37**: 647–657.
48. Tremaroli V, Karlsson F, Werling M *et al.* Roux-en-Y gastric bypass and vertical banded gastroplasty induce long-term changes on the human gut microbiome contributing to fat mass regulation. *Cell Metab* 2015; **22**: 228–238.
49. de Vrese M, Schrezenmeir J. Probiotics, prebiotics, and synbiotics. *Adv Biochem Eng Biotechnol* 2008; **111**: 1–66.
50. Christensen EG, Licht TR, Kristensen M, Bahl MI. Bifidogenic effect of whole-grain wheat during a 12-week energy-restricted dietary intervention in postmenopausal women. *Eur J Clin Nutr* 2013; **67**: 1316–1321.
51. Song MY, Kim BS, Kim H. Influence of *Panax ginseng* on obesity and gut microbiota in obese middle-aged Korean women. *J Ginseng Res* 2014; **38**: 106–115.
52. Kim BS, Song MY, Kim H. The anti-obesity effect of *Ephedra sinica* through modulation of gut microbiota in obese Korean women. *J Ethnopharmacol* 2014; **152**: 532–539.
53. Remely M, Hippe B, Geretschlaeger I, Stegmayer S, Hoefinger I, Haslberger A. Increased gut microbiota diversity and abundance of *Faecalibacterium prausnitzii* and *Akkermansia* after fasting: a pilot study. *Wien Klin Wochenschr* 2015; **127**: 394–398.
54. Han K, Bose S, Kim YM *et al. Rehmannia glutinosa* reduced waist circumferences of Korean obese women possibly through modulation of gut microbiota. *Food Funct* 2015a; **6**: 2684–2692.
55. Karl JP, Fu X, Wang X *et al.* Fecal menaquinone profiles of overweight adults are associated with gut microbiota composition during a gut microbiota-targeted dietary intervention. *Am J Clin Nutr* 2015; **102**: 84–93.
56. Dewulf EM, Cani PD, Claus SP *et al.* Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. *Gut* 2013; **62**: 1112–1121.
57. Sharafedtinov KK, Plotnikova OA, Alexeeva RI *et al.* Hypocaloric diet supplemented with probiotic cheese improves body mass index and blood pressure indices of obese hypertensive patients – a randomized double-blind placebo-controlled pilot study. *Nutr J* 2013; **12**: 138.
58. Omar MOCY, Jones ML, Prakash S, Jones PH. *Lactobacillus fermentum* and *Lactobacillus amylovorus* as probiotics alter body adiposity and gut microflora in healthy persons. *J Funct Foods* 2013; **5**: 116–123.
59. Lee SJ, Bose S, Seo JG, Chung WS, Lim CY, Kim H. The effects of co-administration of probiotics with herbal medicine on obesity, metabolic endotoxemia and dysbiosis: a randomized double-blind controlled clinical trial. *Clin Nutr* 2014; **33**: 973–981.
60. Song MY, Wang JH, Eom T, Kim H. *Schisandra chinensis* fruit modulates the gut microbiota composition in association with metabolic markers in obese women: a randomized, double-blind placebo-controlled study. *Nutr Res* 2015; **35**: 655–663.
61. Han K, Bose S, Wang JH *et al.* Contrasting effects of fresh and fermented kimchi consumption on gut microbiota composition and gene expression related to metabolic syndrome in obese Korean women. *Mol Nutr Food Res* 2015b; **59**: 1004–1008.
62. Uphadyaya B. Impact of dietary resistant starch type 4 on human gut microbiota and immunometabolic functions. Scientific Reports: Nature; 2016.
63. Takahashi S, Anzawa D, Takami K *et al.* Effect of *Bifidobacterium animalis* ssp. lactis GCL2505 on visceral fat accumulation in healthy Japanese adults: a randomized controlled trial. *Biosci Microbiota Food Health* 2016; **35**: 163–171.
64. Voreades N, Kozil A, Weir TL. Diet and the development of the human intestinal microbiome. *Front Microbiol* 2014; **5**: 494.
65. Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. *Nature* 2012; **489**: 220–230.
66. Ursell LK, Clemente JC, Rideout JR, Gevers D, Caporaso JG, Knight R. The interpersonal and intrapersonal diversity of human-associated microbiota in key body sites. *J Allergy Clin Immunol* 2012; **129**: 1204–1208.
67. Arumugam M, Raes J, Pelletier E *et al.* Enterotypes of the human gut microbiome. *Nature* 2011; **473**: 174–180.
68. David LA, Materna AC, Friedman J *et al.* Host lifestyle affects human microbiota on daily timescales. *Genome Biol* 2014; **15**: R89.
69. Koren O, Knights D, Gonzalez A *et al.* A guide to enterotypes across the human body: meta-analysis of microbial community structures in human microbiome datasets. *PLoS Comput Biol* 2013; **9**: e1002863.
70. Choo JM, Leong LE, Rogers GB. Sample storage conditions significantly influence faecal microbiome profiles. *Sci Rep* 2015; **5**: 16350.
71. Moreira AP, Texeira TF, Ferreira AB, Peluzio MC, Alfenas RC. Influence of a high-fat diet on gut microbiota, intestinal permeability and metabolic endotoxaemia. *Br J Nutr* 2012; **108**: 801–809.
72. Kim E, Kim DB, Park JY. Changes of mouse gut microbiota diversity and composition by modulating dietary protein and carbohydrate contents: a pilot study. *Prev Nutr Food Sci* 2016; **21**: 57–61.
73. Conlon MA, Bird AR. The impact of diet and lifestyle on gut microbiota and human health. *Nutrients* 2015; **7**: 17–44.
74. McIntosh FM, Maison N, Holtrop G *et al.* Phylogenetic distribution of genes encoding beta-glucuronidase activity in human colonic bacteria and the impact of diet on faecal glycosidase activities. *Environ Microbiol* 2012; **14**: 1876–1887.
75. Korpela K, Flint HJ, Johnstone AM *et al.* Gut microbiota signatures predict host and microbiota responses to dietary interventions in obese individuals. *PLoS One* 2014; **9**: e90702.
76. de Preter V, Vanhoutte T, Huys G, Swings J, Rutgeerts P, Verbeke K. Baseline microbiota activity and initial bifidobacteria counts influence responses to prebiotic dosing in healthy subjects. *Aliment Pharmacol Ther* 2008; **27**: 504–513.
77. Venkataraman A, Sieber JR, Schmidt AW, Waldron C, Theis KR, Schmidt TM. Variable responses of human microbiomes to dietary supplementation with resistant starch. *Microbiome* 2016; **4**: 1–9.
78. Stenman LK, Burcelin R, Lahtinen S. Establishing a causal link between gut microbes, body weight gain and glucose metabolism in humans – towards treatment with probiotics. *Benefic Microbes* 2015: 1–12.
79. Million M, Angelakis E, Paul M, Armougom F, Leibovici L, Raoult D. Comparative meta-analysis of the effect of Lactobacillus species on weight gain in humans and animals. *Microb Pathog* 2012; **53**: 100–108.
80. Lahtinen SJ, Davis E, Ouwehand AC. Lactobacillus species causing obesity in humans: where is the evidence? *Benefic Microbes* 2012; **3**: 171–174.
81. Park S, Bae JH. Probiotics for weight loss: a systematic review and meta-analysis. *Nutr Res* 2015; **35**: 566–575.
82. Zhang Q, Wu Y, Fei X. Effect of probiotics on body weight and body-mass index: a systematic review and meta-analysis of randomized, controlled trials. *Int J Food Sci Nutr* 2015; **67**: 571–580.
83. Riviere A, Selak M, Lantin D, Leroy F, De Vuyst L. Bifidobacteria and butyrate-producing colon bacteria: importance and strategies for their stimulation in the human gut. *Front Microbiol* 2016; **7**: 979.
84. Beserra BT, Fernandes R, do Rosario VA, Mocellin MC, Kuntz MG, Trindade EB. A systematic review and meta-analysis of the

prebiotics and synbiotics effects on glycaemia, insulin concentrations and lipid parameters in adult patients with overweight or obesity. *Clin Nutr* 2015; **34**: 845–858.
85. Wu GD, Chen J, Hoffmann C *et al.* Linking long-term dietary patterns with gut microbial enterotypes. *Science* 2011; **334**: 105–108.
86. Ridaura VK, Faith JJ, Rey FE *et al.* Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science* 2013; **341** :1241214.
87. Le Roy T, Llopis M, Lepage P *et al.* Intestinal microbiota determines development of non-alcoholic fatty liver disease in mice. *Gut* 2013; **62**: 1787–1794.
88. Vrieze A, Van Nood E, Holleman F *et al.* Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology* 2012; **143**: 913–6.e7.
89. Louis P, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. *Nat Rev Microbiol* 2014; **12**: 661–672.
90. Gagnière J, Raisch J, Veziant J *et al.* Gut microbiota imbalance and colorectal cancer. *World J Gastroenterol* 2016; **22**: 501–518.
91. Schwabe RF, Jobin C. The microbiome and cancer. *Nat Rev Cancer* 2013; **13**: 800–812.
92. Russel R, Gratz SW, Duncan SH *et al.* High-protein, reduced-carbohydrate weight-loss diets promote metabolite profiles likely to be detrimental to colonic health. *Am J Clin Nutr* 2011; **93**: 1062–1072.