Lead Article

Dietary interventions, intestinal microenvironment, and obesity: a systematic review

Johnny G. Santos, Bruna C. Alves, Thais O. Hammes, and Valesca Dall'Alba

Context: *Obesity has been linked to the intestinal microenvironment. Diet plays an important role in obesity and has been associated with microbiota.* ***Objective:*** *This systematic review sought to evaluate the scientific evidence on the effect of dietary modification, including supplementation with prebiotics and probiotics, on microbiota diversity in obesity.* ***Data sources:*** *A systematic search was performed in the MEDLINE and EMBASE databases. Studies were considered eligible if they were clinical trials evaluating dietary intervention and microbiota, body weight, or clinical parameters in obesity.* ***Data extraction:*** *Data were extracted by 2 independent reviewers.* ***Results:*** *From 168 articles identified, 20 were included (n = 931 participants). Increased phyla abundance after food interventions was the main finding in relation to microbiota. Regarding the impact of interventions, increased insulin sensitivity, reduced levels of inflammatory markers, and reduced body mass index were shown in several studies.* ***Conclusions:*** *Interventions that modulate microbiota, especially prebiotics, show encouraging results in treating obesity, improving insulin levels, inflammatory markers, and body mass index. Because the studies included in this review were heterogeneous, it is difficult to achieve conclusive and definitive results.*

INTRODUCTION

According to the World Health Organization, obesity is a serious health problem affecting individuals of all ages. The prevalence of obesity is already >600 million people worldwide, and it has increased substantially.[1] The development of obesity is a complex process that includes imbalances in body regulation of energy intake, expenditure, and storage.

The gut microbiota, the immense amount of microorganisms in the human bowel, has been studied for its role in the pathogenesis of obesity.[2] Investigations in animal models suggest that the gut microbiota affects nutrient acquisition and energy regulation.[3]

Most microorganisms in the gut are bacteria, and a minority are fungi, protozoa, and viruses. Combined with their genetic material, these microbes comprise the gut microbiome.[4,5] It is known that the composition of gut bacteria differs among people, and dietary intake is described as being one of the determining factors.[6]

Studies about the microbiota have found that many parameters may serve as a useful indicator or biomarker of a healthy microbiome, such as abundance, richness, and diversity. Abundance, or related abundance, refers to the quantity of specific bacterial species found in the

Affiliation: *J.G. Santos and V. Dall'Alba* are with the Graduate Program in Food, Nutrition and Health, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil. B.C. Alves and V. Dall'Alba are with the Graduate Program: Sciences of Gastroenterology and Hepatology, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil. *T.O. Hammes and V. Dall'Alba* are with the Nutrition and Dietetics Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil. V. Dall'Alba is with Department of Nutrition, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil.

Correspondence: *B.C. Alves*, Graduate Program: Sciences of Gastroenterology and Hepatology, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos 2400 – 2nd floor, Porto Alegre, RS 90035-003, Brazil. E-mail: bruna.alves@ufrgs.br.

Key words: clinical trials, diet, microbiota, obesity.

©The Author(s) 2019. Published by Oxford University Press on behalf of the International Life Sciences Institute.
All rights reserved. For permissions, please e-mail: journals.permissions@oup.com.

doi: 10.1093/nutrit/nuz022

Downloaded from https://academic.oup.com/nutritionreviews/article-abstract/77/9/601/5514202 by UNT Health Science Center user on 27 January 2020

gut microbiota of an individual or a group of individuals, whereas richness indicates the quantity of different species of bacteria. Diversity, on the other hand, can be defined as the number and the abundance distribution of distinct types of microorganisms within a habitat, and it is useful to describe the complexity of the microbial ecosystem.[7,8]

A highly diverse microbiome seems to promote healthy competition among microbial species, maintaining stability of the gut community.[7] For this reason, diversity seems to be a better parameter to assess the stability of microbiota and the ability to resist perturbation.[7,9]

Study of the relationship between microbiota and obesity has intensified, and the intestinal microenvironment can be considered an ecological factor that modulates the development of obesity. The intestinal microbiota is related to metabolic functions, such as regulation of appetite, inflammation, and glucose homeostasis, as well as adipose tissue functions.[10] It is suggested that lipopolysaccharide (LPS) can be used as a factor in the control of adipogenesis and the endocannabinoid system (eCB), confirming a regulatory connection of the colon microbiota and adipose tissue.[11,12]

Nutritional interventions to modulate the microbiota have been proposed as a therapeutic measure for the control of body weight. Studies have shown that prebiotic intake reduces body weight, body fat percentage, abdominal fat, and serum levels of interleukin 6; positive changes in intestinal microbiota diversity have also been observed.[13,14] Studies with probiotic interventions demonstrate beneficial potential in weight loss, abdominal fat reduction, and reductions in levels of plasma triglycerides and LDL cholesterol.[15–17] Probiotics also seem to improve the intestinal barrier function, which maintains immune tolerance and reduces bacterial translocation.[18] On the other hand, unhealthy diets may be associated with an increase in plasma proinflammatory cytokines, which can change gene expression, inducing the pathogenic state and contributing to the development of obesity.[19]

The microbiota confers effects on both sides of the energy balance, influencing the energy acquisition of diet components and modifying some host genes that regulate energy consumption and storage.[20] Therefore, systematic review was performed to evaluate the effect of dietary modification, including supplementation with prebiotics and probiotics, on gut microbiota diversity and body weight and metabolic changes.

METHODS

To evaluate the influence of dietary modification on gut microbiota and obesity, a systematic review of clinical trials was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement.[21]

Table 1 **PICOS criteria for inclusion of studies**

Parameter	Criteria
Population	Obesity
Intervention	Dietary intake
Comparison	–
Outcome	Microbiota
Study design	Randomized clinical trial

MEDLINE and EMBASE databases were searched for relevant publications in the peer-reviewed literature. PICOS (Population, Intervention, Comparison, Outcomes, and Study design) criteria were used to define the research question (Table 1). The Comparison and the Outcomes were deliberately not stipulated so as to avoid restricting the search. A search strategy using Mesh Terms (MEDLINE) was conducted as follows: ((((“microbiota”[MeSH Terms] OR “microbiotas” OR “microbiome” OR “microbiomes” OR “human microbiome” OR “human microbiomes” OR “microbiomes, human” OR “microbiome, human”)) AND (“Obesity”[Mesh Terms] OR “Obesity, Abdominal”)) AND (“diet”[MeSH Terms] OR “diets”)) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (“clinical trial”[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (“latin square”[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh: noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh])). Databases were last searched in September 2017. The search was limited to studies published as full texts in English, Portuguese, or Spanish. There was no limitation regarding date of publication.

Studies were evaluated on the basis of their titles and abstracts, and those eligible for the systematic review were analyzed on the basis of the full text. Original studies that presented dietary interventions in obese individuals were included whenever there was an evaluation of intestinal microbiota, body weight, and clinical parameters related to obesity. Nonoriginal articles (editorials, letters, and reviews) were excluded from this review. Articles that did not address the outcomes of interest (body weight), that did not correlate with obesity, and that indirectly evaluated the microbiota were excluded.

Data extraction was performed by 2 independent investigators. When there was no concordance, they were clarified by consensus with the group’s senior reviewer.

Downloaded from https://academic.oup.com/nutritionreviews/article-abstract/77/9/601/5514202 by UNT Health Science Center user on 27 January 2020

The risk of bias of each study was assessed following version 5.1.0 of the Cochrane Collaboration's methodology (available at http://handbook-5-1.cochrane.org/). This tool includes different domains to evaluate the quality of study: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective reporting).

RESULTS

The search strategy retrieved 168 publications, 90 of which were excluded after reading titles and an additional 35 were excluded after reading the abstracts and reviewing the type of study design. Thus, following the analysis of titles, abstracts, and study designs, 125 articles were excluded because they did not meet the eligibility criteria or were duplicates. Forty-three references were considered for full-text evaluation, of which 23 were excluded for not directly evaluating microbiota, diet, or weight or because it was a pilot study, study protocol, or nonrandomized clinical trial.

Thus, a total of 20 studies (n = 931) were included in this review. The flow diagram for the search strategy is shown in Figure 1. Tables 2,[13,22–28] 3,[29,30] and 4,[31–40] summarize the characteristics of these studies, and Table 5 presents the main results about microbiota, weight change, and clinical outcomes. The year of publication varied from 2011 to 2017; most were published in 2015. The median duration of intervention was 12 weeks (range = 3–48 wk).

The most frequent intervention, presented in 8 studies, was supplementation with prebiotics such as nonstarch polysaccharides, resistant starch, soluble fiber, or insoluble fiber. In 2 studies, the intervention was supplementation with probiotics, and 10 studies had different methods of dietary intervention. These interventions included Mediterranean diet versus a diet low in fat and rich in complex carbohydrates, comparison between probiotics and medicinal herbs, comparison of different levels of protein, comparison of different levels of carbohydrates, protein supplementation, whole grains, medicinal herbs, and diet with different types of milk.

Anthropometric parameters such as body mass index (BMI), weight, waist circumference, waist/hip ratio, and body fat were used to analyze body composition. Impact on body composition variables after interventions was presented for 2 studies: 1 study found a reduction of body weight, and the other showed a reduction of body weight accompanied by a decrease of body fat percentage, waist circumference, and BMI.[26,37]

Most studies (n = 16) evaluated insulin sensitivity, and 4 studies presented some improvement in plasma insulin levels concomitant with change in the gut microbiota profile. Some studies also evaluated inflammatory markers such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and C-reactive protein (CRP), and 4 studies found reduction in these markers after intervention with prebiotics.

Intestinal microbiota from fecal samples were analyzed in all studies. To analyze the microbiota, 4 studies used the 16S rRNA gene sequencing region V4 method,[25,26,32,34] 2 used 16S rRNA gene sequencing region V3–V4,[31,36] 1 used 16S rRNA gene sequencing region V1–V2,[23] 1 used 16S rRNA gene sequencing region V1–V3 or V4–V6,[13] 3 used microarray,[22,28,30] 1 used whole-genome sequencing,[27] 3 used quantitative polymerase chain reaction (qPCR),[33,37,38] 1 used qPCR for specific groups,[24] 1 used qPCR for specific groups plus denaturing gradient gel electrophoresis (DGGE),[35] and 3 used fluorescence in situ hybridization (FISH).[29,39,40] The change between phyla and bacterial species was observed after intervention in 14 analyzed studies. The diversity of the microbiota did not change in all studies. An increase in microbial diversity was observed in 2 studies, especially in those with interventions based on prebiotic or probiotic consumption.

Risk of selection bias was low in 17 of the 20 included studies. In some studies, the allocation was unclear. Risk of performance and detection bias was low in 13 and 9 studies, respectively. Some studies were not blinded for participants or for outcome assessment. Risk of attrition was low in 14 studies. Loss of outcome data was found in some studies. Only 9 studies had a low risk of reporting bias because many did not show a registered protocol.

DISCUSSION

This systematic review evaluated the associations between dietary modifications, microbiota modulation, and body weight changes. Different dietary components and supplements were evaluated in the included studies: prebiotics, probiotics, and herbal medicines. The most frequent intervention in these trials was prebiotic supplementation, which had a positive effect in modulating the intestinal microenvironment, considering an increase in bacterial diversity and changes in the *Bacteroidetes/Firmicutes* ratio. However, these changes were not always accompanied by weight loss.

Prebiotics, especially lactulose, pectin, inulin, oligosaccharides, gums, and indigestible and nonstarch polysaccharides, are food components that cannot be digested by humans; thus, they stimulate the growth and activity of some bacterial populations in the gut.[41] The consumption of prebiotics has been shown to be a strong stimulus to the growth of the *Bifidobacterium*

Downloaded from https://academic.oup.com/nutritionreviews/article-abstract/77/9/601/5514202 by UNT Health Science Center user on 27 January 2020

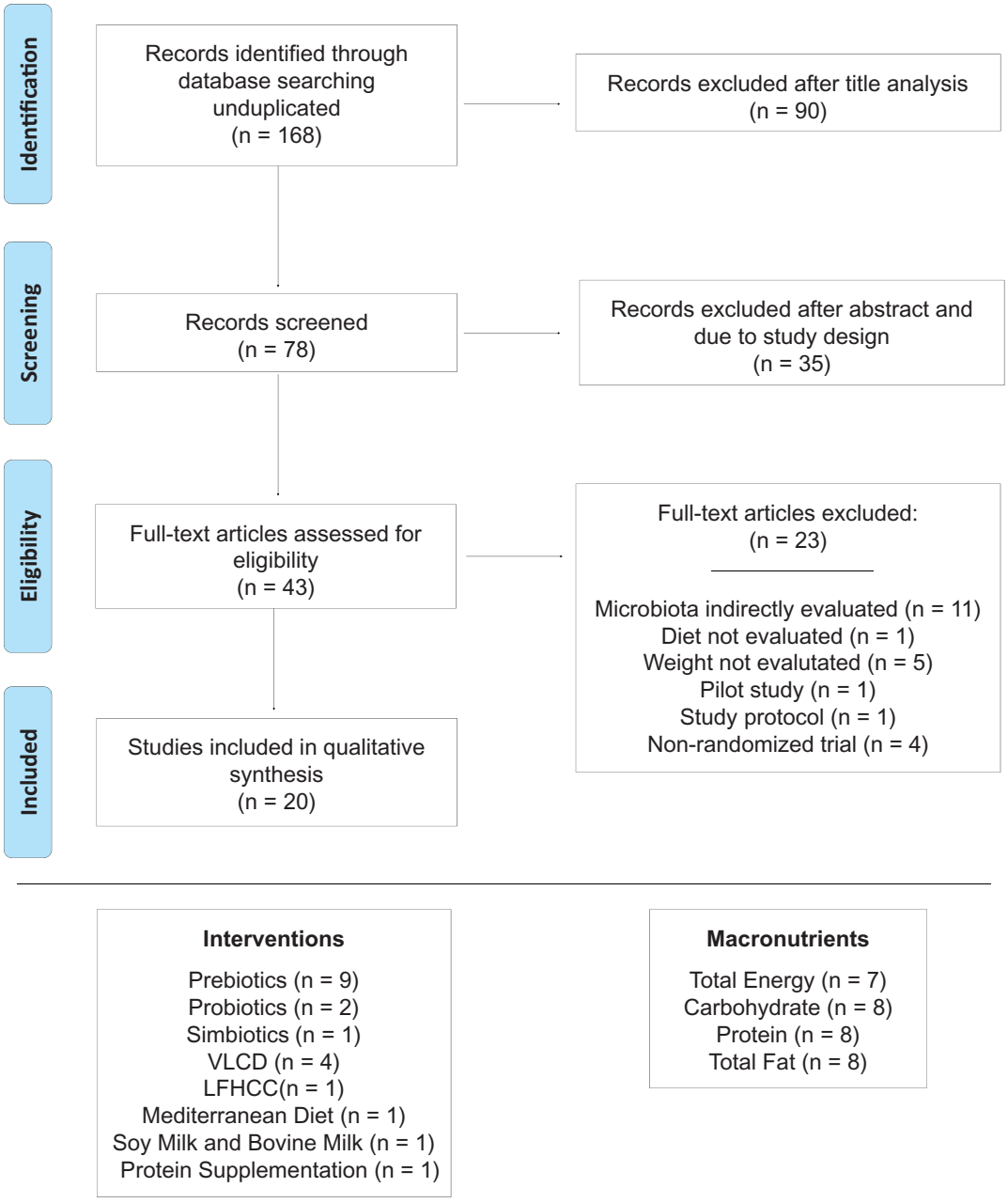

Figure 1 **Flow diagram of the literature search process**. Interventions and macronutrient boxes show the number of interventions included in the study and the number of studies evaluating the dietary composition at the macronutrient level. *Abbreviations:* LFHCC, low-fat high–complex carbohydrate diet; VLCD, very-low-calorie diet.

genus, associated with a reduction of intestinal pH and a decrease of pathogenic bacteria.[42]

It is supposed that microbiota modulation through prebiotic intake occurs indirectly because the products resulting from their degradation will promote a more favorable environment for the selective growth of certain bacteria. Among the mechanisms involved, it is worth highlighting the protective effect against endotoxemia associated with obesity, favoring weight reduction and satiety increase.[43]

Fibers, especially soluble ones, have several physiological effects, such as delay of gastric emptying, reduction of glucose uptake, and improvement of the access of alpha amylase to its substrate. On the other hand, insoluble fibers induce satiety through their intrinsic physical properties, modulating gastric motility and altering the secretion of gut hormones.[44] Thus, this modulation of microbiota would be associated with reduction in risk of developing chronic diseases, such as diabetes mellitus, cardiovascular diseases, obesity, and cancer.[45,46]

Downloaded from https://academic.oup.com/nutritionreviews/article-abstract/77/9/601/5514202 by UNT Health Science Center user on 27 January 2020

Table 2 **Characteristics of clinical trials that evaluated the impact of dietary interventions with prebiotics**

Reference	Studied population	Intervention and time	Groups	Methodology of microbiota analysis	Microbiota outcome	Clinical outcome
Canfora et al (2017)[22]	23 M and 21 F, overweight and obese	Prebiotic 12 wk	GOS (21) Placebo (23) — GOS: 5 g/d, 3 times Placebo: 5 g/d maltodextrin 3 times	Microarray	No change GOS ↑*Bifidobacterium*	No change
Salden et al (2018)[23]	25 M and 22 F, overweight and obese	Prebiotic 6 wk	AX low (16) AX high (15) Placebo (14) — AX low: 7.5 g/d AX AX high: 15 g/d AX Placebo: 15 g/d maltodextrin	16S rRNA sequencing (V1–V2 region)	AX low and AX high: ↓ abundance of Firmicutes ↑ abundance of Bacteroidetes AX high: ↓ Richness and diversity	AX2: ↓ TNF-α ↓IL-2 ↓IFN-ϫ.
Hald et al (2016)[24]	19 metabolic syndrome, overweight and obese	Healthy-carbohydrate diet (HCD): Prebiotic (RS + AX): x Western-style diet (WSD): low fiber 4 wk with washout	HCD (9) WSD (10) — HCD 1 130 kcal 64 g fiber 65% CHO 14% LIP 11% PTN WSD 1 260 kcal 18 g fiber 73% CHO 12% LIP 13% PTN	16S rRNA sequencing (V4 region)	HCD ↓ diversity ↑ *Bifidobacterium* ↓ Anaerostipes, Dorea, Lachnospira, Ruminococcus, Eubacterium ↓*Proteobacteria* ↓ Bacteroides, Parabacteroides, Butyricimonas, Odoribacter, and Paraprevotella ↑SCFA ↓ BCFA Dieta Ocidental ↓ SCFA ↑BCFA	No change
Brahe et al (2015)[25]	53 W, postmenopausal, obese	Probiotic x Prebiotic 6 wk	Probiotic (18) Prebiotic (19) Flaxseed mucilage Placebo (19) (pure maltodextrin) — Probiotic: 9.4 x 10^{10} CFU/d *Lactobacillus paracasei* F19 + maltodextrin + placebo buns Prebiotic: Flaxseed mucilage buns + maltodextrin Placebo: placebo buns + maltodextrin	Whole genome sequencing	Probiotic: ↑ *Eubacterium rectale* and *Ruminococcus torques* Prebiotic: ↓ *Ruminococcus lactaris* ↑ *Parabacteroides merdae and Parabacteroides Johnsonii* ↑*Bilophila Wadsworthia.* Placebo: ↓ *Roseburia hominis, Clostridiales*	Prebiotic: ↑ insulin sensitivity ↓ C-peptide

(continued)

Downloaded from https://academic.oup.com/nutritionreviews/article-abstract/77/9/601/5514202 by UNT Health Science Center user on 27 January 2020

Table 2 **Continued**

Reference	Studied population	Intervention and time	Groups	Methodology of microbiota analysis	Microbiota outcome	Clinical outcome
Lambert et al (2017)[26]	9 M and 41 W, overweight and obese	Prebiotic 12 wk	Pea fiber (22) Placebo (22) — Pea fiber: wafer with 5 g yellow pea fiber 3 times/d Placebo: wafer without pea fiber 3 times/d	qPCR for specific groups	Pea fiber and placebo: ↑ *Clostridium leptum* ↑ *Clostridium* cluster I ↑ *Roseburia* spp.	Pea fiber: ↓ BMI ↓ CRP ↓ IL-6 ↓ TNF-α ↓OGTT
Salonen et al (2014)[27]	14 M, metabolic syndrome, overweight and obese	Prebiotic and calorie restriction 10 wk Crossover design with washout	High nonstarch polysaccharides diet (NSP) High resistant starch diet (RS) Weight loss diet (WL) — NSP 41.7 g NSP + 2.5 RS RS: 16 g NSP + 25.4 g RS WL: 24.8 g NSP + 2.9 g RS	Microarray	NSP: ↑ Lachnospiraceae RS: ↓ diversity ↓ *Clostridium* cluster XIVa WL: ↑ diversity ↑ SCFA	No change
Vulevic et al (2013)[28]	16 M and 29 W, overweight and obese	Prebiotic 12 wk with washout	Bi2muno-GOS (45) x Maltodextrin (45)	FISH	No change	No change
Dewulf et al (2013)[13]	30 W, obese	Prebiotic 12 wk	Prebiotic (15) Placebo (15) — Prebiotic: 16 g/d inulina/oligofrutose: Placebo: maltodextrin	Microarray	Prebiotic: ↑ Firmicutes ↑ Actinobacteria ↓ Bacteroidetes ↑ Bifidobacterium ↑ *Faecalibacterium prausnitzii* ↓ *Bacteroides intestinalis* ↓ *B. vulgatus*	No change

Abbreviations: AX, arabinoxylans; BCFA, branched-chain fatty acid; BMI, body mass index; CFU, colony-forming unit; CHO, carbohydrate; CRP, C-reactive protein; F, female; FISH, fluorescent in situ hybridization; GOS, galacto-oligosaccharides; HCD, healthy carbohydrate diet; IFN-ɤ, interferon gamma; IL, interkeukin; LIP, lipid; M, male; NSP, high nonstarch polysaccharides diet; OGTT, oral glucose tolerance test; PTN, protein; qPCR, quantitative polymerase chain reaction; RS, resistant starch diet; SCFA, short-chain fatty acid; TNF-α, tumor necrosis factor alpha; WSD, Western-style diet; WL, weight loss diet.

Downloaded from https://academic.oup.com/nutritionreviews/article-abstract/77/9/601/5514202 by UNT Health Science Center user on 27 January 2020

Table 3 **Characteristics of clinical trials that evaluated the impact of dietary interventions with probiotics**

Reference	Studied population	Intervention and time	Groups	Methodology of microbiota analysis	Microbiota outcome	Clinical outcome
Sanchez et al (2014)[29]	48 M and 77 W; healthy, overweight, and obeses	Probiotic 24 wk with washout	Intervention (45) x Placebo (48) — Phase 1: calorie restriction of 500 kcal/d Intervention: 1.6 x 10^{10} CFU *Lactobacillus rhamnosus* CGMCC1.3724 (LPR) + 300 mg oligofructose + inulin + 3 mg of magnesium stearate (52) x Placebo: 250 mg of maltodextrin and 3 mg of magnesium stearate (53) Phase 2 – caloric maintenance diet	16S rRNA sequencing (V1–V3 or V4–V6 region)	No change	LPR: ↑ weight loss in women ↓ Lachnospiraceae ↓ leptin
Mobini et al (2016)[30]	35 M and 11 F, type 2 diabetes, overweight and obese	Probiotic 12 wk	*Lactobacillus reuteri* low (14) *L. reuteri* high (15) Placebo (15) — *L. reuteri* low: *Lactobacillus reuteri* DSM 17 938 - 10^{8} CFU/d *L. reuteri* high: *Lactobacillus reuteri* DSM 17 938 - 10^{10} CFU/d Placebo: powder with a mild sweet taste	16S rRNA sequencing (V4 region)	*L. reuteri* low and high: ↑ diversity and abundance of species only in those who improved insulin sensitivity	*L. reuteri* high: ↑ insulin sensitivity index ↑ acid deoxycholic acid

Abbreviations: CFU, colony-forming unit; F, female; LPR, *Lactobacillus rhamnosus* CGMCC1.3724; M, male.

Downloaded from https://academic.oup.com/nutritionreviews/article-abstract/77/9/601/5514202 by UNT Health Science Center user on 27 January 2020

Table 4 **Characteristics of clinical trials that evaluated the impact of other types of dietary interventions**

Reference	Studied population	Intervention and time	Groups	Methodology of microbiota analysis	Microbiota outcome	Clinical outcome
Beaumont et al (2017)[31]	13 M and 25 F, eutrophic and overweight	Protein supplementation 3 wk	Casein (12) Soy (13) Maltodextrin (13) — Diet 50% CHO 35% LIP 15% PTN 1 opaque bag of supplement 3 times/d	16S rRNA sequencing (V3–V4 region)	No change	No change
Karl et al (2017)[32]	49 M and 32 F, eutrophic, overweight and obese	Whole grain 8 wk	Whole grain (40) Refined grain (41) — Whole grain: 40 g/d of fibers Refined grain: 21 g/d fibers	16S rRNA sequencing (V4 region)	No change	Whole grain: ↑ energy content of stool ↑ glucose tolerance (excluding patients who did not adhere to diet)
Haro et al (2016)[33]	20 M, coronary heart disease, obese	Low-fat, high-complex carbohydrate diet (LFHCC) x Mediterranean diet (Med) 48 wk	LFHCC (10) Med (10) — LFHCC 28% LIP 12% MUFA 8% PUFA 8% SFA Med: 35% LIP 22% MUFA 6% PUFA 7% SFA	qPCR	LFHCC: ↑ Abundance *Bacteroides, Eubacterium,* and *Lactobacillus* Med ↑Abundance *Parabacteroides distasonis, Bacteroides thetaiotaomicron, Faecalibacterium prausnitzii, Bifidobacterium adolescentis, and Bifidobacterium longum*	No change
Vitaglione et al (2015)[34]	23 M and 45 F, overweight and obese	Whole grain 8 wk	Whole grain (36): Refined grain (32) — Whole grain: 70 g/d whole-wheat products Refined grain: 60 g/d refined wheat products	16S rRNA sequencing (V4 region)	Whole grain: ↑Prevotella ↑Abundance de *Firmicutes* ↓*Clostridium*	Whole grain: ↓ TNF-α ↑ ferulic acid ↑ IL-10
Song et al (2015)[35]	28 F, overweight and obese	Herbal medicine 12 wk	*Schisandra chinensis* fruit (SCF; 13) Placebo (15) — SCF: 6.7 g/100 mL of dried SCF Placebo: water + sugar + citric acid + red food coloring Diet 20–25 kcal/kg	qPCR for specific groups and DGGE	SCF fruit: ↑ *Bacteroidetes* ↑*Bifidobacterium* ↓ *Firmicutes.*	No change

(continued)

Downloaded from https://academic.oup.com/nutritionreviews/article-abstract/77/9/601/5514202 by UNT Health Science Center user on 27 January 2020

Table 4 **Continued**

Reference	Studied population	Intervention and time	Groups	Methodology of microbiota analysis	Microbiota outcome	Clinical outcome
Han et al (2015)[36]	23 F, obese	Herbal medicine 8 wk	Fresh kimchi (12) Fermented kimchi (11) — Fresh kimchi: 180 g/d of fresh kimchi Fermented kimchi: 180 g/d of fermented kimchi	16S rRNA sequencing (V3–V4 region)	Fresh kimchi: ↓ Firmicutes/Bacteroidetes ↑ Actinobacteria ↑ Proteobacteria Fermented kimchi: ↑ Firmicutes/Bacteroidetes	Fresh kimchi: ↓ waist circumference ↓% body fat ↓diastolic pressure Fermented kimchi: ↓ HDL cholesterol ↓ systolic BP ↓ glucose ↓insulin
Lee et al (2014)[37]	50 F, overweight and obese	Probiotic and herbal medicine 8 wk	Probiotic + BTS (25) Placebo + BTS (25) — Probiotic + BTS: 5 billion *Streptococcus thermophiles* KCTC 11870BP, *Lactobacillus plantarum* KCTC 10782BP, *Lactobacillus acidophilus* KCTC 11906BP, *Lactobacillus rhamnosus* KCTC 12202BP, *Bifidobacterium lactis* KCTC 11904BP, *Bifidobacterium longum* KCTC 12200BP, and *Bifidobacterium breve* KCTC 12201BP + 3 g of *Bofutsushosan* Placebo + BTS: capsules identical in appearance + BTS+ 3 g of *Bofutsushosan* (25) Diet: 20–25 kcal/kg	qPCR	Probiotic + BTS: ↑ *B. longum* ↑ *B. breve* ↑ *B. lactis* ↑ *L. rhamnosus* ↑ *L. plantarum* ↑ Gram negative	Probiotic + BTS: ↓% body fat ↓ waist circumference ↓ BMI Placebo + BTS: ↓% body fat ↓ waist circumference ↓ BMI ↓ HDL Positive correlation between endotoxin and weight
Fernandez-Raudales et al (2012)[38]	64 M, overweight and obese	Soymilk with different levels of β-conglycinin and glycinin compared with bovine milk 12 wk	Low glycinin soymilk (LGM; 19) Conventional soymilk (S; 23) Bovine milk (BM; 22) — LGM: 49.5% β conglycinin 6% glycinin S: 26.5% β-conglycinin 38.7% glycinin BM: 0% β-conglycinin 0% glycinin	qPCR	LGM, S, and BM: ↑ total number of bacteria LGM: ↑ *Bacteroides-Provotella* ↓ *Bifidobacterium* ↓Firmicutes/Bacteroidetes ↓ diversity S: ↓ *Bifidobacterium* ↓ Firmicutes/ Bacteroidetes ↓ diversity BM: ↑ Lactobacillus ↓ diversity	No change

(continued)

Downloaded from https://academic.oup.com/nutritionreviews/article-abstract/77/9/601/5514202 by UNT Health Science Center user on 27 January 2020

Table 4 **Continued**

Reference	Studied population	Intervention and time	Groups	Methodology of microbiota analysis	Microbiota outcome	Clinical outcome
Weickert et al (2011)[39]	26 M and 43 F, overweight and obese	Diet high in cereal fiber or Diet high in protein 18 wk	Control (18) Diet high in cereal fiber (HCF; 16) Diet high in protein (HP; 17) Mix (HCF and HP; 16) — Control: 51% CHO 17% PTN 14.5 g fiber HCF: 51% CHO 17% PTN 42 g fiber HP: 44% CHO 27% PTN 13.5 g fiber Mix 45% CHO 26% PTN 26 g fiber	FISH	No change	HCF: ↑ insulin sensibility after 6 wk
Russell et al (2011)[40]	17 M, obese	High-protein and low-carbohydrate diet (HPLC) x High-protein and moderate-carbohydrate diet (HPMC) 9 wk Crossover design	HPLC HPMC — HPLC 5% CHO 66% LIP 29% PTN 9 g NSP HPMC 35% CHO 37% LIP 28% PTN 13 g NSP Maintenance diet 50% CHO 37% LIP 13% PTN	FISH	HPLC ↓*Roseburia/ Eubacterium rectale, Lachnospiraceae* ↓ % *Bacteroides spp* ↓ total number of bacteria ↓ SCFA ↑ BCFA (isovalerate and isobutyrate)	No change

Abbreviations: BP, blood pressure; BM, bovine milk; BMI, body mass index; BTS, Bofutsushosan; BCFA, branched-chain fatty acids; CHO, carbohydrate; DGGE, denaturing gradient gel electrophoresis; F, female; FISH, fluorescent in situ hybridization; HPLC, high-protein and low-carbohydrate diet; HPMC, high-protein and moderate-carbohydrate diet; HCF, diet high in cereal fiber; HP, diet high in protein; HDL, high-density lipoprotein cholesterol; IL, interkeukin; LFHCC, low-fat, high-complex carbohydrate diet; LIP, lipid; LGM, low glycinin soymilk; MUFA, monounsaturated fatty acids; Med, Mediterranean diet; M, male; NSP, nonstarch polysaccharide; PTN, protein; PUFA, polyunsaturated fatty acid; qPCR, quantitative polymerase chain reaction; SFA, saturated fatty acid; SCF, *Schisandra chinensis* fruit; S, conventional soymilk; SCFA, short-chain fatty acid; TNF-α, tumor necrosis factor alpha.

Downloaded from https://academic.oup.com/nutritionreviews/article-abstract/77/9/601/5514202 by UNT Health Science Center user on 27 January 2020

Table 5 **Major findings on microbiota, weight change, and clinical outcomes of clinical trials**

Reference	Intervention	Change between phyla or species of bacteria or microbiota diversity	Decreased weight	Decreased inflammation	Improvement in insulin sensitivity
Canfora et al (2017)[22]	Prebiotic	Yes	No	No	No
Beaumont et al (2017)[31]	Protein supplementation	No	No	No	No
Karl et al (2017)[32]	Prebiotic	No	No	NA	Yes
Salden et al (2018)[23]	Prebiotic	Yes	No	Yes	No
Mobini et al (2016)[30]	Probiotic	No	No	No	Yes
Haro et al (2016)[33]	Low-fat, high-complex carbohydrate diet (LFHCC) x Mediterranean diet (Med)	Yes	No	NA	No
Hald et al (2016)[24]	Healthy carbohydrate diet: Prebiotic (RS + AX): x Western-style diet: low fiber	Yes	No	NA	NA
Vitaglione et al (2015)[34]	Prebiotic	Yes	No	Yes	No
Brahe et al (2015)[25]	Prebiotic	Yes	No	Yes	Yes
Lambert et al (2017)[26]	Prebiotic	Yes	Yes	Yes	Yes
Han et al (2015)[36]	Herbal medicine	Yes	No	No	Yes
Song et al (2015)[35]	Herbal medicine	Yes	No	NA	NA
Salonen et al (2014)[27]	Prebiotic x caloric restriction	Yes	No	NA	No
Sanchez et al (2014)[29]	Probiotic	No	No	No	No
Lee et al (2014)[37]	Probiotic and herbal medicine	Yes	Yes	NA	NA
Vulevic et al (2013)[28]	Prebiotic	No	No	No	No
Dewulf et al (2013)[13]	Prebiotic	Yes	No	No	No
Fernandez-Raudales et al (2012)[38]	Soymilk with different levels of β-conglycinin and glycinin compared with bovine milk	Yes	No	NA	NA
Weickert et al (2011)[39]	Diet high in cereal fiber or Diet high in protein	No	No	NA	Yes
Russell et al (2011)[40]	High-protein and low-carbohydrate diet x High-protein and moderate-carbohydrate diet	Yes	No	NA	NA

Abbreviations: AX, arabinoxylans; LFHCC, low-fat, high-complex carbohydrate diet; Med, Mediterranean diet; NA, not applicable; RS, resistant starch diet.

Some of these studies have shown positive effects through the direct modulation of microbiota by using probiotics, which are live microorganisms given in adequate quantities to benefit the host. The beneficial influence of probiotics on the intestinal microbiota encompasses factors such as antagonistic effects, competition, and immunological effects, resulting in increased resistance to pathogens.[47] Probiotics help to recompose the intestinal microbiota through bacterial adhesion and colonization in gut mucosa, which prevent the production and adhesion of toxins and the invasion of epithelial cells by pathogenic bacteria, impacting intestinal permeability.[47]

Caloric restriction was also effective for modifying the intestinal microbiota. Hypocaloric diets have been related to increased bacterial diversity, higher concentrations of short-chain fatty acids, and improved insulin sensitivity.[48] In addition, the intestinal microbiota contributes to the obtainment of energy from food by promoting the metabolization of nutrients and vitamins.[49]

Ridaura et al[50] evaluated the interaction of diet, gut microbiota, and body composition. They transplanted fecal microbiota from adult female twin pairs discordant for obesity into germ-free mice fed low-fat mouse chow. They showed that mice harboring the transplanted microbiomes from the obese twins had higher body and fat mass compared with those transplanted with microbiota from lean twins. In addition, obesity-associated metabolic phenotypes were transmissible with fecal transplantation. They also found that the increase of Bacteroidetes in transplanted microbiota from

Downloaded from https://academic.oup.com/nutritionreviews/article-abstract/77/9/601/5514202 by UNT Health Science Center user on 27 January 2020

lean co-twins was dependent on a healthy diet (low saturated fat, high fruits and vegetables). These findings demonstrated the important role of diet on gut microbiota.[50]

In the present study, the phylum that was most associated with elevation of body weight was filo *Firmicutes* followed by *Actinobacteria* and *Proteobacteria*. Evidence suggests that foods with high concentrations of saturated and polyunsaturated fat stimulate the growth of *Firmicutes* filo bacteria, whereas the intake of fruits and vegetables creates an unfavorable environment for its proliferation.[27] In light of these considerations, it is noted that in most studies with reduced intake of fruits and vegetables, body fat and BMI showed a larger increase and percentages of *Bacteroidetes* were smaller than those of *Firmicutes*.

It is observed that there is a fast adaptation of microbiota after the beginning of dietary interventions, which may lead to modifications in the anthropometric profile and clinical features. It is not known how long the effect of intestinal microenvironment modulation persists after the end of the intervention or the exclusion of a dietary component. Some studies indicate a tendency for microorganism rearrangement and a return to the initial pre-intervention status with a consequent return to the initial anthropometric and clinical parameters associated with obesity.[51,52] In this sense, it is often assumed that the treatment of obesity by modulating microbiota would have to occur continuously, being incorporated into each individual's routine.

Some limitations of this study should be addressed. First, there was variability in the methods used to evaluate the microbiota. Although whole-genome sequencing is the best method to evaluate intestinal microbiota, only 3 studies included in this review used that approach. Among the included studies, 16S rRNA gene sequencing was the most used methodology for profiling bacterial communities, but it could lead to under- or overestimation of some species in a microbial community. Because of these methodological limitations, only changes in phyla, instead of bacterial species, were considered as outcomes.[53] Also, dietary interventions varied widely among studies, and some studies evaluated >1 type of dietary component, making evaluation difficult.

It is known that human intestinal microbiota undergoes some type of modulation due to diet modification, such as the inclusion of prebiotics or probiotics in the eating routine. Therefore, it is necessary to explain which dietary intervention leads to the outcome in microbiota that would contribute most effectively to the management of obesity and associated comorbidities.

CONCLUSION

Interventions that modulate the intestinal microbiota, mainly from prebiotics, show encouraging results for the adjuvant management of obesity, improving insulin levels, and reducing inflammatory markers and BMI. However, the studies included in this review were heterogeneous and used multiple sample forms, doses, intervention times, and microbiota evaluation techniques. This makes it difficult to achieve an analysis that provides conclusive and definitive results.

Acknowledgments

Author contributions. J.G.S. and B.C.A. participated in the work's conception, design, data collection, data interpretation and analysis, and writing of the article. T.O.H. participated in the writing and critical revision of the article. V.D. participated in the work's conception, design, data interpretation and analysis, and critical revision of the article. All authors read and approved the final version of the manuscript.

Funding. No external funding was received to support this work.

Declaration of interest. The authors have no relevant interests to declare.

REFERENCES

1. World Health Organization. Obesity and overweight. Available at: http://www.who.int/mediacentre/factsheets/fs311/en/. Accessed April 15, 2017.
2. Ley RE, Bäckhed F, Turnbaugh P, et al. Obesity alters gut microbial ecology. *Proc Natl Acad Sci U S A*. 2005;102:11070–11075.
3. DiBaise JK, Zhang H, Crowell MD, et al. Gut microbiota and its possible relationship with obesity. *Mayo Clin Proc*. 2016;83:460–469.
4. Million M, Lagier JC, Yahav D, et al. Gut bacterial microbiota and obesity. *Clin Microbiol Infect*. 2013;19:305–3132.
5. Ursell LK, Metcalf JL, Parfrey LW, et al. Defining the human microbiome. *Nutr Rev*. 2012;70:S38–S44.
6. Penders J, Thijs C, Vink C, et al. Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics*. 2006;118:511–521.
7. Johnson KV, Burnet PW. Microbiome: should we diversify from diversity? *Gut Microbes*. 2016;7:455–458.
8. Human Microbiome Project Consortium, Huttenhower C, Gevers D, et al. Structure, function and diversity of the healthy human microbiome. *Nature*. 2012;486:207–214.
9. Bäckhed F, Fraser CM, Ringel Y, et al. Defining a healthy human gut microbiome: current concepts, future directions, and clinical applications. *Cell Host Microbe*. 2012;12:611–622.
10. Kobyliak N, Falalyeyeva T, Boyko N, et al. Probiotics and nutraceuticals as a new frontier in obesity prevention and management. *Diabetes Res Clin Pract*. 2018;141:190–199.
11. Dahiya DK, Renuka PM, Shandilya UK, et al. Gut microbiota modulation and its relationship with obesity using prebiotic fibers and probiotics: a review. *Front Microbiol*. 2017;8:563.
12. Geurts L, Neyrinck AM, Delzenne NM, et al. Gut microbiota controls adipose tissue expansion, gut barrier and glucose metabolism: novel insights into molecular targets and interventions using prebiotics. *Benef Microbes*. 2014;5:3–17.
13. 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.

Downloaded from https://academic.oup.com/nutritionreviews/article-abstract/77/9/601/5514202 by UNT Health Science Center user on 27 January 2020

14. Nicolucci AC, Hume MP, Martínez I, et al. Prebiotics reduce body fat and alter intestinal microbiota in children who are overweight or with obesity. *Gastroenterology*. 2017;153:711–722.
15. Jones RB, Alderete TL, Martin AA. Probiotic supplementation increases obesity with no detectable effects on liver fat or gut microbiota in obese Hispanic adolescents: a 16-week, randomized, placebo-controlled trial. *Pediatr Obes*. 2018;13:705–714.
16. Yoo SR, Kim YJ, Park DY. Probiotics, *L. plantarum* and *L. curvatus* in combination alter hepatic lipid metabolism and suppress diet-induced obesity. *Obesity (Silver Spring)*. 2013;21:2571–2578.
17. Huang Y, Wang X, Wang J, et al. *Lactobacillus plantarum* strains as potential probiotic cultures with cholesterol-lowering activity. *J Dairy Sci*. 2013;96:2746–2753.
18. Hemarajata P, Versalovic J. Effects of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. *Therap Adv Gastroenterol*. 2013;6:39–51.
19. Vijay-Kumar M, Aitken JD, Carvalho FA, et al. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science*. 2010;328:228–231.
20. Passos MCF, Moraes-Filho JP. Intestinal microbiota in digestive diseases. *Arq Gastroenterol*. 2017;54:255–262.
21. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700.
22. Canfora EE, van der Beek CM, Hermes GDA, et al. Supplementation of diet with galacto-oligosaccharides increases Bifidobacteria, but not insulin sensitivity, in obese prediabetic individuals. *Gastroenterology*. 2017;153:87–97.
23. Salden BN, Troost FJ, Wilms E, et al. Reinforcement of intestinal epithelial barrier by arabinoxylans in overweight and obese subjects: a randomized controlled trial: arabinoxylans in gut barrier. *Clin Nutr*. 2018;37:471–480.
24. Hald S, Schioldan AG, Moore ME, et al. Effects of arabinoxylan and resistant starch on intestinal microbiota and short-chain fatty acids in subjects with metabolic syndrome: a randomised crossover study. *PLoS One*. 2016;11:e0159223.
25. Brahe LK, Le Chatelier E, Prifti E, et al. Dietary modulation of the gut microbiota—a randomised controlled trial in obese postmenopausal women. *Br J Nutr*. 2015;114:406–417.
26. Lambert JE, Parnell JA, Tunnicliffe JM, et al. Consuming yellow pea fiber reduces voluntary energy intake and body fat in overweight/obese adults in a 12-week randomized controlled trial. *Clin Nutr*. 2017;36:126–133.
27. 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.
28. Vulevic J, Juric A, Tzortzis G, et al. A mixture of trans-galactooligosaccharides reduces markers of metabolic syndrome and modulates the fecal microbiota and immune function of overweight adults. *J Nutr*. 2013;143:324–331.
29. 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.
30. Mobini R, Tremaroli V, Ståhlman M, et al. Metabolic effects of *Lactobacillus reuteri* DSM 17938 in people with type 2 diabetes: a randomized controlled trial. *Diabetes Obes Metab*. 2016;19:579–589.
31. Beaumont M, Portune KJ, Steuer N, et al. Quantity and source of dietary protein influence metabolite production by gut microbiota and rectal mucosa gene expression: a randomized, parallel, double-blind trial in overweight humans. *Am J Clin Nutr*. 2017;106:1005–1019.
32. Karl JP, Meydani M, Barnett JB, et al. Substituting whole grains for refined grains in a 6-wk randomized trial favorably affects energy-balance metrics in healthy men and postmenopausal women. *Am J Clin Nutr*. 2017;105:589–599.
33. 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.
34. Vitaglione P, Mennella I, Ferracane R, et al. Whole-grain wheat consumption reduces inflammation in a randomized controlled trial on overweight and obese subjects with unhealthy dietary and lifestyle behaviors: role of polyphenols bound to cereal dietary fiber. *Am J Clin Nutr*. 2015;101:251–261.
35. Song MY, Wang JH, Eom T, et al. *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.
36. 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*. 2015;59:1004–1008.
37. Lee SJ, Bose S, Seo JG, et al. 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.
38. Fernandez-Raudales D, Hoeflinger JL, Bringe NA, et al. Consumption of different soymilk formulations differentially affects the gut microbiomes of overweight and obese men. *Gut Microbes*. 2012;3:490–500.
39. Weickert MO, Arafat AM, Blaut M, et al. Changes in dominant groups of the gut microbiota do not explain cereal-fiber induced improvement of whole-body insulin sensitivity. *Nutr Metab (Lond)*. 2011;8:90.
40. Russell WR, 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.
41. Guarner F, Khan AG, Garisch J, et al. World Gastroenterology Organisation global guidelines: probiotics and prebiotics. *J Clin Gastroenterol*. 2012;46:468–481.
42. Gullón P, González-Muñoz MJ, Parajó JC. Manufacture and prebiotic potential of oligosaccharides derived from industrial solid wastes. *Bioresour Technol*. 2011;102:6112–6119.
43. Papathanasopoulos A, Camilleri M. Dietary fiber supplements: effects in obesity and metabolic syndrome and relationship to gastrointestinal functions. *Gastroenterology*. 2010;138:62–55.
44. Dall'Alba V, Silva FM, Antonio JP, et al. Improvement of the metabolic syndrome profile by soluble fibre—guar gum—in patients with type 2 diabetes: a randomised clinical trial. *Br J Nutr*. 2013;110:1601–1610.
45. Jonnalagadda SS, Harnack L, Liu RH, et al. Putting the whole grain puzzle together: health benefits associated with whole grains summary of American Society for Nutrition 2010 Satellite Symposium. *J Nutr*. 2011;141:1011S–1022S.
46. Slavin J. Fiber and prebiotics: mechanisms and health benefits. *Nutrients*. 2013;5:1417–1435.
47. Saad S. Probióticos e prebióticos: o estado da arte. *Rev Bras Cienc Farm*. 2006;42:1–16.
48. Valdés JMB, Alonso MCV, Pieiga EM, et al. Alteraciones en la microbiota intestinal por la dieta y su repercusión en la génesis de la obesidad. *Medisan*. 2015;19:1536–1546.
49. Tremaroli V, Backhed F. Functional interactions between the gut microbiota and host metabolism. *Nature*. 2012;489:242–249.
50. Ridaura VK, Faith JJ, Rey FE, et al. Cultured gut microbiota from twins discordant for obesity modulate adiposity and metabolic phenotypes in mice. *Science*. 2013;341:1241214.
51. Eckburg PB, Bik EM, Bernstein CN, et al. Diversity of the human intestinal microbial flora. *Science*. 2005;308:1635–1638.
52. 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.
53. Yang B, Wang Y, Pei-Yuan Q. Sensitivity and correlation of hypervariable regions in 16S rRNA genes in phylogenetic analysis. *BMC Bioinformatics*. 2016;17:135.

Downloaded from https://academic.oup.com/nutritionreviews/article-abstract/77/9/601/5514202 by UNT Health Science Center user on 27 January 2020