Probiotic Foods and Supplements Interventions for Metabolic Syndromes: A Systematic Review and Meta-Analysis of Recent Clinical Trials

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Keywords

Metabolic syndrome · Probiotics · *Lactobacillus* · *Bifidobacterium* · Anthropometric change

Abstract

Background: Individual clinical trials suggested that when treated with probiotic foods or supplements with *Lactobacillus* and *Bifidobacterium*, specific symptoms of metabolic syndrome (*MetS*) could be alleviated, but the results have been inconclusive. **Aims:** The objective of the present meta-analysis was to use anthropometric and biochemical as indicators to evaluate the efficacy of using these probiotic foods or supplements among individuals with *MetS*. **Methods:** PubMed, Cochrane Library, and CINAHL Plus were used to collect randomized controlled trials (RCTs) studies published from January 2000 to January 2018. Studies were included if they had at least one of the following outcome measurements: body mass index (BMI), waist circumference, hip circumference, waist-to-hip ratio, body fat mass (BFM), body fat percentage (BFP), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose, fasting insulin, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-

C), low-density lipoprotein cholesterol (LDL-C), triglycerides, and/or hemoglobin A1c (HbA1c). **Results:** The 356 records were identified during the literature search, of which only 18 met the selection criteria. The 18 RCTs with a total of 1,544 participants were included in this analysis. This meta-analysis indicated that there were no significant differences of BMI, BFM, waist circumference, hip circumference, waist-to-hip ratio, SBP, DBP, fasting glucose, fasting insulin, TC, HDL-C, HbA1c, or triglycerides between the intervention and control groups. Significant standardized mean net differences were found in the BFP and LDL-C between the intervention and control groups. **Conclusions:** The results indicated that probiotic food and supplement with *Lactobacillus* and *Bifidobacterium* could be used as interventions to improve specific anthropometric and biochemical outcomes among individuals with *MetS*. However, probiotic treatment alone could not reduce overall health risks. In addition, there were methodological drawbacks among reviewed studies, and further research is needed.

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Introduction

According to the American Heart Association/National Heart, Lung, and Blood Institute, *metabolic syndrome* (*MetS*) is the failure of normal body metabolism functions that are related to abnormalities of serum triglyceride, lipoprotein, and cholesterol levels [1]. Several studies suggest that *MetS* is a cluster of physiological, biochemical, and metabolic risk conditions, which are often related to cardiovascular diseases, type 2 diabetes mellitus, and obesity [2–4]. In 2016, more than 650 million individuals were obese, and more than 1.9 billion adults were overweight [5]. In the United States, 39.8% in adults and 18.5% in youth were obese [6]. Obesity is associated with severe health risks such as cardiovascular diseases and diabetes [7]. In 2015, cardiovascular disease was the first leading cause of death (258.9 death per 100,000), and diabetes mellitus is the seventh leading cause of death in the United States (24.7 death per 100,000) [8]. Previous studies suggested that waist and hip circumferences, body mass index (BMI), blood pressure, and blood glucose could frequently be used to measure individuals' risk of developing *MetS* [2, 9]. Research showed that 10^{14} microorganisms consisted of more than 50 bacterial phyla live in the human gastrointestinal tract [10, 11]. Previous studies have suggested that gut microbiota play a vital role in the regulation of body metabolism function such as decomposition of carbohydrates, proteins, and lipids, absorption of both energy and nutrients, as well as gut motility [12–15]. Recent studies have suggested that *MetS* was associated with specific abnormalities in gut microbiota [16–18]. Food intake has a significant impact on the formation, composition, and functions of the human digestive tract microbiota [19]. By introducing microorganisms into the digestive tract, it is possible to change gut microbiota and may lead to beneficial changes in the gastrointestinal environment [20]. Recent clinical research has shown that in the novel treatment of *MetS*, the use of probiotic foods or supplements might help patients who have *MetS* to alleviate the severity of symptoms and that probiotics could change both anthropometric and biochemical outcomes of the individuals [21, 22]. Le Barz et al. [23] suggested that probiotics could be used as a complementary treatment for individuals with metabolic-related problems.

Among probiotic foods or supplements, the most common strains such as *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus reuteri*, *Lactobacillus gasseri*, *Lactobacillus paracasei*, *Lactobacillus casei*, *Lactobacillus salivarius*, *Bifidobacterium animalis* subsp. *Lactis*, and *Bifidobacterium bifidum*

are affiliated with the *Lactobacillus* (*L.*) and *Bifidobacterium* (*B.*) genera [24–26]. Previous studies have linked these 2 genera with human gut health and metabolic functions [27, 28]. *Lactobacillus* and *Bifidobacterium* genera are the predominant genera in the intestinal lumen, and *Lactobacillus* is predominant in the mucosa-associated surface [29].

Furthermore, studies show that in recent years, news outlets, commercial websites, and noncommercial websites have made more claims about the beneficial medical effect of using probiotic foods or supplements for treating *MetS* [30, 31]. Nevertheless, to date, no meta-analysis has been conducted to study the efficacy of using *Lactobacillus* and *Bifidobacterium* foods or supplements to alleviate the symptoms of *MetS*. Thus, it is crucial to systematically review the existing evidence regarding the using of probiotics in treating *MetS*. This study was the first to investigate the effect of *Lactobacillus* and *Bifidobacterium* on *MetS*; the authors conducted the meta-analysis with a focus on the changes of several key *MetS* anthropometric measurements and biochemical indicators.

Materials and Methods

Data Sources and Searches

The review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [32]. The protocol of this systematic review and meta-analysis is registered at PROSPERO (International prospective register of systematic reviews), and the registration number is CRD42018086937. Three databases PubMed, Cochrane Library, and CINAHL Plus were used to collect articles for this review. The publications were retrieved from January 2000 to January 2018. The search terms used were as follows: “*Lactobacillus*,” “*Bifidobacterium*,” “metabolic syndrome,” “metabolic dysfunction,” “obesity,” “cultured milk products,” and “probiotics.” Also, “weight loss” and “weight control” were later added to the search term sets.

The inclusion criteria of this article were as follows: studies of randomized controlled trials (RCTs) that compared the effects of using probiotic foods or supplements (regardless of strains, forms, dosages, and duration of treatments) with controls in treating *MetS*. Furthermore, all included studies needed to have at least one of the following anthropometric or biochemical indicators: BMI, body fat mass (BFM), body fat percentage (BFP), waist circumference, hip circumference, waist-to-hip ratio, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose, fasting insulin, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), hemoglobin A1c (HbA1c), or triglycerides. This article included studies with 2 or more treatment arms.

The exclusion criteria of this review were as follows: research subjects were nonhuman; there were no intervention or prevention program being evaluated; studies did not have RCTs as research design (either a cohort study, a case-control study, cross-

Fig. 1. PRISMA 2009 flow diagram.

sectional study, a review, or a commentary article); studies did not have the aforementioned outcome/measurements; or publications were not in English.

The initial search yielded 356 articles, and 57 additional records were identified through Google Scholar. After removing duplicates, 207 records were examined. Based on the information from the titles and abstracts, the authors removed 154 articles because for the following reasons: they were not intervention or prevention programs ($n = 79$), or did not report anthropometric or biochemical changes ($n = 54$), or did not have an appropriate comparison group ($n = 21$). The remaining 53 articles were assessed for eligibility. After full-text examination, 35 articles were excluded from the meta-analysis for the following reasons: conference paper ($n = 9$), unrelated ($n = 6$), non-RCTs ($n = 7$), only study of organs not full human body ($n = 6$), full text in other languages than English ($n = 7$). Thus, 18 articles were included in the qualitative synthesis and quantitative analyses (meta-analysis; Fig. 1).

The selected studies were checked and reviewed independently by 4 researchers. Two of them have expertise in evidence-based medicine, and the other 2 researchers are experts in food microbiology. Three researchers independently conducted the study selection and abstraction of data. Any disagreement about the search strategies among the investigators in data selection was resolved through a panel discussion with the fourth researcher. The following information about eligible articles was collected: study design, duration of treatment, sample size, characteristics of research subjects, dosage, strains of the bacterium, the form of intervention

(food, capsules or pills), and changes of anthropometric and biochemical indicators. The full text of all studies was assessed for eligibility against the inclusion criteria.

Data Extraction and Risk of Bias Assessment

Data were extracted on the allocation, endpoint classification, intervention model, masking, primary purpose of the clinical trial, condition, sample size, age, inclusion criteria of the participants, description of treatment arms, per-day dosage, form, duration, strain of bacterium, anthropometric indicators, biochemical indicators, level of evidence, and risk of bias. Based on the recommendations that were outlined in the Cochrane Handbook, the authors conducted assessments of the risk of bias regarding the following aspect: random sequence generation, allocation concealment, blinding of participants, blinding of research personnel, blinding of outcome assessment, attrition biases, and selective reporting [33].

Measurement of Outcomes

To evaluate the results of the intervention, the authors evaluated the differences in both anthropometric and biochemical indicators in the form of standardized mean net changes. The anthropometric indicators include BMI, waist circumference, hip circumference, waist-to-hip ratio, BFM, BFP, and SBP and DBP. The biochemical indicators include fasting glucose level, fasting insulin level, lipid profile (TC level, HDL-C level, LDL-C level, triglycerides level), and HbA1c.

Qualitative Descriptive Analysis

This meta-analysis provided descriptive analyses of the following perspectives of the reviewed studies: blinding, characteristics of participants, and intervention methods.

Quantitative Statistical Analysis

Mean net change was used to generate results for this meta-analysis with continuous variables. Mean net changes were calculated as the differences of the changes (mean value at endpoint minus mean value at baseline) for both the experimental group and the control group. SE and CI were converted to the SD for further analyses. Regarding heterogeneity, the authors used the fixed-effect model when I^2 statistic $<50\%$, and random-effect model when I^2 statistic $\geq 50\%$. As it was suggested by Higgins [34] and Schroll et al. [35], the use of 50% is rather arbitrary; however, in the published meta-analyses, values greater than 50% are generally considered substantial heterogeneity. For studies that had multiple treatment arms, the authors followed the recommendation in Cochrane Handbook (Section 7.7.3.8, Table 7.7.a), and calculated the means, the SDs, the sample sizes of each, and then combined them into a single experimental group and a single control group for comparison [33]. Since individual meta-analysis measures the same anthropometric or biochemical indicators, the author followed the recommendation in the Cochrane Handbook (Section 9.2.3.2) and calculated the standardized mean differences for each sub meta-analysis. This methodological change also allowed the authors to provide accurate effective sizes for different interventions [33]. All analyses were performed with Review Manager 5.3 [36]. In addition, the fixed and random effects models were weighted by the inverse variance. A p value <0.05 was considered statistically significant.

Results

Overall View

Eighteen RCT studies have met the selection criteria and were reviewed and analyzed. Tables 1–3 present synthesized data extracted from each article in this review. Table 1 shows the following information: study design, program duration, description of the participants which include the number of participants upon completion, age, and health condition; Table 2 shows the descriptions of treatment and control groups (number of participants in each group, daily dosage, strain of microbes, and form of delivery). Table 3 shows the following information regarding the anthropometric and the biochemical changes in reviewed articles.

Study Design

All reviewed articles used randomized allocations, which reduced the risk of bias, and they all employed surrogate endpoints, which provided an easy and fast outcome measurement [37]. These studies were all targeted at providing treatments for participants with symptoms

of *MetS*. Since all reviewed studies have similarities in allocation (randomized), endpoint classification (surrogate), and primary purpose (treatment), the authors in this study did not list this information in the study design section in Table 1. As it was shown in Table 1, only the study by Brahe et al. [38] used single-blinding methods; all other studies used double-blinding in their research ($n = 17$). Ten studies used a 2-treatment-arm design, 5 studies used a 3-treatment-arm design, 2 studies used a 4-treatment-arm design, and one study used a 5-treatment-arm design. According to Cohen et al. [39], by adding an additional treatment arm, researchers can incorporate and evaluate new treatments and reduce the time and cost for determining optimal therapies; however, an additional treatment arm does not always produce critical statistical considerations and could lead to uninterpretable or invalid outcomes.

Level of Evidence and Risk of Bias

Higgins and Green [33] and O'Neil et al. [40] proposed that different research designs could affect the strength of the body of evidence, and they proposed that double-blinded RCTs usually have the highest strength, while single-blinded RCT has moderate strength. As mentioned above, only one study [38] used a single-blind method, and all the others used double-blind methods. Also, all reviewed RCTs had small intervals. Based on the criteria from the Centre for Evidence-Based Medicine [41], these individual RCTs (with narrow CI) had a 1B level of evidence. In the 18 reviewed RCTs, the durations of Sharafedinov et al. [42] (3 weeks) and Lindsay et al. [43] (4 weeks) were below Cochrane recommended duration (6 weeks, Section 8.6, Fig. 8.6.a), which may lead to short-term outcome and attrition bias [33].

Participants

The total participants ($n = 1,544$) include individuals with large visceral fat areas ($n = 210$), individuals with obesity and hypertension ($n = 40$ with arterial hypertonia, $n = 53$ without arterial hypertonia, 93 in total), individuals with hypercholesterolemia ($n = 66$), individuals with abnormally high BMI ($\text{BMI} > 25.0$; $n = 792$), individuals with obesity and fatty liver ($n = 20$), at-risk pregnant and postpartum individuals ($n = 323$), and individuals with Type 2 Diabetes ($n = 40$; Table 1).

Intervention and Control

The participants in the intervention group were given probiotics in the form of foods, pills, or capsules. In

Table 1. Study design, duration, participants description

No.	Author, year	Study design	Duration	Participants description (<i>n</i> = number upon completion)	Completion, <i>n</i>	Age
1	Kadooka et al. [51], 2013	3A; DBSI	12 weeks	Large visceral fat areas (80.2–187.8 cm ²)	210	35–60
2	Sharafedinov et al. [42], 2013	2A; DBSI	3 weeks	Arterial hypertonionia (>130/85 mm Hg)	40	30–69
3	Rerksuppaphol and Rerksuppaphol [48], 2015	2A; DBSI	6 weeks	Hypercholesterolemia (total cholesterol level ≥200 mg/dL W/O lipid-lowering medical treatment)	66	Adult
4	Brahe et al. [38], 2015	3A; SBS	6 weeks	Women, 1 year since last menstruation, no gastrointestinal diseases or chronic diseases, W/O high intake of antibiotics, pro- or prebiotics or fermented food	53	40–70
5	Agerholm-Larsen et al. [61], 2000	5A; DBSI	8 weeks	Normal BP and high BMI 25–37.5, no special diet, normal alcohol consumption, no elite athletes	70	18–55
6	Sanchez et al. [57], 2013	2A; DBSI	24 weeks	Not pregnant, breastfeeding or menopausal, BMI 29–41, W/O complications	125	18–55
7	Vajro et al. [49], 2011	2A; DBSI	8 weeks	BMI >95th, and persisting hypertransaminasemia and bright liver	20	Children
8	Ilmonen et al. [59], 2011	3A; SBS and DBSI	Until the end of exclusive breastfeeding for up to 6 months	At the first trimester of pregnancy, W/O metabolic disease	185	NA
9	Chung et al. [47], 2016	3A; DBSI	12 weeks	BMI 25–35	37	Adult
10	Zarrati et al. [52], 2013	3A; DBSI	8 weeks	24 men and 51 women, age 20–50, BMI 25–35	75	Adult
11	Lindsay et al. [43], 2014	2A; DBSI	4 weeks	Pregnant women, <20 weeks of gestation, BMI 30.0–39.9, singleton pregnancy	138	Adult
12	Göbel et al. [50], 2011	2A; DBSI	12 weeks	BMI percentile which pass through 18.5–25 kg/m ² and above 30 kg/m ²	50	12–15
13	Kadooka et al. [53], 2010	2A; DBSI	12 weeks	BMI 24.2–30.7, and abdominal visceral fat area 81.2–178.5 cm ²	87	33–63
14	Hariri et al. [54], 2015	2A; DBSI	8 weeks	Fasting blood glucose ≥126 mg/dL, and blood sugar (2 h postprandial) ≥200	40	25–65
15	Ivey et al. [64], 2015	4A; DBSI	6 weeks	BMI >25, and elevated waist circumference, and BP >120/80 mm Hg	156	>55
16	Lee et al. [55], 2014	2A; DBSI	8 weeks	Female, BMI >25, and waist circumference >85 cm	36	19–65
17	Ivey et al. [66], 2014	4A; DBSI	6 weeks	BMI >25, and elevated waist circumference, and BP >120/80 mm Hg	156	>55
18	Gomes et al. [56], 2017	2A DBSI	8 weeks	BMI 24.9–40	43	20–59

DBSI, double-blinded (subject and investigator); SBS, single-blinded (subject); 2A, 3A, 4A, and 5A, 2, 3, 4, 5 treatment arms. BMI, body mass index; BP, blood pressure; NA, not applicable.

comparison, the subjects in the control group typically took foods without probiotics or took placebos. The placebos were similar to the probiotic foods, pills, or capsules in look and taste. The probiotics that were used in the intervention groups were from the *Lactobacillus* and

Bifidobacterium genera, which include *L. gasseri*, *L. plantarum*, *L. acidophilus*, *B. bifidum*, *L. paracasei*, *L. rhamnosus*, *L. reuteri*, *L. casei*, *L. salivarius*, and *B. animalis* subsp *lactis* (Table 2).

Table 2. Description of treatment group(s) and control group(s)

No.	Author, year	Treatment group (2): daily dosage; strain; form	Control group(s)
1	Kadooka et al. [51], 2013	Group A: $n = 69$, CFU 10^{10} ; Group B: $n = 71$, CFU 10^6 . <i>L. gasseri</i> strain SBT2055 (LG2055), yogurt	Group C: $n = 70$, PLY W/O LG2055
2	Sharafedinov et al. [42], 2013	Group A: $n = 25$, LOG CFU 10.4, <i>L. plantarum</i> TENSIA, cheese	Group B: $n = 15$, 50 g of cheese W/O <i>L. plantarum</i> TENSIA
3	Rerksuppaphol and Rerksuppaphol [48], 2015	Group A: $n = 33$, CFU 10^9 , <i>L. acidophilus</i> and <i>B. bifidum</i> , capsule	Group B: $n = 33$, PLA
4	Brahe et al. [38], 2015	Group A: $n = 18$, CFU 9.4×10^{10} , <i>L. paracasei</i> F19, food	Group B: $n = 19$, flaxseed mucilage 10 g/day; Group C: $n = 16$, PLA
5	Agerholm-Larsen et al. [61], 2000	Group A: $n = 16$, CFU 2×10^7 , <i>Streptococcus thermophilus</i> and <i>L. acidophilus</i> (StLa), pill; Group B: $n = 14$, CFU 2×10^8 , <i>Streptococcus thermophilus</i> and <i>L. rhamnosus</i> (StLr), pill	Group C: $n = 14$, PLY WI delta-acid-lactone; Group 2: Group D: $n = 16$, <i>Enterococcus faecium</i> and <i>Streptococcus thermophilus</i> (CAUSIDO, G); Group E: $n = 10$, PLA
6	Sanchez et al. [57], 2013	Group A: $n = 62$, CFU 3.24×10^8 , <i>L. rhamnosus</i> CGMCC1.3724 (LPR), capsule	Group B: $n = 63$, PLA
7	Vajro et al. [49], 2011	Group A: $n = 10$, CFU 1.2×10^{11} , <i>L. rhamnosus</i> Strain GG, pill	Group B: $n = 10$, PLA
8	Ilmonen et al. [59], 2011	Group A: $n = 64$, CFU 1.0×10^{10} , dietary COUN and <i>L. rhamnosus</i> GG (ATCC 53103) and <i>B. lactis</i> , capsule	Group B: $n = 64$, COUN and PLA; Group C: $n = 57$, PLA
9	Chung et al. [47], 2016	Group A: $n = 18$, CFU 1×10^9 , <i>L. reuteri</i> JBD301, cream	Group B: $n = 19$, placebo vegetable cream
10	Zarrati et al. [52], 2013	Group A: $n = 25$, PROY and low-calorie diet. Group B: $n = 25$, PROY and regular diet. Yogurt has CFU 2×10^{10} mix of <i>L. acidophilus</i> La5, <i>L. casei</i> DN001, <i>B. lactis</i> BB12	Group C: $n = 25$, PLY WI low-calorie diet
11	Lindsay et al. [43], 2014	Group A: $n = 64$, CFU 1.0×10^9 , <i>L. salivarius</i> UCC118, capsule	Group B: $n = 76$, PLA
12	Göbel et al. [50], 2011	Group A: $n = 27$, CFU 1.0×10^{10} , <i>L. salivarius</i> Ls-33, capsule	Group B: $n = 23$, PLA
13	Kadooka et al. [53], 2010	Group A: $n = 43$, CFU 1.0×10^{11} , <i>L. gasseri</i> SBT2055, yogurt	Group B: $n = 44$, fermented milk W/O <i>L. gasseri</i> SBT2055
14	Hariri et al. [54], 2015	Group A: $n = 20$, dosage not reported; <i>L. planetarium</i> A7, fermented soymilk.	Group B: $n = 20$, regular soymilk
15	Ivey et al. [64], 2015	Group A: $n = 40$, PROY and PROP; Group B: $n = 37$, PROY and PLA; Group C: $n = 39$, control milk and PROP. Both PROY and PROP have CFU 3.0×10^9 of <i>L. acidophilus</i> La5 and <i>B. animalis</i> subsp <i>lactis</i> Bb12	Group C: $n = 40$, control milk WI PLA
16	Lee et al. [55], 2014	Group A: $n = 17$, no exact dosage, mentioned 5 billion viable cells, Bofutsushosan capsule with <i>L. plantarum</i> (KCTC 10782BP), <i>L. acidophilus</i> (KCTC 11906BP), <i>L. rhamnosus</i> (KCTC 12202BP)	Group B: $n = 19$, PLA WI Bofutsushosan
17	Ivey et al. [66], 2014	Group A: $n = 40$, CFU 6.0×10^9 PROY and PROP; Group B: $n = 37$; 3.0×10^9 CFU; PROY and PLA; Group C: $n = 39$; 3.0×10^9 CFU, PROP and milk. Both PROP and PROY have 3.0×10^9 mix of <i>L. acidophilus</i> La5 and <i>B. animalis</i> subsp <i>lactis</i> Bb12	Group D: $n = 40$, control milk WI PLA
18	Gomes et al. [56], 2017	Group A: $n = 21$, CFU 2.0×10^9 , <i>L. acidophilus</i> LA-14, <i>L. casei</i> LC-11, <i>Lactococcus lactis</i> LL-23, <i>B. bifidum</i> BB-06, and <i>B. lactis</i> BL-4 (DaniscoVR), sachet	Group B: $n = 22$, PLA

L, Lactobacillus, B, Bifidobacterium; WI, with, W/O, without; PLA, placebo capsules or pills; PLY, placebo yogurt; PROP, probiotic capsules or pills; PROY, probiotic yogurt; COUN, dietary counselling.

Change of Anthropometric Indicators

In a recent study, Sagun et al. [44] suggested that visceral fat, waist circumferences, hip circumferences, and waist-to-hip ratio were useful noninvasive and nonbiochemical (e.g., plasma glucose, lipids, uric acid, insulin,

and HbA1c) measurements when determining whether individuals were at risk of developing *MetS*. Also, Mooney et al. [45] suggested that in clinical settings, when combining BMI with other anthropometric measurements of body compositions, physicians and health professionals

Table 3. Result of anthropometric changes and biochemical changes

No.	Author, year	Significant anthropometric changes	Nonsignificant anthropometric changes	Significant biochemical changes	Nonsignificant biochemical changes
1	Kadooka et al. [51], 2013	Group A vs. C: BMI; waist and hip CIR, BFM, and BFP Group B vs. C: BMI; waist and hip CIR, BFM, and BFP Within both Group A and B: BMI; waist and hip CIR, BFM, and BFP	NR	NR	NR
2	Sharafedtinov et al. [42], 2013	Group A vs. B: weight and BMI	Group A vs. B: Fat and muscle mass or WHR	NR	Group A vs. B: plasma glucose, plasma lipids, or cholesterol levels
3	Rerksupphaphol and Rerksupphaphol [48], 2015	NR	Group A vs. B: Weight, BMI, or waist and hip CIR	Group A vs. B: TC, LDL-C, and HDL-C	Group A vs. B: serum TAG or fasting blood glucose levels
4	Brahe et al. [38], 2015	NR	NR	Group A vs. B, A vs. C, B vs. C: insulin AUC, Group A vs. B: LDL-C Group A vs. B.: LDL-C	Fasting blood glucose, TC HDL-C or fasting insulin level in any comparison
5	Agerholm-Larsen et al. [61], 2000	Group A vs. B: systolic BP, Group D vs. B: systolic BP, Within Group A, D, and E: weight, Within Group A, D, and E: BFM, Within Group A and D: systolic BP, Within Group A and E: diastolic BP	NR	Group D vs. C, and Group D vs. E: LDL-C	TC, HDL-C, or triacylglycerol in any comparison
6	Sanchez et al. [57], 2013	Group A vs. B: weight and BFM among women	Group A vs. B: weight and BFM for total population	NR	Group A vs. B: TC, HDL-C, fasting glucose or fasting insulin level
7	Vajro et al. [49], 2011	NR	Group A vs. B: BMI or visceral fat area	NR	NR
8	Ilmonen et al. [59], 2011	Group A vs. B, and Group A vs. C: waist CIR	NR	Group A vs. B, Group A vs. C, Group B vs. C: postpartum glucose, mmol/L	NR
9	Chung et al. [47], 2016	Group A vs. B: percentage change in weight and BMI	NR	NR	Group A vs. B: blood lipid profile, fasting blood glucose, blood insulin, or HbA1c
10	Zarrati et al. [52], 2013	Group A vs. C, and Group B vs. C: weight, BMI, waist CIR, and hip CIR	WHR, SBP, or DBP in any comparison	NR	NR
11	Lindsay et al. [43], 2014	NR	NR	NR	Group A vs. B: fasting glucose level, insulin, TC HDL-C, LDL-C, or TAG
12	Göbel et al. [50], 2011	NR	Group A vs. B: BMI, WHR, BFP, BP	NR	Group A vs. B: fasting glucose, insulin, TC, HDL-C, LDL-C, TAG
13	Kadooka et al. [53], 2010	Group A vs. B: BMI, weight, waist and hip CIR, WHR Within Group A: BMI, weight, waist and hip CIR	NR	NR	Group A vs. B: TAG, TC, HDL-C, or LDL-C
14	Hariri et al. [54], 2015	Group A vs. B: systolic BP and diastolic BP, Within Group A: weight, BMI, WHR, systolic BP and diastolic BP, Within Group B: weight and BMI	Group A vs. B: weight, BMI, or WHR	NR	NR
15	Ivey et al. [64], 2015	NR	Group A vs. C, Group B vs. C: BP	NR	Group A vs. C, Group B vs. C: TC, HDL-C, LDL-C or TAG
16	Lee et al. [55], 2014	Within Group A and B: weight, BMI, waist CIR, BFP, BFM	Group A vs. B: weight, BMI, waist CIR, BFP, or BFM	Group A vs. B: HDL-C, Within Group B: blood glucose level, HDL-C, and TC	Group A vs. B: blood glucose level, TAG, or TC
17	Ivey et al. [66], 2014	NR	NR	Group B vs. D: blood glucose	Group A vs. C: HbA1c, blood glucose, or insulin, Group B vs. D: HbA1c or insulin

Table 3. (continued)

No.	Author, year	Significant anthropometric changes	Nonsignificant anthropometric changes	Significant biochemical changes	Nonsignificant biochemical changes
18	Gomes et al. [56], 2017	Group A vs. B: waist CIR, waist-height ratio, conicity index	NR	Group A vs. B: decrease in plasma polyunsaturated fatty acids, increase in the activity of glutathione peroxidase	NR

Cir, circumferences; BFM, body fat mass; BFP, body fat percentage; BP, blood pressure; WHR, waist-to-hip ratio; TAG, triglyceride; NR, not reported; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol.

Fig. 2. Comparison of standardized mean net changes of BMI between probiotic groups and control groups. $\tau^2 = 0.18$, $I^2 = 74\%$, 95% CI -0.68 to 0.01, $Z = 1.91$, $p = 0.06$. No significant difference in the comparison of standardized mean net changes of BMI between probiotic groups and control groups.

could get detailed information about individuals' *MetS*-related health risks. Moreover, when diagnosing *MetS*, the costs of anthropometric measurements were lower than using biochemical measurements [44]. Thus, for health professionals who work in low-income communities or under financial constraints, they could use anthropometric measurements to meet the needs of large epidemiological studies, routine medical practice, or both.

BMI was calculated as the ratio of weight in kilograms divided by the square of the height in meters. A BMI of 25 kg/m² or higher was considered overweight, and a BMI of 30 kg/m² or higher was considered obese [46]. BMI was mentioned as an outcome measurement in 12 studies, which were comprised with 792 study participants. After further examination, 4 studies were excluded from the meta-analysis (Chung et al. [47], no original data; Rerk-supphaphol and Rerk-supphaphol [48], data of BMI was not provided, used BMI z-score, not BMI [49]; Gøbel et al. [50], used BMI-for-age z-score, not BMI).

The remaining 8 studies were further analyzed. Four studies [42, 51–53] reported significant differences in BMI between intervention and control group. While the rest of the studies [54–57] did not find significant BMI changes after the intervention.

When combining the findings from these 8 studies (599 participants), the result suggested that there is no significant ($p = 0.06$; Fig. 2) difference in the comparison of standardized mean net changes of BMI between the control group(s) and the probiotic intervention group(s) groups who used *Lactobacillus* (*L. planetarium*, *L. gasseri*, *L. plantarum*, *L. acidophilus*, *L. rhamnosus*, *L. rhamnosus*, *L. acidophilus*, *L. casei*) and *Bifidobacterium* (*B. lactis*) foods or supplements.

Waist, hip circumference, and waist-to-hip ratio are 3 other useful *MetS* measurements. Janssen et al. [58] suggested that because waist, hip circumference, and waist-to-hip ratio likely reflect the abdominal, and in particular, visceral fat; thus, using these 3 anthropometric measure-

Fig. 3. Comparison of standardized mean net changes of waist circumference between probiotic groups and control groups. $\tau^2 = 0.26$, $I^2 = 81\%$, 95% CI -0.81 to 0.11, $Z = 1.48$, $p = 0.14$. No significant difference in the comparison of standardized mean net changes of waist circumference.

Fig. 4. Comparison of standardized mean net changes of hip circumference between probiotic groups and control groups. $\tau^2 = 0.15$, $I^2 = 78\%$, 95% CI -0.74 to 0.05, $Z = 1.73$, $p = 0.08$. No significant difference in the comparison of standardized mean net changes of hip circumference.

ments could better explain the health risk of *MetS* better than using BMI alone. Six reviewed studies showed significant differences in the waist circumference, hip circumference, or both [51–53, 55, 56, 59]. While other 5 studies found no significant changes in these anthropometric outcome measurements [42, 48, 50, 52, 54].

As shown in Figure 3, in the 6 reviewed studies (476 participants), compared to the control group, the participants who received *Lactobacillus* and *Bifidobacterium* foods or supplements did not experienced a significant changes in their waist circumferences ($p = 0.14$). Similarly, in the 5 reviewed studies (553 participants), probiotics intervention did not cause significant change in hip circumference ($p = 0.08$; Fig. 4). In addition, as shown in Figure 5, in the 5 studies that measured waist-to-hip ratio (267 participants), there was no significant change between the intervention groups and the control groups ($p = 0.62$).

BFM and *BFP* are anthropometric indices that are directly related to the risk of developing *MetS* [60]. Among reviewed studies, 2 studies suggested that there were significant differences in reduction of *BFM*, *BFP*, or both [51, 61], and the other 5 studies did not find significant differences in changes of *BFM* or *BFP* [42, 50, 55–57]. In the 7 reviewed studies (569 participants), the results suggested that there was no significant difference between the intervention groups and the control groups for *BFM* ($p = 0.07$, Fig. 6).

However, in the 6 reviewed studies (519 participants), the result suggested that there is a significant difference in the standardized mean net changes of fat percentage (*BFP*) between probiotic groups and control groups (95% CI -0.58 to -0.02; $p = 0.04$; Fig. 7). The standardized mean difference is -0.30, which suggested that the mean of the intervention group is -0.30 SD away from the mean of the

Fig. 5. Comparison of standardized mean net changes of waist-to-hip ratio between probiotic groups and control groups. $\tau^2 = 0.10$, $I^2 = 57\%$, 95% CI -0.47 to 0.28, $Z = 0.50$, $p = 0.62$. No significant difference in the comparison of standardized mean net changes of waist-to-hip ratio.

Fig. 6. Comparison of standardized mean net changes of BFM between probiotic groups and control groups. $\tau^2 = 0.13$, $I^2 = 69\%$, 95% CI -0.64 to 0.03, $Z = 1.81$, $p = 0.07$. No significant difference in the comparison of standardized mean net changes of BFM.

Fig. 7. Comparison of standardized mean net changes of BFP between probiotic groups and control groups. $\tau^2 = 0.07$, $I^2 = 55\%$, 95% CI -0.58 to -0.02, $Z = 2.09$, $p = 0.04 < 0.05$. Significant differ-

ence in the comparison of standardized mean net changes of BFP. Standardized mean difference = -0.30, which indicates intervention has a small to medium in effect reducing BFP.

Fig. 8. Comparison of standardized mean net changes of SBP between probiotic groups and control groups. $I^2 = 0\%$, 95% CI -0.24 to 0.14, $Z = 0.50$, $p = 0.62 > 0.05$. No significant difference in the comparison of standardized mean net changes of SBP.

Fig. 9. Comparison of standardized mean net changes of DBP between probiotic groups and control groups. $I^2 = 0\%$, 95% CI -0.27 to 0.10, $Z = 0.88$, $p = 0.38 > 0.05$. No significant difference in the comparison of standardized mean net changes of DBP.

control group. In terms of clinical meaning, as it was suggested by Cohen [39], this result suggested the intervention had a small to medium effect on the outcome.

DBP and SBP are usually higher among individuals with *MetS* than those without *MetS* [62]. Untreated diastolic or systolic hypertension significantly increases the risk of cardiovascular death [63]. In the reviewed studies, only Hariri et al. [54] reported a significant decrease of DBP and SBP when participants took *Lactobacillus* and *Bifidobacterium* foods or supplements. Other studies [50, 52, 57, 64] reported no significant differences in blood pressure. Also, Agerholm-Larsen et al. [61] suggested that there was a significant decrease in SBP and a significant increase in DBP between the intervention group and the control group. As it was shown in Figure

8, when combined the results from 6 studies (449 participants), there was no significant differences in SBP ($p = 0.62$). Similarly, there was no significant difference in DBP ($p = 0.38$; Fig. 9) between the intervention and the control groups.

Change of Biochemical Indicators

Abnormal blood values were determined in accordance with the criteria for the *MetS* as defined by the National Cholesterol Education Program [65]. Patients who have *MetS* tend to have unusual value in metabolic-related clinical biochemical markers, such as abnormal fasting glucose, fasting insulin, lipid profile, and HbA1c.

Fasting glucose is a commonly used indicator to determine whether a patient has diabetes or is prediabetic. Ten

Fig. 10. Comparison of standardized mean net changes of fasting glucose between probiotic groups and control groups. $I^2 = 15\%$, 95% CI = -0.09 to 0.22 , $Z = 0.77$, $p = 0.44 > 0.05$. No significant difference in the comparison of standardized mean net changes of fasting glucose level.

studies discussed the efficacy of *Lactobacillus* food and/or supplement intake on fasting glucose. Upon further examination, 3 studies were removed from the meta-analysis. The reasons for the removal include lack of original data [47], data without specific SD of fasting glucose [48], and outcome indicator being serum glucose, not fasting glucose [42]. Among the remaining 7 studies, 5 of them found no significant differences in fasting glucose or blood glucose in between-group comparisons [38, 43, 50, 55, 57]. In the 2014 4-arm study by Ivey et al. [66], the researchers used a 4-arm approach: (A) probiotic yogurt plus probiotic capsules, (B) probiotic yogurt plus placebo capsules, (C) control milk plus probiotic capsules, and (D) control milk plus placebo capsules. The author found significant differences in blood glucose between group B and D ($p < 0.037$), and no significant difference was found between group A and C. To conduct the meta-analysis, the reviewers standardized the unit-of-measurement prior to computations. The fasting glucose level in mmol/L was converted to mg/dL, and the conversion factor was $1 \text{ mmol/L} = 18.0 \text{ mg/dL}$. In the 7 reviewed studies (642 participants), the result suggested that there was no significant difference in the fasting glucose level between the intervention groups and the control groups ($p = 0.44$; Fig. 10).

Fasting insulin is another indicator of health for individuals with *MetS*. An abnormal fasting insulin level indicates a potential risk of developing diabetes; thus, it is crucial for both patients and health-care professionals to take precautionary measures to prevent diabetes when abnormal fasting insulin levels are presented [67]. In the 6 reviewed studies, the authors did not find significant fasting insulin differences between the intervention groups and

control groups [38, 43, 47, 50, 57, 66]. Except for the study without original data conducted by Chung et al. [47]. In the study by Brahe et al. [38], the researchers noticed that there was a significant difference of AUC insulin in between group comparisons; however, they did not find any significant difference in fasting insulin in any between group comparisons. Similarly to the meta-analysis of the fasting glucose level, the reviewers standardized the unit-of-measurement prior to computations. The fasting insulin level in mmol/L was converted to mg/dL prior to computations, and the conversion factor was $1 \text{ mmol/L} = 18.0 \text{ mg/dL}$. The result of the meta-analysis of the 5 reviewed studies (471 participant) suggested that the probiotic intervention did not have significant effect ($p = 0.37$; Fig. 11).

Lipid profile consists of TC, LDL-C, High-HDL-C, and Triglycerides. Regarding the overall effects of probiotic food and supplements on cholesterol levels, only one study showed that interventions had significantly lowered the TC, LDL-C, and HDL-C levels [48]. However, in the other 4 studies, the researchers did not find significant effects on all these 3 (TC, LDL-C, and HDL-C) indicators [47, 54, 62, 64].

Two studies reported significant differences in LDL-C level when they compared the probiotic-intervention group with the control group [38, 61]. Nevertheless, these 2 studies and the study by Sanchez et al. [57] all failed to find any significant changes in the TC and HDL-C between the intervention groups and control groups. In addition, there were no significant differences observed in the TC level in the other 2 studies [42, 55]. In the 7 studies that evaluated the changes of the triglycerides level, none of them reported significant differences [42, 43, 48, 50, 55, 56, 64].

Fig. 11. Comparison of standardized mean net changes of fasting insulin between probiotic groups and control groups. $I^2 = 0\%$, 95% CI = -0.10 to 0.26, $Z = 0.89$, $p = 0.37 > 0.05$. No significant difference in the comparison of standardized mean net changes of fasting insulin level.

Fig. 12. Comparison of standardized mean net changes of TC between probiotic groups and control groups. $\tau^2 = 0.11$, $I^2 = 63\%$, 95% CI -0.50 to 0.03, $Z = 1.77$, $p = 0.08 > 0.05$. No significant difference in the comparison of standardized mean net changes of TC.

In order to perform calculation, the researchers standardized the unit-of-measurement to conduct the meta-analysis, lipid levels in mmol/L were converted to mg/dL, and the conversion factor was 1 mmol/L = 38.7 mg/dL for cholesterol and 1 mmol/L = 88.5 mg/dL for triglycerides. The mean net changes (mean values $\pm$ SD) in the TC, HDL cholesterol, LDL cholesterol, and triglycerides of each study were individually calculated.

As shown in Figure 12, in the 10 reviewed studies (714 participants), there was no significant difference in TC changes between the control group and the intervention group ($p = 0.08$). In addition, as it was shown in Figure 13, there was no significant effect of using probiotics on the HDL-C level ($p = 0.29$).

However, the results in 9 reviewed study (678 participants) showed that probiotic food and supplements had a significant effect on reducing the LDL-C level ($p = 0.02 < 0.05$, $I^2 = 32$, 95% CI -0.34 to -0.03, $Z = 2.36$; Fig. 14). It is worth to point out that the effect size is -0.18, which suggested that the mean of the intervention group is only -0.18 SD away from the mean of the control group. As it was suggested by Cohen et al. [39], this result suggested the intervention only yield a trivial effect on reducing LDL-C.

In terms of the triglycerides, the meta-analysis of 8 reviewed studies (587 participants) did not find any significant effect between probiotic groups and control groups ($p = 0.38$; Fig. 15).

Fig. 13. Comparison of standardized mean net changes of HDL-C between probiotic groups and control groups. $I^2 = 0\%$, 95% CI -0.23 to 0.07, $Z = 1.05$, $p = 0.29 > 0.05$. No significant difference in the comparison of standardized mean net changes of HDL-C.

Fig. 14. Comparison of standardized mean net changes of low-density lipoprotein cholesterol (LDL-C) between probiotic groups and control groups. $I^2 = 32\%$, 95% CI -0.34 to -0.03, $Z = 2.36$, $p = 0.02 < 0.05$. Significant difference in the comparison of standard-

ized mean net changes of LDL-C. However, the standardized mean difference = -0.18, which indicates intervention only has a trivial effect in reducing LDL-C level.

HbA1c was only evaluated in 3 studies [47, 56, 66]. Since there were no original data in the report of Chung et al. [47]; thus, the meta-analysis was performed based on the remaining 2 studies (199 participants) [56, 66]. The results showed no significant difference in *HbA1c* between the probiotic and control groups ($p = 0.20$, Fig. 16).

Discussion

This review and meta-analysis described and evaluated 18 RCTs studies that used *Lactobacillus* or *Bifidobacterium* probiotic foods or supplements as interventions to reduce the health risks among patients with *MetS*. More specifically, the authors used anthro-

Fig. 15. Comparison of standardized mean net changes of triglycerides between probiotic groups and control groups. $I^2 = 0\%$, 95% CI -0.09 to 0.24, $Z = 0.88$, $p = 0.38 > 0.05$. No significant difference in the comparison of standardized mean net changes of triglycerides.

Fig. 16. Comparison of standardized mean net changes of HbA1c between probiotic groups and control groups. $\tau^2 = 0.11$, $I^2 = 65\%$, 95% CI -0.93 to 0.20, $Z = 1.27$, $p = 0.20$. No significant difference in the comparison of standardized mean net changes of HbA1c.

pometric and biochemical indicators as a measurement to evaluate the effectiveness of the intervention outcomes.

Primary mechanisms underlying the antagonistic effects of probiotics include improvement of the gut barrier function, increased competitive adherence to the mucosa and epithelium, gut microbiota modification, and regulation of the gut-associated lymphoid immune system. In this sense, probiotics communicate with the host through intestinal cell patterns recognition receptors, such as Toll-like receptors and nucleotide-binding oligomerization domain-containing protein-like receptors, which modulate important key signaling pathways, such as nuclear factor- κ B and mitogen-activated protein kinase, to enhance or suppress activation and influence downstream pathways [68, 69]. Based on the results, the authors of this review concluded that *Lactobacillus* and

Bifidobacterium foods or supplements could be used as a possible intervention to bring specific beneficial changes for individuals with *MetS*. However, it is also important to point out that the probiotic intervention does little to nothing to improve blood pressure and lipid profiles, except for the LDL-C.

As suggested in the results section, when combining all the data from each RCT, there were significant differences in the following *MetS* indicators: LDL-C and BFP. However, researchers did not find significant differences in BFM, BMI, waist circumference, hip circumference, waist-to-hip ratio, fasting glucose, HbA1c, SBP, DBP, fasting insulin, TC, HDL-C, or triglycerides between the probiotics and placebo groups that were observed. Furthermore, the researchers found several RCTs studies with problems in research design and methodology. As explained in the Results section, all re-

viewed studies were RCTs. Compared to other non-RCT research designs (e.g., observation studies), the RCTs design can provide more evidence-based analysis on the cause-and-effect relationships with minimal bias and confounding factors [70]. According to the Consolidated Standards of Reporting Trials statement [71], one critical part of reporting RCTs is to provide detailed information about the randomization process. Among the 18 reviewed RCTs studies, 12 of them provided explicit and replicable information about the method of randomization. The other 6 RCT studies have only mentioned that their studies were randomized in the methods section or elsewhere in the text or title [49, 51, 53, 55, 61, 64]. Without detailed information about the randomization procedure, it became difficult for the reviewers to evaluate the quality of randomization (e.g., using pseudo-randomization such as time-period randomization).

In terms of sample size calculation, 8 RCT studies did not report any type of power calculations [42, 47, 49, 50, 52, 54, 55, 61]. One study reported post hoc calculation [66]. Five studies reported prior power calculation [43, 51, 57, 59, 64]. The other studies did not specify how they performed the power calculation. The inconsistency in providing sample size calculation should also be pointed out here. Furthermore, the study by Brahe et al. [38] only used a single-blind method, which may increase the likelihood of bias [72].

Another problem in the reviewed studies is that there was no consistency in selecting uniformed outcome measurement. As it was shown in Table 3, there were no anthropometric measurements in 3 studies [38, 43, 66]; meanwhile, 4 studies did not report any biochemical measurements [49, 51, 52, 54]. The lack of consistency in reporting methods made it difficult for the reviewer to assess the overall effectiveness of using *Lactobacillus* and *Bifidobacterium* probiotic foods or supplements in *MetS* intervention.

In terms of food or medication interferences, Ivey et al. [64] suggested that some of their participants in both control and experimental groups used hypolipidemic medication or supplement; however, the researchers did not provide detailed information regarding the exact dosages of the medications or supplements. In addition, Lee et al. [55] suggested that they provided each participant in both control and experimental groups with equal dosage of Bofutsushosan over an 8-week period (3 g per administration, 15 g in total). No other study reported any abnormal usage of medication or supplement.

Conclusion

The results from this systematic review and meta-analysis indicated that probiotic food and supplements with *Lactobacillus* and *Bifidobacterium* genera have the potential to bring beneficial changes in BFP and LDL-C level for individuals with *MetS*. The results also suggested that probiotics did not have a significant effect in improving BFM, BMI, waist circumference, hip circumference, waist-to-hip ratio, fasting glucose, HbA1c, SBP, DBP, fasting insulin, TC, HDL-C, or triglycerides. Based on these 2 conclusions, the authors suggested that the probiotics should only be used as a complementary treatment to improve the overall effectiveness of other medical treatment.

In the future, researchers can improve the scientific rigor of their studies by using the triple-blind method, having large sample sizes with prior power calculation results, and providing complete reports on the randomizing process. Besides, it will be useful for future studies to provide more information regarding the sub-strains of the microbiome, as well as to provide detailed information about the participants. Such information will be useful for researchers to further analyze the data, and it will facilitate the designing of new intervention programs. Lastly, as it was mentioned in the previous chapter [30, 31], the use of probiotics in treating *MetS* has been widely publicized on different media platforms; however, without further studies, several claims remain ambiguous. Thus, to provide accurate and responsible health-related information for the public and to better evaluate the efficacy of using probiotics in *MetS* treatment, researchers should also include more strains of probiotic bacteria in their future RCTs studies.

Ethics Statement

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Y.D. (corresponding author) contributed to the study conception and design, the acquisition of data, the development of the protocol, and the drafting of the manuscript. M.X. (equal contributor) contributed to the development of the protocol,

the analysis and interpretation of the quantitative data, and the drafting of the manuscript. L.C. contributed to the development of the protocol and the critical revising of the final draft of the manuscript. A.B. contributed to the development of the protocol and the analysis and interpretation of the descriptive data.

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