REVIEW

Probiotics Contribute to Glycemic Control in Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

Thanitsara Rittiphairoj,[1,2] Krit Pongpirul,[2,3] Kantima Janchot,[4] Noel T Mueller,[1,5] and Tianjing Li[1,6]

[1] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; [2] Department of Preventive and Social Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [3] Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; [4] Panacee Group Co., Ltd, Bangkok, Thailand; [5] Welch Center for Prevention, Epidemiology and Clinical Research, Baltimore, MD, USA; and [6] Department of Ophthalmology, School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

ABSTRACT

This systematic review aimed to evaluate the effectiveness and safety of probiotics for glycemic control in adults with impaired glucose control, including prediabetes and type 2 diabetes mellitus (T2DM). We searched PubMed, Embase, and Cochrane databases, and trial registries up to February 2019. We included randomized controlled trials (RCTs) of participants with prediabetes or T2DM. Eligible trials compared probiotics versus either placebo, no intervention, or comparison probiotics, or compared synbiotics versus prebiotics. Primary outcomes were mean change in fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) from baseline to short term (<12 wk) and long term (≥12 wk). We performed meta-analyses using the random-effects model. We included 28 RCTs (1947 participants). Overall, probiotics reduced FBG more than the placebo/no intervention group with a mean difference (MD) of −12.99 mg/dL (95% CI: −23.55, −2.42; *P* value: 0.016) over the short term; and −2.99 mg/dL (95% CI: −5.84, −0.13; *P* value: 0.040) over the long term. There was also some evidence for reduced HbA1c in the probiotics group at both short term (MD: −0.17; 95% CI: −0.37, 0.02; *P* value: 0.084) and long term (MD: −0.14; 95% CI: −0.34, 0.06; *P* value: 0.172), however, these did not reach statistical significance possibly because only a few trials reported HbA1c as an outcome. Subgroup analyses showed a greater reduction in HbA1c in participants not receiving insulin therapy than those receiving insulin therapy. Furthermore, the effect of probiotics on the reduction of FBG was more pronounced in participants with FBG >130 mg/dL and those not receiving insulin therapy than their counterparts. Probiotics were also effective in lowering serum cholesterol over the short and long term. In conclusion, we found that probiotics may have a glucose-lowering effect in T2DM participants. The effect appeared to be stronger in participants with poorly controlled diabetes and those not on insulin therapy. Systematic review registration: CRD42019121682. *Adv Nutr* 2021;12:722–734.

Keywords: probiotics, type 2 diabetes mellitus, glycemic control, systematic review, meta-analysis

Introduction

Probiotics—live microbial communities (microbiota) that may benefit host health (1, 2)—are 1 of the most commonly used nutritional supplements worldwide (3). The gut microbiota has been shown to play a role in diabetes—a disease estimated to impact 451 million people in 2017 and projected to impact 693 million by 2045 (3, 4). Several randomized controlled trials (RCTs) have tested whether probiotics can improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Although some RCTs have found that probiotics lower blood sugar (5, 4, 6, 7, 8, 9), overall the evidence is inconsistent (10, 11, 12, 13). Previous systematic reviews and meta-analyses have concluded an overall beneficial effect of probiotics in adults with T2DM. However, the literature searches in these systematic reviews were not comprehensive and the trials included had a short treatment duration and follow-up period (14, 15, 16, 17, 18, 19, 20). Since the publication of these reviews, ≥2 RCTs with a longer treatment duration have been published (6, 9).

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Supplementary Table 1 is available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances.

Address correspondence to KP (e-mail: doctorkrit@gmail.com).

Abbreviations used: FBG, fasting blood glucose; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; MD, mean difference; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus.

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The purpose of this systematic review was to assess the effectiveness and safety of probiotics for glycemic control (fasting glucose and glycated hemoglobin [HbA1c]) over the short term and long term in adults with impaired glucose control, including prediabetes and T2DM. In addition, we examined plasma insulin (μU/mL), triglyceride, cholesterol, LDL cholesterol, HDL cholesterol (mg/dL), and health service outcomes. Finally, we determined whether treatment effects differed by the risk of bias, funding, diabetes severity and treatment, and probiotic strains.

Methods

We registered the systematic review with International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42019121682). We followed a pre-established protocol in conducting the review, which was previously published (21). Briefly, we searched PubMed, Embase, and Cochrane databases, and trial registries up to February 2019. We included RCTs of participants with pre-diabetes or T2DM. Eligible trials either compared probiotics with placebo, comparison probiotics, or no intervention, or they compared synbiotics (probiotics + prebiotics) with pre-biotics. Two reviewers (TR, KJ) independently screened titles and abstracts, reviewed full texts, extracted information, and assessed the risk of bias using Cochrane Risk of Bias 2 (22, 23). The tool is structured into 5 domains through which bias might be introduced into a result: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported results. We rated each domain as either "low risk of bias," "high risk of bias," or "some concerns" following a series of signaling questions. The overall risk of bias for the result is the least favorable assessment across the domains of bias.

We assessed publication bias and reporting bias by comparing information in the trial protocols and/or trial registrations with the publications of trials when they were available. Publication bias is suspected when a trial is completed but there are no publications available. Reporting bias is suspected when outcomes registered or described in the protocols are not reported in the publications.

We examined each outcome, described below, over the short term (<12 wk) and the long term (≥12 wk). Within each time frame, we chose the outcome measurement at the longest follow-up time point. The primary outcomes were mean change in fasting blood glucose (FBG; mg/dL) and mean change in HbA1c (%) from the baseline. For secondary outcomes, we focused on mean change in plasma insulin (μU/mL), triglyceride, cholesterol, LDL cholesterol, and HDL cholesterol (mg/dL) from the baseline. For adverse outcomes, we focused on the proportion of participants that experienced abdominal cramping, abdominal pain, nausea, taste disturbance, soft stools, diarrhea, flatulence, bloating, and systemic infection such as septicemia and endocarditis (24). For health service outcomes, we looked for costs associated with the intervention and mean number of hospital or health professional visits.

For statistical analysis, we used mean difference (MD) for continuous outcomes and risk ratio for binary outcomes. In cases where the MD was not reported, we calculated the MD as the mean (or mean change from baseline) in the intervention group minus the mean (or mean change from baseline) in the comparison group. We calculated SD from the SE or 95% CI whenever possible but did not impute the variability for the MD when they were not reported. We performed meta-analyses using random-effects models. The sources of heterogeneity were qualitatively investigated in the analyses that showed substantial statistical heterogeneity (I^2 was 50–90%). We conducted subgroup analyses by the risk of bias of trials (high risk of bias versus low risk of bias or some concern), funding (funded by food industry versus others), stage of disease (prediabetes versus T2DM), participants' baseline FBG (≤130 mg/dL versus >130 mg/dL), whether participants received insulin therapy at the baseline, type of vehicles for probiotics (foods versus capsules), and whether the probiotics contained the *Bifidobacterium* genus.

Results

Description of studies

Results of the search.

The electronic search yielded 4189 records, of which 66 records of 28 trials were included in our systematic review and 26 trials were included in meta-analyses (2 trials did not provide sufficient data for meta-analysis). We identified 22 ongoing studies and 17 studies that are awaiting classification (**Figure 1**).

Included studies.

We included 28 RCTs published between 2011 and 2019. Most RCTs (26, 90%) were single-center trials. The maximal planned length of follow-up ranged from 6 wk to 9 mo (median: 12; IQR: 8–12 wk). Of the 27 trials that reported receiving financial and nonfinancial support, 11 (39%) received funding from the food industry (**Table 1**).

Participants.

A total of 1947 participants were included. The number of participants per trial ranged from 24 to 234 (median: 64; IQR: 49–79). Half of participants (1031, 53%) were recruited from the Middle East (Iran: 935, 48%; Saudi Arabia: 96, 5%). Other participants were recruited from Austria (30, 1.5%), Brazil (125, 6%), China (234, 12%), Japan (170, 9%), Korea (48, 2.5%), Malaysia (136, 7%), Sweden (46, 2%), Taiwan (74, 4%), and the Ukraine (53, 3%). Participants were both men and women with ages ranging from 35 to 76 y. All participants had been diagnosed either with prediabetes or T2DM for 1–26 y and all were overweight. Most T2DM participants were fair to well-controlled in terms of FBG and HbA1c. All T2DM participants received an oral glucose-lowering medication(s) and one-third (33%; 645) received the additional insulin

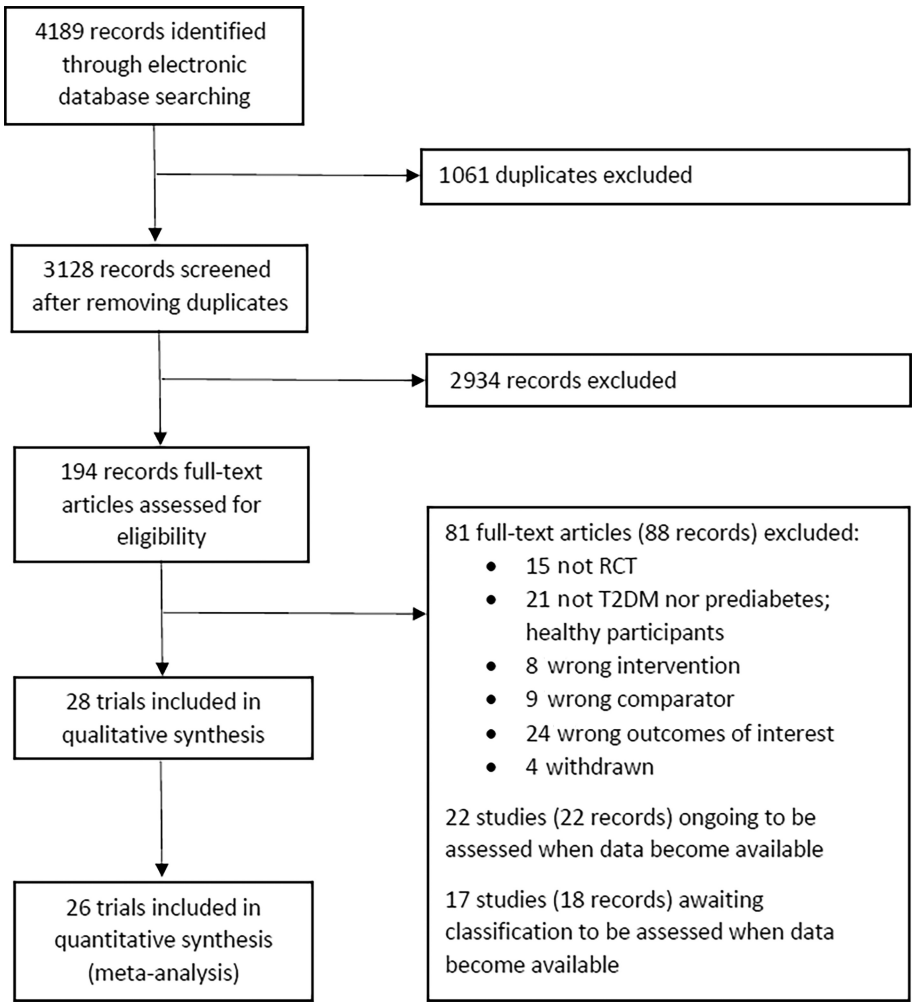

FIGURE 1 Study flow diagram. RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus.

therapy at baseline. No participants with prediabetes were taking type 2 diabetes medication (**Table 2**).

Type of interventions.

We focused on 3 comparisons: (2) probiotics versus placebo or no intervention (21 RCTs), (1) probiotics versus comparison probiotics (5 RCTs), and (3) synbiotics versus prebiotics (2 RCTs). Most of the trials (22, 76%) allowed participants to continue their diabetic standard therapy and remain on their usual diet during the trial. Half (16, 55%) of the trials mentioned that they did not allow pretreatment with antibiotics before and during the trial (**Table 3**).

Probiotics versus placebo or no intervention. Of the 21 RCTs that compared probiotics to placebo or no intervention, 7 (33%) evaluated multistrain probiotics versus placebo or no intervention. The number of strains ranged from 3 to 14 (median: 4; IQR: 4–7). Eleven RCTs (53%) compared single-strain probiotics versus placebo or no intervention. The remaining 3 RCTs (14%) did not report the number of strains. The type of vehicles for probiotics varied including fermented foods (i.e. yogurt, fermented milk, kimchi), functional foods (i.e. honey, bread), and dietary supplements (i.e. probiotic capsules or tablets). The microbial compositions were similar in terms of the genera, which were mainly *Lactobacillus* and *Bifidobacterium*; however, the species and strains differed, and the daily dose ranged from 10^6 to 10^{19} CFU across the trials. The treatment duration also varied across these 21 RCTs: 8 (38%) evaluated short-term treatment duration that ranged from 6 to 8 wk (median: 8; IQR: 7.6–8); 13 (62%) evaluated long-term treatment duration ranging from 12 to 36 wk (median: 12; IQR: 12–16) (Table 3).

Probiotics versus comparison probiotics. Of the 5 RCTs that compared probiotics to comparison probiotics, 4 (80%) evaluated 4-strain probiotics versus 2-strain control probiotics; and 1 (20%) evaluated 2-strain probiotics versus single-strain control probiotics. In these comparisons, all probiotics were fermented foods (i.e. yogurt and fermented milk). The microbial composition of probiotics was similar in terms of the genera, which were *Lactobacillus*, *Bifidobacterium*, and

TABLE 1 Study design of included trials that evaluated the effectiveness and safety of probiotics for glycemic control in patients with type 2 diabetes mellitus[1]

Study	Interventions compared	Allowed antidiabetic standard therapy during the trial	Allowed pretreatment with antibiotics	Multi/single center trial (*n*, recruiting centers)	Country(ies) in which participants were recruited	Maximal planned length of follow-up, wk	Number of participants randomized
Ejtahed et al., 2011 (25)	Probiotics; control probiotics	OGM	NR	Single	Iran	6	64
Ejtahed et al., 2012 (4)	Probiotics; control probiotics	OGM	NR	Single	Iran	6	64
Tripolt et al., 2013 (26)	Probiotics; no intervention	NR	No	Single	Austria	12	30
Mazloom et al., 2013 (13)	Probiotics; placebo	NR	NR	Single	Iran	6	NR
Asemi et al., 2013 (5)	Synbiotics; prebiotics	OGM	NR	Single	Iran	8	60
Barreto et al., 2014 (27)	Probiotics; placebo	NR	NR	Single	Brazil	12	24
Shakeri et al., 2014 (28)	Probiotics; placebo	OGM	NR	Single	Iran	8	78
Mohamadshahi et al., 2014 (7)	Probiotics; control probiotics	OGM	NR	Single	Iran	8	44
Jung et al., 2014 (29)	Probiotics; no intervention	LM, OGM	NR	Single	Korea	12	48
Tajadadi-Ebrahimi et al., 2014 (30)	Probiotics; placebo	OGM	NR	Single	Iran	8	81
Ostadrahimi et al., 2015 (31)	Probiotics; control probiotics	OGM	NR	Single	Iran	8	68
Bayat et al., 2016 (32)	Probiotics; no intervention	OGM	NR	Single	Iran	8	80
Bernini et al., 2016 (33)	Probiotics; no intervention	NR	No	Single	Brazil	45 days	51
Sato et al., 2017 (34)	Probiotics; placebo	LM, OGM, insulin therapy	NR	Single	Japan	16	70
Mobini et al., 2017 (35)	Probiotics; placebo	LM, OGM, insulin therapy	No	Single	Sweden	12	46
Firouzi et al., 2017 (36)	Probiotics; placebo	LM, OGM	No	Single	Malaysia	12	136
Tonucci et al., 2017 (37)	Probiotics; control probiotics	OGM	No	Unclear[2]	Brazil	6	50
Feizollahzadeh et al., 2017 (38)	Probiotics; placebo	OGM, insulin therapy	No	Single	Iran	8	48
Yuan et al., 2017 (39)	Probiotics; placebo	LM, OGM, insulin therapy	No	Multi (7)	China	12	234
Raygan et al., 2018 (40)	Probiotics; placebo	OGM, insulin therapy	No	Single	Iran	12	60
Kassaian et al., 2018 (41)	Probiotics; placebo	NR	No	Single	Iran	24	120
Sabico et al., 2018 (9)	Probiotics; placebo	NR	No	Single	Saudi Arabia	6 months	96
Kobyliak et al., 2018 (12)	Probiotics; placebo	OGM, insulin therapy	No	Single	Ukraine	8	53
Hsieh et al., 2018 (6)	Probiotics; placebo	OGM, insulin therapy	No	Single	Taiwan	9 months	74
Mazruei et al., 2019 (42)	Probiotics; placebo	OGM, insulin therapy	No	Single	Iran	12	60
Naito et al., 2018 (43)	Probiotics; placebo	NR	No	Single	Japan	12	100
Razmpoosh et al., 2019 (44)	Synbiotics; prebiotics	OGM	No	Single	Iran	6	68
Khalili et al., 2019 (45)	Probiotics; placebo	OGM	No	Single	Iran	8	40

[1] LM, lifestyle modification; NR, not reported; OGM, oral glucose-lowering medication.
[2] Participants were recruited from 2 clinics in the same city.

TABLE 2 Baseline participant characteristics of intervention versus comparison of included trials that evaluated the effectiveness and safety of probiotics for glycemic control in patients with type 2 diabetes mellitus[1]

	Age, y		Participants, *n* (% female)		Duration of diabetes, y		BMI, kg/m^2		2-h OGTT, mg/dL		HbA1c, %	
Study	Intervention	Comparison	Intervention	Comparison	Intervention	Comparison	Intervention	Comparison	Intervention	Comparison	Intervention	Comparison
Ejtahed et al., 2011 (25)	50.87 ± 1.40	51.00 ± 1.34	19 (63)	18 (60)	5.82 ± 0.90	4.08 ± 0.78	28.95 ± 0.67	29.14 ± 0.78	NR	NR	NR	NR
Ejtahed et al., 2012 (4)	50.87 ± 7.68	51.00 ± 7.32	19 (63)	18 (60)	5.82 ± 4.95	4.08 ± 4.28	28.95 ± 3.65	29.14 ± 4.30	NR	NR	7.29 ± 1.21	6.87 ± 0.81
Tripolt et al., 2013 (26)	51.00 ± 11.00	55.00 ± 9.00	4 (31)	6 (40)	NR	NR	34.9 ± 5.3	31.4 ± 3.7	7.90 ± 2.30	8.2 ± 2.90	NR	NR
Mazloom et al., 2013 (13)	55.40 ± 8.00	51.80 ± 10.20	26 (76)	NR	NR	27.97 ± 3.81	27.24 ± 2.73	NR	NR	NR	NR	NR
Asemi et al., 2013 (5)	50.51 ± 9.82	52.59 ± 7.14	42 (70)	NR	NR	31.16 ± 6.36	30.17 ± 4.23	NR	NR	NR	7.71 ± 0.37[3]	6.35 ± 0.30[3]
Barreto et al., 2014 (27)	62 (58.3–67)[2]	63 (60.5–75.7)[2]	NR	NR	NA	NA	27.5 (26.0–31.3)[2]	27.5 (24.3–30.0)[2]	NR	NR	NR	NR
Shakeri et al., 2014 (28)	52.30 ± 8.20	53.10 ± 7.50	NR	NR	NR	NR	29.50 ± 5.70	30.6 ± 4.10	NR	NR	NR	NR
Mohamadshahi et al., 2014 (7)	53.00 ± 5.90	49.00 ± 7.08	NR	NR	NR	NR	28.36 ± 4.14	29.22 ± 3.20	NR	NR	8.24 ± 1.68	8.33 ± 1.46
Jung et al., 2014 (29)	63.30 ± 2.00	60.20 ± 1.90	9 (43)	10 (50)	NR	NR	25.90 ± 0.90	25.60 ± 0.70	NR	NR	6.77 ± 0.20[3]	6.77 ± 0.2[3]
Tajadadi-Ebrahimi et al., 2014 (30)	52.00 ± 7.20	53.40 ± 7.50	NR	NR	NR	NR	29.80 ± 5.70	30.50 ± 4.10	NR	NR	NR	NR
Ostadrahimi et al., 2015 (31)	NR	NR	12 (40)	14 (47)	6.47 ± 0.90	7.36 ± 0.84	28.89 ± 4.77	27.47 ± 3.55	NR	NR	7.61 ± 1.22	6.98 ± 1.63
Bayat et al., 2016 (32)	54.10 ± 9.54	46.95 ± 9.34	17 (85)	11 (55)	NR	NR	28.77 ± 4.59	29.75 ± 4.66	NR	NR	7.06 ± 1.58	7.54 ± 2.03
Bernini et al., 2016 (33)	NR	NR	NR	NR	NR	NR	30.8 (27.2–33.7)[2]	35.8 (33.4–44.5)[2]	NR	NR	NR	NR
Sato et al., 2017 (34)	64.00 ± 9.20	65.00 ± 8.3	5 (15)	14 (41)	NR	NR	24.20 ± 2.60	24.60 ± 2.60	NR	NR	NR	NR
Mobini et al., 2017 (35)	64.00 ± 6.00	65.00 ± 5.00	3 (21)	4 (27)	14.40 ± 9.60	18.30 ± 7.30	32.30 ± 3.40	30.70 ± 4.00	NR	NR	8.10 ± 0.70	7.70 ± 0.50
Firouzi et al., 2017 (36)	52.90 ± 9.20	54.2 ± 8.30	65 (48)	NR	NR	29.20 ± 5.60	29.30 ± 5.30	NR	NR	NR	7.46 ± 1.20	7.29 ± 1.60
Tonucci et al., 2017 (37)	51.83 ± 6.64	50.95 ± 7.20	11 (47)	8 (37)	6.0 (2–17)[2]	4.5 (2–15)[2]	27.49 ± 3.97	29.20 ± 5.60	NR	NR	6.07 (5.4–7.0)[2]	5.35 (4.9–6.1)[2]
Feizollahzadeh et al., 2017 (38)	56.90 ± 1.81[3]	53.60 ± 1.60[3]	11 (55)	10 (50)	8.70 ± 2.10	6.90 ± 4.90	26.68 ± 0.71	26.58 ± 0.73	NR	NR	NR	NR
Yuan et al., 2017 (39)	57.43 ± 9.50	57.71 (8.20)	61	56	9.49 ± 6.43	9.20 ± 6.20	25.53 ± 4.26	24.91 ± 2.81	NR	NR	8.00 ± 1.08	7.99 ± 1.03
Raygan et al., 2018 (40)	60.70 ± 9.40	61.8 (9.8)	NR	NR	6.60 ± 1.90	6.80 ± 2.20	30.30 ± 5.20	29.30 ± 4.10	NR	NR	NR	NR
Kassaian et al., 2018 (41)	52.90 ± 6.30	52.97 ± 5.90	14 (52)	16 (57)	NR	NR	29.60 ± 3.50	30.40 ± 3.20	NR	NR	5.68 ± 0.40	5.70 ± 0.40
Sabico et al., 2018 (9)	48.00 ± 8.30	46.60 ± 5.9	20 (51)	18 (46)	NR	NR	29.40 ± 5.20	30.10 ± 5.00	NR	NR	NR	NR
Kobyliak et al., 2018 (12)	52.23 ± 1.74	57.18 ± 2.06	NR	NR	6.16 ± 0.92	5.91 ± 0.87	34.70 ± 1.29	35.65 ± 1.57	NR	NR	8.40 ± 0.22	8.31 ± 0.29
Hsieh et al., 2018 (6)	52.32 ± 10.20	55.77 ± 8.55	10 (46)	9 (41)	NR	NR	28.04 ± 4.29	27.53 ± 3.15	NR	NR	7.91 ± 0.68	7.91 ± 0.62
Mazruei et al., 2019 (42)	62.70 ± 9.10	60.30 ± 8.50	NR	NR	NR	NR	30.30 ± 5.60	31.10 ± 4.60	NR	NR	NR	NR
Naito et al., 2018 (43)	46.60 ± 1.10[3]	47.40 ± 1.00[3]	0	0	NA	NA	29.5 ± 0.40[3]	29.0 ± 0.40[3]	161.50 ± 3.50[3]	165.80 ± 4.60[3]	5.74 ± 0.04[3]	5.79 ± 0.04[3]
Razmpoosh et al., 2019 (44)	58.60 ± 6.50	61.30 ± 5.20	13 (43)	14 (47)	6.20 ± 3.10	5.90 ± 2.90	27.70 ± 4.20	27.20 ± 4.20	NR	NR	NR	NR
Khalili et al., 2019 (45)	43.95 ± 8.14	45.00 ± 5.37	13 (65)	13 (65)	4.00 ± 3.81	3.67 ± 4.00	29.50 ± 3.34	31.94 ± 5.76	NR	NR	7.30 ± 0.65	6.83 ± 0.95

[1] Values are means ± SDs or *n* (%) unless otherwise indicated; HbA1c, glycated hemoglobin; NA, not applicable; NR, not reported; 2-h OGTT = 2-h oral-glucose-tolerance test.
[2] Data reported as median (range).
[3] Data reported as mean ± SE.

TABLE 3 Intervention and comparison of included trials that evaluated the effectiveness and safety of probiotics for glycemic control in patients with type 2 diabetes mellitus[1]

Study	Type of vehicles for probiotics/synbiotics		Microbial composition and content (CFU) per dose		Dose		Frequency of usage		Duration of treatment, week
	Intervention	Comparison	Intervention	Comparison	Intervention	Comparison	Intervention	Comparison	
Ejtahed et al., 2011 (25)	Yogurt	Yogurt	*Lactobacillus acidophilus* La5 (2.2×10^9 CFU); *Bifidobacterium lactis* Bb12 (1.8×10^9 CFU); *Lactobacillus bulgaricus* (NR); *Streptococcus thermophilus* (NR)	*Lactobacillus bulgaricus* (NR); *Streptococcus thermophilus* (NR)	300 g	300 g	once a day	once a day	6
Ejtahed et al., 2012 (4)	Yogurt	Yogurt	*Lactobacillus acidophilus* La5 (2.2×10^9 CFU); *Bifidobacterium lactis* Bb12 (1.8×10^9 CFU); *Lactobacillus bulgaricus* (NR); *Streptococcus thermophilus* (NR)	*Lactobacillus bulgaricus* (NR); *Streptococcus thermophilus* (NR)	300 g	300 g	once a day	once a day	6
Tripolt et al., 2013 (26)	Milk[2]	NA	*Lactobacillus casei* Shirota (6.5×10^9 CFU)	NA	65 mL	NA	thrice a day	NA	12
Mazloom et al., 2013 (13)	Capsules	Capsules	*Lactobacillus acidophilus* (NR); *Lactobacillus bulgaricus* (NR); *Lactobacillus bifidum* (NR); *Lactobacillus casei* (NR)	NA	1.5 g	1.5 g	twice a day	twice a day	6
Lactobacillus bifidum (NR); *Lactobacillus casei* (NR)	Capsules	Capsules	*Bifidobacterium breve* (2×10^{10} CFU); *Lactobacillus casei* (7×10^9 CFU); *Bifidobacterium longum* (7×10^9 CFU); *Lactobacillus acidophilus* (2×10^9 CFU); *Lactobacillus rhamnosus* (1.5×10^9 CFU); *Streptococcus thermophilus* (1.5×10^9 CFU); *Lactobacillus bulgaricus* (2×10^8 CFU)	NA	NR	NR	once a day	once a day	8
Asemi et al., 2013 (5)	Milk[2]	NA	*Lactobacillus plantarum* LP 115 (1×10^9 CFU)	NA	80 mL	80 mL	once a day	once a day	12
Lactobacillus bulgaricus (2×10^8 CFU)	Bread	Bread	*Lactobacillus sporogenes* (4×10^9 CFU)	NA	40 g	40 g	thrice a day	thrice a day	8
Barreto et al., 2014 (27)	Yogurt	Yogurt	*Lactobacillus acidophilus* La5 (5.55×10^8 CFU); *Bifidobacterium lactis* Bb12 (5.55×10^8 CFU); *Lactobacillus delbrueckii* (NR); *Streptococcus thermophilus* (NR)	*Lactobacillus delbrueckii* (NR); *Streptococcus thermophilus* (NR)	150 g	150 g	twice a day	twice a day	8
Shakeri et al., 2014 (28)	Kimchi[4]	NA	NR	NA	NR	NA	thrice a day	NA	12
Mohamadshahi et al., 2014 (7)	Bread	Bread	*Lactobacillus sporogenes* (4×10^9 CFU)	NA	40 g	40 g	thrice a day	thrice a day	8
Jung et al., 2014 (29)	Milk[2]	Milk[2]	*Lactobacillus acidophilus* (1.5×10^{10} CFU); *Lactobacillus casei* (9×10^9 CFU); *Bifidobacterium lactis* (4.8×10^9 CFU); *Streptococcus thermophilus* (NR)	*Streptococcus thermophilus* (NR); *Lactobacillus bulgaricus* (NR)	600 mL	600 mL	twice a day	twice a day	8
Tajadadi-Ebrahimi et al., 2014 (30)	Yogurt	NA	NR	NA	150 g	NA	once a day	NA	8
Ostadrahimi et al., 2015 (31)	Milk[2]	NA	*Bifidobacterium animalis* HN019 (2.72×10^{10} CFU)	NA	80 mL	NA	once a day	NA	45 days
Bayat et al., 2016 (32)	Milk[2]	Milk[3]	*Lactobacillus casei* Shirota (4×10^{10} CFU)	NA	80 mL	80 mL	once a day	once a day	16
Bernini et al., 2016 (33)	Powders	Powders	*Lactobacillus reuteri* DSM 17,938 (10^{10} CFU)	NA	10^{10} CFU	NR	once a day	once a day	12
Sato et al., 2017 (34)	Powders	Powders	*Lactobacillus acidophilus* (10^5 CFU); *Lactobacillus casei* (10^5 CFU); *Lactobacillus lactis* (10^5 CFU); *Bifidobacterium bifidum* (10^5 CFU); *Bifidobacterium longum* (10^5 CFU); *Bifidobacterium infantis* (10^5 CFU)	NA	3×10^{10} CFU	NR	twice a day	twice a day	12
Mobini et al., 2017 (35)	Milk[2]	Milk[2]	*Lactobacillus acidophilus* La-5 (10^9 CFU); *Bifidobacterium animalis* BB-12 (10^9 CFU)	*Streptococcus thermophilus* TA-40 (NR)	120 g	120 g	once a day	once a day	6
Firouzi et al., 2017 (36)	Soymilk	Soymilk	*Lactobacillus plantarum* A7 (2×10^7 CFU)	NA	200 mL	200 L	once a day	once a day	8
Tonucci et al., 2017 (37)	Tablets	Tablets	*Bacillus cereus* ($>0.5 \times 10^6$ CFU); *Bifidobacterium infantis* ($>0.5 \times 10^6$ CFU); *Enterococcus faecalis* ($>0.5 \times 10^6$ CFU); *Lactobacillus acidophilus* ($>0.5 \times 10^6$ CFU)	NA	1.5 g	1.5 g	thrice a day	thrice a day	8
Feizollahzadeh et al., 2017 (38)	Capsules	Capsules	*Bifidobacterium bifidum* (2×10^9 CFU); *Lactobacillus casei* (2×10^9 CFU); *Lactobacillus acidophilus* (2×10^9 CFU)	NA	NR	NR	once a day	NR	12
Yuan et al., 2017 (39)	Powders	Powders	*Lactobacillus acidophilus* (1×10^9 CFU); *Bifidobacterium lactis* (1×10^9 CFU); *Bifidobacterium bifidum* (1×10^9 CFU); *Bifidobacterium longum* (1×10^9 CFU)	NA	6 g	NR	once a day	once a day	24

(*Continued*)

TABLE 3 (*Continued*)

Study	Type of vehicles for probiotics/synbiotics		Microbial composition and content (CFU) per dose		Dose		Frequency of usage		Duration of treatment, week
	Intervention	Comparison	Intervention	Comparison	Intervention	Comparison	Intervention	Comparison	
Raygan et al., 2018 (40)	Powders	Powders	*Bifidobacterium bifidum* W23 (NR); *Bifidobacterium lactis* W52 (NR); *Lactobacillus acidophilus* W37 (NR); *Lactobacillus brevis* W63 (NR); *Lactobacillus casei* W56 (NR); *Lactobacillus salivarius* W24 (NR); *Lactobacillus lactis* W19 (NR); *Lactobacillus lactis* W58 (NR)	NA	5×10^9 CFU	2 g	twice a day	twice a day	6 months
Kassaian et al., 2018 (41)	Powders	Powders	*Lactobacillus* + *Lactococcus* (6×10^{11} CFU); *Propionibacterium* (3×10^{11} CFU); *Bifidobacterium* (1×10^{11} CFU); *Acetobacter* (1×10^7 CFU)	NA	10 g	10 g	once a day	once a day	8
Sabico et al., 2018 (9)	Capsules	Capsules	*Lactobacillus reuteri* GMNL-89 (2×10^9 CFU)	NA	4×10^9 CFU	NR	once a day	once a day	6 months
Kobyliak et al., 2018 (12)	Honey	Honey	*Bacillus coagulans* T4 (2.5×10^9 CFU)	NA	25 g	25 g	once a day	once a day	12
Hsieh et al., 2018 (6)	Milk[2]	Milk[3]	*Lactobacillus casei* Shirota YIT 9029 ($> 1.0 \times 10^{11}$ CFU)	NA	100 mL	100 mL	once a day	once a day	8
Mazruei et al., 2019 (42)	Capsules	Capsules	*Bifidobacterium breve* (3×10^{10} CFU); *Lactobacillus casei* (7×10^9 CFU); *Bifidobacterium longum* (7×10^9 CFU); *Lactobacillus acidophilus* (2×10^9 CFU); *Lactobacillus rhamnosus* (1.5×10^9 CFU); *Streptococcus thermophilus* (1.5×10^9 CFU); *Lactobacillus bulgaricus* (2×10^8 CFU)	NA	NR	NA	twice a day	twice a day	6
Naito et al., 2018 (43)	Capsules	Capsules	*Lactobacillus casei* (10^8 CFU)	NA	10^8 CFU	NR	once a day	once a day	8

[1]NA, not applicable; NR, not reported.
[2]Fermented milk.
[3]Nonfermented milk.
[4]Kimchi and fermented soy-based condiments.

Streptococcus; however, the species and strains varied among trials. The daily dose ranged from 10^9 to 10^{10} CFU. The treatment was short term in all 5 RCTs, ranging from 6 to 8 wk (Table 3).

Synbiotics versus prebiotics. Two RCTs compared prebiotics versus 7-strain synbiotics in dietary supplements. Both trials were similar concerning the microbial composition; however, the daily dose differed between trials. Treatment duration was 6 and 8 wk in these trials (Table 3).

Type of outcomes

Apart from Ejtahed (2011) (25), which measured only mean change in triglyceride, cholesterol, LDL cholesterol, and HDL cholesterol (mg/dL) from the baseline, all included trials measured ≥1 of our primary outcomes of interest. For our secondary outcomes of interest, the number of trials reporting each outcome ranged from 19 to 21. None of the studies reported health service utilization outcomes and half of the studies (15, 52%) reported adverse events (**Table 4**).

Risk of bias in included studies

The overall risk of bias of the included RCTs was either some concern or high (**Figure 2** and **Supplementary Table 1**). Six trials (21%) were rated at a high risk of bias arising from the randomization process. Thirteen trials (46%) were rated at a high risk of bias due to deviation from intended interventions. Seven trials (25%) were rated at a high risk of bias due to missing outcome data. None of the trials was rated at a high risk of bias in the measurement of the outcome and selection of the reported results. We did not find evidence for publication or reporting bias.

Effects of interventions

Comparison I: probiotics versus placebo or no intervention (Table 5).

FBG. Twenty-one RCTs (1529 participants) were included for comparison I. Nine RCTs (428 participants) evaluated FBG in the short term. Eight RCTs reported sufficient data to permit meta-analysis and the average effect from these RCTs was in favor of probiotics (MD: −12.99; 95% CI: −23.55, −2.42; *P* value: 0.016; $I^2 = 65.7\%$). Twelve RCTs (805 participants) evaluated FBG in the long term. All reported sufficient data to permit meta-analysis and the average effect from these RCTs was in favor of probiotics (MD: −2.99; 95% CI: −5.84, −0.13; *P* value: 0.040; $I^2 = 0\%$).

HbA1c. Four RCTs (231 participants) evaluated HbA1c in the short term. All RCTs reported sufficient data to permit meta-analysis. Although the average effect appears to favor probiotics, it did not meet the threshold for statistical significance (MD: −0.17; 95% CI: −0.37, 0.02; *P* value: 0.084; $I^2 = 36.3\%$). Seven RCTs (572 participants) evaluated HbA1c in the long term. All reported sufficient data to permit meta-analysis. Although the average effect favored probiotics, the

TABLE 4 Outcome measures of included trials that evaluated the effectiveness and safety of probiotics for glycemic control in patients with type 2 diabetes mellitus[1]

Study	FBG	Insulin	HbA1c	Cholesterol	Triglyceride	HDL-C	LDL-C
Ejtahed et al., 2011 (25)	—	—	—	✓	✓	✓	✓
Ejtahed et al., 2012 (4)	✓	✓	✓	—	—	—	—
Tripolt et al., 2013 (26)	✓	✓	—	—	—	—	—
Mazloom et al., 2013 (13)	✓	✓	—	✓	✓	✓	✓
Asemi et al., 2013 (5)	✓	✓	✓	✓	✓	✓	✓
Barreto et al., 2014 (27)	✓	✓	—	✓	✓	✓	✓
Shakeri et al., 2014 (28)	✓	—	—	✓	✓	✓	✓
Mohamadshahi et al., 2014 (7)	✓	—	✓	✓	✓	✓	✓
Jung et al., 2014 (29)	✓	✓	✓	✓	✓	✓	✓
Tajadadi-Ebrahimi et al., 2014 (30)	✓	✓	—	—	—	—	—
Ostadrahimi et al., 2015 (31)	✓	—	✓	✓	✓	✓	✓
Bayat et al., 2016 (32)	✓	—	✓	✓	✓	✓	✓
Bernini et al., 2016 (33)	✓	✓	—	✓	✓	✓	✓
Sato et al., 2017 (34)	✓	—	✓	✓	✓	✓	
Mobini et al., 2017 (35)	✓	—	✓	✓	✓	✓	✓
Firouzi et al., 2017 (36)	✓	✓	✓	✓	✓	✓	✓
Tonucci et al., 2017 (37)	✓	✓	✓	✓	✓	✓	✓
Feizollahzadeh et al., 2017 (38)	✓	—	—	—	✓	✓	✓
Yuan et al., 2017 (39)	✓	—	✓	—	—	—	—
Raygan et al., 2018 (40)	✓	✓	—	✓	✓	✓	✓
Kassaian et al., 2018 (41)	✓	✓	✓	—	—	—	—
Sabico et al., 2019 (9)	✓	✓	—	✓	✓	✓	✓
Kobyliak et al., 2018 (12)	✓	✓	✓	—	—	—	—
Hsieh et al., 2018 (6)	✓	✓	✓	✓	✓	✓	✓
Mazruei et al., 2019 (42)	✓	✓	—	✓	✓	✓	✓
Naito et al., 2018 (43)	✓	✓	✓	✓	✓	✓	✓
Razmpoosh et al., 2019 (44)	✓	✓	—	✓	✓	✓	✓
Khalili et al., 2019 (45)	✓	✓	✓	—	—	—	—

[1] FBG, fasting blood glucose; HbA1c, glycated hemoglobin.

difference was not statistically significant (MD: −0.14; 95% CI: −0.34, 0.06; *P* value: 0.172; $I^2 = 72.1\%$).

Secondary outcomes. We found statistically significant differences in mean change in serum cholesterol and LDL cholesterol from baseline in favor of probiotics in the short term and statistically significant differences in mean change in serum insulin, triglyceride, and serum cholesterol from baseline in favor of probiotics in the long term. The estimates and 95% CIs are available in Table 5.

Health services outcomes. No trials reported costs associated with the intervention or mean number of hospital or health professional visits.

Sources of heterogeneity. We concluded that the statistical heterogeneity could be due to differences in participants' ethnicity, blood sugar control, bacterial strains, and dose of probiotics.

Subgroup analysis for comparison I: probiotics versus placebo or no intervention (Table 6).

FBG. In the subgroups of trials without the high risk of bias, trials not funded by the food industry, trials of participants with T2DM, trials testing food-type probiotics, and trials among participants that did not receive insulin therapy, there was a statistically significantly difference in mean change in FBG from baseline, in favor of probiotics, between the probiotics and placebo or no intervention

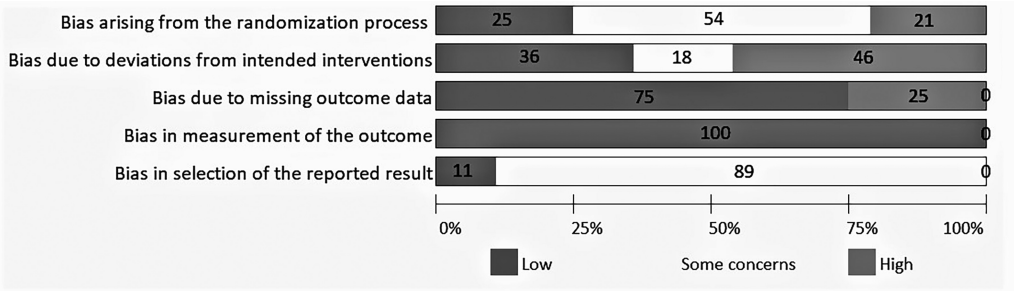

FIGURE 2 Risk of bias.

TABLE 5 Summary estimates for primary and secondary outcomes at short term and long term derived from meta-analyses on 3 comparisons from 26 trials[1]

Intervention	Comparison	Outcomes	Studies, *n*	Participants, *n*	MD	95% CI	*P* value	In favor of	Tau-squared	*I*-squared
Probiotics	Placebo/no intervention	Short term								
		Primary Outcomes								
		Fasting blood glucose	8	428	−12.99	(−23.55, −2.42)	0.016	Probiotics	0.005	65.7
		HbA1c	4	231	−0.17	(−0.37, 0.02)	0.084	—	0.194	36.3
		Secondary Outcomes								
		Serum insulin	5	296	−0.98	(−2.38, 0.42)	0.170	—	0.122	45.0
		Triglyceride	5	281	−20.98	(−63.96, 22.01)	0.339	—	0.021	65.3
		Cholesterol	4	241	−10.69	(−19.53, −1.85)	0.018	Probiotics	0.680	0
		LDL-C	5	281	−9.55	(−17.13, −1.98)	0.013	Probiotics	0.942	0
		HDL-C	5	281	3.25	(−0.05, 6.54)	0.054	—	0.176	36.8
		Long term								
		Primary outcomes								
		Fasting blood glucose	12	805	−2.99	(−5.84, −0.13)	0.040	Probiotics	0.774	0
		HbA1c	7	572	−0.14	(−0.34, 0.06)	0.172	—	0.001	72.1
		Secondary outcomes								
		Serum insulin	9	474	−1.79	(−3.33, −0.24)	0.023	Probiotics	0.011	59.4
		Triglyceride	10	516	−12.39	(−23.78, −0.99)	0.033	Probiotics	0.195	27.0
		Cholesterol	10	516	−4.77	(−9.20, 0.33)	0.035	Probiotics	0.981	0
		LDL-C	8	420	−2.67	(−7.48, 2.14)	0.277	—	0.886	0
		HDL-C	9	488	1.49	(−0.47, 3.46)	0.136	—	0.030	53.0
Synbiotics	Prebiotics	Short term								
		Primary outcomes								
		Fasting blood glucose	2	114	−19.52	(−32.42, −6.62)	0.003	Synbiotics	0.341	0
		HbA1c	1	54	−0.48	(−1.43, 0.47)	0.320	—	.	.
		Secondary outcomes								
		Serum insulin	2	114	−1.66	(−3.72, 0.40)	0.115	—	0.510	0
		Triglyceride	2	114	−8.71	(−28.79, 11.37)	0.395	—	0.568	0
		Cholesterol	2	114	−4.92	(−19.17, 9.33)	0.499	—	0.694	0
		LDL-C	2	114	−3.59	(−13.60, 6.43)	0.483	—	0.870	0
		HDL-C	2	114	0.99	(−2.70, 4.69)	0.598	—	0.560	0
Probiotics	Control probiotics	Long term								
		Primary outcomes								
		Fasting blood glucose	3	165	−8.56	(−37.19, 20.08)	0.558	—	0.017	75.5
		HbA1c	3	165	−0.15	(−0.55, 0.25)	0.452	—	0.547	0
		Secondary outcomes								
		Serum insulin	2	115	0.35	(−1.28, 1.98)	0.672	—	0.853	0
		Triglyceride	3	165	−2.39	(−29.69, 24.91)	0.864	—	0.264	24.9
		Cholesterol	3	165	−9.95	(−31.42, 11.53)	0.364	—	0.061	64.2
		LDL-C	3	165	−2.08	(−14.46, 10.31)	0.742	—	0.208	36.3
		HDL-C	3	165	0.29	(−3.30, 3.88)	0.873	—	0.996	0

[1] There are 20 trials in probiotics versus placebo or no intervention comparison, 2 trials in synbiotics versus prebiotics, and 4 trials in probiotics versus control probiotics (total 26 trials) that reported sufficient data to permit meta-analysis; HbA1c, glycated hemoglobin; MD, mean difference; short term is defined as <12 wk; long term is defined as ≥12 wk.

TABLE 6 Summary estimates on fasting blood glucose and glycated hemoglobin from subgroup analysis and additional analysis on probiotics versus placebo or no intervention comparison[1]

	n, studies	*n*, participants	MD	(95% CI)	*P* value	In favor of	Tau-squared	I-squared	*P* value
Fasting blood glucose									
High risk of bias	10	522	−2.68	(−5.75, 0.39)	0.087	—	0.987	0.0	0.396
Not high risk of bias	10	711	−10.26	(−18.23, −2.30)	0.012	Probiotics	0.003	64.3	
Funded by industry	11	615	−2.99	(−5.84, −0.14)	0.040	Probiotics	0.713	0.0	0.501
Not funded by industry	9	618	−8.12	(−15.76, −0.48)	0.037	Probiotics	0.008	61.2	
T2DM	15	977	−9.14	(−15.12, −3.17)	0.003	Probiotics	0.062	38.9	0.081
Prediabetes	2	153	−2.54	−5.45, 0.37)	0.087	—	0.794	0.0	
Metabolic syndrome	3	103	−0.30	(−6.14, 5.53)	0.919	—	0.928	0.0	
FBG ≤ 130 mg/dL	7	401	−2.58	(−4.99, −0.16)	0.036	Probiotics	0.953	0.0	0.000
FBG > 130 mg/dL	10	530	−16.15	(−24.62, −7.68)	0.000	Probiotics	0.211	25.2	
Foods	11	556	−4.55	(−8.97, −0.12)	0.044	Probiotics	0.140	32.4	0.663
Capsules	9	677	−6.20	(−12.64, 0.24)	0.059	—	0.105	39.4	
Contained *Bifidobacterium*	4	268	−3.53	(−7.42, 0.36)	0.075	—	0.745	0.0	0.828
Do not contain *Bifidobacterium*	6	296	−7.12	(−15.39, 1.15)	0.091	—	0.024	61.3	
Received insulin therapy	8	588	−3.52	(−8.50, 1.45)	0.165	—	0.660	0.0	0.006
Did not received insulin therapy	6	328	−18.40	(−30.20, −6.60)	0.000	Probiotics	0.073	50.4	
Additional analysis: short- and long-term combination	20	1233	−4.95	(−8.36, −1.54)	0.004	Probiotics	0.080	32.6	
Glycated hemoglobin									
High risk of bias	5	318	−0.16	(−0.35, 0.03)	0.098	—	0.009	70.2	0.923
Not high risk of bias	6	485	−0.17	(−0.43, 0.08)	0.182	—	0.025	61.0	
Funded by industry	4	296	−0.01	(−0.17, 0.16)	0.946	—	0.070	57.5	0.002
Not funded by industry	7	507	−0.29	(−0.45, −0.12)	0.001	Probiotics	0.148	36.8	
T2DM	9	650	−0.18	(−0.38, 0.02)	0.078	—	0.001	68.3	0.996
Prediabetes	2	153	−0.11	(−0.23, −0.002)	0.046	Probiotics	0.310	3.1	
FBG ≤ 130 mg/dL	4	262	−0.14	(−0.34, 0.06)	0.161	—	0.004	77.4	0.477
FBG > 130 mg/dL	5	263	−0.16	(−0.42, 0.11)	0.248	—	0.082	51.6	
Foods	4	247	−0.19	(−0.46, 0.09)	0.180	—	0.001	80.7	0.235
Capsules	7	556	−0.16	(−0.32, −0.01)	0.038	Probiotics	0.158	35.4	
Contained *Bifidobacterium*	2	156	−0.19	(−0.35, −0.03)	0.021	Probiotics	0.757	0.0	0.401
Did not contain *Bifidobacterium*	2	138	−0.12	(−0.30, 0.06)	0.180	—	0.264	19.9	
Received insulin therapy	5	428	−0.04	(−0.28, 0.21)	0.759	—	0.031	62.3	0.002
Not received insulin therapy	4	222	−0.34	(−0.58, −0.11)	0.004	Probiotics	0.170	40.3	
Additional analysis: short- and long-term combination	11	803	−0.16	(−0.30, −0.02)	0.023	Probiotics	0.003	61.9	

[1] FBG, fasting blood glucose; MD, mean difference; T2DM, type 2 diabetes mellitus.

comparison. The magnitude of reduction was significantly greater in the subgroup of participants with baseline FBG >130 mg/dL than in participants with baseline FBG ≤130 mg/dL ($P < 0.001$); and significantly greater in the subgroup of participants not receiving insulin therapy at baseline ($P = 0.006$).

HbA1c. In subgroups of trials not funded by the food industry, probiotics that contained *Bifidobacterium*, capsule-type probiotics, trials among prediabetic participants, and trials among participants not receiving insulin therapy, there was a statistically significant difference in mean change in HbA1c from baseline, in favor of probiotics, between

the probiotics and placebo or no intervention comparison. The magnitude of reduction was significantly greater in the subgroups that were not funded by the food industry ($P = 0.002$) and in participants not receiving insulin therapy ($P = 0.002$).

Additional analysis. When all trials were combined regardless of the duration of treatment, we found significant differences in mean change in FBG (MD: −4.95; 95% CI: −8.36, −1.54; *P* value: 0.004; $I^2 = 32.6\%$) and HbA1c from baseline (MD: −0.16; 95% CI: −0.30, −0.02; *P* value: 0.023; $I^2 = 61.9\%$) in favor of probiotics.

Comparison II: synbiotics (probiotics with added prebiotics) versus prebiotics (Table 5).

Two RCTs (114 participants) made this comparison. We found a statistically significant difference in mean change in FBG in favor of synbiotics (MD: −19.52; 95% CI: −32.42, −6.62; *P* value: 0.003; $I^2 = 0\%$) in the short-term trials. We found either no data or no evidence of a difference for other outcomes analyzed (Table 5).

Comparison III: probiotics versus other probiotics (Table 5).

Five RCTs (225 participants) made this comparison. Of these 5 RCTs, 3 reported FBG, 3 reported HbA1c, 4 reported serum insulin, 3 reported triglyceride, 3 reported LDL cholesterol, and 3 reported HDL cholesterol. One RCT did not contribute data to any meta-analysis (7). We found either no data or no evidence of a difference for all outcomes analyzed.

Adverse events.

Of 15 trials (53.6%) that reported adverse events, none reported serious adverse events. Three trials reported minor adverse events observed in the probiotics group which were abdominal cramping, dyspepsia, or diarrhea or soft stools. However, the number of participants reporting minor adverse events was <5% in each trial. We did not have enough data to calculate a between-group difference.

Discussion

We conducted a systematic review to evaluate the effectiveness and safety of probiotics for improving glucose control in adults with impaired blood control, including prediabetes and T2DM. Probiotics were more effective than placebo in reducing FBG from baseline, both over the short term and long term. However, the effect of probiotics over the long term seems to have a less meaningful effect compared with the effect over the short term. Synbiotics were also effective. Subgroup analyses suggested that probiotics might be more effective in adults not on insulin therapy or with poorly controlled T2DM. In addition, probiotics were more effective than placebo in reducing serum cholesterol and LDL cholesterol from baseline in the short term and in reducing triglyceride and serum cholesterol from baseline in the long term.

Previous meta-analyses reported either inconclusive results or modest probiotic effects on glycemic control (14, 15, 16, 17, 18, 19, 20). We found a statistically significant difference in reducing FBG and some effect of reducing HbA1c in type 2 diabetic patients. Previous systematic reviews included between 6 and 12 trials, whereas we included 28 trials, 15 of which were published between 2017 and 2019. Unlike previous systematic reviews, we performed meta-analyses of the effect of probiotics both in the short term and long term to further understand how the effects may vary over time (14, 15, 16, 17, 18, 19, 20). Furthermore, we performed subgroup analyses based on various trial characteristics (e.g. industry funding compared with not) and participant characteristics (e.g. participants receiving insulin therapy compared with not) that have the potential to influence the effect of probiotics on glycemic control.

Mechanisms through which probiotics improve glucose homeostasis likely stem from changing the composition of the host gut microbiota. Altering the gut microbiota can improve intestinal barrier integrity to reduce circulating bacterial endotoxin, and ultimately, reduce systemic inflammation (46, 47, 48). The gut microbiota may also modulate glucagon-like peptide-1 (GLP-1), 1 of the enteroendocrine peptides produced by L-cells in the gut, and alter the secretion of GLP-1 which results in a reduction of gastric emptying time and food intake, and an increase in insulin secretion (49, 50). Also, probiotics may alter microbiota-derived metabolites, such as butyrate and acetate, which have been associated with changes in glucose and lipid metabolism as well as appetite signaling (51).

In the subgroup analyses, we found that the magnitude of the probiotic effect on glycemic outcomes appears to be stronger in participants with poorly controlled diabetes (FBG >130 mg/dL). In addition, the magnitude of reduction in FBG was more pronounced in those not receiving insulin therapy compared with those receiving insulin therapy. T2DM patients who require additional insulin therapy may have compromised β-cell function (52). Probiotics may exert glycemic effects via improved insulin sensitivity and therefore be less likely to have a significant impact on reducing blood glucose in diabetics on insulin.

It should be noted that differences in probiotic strains, host conditions, as well as dietary patterns can affect the composition of gut microbiota which may result in an interindividual difference in response to probiotic treatment (53, 54, 55, 56). Our systematic review highlights the need for future studies to (1) explicitly report specific strains and dosages of each specific bacteria contained in probiotic supplements, (2) carefully monitor participants' dietary intake and antibiotic use to minimize bias and to determine whether there is heterogeneity between interventions, (3) be adequately powered and stratified by severity of T2DM, and (4) use appropriate randomization and allocation concealment as well as blinding of participants, study personnel, and outcome assessors. Moreover, to determine the benefit of probiotics on reducing morbidity and mortality of prediabetes and T2DM, future studies should measure

long-term, patient-centered outcomes and long-term micro- and macrovascular complications, mortality, health services outcomes, and adverse events in addition to lab measures.

There were several limitations of the trials included in our meta-analysis. First, most included trials did not report specific probiotic strain composition, thus our meta-analysis grouped unrelated microorganisms. Also, many of the organisms in the trials reviewed have yet to meet the definition of probiotic and should thus be considered only as putative probiotic organisms. Another limitation of the reviewed studies is that certain racial or ethnic groups were underrepresented. Half of the included trials were conducted in the Middle East, in which dietary, genetic, and gut microbiome profiles of the population may differ from those in other regions. Since individuals may respond to probiotics differently based on the strain of probiotics as well as an individual's genetic, diet, and gut microbiome profile, different responses to probiotics among the studies can be expected (57). Finally, all of the included trials were rated as having some concern or high risk of bias, which reduced the certainty of evidence.

In conclusion, we found that probiotics have a beneficial effect on fasting glucose in adults with T2DM, and the effect was stronger in participants with poorly controlled diabetes and those not on insulin therapy. Probiotics also may have a beneficial glycemic effect in adults with prediabetes, although the number of included trials was too small to demonstrate statistical significance. There was also suggestive evidence that probiotics lower HbA1c, however, these differences did not meet the threshold for statistical significance likely due to the smaller number of trials contributing to the HbA1c analyses. If probiotics are selected to be supplementary therapy for prediabetes and T2DM patients, all factors including its effectiveness, cost, safety, and patients' preference should be considered.

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