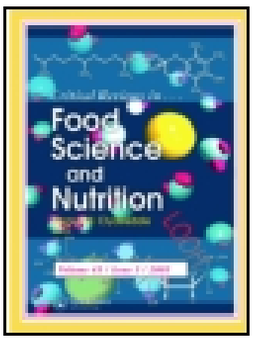

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Probiotics supplementation improves hyperglycemia, hypercholesterolemia, and hypertension in type 2 diabetes mellitus: An update of meta-analysis

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REVIEW

Probiotics supplementation improves hyperglycemia, hypercholesterolemia, and hypertension in type 2 diabetes mellitus: An update of meta-analysis

Tingting Liang[a,b], Lei Wu[a,b], Yu Xi[b], Ying Li[b], Xinqiang Xie[b], Congcong Fan[a,b], Lingshuang Yang[b], Shuanghong Yang[b], Xuefeng Chen[a], Jumei Zhang[b], and Qingping Wu[a,b]

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ABSTRACT

Background: Although many studies have shown that consumption of probiotics is relevant to diabetes, the effects of probiotics improves clinical outcomes in type 2 diabetes have yielded conflicting results. The aim of this meta-analysis was conducted to assess the effects of probiotics supplementation on glycemic, blood lipids, pressure and inflammatory control in type 2 diabetes.

Methods: PubMed, Web of science, Embase and the Cochrane Library databases were searched for relevant studies from February 2015 up to Janurary 2020, with no language restrictions. The pooled results were calculated with the use of a random-effects model to assess the impact of supplemental probiotics on glycemic, blood lipids, pressure and inflammatory control in type 2 diabetes. Additionally, subgroup analysis was conducted based on patients age, body mass index (BMI), country and duration of the probiotics supplement, respectively.

Results: 13 studies were included in this meta-analysis, involving a total of 818 participants in 8 countries. Overall, compared with control groups, the subjects who received multiple species of probiotics had a statistically significant reduction in fasting blood sugar (FBS), homeostasis model assessment of insulin resistance (HOMA-IR), total cholesterol (TC), triglycerides (TG), systolic blood pressure (SBP), diastolic blood pressure (DBP) and tumor necrosis factor (TNF) -α [standardized mean difference (SMD): −0.89 mg/Dl, 95% CI: −1.66, −0.12 mg/dL; SMD: −0.43, 95% CI: −0.63, −0.23; SMD: −0.19 mg/dL, 95% CI: −0.36, −0.01 mg/dL; SMD: −0.23 mg/dL, 95% CI: −0.40, −0.05 mg/dL; SMD: −5.61 mmHg, 95% CI: −9.78, −1.45 mmHg; SMD: −3.41 mmHg, 95% CI: −6.12, −0.69 mmHg; and SMD: 6.92 pg/ml, 95% CI: 5.95, 7.89 pg/ml, respectively]. However, the subjects who received single-species of probiotic or probiotic with co-supplements in food only changed FBS, HOMA-IR, DBP and TG levels. Moreover, subgroup analyses revealed that the effects of probiotics supplementation on FBS, HMOA-IR, SBP and DBP are significantly influenced by patients age, body mass index (BMI), country and duration of the probiotics supplement.

Conclusion: Our analysis revealed that glycemic, lipids, blood pressure and inflammation indicators are significantly improved by probiotic supplementation, particularly the subjects who ages $\leq$ 55, baseline BMI$<$ 30 kg/m^2, duration of intervention more than 8 weeks, and received multiple species probiotic.

KEYWORDS
Probiotics; glycemic; lipids; pressure; inflammation; type 2 diabetes; meta-analysis

Introduction

According to the recent study, 630 million people worldwide will have diabetes mellitus by the year 2045 (Carracher, Marathe, and Close 2018). Type 2 diabetes (T2D), the most common form of diabetes, is a complex metabolic disorder characterized by hyperglycemia, low-grade inflammation, insulin resistance and β-cell failure(Poon, Ong, and Cheung 2011; Nie et al. 2017) and affecting about 10% adults in 2040 (Sun et al. 2018; Yang et al. 2018). Patients with T2D share common characteristics of raised blood sugar, decreased insulin sensitivity, obesity, dyslipidemia, and hypertension, which often appear simultaneously rather than alone (Ridker et al. 2003; Auro et al. 2008). Therefore, it is important to find ways to treat these comorbid diseases simultaneously.

Accumulating evidence indicates that probiotics, living microorganisms in the gut (Allen et al. 2010; Heshmati et al. 2019), can induce many beneficial effects on the host in several diseases, including oral diseases (Terai et al. 2015), intestinal diseases (Hempel et al. 2012; Chmielewska and Szajewska 2010; Moayyedi et al. 2010), allergic diseases (Azimzadeh et al. 2020; Dev et al. 2008), tumors (Bui et al. 2015) and other diseases. There were also a growing body of evidence supports an strong association between probiotics supplementation and chronic metabolic diseases, such as hyperglycemia, hyperlipidemia, and hypertension (Lin et al. 2014; Akbari and Hendijani 2016; Niibo et al. 2019; Li et al.

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2014; Gómez-Guzmán et al. 2015; Brunkwall and Orho-Melander 2017). However, recently, three papers show that the health benefit value of probiotics should first be evaluated by clinical parameters and combined with microbiome data using well-characterized probiotic strains or mixes (Niv et al. 2018; Jotham et al. 2018; Langella and Chatel 2019). Previous human clinical studies using various probiotics have yielded inconsistent voice, Elham et al. (Elham et al. 2018) reported that supplement with 7 viable and freeze-dried strains (including *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Lactobacillus bulgaricus*, *Bifidobacterium breve*, *Bifidobacterium longum*, *Streptococcus thermophilus*) can decrease fasting blood sugar (FBS), and increase high-density lipoprotein cholesterol (HDL-C) levels, no significant alterations were observed other indicators (including insulin, triglycerides, total cholesterol, insulin resistance). While Khalili et al. (2018) demonstrated that *lactobacillus casein* significantly decreased fasting blood sugar, insulin, and insulin resistance. Moreover, Alireza et al. (2015) have identified that probiotic fermented milk containing *Lactobacillus casei*, *Lactobacillus acidophilus* and *Bifidobacteria* can lead a significant reduction of fasting blood glucose and glycated hemoglobin (HbA1c), but serum triglyceride (TG), total cholesterol(TC), low density lipoprotein-cholesterol (LDL-C) and HDL-C levels were not shown significant differences. And also Mohammadi et al. (Mohamadshahi et al. 2014) have suggested that probiotic yogurt caused a significant decrease in HbA1c and tumor necrosis factor (TNF)-α levels. However, Feizollahzadeh et al. (Feizollahzadeh et al. 2017) have revealed that probiotic soy milk containing *Lactobacillus planetarum A7* therapies did not show any significant changes in serum TNF-α and C reactive protein.

Investigate its reason, those studies varied with respect to several parameters, including probiotics consumption patterns, subjects ages, Body Mass Index (BMI), country (influenced by dietary and genetic), diabetes duration, and intervention duration, thereby leading to inconsistent results. In addition, few meta-analyses to date have simultaneous examined the effects of probiotics on systemic levels of hyperglycemia, hyperlipidemia, hypertension and inflammation in type 2 diabetes mellitus.

Our meta-analyses aimed to summary the convincing evidence of current studies to clarify the efficacy of probiotics on glycemic, lipids, blood pressure and inflammatory control in type 2 diabetes mellitus. Furthermore, this meta-analyses through subgroup analysis to investigate the influence of probiotics consumption patterns, subjects ages, BMI, country, and intervention duration on the overall effect of probiotic consumption on glycemic, lipids, blood pressure and inflammatory levels.

Methods

We carried out this study following the guidelines from the Cochrane Handbook for Systematic Reviews of Interventions, version 5.2.0 and reported its findings according to the Preferred Reporting Items for Systematic Review and Meta Analyses (PRISMA) statement (Moher et al. 2015) (see Supplementary material 1).

Search strategy

We searched PubMed, Embase, Web of science and the Cochrane Library up to January, 2020. The following keywords were used in the literature search: ("probiotic" OR "probiotics" OR "*lactobacillus*" OR "*bifidobacteria*") AND ("diabetes" OR "glycemia" OR "glucose" OR "Fasting blood sugar" OR "FBS" OR "Glycosylated hemoglobin A1c" OR "HbA1c" OR "insulin" OR "Homeostasis model assessment-insulin resistance" OR "HOMA-IR" OR "cholesterol" OR "lipids" OR "Total cholesterol" OR "TC" OR "Triglyceride" OR "TG" OR "High density lipoprotein cholesterol" OR "HDL-C" OR "Low density lipoprotein cholesterol" OR "LDL-C" OR "blood pressure" OR "Systolic blood pressure" OR "SBP" OR "Diastolic blood pressure" OR "DBP" OR "inflammatory" OR "TNF-α" OR "C-reactive protein" OR "CRP"). We also attempted to contact the investigators if their clinical end-points were not reported.

Study selection

Studies were selected for inclusion by 2 independent reviewers (TL and YL), subject to approval by a third reviewer (QW). The procedure of study selection is shown in Figure 1. Studies that satisfied the PICOS (participants, interventions, comparators, outcomes, and study design) criteria (Table 1). Inclusion criteria: (1) the study was a controlled clinical trial in humans; (2) participants had to be males or females with type 2 diabetes mellitus; (3) the study included probiotics intervention; and 4) the study included $\geq$1 of the following outcomes: FBS, HbA1c, insulin, HOMA-IR, TC, TG, LDL-C, HDL-C, SBP, DBP, TNF-α, or CRP, or a combination of these. In addition, we excluded the following studies: (1) studies with no placebo controlled or intervention; (2) patients that were belong to gestational diabetes subjects or type 1 diabetes; (3) the mean change, SD in the outcome measure(s) or complete outcomes were not reported; (4) studies that were not randomized controlled trials; and (5) studies that was a animal studies; (6) studies that was a review paper, letter, or conference abstract.

Data extraction and quality assessment

Two investigators (TL and QW) independently using standardized template to extracted detailed information from each included studies. The first author, publication year, sample size, participants, country, gender, age, weight, BMI, diabetes duration, study design, dose and duration of the probiotics supplementation, and outcome measures.

Both authors independently assessed studies quality and risk of bias of each eligible study using the criteria outlined in the *Cochrane manual* (Higgins and Altman 2008). Six criterias were considered: (1) Random sequence distribution generation, (2) Allocation concealment, (3) Blinding, (4) Outcome data, (5) selective reporting, and (6) other bias, and these items were recognized as "yes" (low risk of bias), "no" (high risk of bias), or "unclear".

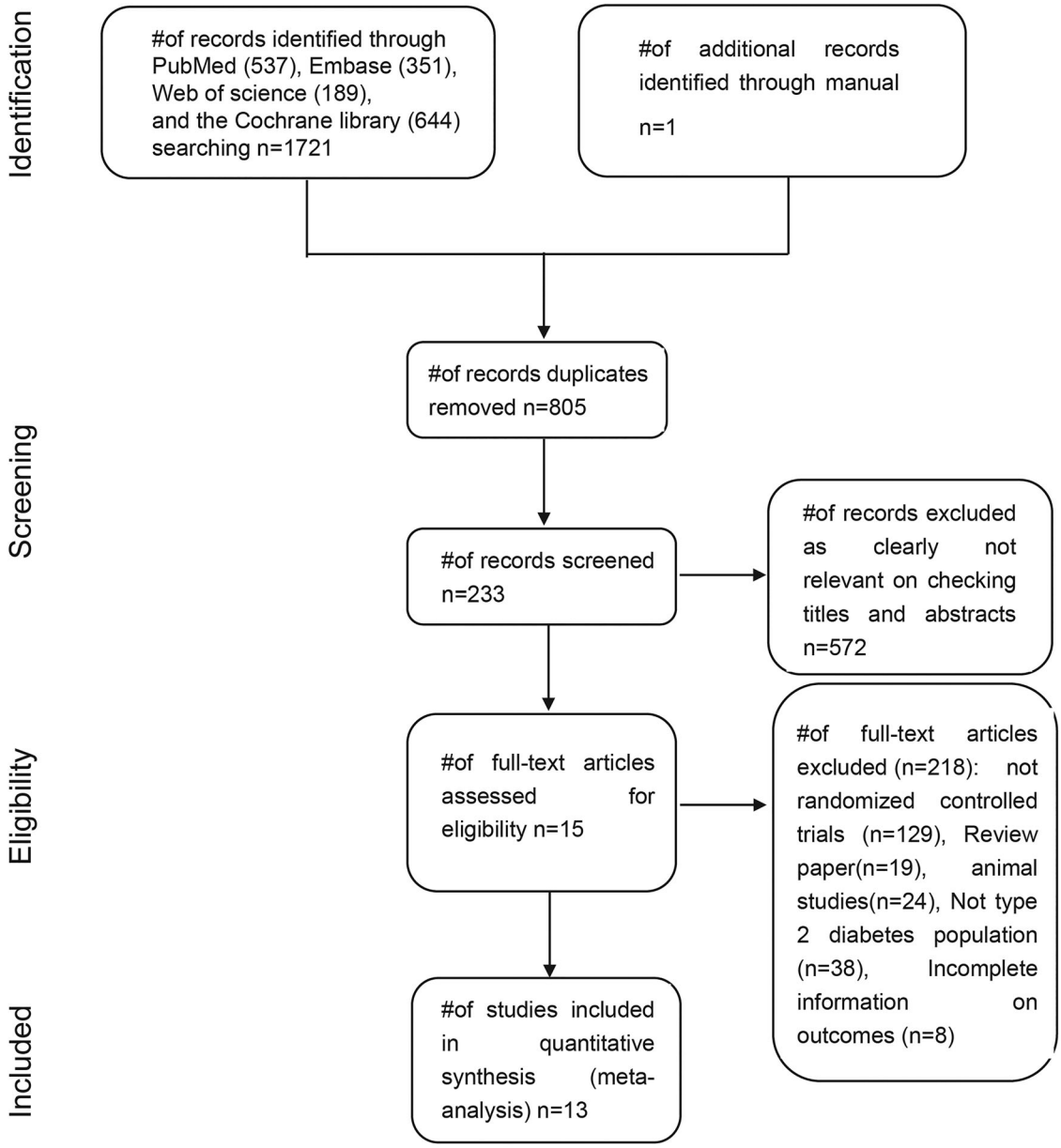

Figure 1. Flow chart depicting the literature search and selection strategy. After applying the inclusion and exclusion criteria, a total of 13 articles were included in the meta-analysis.

Statistical analyses: data synthesis and meta-analysis

STATA software package, version 15.1 (StataCorp, College Station, TX) was used for the majority of statistical analyses. RevMan 5.3 was only used for analysis and graph of risk of bias. The changes of mean and SD values between baseline and the endpoint were calculated (Shuster 2011), we based on the following formula:

Changes of mean (probiotic group)
= (measure at endpoint in the probiotic group)
− (measure at baseline in the probiotic group)

Changes of mean (control group)
= (measure at endpoint in the control group)
− (measure at baseline in the control group)

$$SD^2 = SD1^2 + SD2^2 - 2{*}r * SD1{*}SD2 \ \ (r = 0.5)$$

Before meta-analysis, the FBS levels were collated in mg/dL, when necessary, it can be convert glucose concentrations from mmol/L to mg/dL. Insulin levels were collated in mU/mL, where necessary, it can be convert insulin concentrations from pmol/L to mU/mL. The TC, TG, HDL-C and LDL-C levels were collated in mg/dl, when necessary, it can be convert TC, TG, HDL-C, LDL-C concentrations from mmol/L to mg/dl. The SBP and DBP levels were presented in mmHg. TNF-α levels were presented in pg/ml, and CRP values presented in mg/L.

A random effects meta-analysis was used for the standardized mean difference (SMD), with 95% confidence intervals for continuous outcomes, a p value of <0.05 was considered statistically significant . Heterogeneity of the studies was evaluated by the use of the I^2 statistic, and I^2 in 0–25%,

Table 1. PICOS criteria for inclusion and exclusion of studies.

Parameter	Defined criteria for current study
Participants	Type 2 diabetic patients
Intervention	Single strain probiotic, or multi-strain probiotic, or probiotic with co-supplements
Comparator	Placebo (no microorganisms) consumed
Outcomes	Fasting blood sugar (FBS), HbA1c, Insulin, homeostasis model assessment of insulin resistance (HOMA-IR), Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), systolic blood pressure (SBP), diastolic blood pressure (DBP) and tumor necrosis factor (TNF) -α, C-reactive protein (CRP) (effects on glycemic, blood lipids, hypertension control were considered in screening steps)
Study design	Controlled clinical human trials

26–75%, and 76–100% considering as low, moderate, or high degree of heterogeneity(Higgins et al. 2003; Dan, White, and Riley 2012), respectively, and $P < 0.05$ or I^2 >50% indicated that heterogeneity existed. In addition, subgroup analyses to search for sources of heterogeneity and meta-regression were also performed (Higgins 2009). Potential publication bias in each analysis was evaluated qualitatively by using the funnel plots and quantitatively by using the Egger's tests (Seagroatt and Stratton 1998). To assess the effect of individual studies on overall results of meta-analysis, a one by one study sensitivity analysis was performed.

Results

Selected studies

The flow diagram of the literature search process is summarized in Figure 1. From a total of 1721 articles obtained in PubMed, Embase, Web of science, and the Cochrane Library, 1 article was identified through manual. After removing duplicate articles and screening the articles by reading the title and abstract, a total of 233 papers were inclusion. After reading full-text articles, 218 records were removed, including not randomized controlled trials (129), review papers (19), animals studies (24), not type 2 diabetes population (38), and incomplete information on outcomes (8). Finally, 13 papers were met eligibility criteria for inclusion in the meta analysis.

Studies characteristics and their quality assessment

The characteristics of included studies are presented in Table 2. In these 13 trials, including 2 intervention studies that used single species probiotic (Khalili et al. 2018; Mobini et al. 2017), and 8 intervention studies that used multiple species probiotic (Madempudi et al. 2019; Elham et al. 2018; Kobyliak et al. 2018; Sabico et al. 2017; Tajabadi-Ebrahimi et al. 2016; Firouzi et al. 2017; Tonucci et al. 2017; Alireza et al. 2015), and 3 publications in which probiotic was administered together with food (e.g. milk, soybean milk et al.), it was named a co-supplement (Asemi et al. 2016; Hove et al. 2015; Feizollahzadeh et al. 2017). The samples size varied, ranging from 29 to 136 participants. In total, 818 participants were assigned to either a probiotic intervention or a control group. Of which these participants diabetes duration were from 3 years to 18 years. 5 studies of which participants were subjects aged ≤55 y, and 6 studies were >55 y of age. Moreover, 6 studies involved the mean BMI ≥ 30, 7 interventions were the mean BMI < 30. In addition, of these studies, one in Ukraine, one in Saudi Arabia, one in Malaysia, one in Brazil, one in Sweden, one in Denmark, one in India, and other 6 studies were performed in Iran. What's more, the duration of probiotic supplementation ranged from 6 to 12 weeks. 6 studies of which duration of interventions exceed 8 weeks, and 7 studies lower than 8 weeks.

According to the Cochrane manual, our results of risk-of-bias assessment are presented in Figure 2. All the 13 studies reported random sequence generation and blinding of outcome assessment. Only 1 study had a high risk of bias regarding blinding of participants and personnel (Khalili et al. 2018). In 3 studies, several patients did not complete the study, and had a high bias of incomplete outcome data (Madempudi et al. 2019; Feizollahzadeh et al. 2017; Asemi et al. 2016). Selective reporting bias was found in the 1 trial of the 13 included studies (Madempudi et al. 2019). Most of trials had no other bias in 13 trials. On the basis of critical appraisal, no studies were excluded.

Effects of probiotics on glucose metabolism

Effect of probiotics on FBS

To determine whether probiotics supplementation affects hyperglycemia, FBS data were extracted from the eligible studies. The effect of probiotics on FBS was reported in 13 interventions, including 2 studies that used single species probiotic, 8 studies that used multiple species probiotic and 3 studies that used probiotics with a co-supplement (Figure 3A). The following analysis revealed a significant reduction in FBS when used single species probiotic, with a standard mean difference (SMD) of −0.60 mg/dL (95% CI: −1.08, −0.12 mg/dL; $I^2 = 0.0\%$, $p = 0.583$) between the probiotics and control groups. In addition, we found a significant reduction in FBS that used multiple species probiotic, with a standard mean difference (SMD) of −0.89 mg/dL (95% CI: −1.66, −0.12 mg/dL; $I^2 = 94.4\%$, $p = 0.000$) between the probiotics and control groups. However, when probiotic with co-supplements group, there was no significant between probiotics and control groups (SMD: −1.30 mg/dL; 95% CI: −3.11, 0.51 mg/dL; $I^2 = 95.8\%$, $p = 0.000$). In the overall, probiotics group was significantly lower than control group (SMD: −0.91 mg/dL; 95% CI: −1.48, −0.33 mg/dL; $I^2 = 93.1\%$, $p = 0.000$).

Effect of probiotics on HbA1c

Next, we examined whether probiotics supplementation affects long-term glycemic regulation by extracting and analyzing HbA1c data. The effect of probiotic on HbA1c was

Table 2. Characteristics of the studies included in this meta-analysis.[a]

Author/ year	Intervention/ Control (size)	Participants/ Country	Age (year)	Female/ Male	Weight (kg)	BMI (kg/m^2)	Diabetes duration (Year)	Probiotic/Control	Dose	Design	Duration	Measure outcomes
Madempudi et al. 2019	Probiotics (37)	T2DM/ India	53.60	7/30	69.20	26.43	NA	*L. salivarius* UBLS22, *L. casei* UBLC42, *L. plantarum* UBLP40, *L. acidophilus* UBLA34, *B. breve* UBBr01, and *B. coagulans* Unique IS2	3.0 × 1010 cfu capsules	R, PC, DB	12 wks	FBS/ HbA1c/ Insulin/ HOMA-IR/ TC/TG/HDL-C/LDL-C
	Control (37)	T2DM/ India	50.50	9/28	68.00	25.97	NA	Placebo	2 capsules			
Khalili et al. 2019	Probiotics (20)	T2DM/ Iran	43.95 ± 8.14	13/7	77.15 ± 13.58	29.50 ± 3.34	4.00± 3.81	*Lacidophilus casei*	10^8 cfu capsules	R, PC, DB	8 wks	FBS/ HbA1c/
	Control (20)	T2DM/ Iran	45.00 ± 5.37	13/7	83.45 ± 15.84	31.94 ± 5.76	3.67 ± 4.00	Placebo	capsules			Insulin/ HOMA-IR/ SBP/DBP/
Elham et al. 2018	Probiotics (30)	T2DM/ Iran	58.60 ± 6.50	13/17	75.20 ± 15.60	27.70 ± 4.20	6.20± 3.10	*Lacidophilus*+ *L. casei*+*L. rhamnosus*+*L. bulgaricus*+*B. breve*+*B. longum*+ *Streptococcus thermophilus*	3.9 × 1010 cfu capsules	R, C, DB	6 wks	FPG/ Insulin/ HOMA-IR /TC/TG/HDL-C/LDL-C
	Control (30)	T2DM/ Iran	61.30 ± 5.20	14/16	74.10 ± 9.20	27.20 ± 4.20	5.90± 2.90	Placebo	capsules			
Kobyliak et al. 2018	Probiotics (31)	T2DM/ Ukraine	52.23 ± 1.74	NA	99.32 ± 3.23	34.70 ± 1.29	6.16± 0.92	*Lactobacillus*+*Lactococcus*+ *Bifidobacterium*+ *Propionibacterium*+ *Acetobacter*	10g/d	SC, DB, PC, P	8 wks	FBS/ HbA1c/ Insulin/ TNF-α
	Control (22)	T2DM/ Ukraine	57.18 ± 2.06	NA	96.95 ± 4.35	35.65 ± 1.57	5.91± 0.87	placebo	10g/d			
Sabico et al. 2017	Probiotics (39)	T2DM/ Saudi Arabia	48.00 ± 8.30	20/19	75.60 ± 11.00	29.40 ± 5.20	NA	*B. bifdum* W23, *B. lactis* W52, *L. acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, *L. lactis* W19 and *L. lactis* W58	5 × 109 cfu/d sachets	SC, DB, R, PC	12 wks	Glucose/ Insulin/ HOMA-IR/ TC/ TG/ HDL-C/LDL-C/SBP/DBP
	Control (39)	T2DM/ Saudi Arabia	46.60 ± 5.90	18/21	79.50 ± 15.70	30.10 ± 5.00	NA	placebo	sachets			
Feizollahzadeh et al. 2017	Probiotics (20)	T2DM/ Iran	56.9 ± 1.81	11/9	70.84 ± 2.41	26.68 ± 0.71	8.70 ± 2.10	soy milk containing *L. planetarum* A7	200 mL/d 2 × 107 cfu	R, DB, PC	8 wks	FBS/TG/HDL-C/LDL-C/ CRP/ Serum TNF-α
	Control (20)	T2DM/ Iran	53.60 ± 1.60	10/10	71.61 ± 2.55	26.58 ± 0.73	6.90 ± 4.90	pure soy milk	200 mL/d			
Tajabadi-Ebrahimi et al. 2016	Probiotics (30)	T2DM/ Iran	64.20 ± 12.00	NA	79.2 ± 15.4	32.30 ± 6.00	NA	*L. acidophilus*, *L. casei*, *B. bifdum*	2 × 109 cfu	R, DB, PC	12 wks	FPG/Insulin/HOMA-IR/ TC/TG/ HDL-C/LDL-C
	Control (30)	T2DM/ Iran	64.00 ± 11.70	NA	74.3 ± 13.7	29.60 ± 4.60	NA	placebo	capsules			
Firouzi et al. 2017	Probiotics (68)	T2DM/ Malaysia	52.90 ± 9.20	NA	74.60 ± 15.10	29.20 ± 5.60	NA	*L. acidophilus*, *L. casei*, *L. lactis. Bifdobacterium, Actinobacteria*, *B. bifdum*, *B. longum and B. infantis.*	10^{10} cfu 500mL/d	R, DB, PC	12 wks	FBG/ HbA1c/ insulin/ HOMA-IR/ TC/TG/HDL-C/LDL-C/SBP/ DBP/CRP
	Control (68)	T2DM/ Malaysia	54.20 ± 8.30	NA	76.60 ± 15.60	29.30 ± 5.30	NA	placebo	500mL/d			
Tonucci et al. 2015	Probiotics (23)	T2DM/ Brazil	51.83 ± 6.64	11/12	71.70 ± 12.43	27.49 ± 3.97	6.00± 2.00	probiotic fermented milk (*L. acidophilus* La-5+*B. animalis* subsp lactis BB-12)	120g/d	DB, R, PC	6 wks	FPG/HbA1c/ insulin/ HOMA-IR/ TC/TG/HDL-C/LDL-C
	Control (22)	T2DM/ Brazil	50.95 ± 7.20	8/14	77.15 ± 13.85	27.94 ± 4.15	4.50± 2.00	conventional fermented milk	120 g/d			
Alireza et al. 2015	Probiotics (30)	T2DM/ Iran	NA	12/18	77.46 ± 13.26	28.89 ± 4.77	6.47± 0.90	fermented milk (kefir) contain *L. casei*, *L. acidophilus* and *Bifidobacteria*	600mL/d	R, DB, PC	8 wks	Glucose/HbA1C/ TC/TG/HDL-C/ LDL-C
	Control (30)	T2DM/ Iran	NA	14/16	74.92 ± 11.48	27.47 ± 3.55	7.36± 0.84	fermented milk(dough)	600mL/d			
Mobini et al. 2017	Probiotics (14)	T2DM/ Sweden	64.00 ± 6.00	3/11	101.40 ± 18.00	32.30 ± 3.40	14.40 ± 9.60	*L. reuteri* DSM 17938	10^{10}cfu/d	R, DB, PC	12 wks	FPG/HbA1c/ insulin/ TC/TG/HDL-C/LDL-C/SBP/DBP/CRP
	Control (15)	T2DM/ Sweden	65.00 ± 5.00	4/11	93.50 ± 12.10	30.70 ± 4.00	18.30 ± 7.30	placebo	NA			
Asemi et al. 2016	Probiotics (51)	T2DM/ Iran	NA	NA	77.59 ± 13.65	30.15 ± 5.07	NA	synbiotic food with *Lactobacillus sporogenes*	1 × 107 cfu	R, DB, PC	6 wks	FPG / insulin/ HOMA-IR/TC/TG/ HDL-C/LDL-C/SBP/DBP/CRP
	Control (51)	T2DM/ Iran	NA	NA	78.28 ± 13.42	30.15 ± 5.07	NA	control food	9g			
Hove et al. 2015	Probiotics (23)	T2DM/ Denmark	58.50 ± 7.70	NA	93.20 ± 17.90	29.20 ± 3.80	NA	milk fermented with *L. helveticus*	300 mL	R, DB, P, PC	12 wks	Glucose/HbA1c/Insulin/HOMA-IR/ TC/TG/HDL-C/LDL-C/CRP/ TNF-α
	Control (18)	T2DM/ Denmark	60.60 ± 5.20	NA	85.20 ± 9.50	27.70 ± 3.30	NA	artificially acidified milk	300 mL			

[a]Data are presented as means ± SDs or as a range. T2DM, type 2 diabetes mellitus; FBS, fasting blood sugar; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure, DBP, diastolic blood pressure; TNF-α, tumor necrosis factor α; CRP, C-reactive protein; P, parallel; R, randomized; PC, placebo-controlled study; DB, double-blinded.

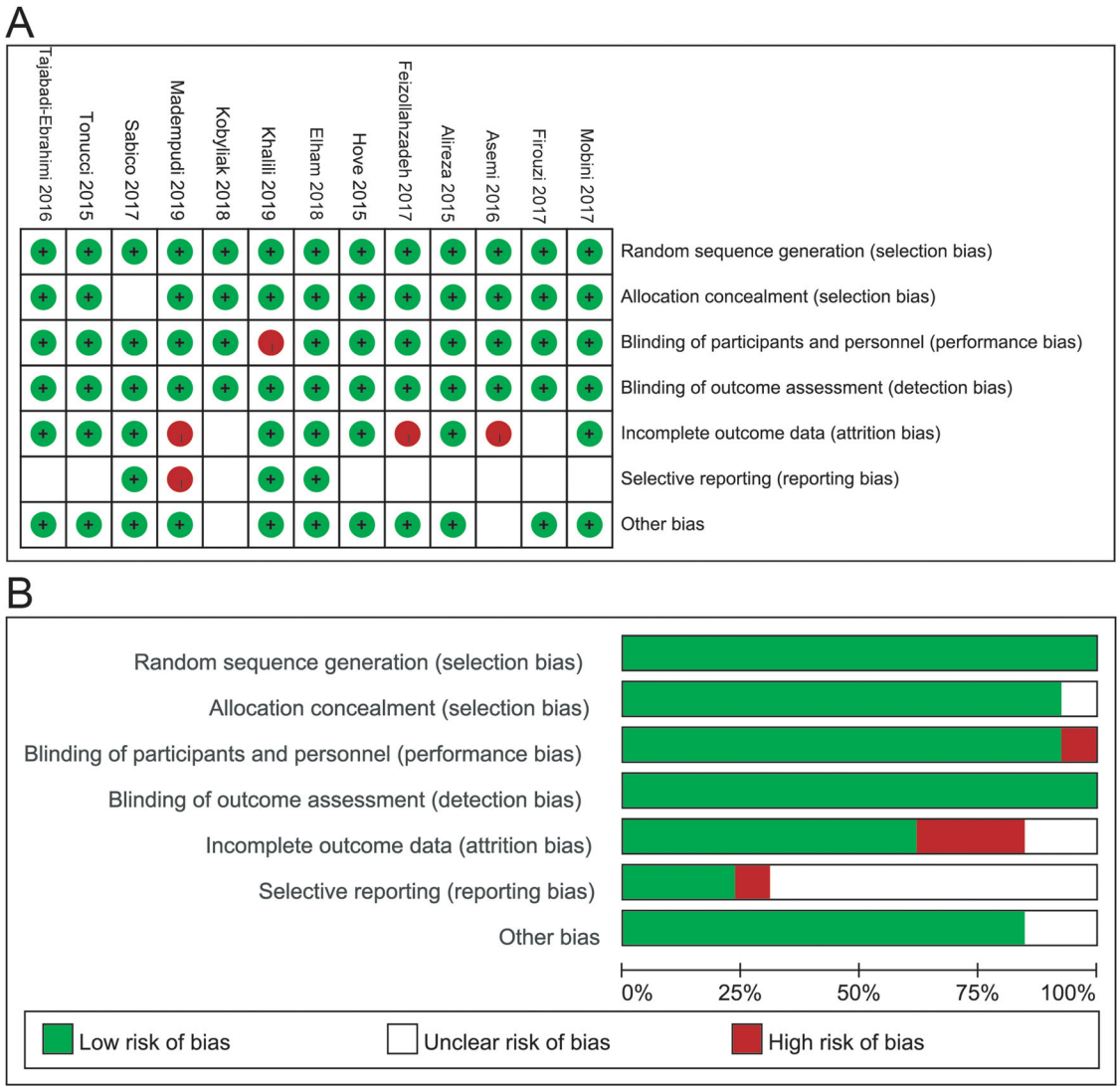

Figure 2. Risk of bias assessment for included studies. (A) Risk of bias summary: the judgements about each risk of bias item for each included study. The color green, red and blank represent low, high and unclear risk of bias, respectively. (B) Risk of bias graph: the judgements about each risk of bias item presented as percentages across all included studies. There are three bias assessment criteria "Low", "High" and "Unclear" for each point, shown as the color green, red and blank, respectively.

reported in 7 interventions, including 2 studies that used single species probiotic, 4 studies that used multiple species probiotic and 1 study that used probiotic with a co-supplement (Figure 3B). Our analysis revealed that there was no significant difference between probiotics group (single species probiotic, multiple species probiotic and probiotic with a co-supplement) and control group. (SMD: −0.36%; 95% CI: −1.30%, 0.58%, I^2= 73.1%, p = 0.054; SMD: −0.07%; 95% CI: −0.90%, −0.77%, I^2= 89.6%, $p = 0.000$; SMD: −0.15%; 95% CI: −0.77%, −0.47%, respectively). In the overall, ungrouped analysis (SMD: −0.16%; 95% CI: −0.68%, 0.36%; I^2 = 81.9%, $p = 0.000$).

Effect of probiotics on insulin

Next, we examined whether probiotics supplementation affects circulating insulin by extracting and analyzing insulin concentrations. The effect of probiotic on insulin was reported in 11 interventions, including 2 studies that used single species probiotic, 7 studies that used multiple species probiotic and 2 studies that used probiotic with a co-supplement (Figure 3C). Our analysis showed no significant reduction in insulin when probiotic was either single species (SMD: −0.14 mU/L; 95% CI: −0.70, 0.41 mU/L; I^2 = 26.3%, $p = 0.244$) or used multiple species probiotic (SMD: 0.08 mU/L; 95% CI: −0.49, 0.64 mU/L; I^2 = 89.6%, $p = 0.000$), or used with a co-supplement (SMD: −0.18 mU/L; 95% CI: −1.12, 0.77 mU/L; I^2 = 84.9%, $p = 0.000$). Moreover, we found there was no significant reduction in insulin based on an overall, ungrouped analysis (SMD: −0.01 mU/L; 95% CI: −0.41, 0.39 mU/L; I^2 = 85.0%, $p = 0.000$).

Effect of probiotics on HOMA-IR

We also examined whether probiotics supplementation affects insulin sensitivity by extracting HOMA-IR data from the eligible studies. The effect of probiotic on HOMA-IR was reported in 8 interventions, including 1 study that used single species probiotic, 5 studies that used multiple species probiotic and 2 studies that used probiotics with a co-

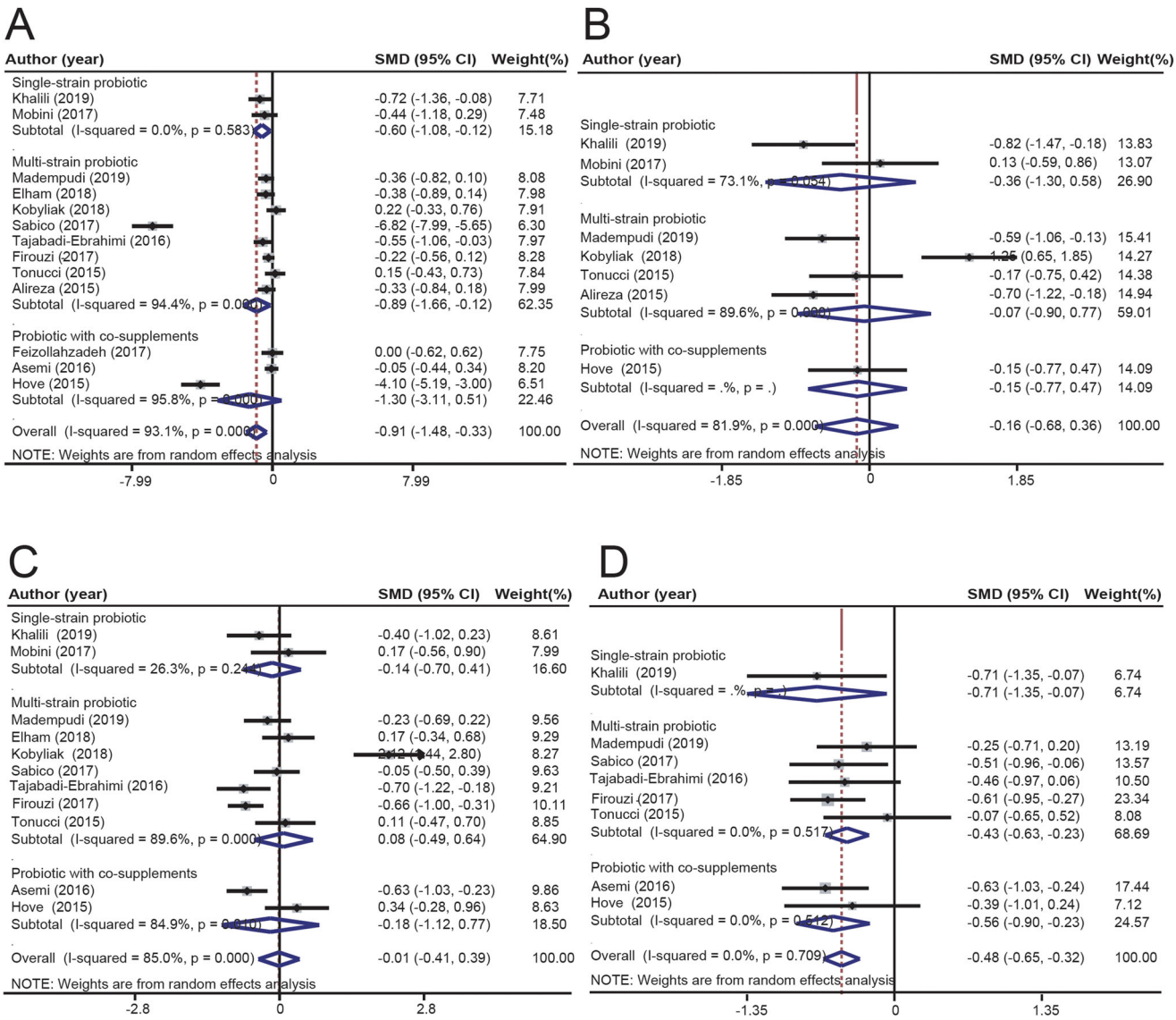

Figure 3. Forest plots for the effect of probiotics supplementation on FBS(mg/dL)(A), HbA1c(%)(B), Insulin (mU/mL)(C), and HOMA-IR(D), compared to controls in pooled analysis. For each study, the solid black diamonds represent the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of this effect. The open diamonds represent the subgroup and overall SMD determined with a random-effects model.

supplement (Figure 3D). We found a significant reduction in HOMA-IR when was used with single species probiotic (SMD: −0.71; 95% CI: −1.35, −0.07), or when was used with multiple species probiotic (SMD: −0.43; 95% CI: −0.63, −0.23; I^2 = 0.0%; $p = 0.517$), or when probiotic was used with a co-supplement (SMD: −0.56; 95% CI: −0.90, −0.23; I^2 = 0.0%; $p = 0.512$). And that in the overall, probiotics caused a significant reduction in HOMA-IR (SMD: −0.48; 95% CI: −0.65, −0.32; I^2= 0.0%; $p = 0.709$).

Effects of probiotics on lipids metabolism

Effect of probiotics on TC

To determine whether probiotics supplementation affects hyperlipidemia, TC data were extracted from the eligible studies. The effect of probiotics on TC was reported in 10 interventions, including 1 study that used single species probiotic, 7 studies that used multiple species probiotic and 2 studies that used probiotics with a co-supplement (Figure 4A). The following analysis revealed there was no significant reduction in TC when used single species probiotic, with a standard mean difference (SMD) of −0.11 mg/dL (95% CI: −0.84, 0.62 mg/dL) between the probiotics and control groups. In addition, our analysis showed significant reduction in TC that used multiple species probiotic (SMD: −0.19%; 95% CI: −0.36, −0.01 mg/dL; I^2 = 0.0%, $p = 0.871$), or when probiotic was used with co-supplements group (SMD: 0.01 mg/dL; 95% CI: −0.32, 0.33 mg/dL; I^2 = 0.0%, $p = 0.981$). In the overall, probiotics group was lower than control group, but there was no significant (SMD: −0.14 mg/dL; 95% CI: −0.29, 0.01 mg/dL; I^2 = 0.0%, $p = 0.941$).

Effect of probiotics on TG

Next, we examined whether probiotics supplementation affects long-term lipidemia regulation by extracting and analyzing TG data. The effect of probiotic on TG was reported in 11 interventions, including 1 study that used single

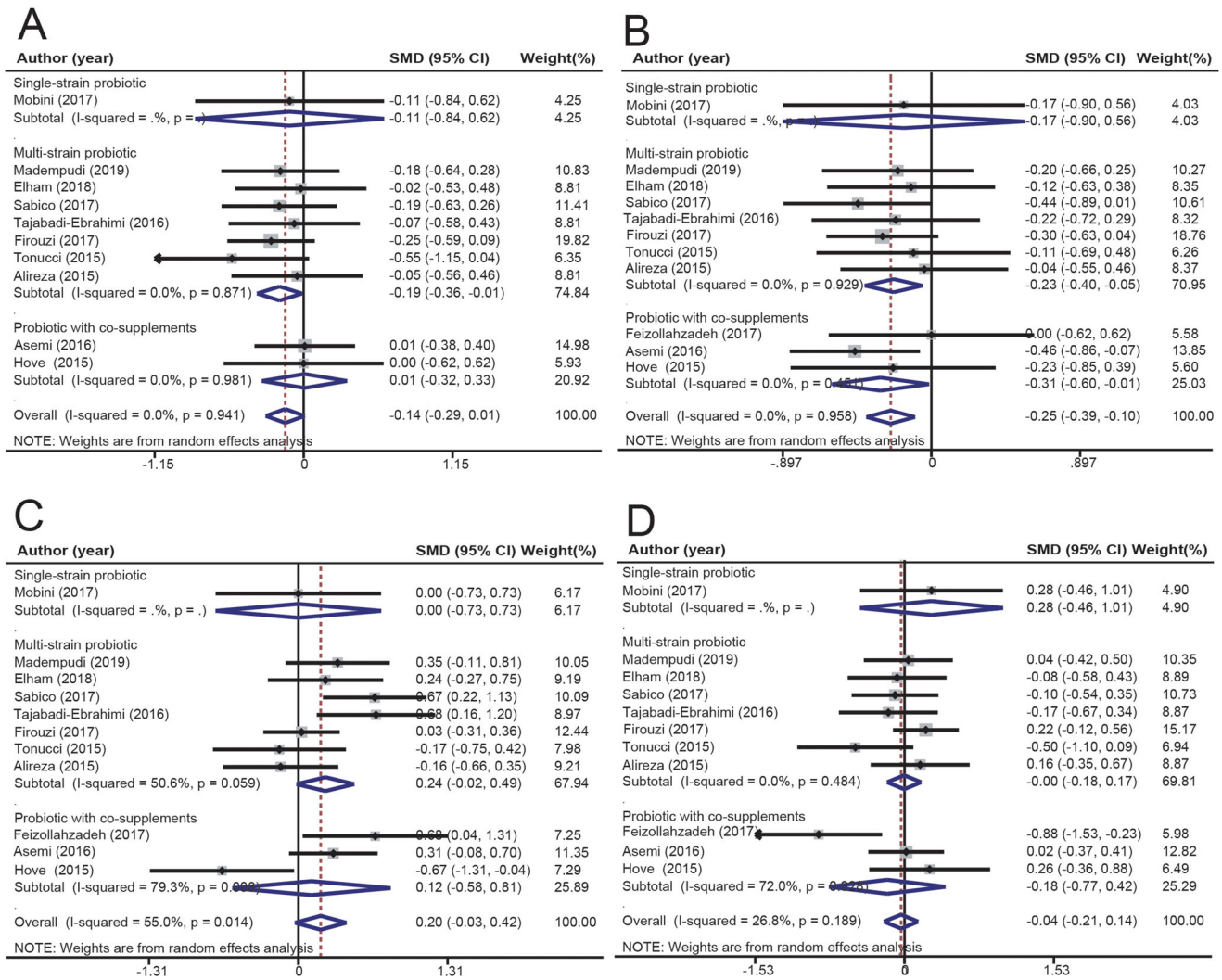

Figure 4. Forest plots for the effect of probiotics on TC (mg/dL) (A), TG(mg/dL) (B), HDL-C(mg/dL) (C), and LDL-C(mg/dL) (D) compared to controls in pooled analysis. For each study, the solid black diamonds represent the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of this effect. The open diamonds represent the subgroup and overall SMD determined with a fixed-effects model.

species probiotic, 7 studies that used multiple species probiotic and 3 studies that used probiotic with a co-supplement (Figure 4B). Our analysis revealed that there was no significant difference when was used single species probiotic (SMD: −0.17 mg/dL; 95% CI: −0.90, 0.56 mg/dL). However, we found a significant reduction when probiotic was used multiple species (SMD: −0.23 mg/dL; 95% CI: −0.40, −0.05 mg/dL, I^2=0.0%, $p = 0.929$), or used probiotics with a co-supplement (SMD: −0.31 mg/dL; 95% CI: −0.60, −0.01 mg/dL, I^2=0.0%, $p = 0.451$). In the overall, there was a significant between probiotics and control groups (SMD: −0.25 mg/dL; 95% CI: −0.39, −0.10 mg/dL; I^2 = 0.0%, $p = 0.958$).

Effect of probiotics on HDL-C

Next, we examined whether probiotics supplementation affects circulating HDL-C by extracting and analyzing HDL-C concentrations. The effect of probiotic on HDL-C was reported in 11 interventions, including 1 study that used single species probiotic, 7 studies that used multiple species probiotic and 3 studies that used probiotic with a co-supplement (Figure 4C). Our analysis showed no significant increase were observed in HDL-C when probiotic was either single species, or multiple species, or used with a co-supplement (SMD: −0.00 mg/dL; 95% CI: −0.73, 0.73 mg/dL; SMD: 0.24 mg/dL; 95% CI: −0.02, 0.49 mg/dL; I^2 = 79.3%, $p = 0.000$; SMD: 0.12 mg/dL; 95% CI: −0.58, 0.81 mg/dL; I^2 = 79.3%, $p = 0.000$). And also we found there was no significant increase in HDL-C based on an overall (SMD: 0.20 mU/L; 95% CI: −0.03, 0.42 mg/dL; I^2 = 55.0%, $p = 0.014$).

Effect of probiotics on LDL-C

We also examined whether probiotic supplementation affects lipids by extracting LDL-C data from the eligible studies. The effect of probiotic on LDL-C was reported in 11 interventions, including 1 study that used single species probiotic, 7 studies that used multiple species probiotic and 3 studies that used probiotics with a co-supplement (Figure 4D). No significant changes were observed in LDL-C when either used single species probiotic (SMD: 0.28 mg/dL; 95% CI: −0.46, 1.01 mg/dL), or when used multiple species probiotic(SMD: −0.00 mg/dL; 95% CI: −0.18,

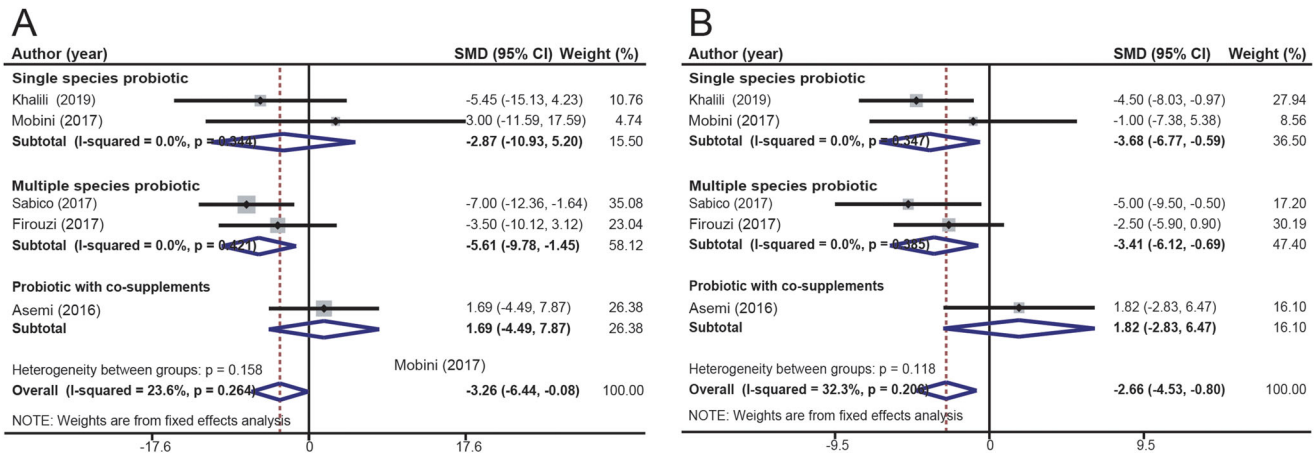

Figure 5. Forest plot for the effect of probiotics on SBP(mmHg) (A) and DBP(mmHg) (B) compared to controls. For each study, the solid black diamonds represent the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of this effect. The open diamonds represent the subgroup and overall SMD determined with a fixed-effects model.

0.17 mg/dL; I^2 = 0.0%; $p = 0.484$), or when probiotic was used with a co-supplement (SMD: −0.18 mg/dL; 95% CI: −0.77, 0.42 mg/dL; I2 = 72.0%; $p = 0.028$). And that the overall, our analysis showed that probiotics showed no significant reduction in LDL-C (SMD: −0.04 mg/dL; 95% CI: −0.21, 0.14 mg/dL; I^2= 26.8%; $p = 0.189$).

Effects of probiotics on blood pressure metabolism

Effect of probiotics on SBP

To determine whether probiotics supplementation affects hypertension, SBP data were extracted from the eligible studies. The effect of probiotics on SBP was reported in 5 interventions, including 2 studies that used single species probiotic, 2 studies that used multiple species probiotic and 1 study that used probiotics with a co-supplement (Figure 5A). Our analysis result showed there was no significant reduction in SBP when either used single species probiotic (SMD: −2.87 mmHg, 95% CI: −10.93, 5.20 mmHg; I^2 = 0.0%; $p = 0.486$), or when probiotic was used with co-supplements group (SMD: 1.69 mmHg; 95% CI: −4.49, 7.87 mmHg; $p = 0.592$) between the probiotics and control groups. However, our analysis showed a significant reduction in SBP that used multiple species probiotic (SMD: −5.61 mmHg; 95% CI: −9.78, −1.45 mmHg; I^2 = 0.0%, $p = 0.008$). In the overall, probiotics group was significantly lower than control group in SBP (SMD: −3.26 mmHg; 95% CI: −6.44, −0.08 mmHg; I^2 = 23.6%, $p = 0.044$).

Effect of probiotics on DBP

We also examined whether probiotic supplementation affects blood presure by extracting DBP data from the eligible studies. The effect of probiotic on DBP was reported in 5 interventions, including 2 studies that used single species probiotic, 2 studies that used multiple species probiotic and 1 study that used probiotics with a co-supplement (Figure 5B). Our analysis showed a significant changes in DBP when either used single species probiotic (SMD: −3.68 mmHg; 95% CI: −6.77, −0.59 mmHg; $p = 0.020$), or when used multiple species probiotic (SMD: −3.41 mmHg; 95% CI: −6.12, −0.69 mmHg; I^2 = 0.0%; $p = 0.014$). Nevertheless, when probiotic was used with a co-supplement did not show a significant reduction compared with control groups (SMD: −1.82 mmHg; 95% CI: −2.83, 6.47 mmHg; $p = 0.443$). In the overall, our analysis suggested that probiotics showed a significant reduction in DBP (SMD: −2.66 mmHg; 95% CI: −4.53, −0.80 mmHg; I^2= 32.3%; $p = 0.005$).

Effects of probiotics on inflammatory biomarkers

Effect of probiotics on TNF-α

Given that previous studies suggest that chronic inflammation is closely associated with the risk of diabetes, we investigated the effect of probiotics on the level of circulating TNF-α. The effect of probiotics on TNF-α was reported in 3 interventions, including 1 study that used multiple species probiotics, and 2 studies that used probiotics with a co-supplement (Figure 6A). Our analysis revealed a significant increase in TNF-α when used multiple species probiotics (SMD: 6.92 pg/ml; 95% CI: 5.95, 7.89 pg/ml; $p = 0.000$) compared with control group. There was no significant difference when probiotics was used with a co-supplement (SMD: −109.85 pg/ml; 95% CI: −324.40, 104.69 pg/ml; I^2 = 100%; $p = 0.316$), and in the overall, a significant reduction were found in TNF-α when used probiotics (SMD: −70.80 pg/ml; 95% CI: −116.39, −25.22 pg/ml; I^2= 100%; $p = 0.002$).

Effect of probiotics on CRP

In this meta-analysis, we also evaluated whether probiotic supplementation affects the concentration of circulating CRP. The effect of probiotic supplementation on CRP was reported in 5 interventions, including 1 study that used single species probiotic, 1 study that used multiple species probiotics, and 3 studies that used probiotics with a co-supplement (Figure 6B). Our analysis revealed that there were no significant reduction in CRP when used single species probiotic (SMD: −0.17 mg/L; 95% CI: −0.90, −0.56 mg/L; $p = 0.648$), or when used multiple species probiotic (SMD: −0.06 mg/L; 95% CI: −0.68, 0.56 mg/L; $p = 0.849$), or when probiotic used with a co-supplement (SMD: −0.06 mg/L; 95% CI: −0.18, 0.30 mg/L; I^2 = 0.0%;

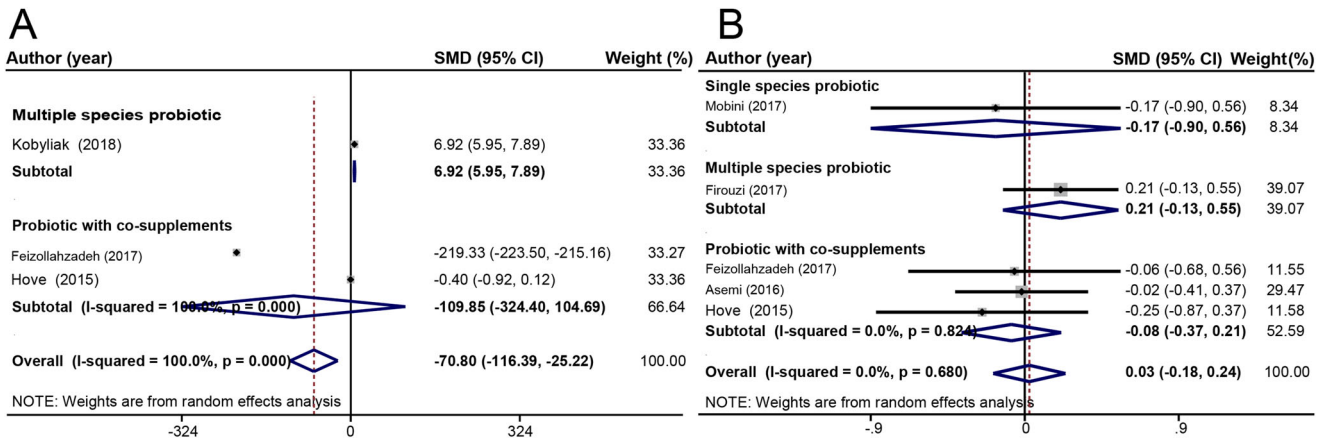

Figure 6. Forest plot for the effect of probiotics on TNF-α (pg/ml) and CRP (mg/l) compared to controls. For each study, the solid black diamonds represent the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of this effect. The open diamonds represent the subgroup and overall SMD determined with a random-effects model.

$p = 0.619$), and in the overall, no significant decreased in CRP (SMD: 0.03 mg/L; 95% CI: −0.18, 0.24 mg/L; $I^2 =$ 0.0%; $p = 0.804$) between probiotic and control group.

Subgroup and meta-regression analyses of probiotics on glucose metabolism

We also performed subgroup analyses on studies that used probiotics for the 4 glycemic indicators stratified according to 4 specific factors. In addition, a meta-regression analysis was performed to research the sources of heterogeneity. It revealed that subjects come from Eastern decreased more insulin concentrations than from Western after probiotic supplementation ($P = 0.027$), this suggest that subjects race may be a possible factor affecting heterogeneity (Table 3).

Subgroup analyses based on human age years

First, we examined whether human ages influenced the hypoglycemic effects of probiotic supplementation (Table 3). Notably, the effect of probiotic supplementation on FBS was stronger significantly among human age years ≤ 55 than among subjects age years> 55 ($p = 0.029$). Moreover, the effect of probiotic supplementation on HMOA-IR was stronger significantly among human age years ≤ 55 than among subjects age years > 55 ($p = 0.000$).

Subgroup analyses based on human baseline BMI

We also performed a subgroup analysis to determine whether the human baseline BMI affected outcome by comparing studies with low BMI (<30) and high BMI (≥30) (Table 3). The effect of probiotic supplementation on FBS was significant difference among <30 than among subjects BMI ≥ 30 ($p = 0.003$). However, the effect of probiotic supplementation on HMOA-IR was also significant difference among BMI ≥ 30 than among subjects BMI < 30 ($p = 0.000$).

Subgroup analyses based on geographic area

We also examined whether geographic area influenced the hypoglycemic effects of probiotics supplementation (Table 3). We compared the effects of probiotic in studies in which the intervention was conducted in Eastern (Iran, Malaysia, Saudi Arabia, India) and Western (Denmark, Sweden, Brazil, and Ukraine) countries. The effect of probiotic supplementation on FBS was significant difference among subjects come from Eastern than among subjects come from Western ($p = 0.002$). There was also a significant between subjects come from Eastern and Western in HMOA-IR ($p = 0.000$).

Subgroup analyses based on the duration of probiotic intervention

Next, we determined whether the duration of the intervention influenced the hypoglycemic effects of probiotic supplementation (Table 3). We compared the effects of probiotics in studies in which the intervention was relatively brief (≤8 weeks) with studies that involved a relatively long intervention (>8 weeks). There was a significant difference between two different duration of the intervention in FBS and HOMA-IR ($p = 0.002$, $p = 0.000$). Additionally, we can be found that more duration of probiotic intervention can decrease more FBS concentration and HOMA-IR.

Subgroup and meta-regression analyses of probiotics on lipids metabolism

We also performed subgroup analyses on studies that used probiotics for the 4 blood lipids indicators stratified according to 4 specific factors. In addition, a meta-regression analysis was performed to research the sources of heterogeneity. It revealed that subjects come from Eastern increased more HDL-C concentrations than from Western after probiotic supplementation ($P = 0.032$), this further more suggest that subjects race may be a possible factor affecting heterogeneity (Table 3).

Subgroup analyses based on human age years

First, we examined whether human ages influenced the lipid-lowering effects of probiotic supplementation (Table 3). Notably, the effect of probiotic supplementation on TG

Table 3. Subgroup analysis of 10 indicators.[a]

	n	SMD(95% CI)	I^2 (%)	*p* value[b]	*p* value[c]	*p* value[d] (Meta-regression)
FBS						
Age						
years $\leq$ 55	5	−1.19 (−2.50, 0.12)	92.9	0.074	0.029	0.625
Years $>$ 55	4	−0.18 (−0.47, 0.10)	39.6	0.206		
Baseline BMI						
BMI $\geq$ 30	3	−0.14 (−0.41, 0.14)	96.3	0.005	0.003	0.583
BMI $<$ 30	7	−1.61 (−2.75, −0.48)	0.00	0.333		
Country						
Eastern	9	−0.99 (−2.30, 0.32)	93.8	0.011	0.002	0.820
Western	4	−0.89 (−1.57, −0.21)	93.6	0.138		
Duration of intervention						
$\leq$8 wks	7	−0.69 (−1.38, −0.00)	95.1	0.050	0.002	0.055
$>$8 wks	6	−1.12 (−2.11, −0.12)	90.2	0.028		
HbA1c						
Age						
years $\leq$ 55	3	−0.45 (−0.99, 0.09)	93.0	0.926	0.567	0.355
Years $>$ 55	2	−0.06 (−1.29, 1.18)	44.4	0.101		
Baseline BMI						
BMI $\geq$ 30	2	0.08 (−0.71, 0.86)	70.1	0.436	0.857	0.890
BMI $<$ 30	4	−0.32 (−1.14, 0.49)	87.2	0.851		
Country						
Eastern	4	−0.40 (−0.78, −0.01)	39.4	0.042	0.548	0.143
Western	3	0.13 (−1.02, 1.28)	91.6	0.829		
Duration of intervention weeks						
$\leq$8	4	0.10 (−0.78, 0.98)	86.8	0.821	0.548	0.780
$>$8	3	−0.52(−0.83, −0.22)	0.00	0.001		
Insulin						
Age						
years $\leq$ 55	5	−0.00 (−0.83, 0.83)	92.7	0.998	0.841	0.549
Years $>$ 55	4	−0.10 (−0.18, 0.38)	0.00	0.483		
Baseline BMI						
BMI $\geq$ 30	3	−0.14 (−0.70, 0.41)	73.7	0.615	0.132	0.456
BMI $<$ 30	5	−0.27 (−0.66, 0.12)	65.7	0.169		
Country						
Eastern	7	−0.05(−−0.56, 0.47)	88.9	0.967	0.958	0.027
Western	4	0.01(−0.58, 0.61)	76.6	0.862		
Duration of intervention						
$\leq$8 wks	6	0.10 (−0.61, 0.81)	91.5	0.784	0.958	0.356
$>$8 wks	5	−0.13 (−0.45, 0.19)	48.0	0.428		
HMOA − IR						
Age						
years $\leq$ 55	5	−0.46 (−0.67, −0.25)	0.00	0.000	0.000	0.755
Years $>$ 55	2	−0.43 (−0.82, −0.03)	0.00	0.034		
Baseline BMI						
BMI $\geq$ 30	1	−0.63 (−1.03, −0.24)	–	0.002	0.000	0.578
BMI $<$ 30	3	−0.40 (−0.64, −0.17)	28.0	0.001		
Country						
Eastern	6	−0.53(−0.71, −0.35)	0.00	0.000	0.000	0.178
Western	2	−0.22 (−0.64, 0.21)	0.00	0.321		
Duration of intervention						
$\leq$8 wks	4	−0.46 (−0.69, −0.24)	0.00	0.000	0.000	0.809
$>$8 wks	4	−0.51 (−0.75, −0.28)	0.00	0.000		
TC						
Age						
years $\leq$ 55	4	−0.16(−0.38, 0.06)	0.00	0.876	0.057	0.323
Years $>$ 55	4	−0.10 (−0.37, 0.17)	0.00	0.962		
Baseline BMI						
BMI $\geq$ 30	2	−0.01 (−0.32, 0.29)	0.00	0.855	0.042	0.511
BMI $<$ 30	6	−0.21 (−0.41, −0.01)	0.00	0.828		
Country						
Eastern	7	−0.13 (−0.32, 0.05)	0.00	0.838	0.053	0.534
Western	3	−0.16 (−0.41, 0.10)	0.00	0.697		
Duration of intervention						
$\leq$8 wks	5	−0.11 (−0.34, 0.11)	0.00	0.982	0.033	0.708
$>$8 wks	5	−0.17 (−0.37, 0.04)	0.00	0.561		
TG						
Age						
years $\leq$ 55	4	−0.21 (−0.44, −0.01)	0.00	0.924	0.012	0.452
Years $>$ 55	4	−0.16 (−0.46, 0.14)	0.00	0.950		
Baseline BMI						
BMI $\geq$ 30	2	−0.30 (−0.73, 0.14)	0.00	0.942	0.000	0.230
BMI $<$ 30	7	−0.24 (−0.42, −0.06)	0.00	0.218		
Country						
Eastern	8	−0.27 (−0.43, −0.11)	0.00	0.902	0.000	0.621

(*continued*)

Table 3. Continued.

	n	SMD(95% CI)	I^2 (%)	*p* value[b]	*p* value[c]	*p* value[d] (Meta-regression)
Western	3	−0.11 (−0.46, 0.24)	0.00	0.875		
Duration of intervention						
≤8 wks	6	−0.22 (−0.43, −0.01)	0.00	0.953	0.001	0.474
>8 wks	5	−0.27 (−0.47, −0.06)	0.00	0.707		
HDL-C						
Age						
years ≤ 55	4	0.11 (−0.11, 0.34)	0.00	0.503	0.277	0.838
Years > 55	4	0.19 (−0.46, 0.83)	76.8	0.005		
Baseline BMI						
BMI ≥ 30	3	0.41 (0.08, 0.74)	0.00	0.334	0.289	0.412
BMI < 30	7	0.04 (−0.26, 0.34)	59.5	0.022		
Country						
Eastern	8	0.27 (0.06, 0.47)	35.1	0.149	0.088	0.032
Western	3	−0.06 (−0.81, 0.69)	77.3	0.012		
Duration of intervention						
≤8 wks	6	0.19 (−0.08, 0.46)	38.3	0.151	0.066	0.720
>8 wks	6	0.22 (−0.20, 0.64)	71.6	0.007		
LDL-C						
Age						
years ≤ 55	4	−0.01 (−0.29, 0.27)	32.9	0.215	0.551	0.632
Years > 55	4	0.14 (−0.64, 0.37)	61.5	0.050		
Baseline BMI						
BMI ≥ 30	2	0.07 (−0.12, 0.25)	81.4	0.020	0.822	0.698
BMI < 30	7	−0.39 (−1.27, 0.48)	0.00	0.460		
Country						
Eastern	8	−0.37 (−1.02, 0.28)	0.00	0.895	0.693	0.850
Western	3	−0.05 (−0.11, 0.21)	69.2	0.039		
Duration of intervention						
≤8 wks	6	−0.04 (−0.24, 0.16)	0.00	0.574	0.189	0.159
>8 wks	5	−0.06 (−0.41, 0.28)	48.9	0.045		
SBP						
Age						
years ≤ 55	3	−0.33 (−0.57, −0.08)	0.00	0.010	0.035	0.360
Years > 55	1	0.15 (−0.58, 0.88)	–	0.689		
Baseline BMI						
BMI ≥ 30	2	0.12 (−0.23, 0.46)	0.00	0.509	0.783	0.443
BMI < 30	1	−0.18 (−0.51, 0.16)	–	0.301		
Country						
Eastern	4	−0.22 (−0.51, 0.07)	43.5	0.134	0.177	0.470
Western	1	0.15 (−0.58, 0.88)	–	0.689		
Duration of intervention						
≤8 wks	3	−0.25 (−0.70, 0.20)	62.1	0.269	0.177	0.529
>8 wks	2	−0.12 (−0.43, 0.19)	0.00	0.440		
DBP						
Age						
years ≤ 55	3	−0.42 (−0.70, −0.14)	14.9	0.003	0.002	0.536
Years > 55	1	−0.11 (−0.84, 0.62)	–	0.759		
Baseline BMI						
BMI ≥ 30	2	0.09 (−0.25, 0.44)	0.00	0.595	0.576	0.398
BMI < 30	1	−0.25 (−0.58, 0.09)	–	0.151		
Country						
Eastern	4	−0.29 (−0.65, 0.06)	62.0	0.106	0.087	0.752
Western	1	−0.11 (−0.84, 0.62)	–	0.759		
Duration of intervention						
≤8 wks	3	−0.34 (−0.89, 0.22)	74.7	0.234	0.087	0.836
>8 wks	2	−0.22 (−0.53, 0.08)	0.00	0.152		

[a]FBS, fasting blood sugar; HbA1c, glycated hemoglobin; HOMA − IR, homeostasis model assessment of insulin resistance; TC, total cholesterol; TG, triglycerides; HDL − C, high − density lipoprotein cholesterol; LDL − C, low − density lipoprotein cholesterol; SBP, systolic blood pressure, DBP, diastolic blood pressure; SMD, standardized mean difference.

[b] *p* values for heterogeneity within each subgroup, $p < 0.05$ indicate significant differences within each subgroup.

[c] *p* values for subgroup differences between groups, $p < 0.05$ indicate significant differences within each subgroup.

[d]*P* values for meta − regression differences between sugroups, $P < 0.05$ indicate that this factor may be one of the reasons for the high heterogeneity.

was significant among human age years ≤ 55 than among subjects age years > 55 ($p = 0.026$).

Subgroup analyses based on human baseline BMI

We also performed a subgroup analysis to determine whether the human baseline BMI affected outcome by comparing studies with low BMI (<30) and high BMI (≥30) (Table 3). The effect of probiotic supplementation on TG was significant difference among BMI ≥30 than among subjects BMI < 30 ($p = 0.000$).

Subgroup analyses based on geographic area

We also examined whether geographic area influenced the lipid-lowering effects of probiotics supplementation

(Table 3). The effect of probiotic supplementation on TG was significant difference among subjects come from Eastern than among subjects come from Western ($p = 0.000$).

Subgroup analyses based on the duration of probiotic intervention

Next, we determined whether the duration of the intervention influenced the lipid-lowering effects of probiotic supplementation (Table 3). There was a significant difference between two different duration of the intervention in TG ($p = 0.001$), we also can be found that more duration of probiotic intervention can decrease more concentration of TG.

Subgroup and meta-regression analyses of probiotics on blood pressure metabolism

We also performed subgroup analyses on studies that used probiotics for the 2 blood pressure indicators stratifed according to 4 specific factors. In addition, a meta-regression analysis was performed to research the sources of heterogeneity. Notably, the effect of probiotic supplementation on SBP and DBP were stronger significantly among human age years $\leq$ 55 than among subjects age years $>$ 55 ($p = 0.035$, $p = 0.002$, respectively). However, blood pressure indicators with no significant difference in human baseline BMI, geographic area, and the duration of probiotic intervention (Table 3).

Publication bias and sensitivity analysis

Next, we examined publication bias by generating funnel plots (Supplementary Figures 1–3) and performing Egger's test (quantitative). For the probiotic supplementation improves glycemic control, our analysis revealed a significant difference publication bias in FBS and insulin ($P = 0.009$ and $P = 0.045$, respectively), but revealed no significant differences of publication bias for HbA1c ($P = 0.713$), HOMA-IR ($P = 0.268$). For the probiotic supplementation improves blood lipids, blood pressure and inflammation control, our analysis showed no significant publication bias for TC, TG, HDL-C, LDL-C, SDP and DBP ($P = 0.973$, $P = 0.079$, $P = 0.748$, $P = 0.262$, $P = 0.957$ and $P = 0.517$, respectively). For the probiotic supplementation improves inflammation control (TNF-α and CRP), only 2–5 studies have been found, so publication bias have not done. Finally, in order to explore the publication bias in FBS and insulin, a sensitivity analysis have been calculated, and it revealed that no single study likely affected the pooled results or total effect size (Supplementary Figures 4–6).

Discussion

Previous studies have reported that gut microbiota modification by consumption of probiotics may regulate hyperglycemia and other metabolic disorders in T2DM (Delzenne et al. 2015; Everard et al. 2013; Kootte et al. 2012). Therefore, we analyzed the effects of probiotics on blood glucose, lipid, pressure, and inflammation metabolic profiles in T2DM. This meta-analysis described and evaluated 13 RCTs studies involving a total of 818 participants spanning 8 countries. The results of our meta-analysis shows that probiotic supplementation have a potentially beneficial effect on FBS, HOMA-IR, TC, TG, SBP, DBP and TNF-α.

In mammals, probiotics plays an important role in blood glucose, lipid, pressure, and inflammation metabolic profiles in T2DM (He, Zhang, and Han 2017; Tian, Hai-Mei, and Ji-An 2011; Sabico et al. 2019; Majid et al. 2014). The exact mechanisms of the effect of probiotics on glucose parameters, lipid profiles and blood pressure in T2DM are unknown. Nevertheless, more and more studies showed that probiotic *lactobacilli* and *bifidobacteria* could particularly change the intestinal microbiota (increased the good bacteria and reduced the harmful bacteria), modulate the host immune response, and play a positive role in T2DM treatment(Ushkalova 2014; Harsh et al. 2013), it was shown in Figure 7. More evidence suggests that probiotics could regulate the levels of metabolic endotoxin (lipopolysaccharide, LPS), intestinal permeability and intestinal peptides (GLP-1 and PYY) (Griffiths et al. 2004; Siebler, Galle, and Weber 2008; Hariom, Shalini, and Sinha 2007). Probiotics also improve insulin resistance and inflammation by regulating the expression of TNF- α and reducing the binding activity of Nuclear factor kB (NF-kB) (Ma, Hua, and Li 2008). Recent studies reported that the anti-diabetic effect of probiotics may be due to the microbial metabolites (including short chain fatty acids(SCFAs) and total biles acids (TBA)) on biological signaling pathways, and which can regulate ubiquitinase and protease genes, and change autonomic nervous activity (Al-Salami et al. 2008; Yamano et al. 2006; Alip et al. 2008), thus inhibiting and delaying the absorption of glucose in the intestine. In addition, previous meta-analysis have shown that the mechanism of probiotics supplementation on glycemic control through oxidative stress pathways (Hajifaraji et al. 2018). probiotic consumption can significantly regulate the biomarkers of oxidative stress, including antioxidant resistance (total antioxidant capacity (TAC)), and antioxidant enzymes (glutathione (GSH), superoxide dismutase (SOD) and nitric oxide (NO)) (Heshmati et al. 2018). Samah et al. have suggested that probiotic intake significantly decreased the insulin resistance may be due to a reduce the levels of blood glucose, insulin, and an increase total antioxidant capacity (Samah et al. 2016). Thus, the exact mechanism of probiotic glycemic control need been further studied.

This meta-analysis results of glycemic suggested that probiotic supplementation may significantly reduced FBS or HOMA-IR, while it has no effect on insulin or HbA1c levels. And our some results are inconsistent with previous some reviews. Ruan et al. (2015) found that probiotics not only have a significant effect on fasting glucose and HOMA-IR, but also reduced fasting insulin. Whereas, Dong et al. (Dong et al. 2019) indicated that probiotics reduced levels of HbA1c and HOMA-IR, but there were no significant differences of fasting glucose, fasting insulin between the intervention and control groups. Yao et al. (2017) reported that the effect of probiotics was significant on reducing HbA1c level, fasting insulin level, and HOMA-IR, and did not have

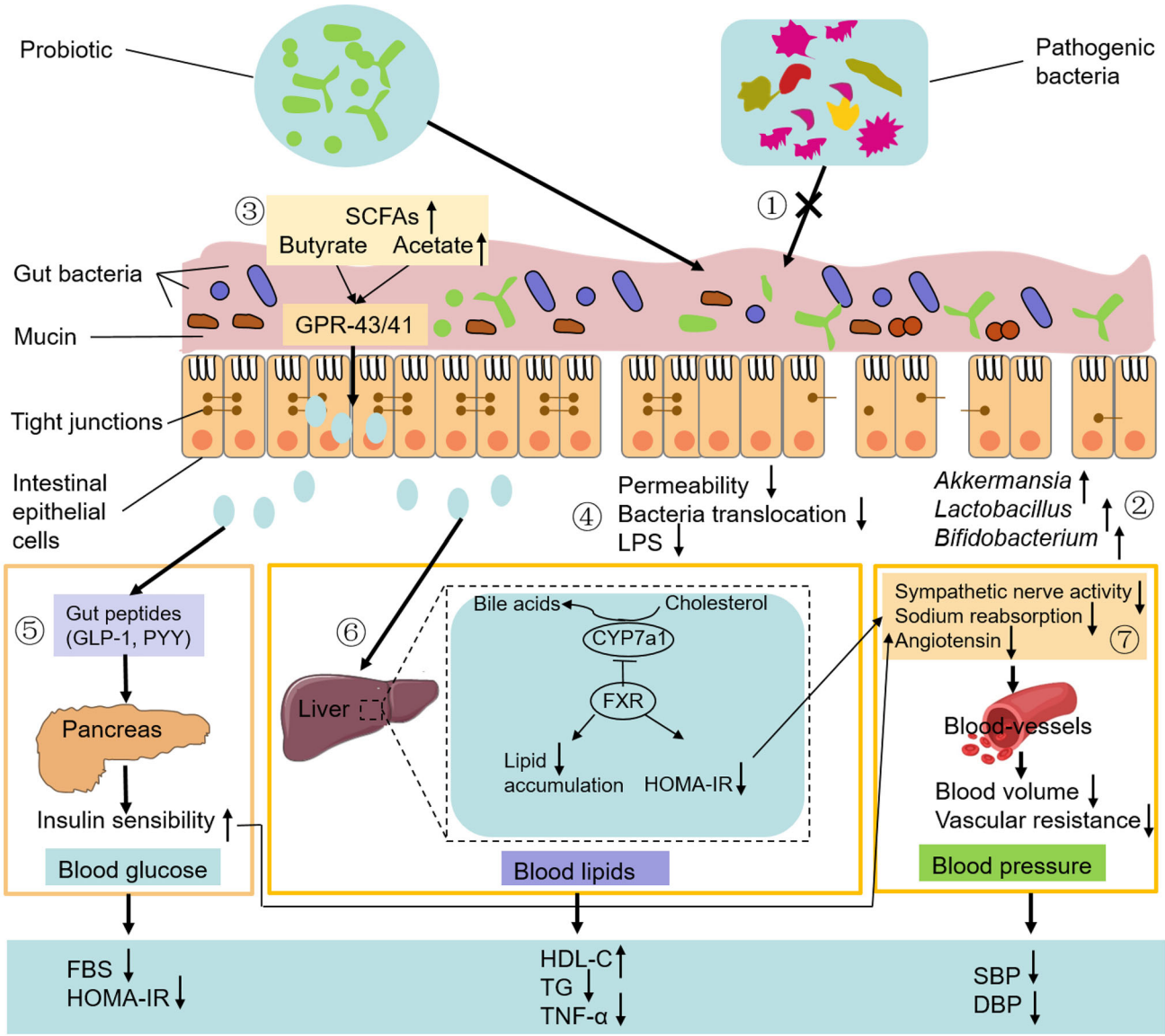

Figure 7. The mechanisms and results of the effect of probiotics on glucose parameters, lipid profiles and blood pressure in T2DM. Intake of probiotics can ① prevent pathogenic bacteria from entering the intestinal mucosal, ② modulate the intestinal microbiota (increased the good bacterias), ③ increase production of metabolites short chain fatty acids (SCFAs) levels, and ④ decrease the permeability of the intestinal barrier, which may reduce translocation of bacteria and liposaccharide (LPS). ⑤ On the one hand, the SCFAs can activate the receptor of GPR-43/41, which can lead to the production of gut peptides (e.g. GLP-1, PYY), it increasing the sensitivity of pancreas to insulin, thereby reduce the levels of FBS and HOMA-IR. ⑥ On the other hand, the SCFAs can provide energy for the liver, and increase hypersensitive of FXR, which can promote the conversion of cholesterol to bile acids, reduce the lipids accumulation and HOMA-IR, and thus decrease the levels of TG and TNF-α, and increase levels of HDL-C. ⑦ The increase of insulin sensitivity and the decrease of insulin resistance can reduce the sympathetic activity, the reabsorption of sodium and the level of angiotensin, which can reduce the blood vessel volume and resistance, and lower the levels of blood pressure (DBP and SBP).

a significant effect on FBG levels. Nikbakht et al. (2018) demonstrated that reduction in FBG observed from consumption of probiotics statistically significant. However, in contrast to the findings of these reviews, Elena et al. (Barengolts et al. 2019) suggested that there were no effects of probiotic yogurt on all glycemic indicators, including fasting blood glucose, fasting insulin, and insulin resistance. We found that these reviews included studies which have varied factors, such as sample size, subjects race, age et al, especially probiotics consumption patterns, this may have led to different results.

The subgroup analysis results of our study suggested that consuming multiple strains probiotic resulted in a higher reduction in FBG, compared with single species probiotics and co-supplements with foods, which might be due to multi-strain probiotics have synergistic interaction among different strains, or a higher concentration of live cultures (Chapman, Gibson, and Rowland 2011). Moreover, subjects ages $\leq$55 showed higher reduction in FBS and HMOA-IR compared with the ages >55. A previous study have reported that there was a case report of liver abscess and bacteremia in 74-year-old woman with non-insulin-dependent diabetes who received a probiotic supplement containing *Lactobacillus* species (Land et al. 2005). Thus, it is still necessary to evaluate the long-term safety of probiotic supplementation in diabetic patients, especially in the elderly. In addition, the results obtained from subgroup analysis of trials with baseline BMI $\geq$ 30 kg/m^2 illustrates a significant

Table 4. The main results of probiotics supplementation on glycemic, blood lipids, blood pressure and inflammatory in type 2 diabetes.[a]

Indexes		Effectness	Results of subgroup analyses
Blood glucose	FBS	Down	Single or multiple strain species probiotic; subjects age $\leq$ 55; BMI <30 kg/m^2; Eastern country; duration of intervention > 8 weeks
	HbA1c	—	—
	Insulin	—	—
	HOMA-IR	Down	Single or multiple strain species probiotic, probiotic with co-supplements; Subjects age $\leq$ 55; baseline BMI $\geq$30 kg/m^2; Eastern country; duration of intervention > 8 weeks
Blood lipids	TC	Down	Multiple strain species probiotic; baseline BMI < 30; duration of intervention > 8 weeks
	TG	Down	Multiple strain species probiotic or probiotic with co-supplements; Subjects age $\leq$ 55; baseline BMI $\geq$30 kg/m^2; Eastern country; duration of intervention > 8 weeks
	HDL-C	—	—
	LDL-C	—	—
Blood pressure	SBP	Down	Subjects age $\leq$ 55
	DBP	Down	Subjects age $\leq$ 55
Inflammation cytokines	TNF-α	Down	—
	CRP	—	—

[a] FBS, fasting blood sugar; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure, DBP, diastolic blood pressure; TNF-α, tumor necrosis factor α; CRP, C-reactive protein.

reduction in HMOA-IR compared to those with lower BMI. It is possible that the beneficial effect of probiotics consumption is masked by the adverse effect of higher body weight and BMI. There is strong evidence suggesting increased body weight or BMI can induce insulin sensitivity and lower insulin production (Jean-Philippe et al. 2006). What's more, we found that the effects of probiotics on glycemic are also influenced by the subjects race, and subjects from Eastern country induce a higher reduction of FBS and HOMA-IR than western country. However, our study indicated that the most of the clinical trials were performed in Asian countries, with relatively few studies performed in western countries. Thus, well designed placebo-controlled trials with larger sample sizes in a variety of geographic regions should be conducted in order to overcome this limitation. Finally, our study suggested that duration of intervention of probiotic appears to be more reduction when it is supplied for more than 8 weeks. This result was consistent with a meta-analysis in last year. And those results illustrates that a longer duration of intervention of probiotic may be required to induce gut microbiota changes and beneficial effects on glucose metabolism.

A recent meta-analysis showed that probiotics supplementation can reduced LDL cholesterol, no significant differences of TC, HDL-C, or triglycerides (Dong et al. 2019). And Wu et al. (2017) suggested that probiotic *Lactobacillus* consumption significantly reduced TC and LDL-C, while no significant effects were found on TG and HDL-C levels. However, because subjects age, BMI, country, the dose, diabetes duration and duration intervention vary among studies, the overall role of probiotic on preventing and treating diabetes has also remained inconclusive. Yao et al. (2017) found that the effects of probiotics on lipid profile (TC, TG, LDL-C, HDL-C) were non-significant. A most recent meta-analysis also demonstrated similar results which supplementation with probiotics did not have a significant effect on lipids profile (Kasińska and Drzewoski 2015). However, in our study, the level of TC and TG was significantly improved in the probiotic treatment, and HDL-C, LDL-C were non-significant between probiotic and control traetment. These results were inconclusive due to varied factors, there were different sample sizes, subjects status, subjects race, and et al. we found that subjects ages $\leq$55, Eastern people, intervention of probiotic more than 8 weeks, illustrates a significant lower in TG, while, we also found that baseline BMI $\geq$ 30kg/m^2 had a higher reduction than BMI < 30kg/m^2, this inconsistent with glycemic index, and need been further studied.

Recently, it is reported that beneficial metabolic effects of Angiotensin-converting enzyme (ACE) inhibitors on blood pressure in patients with T2DM (Raj and Andreas 2005; Scheen 2004; Katsunori, Osamu, and Yoshifusa 2008). It may be due to bioactive peptides in the probiotics inhibiting ACE may reduce blood pressure levels in patients with diabetes. Our results demonstrated that SBP and DBP reduced in patients who received multiple species probiotic, and DBP also decreased when using the single species probiotic. Previous studies have investigated the effects of probiotics supplementation on the blood pressure (SBP and DBP). Similar results reported that the beneficial effects of probiotics in most studies (Khalesi et al. 2014; Jia-Yi et al. 2013), they observed that multistrain probiotic mixtures showed greater effiency than single species probiotic. Whereas other studies found less pronounced effects on blood pressure control (Dong et al. 2019; Khalili et al. 2018). Further evidence are needed to confirm these findings. These different results may be due to subjects age, our meta-analysis showed that subjects ages $\leq$ 55 had a higher reduction than ages > 55.

It is well known that alterations in glucose, blood lipid, pressure homeostasis are negatively associated with low-grade inflammation promoted by gut microbiota-derived

lipopolysaccharide or endotoxin (Cani et al. 2012). And some studies have suggested that consumption of probiotics could decrease pro-inflammatory factors in humans (Mohamadshahi et al. 2014). We hypothesized that effect of probiotics on metabolic syndrome control could be through immune-modulatory effects. To capture these interrelations were selected two pro-inflammatory mediator, including TNF-α, and CRP. This meta analysis suggested that probiotics treatment reduced TNF-α levels, but no significant effects was observed on CRP. We guess that the glucose, lipid, pressure lowering of probiotics by regulating the TNF-α metabolic pathway in type 2 diabetes mellitus.

A previous meta analysis only reported that the effect of probiotics and synbiotics on FBG, and other metabolic factors, such as HbA1c, insulin, HMOA-IR were not measured (Saman et al. 2018), the effect of consuming probiotics on other metabolic factors needs further evaluate. To our knowledge, this study is the first to investigate the effect of probiotics on glycemic, blood lipids, blood pressure outcomes simultaneously, compared to previous published results. However, there are several important limitations in this meta analysis. First, our meta-analysis was not registered such as in a prospective register PROSPERO, it was a limitation. Second, included in this studies were different in their methodological assessment, and some did not provide complete outcome data, and some studies were unclear in the risk of bias related to selective outcome reporting. This leads us not to adequately assess included articles quality, and it may influence the reliability of our results. Third, high heterogeneity was found in some parameters included in our analysis, there was encountered perhaps due to various regimens, doses, duration, center settings, populations enrolled etc. For example, some studies had low number of participants. Thus, it is still necessary to design trails with larger sample sizes, this way can increase the validity of results. Fourth, the majority of the subjects initial condition varied, including subjects ages, gender, baseline BMI, race, and diabetes duration. Thus, well-designed trials with larger sample sizes in a variety of subjects should be conducted in order to overcome these limitations.

Conclusion

The results of our meta-analysis indicate that probiotics supplementation has beneficial effect on glycemic, blood lipids, and blood pressure control, it was shown in Table 4. We observed that consuming probiotics had effects on FBS, HOMA-IR, TG, SBP, DBP and TNF-α. In addition, our subgroup analyses revealed that probiotics intake patterns, subjects ages, baseline BMI, race, and duration of intervention effects on these indexes. Particularly, multispecies probiotics, subjects ages $\leq$55, subjects baseline BMI $<$ 30kg/m^2, and duration of intervention more than 8 weeks, which more beneficial to the improvement of the glycemic, blood lipids, blood pressure, and inflammatory cytokines. Take together, these results indicate that probiotics supplementation may be used as an adjuvant therapy for preventing in type 2 diabetes mellitus. Future studies at clinical with a variety of subjects conditions, different dose of probiotics and durations of intervention are required to confirm the beneficial effect of probiotics on glycemic, blood lipids, blood pressure control.

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Disclosure statement

No conflict of interest to declare.

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