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Effect of Probiotics on Glucose and Lipid Metabolism in Type 2 Diabetes Mellitus: A Meta-Analysis of 12 Randomized Controlled Trials

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: It has been unclear whether supplemental probiotics therapy improves clinical outcomes in type 2 diabetic patients. This meta-analysis aimed to summarize the effect of probiotics on glucose and lipid metabolism and C-reactive protein (CRP) from 12 randomized controlled trials (RCTs).

Material/Methods: An up-to-date search was performed for all relevant RCTs up to April 2016 from PubMed, Embase, and Cochrane Library. Standardized mean difference (SMD) and weighted mean difference (WMD) were calculated for a fixed-effect and random-effect meta-analysis to assess the impact of supplemental probiotics on fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), lipid profile, and CRP level.

Results: A total of 12 studies (684 patients) were entered into the final analysis. The effect of probiotics was significant on reducing HbA1c level (standardized mean difference [SMD], –0.38; confidence interval [CI], –0.62 to –0.14, P=0.002; I^2=0%, P=0.72 for heterogeneity), fasting insulin level (SMD, –0.38; CI –0.59 to –0.18, P=0.0003; I^2=0%, P=0.81 for heterogeneity), and HOMA-IR (SMD, –0.99; CI –1.52 to –0.47, P=0.0002; I^2=86%, P<0.00001 for heterogeneity). Pooled results on effects of probiotics on FPG, CRP, or lipid profile were either non-significant or highly heterogeneous.

Conclusions: This meta-analysis demonstrated that probiotics supplementation was associated with significant improvement in HbA1c and fasting insulin in type 2 diabetes patients. More randomized placebo-controlled trials with large sample sizes are warranted to confirm our conclusions.

MeSH Keywords: Diabetes Mellitus, Type 2 • Meta-Analysis • Probiotics

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Background

Diabetes mellitus (DM) is becoming a serious international public health problem. As reported by the International Diabetes Federation (2013), the world-wide diabetic population is now 382 million and will reach 592 million by 2035. Diabetes has cost 548 billion USD and led to 5.1 million deaths by the end of 2013 [1]. The pathogenesis of type 2 diabetes (T2D) involves both genetic and environmental factors [2–4], among which gut microorganisms play an important role [5,6]. The human gut hosts trillions of microorganisms, including thousands of bacterial species [7], affecting a large number biological functions and metabolism in humans [8]. Cani et al. first demonstrated the direct role of gut bacteria in insulin resistance in 2007 [9]. They found that a high-fat diet increased certain gut bacterial species that generate higher levels of lipopolysaccharide, triggering the progression of insulin resistance [9]. Later studies also found that the gut microbiota contributes to glucose hemostasis through numbers of different bacterial metabolites [10]. More importantly, administration of probiotics in a mouse model effectively inhibited gluconeogenesis in type 2 diabetes [11], indicating its glucose-lowering effect might contribute to its inhibition of tumorigenesis [12,13]. Randomized controlled trials in humans have also shown potential benefits of probiotics in type 2 diabetes. Previous systematic reviews have evaluated the effect of probiotics on blood glucose, insulin, and C-reactive protein (CRP) in type 2 diabetes; however, they had a small number of cases and lacked convincing evidence [14–16]. Therefore, we aimed to summarize the effect of probiotics on type 2 diabetes by conducting a meta-analysis.

Material and Methods

This study protocol was established based on the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions [17].

Study selection

All randomized controlled trials (RCTs) investigating the effect of probiotics as a dietary supplementation on glucose and lipid metabolism and inflammatory markers in patients with type 2 diabetes mellitus were eligible for enrolment in this meta-analysis. We excluded the studies presented only as abstracts with no subsequent full report of findings, on-going clinical studies, quasi-randomized study design, review papers, non-English literature, studies involving patients with GDM, type 1 diabetes mellitus (T1DM), and any other metabolic diseases such as obesity or hypercholesterolemia.

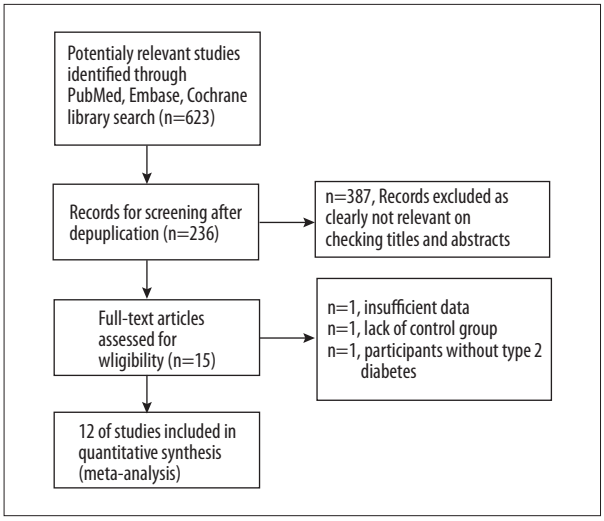

Figure 1. PRISMA 2009 flow diagram.

Search strategy

We searched PubMed, MEDLINE, EMBASE, and Cochrane library databases up to April 2016. Data from newly available studies were also accessed by searching editorials and web-based information. The terms for searching were: ('probiotics') AND ('supplementation') AND ('type 2 diabetes mellitus') AND ('glycemic-related parameters') AND ('inflammatory markers') AND (randomized OR blind OR placebo OR meta-analysis). We also attempted to contact the investigators if their clinical endpoints were not reported.

Selection criteria

Two independent authors (KY and XZ) identified eligible articles and a third investigator (QH) resolved any disagreements. The process of study selection is shown in Figure 1. The study selection process was based on preferred reporting items for systematic reviews and meta-analyses (PRISMA) [18].

Study quality assessment

Data were extracted, including baseline information of the study population, types of probiotics administration, and clinical outcomes. The study quality was determined according to the Cochrane Handbook [17] (Figure 2). Randomization was assessed and considered adequate for 2 out of 12 trials.

Clinical endpoints

The main clinical endpoints in this study were FPG, HbA1c, fasting insulin level, homeostasis model assessment of insulin resistance (HOMA-IR), CRP, and the levels of triglycerides, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C).

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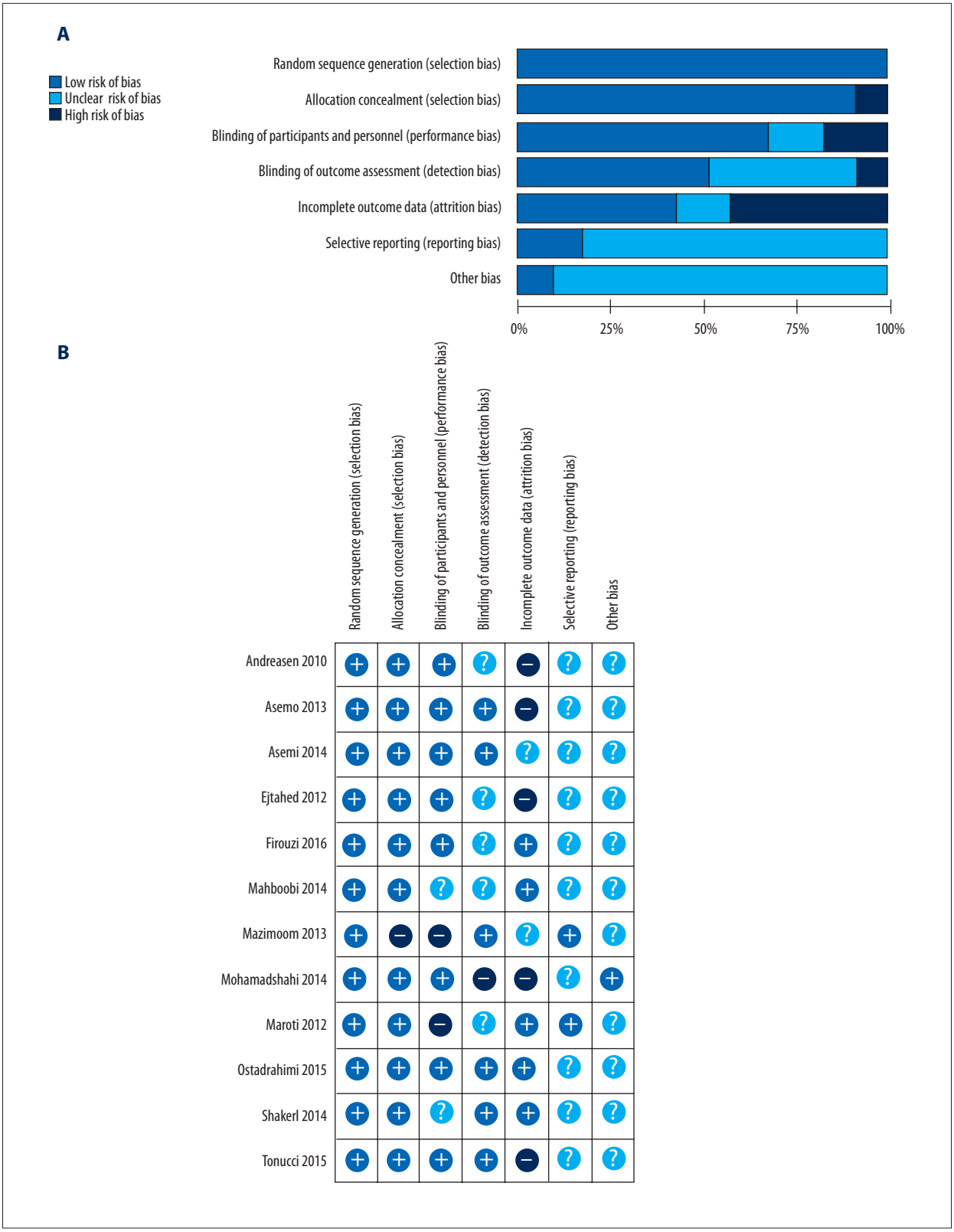

Figure 2. Risk of bias graph (**A**) and risk of bias summary (**B**) in 12 randomized controlled trials.

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Data synthesis and analysis

RevMan 5.3 (Nordic Cochrane Centre) was used for data synthesis and analysis. A fixed-effects or random-effects meta-analysis was performed for the standardized mean difference (SMD) or weighted mean difference (WMD), with 95% confidence intervals for continuous outcomes. All reported *P* values were two-sided, with a significance level set at $P<0.05$. Heterogeneity of studies was calculated by I^2 statistics and an I^2 of 0–25%, 25–50%, and 50–75% were considered as low, moderate, and high levels of heterogeneity, respectively.

Results

Study description

Originally, a total of 623 RCT studies were searched and 12 RCTs satisfied the inclusion criteria (Table 1). Table 1 shows the baseline characteristics of the 12 included RCTs [19–30]. Hariri (2015) [31] and Yan (2015) [32] were very small trials and their clinical endpoints were different. Therefore, they were not included in this analysis.

Probiotics and glucose metabolism

The pooled results of probiotics and glucose metabolism are presented in Figure 3. Nine studies reported the effect of probiotics on fasting plasma glucose levels. As shown in Figure 3A, 7 trails demonstrated significantly decreased glucose levels in the probiotics group, with a pooled standardized mean difference of –0.18 mg/dl (95% CI –0.35, –0.01; $P=0.04$). However, there was also significant heterogeneity ($I^2=64\%$, $P=0.004$).

Glycated hemoglobin reflects the average blood glucose level in the past 3 months. Four studies compared the change of HbA1c between the probiotics and control groups (Figure 3B). There was a statistically significant reduction in HbA1c in the probiotics group, with a pooled standardized mean difference of –0.38% (95% CI –0.62, –0.14; $P=0.002$) and a non-significant heterogeneity ($I^2=0\%$, $P=0.72$) compared to control.

Regarding the change in fasting insulin level, 5 studies reported the effect of probiotics on fasting insulin compared to control (Figure 3C). Probiotics significantly reduced fasting insulin levels, with a pooled standardized mean difference of –0.38 (95% CI –0.59, –0.18; $P=0.003$) and a non-significant heterogeneity ($I^2=0\%$, $P=0.81$). Similarly, 5 studies reported HOMA-IR results (Figure 3D). As a result, probiotics statistically reduced HOMA-IR level (pooled effect of –0.99, 95% CI –1.52, –0.4; $P=0.0002$). However, there was also significant heterogeneity ($I^2=86\%$, $P<0.00001$).

Probiotics and lipid metabolism

The effect of probiotics on lipid profile is presented in Figure 4. Ten trails were included in this analysis for evaluating the effects of probiotics on triglyceride levels (Figure 4A). Of these, 8 RCTs showed a significant decrease in triglyceride levels in the probiotics group compared to the control group. However, the total effect was found to be non-significant and there was significant heterogeneity (SMD, –0.23; 95% CI –0.48, 0.02; P=0.07; $I^2=52\%$, $P=0.03$ for heterogeneity).

Ten studies evaluated the effects of probiotics on total cholesterol levels (Figure 4B). Eight of these were included in this meta-analysis, and there was a significant decrease in total cholesterol level in the probiotics group compared to the control group. However, the overall effect was non-significant and the heterogeneity was marginally significant (SMD, –0.18; 95% CI –0.42, 0.06; $P=0.14$; $I^2=47\%$, $P=0.05$ for heterogeneity). The effect of probiotics on low- and high-density lipoprotein cholesterol are presented in Figures 4C and 4D. Among 9 RCTs included (Figure 4C), 5 studies showed a significant decrease in LDL-C levels in the probiotics group. However, no significance in the overall effect was found between the probiotics group and the control group (SMD, –0.03; 95% CI –0.20, 0.14; $P=0.73$, $I^2=3\%$, $P=0.41$ for heterogeneity). Regarding the effect of probiotics on HDL-C levels (Figure 4D), the total effect was marginally significant (SMD, 0.19; 95% CI 0.02, 0.35; $P=0.02$) and a moderate level of heterogeneity was also found ($I^2=29\%$, $P=0.18$).

Probiotics and C-reactive protein level

In this meta-analysis, we also investigated the effect of probiotics on CRP level and found 4 studies reported these effects (Figure 5). Probiotics significantly reduced CRP level, with a pooled mean difference of –1.34 mg/l (95% CI –1.76, –0.92; $P<0.00001$) and significant heterogeneity ($I^2=90\%$, $P<0.00001$).

Discussion

T2D is a metabolic disease characterized by hyperglycemia and insulin resistance, and associated with metabolic disturbance of blood lipids [1–3]. It causes severe pain to patients and imposes a heavy burden on families and society. In recent years, many studies have reported that probiotics have variety of effects on metabolic disturbance in T2D [10,11]. Therefore, we systematically analyzed these studies and evaluated the effect of probiotics on glucose and lipid metabolic profiles in T2D.

In this meta-analysis evaluating 12 randomized control trials with a total population of 684 diabetes patients, we demonstrated that probiotics supplementation significantly reduced

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Table 1. Study characteristics of 12 randomized control trials in this meta-analysis.

Studies	Participants (P/C)	Country	Design	Age (P/C)	Intervention	Weeks	Measure outcones
Andreasen 2010	Type 2 diabetes mellitus (21/24 adult patients)	Denmark	Randomized, placebo-controlled, double blinded trial	55±14/ 60±13	L.acidophilus NCFM	4	HOMA-IR, CRP
Asemi 2013	Type 2 diabetes mellitus (27/27 patients)	Iran	Randomized, placebo-controlled, double blinded trial	50.5±9.8/ 52.6±7.1	*L. acidophilus* (2×10^9 CFU), *L. casei* (7×10^9 CFU), *L. rhamnosus* (1.5×10^9 CFU), *L. bulgaricus* (2×10^8 CFU), *B. breve* (2×10^{10} CFU), *B. longum* (7×10^9 CFU), *S. thermophilus* (1.5×10^9 CFU), and 100 mg fructo-oligosaccharide	8	FPG, HbA1c, insulin, total cholesterol, triglycerides, LDL-C, HDL-C
Asemi 2014	Type 2 diabetes mellitus (62/62 patients)	Iran	Randomized, double-blinded, crossover controlled clinical trial	53.1±8.7/ 52.6±4.1	Probiotic viable and heat resistant Lactobacillus sporogenes (1×10^7 CFU), 0.04 g inulin (HPX) as prebiotic with 0.38 g isomalt, 0.36 g sorbitol and 0.05 gstevia as sweetener per 1 g	6	FPG, insulin, total cholesterol, triglycerides, LDL-C, HDL-C
Ejtahed 2012	Type 2 diabetes mellitus (30/30 patients)	Iran	Double-blinded, randomized controlled clinical trial	50.9±7.7/ 51.0±7.3	300 g/d of probiotic yogurt containing *L. acidophilus* La5 and *B. lactis* Bb 12	6	FPG, insulin, HbA1c
Firouzi 2016	Type 2 diabetes mellitus (48/53 patients)	Malaysia	Randomized, double-blinded, parallel-group controlled clinical trial	52.9±9.2/ 54.2±8.3	Provideda 3×10^{10} dose of six viable microbial cell preparation strains: three strains from the genus *Lactobacillus*, *Firmicutes phyla* (*Lactobacillus acidophilus, Lactobacilluscasei, Lactobacillus lactis*) and three strains from the genus *Bifidobacterium* and *Actinobacteriaphyla* (*Bifidobacterium bifidum, Bifidobacterium longum* and *Bifidobacteriuminfantis*)	12	FPG, insulin, HOMA-IR, HbA1c, total cholesterol, triglycerides, LDL-C, HDL-C
Mahaboobi 2014	Type 2 diabetes mellitus (28/27 paitients)	Iran	Randomized, double-blinded, controlled clinical trial	51.0±1.4/ 50.4±1.3	Probiotic capsules contained 7×10^9 colonyforming unit (CFU) *L. casei*, 2×10^9 CFU *L. Acidophilus*, 1.5×10^9 CFU *L. rhamnosus*, 2×10^8 CFU *L. bulgaricus*, 2×10^{10} CFU *B. breve*, 7×10^9 CFU *B. longum*, 1.5×10^{10} CFU *S. thermophilus*	8	Total cholesterol, triglycerides, LDL-C, HDL-C

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Table 1 continued. Study characteristics of 12 randomized control trials in this meta-analysis.

Studies	Participants (P/C)	Country	Design	Age (P/C)	Intervention	Weeks	Measure outcones
Mazloom 2013	Type 2 diabetes mellitus (16/18 paitients)	Iran	Randomized, single-blinded, controlled clinicaltrial	55.4±8.0/ 51.8±10.2	The lactobacillus probiotics contained *L. acidophilus, L. bulgaricus, L. bifidum*, and *L. casei*	6	FPG, Insulin, HOMA-IR, HbA1c, total cholesterol, triglycerides, LDL-C, HDL-C
Mohamadshahi 2014	Type 2 diabetes mellitus (16/18 paitients)	Iran	Randomized, double-blinded, controlled clinicaltrial	Mean age 51	300 g probiotic yogurt containing 3.7×10^6 cfu/mg of both *L. acidophilus* La-5 and *B. lactis* Bb-12	8	FPG, insulin, HOMA-IR, HbA1c, total cholesterol, triglycerides, LDL-C, HDL-C
Moroti 2012	Type 2 diabetes mellitus (10/10 patients)	Brazil	Randomized, placebo-controlled, double blinded trial	55.5±2.0/ 56.9±1.7	Symbiotic shake containing 4×10^8 UFC/100 mL *L. acidophillus*, 4×10^8 UFC/100 mL *B. bifidum* and 1 g/100 mL of fructooligosaccharides	4	FPG, total cholesterol, triglycerides, HDL-C
Ostadrahimi 2015	Type 2 diabetes mellitus (30/30 paitients)	Iran	Randomised, placebo-controlled, double blinded trial	Range from 35 to 65	Probiotic fermented milk (kefir) containing *L. casei, L. acidophilus* and *Bifidobacteria*	8	FPG, HbA1c, total cholesterol, triglycerides, LDL-C, HDL-C
Shakeri 2014	Type 2 diabetes mellitus (26/26 paitients)	Iran	Randomized, placebo-controlled, double blinded trial	52.3±8.2/ 53.1±7.5	Probiotic bread contained *L. sporogenes* (1×10^8 CFU) per 1 g	8	FPG, total cholesterol, triglycerides, LDL-C, HDL-C
Tonucci 2015	Type 2 diabetes mellitus (23/22 paitients)	Brazil	Randomized, placebo-controlled, double blinded trial	51.8±6.6/ 51.0±7.2	Fermented milk containing Lactobacillus acidophilus La-5 and *B. animalissubsplactis* BB-12 (10^9 colony-forming units/d, each)	6	FPG, insulin, HOMA-IR, HbA1c, total cholesterol, triglycerides, LDL-C, HDL-C

Age was presented as mean ±SD or as otherwise indicated; P/C – patient/control; HOMA-IR – homeostasis model assessment of insulin resistance; CRP – C-reactive protein; FPG – fasting plasma glucose; HbA1c – glycated hemoglobin; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol.

glucose level and alleviated insulin resistance. However, the effects of probiotics on lipid metabolism and CRP level were not convincing.

Previous meta-analyses with smaller numbers of studies have concluded that probiotics improve insulin resistance and reduce the level of glycated hemoglobin [14–16]. A most recent meta-analysis, with 11 RCTs and 614 subjects, also demonstrated similar results [14]. They found that probiotics supplementation significantly reduced FPG, HbA1c, insulin, and HOMA-IR in diabetic patients. Our study further confirmed these findings; however, our pooled results on fasting glucose and HOMA-IR demonstrated a high level of heterogeneity, indicating that further RCTs with larger populations are needed for confirmation of these results.

No significant relationships between probiotics intake and improved lipid metabolism were found in our study, despite the fact that the present meta-analysis in general participants suggested probiotics intake significantly reduced total cholesterol and LDL-C levels [33,34]. The underlying reason might be the difference in participant characteristics between the present study and other studies. Hence, our statistical power for detecting an effect of probiotics on lipid metabolism in type 2 diabetic patients may be lower. Interestingly, neither of these 2 studies found any relationships between probiotics and levels of triglycerides or HDL-C. Future clinical trials and animal studies are warranted to elucidate the effect of probiotics on lipid metabolism.

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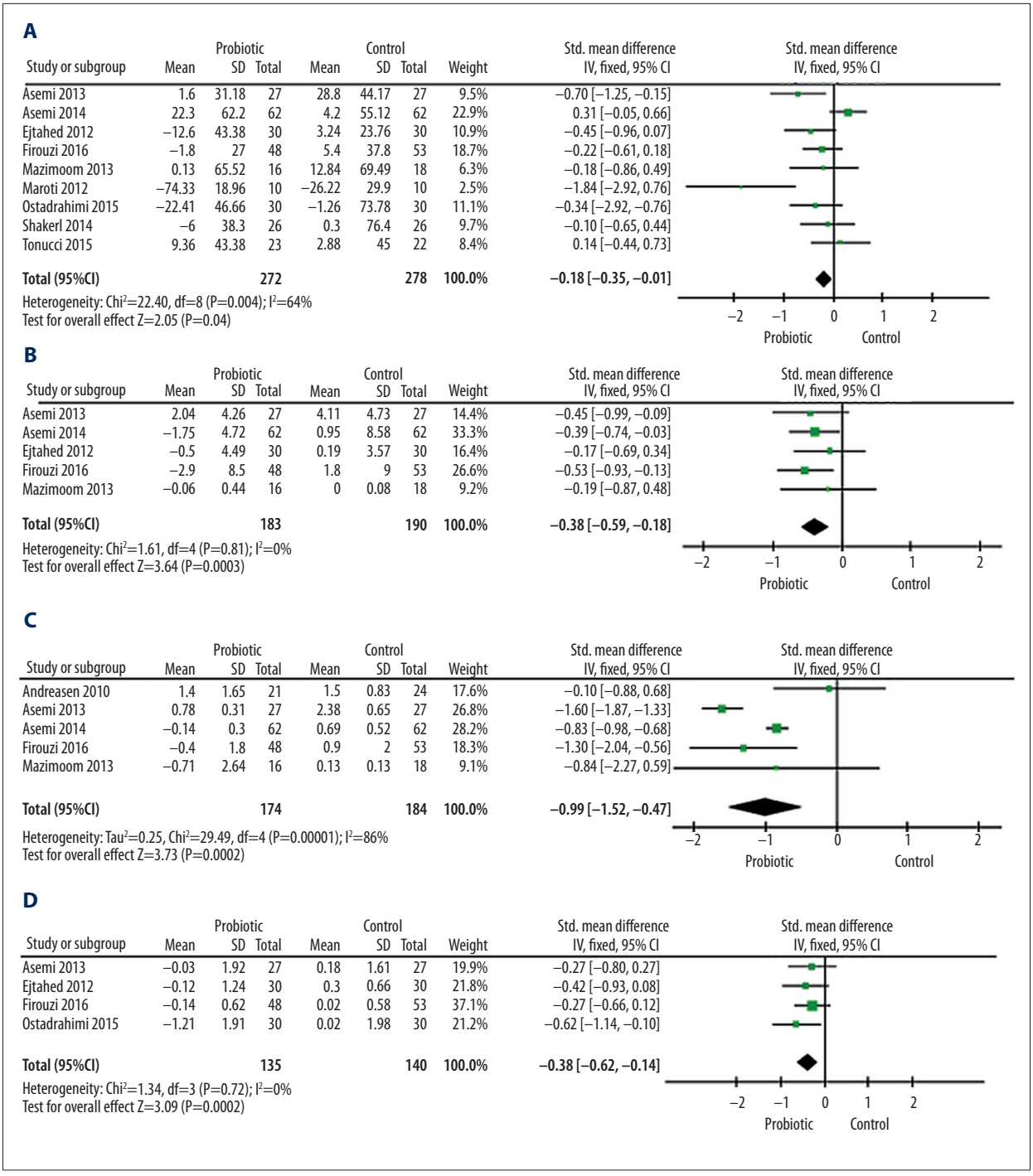

Figure 3. Forest plots for the effect of probiotics on fasting plasma glucose (**A**), glycated hemoglobin (**B**), fasting insulin levels (**C**), and insulin resistance (**D**) compared to controls in pooled analysis.

Our results also demonstrated insufficient evidence on probiotics reducing CRP levels, with a high level of heterogeneity. CRP is an important inflammatory marker for diabetes progression and complications [35,36]. A previous meta-analysis also presented non-significant effects of probiotics on CRP levels [15]. These results suggest that although probiotics have an important role in intestinal immunological modulation [37], the evidence for an effect on CRP level is scarce. More inflammatory markers screening may help expand our understanding of the regulation of probiotics on immunological modulation.

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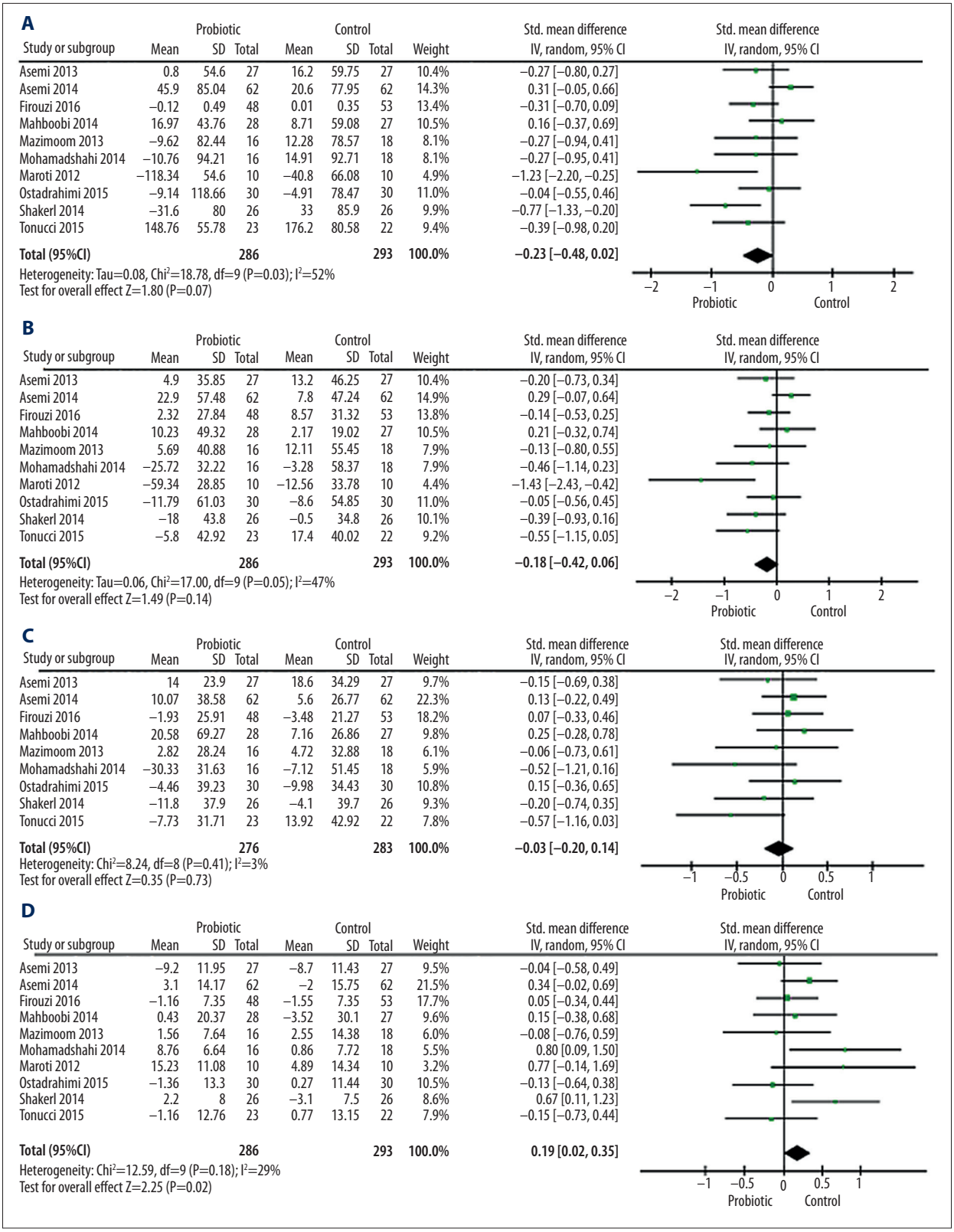

Figure 4. Forest plots for the effect of probiotics on triglycerides (**A**), total cholesterol (**B**), low-density lipoprotein cholesterol (**C**), and high-density lipoprotein cholesterol (**D**) compared to controls in pooled analysis.

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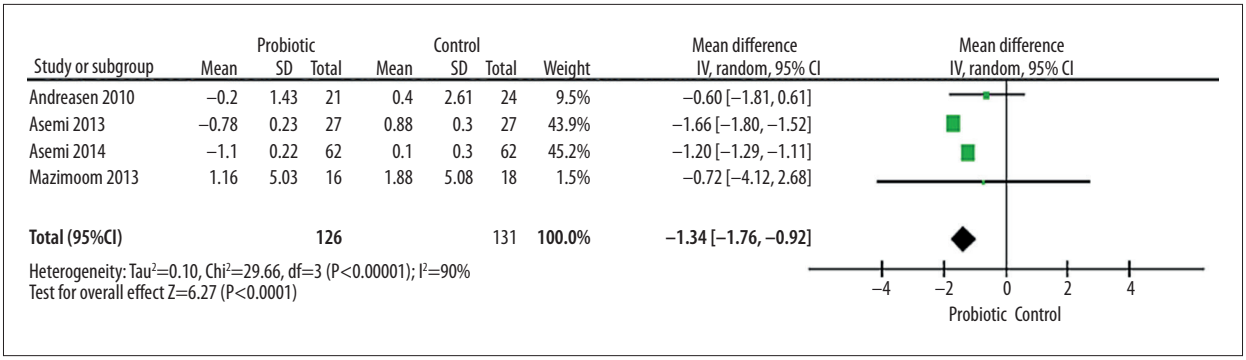

Figure 5. Forest plot for the effect of probiotics on C-reactive protein compared to controls.

The mechanism of these effects of probiotics remains unclear. One possibility was pointed out by Le Chatelier et al., who suggested the role of gut bacterial species richness in body weight and fat content in humans, which may further lead to other adiposity-related metabolic disorders [38]. Therefore, increasing the diversity of gut bacterial species by taking probiotics may have the reverse effect in alleviating metabolic disorders. On the other hand, animal studies have also provided insights [39–41]. Naito et al. showed that obese mice fed *Lactobacillus casei* strain Shirota had better insulin resistance through decreasing plasma levels of lipopolysaccharide-binding protein, a marker of endotoxemia [39], rather than reducing abdominal fat. Chen et al. demonstrated that in rats fed a high-fat diet, supplementation with *Bifidobacterium longum* led to reduced intestinal inflammatory activity index [40], which may also be the underlying mechanism by which probiotics affect glucose and lipid metabolism.

Limitations

Our study has several limitations. First, the doses of probiotics as dietary supplementation in the 12 included RCTs were not identical; therefore, it was not possible to determine the optimal dose for diabetic patients. Secondly, the researchers in these studies expected patients to have higher compliance, which contributes to positive results, producing a potentially higher selection bias. Finally, due to the excessive attention of researchers, the strength of the results is overestimated and the reliability of the results is reduced.

Conclusions

The present meta-analysis demonstrated that probiotics supplementation significantly reduced glucose level and alleviated insulin resistance, thereby potentially improving the clinical prognosis of type 2 diabetes. The evidence that probiotics improve lipid profiles in type 2 diabetic patients was not convincing. These results may provide evidence for encouraging use of probiotics in patients with type 2 diabetes mellitus. However, more randomized placebo-controlled trials with larger sample sizes are warranted to confirm these conclusions.

Disclosures

The authors declare they have no conflicts of interest regarding this study.

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