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The Effects of Synbiotic Supplementation on Glucose Metabolism and Lipid Profiles in Patients with Diabetes: a Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract Although several studies have evaluated the effect of synbiotic intake on metabolic profiles in patients with diabetes, findings are inconsistent. This systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted to summarize the evidence on the effect of synbiotic intake on metabolic profiles in patients with diabetes. The PubMed, EMBASE, Web of Science, and Cochrane Library databases were systematically searched. All RCTs published up to 12 November 2016 were included. Two review authors independently assessed study eligibility, extracted data, and evaluated risk of bias of included studies. Heterogeneity was measured with a Q test and with I_2 statistics. Data were pooled by using the fix or random-effect model based on the heterogeneity test results and expressed as standardized mean difference (SMD) with 95% confidence interval (CI). A total of seven randomized controlled trials were included. Synbiotic consumption significantly changed glucose metabolism, including fasting plasma glucose (FPG) (SMD = −0.29; 95% CI, −0.47, −0.10), insulin concentrations (SMD = −0.84; 95% CI, −1.61, −0.06), homeostasis model assessment of insulin resistance (HOMA-IR) (SMD = −0.80; 95% CI, −1.58, −0.03), homeostatic model assessment-B cell function (HOMA-B) (SMD = −0.36; 95% CI, −0.71, −0.01), quantitative insulin sensitivity check index (QUICKI) (SMD = 0.46; 95% CI, 0.09, 0.82), and significantly improved lipid profiles, such as triglycerides (SMD = −0.36; 95% CI, −0.55, −0.17), very low density lipoprotein-cholesterol (SMD = −0.31; 95% CI, −0.55, −0.08), and total cholesterol (SMD = −0.32; 95% CI, −0.67, −0.03), but had no effect on low density lipoprotein-cholesterol (SMD = −0.07; 95% CI, −0.58, 0.43) and high density lipoprotein-cholesterol concentrations (SMD = −0.25; 95% CI, −0.81, 0.31). Synbiotic may result in an improvement in FPG, insulin, HOMA-IR, HOMA-B, QUICKI, triglycerides, and total cholesterol.

Keywords Synbiotic · Glucose metabolism · Lipid profiles · Meta-analysis · Diabetes

Introduction

Impaired glucose metabolism, insulin resistance, and dyslipidemia are causally related to a greater risk of several chronic disorders, including diabetes, obesity, fatty liver, and cardiovascular diseases (CVDs) [1]. Blood glucose and lipid profiles can be controlled by proper eating pattern to prevent or control diabetes or related disorders [2]. In addition, existing evidence suggests that supplements such as omega-3 fatty acids [3], vitamin D [4], and dairy products [5] can improve glycemic control and lipid profiles or reduce risk of diabetes and CVD.

Probiotic and synbiotic are suggested to manage metabolic profiles of patients suffering from diseases related to metabolic syndrome. Synbiotics refer to nutritional supplements that are combining probiotics and prebiotics in a form of synergism [6]. Few studies have evaluated the effects of synbiotic-containing products on glucose metabolism and lipid profiles among patients with type 2 diabetes mellitus (T2DM) [7] and pregnant women [8]; however, findings were inconsistent. Such

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controversial findings complicate approaches to and conclusions about synbiotic use. In a meta-analysis by Beserra et al. [9], synbiotic supplementation among overweight or obese adults resulted in reductions in plasma fasting insulin and triglyceride fractions, while prebiotic supplementation resulted in reduction of triglycerides, plasma total cholesterol, and low density lipoprotein (LDL)-cholesterol levels and increased high density lipoprotein (HDL)-cholesterol level. In another study by Ruan et al. [10], reduced fasting glucose, insulin concentrations, and homeostasis model assessment of insulin resistance (HOMA-IR) were observed among percipients who consumed probiotic supplement compared with controls. Synbiotics are being used to modulate gut microbiota with favorable benefits for glucose homeostasis parameters and lipid profiles through mechanisms such as the production of short-chain fatty acid (SCFA), carbon disulfide, and methyl acetate [11] and decreased expression of inflammation-relevant genes [12], energy harvest, storage and expenditure from diet, satiety hormone balance, regulation of lipid synthesis, and improvement of markers of insulin metabolism and modulating the immune function [13].

Numerous randomized controlled trials (RCTs) have been conducted to determine whether synbiotic supplementation has a causal effect on glucose metabolism and lipid profiles. This study aimed to systematically review the current evidence on the effect of synbiotic supplementation on glucose metabolism and lipid profiles in RCTs among patients with diabetes and to summarize the available findings in a meta-analysis, if possible.

Methods

Search Strategy

Relevant studies were systematically searched from online databases PubMed, EMBASE, Web of Science, and Cochrane Library databases up to 12 November 2016. The search was conducted based on PICOS elements (Table 1). Search terms included patients ["diabetes" OR "T2DM" OR "gestational diabetes mellitus (GDM)"], intervention ("synbiotic" OR "symbiotic" AND "supplementation" OR "intake"), and outcomes ["fasting plasma glucose (FPG)" OR "insulin" OR "homeostatic model assessment-B cell function (HOMA-B)" OR "homeostatic model assessment-B cell function (HOMA-B)" OR "total-cholesterol" OR "triglycerides" OR"LDL-cholesterol" OR "HDL-cholesterol" OR "VLDL-cholesterol" OR "quantitative insulin sensitivity check index (QUICKI)"]. Search was conducted by two independent researchers. References cited in the selected studies were manually searched for additional relevant articles. Additionally, the relevant research centers and experts of the field were contacted to find unpublished studies. Our search was restricted to studies published in the English language.

Table 1 PICOS criteria used to define the research question for the systematic review criteria description

Population	Adult populations (aged >18 years) with diabetes [type 2 diabetes mellitus (T2DM) and gestational diabetes mellitus (GDM)]
Interventions	Synbiotic capsules/synbiotic food
Comparison group	Placebo capsules/placebo food
Outcomes	Glucose metabolism including fasting plasma glucose (FPG), insulin concentrations, homeostasis model assessment of insulin resistance (HOMA-IR), homeostatic model assessment-B cell function (HOMA-B), quantitative insulin sensitivity check index (QUICKI), and lipid profiles such as triglycerides, VLDL-cholesterol, total cholesterol, LDL-cholesterol, and HDL-cholesterol concentrations) at baseline and at the end of the intervention
Study design	All randomized controlled trials

Selection Criteria

The eligibility criteria were human RCTs, patients with T2DM or GDM, and administration of synbiotic or symbiotic supplements. Studies that did not reported mean changes of glucose metabolism and lipid profiles, along with standard deviation (SD) for the intervention and control groups, the abstracts of seminars without full text, case reports, and studies that did not obtain the minimum required score of quality assessment process were excluded.

Quality Assessment

Data extraction and study quality assessment were conducted by two independent reviewers (ZA and MA), according to Cochrane Collaboration risk of bias tool. The scale includes three domains related to quality of clinical trials: (1) random sequence generation description (0 = no description, 1 = inadequate description, 2 = adequate description), (2) blinding process (2 = double blinding with adequate description, 1 = double blinding with inadequate description, 0 = wrong usage of double blinding), and (3) withdrawal of patients (1 = the number and reasons of patients withdrawal described, 0 = otherwise). In the event of disagreement, resolved by discussion until consensus was reached.

Statistical Methods

RevMan software (Cochrane Review Manager, version 5.2) and STATA version 12.0 (Stata Corp., College Station, TX) were used for data analyses. Heterogeneity was evaluated through the Cochran (Q) and I-squared tests (I_2). Given the existing heterogeneity between studies, when I_2 exceeds 50% or $P < 0.05$, the random-effect model was used; otherwise, the fixed-effect

model was applied. Inverse variance method and Cohen statistics were used for estimation of standardized mean difference (SMD) and 95% CI for verifying the outcome behavior of each study group (intervention/control). Sensitivity analyses also undertook in the trials one by one to evaluate the reliability of the pooled mean difference. In addition, the Cochrane Collaboration risk of bias tool was used to assess the methodological quality of the RCTs. Potential publication bias was assessed through visual inspection of funnel plots and quantitatively assessed using Egger's tests.

Results

Search Results and Trial Flow

A total of 1328 studies were identified through the database search. Of these, 302 duplicate articles, 261 not randomized controlled trials, and 4 review articles were excluded. After reading titles and abstracts, 761 articles were excluded and 23 full text articles were assessed for eligibility. One article was included form the references cited in the selected studies. The remaining 23 articles were retrieved for further review, and 9 were deemed relevant. Of these, we excluded 14 articles that examined non-diabetic patients (n = 3), did not presented required data for meta-analyses (n = 11), and did not administrated symbiotic (n = 2). Finally, seven studies were found to be appropriate for in this meta-analysis [8, 14–19] (Fig. 1).

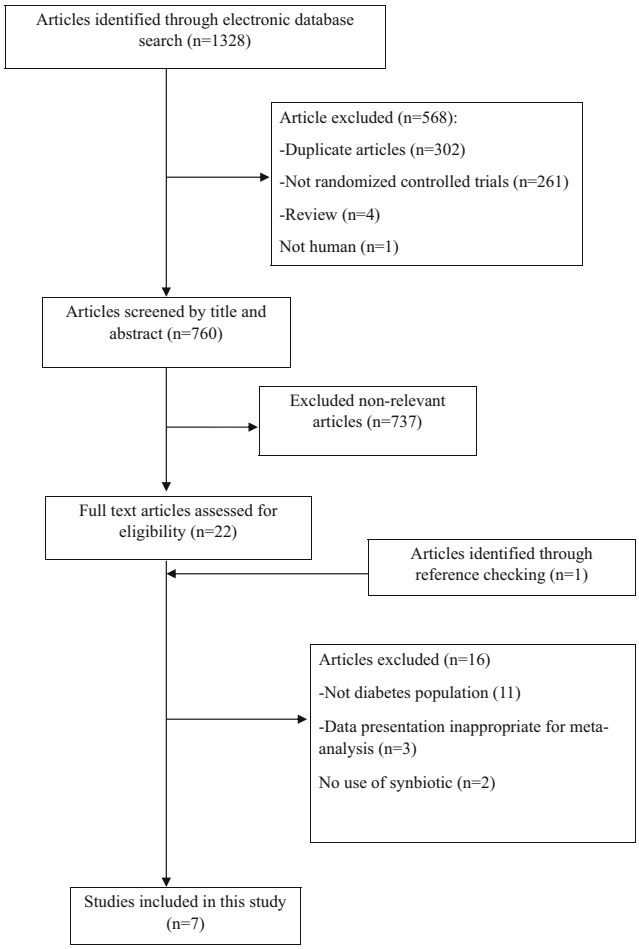


Fig. 1 Literature search and review flow chart for selection of studies

Characteristics of Included Studies

Totally, seven studies with 482 participants were included in the final meta-analysis. Six studies were double blind, and one study was single blind [17]. Four studies used parallel design, and two used crossover design [15, 16]. The intervention duration varied from 6 to 12 weeks. Six studies have investigated the effects of synbiotic supplementation on glucose metabolism and lipid profiles in patients with T2DM and one study in patients with GDM [14]. Six studies have reported changes in FPG, triglycerides, total cholesterol, and HDL-cholesterol, and five studies have reported changes in insulin concentrations, HOMA-IR, and LDL-cholesterol, and four studies have reported changes in HOMA-B, QUICKI, and very low density lipoprotein (VLDL)-cholesterol levels. The synbiotic species and used dosage were varied between studies. Five studies have used combination of more than two strains, whereas two studies have used a single species of probiotics [15, 16]. Total daily dose of probiotic intake was varied from 10^6 colony-forming units (CFU) to 10^8 CFU, except for one study that has used 1500 mg probiotic capsule twice daily. Participants of three studies in the intervention group consumed synbiotic capsules, and those in the control group consumed placebo capsules. Participants of four studies in the intervention group consumed synbiotic food, and those in the control group consumed control food. The characteristics of included studies are presented in Table 2. The methodological quality based on authors' judgments about each risk of bias item for each included study is shown in Fig. 2.

Pooled Effects of Synbiotic on Glucose Metabolism

Figure 3 shows the forest plots for effect of synbiotic on glucose metabolism parameters. We observed that synbiotic consumption significantly improved glucose metabolism, such as FPG (SMD −0.29; 95% CI, −0.47, −0.10), insulin concentrations (SMD = −0.84; 95% CI, −1.61, −0.06; I_2 = 92.6%, P < 0.001), HOMA-IR (SMD = −0.80; 95% CI, −1.58, −0.03; I_2 = 92.6%, P < 0.001), HOMA-B (SMD = −0.36; 95% CI, −0.71, −0.01; I_2 = 53.0%, P = 0.094), and QUICKI (SMD = 0.46; 95% CI, 0.09, 0.82; I_2 = 55.7%, P = 0.08). Evidence of inter-study heterogeneity was observed across studies on glucose metabolism parameters; therefore, the random-effect model was used. Sensitivity analysis was performed by removing the trials one by one to evaluate the reliability of the pooled standardize mean difference; expect

Table 2 Characteristics of included studies

Ref.	Intervention/control (sample size)	Duration (weeks)	Age (years)	Strain	Dosage (CFU/g)	Number of bacteria
Ahmadi et al. [14]	Synbiotic capsules/placebo capsules (35/35)	<8	18–40	*Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum*	2×10^9	>2
Asemi et al. [15]	Synbiotic food/control food (62/62)	<8	35–70	*Lactobacillus sporogenes*	1×0^7	≤2
Asemi et al. [16]	Synbiotic fortified/placebo capsules (51/51)	<8	35–70	*Lactobacillus sporogenes*	1×10^7	≤2
Moroti et al. [17]	Symbiotic shake/placebo shake (10/10)	<8	50–65	*Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *oligofructose*	10^8	≤2
Tajadadi-Ebrahimi et al. [18]	Synbiotic bread/control bread (27/27)	≥8	35–70	*Lactobacillus sporogenes*	1×10^8	≤2
Shakeri et al. [8]	Synbiotic bread/control bread (26/26)	≥8	35–70	*Lactobacillus sporogenes*	1×10^8	≤2
Tajadadi-Ebrahimi et al. [19]	Synbiotic capsules/placebo capsules (30/30)	≥8	40–85	*Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum*	2×10^9	>2

Asemi et al. [15] study, results remained consistent after removing the trials for insulin and HOMA-IR.

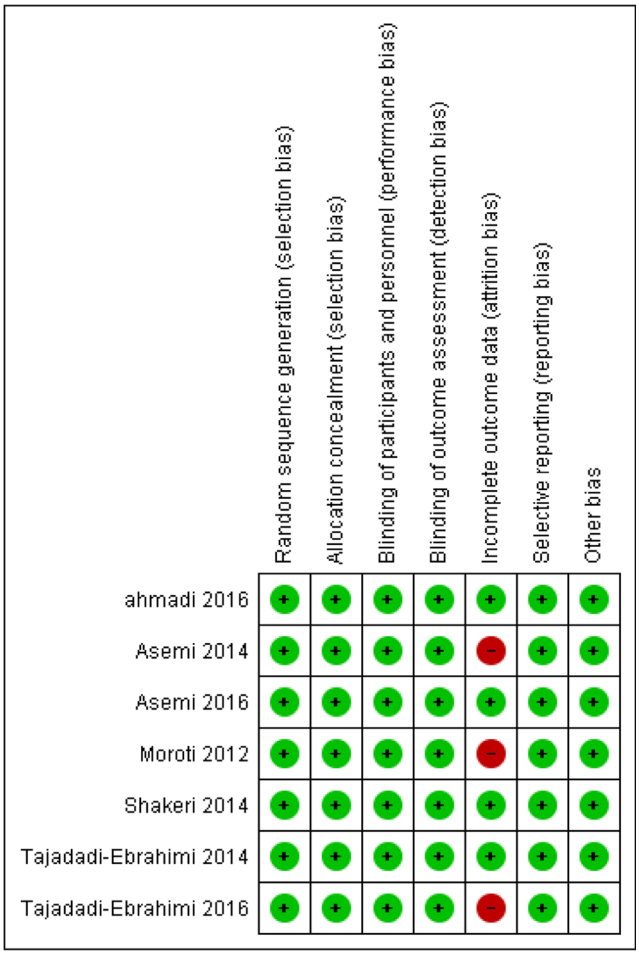


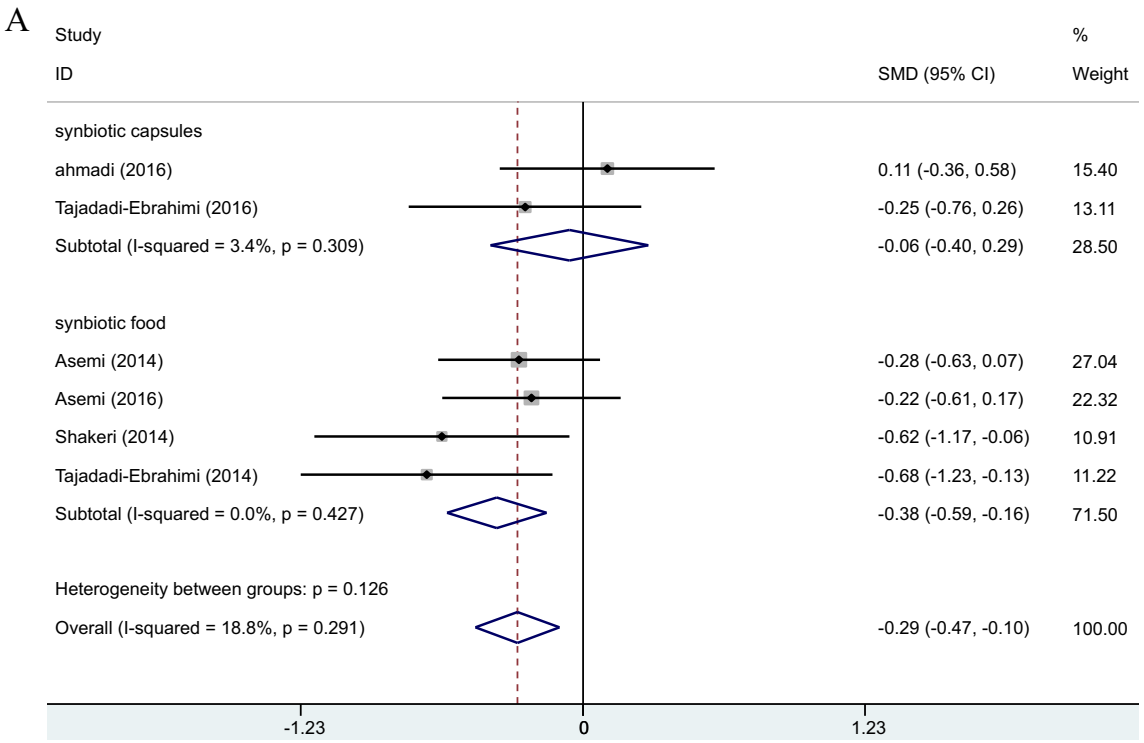
Fig. 2 The methodological quality of included studies

Pooled Effects of Synbiotic on Lipid Profiles

Similar results were observed for lipid profiles. The effect of synbiotic supplementation on triglycerides and VLDL-cholesterol levels was examined in seven RCTs; significant decrease in SMD −0.32 (95% CI, −0.67, −0.03), −0.36 (95% CI, −0.55, −0.17), and −0.31 (95% CI, −0.55, −0.08) was observed between intervention and placebo groups for any of the lipid profiles, respectively (Table 3). Due to heterogeneity of studies, the results of total cholesterol studies were combined by using random-effect model (I_2 = 66.4%, P = 0.011). Synbiotic consumption significantly decreased triglycerides (SMD = −0.36; 95% CI, −0.55, −0.17), VLDL-cholesterol (SMD = −0.31; 95% CI, −0.55, −0.08), and total cholesterol (SMD = −0.32; 95% CI, −0.67, −0.03), but had no significant effect on LDL-cholesterol (SMD = −0.07; 95% CI, −0.58, 0.43) and HDL-cholesterol concentrations (SMD = −0.25; 95% CI, −0.81, 0.31) (Fig. 4). Sensitivity analysis showed that removing studies with high heterogeneity in lipid profiles did not change the pooled effect.

Meta-Regression and Subgroup Analyses

Subgroup analyses for all metabolic profiles were done based on bacteria strain (Figs. 3 and 4). The univariate meta-regression analyses based on bacteria strain, time of intervention, and the number of bacteria did not show any statistically significant subgroup-effect interactions on lipid profiles ($P \geq 0.05$ for all comparisons). However, among glucose metabolism, parameters as FPG based on time of intervention and insulin by bacteria strain and the number of bacteria had statistically significant subgroup-effect interactions ($P < 0.05$) (Table 4).



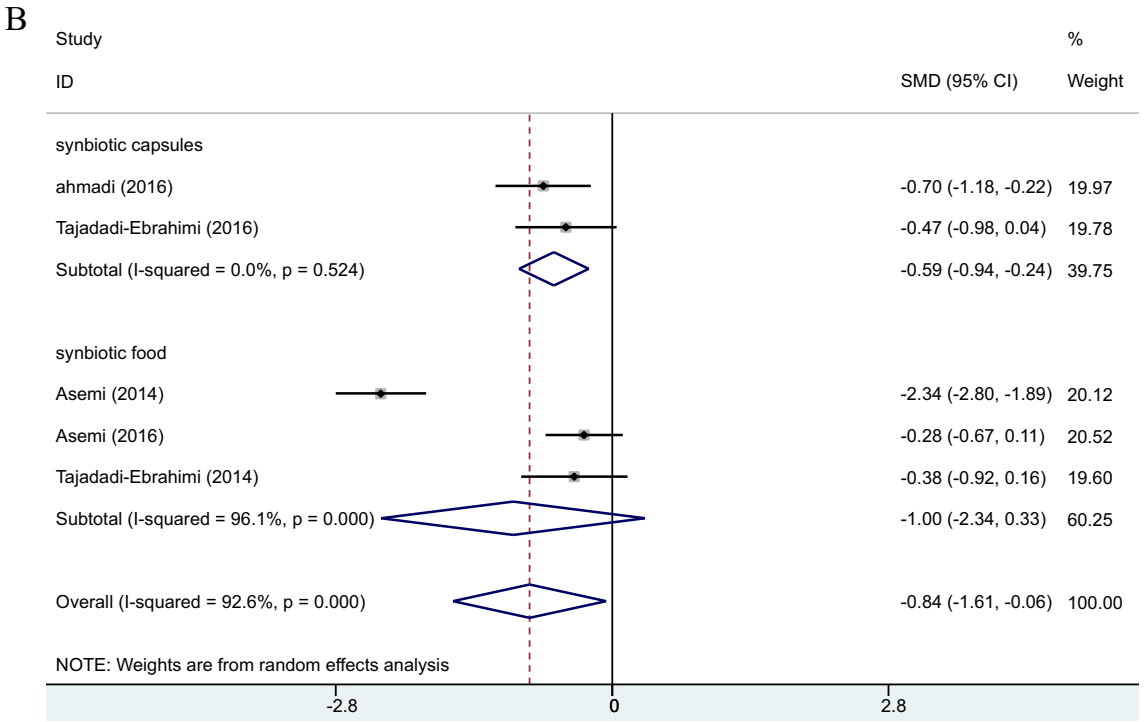


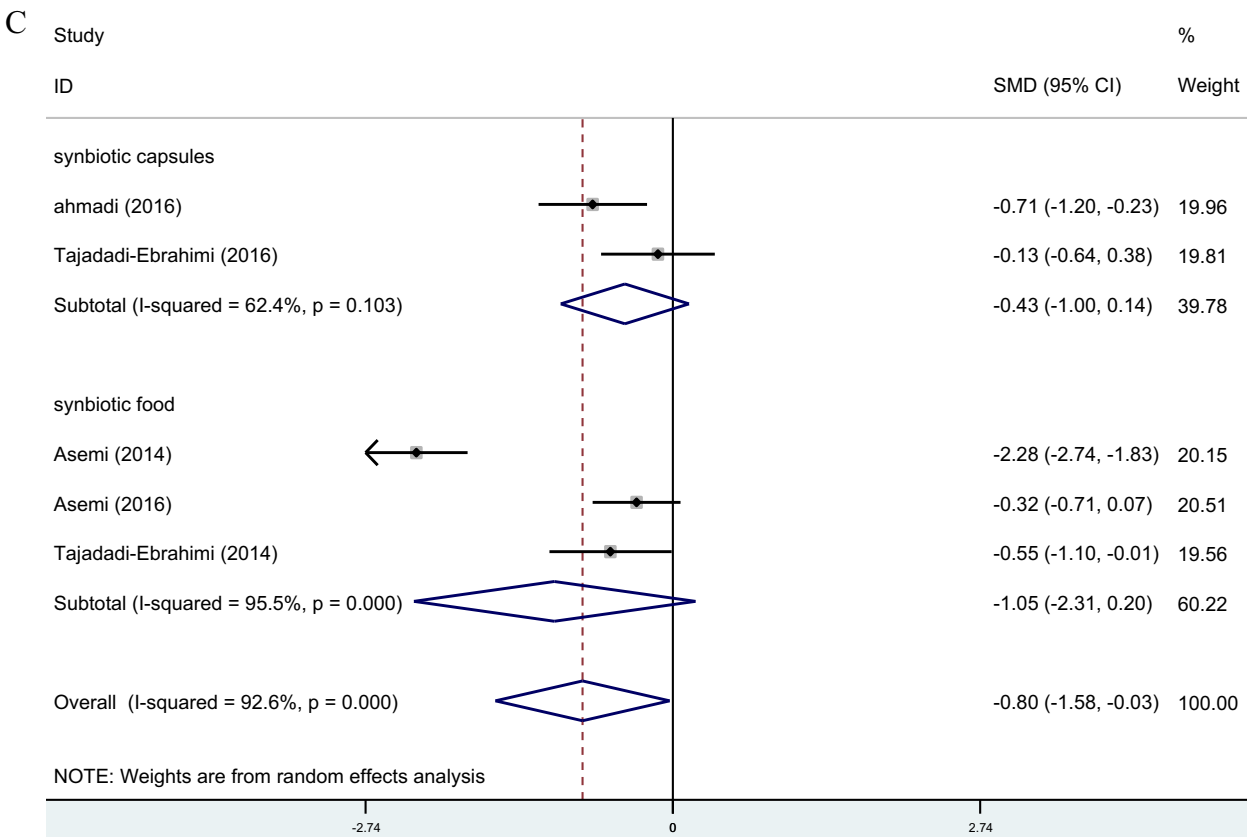
Fig. 3 **a**–**e** Meta-analysis glycemic parameters' standardized mean difference estimates for **a** FPG, **b** for insulin, **c** for HOMA-IR and **d** HOMA-B, and **e** for QUICKI in synbiotic and placebo groups (CI = 95%)

Publication Bias

The Egger's regression was performed to detect potential publication bias. Egger's regression indicated no significant publication bias for all indices ($B = 1.67$, $P = 0.605$).

Discussion

To our knowledge, this is the first meta-analysis of RCTs that examined the effect of synbiotic supplementation on glucose metabolism and lipid profiles among patients with diabetes.



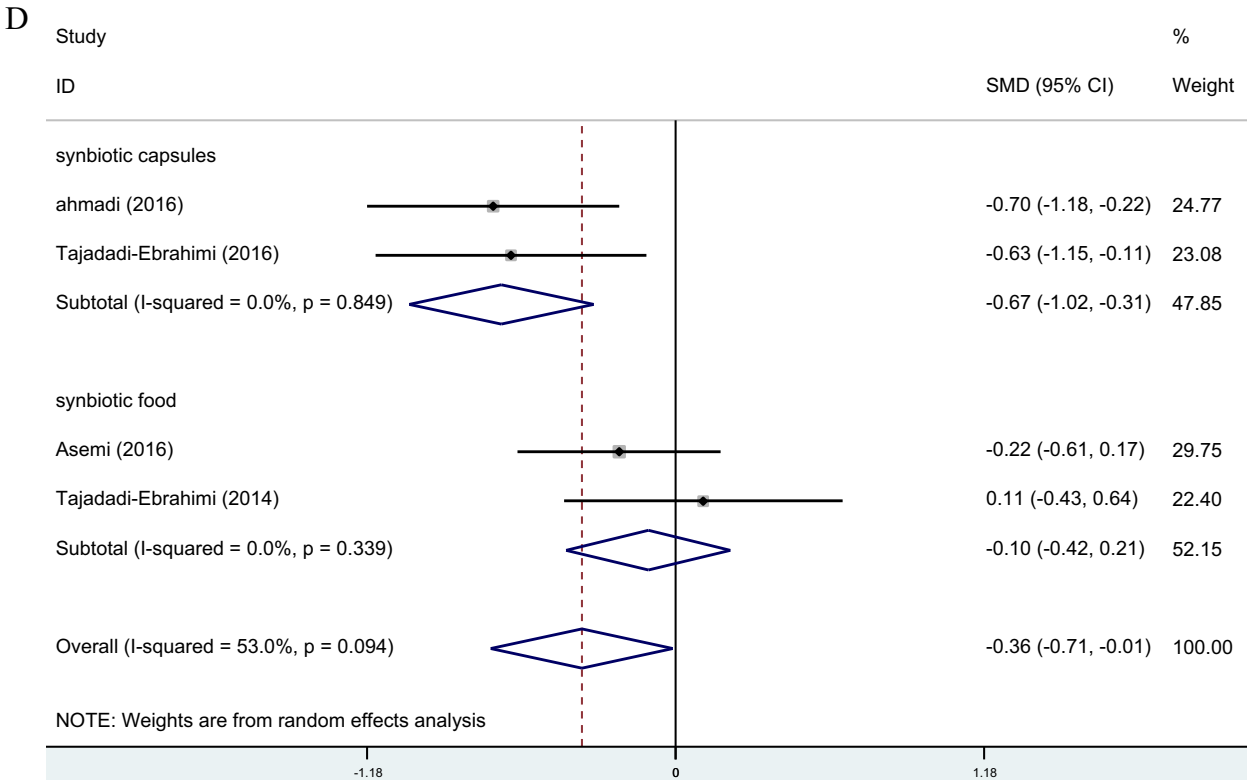


Fig. 3 (continued)

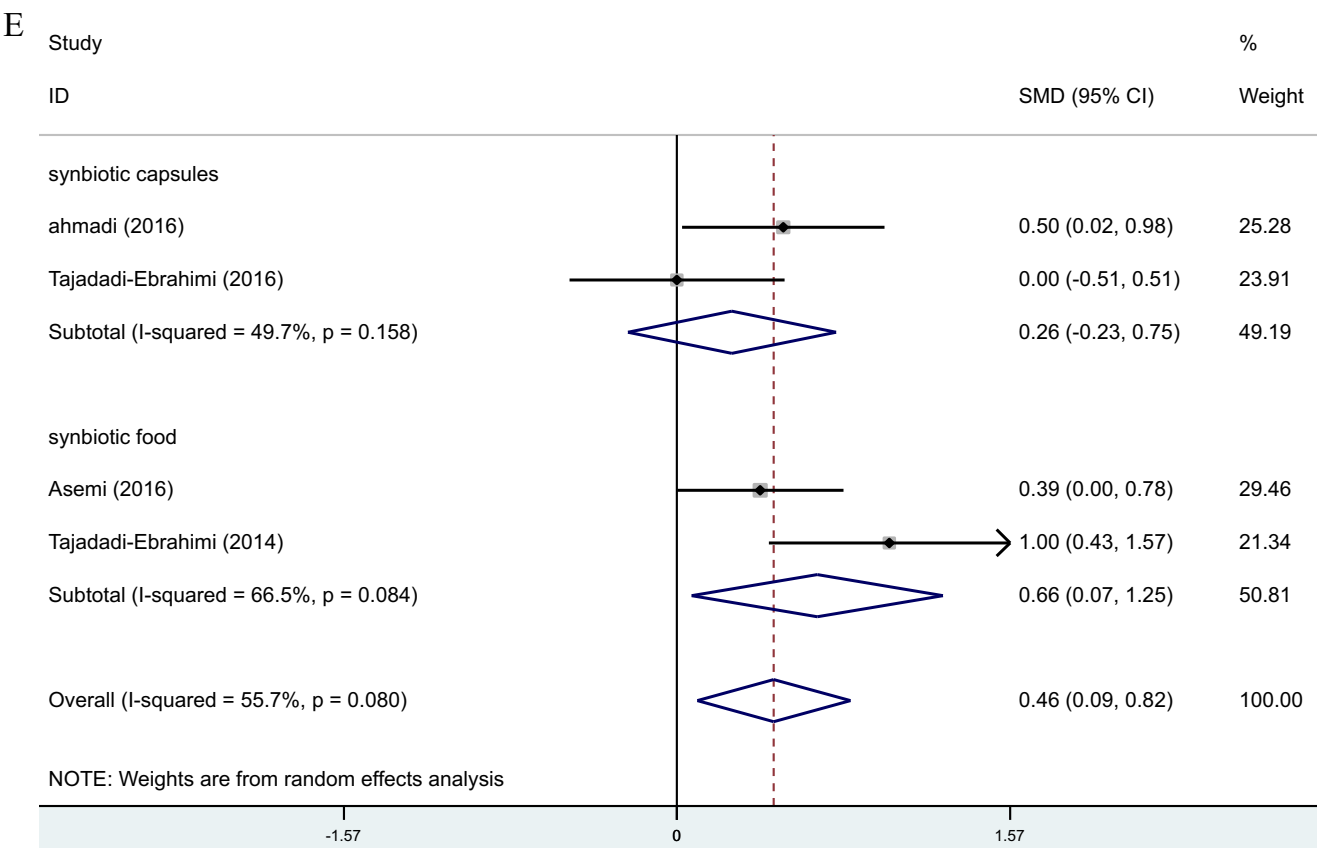


Fig. 3 (continued)

We show that synbiotic supplementation may result in an improvement in FPG, insulin, HOMA-IR, HOMA-B, QUICKI, triglycerides, total cholesterol, and VLDL-cholesterol levels, but did not affect LDL-cholesterol and HDL-cholesterol levels in patients with diabetes.

The hypothesis that probiotics and synbiotics may be involved in the maintenance of healthy gut microbiota and the management of glucose metabolism and lipid profiles has received much attention. In a study by Gomes et al. [20], the ratio of bacteroidetes species in T2DM was correlated positively with fasting plasma glucose. The alterations in gut microbiota have recently been reported in subjects with T2DM, and this may be reversible with probiotic intake [21]. The results of our meta-analysis revealed that synbiotic supplementation significantly reduced FPG, insulin levels, HOMA-IR, and HOMA-B and increased QUICKI score in patients with diabetes. In a recent meta-analysis by Kasinska et al. [22], a significant effect of probiotic supplementation on reducing HbA1c levels and HOMA-IR was observed; however, there was no effect on FPG and insulin concentrations. In another meta-analysis study by Beserra et al. [9], synbiotic intake in adults with overweight or obesity significantly decreased insulin and triglyceride levels and prebiotic supplementation decreased total cholesterol and LDL-cholesterol values in overall analysis, and decreased triglycerides and increased HDL-cholesterol values in patients with diabetes. In addition, a meta-analysis by Samah et al. [23] showed that FGD was significantly lower following consumption of probiotic supplements. The findings of our meta-analysis are in agreement with the previous review, suggesting that a combination of probiotic species in synbiotic supplements is more effective than single-species probiotics [24].

An interesting observation in the current meta-analysis was that synbiotic supplementation was associated with improvement in HOMA-IR among participants with impaired glucose tolerance and insulin resistance at baseline, a common feature in T2DM patients. Insulin resistance is pathogenic for several prevalent disorders such as T2DM, CVD, polycystic ovary syndrome, non-alcoholic fatty liver disease, and several cancers [25]. Accurate mechanism of synbiotic function on glucose metabolism is unclear. The glucose-lowering effects of synbiotics may be related to the reduction in oxidative stress activities [26]. Previous studies have shown that specific strains of lactic acid bacteria have antioxidant properties [27, 28]. For instance, Yadav et al. [29] revealed that probiotic dahi-supplemented diet, a fermented milk containing

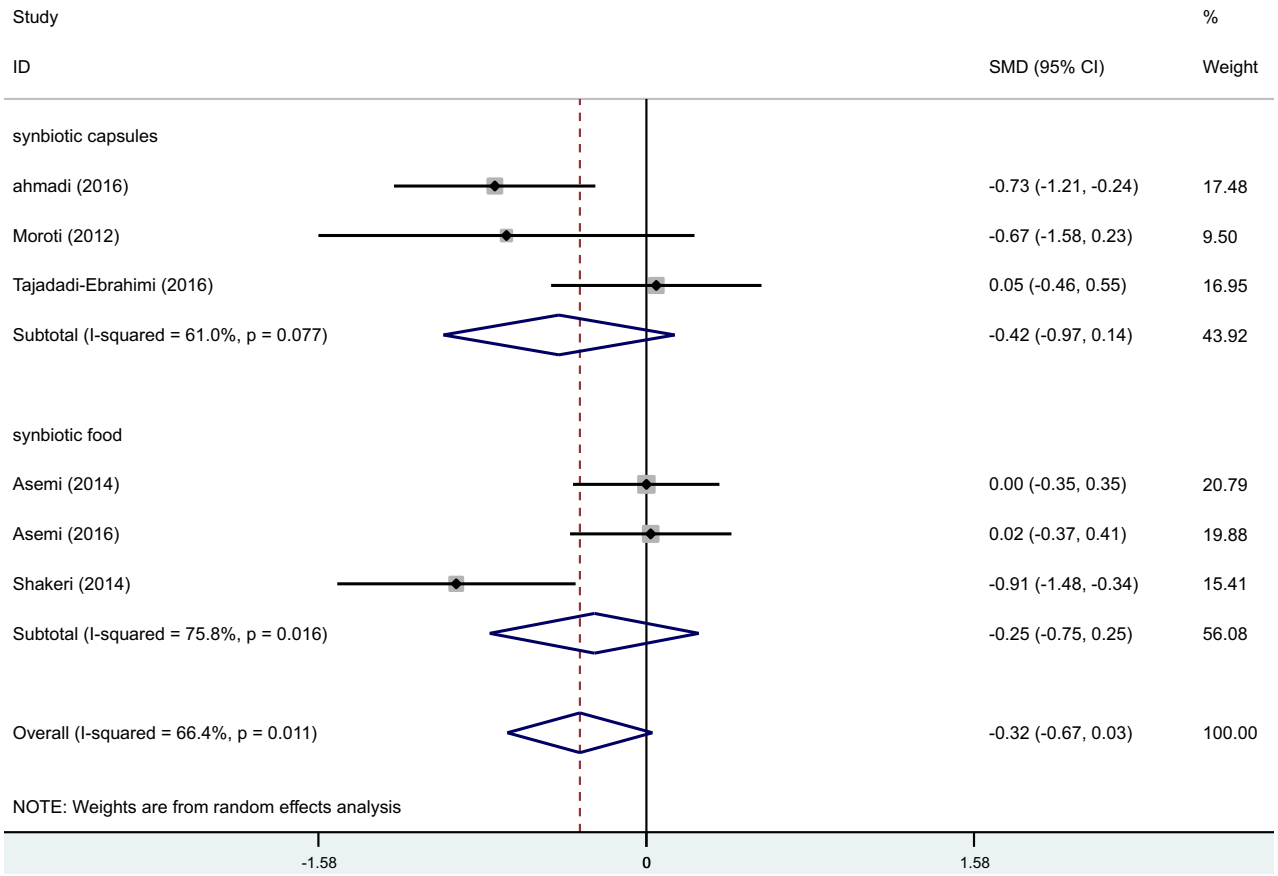
Table 3 Estimation of the standardized difference means of related indictors and confidence interval 95% before and after synbiotic consumption between the intervention and placebo groups

Parameter		Number of study	Standardized mean difference	95% CI	Heterogeneity		
					I-squared (%)	*Q*	*P* value
FPG	Intervention group (after vs. before)	6	0.24	−0.69, 1.16	95.4	109.9	<0.001
	Placebo group (after vs. before)	6	0.21	0.03, 0.40	0.0	4.5	0.471
	Intervention group vs. placebo group	6	−0.29	−0.47, −0.10	18.8	6.16	0.291
Insulin	Intervention group (after vs. before)	5	−0.82	−1.83, 0.19	95.5	89.12	<0.001
	Placebo group (after vs. before)	5	0.53	0.19, 0.86	64.2	11.17	0.025
	Intervention group vs. placebo group	5	−0.84	−1.61, −0.06	92.6	54.23	<0.001
HOMA-IR	Intervention group (after vs. before)	5	−0.33	−0.53, −0.14	27.9	5.55	0.236
	Placebo group (after vs. before)	5	0.58	0.07, 1.09	84.0	25.02	<0.001
	Intervention group vs. placebo group	5	−0.80	−1.58, −0.03	92.6	54.40	<0.001
HOMA-B	Intervention group (after vs. before)	4	−0.20	−0.43, 0.03	1.6	3.05	0.384
	Placebo group (after vs. before)	4	0.32	0.09, 0.55	0.0	1.47	0.690
	Intervention group vs. placebo group	4	−0.36	−0.71, −0.01	53.0	6.38	0.094
QUICKI	Intervention group (after vs. before)	4	0.30	−0.07, 0.66	58.1	7.15	0.067
	Placebo group (after vs. before)	4	−0.24	−0.48, −0.01	0.00	1.66	0.674
	Intervention group vs. placebo group	4	0.46	0.09, 0.82	55.7	6.77	0.080
Total cholesterol	Intervention group (after vs. before)	6	0.36	−0.83, 1.55	96.7	151.31	<0.001
	Placebo group (after vs. before)	6	0.16	−0.35, 0.66	84.0	31.26	<0.001
	Intervention group vs. placebo group	6	−0.32	−0.67, −0.03	66.4	14.87	0.011
Triglycerides	Intervention group (after vs. before)	6	0.38	−0.89, 1.65	97.0	168.21	<0.001
	Placebo group (after vs. before)	6	0.45	−0.07, 0.97	84.5	32.32	<0.001
	Intervention group vs. placebo group	6	−0.36	−0.55, −0.17	29.7	7.11	0.213
LDL-cholesterol	Intervention group (after vs. before)	5	0.48	−0.51, 1.48	95.5	89.34	<0.001
	Placebo group (after vs. before)	5	0.27	−0.25, 0.78	84.8	26.35	<0.001
	Intervention group vs. placebo group	5	−0.07	−0.58, 0.43	84.4	25.58	<0.001
HDL-cholesterol	Intervention group (after vs. before)	6	0.51	−0.33, 1.34	93.9	81.70	<0.001
	Placebo group (after vs. before)	6	−0.54	−0.97, −0.11	77.4	22.09	0.001
	Intervention group vs. placebo group	6	−0.25	−0.81, 0.31	87.0	38.49	<0.001
VLDL-cholesterol	Intervention group (after vs. before)	4	−0.09	−0.33, 0.14	0.0	2.65	0.449
	Placebo group (after vs. before)	4	0.36	0.12, 0.59	0.00	0.36	0.948
	Intervention group vs. placebo group	4	−0.31	−0.55, −0.08	44.6	5.42	0.144

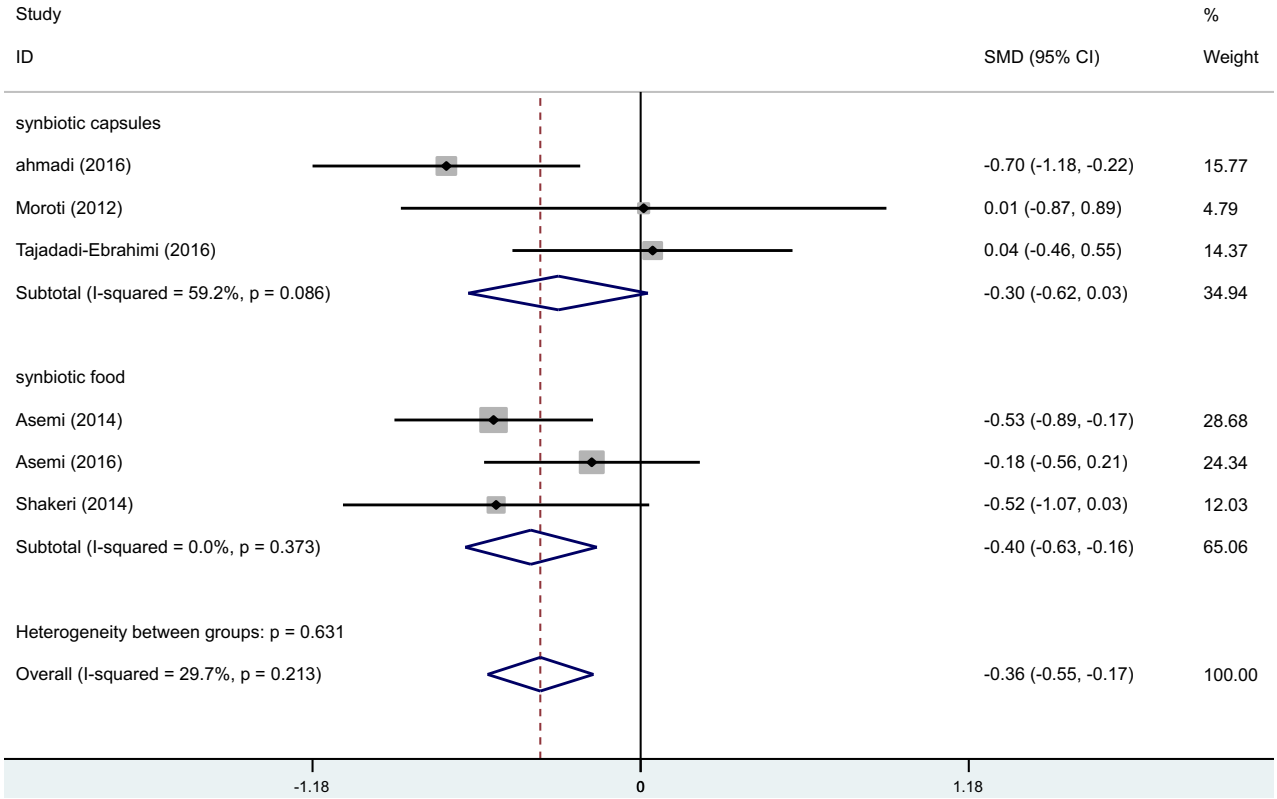
Lactobacillus acidophilus and *Lactobacillus casei*, delayed the progression of glucose intolerance, hyperglycemia, and hyperinsulinemia via decreased oxidative stress in animal models. In addition, synbiotics may have antidiabetic effects through modulating immune responses and systemic low-grade inflammation, in particular by reducing inflammatory cytokines [30] and suppressing the nuclear factor kappa light

Fig. 4 **a**–**e** Meta-analysis lipid profiles' standardized mean difference estimates for **a** total cholesterol, **b** for triglycerides, **c** for LDL-cholesterol, **d** for HDL-cholesterol, and **e** for VLDL-cholesterol in synbiotic and placebo groups (CI = 95%). *FPG* fasting plasma glucose, *HOMA-IR* homeostasis model assessment of insulin resistance, *HOMA-B* homeostatic model assessment-B cell function, *QUICKI* quantitative insulin sensitivity check index

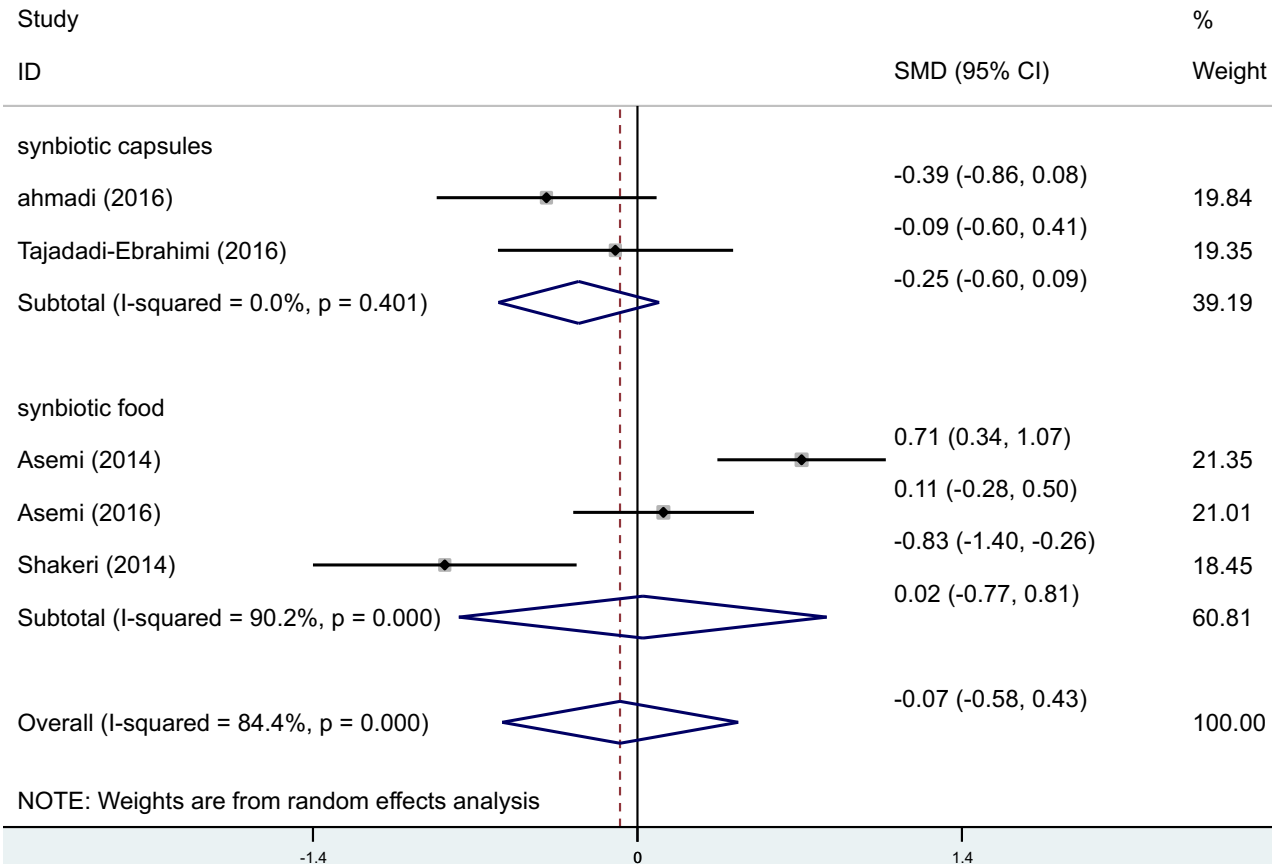
A


Study
ID
SMD (95% CI)
%
Weight
synbiotic capsules
ahmadi (2016)
-0.73 (-1.21, -0.24)
17.48
Moroti (2012)
-0.67 (-1.58, 0.23)
9.50
Tajadadi-Ebrahimi (2016)
0.05 (-0.46, 0.55)
16.95
Subtotal (I-squared = 61.0%, p = 0.077)
-0.42 (-0.97, 0.14)
43.92
synbiotic food
Asemi (2014)
0.00 (-0.35, 0.35)
20.79
Asemi (2016)
0.02 (-0.37, 0.41)
19.88
Shakeri (2014)
-0.91 (-1.48, -0.34)
15.41
Subtotal (I-squared = 75.8%, p = 0.016)
-0.25 (-0.75, 0.25)
56.08
Overall (I-squared = 66.4%, p = 0.011)
-0.32 (-0.67, 0.03)
100.00
NOTE: Weights are from random effects analysis
-1.58
0
1.58

B


Study
ID
SMD (95% CI)
%
Weight
synbiotic capsules
ahmadi (2016)
-0.70 (-1.18, -0.22)
15.77
Moroti (2012)
0.01 (-0.87, 0.89)
4.79
Tajadadi-Ebrahimi (2016)
0.04 (-0.46, 0.55)
14.37
Subtotal (I-squared = 59.2%, p = 0.086)
-0.30 (-0.62, 0.03)
34.94
synbiotic food
Asemi (2014)
-0.53 (-0.89, -0.17)
28.68
Asemi (2016)
-0.18 (-0.56, 0.21)
24.34
Shakeri (2014)
-0.52 (-1.07, 0.03)
12.03
Subtotal (I-squared = 0.0%, p = 0.373)
-0.40 (-0.63, -0.16)
65.06
Heterogeneity between groups: p = 0.631
Overall (I-squared = 29.7%, p = 0.213)
-0.36 (-0.55, -0.17)
100.00
-1.18
0
1.18

C



D

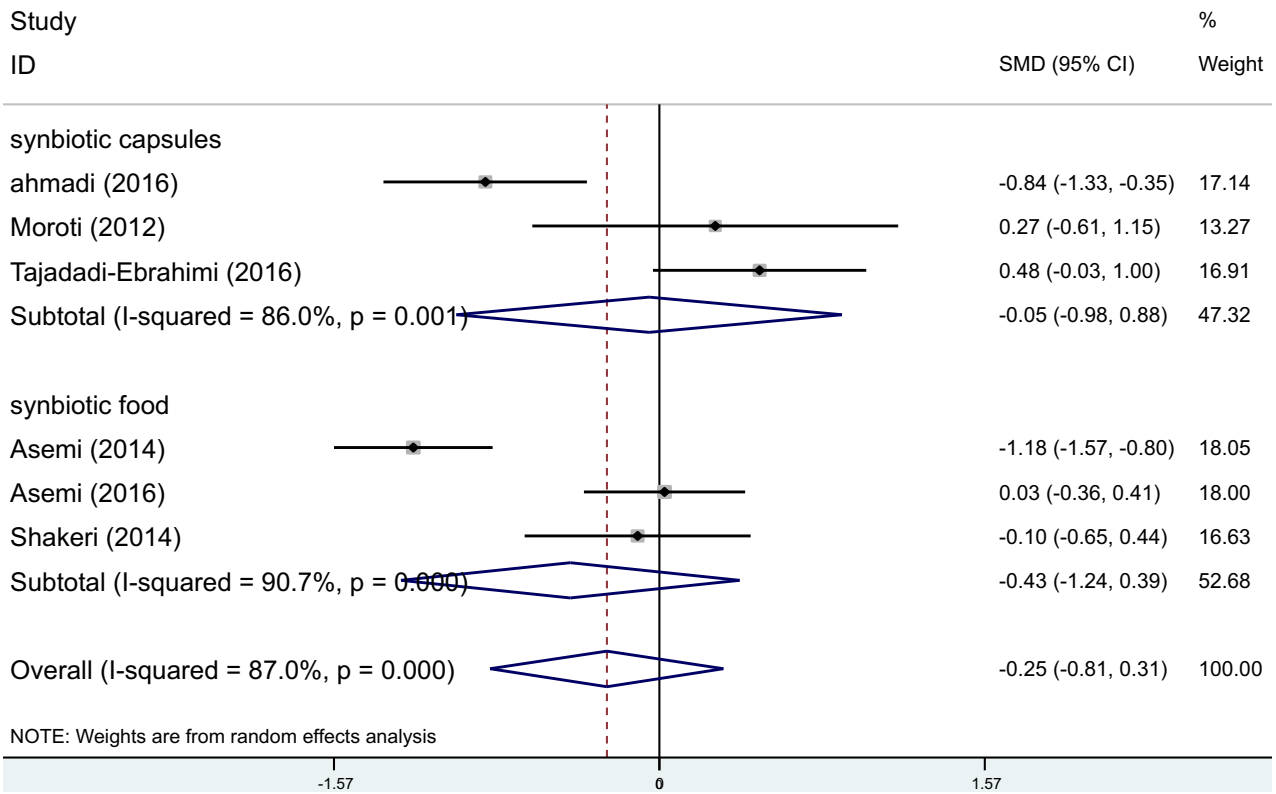


Fig. 4 (continued)

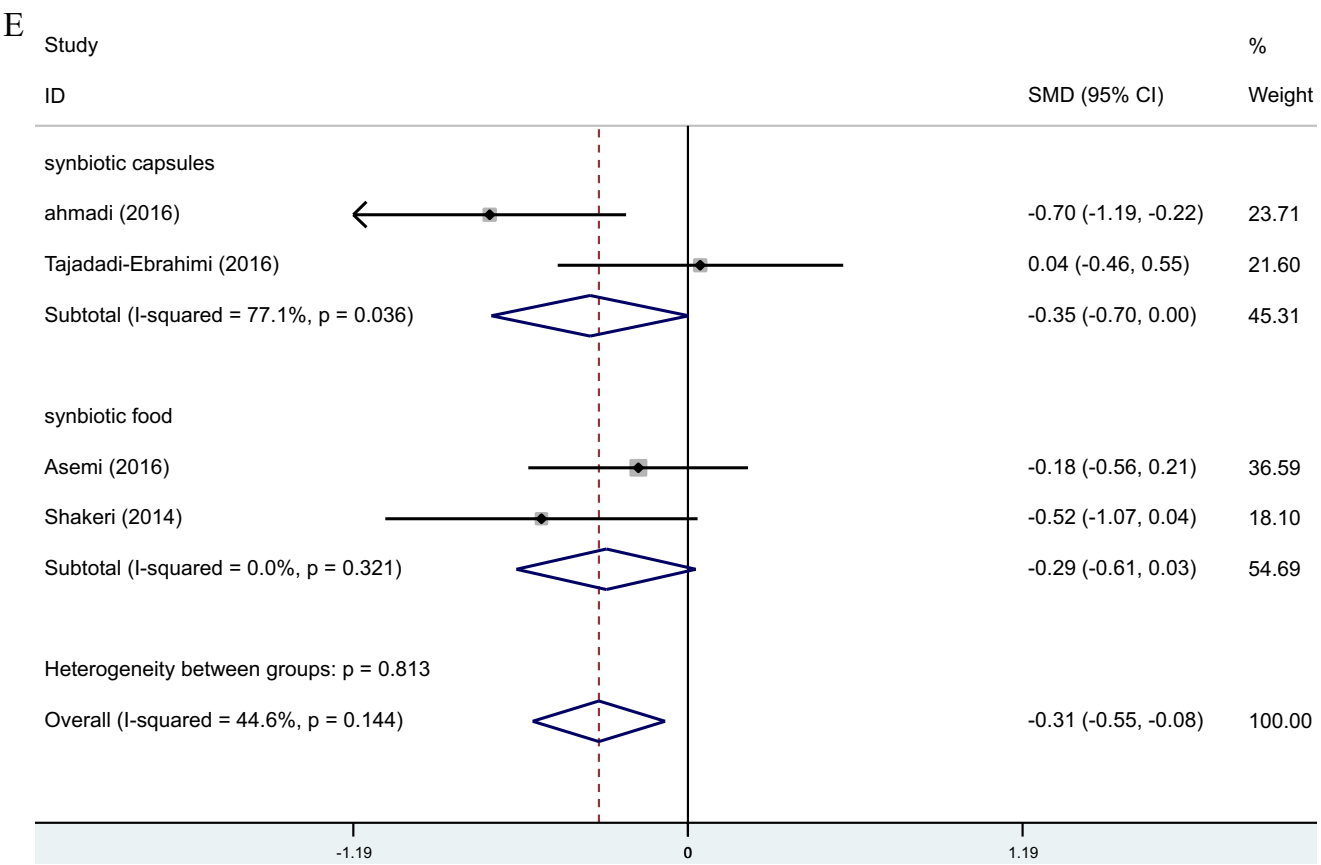


Fig. 4 (continued)

chain enhancer of activated B cell (NF-κB) pathway [31]. Furthermore, probiotic and inulin intake may improve insulin resistance through upregulation in the expression of peroxisome proliferator-activated receptor gamma (PPAR-γ) gene [32, 33]. Wang et al. [34] found that *L. casei* significantly increased the expression of PPAR-γ gene in a rat model of acute liver failure induced by lipopolysaccharide and d-galactosamine for 30 days. Downregulation in the expression of hepatic genes involved in lipogenesis and fatty acid elongation/desaturation by inulin may also result in improvement in markers of insulin metabolism [35].

We found that synbiotic supplementation in patients with diabetes significantly reduced triglycerides, total cholesterol, and VLDL-cholesterol levels, but did not alter LDL-cholesterol and HDL-cholesterol levels. Although several meta-analyses studies have demonstrated that probiotic supplementation is effective for the improvement of hyperlipidemia, the characteristics of subjects who consume probiotics with the most beneficial effects remained unclear. In a meta-analysis of 30 RCTs with 1624 participants by Cho et al. [36], probiotic supplementation resulted in statistically significant decreases in total cholesterol and LDL-cholesterol compared to control subjects by 7.8 and 7.3 mg/dL, respectively, but did not affect HDL-cholesterol or triglyceride concentrations. In another meta-analysis study of 33 RCTs by Shimizu et al. [37], probiotic interventions, including fermented milk products and probiotics, led to significant changes in total cholesterol and LDL-cholesterol levels; however, it did not influence HDL-cholesterol and triglyceride levels. However, Agerholm-Larsen et al. [38] revealed that the duration of probiotic consumption had no significant effect on total cholesterol and LDL-cholesterol reduction using regression analysis. This difference in findings with other studies was likely due to a short duration (4–8 weeks) of supplementation in trial conducted by Agerholm-Larsen et al. Long-term (>4 weeks) synbiotic supplementation was more effective in reduction of lipid profiles, which could be useful in reduced risk of CVD. Synbiotic intake may decrease triglycerides and VLDL-cholesterol values through lipolysis of triglycerides and transform triglyceride-rich particles into small [39], suppressing the NF-κB pathway [31], and gut microbiota-SCFA-hormone axis [40]. Several possible mechanisms proposed for the removal of cholesterol from media, such as assimilation of cholesterol during growth by *L. acidophilus* [41], binding of cholesterol to the cellular surface, disruption of cholesterol micelles [42], and deconjugation of bile salt and bile salt hydrolase activity [41]. The meta-analysis findings regarding potential benefit of probiotics to manage or prevent metabolic disorders are influenced by differences in the study design, inclusion criteria of the studies, and method for data analysis. One

Table 4 Factors associated with the heterogeneity by using univariate meta-regression model

Mean	Variables	*B*	*P* value
FPG	Strain	15.06	0.378
	Time of intervention	26.12	0.042
	Number of bacteria	15.06	0.378
Insulin	Strain	−2.37	0.041
	Time of intervention	−0.31	0.883
	Number of bacteria	−2.37	0.041
HOMA-IR	Strain	0.33	0.495
	Time of intervention	−0.58	0.169
	Number of bacteria	0.33	0.495
HOMA-B	Strain	−22.57	0.051
	Time of intervention	−3.99	0.829
	Number of bacteria	−22.57	0.051
QUICKI	Strain	−0.01	0.106
	Time of intervention	0.01	0.709
	Number of bacteria	−0.01	0.106
Total cholesterol	Strain	−5.95	0.711
	Time of intervention	3.35	0.845
	Number of bacteria	−1.41	0.935
Triglycerides	Strain	2.92	0.896
	Time of intervention	−1.38	0.954
	Number of bacteria	−10.82	0.642
LDL-cholesterol	Strain	−1.07	0.939
	Time of intervention	11.74	0.361
	Number of bacteria	−1.07	0.939
HDL-cholesterol	Strain	0.22	0.955
	Time of intervention	−2.63	0.528
	Number of bacteria	−2.68	0.518
VLDL-cholesterol	Strain	0.14	0.984
	Time of intervention	−3.36	0.618
	Number of bacteria	0.14	0.984

consideration is that the studies were conducted in many different geographic areas; therefore, the metabolic modifier factors, such as diet, lifestyle, and genetic background, are different. For example, the effectiveness of probiotic intervention could depend on the patient's intestinal microbiome, and this is highly regulated by the factors, including age, diet, lifestyle, and genetics [43]. Of these, diet is easiest to modify and presents the simplest route for therapeutic intervention. In a study by Wu et al. [44], it observed that microbiome composition changed detectably within 24 h of initiating a high-fat/low-fiber or low-fat/high-fiber diet but that enterotype identity remained stable during the 10-day study. Therefore, alternative enterotype states are related to long-term diet [44]. In addition, functional immaturity of the immune system and intestinal epithelium can affect the aberrant intestinal colonization pattern occurring in preterm neonates [45]. Drugs, especially chronic medication, can exert a strong impact on intestinal microbiota [46]. A misbalance of this intestinal microbial community can act as an important source of infection, or inflammation, and can be involved, as well, in gastrointestinal diseases and other extra-intestinal disorders. Probiotic intervention might also be more effective when provided with a prebiotic in a synbiotic combination, but the effectiveness of this intervention could depend dramatically on diet or genetics. We have previously shown that consumption of the synbiotic bread compared with probiotic bread and placebo among diabetic patients had more beneficial effects on insulin metabolism [19]. Prior studies have reported that inclusion of prebiotic substances like inulin can stimulate the growth and/or metabolic activity of the selected bacterial groups including bifidobacteria or lactobacilli and might increase production of SCFA in the colon [47, 48]. Different probiotics might be more beneficial when considering what the endogenous microbiome is. The effectiveness of different types of probiotics or prebiotics can be different in diverse populations, as the endogenous microbiome is affected by the person's diet or genetic background. For instance, the consumption of probiotic containing *L. acidophilus* and *Bifidobacterium lactis* in patients with T2DM improved fasting blood glucose and antioxidant status [26], whereas probiotic supplementation containing *L. acidophilus* and *B. lactis* in overweight men and women did not affect glycemic control [49]. Therefore, a specific type of probiotic might not be useful or effective for all.

Synbiotic supplementation may result in an improvement in FPG, insulin, HOMA-IR, HOMA-B, QUICKI, triglycerides, total cholesterol, and VLDL-cholesterol levels, but did not affect LDL-cholesterol and HDL-cholesterol levels in patients with diabetes. Additional prospective studies regarding the effect of synbiotic intake on glucose homeostasis parameters and lipid profiles in patients with diabetes are necessary.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

For Studies with Human Subjects All procedures in selected papers followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

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