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META-ANALYSIS

The effect of probiotics, prebiotics or synbiotics on metabolic outcomes in individuals with diabetes: a systematic review and meta-analysis

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Abstract

Aims/hypothesis The aim was to conduct a systematic review and meta-analysis of randomised controlled clinical trials assessing the effect of probiotic, prebiotic or synbiotic supplementation on gut microbiota and glucose control and lipid levels in individuals with diabetes.

Methods MEDLINE, EMBASE and the Cochrane Library were searched. The eligibility criteria for the studies was involvement of participants with a diagnosis of type 1 or type 2 diabetes. Metabolic outcomes (glucose control, insulinaemia, and lipid profile) of any probiotic, prebiotic or synbiotic supplementation related to modification of gut microbiota (prebiotics, probiotics and synbiotics) were analysed. We provided a narrative synthesis and meta-analysis of the findings on metabolic outcomes from the studies. Metabolic outcomes were extracted post-intervention and expressed as mean differences (MDs) and 95% CIs between treatment and comparator groups. We pooled the results using a random-effects meta-analysis. The meta-analysis was conducted using Review Manager (RevMan) software.

Results After the removal of duplicates and ineligible studies, 5219 studies were retained for review of titles and abstracts. The number of articles was reduced to 130 by review, for which the full-text articles were obtained and reassessed, 38 of which were included in the final meta-analysis. Overall, the use of prebiotics, probiotics or synbiotics reduced HbA_{1c} levels, but did not reach the threshold for significance (−2.17 mmol/mol, 95% CI −4.37, 0.03; $p = 0.05$, [−0.20%, 95% CI −0.40 to 0.00; $p = 0.05$, $I^2 = 66\%$]) and had no effect on LDL-cholesterol levels (−0.05 mmol/l; 95% CI −0.14, 0.05, $p = 0.35$, $I^2 = 37\%$). However, their consumption decreased levels of fasting blood glucose (−0.58 mmol/l; 95% CI −0.86, −0.30; $p < 0.01$, $I^2 = 60\%$), total cholesterol (−0.14 mmol/l; 95% CI −0.26, −0.02, $p = 0.02$, $I^2 = 39\%$), triacylglycerols (−0.11 mmol/l; 95% CI −0.20, −0.02, $p = 0.01$, $I^2 = 21\%$) and insulinaemia (−10.51 pmol/l; 95% CI −16.68,−4.33, $p < 0.01$, $I^2 = 74\%$), and increased HDL-cholesterol levels (0.04 mmol/l; 95% CI 0.01, 0.07, $p < 0.01$, $I^2 = 24\%$).

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Research in context

What is already known about this subject?

- Gut microbiota may play a role in the development of obesity and diabetes mellitus; bioactive agents, such as probiotics, prebiotics or synbiotics, could play a role in the prevention and treatment of diabetes

What is the key question?

- Is probiotic, prebiotic or synbiotic supplementation associated with improved glucose control and lipid levels in individuals with diabetes?

What are the new findings?

- Consumption of prebiotics, probiotics or synbiotics did not lead to changes in HbA_{1c} or LDL-cholesterol levels
- Consumption of prebiotics, probiotics and synbiotics decreased fasting blood glucose, total cholesterol, triacylglycerol levels and insulinaemia
- Consumption of prebiotics, probiotics and synbiotics increased HDL-cholesterol levels

How might this impact on clinical practice in the foreseeable future?

- Consumption of probiotics, prebiotics and synbiotics may be a potential adjuvant treatment for improving metabolic outcomes

Conclusions/interpretation In individuals with diabetes mellitus, supplementation with probiotics, prebiotics or synbiotics improved metabolic variables, although the magnitude of this effect is low. Our results suggest that consumption of probiotics, prebiotics or synbiotics may be a potential adjuvant treatment for improving metabolic outcomes.
Registration PROSPERO ID CRD42017080071.

Keywords Blood glucose · Cholesterol · Diabetes mellitus · HbA_{1c} · *Lactobacillus* · Meta-analysis · Microbiota · Systematic review · Triacylglycerols

Abbreviations

LPS	Lipopolysaccharide
MD	Mean difference
RoB2	Risk-of-bias tool

Introduction

Diabetes mellitus has become a global pandemic, largely because of the increasing prevalence of obesity and unhealthy lifestyles [1]. Recent studies suggest that the gut microbiota may play a role in obesity [2], metabolic syndrome and diabetes mellitus [3]. Altered microbiota composition features in the progression of type 2 diabetes, with an increasing loss of gut microbial diversity, which is related to insulin resistance and enhanced circulating inflammation markers [4]. Although controversial, because it has not been demonstrated in humans, altered microbiota would be related to increased intestinal permeability, development of metabolic endotoxaemia and inflammation, presumably because of the translocation of bacterial products, such as lipopolysaccharides (LPS) originating in the gut, which in turn would trigger the development of diabetes [5]. In women, type 2 diabetes is positively associated with metabolic endotoxaemia, and IL-6 levels are found to be increased [6]. Thus, the gut microbiota is suggested to drive the pathogenesis of metabolic diseases, including type 2 diabetes.

Bioactive agents, such as probiotics (live microorganisms that when administered in adequate amounts may confer a health benefit on the host) [7], prebiotics (a substrate that is selectively utilised by the microorganisms of the host, conferring a health benefit) [8] or synbiotics (a probiotic–prebiotic combination), could improve the gut microbiota. This change in gut microbiota could, at least to some extent, improve the metabolic control of individuals with type 2 diabetes [9], reducing plasma levels of bacterially derived LPS and improving the gut barrier function, as shown in genetically obese mice [10]. Thus, these bioactive agents could playing a role in the prevention and treatment of diabetes.

Several experimental studies on animal models of diabetes (fructose-induced, alloxan-induced, high-fat diet-induced, genetic models) have demonstrated the benefits of specific probiotic bacterial strains on glucose control. Benefits have been shown with probiotics containing *Lactobacillus*

acidophilus and *Lactobacillus casei* [11], *Lactobacillus plantarum* TN627 strain [12], *Lactobacillus plantarum* DSM 15313 [13], *Lactobacillus gasseri* BNR17 [14], *Lactobacillus reuteri* [15] and *Lactobacillus rhamnosus*, but not with *Lactobacillus bulgaricus* [16]. Other metabolic effects have been reported with the use of probiotics in experimental studies on diabetes. *Bifidobacterium lactis* was associated with low levels of lipids and insulinaemia [17]; *L. casei* CCFM0412 improved glucose tolerance, lowered lipid levels, enhanced immune regulation and reduced oxidative stress [18]; and *Lactobacillus johnsonii* led to upregulated expression of proteins involved in intercellular tight junction assembly and maintenance in the gut [19].

Studies on consumption of probiotics or synbiotics by individuals with diabetes have provided conflicting results, with some reporting improved metabolic control [20–22] and others not [23, 24]. A recent systematic review suggested that supplementation with probiotics and synbiotics could be beneficial in lowering fasting blood glucose in adults with high baseline fasting blood glucose [25]; however, the included studies evaluated individuals with other conditions in addition to those with diabetes, and no information was provided on glucose control and lipid profile. Because of the lack of consistent data in the literature, the current systematic review and meta-analysis aimed to evaluate the impact of probiotic, prebiotic or synbiotic supplementation related to modification of gut microbiota on glucose control and lipid levels in individuals with diabetes. This study may have important implications for the development of a probiotic treatment for diabetes and may form a rational basis for the selection of specific probiotic agents to boost gut mucosal regulatory responses.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement was followed as a guideline for conducting and reporting this systematic review and meta-analysis [26].

This systematic review is registered in the International Prospective Register for Systematic Review (PROSPERO) database under number CRD42017080071.

Eligibility criteria The inclusion criteria were as follows: studies with adult participants with type 1 or 2 diabetes diagnosis and a focus on metabolic outcomes (glucose control, insulinaemia and lipid profile) that involved any probiotic, prebiotic or synbiotic supplementation or combination of interventions with the aim of adjusting the gut microbiota. Studies reporting gestational or other diabetes types were excluded. Because of the diverse range of possible interventions, to avoid exclusion of relevant data we did not restrict the intervention type in the search, but only randomised clinical trials were included. Only studies published in English, Spanish or Portuguese were included. We did not include conference abstracts.

Information sources and search In the article search process, we used the terms 'diabetes mellitus' and 'microbiota' in the selected databases. To extend our search strategy, we did not use any terms referring to the control or study design. MEDLINE, EMBASE and the Cochrane Library were searched using a combination of MeSH headings, keywords and related entry terms to identify the potentially relevant studies. The complete search strategy used for the PubMed database is shown in electronic supplementary material (ESM) text 1.

The search process was completed by October 2017, and updated in September 2019 and, again, in July 2020. After combining the search results of different databases, the duplicates were removed. Records were managed using EndNote X7. Manual search (i.e., reference lists and citation searching) of studies fulfilling the eligibility criteria was also carried out.

Study selection and data collection process Two authors (PMB and RR) independently screened the titles and abstracts of all the studies generated by the search to identify studies that met the inclusion criteria outlined above. The reviewers were not blinded to the authors, institutions or the name of the journals the manuscripts were published in. Papers with abstracts that did not provide enough information regarding the inclusion and exclusion criteria were retrieved for full-text evaluation. The full-text articles were assessed independently by the same two authors (PMB and RR) to decide whether or not they should be retained. Any disagreement was resolved by a third independent author (GHT).

A standardised, pre-piloted form (Excel) was used to extract data from the included studies for evidence synthesis. The following information was extracted from included studies: first author's name, publication year, title, objective, intervention type, study design, daily dose, pharmaceutical formulation, sample size, follow-up time, disease duration and evaluated outcomes. Means ± standard deviations post-intervention were extracted for continuous variables related to metabolic evaluation (levels of plasma glucose and HbA_{1c}, insulinaemia, lipid profile) and BMI. Relevant data were extracted from studies by two separate investigators (PMB and RR). Any disagreement was resolved by a third independent author (AFM). The corresponding author was contacted as needed to obtain data not included in the published report.

Risk of bias and publication bias assessment The risk-of-bias assessment in the included studies was performed according to the revised Cochrane risk-of-bias tool (RoB2) [27]. A standardised, pre-piloted form (Excel) was used to extract data from the included studies for assessment of study quality. Each study was evaluated for the following items: bias arising

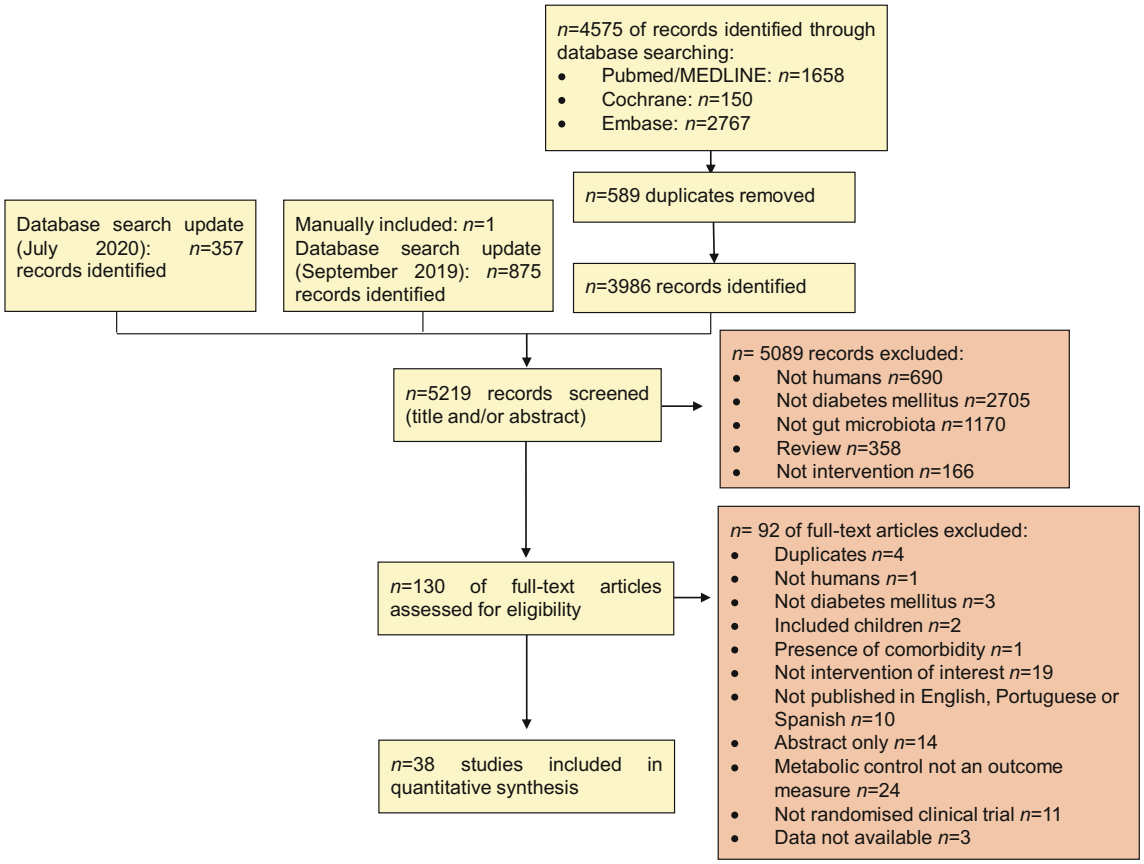


Fig. 1 Flowchart to illustrate how articles were identified and selected for inclusion in the meta-analysis

from the randomisation process, bias because of deviations from intended interventions (effect of assignment to intervention), bias because of missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each domain was composed of multiple questions, and using an algorithm, they were judged as having low risk, some concerns or high risk of bias. The risk-of-bias assessment was performed by two independent reviewers (MS and GL). Publication bias was assessed using a contour-enhanced funnel plot of each trial's effect size against the standard error of the estimate.

Data analysis We aimed to provide a narrative synthesis of the findings from the included studies, structured around the type of outcome. The meta-analysis was conducted using Review Manager (RevMan) software, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Metabolic outcomes and BMI were expressed as mean differences (MDs) and 95% CIs between treatment and comparator groups. We pooled the results using a random-effects model.

Statistical heterogeneity of the treatment effect among studies was assessed using both the χ^2 test and the I^2 statistic. We considered an I^2 value of >75% indicative of considerable heterogeneity, according to the Cochrane Handbook for Systematic Reviews of Interventions [28]. A p value of <0.05 was considered to indicate a statistically significant effect. We explored heterogeneity between studies using two strategies. First, we re-ran the meta-analyses by assessing the effect of individual studies on the overall results of the meta-analysis, removing one study at a time to check if any specific study explained the heterogeneity. Second, we performed sensitivity analyses to evaluate subgroups of studies most likely to yield valid estimates of the intervention based on prespecified relevant information as follows: (1) specific probiotic species, excluding trials that did not involve *Lactobacillus*; (2) risk of bias, excluding high-risk trials; (3) presence vs absence of a simultaneous cointervention; (4) placebo use; and (5) blinding.

Results

Study selection The electronic search returned 4575 potentially relevant studies from searches of the databases (PubMed/MEDLINE = 1658, Cochrane = 150, and EMBASE = 2767). Additional searches identified 1232 studies (last search was conducted in July 2020). One additional study was identified by manual search of the reference lists of the selected studies and was included. After the removal of duplicates and

Table 1 General characteristics of studies with probiotic, prebiotic or synbiotic interventions and metabolic outcomes in patients with diabetes mellitus

Study	Design	Intervention	Follow-up	*n*	Primary outcome	Metabolic outcomes
Asemi et al (2013) [40]	Randomised, double-blind, placebo-controlled, clinical trial	Synbiotic: *Lactobacillus acidophilus*, *L. casei*, *L. rhamnosus*, *L. bulgaricus*, *Bifidobacterium breve*, *B. longum*, *Streptococcus thermophilus* and fructo-oligosaccharide	8 weeks	Placebo: 27 Intervention: 27	Not stated	HbA_{1c}, FBG, TC, LDL-C, HDL-C, triacylglycerols, insulinaemia
Asemi et al (2014) [59]	Randomised, double-blind, crossover, placebo-controlled, clinical trial	Synbiotic: *L. sporogenes* and inulin	6 weeks	Placebo: 31 Intervention: 31	Not stated	FBG, TC, LDL-C, HDL-C, triacylglycerols, insulinaemia
Asemi et al (2016) [20]	Randomised, double-blind, placebo-controlled, crossover, clinical trial	Synbiotic: *L. sporogenes*, inulin and β-carotene	6 weeks	Placebo: 49 Intervention: 50	Not stated	FBG, TC, LDL-C, HDL-C, triacylglycerols, insulinaemia
Bayat et al (2016) [21]	Randomised, placebo-controlled, parallel-group, clinical trial	Synbiotic: *Cucurbita ficifolia* (green pumpkin) and probiotic yogurt	8 weeks	Placebo: 20 Intervention: 20	Not stated	HbA_{1c}, FBG, TC, LDL-C, HDL-C, triacylglycerols
Ebrahimi et al (2017) [41]	Randomised, double-blind, clinically controlled trial	Synbiotic: Lactobacillus family, Bifidobacterium family, *S. thermophilus* and fructo-oligosaccharide	9 weeks	Placebo: 35 Intervention: 35	Not stated	HbA_{1c}, FBG, TC, LDL-C, HDL-C, triacylglycerols
Ejtahed et al (2011) [22]	Randomised, double-blind, placebo-controlled, clinical trial	Probiotic: *L. bulgaricus*, *S. thermophiles*, *B. lactis* and *L. acidophilus*	6 weeks	Placebo: 30 Intervention: 30	Not stated	TC, LDL-C, HDL-C, triacylglycerols
Ejtahed et al (2012) [31]	Randomised, double-blind, placebo-controlled, clinical trial	Probiotic: *L. bulgaricus*, *S. thermophiles*, *B. lactis* and *L. acidophilus*	6 weeks	Placebo: 30 Intervention: 30	Not stated	HbA_{1c}, FBG, insulinaemia
Feizollahzadeh et al (2017) [36]	Randomised, double-blind, parallel-group, placebo-controlled, clinical trial	Probiotic: *L. plantarum*	8 weeks	Placebo: 20 Intervention: 20	Not stated	FBG, LDL-C, HDL-C, triacylglycerols
Firouzi et al (2017) [49]	Randomised clinical trial	Probiotic: *L. acidophilus*, *L. casei*, *L. lactis*, *B. bifidum*, *B. longum* and *B. infantis*	12 weeks	Placebo: 53 Intervention: 48	Glucose control	HbA_{1c}, FBG, TC, LDL-C, HDL-C, triacylglycerols, insulinaemia
Gargari et al (2013) [58]	Randomised, triple-blind, placebo-controlled trial	Prebiotic: Inulin	2 months	Placebo: 25 Intervention: 24	Antioxidant status	HbA_{1c}, FBG, insulinaemia
Gonai et al (2017) [38]	Double-blind, placebo-controlled trial	Prebiotic: Galacto-oligosaccharide	4 weeks	Placebo: 27 Intervention: 28	Not stated	HbA_{1c}, FBG, LDL-C, HDL-C, triacylglycerols
Horvath et al (2019) [54]	Randomised, double-blind, placebo-controlled pilot study	Synbiotic: *B. bifidum* W23, *B. lactis* W51, *B. lactis* W52, *L. acidophilus* W37, *L. casei* W56, *L. brevis* W63, *L. salivarius* W24, *Lactococcus*. lactis W58, *Lactococcus*. lactis W19, galacto-oligosaccharides and fructo-oligosaccharides	6 months	Placebo: 14 Intervention: 12	Glucose metabolism	HbA_{1c}, FBG, insulinaemia
Hove et al (2015) [23]	Randomised, double-blind, placebo-controlled, 2 × 2 factorial study	Probiotic: *L. helveticus*	12 weeks	Placebo: 23 Intervention: 18	Blood pressure	HbA_{1c}, FBG, TC, LDL-C, HDL-C, triacylglycerols, insulinaemia
Khalili et al (2019) [43]	Randomised, parallel-group, placebo-controlled trial	Probiotic: *L. casei*	8 weeks	Placebo: 20 Intervention: 20	SIRT1 and fetuin-A levels	HbA_{1c}, FBG
Kobyliak et al (2018) [53]	Randomised, double-blind, single-centre, clinical trial	Probiotic: 14 probiotic bacteria genera *Bifidobacterium*, *Lactobacillus*, *Lactococcus*, *Propionibacterium*	8 weeks	Placebo: 22 Intervention: 31	HOMA-IR	HbA_{1c}, FBG, insulinaemia
Mafi et al (2018) [44]	Randomised, double-blind, placebo-controlled trial	Probiotic: *L. acidophilus* strain ZT-L1, *B. bifidum* strain ZT-B1, *L. reuteri* strain ZT-Lre, and *L. fermentum* strain ZT-L3	12 weeks	Placebo: 30 Intervention: 30	HOMA-IR	HbA_{1c}, FBG, TC, LDL-C, HDL-C, triacylglycerols, insulinaemia
Madempudi et al (2019) [47]	Randomised, double-blind, placebo-controlled study	Synbiotic: *L. salivarius* UBLS22, *L. casei* UBLC42, *L. plantarum* UBLP40, *L. acidophilus* UBLA34, *B. breve* UBBr01, *Bacillus coagulans* Unique IS2, and fructo-oligosaccharide	12 weeks	Placebo: 39 Intervention: 40	HbA_{1c}	HbA_{1c}, FBG, TC, LDL-C, HDL-C, triacylglycerols, insulinaemia

Table 1 (continued)

Study	Design	Intervention	Follow-up	*n*	Primary outcome	Metabolic outcomes
Mazloom et al (2013) [24]	Single-blind clinical trial	Probiotic: *L. acidophilus*, *L. bulgaricus*, *L. bifidum* and *L. casei*	6 weeks	Placebo: 18 Intervention: 16	Not stated	FBG, TC, LDL-C, HDL-C, triacylglycerols, insulinaemia
Mirmiranpour et al (2019) [48]	Randomised, double-blind, placebo-controlled study	Synbiotic: *L. acidophilus* and powdered cinnamon	3 months	Placebo: 27 Intervention: 30	Not stated	HbA_{1c}, FBG
Mobini et al (2017) [55]	Randomised, double-blind, placebo-controlled trial	Probiotic: *L. reuteri*	12 weeks	Placebo: 15 Intervention: 14	Glucose control	FBG, TC, LDL-C, HDL-C, triacylglycerols
Mohamadshahi et al (2014) [32]	Randomised, double-blind, placebo-controlled, clinical trial	Probiotic: *L. acidophilus* and *B. lactis*	8 weeks	Placebo: 22 Intervention: 22	Not stated	TC, LDL-C, HDL-C, triacylglycerols
Moroti et al (2012) [37]	Randomised, double-blind, placebo-controlled study	Synbiotic: *L. acidophilus*, *B. bifidum* and fructo-oligosaccharides	30 days	Placebo: 10 Intervention: 10	Not stated	FBG, TC, HDL-C, triacylglycerols
Ostadrahimi et al (2015) [33]	Randomised, double-blind, placebo-controlled, clinical trial	Probiotic: *L. acidophilus*	8 weeks	Placebo: 30 Intervention: 30	Not stated	HbA_{1c}, FBG, TC, LDL-C, HDL-C, triacylglycerols
Pedersen et al (2016) [50]	Randomised, double-blind, placebo-controlled, parallel study	Prebiotic: galacto-oligosaccharide	12 weeks	Placebo: 15 Intervention: 14	Intestinal permeability	HbA_{1c}, FBG, TC, LDL-C, HDL-C, triacylglycerols, insulinaemia
Raygan et al (2018) [30]	Randomised, double-blind, placebo-controlled, clinical trial	Probiotic: *L. acidophilus*, *B. bifidum*, *L. reuteri* and *L. fermentum* plus vitamin D_3	12 weeks	Placebo: 30 Intervention: 30	Glucose control	FBG, TC, LDL-C, HDL-C, triacylglycerols, insulinaemia
Razmpoosh et al (2019) [45]	Randomised, double-blind, clinical trial	Synbiotic: *L. acidophilus*, *L. casei*, *L. rhamnosus*, *L. bulgaricus*, *Bifidobacterium breve*, *Bifidobacterium longum*, *S. thermophilus* and fructo-oligosaccharide with lactose	6 weeks	Placebo: 30 Intervention: 30	Glucose control and lipid profile	HbA_{1c}, FBG, TC, LDL-C, HDL-C, triacylglycerols, insulinaemia
Roshanravan et al (2017) [56]	Randomised, double-blind, placebo-controlled, clinical trial	Prebiotic and posbiotic: butyrate and inulin	45 days	Placebo: 15 Intervention: 14	Not stated	HbA_{1c}, FBG, TC, LDL-C, HDL-C, triacylglycerols, insulinaemia
Sabico et al (2017) [51]	Randomised, single-centre, double-blind, placebo-controlled study	Probiotic: *B. bifidum* W23, *B. lactis* W52, *L. acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, *Lactococcus lactis* W19 and *Lactococcus lactis* W58	12 weeks	Placebo: 39 Intervention: 39	Not stated	FBG, TC, LDL-C, HDL-C, triacylglycerols, insulinaemia
Sabico et al (2019) [52]	Randomised, single-centre, double-blind, placebo-controlled clinical trial	Probiotic: *B. bifidum* W23, *B. lactis* W52, *L. acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, *Lactococcus lactis* W19 and *Lactococcus lactis* W58	6 months	Placebo: 30 Intervention: 31	Not stated	FBG, TC, LDL-C, HDL-C, triacylglycerols, insulinaemia
Sanborn et al (2020) [46]	Randomised, double-blind, placebo-controlled, clinical trial	Probiotic: *L. rhamnosus* GG	3 months	Placebo: 42 Intervention: 51	Not stated	HbA_{1c}, FBG
Sato et al (2017) [34]	Interventional randomised control study	Probiotic: *L. casei* strain Shirota	16 weeks	Placebo: 34 Intervention: 34	Bacterial translocation	HbA_{1c}, FBG, TC, HDL-C, triacylglycerols
Shakeri et al (2014) [60]	Randomised, double-blind, placebo-controlled, clinical trial	Synbiotic: *L. sporogenes* and inulin	8 weeks	Placebo: 26 Intervention: 26	Not stated	FBG, TC, LDL-C, HDL-C, triacylglycerols
Sheth et al (2015) [57]	Randomised, placebo-controlled, trial	Synbiotic: two species of *Lactobacillus*, *Bifidobacterium* each, one species of *Streptococcus*, one species of yeast and Fructo-oligosaccharide	45 days	Placebo: 10 Intervention: 25	Not stated	HbA_{1c}, FBG
Tajabadi-Ebrahimi et al (2017) [42]	Randomised, double-blind, placebo-controlled trial	Synbiotic: *L. acidophilus*, *L. casei*, *B. bifidum* and inulin	12 weeks	Placebo: 30 Intervention: 30	Insulinaemia	FBG, TC, LDL-C, HDL-C, triacylglycerols, insulinaemia
Tajadadi-Ebrahimi et al (2014) [61]	Randomised, double-blind, placebo-controlled, clinical trial	Synbiotic: *L. sporogenes* and inulin	8 weeks	Placebo: 27 Intervention: 27	Not stated	FBG, insulinaemia

Table 1 (continued)

Study	Design	Intervention	Follow-up	*n*	Primary outcome	Metabolic outcomes
Tonucci et al (2017) [35]	Randomised, double-blind, placebo-controlled trial	Probiotic: *L. acidophilus* La-5 and *B. animalis* subsp. lactis BB-12	6 weeks	Placebo: 22 Intervention: 23	Serum IL-6	HbA_{1c}, FBG, TC, LDL-C, HDL-C, triacylglycerols, insulinaemia
Xu et al (2015) [39]	Randomised, double-blind, placebo-controlled clinical trial	Prebiotic: Chinese herbal formula	12 weeks	Placebo: 41 Intervention: 44	Glucose control	HbA_{1c}, FBG, TC, LDL-C, HDL-C, triacylglycerols
Zare Javid et al (2020) [29]	Double-blind clinical trial	Synbiotic: *L. sporogenesis* GBI-30, maltodextrin and fructo-oligosaccharide	8 weeks	Placebo: 22 Intervention: 22	FBG	HbA_{1c}, FBG, TC, LDL-C, HDL-C, triacylglycerols, insulinaemia

Most participants met the diagnostic criteria for type 2 diabetes; only one study with type 1 diabetes was found [29]. FBG, fasting blood glucose; LDL-C, LDL-cholesterol; HDL-C, HDL-cholesterol; SIRT-1, sirtuin 1; TC, total cholesterol

ineligible studies, 5219 studies were retained for review of titles and abstracts. The number of articles was reduced to 130 by review, for which the full-text articles were obtained and reassessed, 38 of which were included in the final meta-analysis. A detailed flowchart showing the study search and selection process is presented in Fig. 1.

Study characteristics The characteristics of the included studies are described in Table 1. A total of 2086 randomised participants from the eligible trials were included in this meta-analysis. Most participants met the diagnostic criteria for type 2 diabetes as set out by each study; only one study included individuals with type 1 diabetes [29]. The first trial to evaluate the impact of a probiotic intervention on metabolic control was published in 2011, evaluating lipid levels as outcomes. Twenty-eight of the included studies were published in the last 5 years.

The durations of the interventions varied from 30 days to 6 months. In 18, 5 and 15 trials, probiotics, prebiotics and synbiotics were used as the intervention. In 12 trials, supplementation involved a single probiotic species, while 20 studies used multiple strains of probiotic bacteria. No study in this meta-analysis included more than one dose of probiotics. Only two studies presented data on co-interventions; one used esomeprazole [23], the other, vitamin D_3 [30]. No major adverse effects were reported (ESM Table 1).

Concerning liquid formulations, five trials used probiotic yogurt [21–23, 31, 32], three studies used fermented milk [33–35], one used soy milk [36], one used a shake [37], one used a syrup [38] and one used a decoction [39] as the carrier. Regarding solid pharmaceutical formulations, ten studies used capsules [24, 40–48], six studies used sachets [49–54], and five used powder package [29, 55–58] as the source of probiotics. Four studies used other types of foods for supplementation [20, 59–61]. One study did not report the formulation used [30].

In all the studies, a final assessment was carried out and the following outcomes were reported: HbA_{1c} ($n = 13$ for more than 12 weeks of treatment; one that evaluated individuals with type 1 diabetes was not included in the insulinaemia analysis), fasting blood glucose ($n = 36$), insulinaemia ($n = 22$), total cholesterol ($n = 27$), LDL-cholesterol ($n = 27$), HDL-cholesterol ($n = 29$) and triacylglycerols ($n = 29$).

Risk of bias and publication bias assessment All included studies were assessed for methodological quality using the Cochrane RoB2 tool (ESM Fig. 1, ESM Table 2).

The risk of bias as per the RoB2 evaluation tool was overall low in 13.2% of studies, indicated some concerns in 47.4%, and high in 39.5% of the studies. Most of the studies had a low risk of bias because of deviations from intended interventions (92%), missing outcome data (82%) and measurement of the outcomes (87%). In the domain of bias arising from the randomisation process, 50% of the studies were considered as indicating some concerns. In selection of the reported result, 48% of the studies were judged as having low risk of bias, mostly because of an incomplete or absent study protocol.

Fig. 2 Absolute changes in (**a**) HbA_{1c}, (**b**) fasting blood glucose and (**c**) insulinaemia in individual studies on supplementation with probiotics, prebiotics or synbiotics. 'IV, Random' refers to a random-effects meta-analysis with weights based on inverse variances

The possibility of publication bias was evaluated by using a funnel plot for the primary outcome, HbA_{1c} and fasting blood glucose (ESM Fig. 2a, b). The points for the missing studies would be on the bottom left side of the plot. Since most of this area contains regions of high significance, publication bias is unlikely to be the underlying cause of this asymmetry. Given the limited number of studies included in the primary outcome meta-analysis, no further tests were run to distinguish between chance and real asymmetry.

Synthesis of results The data from the meta-analysis on the impact of probiotics and synbiotics on glucose control are presented in Fig. 2 and on lipid profile in Fig. 3. Only studies with a duration of more than 12 weeks were considered for the meta-analysis of HbA_{1c}; probiotics/prebiotics/synbiotics did not decrease HbA_{1c} levels (−2.17 mmol/mol, 95% CI −4.37, 0.03; $p = 0.05$; p for heterogeneity <0.01 [−0.20%, 95% CI −0.40 to 0.00; $p = 0.05$, $I^2 = 66\%$], Fig. 2a).

Consumption of probiotics, prebiotics or synbiotics decreased fasting blood glucose levels (−0.58 mmol/l, 95% CI −0.86, −0.30; $p < 0.01$, $I^2 = 60\%$; p for heterogeneity <0.01, Fig. 2b) and insulinaemia (−10.51 pmol/l; 95% CI −16.68, −4.33, $p < 0.01$, $I^2 = 74\%$; p for heterogeneity <0.01, Fig. 2c). The study that evaluated individuals with type 1 diabetes was not included in the insulinaemia analysis. Probiotics, prebiotics or synbiotics had no effect on BMI (−0.06 kg/m^2, 95% CI −0.53, 0. 41; $p = 0.81$, $I^2 = 0\%$; p for heterogeneity = 0.87) (ESM Fig. 3).

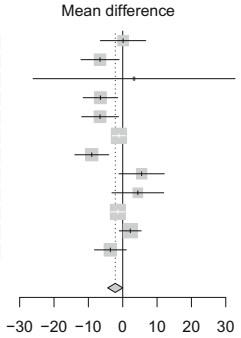
Consumption of probiotics, prebiotics or synbiotics decreased total cholesterol (−0.14 mmol/l; 95% CI −0.26, −0.02, $p = 0.02$, $I^2 = 39\%$; p for heterogeneity = 0.02; Fig. 3a) and triacylglycerol levels (−0.11 mmol/l; 95% CI −0.20, −0.02, $p = 0.01$, $I^2 = 21\%$; p for heterogeneity = 0.16; Fig. 3d), while HDL-cholesterol was increased (0.04 mmol/l; 95% CI 0.01, 0.07, $p < 0.01$, $I^2 = 24\%$; p for heterogeneity = 0.12; Fig. 3c). However, consumption of probiotics, prebiotics or synbiotics had no effect on LDL-cholesterol levels (−0.05 mmol/l; 95% CI −0.14, 0.05, $p = 0.35$, $I^2 = 37\%$; p for heterogeneity = 0.03; Fig. 3b).

When studies were omitted individually from the meta-analysis to assess possible individual influences on outcomes, the heterogeneity was unchanged. The sensitivity analyses conducted to assess results using *Lactobacillus*, presence vs

a

Study	Experimental Mean	SD	*n*	Control Mean	SD	*n*	Weight (%)	Mean difference	95% CI
Firouzi et al (2017) [49]	56.50	15.3	48	56.40	18.6	53	6.4	0.10	[−6.52; 6.72]
Gargari et al (2013) [58]	60.60	7.5	24	67.20	11.9	25	7.8	−6.60	[−12.15; −1.05]
Horvath et al (2019) [54]	67.20	47.0	12	63.90	24.0	14	0.5	3.30	[−26.11; 32.71]
Hove et al (2015) [23]	54.10	6.6	18	60.60	9.8	23	8.5	−6.50	[−11.53; −1.47]
Madempudi et al (2019) [47]	60.60	8.6	40	67.20	14.8	39	8.1	−6.60	[−11.96; −1.24]
Mafi et al (2018) [44]	50.80	4.4	30	51.90	3.3	30	13.7	−1.10	[−3.07; 0.87]
Mirmiranpour et al (2019) [48]	60.20	12.1	30	69.20	6.4	27	8.7	−9.00	[−13.96; −4.04]
Mobini et al (2017) [55]	66.10	10.9	14	60.60	6.6	15	6.4	5.50	[−1.11; 12.11]
Pedersen et al (2016) [50]	53.00	12.2	14	48.60	7.9	15	5.5	4.40	[−3.14; 11.94]
Sanborn et al (2020) [46]	37.90	3.7	51	39.30	6.1	42	13.5	−1.40	[−3.51; 0.71]
Sato et al (2017) [34]	54.10	7.7	34	51.90	5.5	34	11.7	2.20	[−0.98; 5.38]
Xu et al (2015) [39]	56.90	8.6	44	60.50	12.7	41	9.1	−3.60	[−8.24; 1.04]
Random effects model			359			358	100.0	−2.17	[−4.37; 0.03]

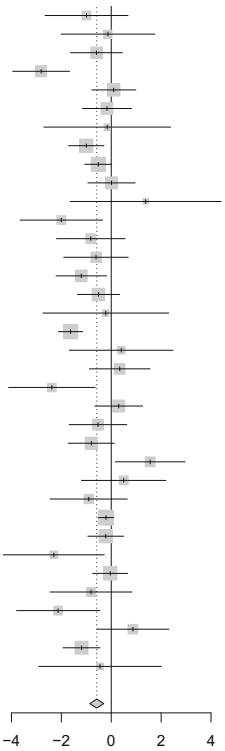
Heterogeneity: I^2 = 66%, τ^2 = 8.1879, χ^2_{11} = 32.35 (p < 0.01)
Test for overall effect: z = −1.93 (p = 0.05)



b

Study	Experimental Mean	SD	*n*	Control Mean	SD	*n*	Weight (%)	Mean difference	95% CI
Asemi et al (2013) [40]	8.07	2.7	27	9.06	3.5	27	1.9	−0.99	[−2.65; 0.67]
Asemi et al (2014) [59]	9.45	3.9	31	9.58	3.6	31	1.6	−0.13	[−2.00; 1.74]
Asemi et al (2016) [20]	7.54	2.1	50	8.13	3.1	49	3.2	−0.59	[−1.63; 0.45]
Bayat et al (2016) [21]	6.38	1.2	20	9.19	2.3	20	3.0	−2.81	[−3.95; −1.67]
Ebrahimi et al (2017) [41]	7.33	2.1	35	7.23	1.6	35	3.7	0.10	[−0.79; 0.99]
Ejtahed et al (2012) [31]	7.35	2.4	30	7.52	1.3	30	3.4	−0.17	[−1.15; 0.81]
Feizollahzadeh et al (2017) [36]	7.33	3.9	20	7.49	4.3	20	1.0	−0.16	[−2.70; 2.38]
Firouzi et al (2017) [49]	7.21	1.2	48	8.21	2.3	53	4.2	−1.00	[−1.71; −0.29]
Gargari et al (2013) [58]	8.14	1.1	24	8.66	0.8	25	4.8	−0.52	[−1.06; 0.02]
Gonai et al (2017) [38]	7.68	1.7	28	7.67	1.9	27	3.5	0.01	[−0.94; 0.96]
Horvath et al (2019) [54]	10.43	4.6	12	9.05	3.0	14	0.7	1.38	[−1.64; 4.40]
Hove et al (2015) [23]	7.91	1.9	18	9.91	3.4	23	1.9	−2.00	[−3.65; −0.35]
Khalili et al (2019) [43]	7.54	2.4	20	8.36	2.0	20	2.4	−0.82	[−2.20; 0.56]
Kobyliak et al (2018) [53]	8.31	2.5	31	8.92	2.3	22	2.6	−0.61	[−1.90; 0.68]
Madempudi et al (2019) [47]	7.01	1.5	40	8.21	2.9	39	3.3	−1.20	[−2.21; −0.19]
Mafi et al (2018) [44]	6.85	1.7	30	7.36	1.7	30	3.8	−0.51	[−1.36; 0.34]
Mazloom et al (2013) [24]	8.81	3.6	16	9.03	3.9	18	1.0	−0.22	[−2.74; 2.30]
Mirmiranpour et al (2019) [48]	8.21	0.2	30	9.84	1.3	27	5.0	−1.63	[−2.12; −1.14]
Mobini et al (2017) [55]	12.29	2.7	14	11.89	3.0	15	1.4	0.40	[−1.68; 2.48]
Moroti et al (2012) [37]	6.48	1.0	10	6.14	1.7	10	2.8	0.34	[−0.88; 1.56]
Ostadrahimi et al (2015) [33]	7.73	2.6	30	10.11	4.1	30	1.8	−2.38	[−4.11; −0.65]
Pedersen et al (2016) [50]	6.79	1.5	14	6.49	1.1	15	3.5	0.30	[−0.66; 1.26]
Raygan et al (2018) [30]	6.38	2.6	30	6.91	1.9	30	2.9	−0.53	[−1.69; 0.63]
Razmpoosh et al (2019) [45]	7.31	1.7	30	8.11	1.9	30	3.6	−0.80	[−1.72; 0.12]
Roshanravan et al (2017) [56]	8.82	2.4	14	7.26	1.3	15	2.4	1.56	[0.16; 2.96]
Sabico et al (2017) [51]	8.49	3.5	39	7.99	4.1	39	1.9	0.50	[−1.19; 2.19]
Sabico et al (2019) [52]	7.19	2.8	31	8.09	3.3	30	2.1	−0.90	[−2.45; 0.65]
Sanborn et al (2020) [46]	5.36	0.6	51	5.57	0.9	42	5.4	−0.21	[−0.52; 0.10]
Sato et al (2017) [34]	7.39	1.2	34	7.61	1.8	34	4.2	−0.22	[−0.94; 0.50]
Shakeri et al (2014) [60]	7.05	2.2	26	9.35	4.8	26	1.4	−2.30	[−4.32; −0.28]
Sheth et al (2015) [57]	8.15	0.9	25	8.19	1.0	10	4.3	−0.04	[−0.74; 0.66]
Tajabadi−Ebrahimi et al (2017) [42]	7.21	2.2	30	8.02	4.0	30	1.9	−0.81	[−2.46; 0.84]
Tajadadi−Ebrahimi et al (2014) [61]	7.31	2.0	27	9.44	4.0	27	1.9	−2.13	[−3.80; −0.46]
Tonucci et al (2017) [35]	8.41	2.4	23	7.54	2.5	22	2.3	0.87	[−0.57; 2.31]
Xu et al (2015) [39]	7.55	1.3	44	8.74	2.1	41	4.1	−1.19	[−1.93; −0.45]
Zare Javid et al (2020) [29]	9.08	4.2	22	9.53	4.1	22	1.1	−0.45	[−2.91; 2.01]
Random effects model			1004			978	100.0	−0.58	[−0.86; −0.30]

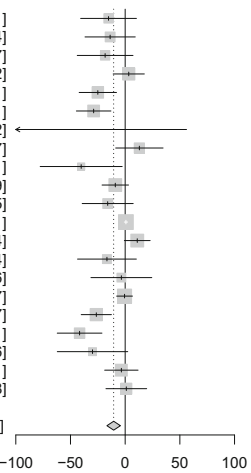
Heterogeneity: I^2 = 60%, τ^2 = 0.3504, χ^2_{35} = 87.49 (p < 0.01)
Test for overall effect: z = −4.05 (p < 0.01)



c

Study	Experimental Mean	SD	*n*	Control Mean	SD	*n*	Weight (%)	Mean difference	95% CI
Asemi et al (2013) [40]	53.75	40.1	27	68.96	54.5	27	3.6	−15.21	[−40.73; 10.31]
Asemi et al (2014) [59]	48.96	27.9	31	62.71	59.0	31	4.0	−13.75	[−36.74; 9.24]
Asemi et al (2016) [20]	69.45	61.5	50	87.78	67.8	49	3.6	−18.33	[−43.83; 7.17]
Ejtahed et al (2012) [31]	48.41	31.2	30	45.14	24.8	30	6.1	3.27	[−10.98; 17.52]
Firouzi et al (2017) [49]	70.84	43.8	48	95.84	43.8	53	5.4	−25.00	[−42.09; −7.91]
Gargari et al (2013) [58]	64.52	22.2	24	93.34	33.3	25	5.7	−28.82	[−44.63; −13.01]
Horvath et al (2019) [54]	159.74	132.6	12	430.59	607.5	14	0.0	−270.85	[−597.82; 56.12]
Hove et al (2015) [23]	51.95	38.5	18	38.96	30.4	23	4.3	12.99	[−8.69; 34.67]
Kobyliak et al (2018) [53]	100.42	54.6	31	140.64	77.1	22	2.1	−40.22	[−77.73; −2.71]
Madempudi et al (2019) [47]	53.48	26.1	40	62.51	28.8	39	6.7	−9.03	[−21.15; 3.09]
Mafi et al (2018) [44]	99.31	41.0	30	115.29	50.7	30	4.0	−15.98	[−39.31; 7.35]
Mazloom et al (2013) [24]	2.43	3.1	16	1.74	0.6	18	9.0	0.69	[−0.83; 2.21]
Pedersen et al (2016) [50]	94.04	18.7	14	82.99	13.0	15	6.8	11.05	[−0.74; 22.84]
Raygan et al (2018) [30]	75.71	51.4	30	92.37	54.9	30	3.3	−16.66	[−43.56; 10.24]
Razmpoosh et al (2019) [45]	65.28	38.9	30	68.76	67.4	30	3.2	−3.48	[−31.32; 24.36]
Roshanravan et al (2017) [56]	35.42	11.7	14	35.98	7.5	15	8.1	−0.56	[−7.79; 6.67]
Sabico et al (2017) [51]	47.92	27.1	39	74.31	34.7	39	6.2	−26.39	[−40.21; −12.57]
Sabico et al (2019) [52]	42.36	30.6	31	84.03	48.6	30	4.5	−41.67	[−62.13; −21.21]
Tajabadi−Ebrahimi et al (2017) [42]	107.65	55.6	30	137.51	70.8	30	2.6	−29.86	[−62.08; 2.36]
Tajadadi−Ebrahimi et al (2014) [61]	54.87	15.3	27	58.34	37.5	27	5.8	−3.47	[−18.75; 11.81]
Tonucci et al (2017) [35]	47.23	31.9	23	46.18	31.9	22	5.0	1.05	[−17.58; 19.68]
Random effects model			595			599	100.0	−10.51	[−16.68; −4.33]

Heterogeneity: I^2 = 74%, τ^2 = 109.3284, χ^2_{20} = 76.80 (p < 0.01)
Test for overall effect: z = −3.34 (p < 0.01)



absence of a simultaneous cointervention, risk of bias, type of placebo used and blinding, slightly changed heterogeneity, with no significant overall effect on the results (data not shown).

Discussion

In the field of diabetes there is growing interest in the modulation of gut microbiota through supplementation with

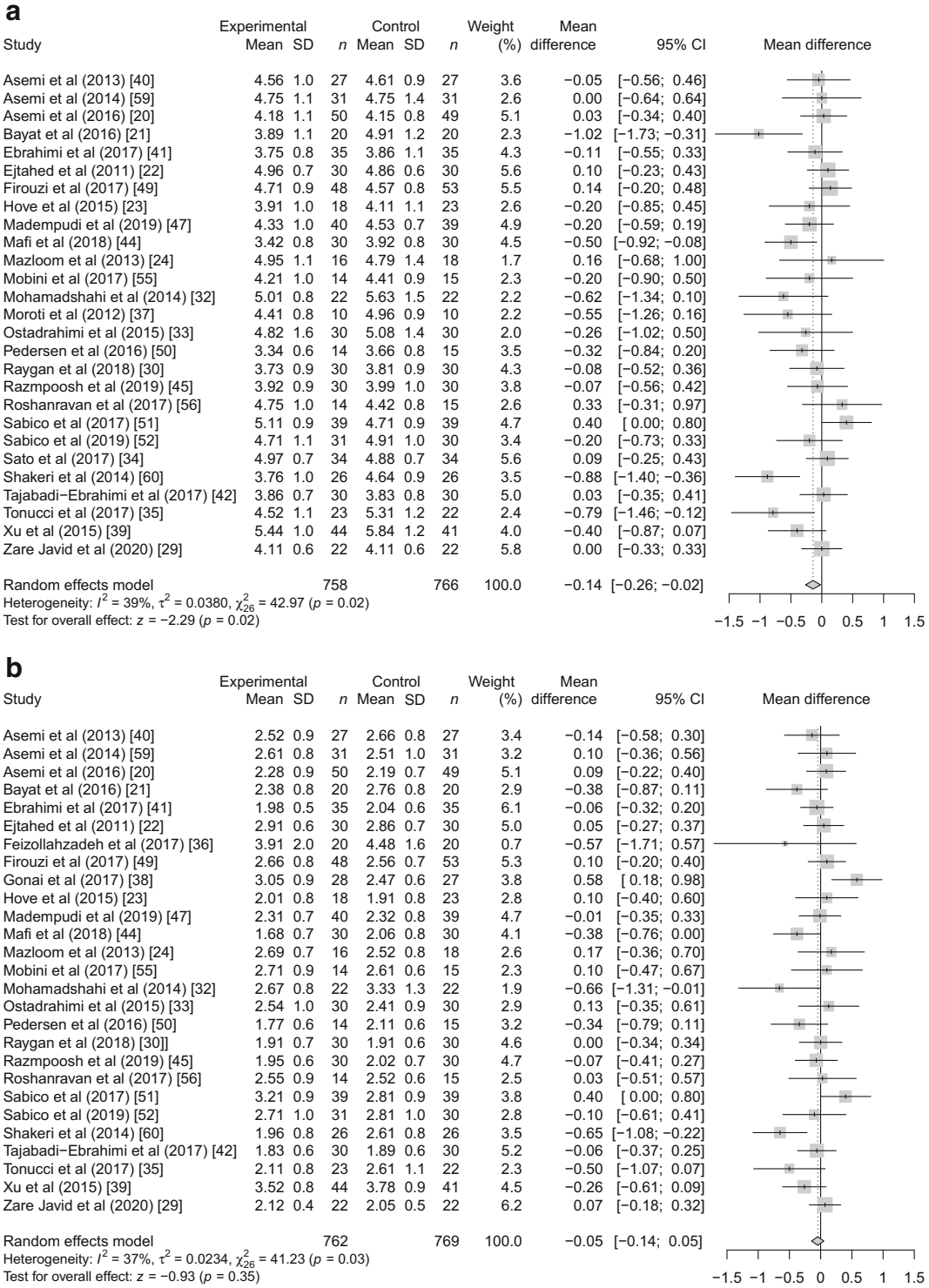


Fig. 3 Absolute changes in lipid profile of individual studies on supplementation with probiotics, prebiotics or synbiotics. (**a**) Total cholesterol, (**b**) LDL-cholesterol, (**c**) HDL-cholesterol (**d**) Triacylglycerols. 'IV, Random' refers to a random-effects meta-analysis with weights based on inverse variances

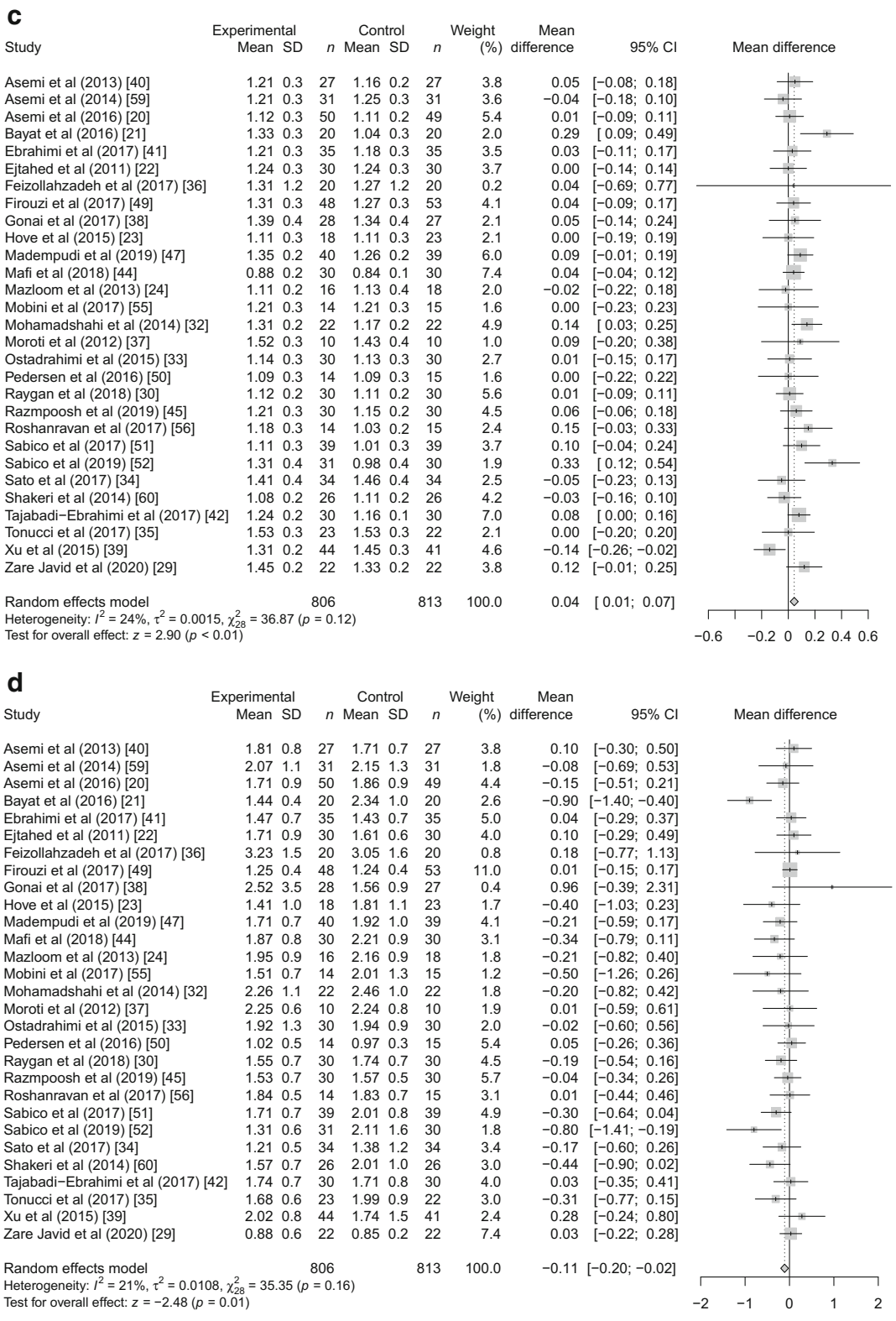


Fig. 3 (continued)

probiotics, prebiotics or synbiotics, which is motivated by the possibility of gut microbiota helping individuals with diabetes mellitus achieve favourable metabolic control. To the best of our knowledge, our meta-analysis represents the most comprehensive synthesis to date on the effects of consumption of probiotics, prebiotics and synbiotics on glucose control and

lipid changes in individuals with diabetes mellitus. Overall, the evidence generated by this review indicates that probiotics, prebiotics and synbiotics do not change LDL-cholesterol levels, they non-significantly decrease HbA_{1c}, and they significantly reduce fasting plasma glucose, serum insulin, total cholesterol and triacylglycerol levels and increase HDL-cholesterol levels.

Although supplementation reduced fasting plasma glucose, it did not significantly reduce HbA_{1c}, which is the standard measure for evaluating long-term glucose control in diabetes. Moreover, the majority of the studies that evaluated insulinaemia as an outcome showed that the interventions resulted in lower insulinaemia, i.e. reduced the severity of insulin resistance. These results were supported by the plasma glucose reduction observed following probiotic, prebiotic or synbiotic supplementation in the majority of studies with reported positive insulin response. Although we have not explored changes in the gut flora in this study, the mechanism of the effect of probiotics on glucose control may be the result of changes in microbiota composition. Several studies in the literature have suggested that consuming probiotics may not lead to a sustainable change in the diversity and the number of bacteria in the gut [62, 63]; however, even the transition of bacteria through the gut may have some benefits on glycaemic control. This may also explain why long-term changes in HbA_{1c} were not observed in this study. The bacterial strains of *L. plantarum*, *Lactobacillus fermentum*, *L. casei* and *L. rhamnosus* have shown, in vitro, potent and broad-spectrum inhibitory activities on intestinal α-glucosidase enzymes as well as the potential to reduce blood glucose in vivo [64]. Thus, supplementation with these strains, observed in at least ten included studies (some studies did not specify the strain of *Lactobacillus*), could partially explain the results. Furthermore, only eight studies evaluated HbA_{1c} after treatment for more than 12 weeks, but 31 studies evaluated fasting plasma glucose, so it is possible that if all these studies were conducted for more than 12 weeks and evaluated HbA_{1c}, a decrease in HbA_{1c} would have been observed.

Low levels of lactate- and butyrate-producing species have previously been associated with adverse impacts on intestinal epithelial barrier function and gut permeability, along with inflammation [65]. However, it is currently unclear whether inflammation can lead to increased intestinal permeability or if it has the opposite effect, since the gut inflammatory responses include an innate immune response mechanism involving Toll-like receptors, producing proinflammatory cytokines and increasing endotoxaemia [66]. A study that evaluated permeability to bacterial products by measuring circulating LPS-binding protein (which facilitates the interaction between LPS and various receptors), intestinal fatty acid binding protein and derived intestinal permeability risk score, reported that all measures were higher in individuals with type 2 diabetes compared with healthy individuals [67]. Moreover, in one study, individuals with type 2 diabetes presented a high rate of gut bacteria in the circulation, providing indirect evidence of bacterial translocation from the gut to the bloodstream [68], which could be related to inflammation and insulin resistance [69]. The inflammatory pathways related to ligands such as bacterial LPS are associated with reduced glucose uptake in insulin-sensitive tissues, increasing insulin requirement [70]. Therefore, probiotic supplementation could be beneficial in reducing inflammation and insulin sensitivity, similar to our results, which showed a reduction in serum insulin levels.

Furthermore, diabetes medication type could be a possible confounder related to the the lack of association for HbA_{1c} because drug-induced modulation of the gut microbiota could be a mechanism by which drugs exert their therapeutic effect in individuals with diabetes, as observed in a cross-sectional study in which individuals with type 2 diabetes using metformin experienced a reduction in the relative abundance of purportedly beneficial mucin-degrading and short-chain fatty acid-producing bacteria [71]. The information about medication type was not clear in most studies analysed and could have interfered with the results of studies evaluating HbA_{1c} as an outcome. In addition, baseline HbA_{1c} level was higher than 8% in only two studies [39, 58], and it is well known that there is an association between baseline HbA_{1c} and absolute change in HbA_{1c} level in response to glucose-lowering interventions [72].

Despite the small effect sizes, the results highlight an interesting effect of the use of probiotic, prebiotic or synbiotic supplements on lipid profile, which was enhanced (total cholesterol and triacylglycerol levels were decreased, whereas HDL-cholesterol levels were increased). As an enhanced lipid profile is usually associated with a low incidence of diabetes-related complications, it is tempting to speculate that these results could be reproduced [73]. However, clinical outcomes were not evaluated in the majority of the studies we retrieved, and the follow-up period was too short to determine any long-term effects on morbidity/mortality. Interestingly, a meta-analysis of prospective cohort studies showed that the consumption of fermented milk was associated with a reduced risk of stroke, ischaemic heart disease and cardiovascular mortality events [74]. Therefore, probiotics and synbiotics could be additional treatments for individuals known to be at high risk of cardiovascular events and could be even combined with medications to treat dyslipidaemia.

A recent systematic review and meta-analysis investigated the predictive role of triacylglycerols as a risk factor for cardiovascular disease in people with type 2 diabetes and found that high serum triacylglycerol levels were associated with poor diabetes control and increased risk of cardiovascular disease [75]. Individuals with low levels of HDL-cholesterol have been reported to exhibit a deterioration in beta cell function [76], therefore decreasing triacylglycerol and increasing HDL-cholesterol levels with the use of probiotics, prebiotics or synbiotics may be helpful.

Our study has some limitations. Data extraction was not blinded, which is a potential source of bias, and the sample sizes of the studies were small. In addition, substantial heterogeneity was identified in the meta-analyses, and to address this, we performed sensitivity analyses to identify the differences between the studies. Moreover, it was a challenge to summarise the results of this review, since different probiotic bacteria were used in the supplements, including several *Lactobacillus*, *Bifidobacterium* and *Streptococcus* strains, some of them together with prebiotics, which may have increased the heterogeneity. Another important factor to consider in the interpretation of our findings is the doses of probiotics, prebiotics and synbiotics, which showed considerable variation among studies, and most studies did not mention the doses used. Another challenge was the wide range of duration of supplementation. Finally, the general quality of the studies led to increased risk of bias in some studies, which may have contributed to the heterogeneity in our analyses.

The strength of this systematic review is that we studied individuals with diabetes and our findings indicate the potential clinical use of probiotics, prebiotics and synbiotics in this group of individuals. Furthermore, we investigated multiple inter-related metabolic outcomes, so that concomitant effects would corroborate the effect of consistent use of probiotics, prebiotics or synbiotics. As we analysed a significant number of studies ($n = 38$), this suggests that the conclusions can be considered reliable.

In conclusion, in individuals with type 2 diabetes mellitus, use of probiotics, prebiotics or synbiotics was associated with improvements in metabolic variables, although the magnitude of these effects was low. Accounting for all included outcomes, our results support the use of probiotics, prebiotics and synbiotics as an adjuvant treatment for metabolic control in type 2 diabetes. The best bacterial strain and concentration remains to be determined. This review highlights the need for further intervention studies to determine the importance of specific bacterial strains, doses and treatment durations.

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Data availability Data are available on request from the authors.

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Authors' relationships and activities The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement BS had full access to all of the data in the study, supervised study and takes responsibility for the integrity of the data and the accuracy of the data analysis. PMB, GHT, AFM and BS designed study. PMB, RR, MS and GL acquired data. PMB analysed data. PMB, GHT, AFM and BS interpreted data. PMB drafted the manuscript. PMB, GHT, RR, MS, GL, AFM and BS revised the manuscript for important intellectual content and approved the version to be published.

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