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Meta-analyses

Probiotics and synbiotics for glycemic control in diabetes: A systematic review and meta-analysis of randomized controlled trials

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SUMMARY

Background & aims: The escalating prevalence of diabetes mellitus may benefit from add-on therapeutic approaches. Given the recognized need for an updated synthesis of the literature, this systematic review and meta-analysis aimed to synthesize and critically assess the available randomized controlled trials (RCTs) that investigate the efficacy of probiotics and synbiotics on glycemic control in patients with Type 1 (T1DM) and Type 2 (T2DM) diabetes mellitus.

Methods: Comprehensive searches were conducted on PubMed, Embase, CINAHL, Scopus, and Web of Science, focusing on adults with T1DM or T2DM. All comparators were deemed eligible. Primary outcomes included changes in glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and insulin levels. Only RCTs were included, and the Cochrane RoB2 tool assessed the risk of bias. Random-effect models facilitated data analysis, supplemented by sensitivity, subgroup analyses, and meta-regressions.

Results: A total of 537 records were screened, resulting in 41 RCTs for analysis, which comprises 2991 (54% females) patients with diabetes. The meta-analysis revealed statistically significant improvements in HbA1c (standardized mean difference (SMD) = −0.282, 95% CI: [-0.37, −0.19], $p < 0.001$), FPG (SMD = −0.175, 95% CI: [-0.26, −0.09], $p < 0.001$), and insulin levels (SMD = −0.273, 95% CI: [-0.35, −0.20], $p < 0.001$). A medium degree of heterogeneity between studies was found in HbA1c ($I^2 = 62.5\%$), FPG ($I^2 = 71.5\%$), and insulin levels ($I^2 = 66.4\%$) analyses. Subgroup analyses indicated that the efficacy varied based on the type of strains used and the country. Multispecies strains were particularly effective in improving HbA1c levels.

Conclusion: The study findings suggest that probiotics and synbiotics may be effective as complementary therapies for managing diabetes. Additionally, the study underscores the need for further tailored research that considers variables such as strain types and geographical factors to deepen the understanding of the role of these interventions in diabetes care.

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1. Introduction

The global prevalence of diabetes, encompassing both Type 1 (T1DM) and Type 2 (T2DM), has witnessed a significant surge, affecting an estimated 465 million adults aged 20–79 years, according to recent available data [1]. Projections indicate that this number will escalate to 578 million by 2030 and 700 million by 2045 [1]. These epidemiological trends underscore the pressing challenges diabetes poses to the medical community, necessitating continual advancements in therapeutic strategies [2]. While contemporary management approaches have achieved notable progress in glycemic control, in some cases, they still fail to ensure optimal patient outcomes [3]. Consequently, a substantial segment of the diabetic population still grapples with suboptimal glycemic control [2,3]. The complexity of achieving optimal glycemic control highlights the need to explore supplementary or alternative ways

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to offer more therapeutic strategies. In this context, the gut microbiome and probiotics have emerged as potential game-changers, offering a fresh lens through which diabetes management can be viewed [4].

The gut microbiome, an intricate consortium of microorganisms inhabiting intestines, has increasingly been recognized for its pivotal role in metabolic health [5]. T1DM is characterized by the body's immune system targeting insulin-producing beta cells, leading to an insulin deficiency. The gut microbiome in T1DM exhibits specific alterations, suggesting a potential link between microbiota shifts and autoimmune responses that influence the severity of the disease [5]. Conversely, T2DM, characterized by metabolic disturbances, is primarily associated with insulin resistance due to factors such as genetics and lifestyle. In T2DM, gut dysbiosis has been observed, contributing to increased gut permeability and chronic inflammation, further exacerbating insulin resistance [6]. Probiotics, which are live microorganisms that confer health benefits to the host, present a potential therapeutic strategy in both T1DM and T2DM: they help to restore the balance of the gut microbiome, improve gut barrier function, and reduce inflammation, thereby potentially aiding in the management and even prevention of diabetes [5,6]. In addition to probiotics, there is a growing interest in the study of synbiotics, which are combinations of probiotics and prebiotics enhancing each other's effects [7]. Given the potential of probiotics in diabetes management, the combined effect of synbiotics could theoretically offer even more pronounced benefits in conditions that require a more holistic approach to gut health and metabolic regulation [8]. Considering the intricate dietary challenges faced by people with diabetes, who require adequate self-care behaviors to navigate and manage their condition effectively, the potential benefits of probiotics and synbiotics become even more pertinent [9].

Over the past decade, a growing body of research has sought to elucidate the potential of probiotics in modulating glycemic control. Several studies have reported promising results, with specific probiotic strains demonstrating the ability to improve insulin sensitivity, reduce inflammatory markers, and even modulate postprandial glucose responses [10,11]. On the other hand, other studies have yielded inconclusive or even contradictory results [11]. Factors such as the diversity of probiotic strains used, variations in study design, sample size, duration, and differences in the populations studied contributed to these discrepancies [12]. Furthermore, the mechanisms through which probiotics affect glycemic control remain only partially understood. While some studies suggest direct interactions with gut epithelial cells, others point to indirect effects mediated through changes in the gut microbiota composition [13]. In addition to probiotics, there is a growing interest in the study of synbiotics, which are combinations of probiotics and prebiotics.

Furthermore, current literature syntheses and meta-analyses reveal a fragmented understanding of the role of probiotics and synbiotics in managing glycemic control, especially regarding their combined effects [7,11,12]. Indeed, foundational meta-analyses and systematic reviews often do not reflect the latest advancements due to their publication timelines [7,11,12]. Moreover, the available meta-analyses narrow their focus to either T1DM or T2DM without adequately bridging these insights to offer a unified and up-to-date perspective on the available literature [14–17].

This trend was recently captured by an umbrella meta-analysis [18], which predominantly focused on T2DM, obesity, polycystic ovary syndrome, and pregnant women with or without gestational diabetes mellitus, yet did not include T1DM, highlighting a significant gap in the literature in summarizing literature that also includes T1DM. Emerging evidence supports the beneficial effects of probiotics on autoimmune diseases, such as T1DM, including their positive impact on cardiometabolic disorders [19,20]. This evidence further emphasizes the need to include both types of diabetes in our analysis, as T1DM, an autoimmune condition, may also benefit from probiotic supplementation, influencing glycemic control. Thus far, the recently published umbrella meta-analysis reported a significant reduction in fasting plasma glucose (FPG) levels across 45 studies involving 29,190 participants, demonstrating probiotic supplementation's efficacy on this specific outcome, while their role remains unclear in relation to other outcomes [18]. However, it also revealed substantial heterogeneity and did not control for overlapping primary studies in its pooled effect sizes. This limit, coupled with the presence of publication bias as indicated by the funnel plot asymmetry and the unaltered results after trim and fill analysis, suggests room for an up-to-date systematic review focused exclusively on primary studies. The need for an up-to-date systematic review that includes analysis of primary studies and studies including T1DM is further widened by the predominant emphasis on gut microbiota changes in the available literature, leaving a crucial aspect of direct glycemic outcomes thus far underexplored [15]. For this reason, the main aim of this systematic review and meta-analysis is to comprehensively synthesize and critically assess the available primary randomized controlled trials (RCTs) that investigate the efficacy of probiotics and synbiotics on glycemic control in both T1DM and T2DM and to aggregate the outcomes from these studies quantitatively.

2. Methods

2.1. Study design

This systematic review and individual-participant data (IPD) meta-analysis was designed in adherence to the Cochrane Handbook for Systematic Reviews of Interventions guidelines [21]. The reporting of this study aligns with the PRISMA 2020 statement to ensure transparency, rigor, and reproducibility [22]. The review protocol was proactively registered in PROSPERO (CRD42023396348). The main research question was: “What are the combined findings of published RCTs investigating the effect of probiotics (any strain) or synbiotics versus any comparator on glycemic control in adults with diagnosed diabetes (T1DM or T2DM)?”

2.2. Search strategy and eligibility criteria

The main research question was framed using the “Population, Intervention, Comparison, Outcome, Study type” (PICOS) framework [21]. The target population comprised adults diagnosed with either T1DM or T2DM. The primary intervention under examination was the add-on administration of probiotics, encompassing any strain and/or synbiotics to patient treatment. These are compared against any other treatments or placebos present in the studies. Our primary outcome of interest is glycemic control, represented by Glycated Hemoglobin (HbA1c) levels, FPG, and serum insulin levels. The study selection was strictly limited to RCTs as these designs are best suited to investigate the efficacy of interventions.

Two independent reviewers (IB and RC) conducted a systematic and comprehensive literature search across PubMed, Embase, CINAHL, Scopus, and Web of Science (WoS) from the databases' inception to October 2023. A combination of MeSH terms and free text, including “diabetes”, “probiotics”, “synbiotics”, and “randomized controlled trials” was employed. Boolean operators were used for sensitivity (“OR”) and precision (“AND”), tailored to each database's syntax. The detailed search strategy is described in Supplementary File 1. The reference lists of prior systematic

reviews and pertinent articles were also examined to ensure a thorough search [7,11,12].

The inclusion criteria were selected to include (a) RCTs on (b) adults (≥18 years) with T1DM or T2DM and (c) examining the addition of probiotics and/or synbiotics to their treatment. Studies should compare these interventions to other treatments, placebos, or standard diabetic care, focusing on outcomes like HbA1c, FPG, and serum insulin levels. However, according to the exclusion criteria, certain studies were unsuitable for this review: we excluded non-randomized studies, observational studies, case reports, and reviews. Additionally, any study that failed to report on our specified outcomes of interest was left out. In conducting this systematic review, no language restrictions were imposed. Nevertheless, articles written in languages other than English were excluded if their full-text versions were not accessible online, given the impracticality of translating non-HTML format articles into English.

3. Outcomes

In this review, the primary outcome of interest was glycemic control, which was operationalized into three specific measures: HbA1c levels, FPG, and serum insulin levels. In assessing glycemic control, HbA1c levels serve as an indicator of the mean blood sugar over an approximate three-month span. FPG offers a precise measure of blood glucose following an overnight fast, elucidating the body's inherent glucose homeostasis in a fasting state. Lastly, serum insulin levels shed light on endogenous insulin secretion and its subsequent interaction with glucose, a critical component in the clinical evaluation of metabolic responses. These measures of glycemic control are outcomes frequently employed in RCTs, and they are mainly reported as continuous measures, allowing for nuanced analyses and interpretations in evaluating the efficacy of interventions targeting glucose metabolism and regulation.

3.1. Data extraction

Participants' setting and health status, along with demographic specifics such as age, sex, and country of origin, were extracted to ensure the study's applicability to diverse populations and to discern variations across studies. The methodological approach of each study was identified, emphasizing its design (e.g., parallel-group designs, other designs). Interventions were detailed to facilitate potential replication, encompassing aspects like strains, concentration, dose, frequency, duration, and other relevant components. Outcomes from each study were systematically listed, including time points of follow-ups. Lastly, any additional observations or comments not captured in the primary a priori categories were integrated into a note field.

The mean and standard deviation of each available outcome, preferably at the 12-week follow-up, were extracted for the meta-analysis, considering the intention-to-treat framework to guide extraction. In cases where studies did not extend to 12 weeks, data from the last available follow-up were considered. The choice of the 12-week duration was twofold: clinically, this period is significant as it allows for observable physiological changes and adaptations to interventions, and statistically, 12 weeks emerged as the median follow-up time across the studies, providing a consistent benchmark. When including a study with multiple intervention groups in a meta-analysis, “double-counting” participants in shared intervention groups was avoided. We included each pair-wise comparison separately but divided the shared intervention groups approximately evenly among the comparisons to address the unit-of-analysis error [21]. Furthermore, both categorical and quantitative potential moderators were also extracted. The categorical potential moderators were the country of the study, the specific strain of the probiotic used (multispecies, unspecified, or monospecies), the type of experimental product (whether probiotics or synbiotic), and the nature of the control (either inactive or active). Additionally, the pooled mean of the Body Mass Index (BMI) and the pooled proportion of male participants were recorded as continuous variables. Other crucial data included the year of publication, the exact time point of the follow-up when it was less than 12 weeks, and the pooled mean age of participants. These parameters were deemed essential to ensure a comprehensive and nuanced understanding of the studies and their outcomes.

3.2. Risk of bias assessment

The Cochrane Risk of Bias tool 2.0 (RoB2) was employed to assess the risk of bias in the included studies [23]. This comprehensive tool evaluates the potential biases in the following domains: the randomization process (D1), deviations from the intended interventions (D2), instances of missing outcome data (D3), the methodology of outcome measurement (D4), and the selection criteria for reported results (D5). Subsequently, each domain was classified based on the risk of bias, with possible ratings being low, uncertain, or high. This systematic approach ensures a rigorous and consistent evaluation of the potential biases present in each study, enhancing the reliability and validity of the review's results. The risk of bias for each included study was assessed independently by two researchers (IB, DF) to adhere to the highest methodological standards in our systematic review and meta-analysis. Any discrepancies or contradictions identified during this independent evaluation were initially discussed between the two researchers for resolution. If a consensus could not be reached on any point of disagreement, a third (RC) impartial researcher was engaged to provide a decisive judgment.

3.3. Data analysis

Random-effects models were deemed appropriate for each outcome, anticipating potential variations in populations and intervention products, as they account for true variability between studies. These models inherently assumed that the variability between studies was not negligible. The primary analysis utilized random-effects models to ascertain the RCTs’ effect size (theta) for each outcome. These models estimated the standardized mean difference (SMD) and its 95% confidence interval (CI) using the Restricted Maximum Likelihood (REML) approach, incorporating DerSimonian and Laird estimates. The direction of effect was configured such that an SMD below zero indicated a favorable intervention outcome.

A predefined sensitivity analysis was set to assess the impact of individual studies on the overall estimation. Cochran's Q test was employed to evaluate statistical heterogeneity, complemented by the assessment of between-study variance (tau^2), the proportion of total variation across studies attributed to heterogeneity (I^2), and the ratio of total variation inclusive of heterogeneity to that exclusive of it (H^2). In our statistical analyses, we assessed publication bias through both graphical and quantitative methods. Initially, we utilized funnel plots to visually examine the distribution of effect sizes against their standard errors, which may indicate potential asymmetry suggestive of publication bias. Subsequently, Egger's regression test was employed to statistically evaluate the symmetry of the funnel plot, providing a more objective measure of publication bias presence. When indications of publication bias were observed, we proceeded with a trim-and-fill analysis. This method quantitatively estimates the number of potentially omitted studies that might lead to asymmetry in the funnel plot and then

imputes these studies to "trim and fill" the plot accordingly. The adjusted effect sizes were then recalculated after accounting for publication bias, reflecting a more accurate estimate. This comprehensive approach, incorporating both the funnel plot for initial visual assessment and Egger's test for statistical confirmation, followed by the trim-and-fill analysis for correction, ensures a comprehensive assessment of the publication bias in the results of this study.

Five subgroup analyses were performed, incorporating tests of group differences based on available data. These analyses considered the type of bacterial strain, experimental product, control group, RoB2 scores, and country of study execution. Additionally, there was an initial intention to perform a subgroup analysis to differentiate between T1DM and T2DM, contingent on the availability of data. However, this analysis proved to be infeasible due to the combined reporting of results in studies that included mixed samples of both T1DM and T2DM patients. To elaborate, the aggregate data from the primary RCTs pertained to 84 out of the 2991 patients, accounting for 2.8% of the total sample. Furthermore, meta-regression models incorporated variables such as pooled mean BMI, pooled proportion of male participants, publication year, follow-up time points shorter than 12 weeks, and pooled mean participant age to elucidate potential sources of heterogeneity in the effect sizes across the included studies. The meta-regressions were interpreted and reported using regression coefficients, standard errors, z-values, and 95% CIs. Furthermore, the assessment of residual variance, the coefficient of determination, the likelihood ratio test, and the examination of residuals following diagnostics were employed to evaluate the fit and robustness of each model. Statistical analyses were conducted using Stata 18 (StataCorp LLC, College Station, TX, USA) with the "metan.ado" file.

3.4. Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

4. Results

The search yielded 41 records from PubMed, 232 from Embase, 38 from CINAHL, 184 from Scopus, and 42 from WoS, for a total of 537 records (Fig. 1). Upon the removal of 198 duplicate records, 339 records remained for screening. Of these, 304 were excluded due to various reasons such as not being an RCT (n = 100), not focusing on T1DM or T2DM, not including participants aged 18 or older (n = 109), not incorporating probiotics/synbiotics (n = 48), not addressing glycemic control (n = 44), or being written in a language and format that not allowed authors to translate records into English (n = 2). Subsequently, 36 reports were retrieved for a more detailed assessment of the full texts. Five records were excluded due to reasons such as involving a population aged 18 or younger (n = 1), not including probiotics (n = 1), not providing numerical results for glycemic control (n = 1), being retracted (n = 1), or presenting identical overlapping results with another eligible study (n = 1). In this last case, we followed the recommendation from the Cochrane Handbook for Systematic Reviews of Interventions when it addressed the issue of identifying multiple reports from the same study: we included only the first publication because the second publication yielded identical results from the same study [21]. Furthermore, citation searching identified ten records, all assessed for eligibility and deemed suitable. Consequently, 41 studies were included in the review. Differences of opinion concerning the

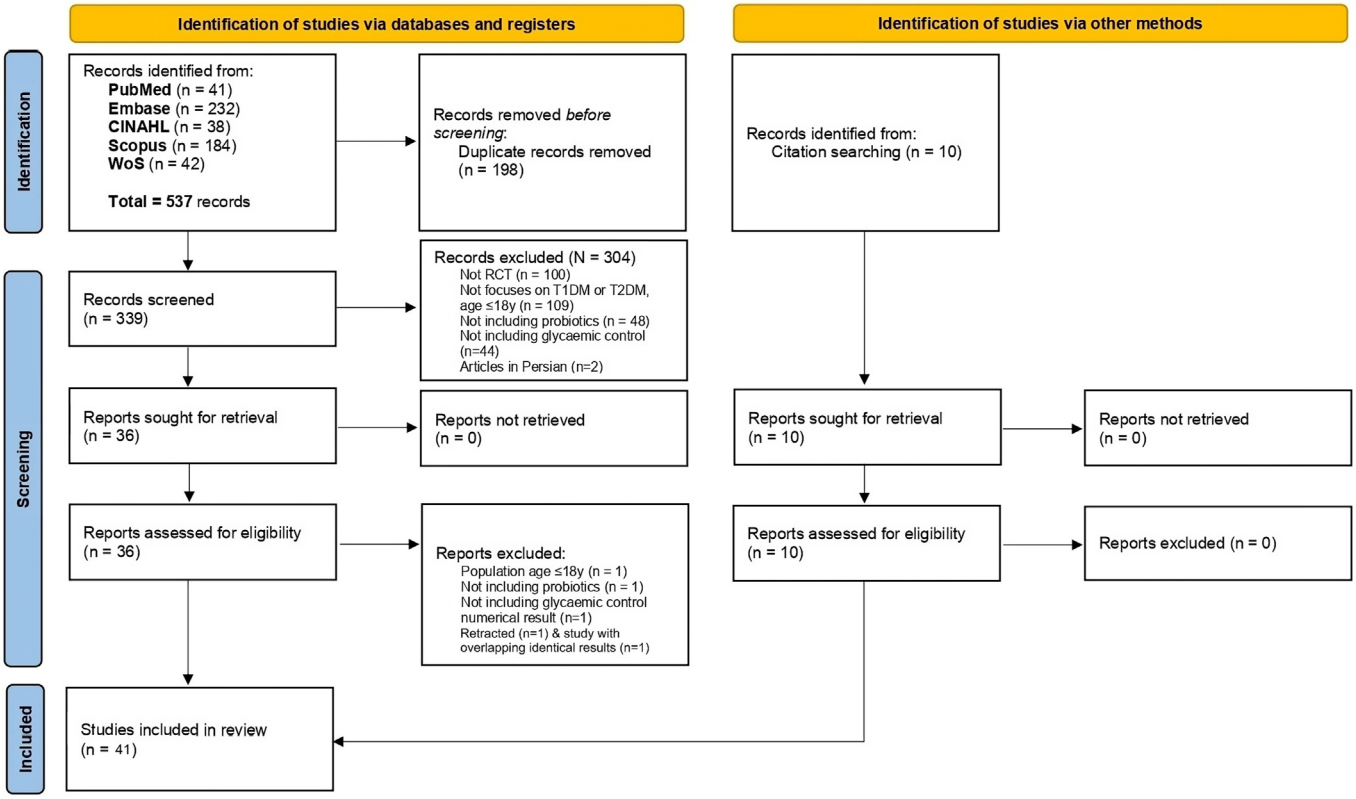

Fig. 1. PRISMA flow-diagram.

inclusion of abstracts and full-text articles were settled through consensus discussions and involving a third reviewer (DA).

This systematic review included 41 studies [24], [–] [64] which comprises 2991patients (54% females). These studies were conducted in various countries, with the majority (23 studies; 56.1%) conducted in Iran (Table 1) [24,26–28,30–33,36,37,40,41,43–45,47–50,60,62–64]. Other countries where the studies were conducted include countries such as Malaysia, Austria, Ukraine, Sweden and Denmark. The studies employed various research methods. The most common method used was a single-center, parallel-group, randomized, double-blind, placebo-controlled trial. Participants in these studies were often described considering several variables, including sex, time from diagnosis, BMI, and age. Randomization was typically achieved using computer-generated random numbers. The interventions used in the studies varied in relation to the adopted strain(s) (mainly various strains of Lactobacillus), with some studies not specifying the species or strains used. The outcomes were generally related to the effects of probiotics or synbiotics on various health indicators, including FPG, HbA1c, and serum insulin levels.

The studies included which evaluated the efficacy of probiotics/synbiotics on HbA1c were 28 [24,25,31,34–39,42,43,45–47,50–64]. As depicted in Fig. 2, the overall effect size (SMD) was −0.282, with a 95% CI of −0.428 to −0.137. The test for the overall effect was significant ($z = -3.798$, $p < 0.001$), indicating a statistically significant impact on HbA1c. Heterogeneity measures revealed a Cochran's Q value of 96.10 (degrees of freedom, $df = 36$, $p < 0.001$), an H value of 1.634, and an I^2 of 62.5%, with a tau^2 estimate of 0.1182. The sensitivity analysis revealed that the omission of any single study did not significantly alter the combined estimate. The combined effect size remained consistent, with an overall estimate of −0.282 and a 95% CI ranging from −0.428 to −0.137. The funnel plot and the trim-and-fill analysis showed no imputed studies, indicating a low likelihood of publication bias (Supplementary File 2).

The subgroup analysis involving the types of strains revealed distinct patterns among multispecies, not specified, and monospecies (Supplementary File 3). The multispecies subgroup showed a significant SMD of −0.305, a 95% CI of −0.491 to −0.120, and a high heterogeneity ($I^2 = 66.8\%$). The "not specified" subgroup had a non-significant SMD of −0.167 and lower heterogeneity ($I^2 = 36.7\%$). The monospecies subgroup had an SMD of −0.249, with moderate heterogeneity ($I^2 = 61.3\%$). Tests for subgroup effects were significant for the multispecies group ($p = 0.001$) but not for the other subgroups.

The subgroup analysis involving probiotics and synbiotics showed SMDs of −0.220 and −0.469, respectively (Supplementary File 3). The z-tests for subgroup effect sizes were significant for probiotics ($z = -2.963$, $p = 0.003$) and synbiotics ($z = -2.403$, $p = 0.016$), indicating that the effects are not likely due to chance. Both subgroups and the overall analysis were statistically significant, with varying degrees of heterogeneity: 49.5% for probiotics and 78.2% for synbiotics.

When analyzing subgroups related to the type of control, the inactive control subgroup had a significant negative effect size ($SMD = -0.308$, $z = -3.099$, $p = 0.002$), while the active control subgroup also showed a significant but smaller negative effect size ($SMD = -0.174$, $z = -2.284$, $p = 0.022$). Heterogeneity was high in the inactive subgroup ($I^2 = 69.2\%$, $p < 0.001$) but negligible in the active subgroup ($I^2 = 0.0\%$, $p = 0.494$).

The subgroup analysis by country, with Iran having the largest number of studies ($n = 13$) and a significant negative effect size ($SMD = -0.355$, $z = -3.767$, $p < 0.001$). Heterogeneity varied across countries, with India showing the highest ($I^2 = 91.3\%$, $p < 0.001$) and several countries like Malaysia, Austria, and Denmark having only single studies, thus not allowing for heterogeneity calculations. Overall, the meta-analysis showed a significant negative effect size ($SMD = -0.282$, $z = -3.798$, $p < 0.001$) with moderate heterogeneity ($I^2 = 62.5\%$, $p < 0.001$).

The random-effects meta-regression analysis indicated that none of the predictors, such as BMI, gender proportion, risk of bias, year of study, time point, and mean age, showed a statistically significant effect on the meta-analyzed effect size, as evidenced by the high p-values (e.g., $p = 0.512$ for BMI, $p = 0.881$ for gender proportion). The model's R-squared value was 0.0%, indicating that the predictors did not explain any of the variances in the effect size, and the overall model fit was not significant (Wald $chi^2_{(6)} = 2.72$, $Prob > chi^2 = 0.8433$).

4.1. Efficacy of probiotics/synbiotics on FPG

The studies included in this meta-analysis were 41 [24–64]. As depicted in Fig. 3, the SMD was −0.175, with a 95% CI ranging from −0.318 to −0.032. The test for the overall effect was statistically significant ($z = -2.393$, $p = 0.017$). Heterogeneity measures revealed a Cochran's Q value of 172.04 (degrees of freedom, $df = 49$, $p < 0.001$), an H value of 1.874, and an I^2 of 71.5%, with a tau^2 estimate of 0.1785. The sensitivity analysis, which omitted each study one at a time, showed that the combined effect size estimate remained relatively consistent across the studies. The combined effect size ranged from −0.158 to −0.226, indicating that no single study significantly influenced the overall result. The funnel plot and the trim-and-fill analysis showed no imputed studies, indicating a low likelihood of publication bias (Supplementary File 2).

The subgroup analysis involving the types of strains revealed nuanced differences among the subgroups based on the type of strain used in the studies (Supplementary File 3). The multispecies subgroup showed a non-significant SMD of −0.029 with a 95% CI of −0.246 to 0.188, accompanied by a high level of heterogeneity ($I^2 = 79.9\%$). The "not specified" subgroup had a significant SMD of −0.505 with a 95% CI of −0.937 to −0.073 and moderate heterogeneity ($I^2 = 51.4\%$). The monospecies subgroup exhibited a significant SMD of −0.308 with a 95% CI of −0.476 to −0.140 and lower heterogeneity ($I^2 = 34.6\%$). Tests for subgroup effects were significant for the "not specified" and monospecies groups ($p = 0.022$ and $p < 0.001$, respectively) but not for the multispecies group ($p = 0.794$). Cochran's Q statistics further confirmed the presence of heterogeneity within and between the subgroups.

The subgroup analysis involving probiotics and synbiotics interventions revealed distinct patterns. The Probiotic subgroup showed a non-significant SMD of −0.169 with a 95% CI of −0.363 to 0.025 and a high level of heterogeneity ($I^2 = 77.6\%$) (Supplementary File 3). The Synbiotic subgroup had a marginally significant SMD of −0.165, a 95% CI of −0.329 to −0.001, and lower heterogeneity ($I^2 = 30.9\%$). The z-tests for subgroup effect sizes were not significant for probiotics ($z = -1.706$, $p = 0.088$). However, they were significant for synbiotics ($z = -1.970$, $p = 0.049$), suggesting that the effects for Synbiotics are less likely to be due to chance.

When analyzing subgroups related to the type of control, the inactive control subgroup had a significant negative effect size ($SMD = -0.230$, $z = -3.763$, $p < 0.001$). In contrast, the active control subgroup did not show a significant effect size ($SMD = 0.184$, $z = 0.647$, $p = 0.518$). Heterogeneity was moderate in the inactive subgroup ($I^2 = 47.3\%$, $p = 0.001$) and high in the active subgroup ($I^2 = 91.5\%$, $p < 0.001$).

The subgroup analysis by country revealed varying effect sizes and levels of statistical significance. For instance, studies from Iran showed a non-significant negative effect size ($SMD = -0.188$, $z = -1.622$, $p = 0.105$) with high heterogeneity ($I^2 = 79.1\%$, $p < 0.001$). In contrast, studies from Malaysia and Denmark showed significant negative effect sizes with z-scores of −2.649 and −2.295,

Table 1
Summary of study characteristics (n = 41).

Study ID	Aim	Country	Participants	Methods	Interventions	Probiotics/Synbiotic composition	Outcomes
Asemi et al. **2013**	To investigate how multispecies probiotic supplements affect metabolic profiles, high-sensitivity C-reactive protein, and oxidative stress in patients with T2DM	Iran	Patients with T2DM **Total:** n = 60 (42 females); **Probiotics**: n = 30 (21 females; 50,51 ± 9.82 years); **Placebo**: n = 30 (21 females; 52.59 ± 7.14 years).	Single-center, parallel-group, randomized, double-blind, placebo-controlled clinical trial.	One probiotic supplement/ placebo capsule per day for 8 weeks	Multispecies probiotic capsule: - *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) - *Bifidobacterium breve* (2 × 10^10 CFU) - *B. longum* (7 × 10^9 CFU) - *Streptococcus thermophilus* (1.5 × 10^9 CFU)	Multispecies probiotic supplementation after 8 weeks of intaking prevented a rise in fasting blood glucose compared with placebo.
Asemi et al. **2014**	To investigate how synbiotic food consumption affects metabolic profiles, hs-CRP and biomarkers of oxidative stress in patients with T2DM.	Iran	Patients with T2DM, age range 35 −70 years **Total:** n = 70, 62 analyzed (19 females, 53.1 ± 8.7 years) **Synbiotic:** n = 31 (62 patients after crossover) **Control:** n = 31 (62 patients after crossover)	Single-center, crossover, randomized, double-blind, controlled trial.	One package (9 g) of synbiotic/ control food three times a day for 6 weeks. After a 3-week washout period, subjects were crossed over to the alternate treatment arm for an additional 6 weeks.	Monospecies synbiotic package (9 g): - Lactobacillus sporogenes (9 × 10^7 CFU) −0.36 g inulin as prebiotic	Consumption of a synbiotic food, compared to the control, resulted in a significant decrease in serum insulin levels (P = 0.03), but the effect on FPG was not significant (P = 0.09).
Asemi et al. **2016**	To investigate how beta-carotene-fortified synbiotic food intake affects metabolic status in patients with T2DM.	Iran	Patients with T2DM, age range 35 −70 years **Total:** n = 51 (32 females, 52.9 ± 8.1 years) **Synbiotic:** n = 25 (51 patients after crossover) **Control:** n = 26 (51 patients after crossover)	Single-center, crossover, randomized, double-blind, controlled trial.	One package (9 g) of betacarotene fortified synbiotic/control food three times a day for 6 weeks. After a 3-week washout period, subjects were crossed over to the alternate treatment arm for an additional 6 weeks.	Monospecies synbiotic package (9 g): - Lactobacillus sporogenes (9 × 10^7 CFU) −0.9 g inulin as prebiotic −0.45 g beta-carotene	Beta-carotene fortified synbiotic food consumption resulted in a significant decrease in serum insulin (P = 0.002) compared to the control food, but no significant effect of beta-carotene fortified synbiotic food consumption on FPG (P = 0.05).
Bayat A. 2016	To investigate how *Cucurbita ficifolia* (=green pumpkin) and/or probiotic yogurt consumption affect glycemic control, lipid profile, and inflammatory markers in patients with T2DM	Iran	Non-smokers, non-drinkers, and under metformin or glibenclamide therapy patients with T2DM. **Total**: n = 80 (52 females); ***C. ficifolia*:** n = 20 (8 females; 51.8 ± 2.24 years); **Yogurt**: n = 20 (17 females; 54.1 ± 9.54 years); ***C. ficifolia* + yogurt**: n = 20 (16 females; 53.65 ± 6.99 years); **Control**: n = 20 (11 females; 46.95 ± 9.34 years).	Single-center, parallel-group, randomized, open-label, controlled trial.	Each arm has a dietary intervention for 8 weeks (at lunch): 1. *C. ficifolia* (100 g) 2. probiotic yogurt (150 g) 3. *C. ficifolia* (100 g) and probiotic yogurt (150 g) 4. Dietary advice	*No species or strains specified*	All interventions significantly decreased the fasting blood glucose (FPG) (p = 0.001 in *C. ficifolia*, p = 0.014 in yogurt, p = 0.000 in *C. ficifolia* and yogurt) in comparison to control group, and HbA1c (p = 0.001 in *C. ficifolia*, p = 0.002 in yogurt, p = 0.000 in *C. ficifolia* and yogurt).
Ebrahimi et al. **2017**	To investigate how synbiotics supplements affect glycemic control, lipid profiles, and microalbuminuria in non-obese patients with T2DM	Iran	Non-obese patient (BMI <35 kg/m^2) with T2DM and microalbuminuria. **Total**: n = 82 (38 females); **Synbiotic**: n = 35 (12 females; 58.71 ± 8.20 years); **Placebo**: n = 35 (16 females; 58.63 ± 8.06 years).	Single-center, parallel-group, randomized, double-blind, placebo-controlled trial.	1 Synbiotic/placebo capsule daily for 9 weeks	Multispecies synbiotic capsule (500 mg): - Lactobacillus family - Bifidobacterium family - *Streptococcus thermophilus* - Prebiotic: Fructo oligosaccharide	Synbiotics significantly decreased HbA1c (p < 0.001) and FPG (p = 0.05) in comparison to placebo.
Ejtahed et al. **2012**	To investigate how probiotic supplements and conventional yogurt affect blood glucose and antioxidant status in patients with T2DM.	Iran	Patients with T2DM, age range 30 −60 years, BMI <35 kg/m^2. **Total:** n = 72 (60 analyzed) **Probiotic yogurt:** n = 30 (19 females, 50.87 ± 7.68 years) **Conventional yogurt:** n = 30 (18 females, 51.00 ± 7.32 years)	Single-center, parallel-group, randomized, double-blind, controlled trial.	300 g of probiotic/conventional yogurt per day for 6 weeks	Multispecies probiotic yogurt (300 g): - B. lactis Bb12 (3 × 10^8 CFU) - *L. acidophilus* La5 (3 × 10^8 CFU)	Between-group analysis, FPG and HbA1c significantly decreased in the probiotic group compared with the control group, while Insulin concentration did not differ. In within-group

							analysis, the intervention group showed a decrease in FPG, HbA1c and insulin from the baseline value.
Feizollahzadeh et al. **2017**	To investigate how probiotic soy milk affect inflammation, lipid profile, FPG, and serum adiponectin among patients with T2DM.	Iran	Patients with T2DM, age range 35 −68 years. **Total:** n = 48 (40 analyzed) **Probiotic soy milk:** n = 20 (11 females, 56.90 ± 1.81 years) **Conventional soy milk:** n = 20 (10 females, 53.6 ± 1.6 years)	Single-center, parallel-group, randomized, double-blind, controlled trial.	200 ml conventional/probiotic soy milk per day for 8 weeks	Monospecies probiotic soy milk (200 ml): *Lactobacillus plantarum* A7 (2×10^7 CFU)	In between groups analysis, no significant changes in FPG (P = 0.406).
Firouzi et al. **2017**	To investigate how probiotics supplements affect glycemic control and other diabetes-related outcomes in patients with T2DM.	Malaysia	Patients with T2DM **Total**: n = 136 (71 females); **Probiotics**: n = 68 (37 females; 52.9 ± 9.2 years); **Placebo**: n = 68 (34 females; 54.2 ± 8.3).	Single-center, parallel-group, randomized, double-blind, placebo-controlled trial.	1 sachet of probiotics/placebo twice per day (morning and evening) before or after meal for 12 weeks	Multispecies probiotic sachet: - *Lactobacillus acidophilus* ($0,5 \times 10^10$ CFU) - *Lactobacillus casei* ($0,5 \times 10^10$ CFU) - Lactobacillus lactis ($0,5 \times 10^10$ CFU) - *Bifidobacterium bifidum* ($0,5 \times 10^10$ CFU) - *Bifidobacterium longum* ($0,5 \times 10^10$ CFU) - Bifidobacterium infantis ($0,5 \times 10^10$ CFU)	Probiotics significantly decreased HbA1c ($p < 0.05$) in comparison to placebo by PP analysis, while there were no significant differences between the two groups by ITT analysis.
Ghafouri et al. **2019**	To investigate how synbiotic bread with lactic acid consumption affect glycemic status, inflammation, and antioxidant capacity in patients with T2DM.	Iran	Patients with T2DM **Total**: n = 100 (43 females); **Lactic acid bread**: n = 25 (55.00 ± 0.97 years); **Synbiotic bread**: n = 25 (54.92 ± 1.02 years); **Sinbiotic + lactic acid bread**: n = 25 (53.88 ± 1.09 years); **Control bread**: n = 25 (54.6 ± 0.83 years)	Single-center, parallel-group, randomized, double-blinded, controlled trial.	Each arm has daily consumption of one type of bread for 8 weeks: 1. Lactic acid bread: beta-glucan (3 g), lactic acid (4 g); 2. Synbiotic bread: beta glucan (3 g), *Bacillus coagulans* (1×10^8 CFU), inulin (10 g); 3. Synbiotic + lactic acid bread: beta glucan (3 g), probiotic, inulin (10 g), lactic acid (4 g); 4. Control bread: beta glucan (3 g).	Monospecies synbiotic bread: - *Bacillus coagulans* (1×10^8 CFU) - Prebiotic: inulin (10 g);	HbA1c decreased significantly compared to baseline in the synbiotic + lactic acid bread group ($p < 0.001$), and in the synbiotic bread group ($P < 0.001$) after 8 weeks of intervention. HbA1c was significantly lower in the Synbiotic + lactic acid bread and synbiotic bread groups compared to the control group.
Horvath et al. **2020**	To investigate how symbiotic supplement affect glucose metabolism, gut microbiota, gut permeability, neutrophil function and quality of life in patients with diabesity.	Austria	Patients with diabesity (T2DM + BMI 30−40 kg/m^2) **Total**: n = 41 (7 females over 26 analyzed patients); **Synbiotics**: n = 21 (1 female, 61 (56 −65) years, over 12 analyzed patients); **Placebo**: n = 20 (6 females, 59 (54 −63) years, over 14 analyzed patients).	Single-center, parallel-group, randomized, double-blind, placebo-controlled trial.	The probiotic/placebo powder was dispensed in sachets which the patients dissolved every morning in 250 ml of water and drank after 10 min of activation time, for 24 weeks. Also, the prebiotic/placebo daily dose (8 g of active prebiotic Galacto-oligosaccharides P11 (GOS) and Fructo-oligosaccharides P6 (FOS)) was dissolved in 250 −500 ml of water and taken in the evening, for 24 weeks.	Multispecies probiotic sachet (1.5×10^10 CFU): - *B. bifidum* W23, - B. lactis W51, - B. lactis W52, - *L. acidophilus* W37, - *L. casei* W56, - *L. brevis* W63, - *L. salivarius* W24, - Lc. lactis W58 and W19.	No significant change in glucose metabolism was detected in the synbiotics group compared to the placebo group.
Hove et al. **2015**	To investigate how fermented milk (Cardi04 yogurt) consumption affect blood pressure, glycaemic control and cardiovascular risk factors in patients with T2DM.	Denmark	Patients with T2DM, age range 40 −70 years **Total**: n = 41; **Cardi04 yogurt**: n = 23 (58.5 ± 7.7 years); **Placebo**: n = 18 (60.6 ± 5.2 years).	Single-center, parallel-group, randomized, double-blind, placebo-controlled trial. 2 × 2 factorial design in which 20 patients were randomized to receive esomeprazole and 21 to placebo.	Bottles containing 300 ml of fermented milk Cardi04 yogurt/ placebo (identical) consumed every morning for 12 weeks.	Monospecies probiotic fermented milk: *L. helveticus* Cardi04 and added artificial sweetener (sucralose).	The change in fasting blood glucose concentration was significantly different (p = 0.022) between the two groups, with a larger increase in the placebo group during the 12-week intervention.

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Table 1 (*continued*)

Study ID	Aim	Country	Participants	Methods	Interventions	Probiotics/Synbiotic composition	Outcomes
Hsieh et al. **2018**	To investigate how oral consumption of *L. reuteri* strains ADR-1 and ADR-3, affect cholesterol, HbA1c and other metabolic markers, inflammatory cytokines or antioxidant proteins, and intestinal flora.	Taiwan	Patients with T2DM, age range 25 −70 years, BMI >18.5 kg/m^2 **Total**: n = 74 (30 females over 68 analyzed patients); **Live L. *reuteri* ADR-1**: n = 25 (10 females, 52.32 ± 10.20 years, over 22 analyzed patients); H**eat-killed *L. reuteri* ADR-3**: n = 25 (11 females, 53.88 ± 7.78 years, over 24 analyzed patients); **Placebo**: n = 24 (9 females, 55.77 ± 8.55 years, over 22 analyzed patients).	Single-center, parallel-group, randomized, double-blind, placebo-controlled trial. Random allocation into 3 groups in a ratio of 1:1:1.	One probiotic supplement/ placebo capsule per day for 24 weeks.	Monospecies probiotic capsule: - living *L. reuteri* ADR-1 (4 × 10^9 CFU); - heat-killed *L. reuteri* ADR-3 (2 × 10^{10} cells).	The HbA1c net change level in the *L. reuteri* ADR-1 consumption group was significantly reduced at V2, V3, and V4. Only participants from the live *L. reuteri* ADR-1 intake group displayed a decreased trend in the HbA1c level. No significant net change in HbA1c at any time points in the heat-killed *L. reuteri* ADR-3 consumption group. The net changes in insulin and FPG among groups were not significant in comparison with those in the placebo group.
Jiang et al. **2021**	To investigate how probiotic consumption affect glycemic control and renal function in patients with diabetic nephropathy.	China	Patients with T2DM, age range 18 −75 years, and diabetic nephropathy **Total**: n = 101 randomized; 76 analyzed (49 females over 76 analyzed); **Probiotics**: n = 42 (27 females, 55.96 ± 8.45 years); **Placebo**: n = 34 (22 females, 56.12 ± 8.23 years)	Single-center, parallel-group, randomized, double-blind, placebo-controlled trial. Random allocation in a ratio of 1:1.	One probiotic supplement/ placebo capsule per day for 12 weeks.	Multispecies probiotic capsule (3.2 × 10^9 CFU): - *Bifidobacterium bifidum* (1.2 × 10^9 CFU), - *Lactobacillus acidophilus* (4.2 × 10^9 CFU), - *Streptococcus thermophilus* (4.3 × 10^9 CFU).	The administration of probiotics demonstrated a significant reduction in FPG and HbA1c ($P < 0.05$). No differences between the probiotics group and the placebo group at 12 weeks. No significant changes in any parameter within the placebo group.
Kanazawa et al. **2021**	To investigate how daily intake of synbiotic supplementation affect chronic inflammation, gut microbiota, fecal organic acids, and bacterial translocation in obese patients with T2DM.	Japan	Patients with T2DM, BMI ≥25 kg/m^2, age range 30–80 years **Total**: n = 88 randomized (21 females) **Synbiotics**: n = 44 randomized (13 females; 61.1 ± 11.0 years) **Control**: n = 42 (8 females; 55.9 ± 10.7 years)	Multi-center, parallel-group, randomized, open-label, controlled trial.	Synbiotic supplement twice a day (2.0 g dry powder + 5.0 g GOS - galactooligosaccharides - at breakfast and 1.0 g dry powder + 2.5 g GOS at dinner) for 24 weeks; The control group was told not to take any synbiotics.	Multispecies synbiotic supplement (3 g dry powder/ day): - Lacticaseibacillus paracasei YIT 9029 (3 × 10^8) - *Bifidobacterium breve* YIT 12272 (3 × 10^8) Plus, prebiotic: 7.5 g GOS per day	The synbiotic group showed significantly higher levels of FPG and HbA1c at 12 weeks compared with the control group ($p < 0.05$), and also a significant positive change in HbA1c from baseline to 12 weeks ($p < 0.05$). However, glycemic control at 24 weeks did not differ between the two groups.
Khalili et al. **2019**	To investigate how probiotic supplementation on the glycemic control and SIRT1 and fetuin-A levels in patients with T2DM.	Iran	Patients with T2DM, BMI <35 kg/m^2, age range 30–50 years, not smoking. **Total**: n = 40 (26 females); **Probiotic**: n = 20 (13 females; 43.95 ± 8.14 years); **Placebo**: n = 20 (13 females; 45.00 ± 5.37 years).	Single-center, parallel-group, randomized, double-blind, placebo-controlled trial.	One probiotic supplement/ placebo capsule per day for 8 weeks.	Monospecies probiotic capsule: *L. casei* (10^8 CFU)	FPG, serum insulin levels significantly reduced in the intervention group. The between-group differences were significant. Evaluation of HbA1c after treatment showed no significant reduction in the probiotic group.

Kobyliak et al. **2018**	To investigate how probiotic consumption affect insulin resistance, and, to investigate its effects on other glycemic control-related parameters, anthropomorphic variables and cytokines.	Ukraine	Patients with T2DM **Total**: n = 53 *all analyzed*; **Probiotic**: n = 31 (52.23 ± 1.74 years); **Placebo**: n = 22 (57.18 ± 2.06 years).	Single-center, parallel-group, randomized, double-blind, placebo-controlled trial.	One sachet (10 g) of synbiotic or placebo per day for 8 weeks.	Multispecies synbiotic supplement (10 g dry powder): −14 alive probiotic strains of Lactobacillus - Lactococcus (6 × 10^11 CFU), - Bifidobacterium (1 × 10^11 CFU), - Propionibacterium (3 × 10^11 CFU), - Acetobacter (1 × 10^7 CFU) genera.	HbA1c insignificantly decreased by 0.09% and 0.24%, respectively, in placebo and synbiotic groups. No significant changes for FPG and insulin in both within and between group analyses.
Kobyliak et al. **2020**	To investigate how probiotics with omega-3 PUFA consumption as an adjunction to the standard anti-diabetic therapy affect insulin resistance, glycemic control parameters, β-cells functional activity, anthropometric parameters and markers of a chronic systemic inflammatory response in patients with T2DM.	Ukraine	Patients with T2DM, age range 18 −75 years **Total**: n = 56; *54 analyzed*; **Symbiter Omega**: n = 28 (56.29 ± 11.14 years); **Placebo**: n = 26 (55.73 ± 8.75 years).	Single-center, parallel-group, randomized, double-blind, placebo-controlled trial.	One sachet (10 g) of synbiotic-Omega or placebo per day for 8 weeks.	Multispecies synbiotic supplement (10 g dry powder): - Lactobacillus (1x10^10 CFU), - Bifidobacterium (1x10^10 CFU), - Lactococcus (1x10^9 CFU), - Propionibacterium (1x10^9 CFU), - Acetobacter (1x10^6 CFU), - omega-3 concentration 0.5 −5%	Significant reduction of HbA1c (p = 0.006) and improvement of insulin sensitivity (P = 0.010) after 8 weeks of combined treatment with synbiotic and omega-3. Placebo: insignificant difference for both primary outcomes.
Madempudi et al. **2019**	To investigate how probiotic formulation UB0316 affect glycemic control, body weight, blood lipid profile, and quality of life in patients with T2DM on stable metformin therapy.	India	Patients with T2DM on stable metformin (500 mg) monotherapy, age range 18−65 years, BMI range 23−32 kg/m^2 **Total**: n = 79 (17 females; 52.40 years); **Probiotics**: n = 40 (7 females; 54.10 years) **Placebo**: n = 39 (10 females; 50.60 years)	Multicenter, parallel-group, randomized, double-blind, placebo-controlled trial.	One probiotic supplement/ placebo capsule twice a day (after any principal meal) for 12 weeks.	Multispecies probiotic capsule (100 mg): - *L. salivarius* UBLS22 (3 × 10^10 CFU), - *L. casei* UBLC42 (3 × 10^10 CFU), - *L. plantarum* UBLP40 (3 × 10^10 CFU), - *L. acidophilus* UBLA34 (3 × 10^10 CFU), - *B. breve* UBBr01 (3 × 10^10 CFU), - *B. coagulans* Unique IS2 (3 × 10^10 CFU).	Probiotics significantly reduced HbA1c as compared to placebo (P = 0.0023). Changes recorded in FPG), HOMA-IR, and insulin levels were not significantly altered as compared to placebo.
Mafi et al. **2018**	To investigate how probiotics supplementation affect the metabolic and genetic control in patients with diabetic nephropathy.	Iran	Patients with Diabetic (T1DM, T2DM) nephropathy, age range 45 −85 years **Total:** n = 60 (4 T1DM); **Probiotics**: n = 30 (58.9 ± 8.8 years); **Placebo**: n = 30 (60.9 ± 4.4 years).	Single-center, parallel-group, randomized, double-blind, placebo-controlled trial.	One probiotic supplement/ placebo capsule per day for 12 weeks.	Multispecies probiotic capsule: - *Lactobacillus acidophilus* ZT-L1 (2 × 10^9 CFU), - *Bifidobacterium bifidum* ZT-B1 (2 × 10^9 CFU), - *Lactobacillus reuteri* ZT-Lre (2 × 10^9 CFU), - *Lactobacillus fermentum* ZT-L3 (2 × 10^9 CFU).	FPG (p = 0.01), serum insulin concentration (p = 0.01), and HOMA-IR (p = 0.007) significatively reduced in the group with probiotic supplementation compared with the placebo group. But, HbA1c (p = 0.06) did not significately differ between groups.
Mazloom et al. **2013**	To investigate the effect of probiotics on lipid profile, glycemic control, insulin level, oxidative stress, and inflammatory markers in patients with T2DM.	Iran	Patients with T2DM, age range 25 −65 years, time since diagnoses <15 years. **Total:** n = 34 (26 females); **Probiotics**: n = 16 (55.4 ± 8 years); **Placebo:** n = 18 (51.8 ± 10.2 years).	Single-center, parallel-group, randomized, single-blind, placebo-controlled trial.	One probiotic supplement/ placebo capsule twice-a-day (after any principal meal) for 6 weeks.	Multispecies probiotic capsule (1500 mg): - Lactobacillu acidophilus, - Lactobacillu bulgaricus, - Lactobacillu bifidum, - Lactobacillu casei.	FPG, fasting insulin level, Insulin-sensitivity (quantitative insulin sensitivity check index = QUICKI) and HOMA IR did not change significantly after probiotic treatment (p > 0.05).

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Table 1 (*continued*)

Study ID	Aim	Country	Participants	Methods	Interventions	Probiotics/Synbiotic composition	Outcomes
Mazruei et al. **2019**	To investigate how probiotic (*Bacillus coagulans*) honey intake affect metabolic status in patients with diabetic nephropathy.	Iran	Patients with Diabetic (T1DM, T2DM) nephropathy, age range 45 −85 years **Total:** n = 60; **Probiotic honey:** n = 30 (62.7 ± 9.1 years); **Standard honey:** n = 30 (60.3 ± 8.5 years).	Single-center, parallel-group, randomized, double-blind, placebo-controlled trial.	25 g of probiotic/standard honey per day for 12 weeks.	Monospecies probiotic honey (25 g): - *Bacillus coagulans* T4 (IBRC-N10791) (25 × 10^8 CFU).	Serum insulin levels ($p = 0.004$) and HOMA-IR ($p = 0.002$) decreased after treatment in the group of probiotic honey compared with the control honey. QUICKI improved ($p = 0.004$) in the group of probiotic honey compared with the control honey. Probiotic honey intake had no significant effects on FPG ($p = 0.14$).
Mirmiranpour et al. **2020**	To investigate how probiotic supplement, cinnamon powder, and their combinations affect the glycemic and antioxidant indices in patients with T2DM.	Iran	Patients with T2DM, no insulin use, age range 40–60 years, HbA1c of 7 −8%. **Total**: n = 136 randomized; 115 analyzed (66 females); **Synbiotic**: n = 34; 30 analyzed (15 females; 58.4 ± 11.4 years); **Probiotics**: n = 34; 30 analyzed (16 females; 58.8 ± 12.8 years); **Cinnamon**: n = 33; 28 analyzed (20 females; 59.7 ± 12.2 years); **Control**: n = 33; 27 analyzed (15 females; 58.2 ± 11.8 years).	Single-center, parallel-group, randomized, double-blind, controlled trial.	Each arm has daily consumption of one capsule per day for 12 weeks: 1. Synbiotic = probiotic +0.5 g of powdered cinnamon; 2. Probiotic 3. Cinnamon = 0.5 g of powdered cinnamon; 4. Control = placebo with 0.5 g of rice flour powder.	Monospecies probiotic supplement: *Lactobacillus acidophilus* (1 × 10^8 CFU);	FPG level was decreased significantly in probiotic, cinnamon, and synbiotic supplementation groups compared with control ($P = 0.001$, $P = 0.063$ and $P = 0.001$ respectively). HbA1c in probiotic, cinnamon, and synbiotic groups were also decreased ($P = 0.001$, $P = 0.001$ and $P = 0.04$, respectively).
Mobini et al. **2017**	To investigate how 12-week oral probiotic supplementation affects HbA1c levels in patients with T2DM on insulin therapy.	Sweden	Patients with T2DM on insulin therapy, age range 50–75 years, abdominal obesity (women: waist >80 cm; men: waist >94 cm), BMI range 25–45 kg/m^2 **Total**: n = 46 randomized; 44 analyzed (10 females); **Low-dose probiotic**: n = 16; 15 analyzed (3 females; 66 ± 6 years); **High-dose probiotic**: n = 15; 14 analyzed (3 females; 64 ± 6 years); **Placebo**: n = 15 (4 females; 65 ± 5 years).	Single-center, parallel-group, randomized, double-blind, placebo-controlled trial.	One low/high dose probiotic/placebo stick per day for 12 weeks.	Monospecies probiotic supplement: - Low-dose *L. reuteri* DSM 17938 (1 × 10^8 CFU). - high-dose *L. reuteri* DSM 17938 (1 × 10^8 CFU)	No effects on HbA1c and FPG between the groups at baseline, after 12 weeks of *L. reuteri* supplementation, or at the intermediate time points.
Mohamad-Shahi et al. **2014**	To investigate how probiotic yogurt consumption affect inflammatory factors and glycosylated hemoglobin in patients with T2DM.	Iran	Patients with T2DM, BMI≥25 kg/m^2 **Total:** n = 44; 42 analyzed (32 females); **Conventional yogurt:** n = 22 (49.00 ± 7.08 years); **Probiotic yogurt**: n = 22 (53.00 ± 5.9 years).	Single-center, parallel-group, randomized, double-blind, controlled trial. Blocked randomization.	300 g probiotic/conventional yogurt per for 8 weeks	Conventional yogurt (300 g): - *Lactobacillus delbrueckii* subsp. Bulgaricus - *Streptococcus thermophilus* Probiotic yogurt (300 g): - conventional yogurt - Bifidobacterium lactis Bb12 (DSM 10140) (3.7 × 10^6 CFU) - *Lactobacillus acidophilus* La5 (3.7 × 10^6 CFU)	HbA1c levels were significantly reduced in the intervention group compared with the control group. HbA1c levels were decreased in subjects in the intervention group post-probiotic consumption ($p = 0.032$). However, no significant differences were observed in FPG levels between the two groups at the end of the study.

Mohseni et al. **2018**	To investigate how probiotic supplementation affect wound healing and metabolic status in subjects with diabetic foot ulcer (DFU).	Iran	Patients with grade 3 Diabetic foot ulcer (DFU), age range 40–85 years. **Total:** n = 60 (20 females); **Probiotic:** n = 30 (10 females, 62.6 ± 9.7 years); **Placebo:** n = 30 (10 females, 58.5 ± 11.0 years).	Single-center, parallel-group, randomized, double-blind, placebo-controlled trial.	One probiotic/placebo capsule per day for 12 weeks.	Multispecies probiotic capsule: - *Lactobacillus acidophilus* (2×10^9 CFU/g), - *Lactobacillus casei* (2×10^9 CFU/g), - Lactobacillus Fermentum (2×10^9 CFU/g), - *Bifidobacterium bifidum* (2×10^9 CFU/g).	Probiotic supplementation significantly decreased HbA1c and FPG in the intervention group compared to control group (P = 00.003, P = 00.03, respectively).
Ostadrahimi et al. **2015**	To investigate how probiotic fermented milk (kefir) affect glucose and lipid profile control in patients with T2DM.	Iran	Patients with T2DM, age range 35–65 years. **Total:** n = 60 (26 females) **Probiotic Fermented Milk:** n = 30 (12 females); **Conventional Fermented Milk:** n = 30 (14 females);	Single-center, parallel-group, randomized, double-blind, controlled trial. Block randomization procedure with matched subjects in each block based on sex, age and duration of disease, performed by Random Allocation Software	600 ml probiotics/conventional fermented milk twice a day (at lunch and dinner) for 8 weeks	Convetional femented milk (600 ml): - Streptococcus thermophiles - Lactobacillus bulgaricus Probiotic fermented milk (600 ml): - Streptococcus thermophiles; - *Lactobacillus casei* (6×10^8 CFU); - *Lactobacillus acidophilus* (6×10^8 CFU); - Bifidobacterium lactis (6×10^8 CFU)	FPG not decreased in probiotic fermented milk (P = 0.05). Between-group analysis for FPG was statistically significant (P = 0.01). HbA1c was reduced within probiotic fermented milk group (P = 0.001). Decreased HbA1C between the two groups was significant after adjusting for serum levels of glucose, baseline values of HbA1c and energy intake.
Perraudeau et al. **2020**	To inestigate how enteral exposure to microbes can safely improve clinical measures of glycemic control.	US	Patients with T2DM, BMI range 25–45 kg/m^2. **Total:** n = 76 (59 analyzed); **Placebo:** n = 26 (15 females, 53.7 ± 1.5 years); **WBF-010:** n = 27 (18 females, 49.3 ± 2.3). **WBF-011:** n = 23 (13 females, 51.3 ± 1.7)	Multicenter, parallel-group, randomized, double-blind, placebo-controlled trial.	Three capsules of either placebo, microbiome formulation WBF-010 or microbiome formulations WBF-011, two times a day (within 30 min of morning and evening meals), for 12 weeks.	Multispecies probiotic capsule WBF-010: - *Clostridium beijerinckii*, - *Clostridium butyricum*, - Bifidobacterium infantis Multispecies probiotic capsule WBF-011: - *Akkermansia muciniphila*, - Anaerobutycum hallii, - *Clostridium beijerinckii*, - *Clostridium butyricum*, - Bifidobacterium infantis	FPG and HbA1c were both decreased in the WBF-010 group compared to the placebo group, but not significantly. Compared with the placebo, a statistically significant decrease in FPG and HbA1c was observed in WBF-011 group.
Raygan et al. **2018**	To investigate how probiotic supplementation affect metabolic profiles in diabetic patients with coronary heart disease (CHD).	Iran	Patients with T2DM and coronary heart disease (CHD), age range 40–85 years **Total:** n = 60; **Placebo:** n = 30 (61.8 ± 9.8 years); **Probiotic:** n = 30 (60.7 ± 9.4 years).	Single-center, parallel-group, randomized, double-blind, placebo-controlled trial.	One probiotic/placebo capsule per day for 12 weeks	Multispecies probiotic capsule: - *Bifidobacterium bifidum* (2×10^9 CFU), - *Lactobacillus casei* (2×10^9 CFU), - *Lactobacillus acidophilus* (2×10^9 CFU)	Probiotic supplementation significantly decreased FPG (P = 0.005), serum insulin levels (P = 0.01), HOMA-IR (P = 0.03) and total-/HDL-cholesterol ratio (P = 0.02), and significantly increased QUICKI (P = 0.02) and HDL-cholesterol levels (P = 0.04) compared with the placebo.
Razmpoosh et al. **2019**	To investigate how multi-strain probiotics affect FPG, plasma insulin and lipid profile among patients with T2DM.	Iran	Patients with T2DM, age range 30–75 years. **Total:** n = 68 (60 analyzed); **Placebo:** n = 30 (14 females, 61.3 ± 5.2 years); **Probiotic:** n = 30 (13 females, 58.6 ± 6.5years).	Single-center, parallel-group, randomized, double-blind, placebo-controlled trial.	Two probiotic/placebo capsules per day for 6 weeks	Multispecies probiotic capsule: - *Lactobacillus acidophilus* (2×10^9 CFU), - *Lactobacillus casei* (7×10^9 CFU), - *Lactobacillus rhamnosus* (1.5×10^9 CFU), - Lactobacillus bulgaricus (2×10^8 CFU), - *Bifidobacterium breve* (3×10^10 CFU), - *Bifidobacterium longum* (7×10^9 CFU),	Results show that although there was an increase in insulin levels in the probiotic group, these results were not statistically significant (P > 0.05). There was no statistically significant difference in FPG levels between group analyses at the end of the study (P = 0.12).

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Table 1 (*continued*)

Study ID	Aim	Country	Participants	Methods	Interventions	Probiotics/Synbiotic composition	Outcomes
						- *Streptococcus thermophilus* (1.5×10^9 CFU),	
Rustanti et al. **2022**	To investigate how probiotic consumption affect metabolic profiles and glyceamic modulation of women with T2DM.	Indonesia	Women with T2DM, age range 20 −50 years, BMI <3 kg/m^2 **Total:** n = 40 (36 analyzed); **Placebo:** n = 18 (43.44 ± 4.44 years); **Probiotic:** n = 18 (44.11 ± 3.31 years).	Multicenter, parallel-group, randomized, double-blind, placebo-controlled trial.	1 g skim milk powder only/plus 10^10 CFU/g *L. plantarum* Dad-13, pe day for 11 weeks.	Monospecies probiotic supplement: *Lactobacillus plantarum* (10^10 CFU)	FPG and HbA1c levels dropped considerably in the probiotic group, but changes did not differ substantially between groups (P = 0.393, P = 0.533, respectively).
Sabico et al. **2017**	To investigate how multi-strain probiotics supplementation affect circulating endotoxin levels and other cardiometabolic biomarkers in patients with T2DM.	Saudi Arabia	Patients with T2DM, age range 35 −60 years. **Total completed:** n = 96 (78 analyzed) **Probiotic:** n = 39 (20 females, 48.0 ± 8.3 years) **Placebo:** n = 39 (18 females, 46.6 ± 5.9 years)	Single-center, parallel-group, randomized, double-blind, placebo-controlled trial.	One sachet of probiotic powder/ placebo twice a day (dissolving contents in a glass of water) once before breakfast and before going to bed for 12 weeks.	Multispecies probiotic sachet (total 5×10^9 CFU): - *Bifidobacterium bifidum* W23, - Bifidobacterium lactis W52, - *Lactobacillus acidophilus* W37, - *Lactobacillus brevis* W63, - *Lactobacillus casei* W56, - *Lactobacillus salivarius* W24, - *Lactococcus lactis* W19 - *Lactococcus lactis* W58.	In between-groups analysis, no differences were observed in FPG and insulin. In within-groups analysis, there was significantly higher FPG levels in the placebo group after 3 months of intervention (P = 0.02), while FPG and insulin were significantly lower after 3 months in the probiotics group.
Shakeri et al. **2014**	To investigate how daily consumption of synbiotic bread affect blood lipid profiles of patients with T2DM.	Iran	Patients with T2DM **Total:** n = 78 (63 females) **Synbiotic bread:** n = 26 (52.3 ± 10.8 years) **Probiotic bread group:** n = 26 (52.3 ± 8.2 years) **Control bread:** n = 26 (53.1 ± 7.5 years)	Single-center, parallel-group, randomized, double-blind, controlled trial.	40 g of synbiotic/probiotic/ control bread three times a day for 8 weeks	Monospecies synbiotic/ probiotic bread (40 g): - Lactobacillus sporogenes (4×10^9 CFU) −2,8 g inulin (HPX) as prebiotic	No significant effect of synbiotic bread consumption on FPG (P = 0.06).In between groups analysis, synbiotic and probiotic groups did not differed.
Sheth et al. **2015**	To investigate how synbiotic supplementation affect glycaemia, gut health and Short chain fatty acid (SCFA) levels in pre hypertensive T2DM.	India	Pre-hypertensive adults with T2DM, age range 35−55 years. **Total:** n = 35 **Control:** n = 10 **Synbiotic:** n = 50	Single-center, parallel-group, randomized, open-label, controlled trial.	One product with 1 g freeze dried synbiotic per day (along with meals) for 45 days.	Multispecies synbiotic supplement: - Two species of *Lactobacillus*, *Bifidobacterium* each, - One species of *Streptococcu,* - one species of yeast −300 mg Fructo oligosaccharide as prebiotic	Intervention with synbiotic supplementation resulted in a significant reduction in FBS, HbA1c, by 3.3%, 14%, respectively.
Soleimani et al. **2019**	To investigate how synbiotic supplementation affect metabolic profiles of diabetic patients on hemodialysis.	Iran	Diabetic (T1DM and T2DM) patients on hemodialysis. **Total:** n = 60 (4 T1DM); **Placebo:** n = 30 (9 females, 62.8 ± 14.8 years); **Synbiotic:** n = 30 (9 females, 62.8 ± 12.7 years).	Single-center, parallel-group, randomized, double-blind, placebo-controlled trial.	One synbiotic/placebo capsule per day for 12 weeks	Multispecies synbiotic capsule: - Lactobacillus acidophillus (2×10^9 CFU/g) - *Lactobacillus casei* (2×10^9 CFU/g) - *Bifidobacterium bifidum* (2×10^9 CFU/g) −0.8 g/day of inulin as prebiotic	In between group analysis, patients who received synbiotic supplementation had significantly decreased FPG (P = 0.01), serum insulin levels (P < 0.001) and HbA1c (P = 0.01) compared with the placebo.
Soleimani et al. **2017**	To investigate how probiotic supplementation affect glycemic status, lipid concentration, biomarkers of inflammation, and oxidative stress in diabetic patients on hemodialysis.	Iran	Diabetic (T1DM and T2DM) patients on hemodialysis, age range 18−80 years. **Total:** n = 60 (6 T1DM) **Placebo:** n = 30 (10 females, 59.4 ± 16.0 years); **Probiotic:** n = 30 (10 females, 54.0 ± 16.0 years).	Single-center, parallel-group, randomized, double-blind, placebo-controlled trial.	One probiotic/placebo capsule per day for 12 weeks	Multispecies probiotic capsule: - Lactobacillus acidophillus (2×10^9 CFU/g) - *Lactobacillus casei* (2×10^9 CFU/g) - *Bifidobacterium bifidum* (2×10^9 CFU/g)	In between group analysis, patients who received probiotic supplements compared with placebo had significantly decreased FPG levels (P = 0.006), serum insulin levels (P < 0.001) and HbA1c (P = 0.02).

Tajabadi-Ebrahimi et al. **2014**	To investigate how daily consumption of synbiotic bread affect metabolic status of patients with T2DM.	Iran	Patients with T2DM, age 35−70 years. **Total:** n = 81 **Synbiotic bread:** n = 27 (22 females, 51.3 ± 10.4 years) **Probiotic bread:** n = 27 (22 females, 52.0 ± 7.2 years) **Control bread:** n = 27 (22 females, 53.4 ± 7.5 years)	Single-center, parallel-group, randomized, double-blind, controlled trial. .	40 g of synbiotic/probiotic/ control bread three times a day for 8 weeks	Monospecies synbiotic/ probiotic bread (40 g): - Lactobacillus sporogenes (4×10^9 CFU) −2,8 g inulin (HPX) as prebiotic	Consumption of the synbiotic bread resulted in a significant reduction in serum insulin levels (P = 0.007) compared to the probiotic and control bread, while no significant effect of synbiotic bread consumption on FPG (P = 0.75) was seen compared to the probiotic and control breads.
Tajabadi-Ebrahimi et al. **2017**	To investigate how synbiotic administration affect metabolic profile of overweight patients with T2DM and Coronary Heart Disease (CHD).	Iran	Patients with T2DM and stable CHD, age range 40−85 years, BMI ≥25 kg/m^2. **Total:** n = 60 **Synbiotic:** n = 30 (64.2 ± 12.0 years) **Placebo:** n = 30 (64.0 ± 15.7 years)	Single-center, parallel-group, randomized, double-blind, placebo-controlled trial.	One synbiotic/placebo capsule per day for 8 weeks	Multispecie synbiotic capsule: - *Lactobacillus acidophilus* (2×10^9 CFU/g), - *Lactobacillus casei* (2×10^9 CFU/g), - *Bifidobacterium bifidum* (2×10^9 CFU/g),	Compared with placebo, the probiotic group had lower FPG levels (P = 0.03) and insulin concentrations (P = 0.01).
Toejing et al. **2021**	To investigate how probiotic *L. paracasei* HII01 consumption affect glycemia in T2DM patients.	Thailand	Patients with T2DM, age range 20 −70 years. **Total:** n = 50 (36 analyzed) **Probiotic:** n = 18 (12 females, 63.50 ± 5.94years) **Placebo:** n = 18 (16 females, 61.78 ± 7.73 years)	Single-center, parallel-group, randomized, double-blind, placebo-controlled trial.	One aluminum foil envelope per day (20 min before dinner or sleeping), containing either probiotic or placebo with clean drinking water for 12 weeks	Monospecies probiotic supplement: - *Lactobacillus paracasei* HII01 (5×10^{10} CFU)	FPG level in probiotic within-group analysis significantly reduced compared to baseline (P < 0.05), and also in between group analysis compared with placebo (P < 0.05). No significant difference between the groups regarding HbA1C (P = 0.468).
Tonucci et al. **2017**	To investigate how the intake of fermented goat milk affect glycemic control, lipid profile, inflammation, oxidative stress and fecal SCFA (Short chain fatty acid) in patients with T2DM.	Brazil	patients with T2DM, age range 35 −60 years, BMI <35 kg/m^2 **Total:** n = 50 (45 analyzed); **Conventional fermented milk:** n = 22 (8 females, 50.95 ± 7.20 years); **Probiotic fermented milk:** n = 23 (11 females, 51.83 ± 6.64 years).	Single-center, parallel-group, randomized, double-blind, placebo-controlled trial.	120 g of probiotic/conventional fermented milk per day for 6 weeks	Conventional fermented milk (120 g): - *Streptococcus thermophilus* TA-40 Probiotic fermented milk (120 g): - *Lactobacillus acidophilus* La-5 (10^9 CFU); - *Bifidobacterium animalis* subsp. lactis BB-12 (10^9 CFU)	The consumption of probiotic fermented milk did not significantly decrease HbA1c levels (p = 0.06), but in the between groups analysis, there was a significant difference (P = 0.02). The FPG and insulin concentrations did not change significantly throughout the follow-up period in both groups (P > 0.05).
Valishetti et al. **2022**	To investigate the effect of probiotics as an add-on treatment to metformin in patients with T2DM.	India	Patients with T2DM **Total**: n = 150 (66 females); **Probiotics + Metformin**: n = 75 (34 females; 50.90 ± 6.24 years); **Metformin:** n = 75 (32 females; 51.06 ± 5.42 years)	Single-center, parallel-group, randomized, open-label, controlled trial.	Study group: Tab. Metformin 500 mg twice daily with meals and Cap. Probiotics 1 capsule twice daily with meals for 12 weeks. Control group: Tab. Metformin 500 mg twice daily with meals for 12 weeks.	*No species or strains specified*	Probiotics as an add-on therapy with metformin was observed to lower HbA1c, FPG and postprandial blood glucose levels when compared to metformin alone. No significant changes for FPG and HbA1c in between group analysis (p > 0,05). However, the probiotics study group had fewer reported gastrointestinal adverse effects associated with metformin treatment.

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Table 1 (*continued*)

Study ID	Aim	Country	Participants	Methods	Interventions	Probiotics/Synbiotic composition	Outcomes
Zhang et al. **2020**	To investigate and compare how probiotics + berberine (BBR), berberine-only or probiotics-only, or placebo affect glycaemic haemoglobin (HbA1c) among patients with T2DM.	China	Patients with T2DM, age range 20 –70 years, BMI range 19–35 kg/m^2 **Total:** n = 409 (405 analyzed); **Prob + BBR:** n = 106 (46 females, 53.5 (47–60) years); **Prob alone:** n = 102 (37 females, 54 (45–59) years); **BBR alone**: n = 98 (42 females, 54 (46–61) years); **Plac:** n = 103 (42 females, 54 (46 –61) years);	Multicenter, parallel-group, randomized, double-blind, placebo-controlled trial.	Each arm has daily consumption of supplements for 12 weeks: - (Prob + BBR)= Barberine (0.6 g per 6 pills, twice daily before meal) plus probiotics (4 g per 2 strips of powder, once daily at bedtime) plus Placebo - (BBR)= Barberine (0.6 g per 6 pills, twice daily before meal) plus Placebo - (Plac) = Placebo plus Placebo	Multispecies probiotic sachet (total 5 × 10^10 CFU): - *Bifidobacterium longum* BL88-Onlly - *Bifidobacterium breve* BB8 - Lactococcus gasseri LG23 - *Lactobacillus rhamnosus* LR22 - *Lactobacillus salivarius* LS86 - *Lactobacillus crispatus* LCR15 - *Lactobacillus plantarum* LP-Onlly - *Lactobacillus fermentum* LF33 - *Lactobacillus casei* LC18	The change in HbA1c showed a significant difference between the four treatment groups (P < 0.001): recuction of HbA1c in the Prob + BBR group was significantly greater than that in the Plac group (P < 0.001) and the Prob group (P < 0.001), but no difference was found between those of the Prob + BBR and BBR groups (P = 0.70) or between the Prob and Plac groups (P = 0.53). Similar improvements were found in FPG.

Abbreviations. BMI: Body mass index, T2DM: Type 2 Diabetes Mellitus, T1DM: Type 1 Diabetes Mellitus, CFU: Colony Forming Units, FPG: Fasting Plasma Glucose.

respectively, and p-values of 0.008 and 0.022. Some subgroups (e.g., Malaysia, Austria, Denmark) contained only a single valid estimate. Significant between-subgroup heterogeneity (Value = 31.89, df = 14, p = 0.004) indicated that the effect sizes varied significantly across different countries.

The random-effects meta-regression analysis included 42 observations and revealed that none of the predictors significantly impacted the meta-analyzed effect size. The model's R-squared value was 0.69%, suggesting that the predictors explained less than 1% of the variance in the effect size. The overall model fit was not statistically significant. The test for residual homogeneity was significant (Q_res = chi$^2_{(35)}$ = 136.61, Prob > Q_res <0.001), indicating substantial heterogeneity among the studies.

4.2. Efficacy of probiotics/synbiotics on serum insulin level

The studies included in this meta-analysis were 23 [24,26,27,29,31–37,40,41,44,48–51,54,57–61,64]. As shown in Fig. 4, the overall SMD was −0.273, with a 95% confidence interval ranging from −0.435 to −0.111. The test for the overall effect was statistically significant (z = −3.310, p = 0.001). Heterogeneity measures revealed a Cochran's Q value of 83.28 (degrees of freedom, df = 28, p < 0.001), an H value of 1.725, and an I^2 of 66.4%, with a tau^2 estimate of 0.1243. The sensitivity analysis, which omitted each study one at a time, showed that the combined effect size estimate remained relatively consistent across the studies. The combined effect size ranged from −0.235 to −0.310, indicating that no single study significantly influenced the overall result. After the trim-and-fill procedure, eight imputed simulated studies were added, showing an adjusted SMD of −0.447 (95% CI = −0.624, −0.270). The increase in the magnitude of the effect size in the “observed + imputed” model (trim-and-fill) compared to the “observed” model suggested that the intervention's efficacy may have been underestimated in the published literature, possibly due to publication bias (Supplementary file 2).

The subgroup analysis based on the strain type used in the studies revealed distinct patterns among the subgroups (Supplementary File 3). The multispecies subgroup had a significant SMD of −0.250 with a 95% CI ranging from −0.426 to −0.073. The heterogeneity within this subgroup was moderate, with an I^2 value of 58.8%. Tests for the subgroup effect size were significant (z = −2.772, p = 0.006). The monospecies subgroup showed a non-significant SMD of −0.321 with a 95% CI ranging from −0.660 to 0.018. The heterogeneity within this subgroup was high, with an I^2 value of 75.4%. Tests for the subgroup effect size were not significant (z = −1.857, p = 0.063).

The subgroup analysis involving probiotics and synbiotics interventions also revealed distinct patterns (Supplementary File 3). The probiotic subgroup showed a significant SMD of −0.246 with a 95% CI ranging from −0.386 to −0.107. The heterogeneity within this subgroup was moderate, with an I^2 value of 38.5%. The test for the subgroup effect was significant (z = −3.456, p = 0.001). The synbiotic subgroup exhibited a non-significant SMD of −0.329 with a 95% CI ranging from −0.801 to 0.143. The heterogeneity within this subgroup was high, with an I^2 value of 84.8%. The test for the subgroup effect was not significant (z = −1.365, p = 0.172).

Considering the type of control, the inactive control subgroup showed a significant SMD of −0.296 with a 95% CI ranging from −0.480 to −0.111 (Supplementary File 3). The heterogeneity within this subgroup was high, with an I^2 value of 68.7%. The test for the subgroup effect was significant (z = −3.143, p = 0.002). The subgroup that used active controls exhibited a non-significant SMD of −0.148 with a 95% CI ranging from −0.478 to 0.182. The heterogeneity within this subgroup was moderate, with an I^2 value of

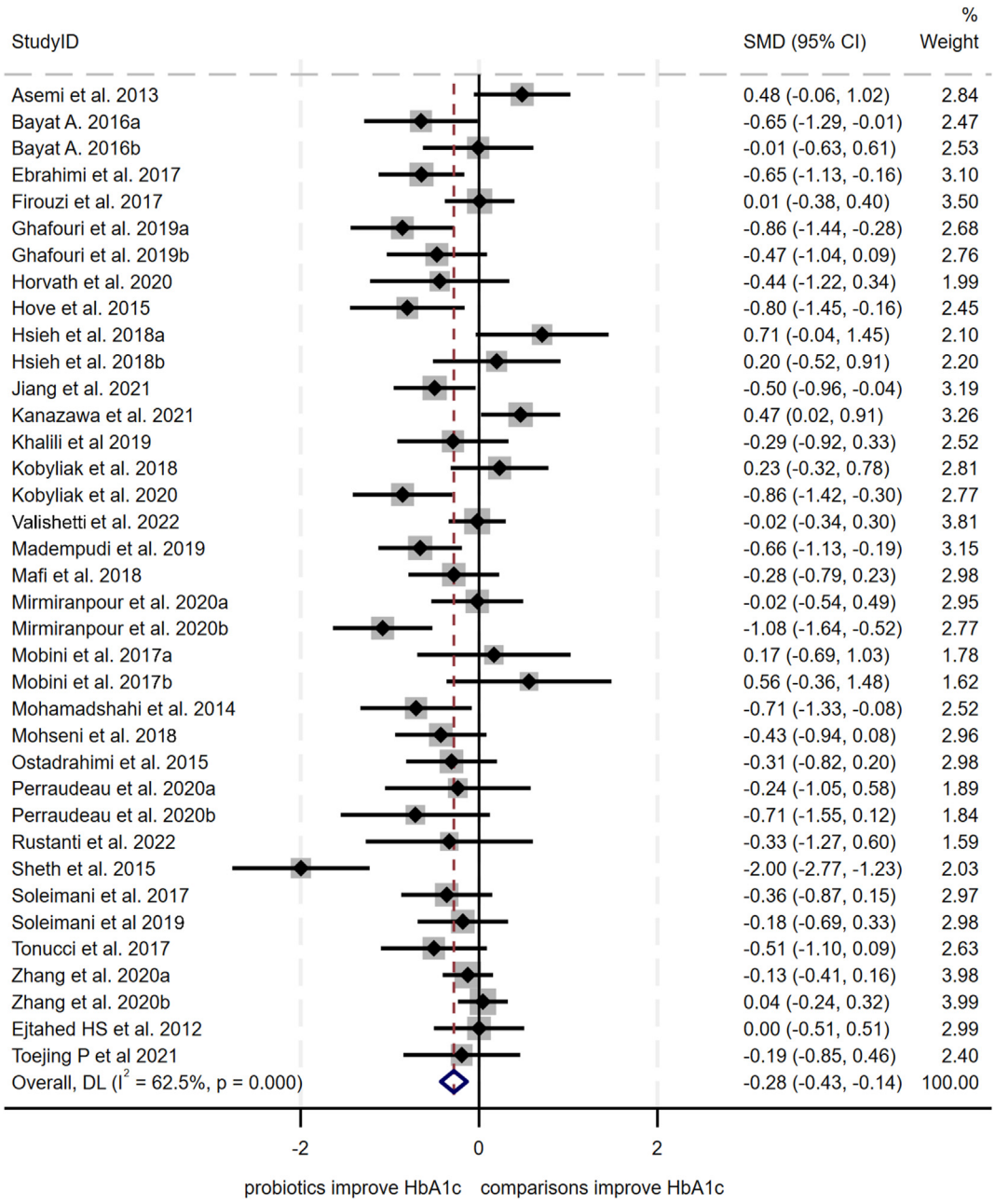

Fig. 2. Meta analysis, outcome: Hb1Ac

50.2%. The test for the subgroup effect was not significant ($z = -0.880$, $p = 0.379$).

Involving the geographical location in the subgroup analysis, the studies conducted in Iran showed a significant SMD of −0.346 with a 95% CI ranging from −0.550 to −0.142. The heterogeneity within this subgroup was high, with an I^2 value of 63.1%. The test for the subgroup effect was significant ($z = -3.331$, $p = 0.001$). Other countries (e.g., Malaysia, Austria, Denmark) contained only one study. Due to this, common-effect models were fitted for these subgroups.

The random-effects meta-regression analysis included 24 observations and revealed that none of the predictors significantly impacted the meta-analyzed effect size. The model's R-squared value was 0.0%, and the overall model fit was not statistically significant. The test for residual homogeneity was significant (Q_res = $chi^2_{(17)}$ = 67.21, Prob > Q_res <0.001), indicating substantial heterogeneity among the studies.

As shown in Supplementary File 4 the majority of the studies (n = 34; 82.9%) presented "Some Concerns" in their overall risk of bias [24–38,40,42,43,45–51,53,55,57–60,62–64], predominantly attributed to the randomization process, deviations from intended interventions, and missing outcome data. The second and latter dimensions were assessed considering "the effect of assignment to the interventions" at baseline (the "intention-to-treat effect"). However, all studies exhibited a "Low Risk" concerning measuring the outcome and selecting the reported result [24–64]. A limited number of studies were categorized with a "High" overall risk of bias (n = 4, 9.7%) [39,52,56,61], which necessitates caution in the interpretation and generalizability of their findings. In general, while the studies included in this review generally demonstrate a

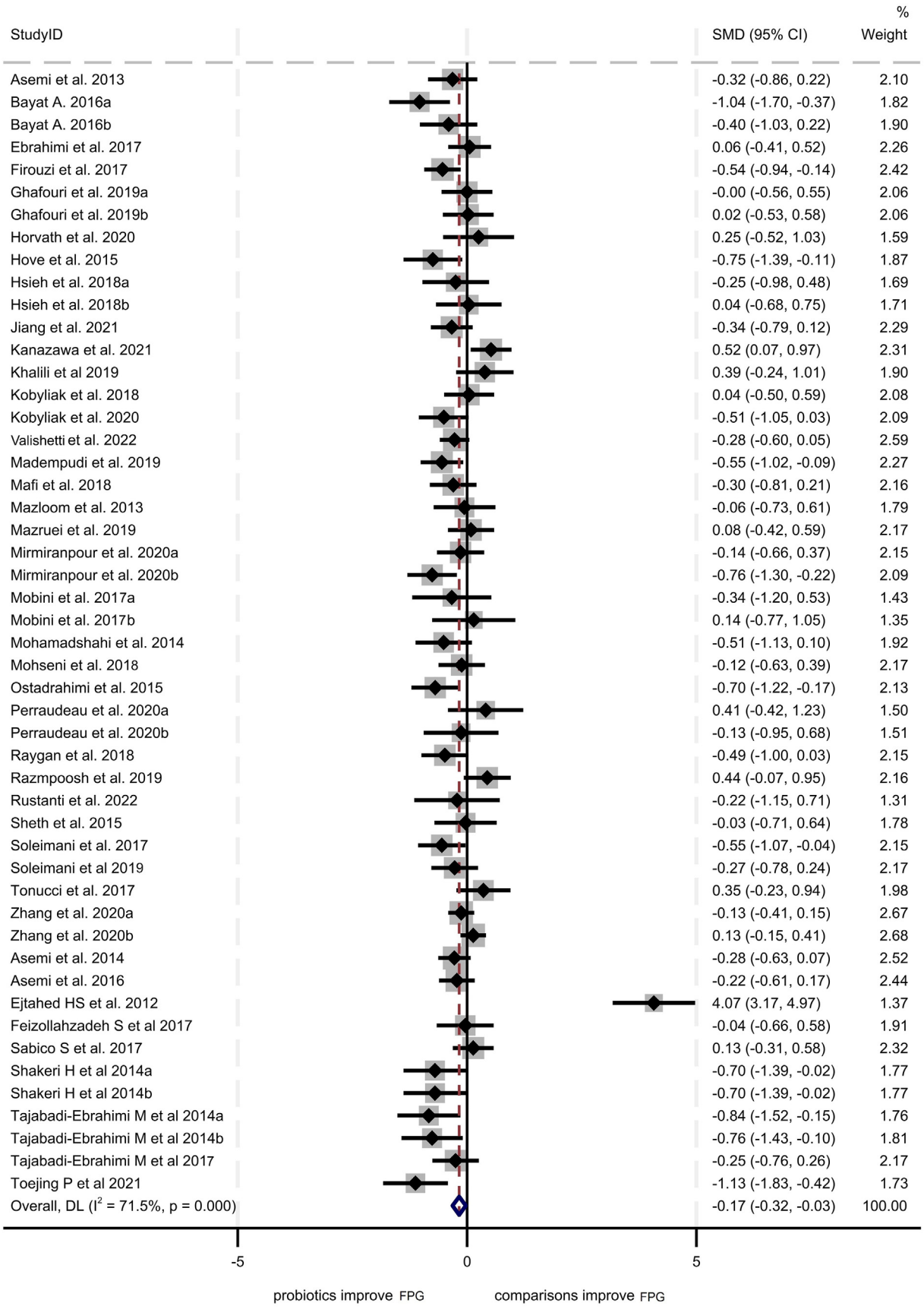

Fig. 3. Meta analysis, outcome: FPG

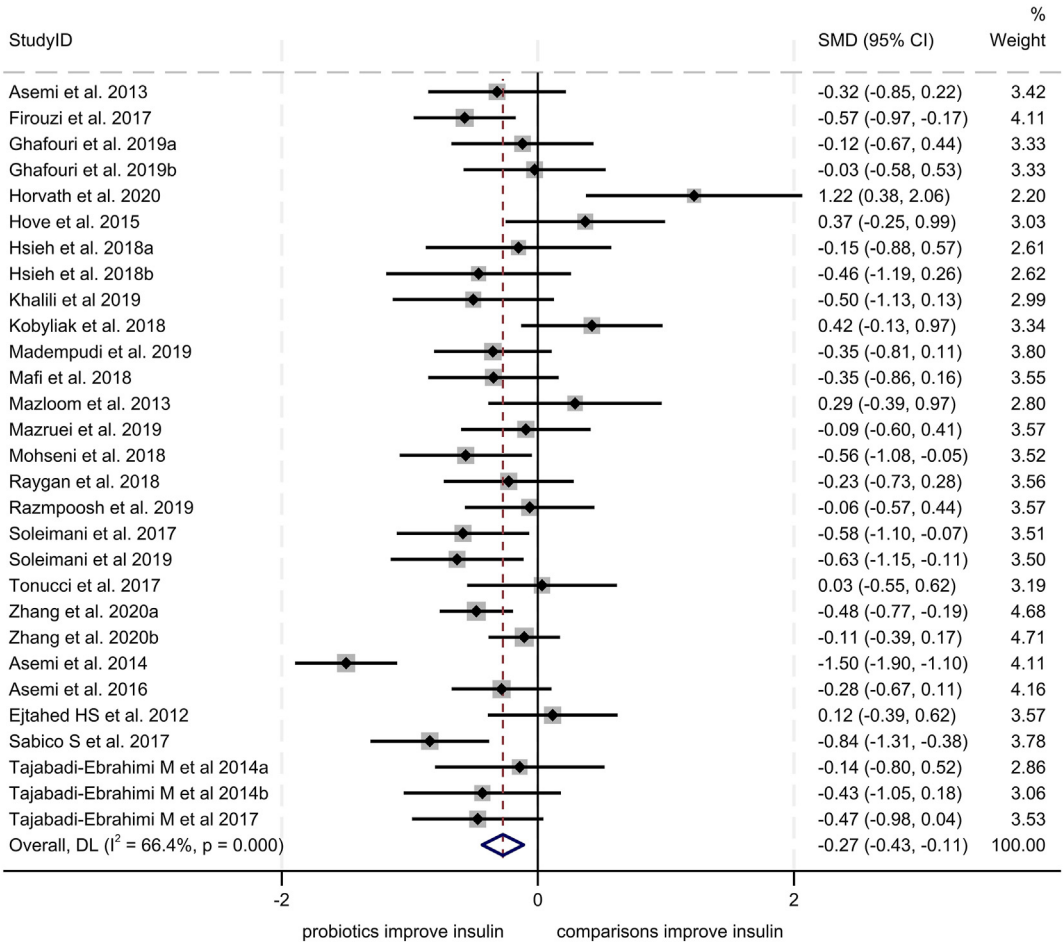

Fig. 4. Meta analysis, outcome: insulin levels

reasonable level of methodological rigor, there are specific domains where caution is advised concerning the randomization process (some concerns = 25 studies; 61%), deviations from intended interventions (some concerns = 20 studies; 49%), and missing outcome data (some concerns = 29 studies; 71%).

5. Discussion

In the contemporary landscape of diabetes research, this systematic review focused on probiotics and synbiotics as potential vanguards in diabetes management in T1DM and T2DM. The results contribute to the growing evidence that underscores the therapeutic potential of microbiota modulation in metabolic diseases, thereby opening new avenues for more targeted and effective treatment strategies [3]. This meta-analysis showed significant improvements across three pivotal diabetes outcomes: HbA1c, FPG, and serum insulin levels, enriching the current understanding of the role of probiotics and synbiotics in diabetes management.

Specifically, for HbA1c, a moderate effect size (SMD = −0.282) was noted. This effect was consistent across various subgroups, including types of strains and the nature of the control group. However, the heterogeneity in the results suggests that the efficacy may vary depending on multiple factors, such as the type of diabetes and the specific strains of probiotics or synbiotics used. These results align with the growing body of literature that highlights the potential benefits of probiotics and synbiotics in diabetes management, particularly in improving glycemic control [3,4,13].

Our meta-analysis's impact on FPG and serum insulin levels was noteworthy, albeit with more variability than HbA1c. While the overall effect size for FPG was small (SMD = −0.175), it was statistically significant. This finding aligns with a previous systematic review by Bock and colleagues [65], which reported a significant decrease in FPG levels by 0.58 mmol/l. For serum insulin levels, our meta-analysis revealed a moderate but statistically significant effect size (SMD = −0.273), indicating a potential role for probiotics and synbiotics in insulin regulation. This result is also consistent with the systematic review by Bock et al. [65], which noted a significant reduction in insulinemia by 10.51 pmol/l. The current study extends this understanding through a comprehensive focus on both types of interventions and by considering a broader range of subgroups that were not previously tested in the literature. This nuanced approach corroborates not only previous findings [65] but also reveals new insights, particularly favoring synbiotics in some cases. Specifically, our subgroup analysis indicated that synbiotics were particularly effective in improving insulin levels, with a moderate but statistically significant effect size (SMD = −0.273 that may be subjected to an underestimation considering the performed trim-and-fill analysis), suggesting that synbiotics may offer additional benefits over probiotics alone in regulating insulin levels.

This study underscored the importance of considering various subgroups when evaluating the efficacy of probiotics and synbiotics in diabetes management. The type of bacterial strain used in interventions generally emerged as a significant determinant. Specifically, certain Lactobacillus strains (e.g., *Lactobacillus acidophilus*, *Lactobacillus casei*) and Bifidobacterium lactis showed pronounced

effects, especially in multispecies formulations confirming preclinical results [66]. This suggests that the therapeutic potential of these add-on interventions might be strain-specific, warranting further exploration into the mechanistic roles of individual strains. In particular, multispecies strains significantly impacted HbA1c levels but were less effective in altering FPG levels. This result suggests that multispecies strains may be more specialized in targeting HbA1c, a marker of long-term glycemic control, than FPG [67]. On the other hand, monospecies strains showed a more consistent effect across different outcomes, indicating their broader applicability in diabetes management. These subgroup results are particularly valuable as they allow for more targeted recommendations and could guide future research in identifying the most effective strains for specific outcomes. However, the absence of specific information on dietary therapy in many studies could act as a confounder, similar to how diabetes medication type has been identified as a potential confounder in previous research [65]. For instance, drug-induced modulation of the gut microbiota could be a mechanism by which medications like metformin exert their therapeutic effects, as observed in studies where metformin use led to a reduction in the relative abundance of beneficial mucin-degrading and short-chain fatty acid-producing bacteria [68]. Most studies' lack of clarity about medication type could have interfered with the results, especially when evaluating outcomes like HbA1c levels. Moreover, baseline HbA1c levels were higher than 8% in only a few studies, and it is well-established that there is an association between baseline HbA1c and the absolute change in HbA1c levels in response to glucose-lowering interventions [69]. For this reason, caution is required when interpreting the pooled results of this study.

Moreover, geographical variations observed in our subgroups could point to the role of environmental, dietary, or genetic factors in modulating the efficacy of these interventions, an area that warrants further investigation. Notably, most of the studies in our meta-analysis were conducted in Iran [24,26–28,30–33,36,37,40,41,43,44,47–50,60,62–64], potentially introducing regional bias.

In light of the findings of this meta-analysis, future directions in this research area should focus on several key aspects. There is a pressing need for studies that employ rigorous methodologies, including randomized controlled trials with larger sample sizes, to validate the efficacy of probiotics and synbiotics in diabetes. Future research should aim to elucidate the mechanisms underlying the observed effects, possibly exploring the role of gut microbiota in metabolic regulation. In addition, given the geographical bias observed in our study, it is crucial to conduct research in diverse populations to assess the generalizability of the results. Lastly, more comprehensive subgroup analyses, considering factors such as medication type, diet, and baseline health markers, could offer invaluable insights into the personalized application of these interventions. Advancing in these directions will corroborate existing findings and pave the way for more targeted and effective therapeutic strategies in diabetes care.

While our meta-analysis offers valuable insights into the potential role of probiotics and synbiotics in diabetes management, it is not without limitations. First, heterogeneity across the included studies, particularly in the randomization process and missing outcome data, raises concerns about the generalizability of our findings. The presence of heterogeneity suggests that the results from different studies might be influenced by varying study designs, participant characteristics, or intervention protocols. To address this, future research should prioritize rigorous study designs with clear inclusion and exclusion criteria, standardized intervention protocols, and consistent outcome measurements. This will not only enhance the reliability and validity of the findings but also facilitate meta-analyses and systematic reviews by reducing inter-study variability. Moreover, addressing these issues will provide a clearer picture of the true effects of probiotics and synbiotics on diabetes outcomes and allow for more accurate comparisons across studies, ultimately leading to more informed clinical and policy decisions.

Second, most of the studies in our analysis were conducted in Iran, which may limit the applicability of the results to other populations with different genetic and environmental factors. The predominance of studies from Iran might limit the results' applicability to diverse global populations with varying genetic and environmental factors. Future studies should aim for a diverse geographical representation to understand how probiotics and synbiotics interventions perform across different populations and environmental conditions. In addition, even though our analyses suggest limited publication bias, the potential for such bias cannot be entirely excluded. Caution is warranted when interpreting the pooled results, as studies with non-significant or negative results might not have been published, potentially skewing the overall effect size.

Third, the baseline HbA1c levels were not consistently reported across studies, making it difficult to assess the absolute change in HbA1c in response to interventions. Consistent reporting of baseline HbA1c levels in future studies will enable a more accurate assessment of the absolute change and allow for better comparisons across studies. The current inconsistency could also mask potential variations in response based on initial glycemic control levels.

Fourth, our meta-analysis did not differentiate between T1DM and T2DM due to the aggregate presentation of results in studies with mixed samples (2.8% of the total sample). The distinction between the two samples could have provided more nuanced insights into the efficacy of the interventions for each type of diabetes. This is a significant limitation as T1DM and T2DM have distinct pathophysiologies, treatment modalities, and potential responses to interventions. As a result, the mechanisms by which probiotics and synbiotics might influence glycemic control could vary between these two types of diabetes. In this regard, future research should be designed to differentiate between the effects of interventions on T1DM and T2DM. In addition, while T1DM is typically prevalent among children and adolescents under 18 years of age, our findings pertain to adult populations due to the inclusion criteria aimed at increasing the internal validity of our results. Therefore, the results from this review do not represent the effects of probiotics and synbiotics on the younger population.

Finally, a significant limitation of our meta-analysis is the omission of several potential confounding variables that are known to influence diabetes outcomes. Specifically, we did not account for factors such as diet, physical activity, medication type, and duration of diabetes. The dietary habits and physical activity levels of the participants could significantly impact metabolic health and glycemic control, thereby influencing the outcomes of interventions involving probiotics and synbiotics. Additionally, the type of diabetes medication used by the participants might modulate the gut microbiota and interact with the effects of the interventions, potentially confounding the results. However, our focus on including only RCTs in the meta-analysis may mitigate some of these concerns, though not entirely. More precisely, by design, RCTs aim to minimize biases by randomly allocating participants to intervention and control groups and ensuring that known and unknown confounding factors are equally distributed between the groups. This random allocation helps in isolating the effect of the intervention from other external factors. Yet, it is important to understand that RCTs are not entirely free from limitations as indicated in the assessment for the risk of bias in the included

studies ("some concerns" related to the randomization process were detected in 61% of the included RCTs). Thus, while RCTs provide a higher level of evidence compared to other study designs, they do not completely eliminate the risk of confounding or other biases. More precisely, another critical element which required attention when interpreting results from this review is the lack of consideration for the role of dietary protein sources, specifically the distinction between animal-based and plant-based proteins, in diabetes prevention and management. Recent research has highlighted the potential benefits of shifting towards plant-based protein sources in terms of improved glycemic control [70]. This aspect should have been integrated into our analysis to offer a more comprehensive perspective on diabetes management.

Future research should comprehensively account for these potential confounding variables and integrate the role of dietary protein sources into their analyses. It is important to note that these oversimplifications were not deliberate choices by the authors but rather reflected the lack of control for these variables in the included primary research studies. This limitation underscores the need for more robust, well-designed primary studies that incorporate a comprehensive analysis of these potential confounding factors to validate and extend the existing results. Future research should aim to control for these variables to elucidate the true impact of probiotics and synbiotics on diabetes outcomes and to avoid drawing misleading conclusions.

Finally, the increasing prevalence of diabetes and emerging evidence supporting the role of probiotics and synbiotics in its management highlight the necessity for this systematic review and meta-analysis. Our findings revealed statistically significant improvements in key diabetes-related outcomes such as HbA1c, FPG, and serum insulin levels, affirming the potential of these interventions as possible add-on therapies in diabetes care that have to be intended as complementary approaches. In this regard, it is crucial to acknowledge that both T1DM and T2DM are multifactorial diseases, and while probiotics and synbiotics show promise as add-on therapies, they are not a standalone solution in diabetes care. The study's in-depth subgroup analyses further enriched the current understanding, showing that the efficacy of these interventions could vary based on factors like the type of strains used and geographical location. For clinicians, these results suggest that incorporating probiotics or synbiotics into treatment plans as complementary might be a viable strategy for enhancing glycemic control, although more tailored research is needed. For researchers, our study highlights the importance of considering multiple variables, including strain types and geographical factors, in future investigations to further clarify the role of probiotics and synbiotics as complementary approaches in diabetes management.

Contributors

RC and IB designed the study. IB, RC, DF, GP and GDA participated in the systematic review of literature and study selection. ML and DA had full access to anonymised individual-participant data and verified the data. RC and IB performed analyses, while DF and DA supervised analyses. RC, IB, DF, ML and DA were involved in writing the first draft of the manuscript. All other authors substantially contributed to the drafting of the work with critical revision for important intellectual content. All authors read and approved the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. RC attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data availability statement

The data underlying this article are available in the article and its online supplementary material.

Conflict of interest

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2024.03.006.

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