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The effect of microbiome-modulating probiotics, prebiotics and synbiotics on glucose homeostasis in type 2 diabetes: A systematic review, meta-analysis, and meta-regression of clinical trials

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ABSTRACT

Aim/hypothesis: The globally escalating diabetes epidemic is responsible for significant morbidity and mortality. Microbiome-modulating nutraceuticals have been investigated for their potential to restore metabolic and floral homeostasis in type 2 diabetic patients

Methods: A systematic review, meta-analyses and meta-regressions were conducted to investigate the effect of probiotics, prebiotics, and synbiotics on various biomarkers of glucose homeostasis based on a multi-database search of clinical trials published through April 10, 2022. Data was pooled using random effects meta-analyses and reported as mean differences with 95% confidence intervals (CIs), followed by univariate linear model meta-regression.

Results: Data from 68 trial comparisons across 58 studies (n = 3835) revealed that, compared to placebo/control group, administration of pro/pre/synbiotics was associated with statistically significant changes in fasting plasma glucose (−12.41 mg/dl [95% CI: −15.94; −8.88], p 0.0001), glycated hemoglobin (−0.38% [95% CI: −0.47; −0.30], p 0.0001), fasting insulin (−1.49 μU/mL [95% CI: −2.12; −0.86], p 0.0001), HOMA-IR (−0.69 [95% CI: −1.16; −0.23], p = 0.0031) and QUICKI (0.0148 [95% CI: 0.0052; 0.0244], p = 0.0025), but not C-peptide (−0.0144 ng/mL [95% CI: −0.2564; −0.2275], p = 0.9069). Age, baseline BMI, baseline biomarker value, pro/prebiotic dosage, trial duration, nutraceutical type, and recruitment region significantly affected the potential of pro/pre/synbiotics use as personalized diabetes adjunct therapy. Lastly, we discuss unexplained observations and directives for future trials, with the aim of maximizing our understanding of how microbiome-modulating nutraceuticals can treat various metabolic diseases

Conclusions: Pro/pre/synbiotic supplementation improved glucose homeostasis in diabetic patients. Our results support their potential use as adjunct therapy for improving glycemia and insulinemia alongside pharmacological therapeutics.

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder associated with hyperglycemia and may be a result of increased resistance or decreased secretion of insulin [1]. Type 2 diabetes (T2D) is the most common type of DM and is attributable to insulin resistance. However, in addition to the endocrine system and the pancreas, its pathology involves other multiorgan systems, contributing to severe complications and an increased risk of cardiovascular disease, hypertension, end-stage renal disease, and obesity [2]. More than 8.5% of United States (US) adults have been diagnosed with T2D, with disproportionate prevalence among individuals above 65 years of age and those with a higher body

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mass index (BMI) [3]. The burden of this disease varies between different populations, and both public healthcare and clinical policies must reflect acknowledgement of this fact to effectively treat and prevent the T2D epidemic that claims more than one million deaths annually [4].

T2D risk is multifactorial and is affected by a plethora of well-cited risk factors, including diet, lifestyle, abdominal obesity, age, family history, hypertension, and dyslipidemia, among others [1,4–6]. Another risk of developing T2D involves the gut microbiome balance and regulation. A decrease in butyrate-producing bacteria, such as *Eubacterium rectale* and *Faecalibacterium prausnitzii*, and an increase in harmful bacteria, such as *Clostridium symbiosum* and *Escherichia coli,* is correlated to gut dysbiosis in T2D patients [5]. It has also been shown that the gut environment of T2D patients is hostile and defensive against stresses that cause oxidative damage and microbes. Based on the gut microbiome, there is a classifier system to categorize T2D patients and differentiate against them with high specificity [5]. Further reading into the pathophysiology of T2D and its relationship to the gut microbiome is provided in Supplementary Table ST1. Modulation and re-regulation of the gut microbiome have thus risen as promising methods to help prevent, manage, and serve as an adjunct therapy in T2D [7].

Probiotics (live microorganisms), prebiotics (fermented ingredients), and synbiotics (a combination of pro/prebiotics) are bioactive agents that present potential benefits to the structure and/or function of the gastrointestinal flora [8]. Recent studies have commented on their potential use as safe next-generation therapeutics for many diseases [9]. Multiple experimental studies on diabetic animal models revealed that specific bacterial strains and indigestible ingredients have the ability to enhance glucose tolerance, decrease lipid levels, stimulate the immune system, and reduce oxidative stress [10]. Therefore, pro/pre/synbiotics adjunction may help overcome some of the challenges posed by existing treatments for T2D, which include chronic adverse effects, high cost of newer medications, patients' low self-efficacy, and the need for life-long adherence to pharmaceuticals [11,12]. Despite many clinical trials demonstrating the benefits of using certain biotics in patients with T2D, different studies have highlighted varying effects of pro/pre/synbiotics. This is because of the range of compositions and concentrations of treatments administered to their subjects, making it difficult to estimate the significant selectivity and specificity of such treatments [13]. To date, there are no quantitative studies that comparatively investigate the efficacy of supplementation with varying combinations of pro/pre/-synbiotics in the management of diabetic patients' glycemic indexes with sufficient depth. This study aims to seal that gap by exploring and assessing current evidence of the effectiveness of pro/pre/synbiotic formulations on various biomarkers of glycemia and insulinemia (Supplementary Table ST2). Our results will add to existing evidence of the ability of such nutraceuticals to complement current treatment regimens, formulate more insightful nutraceutical dosages and mixtures, and further our understanding of how modulation of the gut microbiota can benefit human health.

2. Methods

2.1. Study protocol

This systematic review was conducted in accordance with the Cochrane Collaboration Handbook guidelines and was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA); the PRISMA checklist is available as Supplementary Table ST3. The protocol for this systematic review and meta-analysis has been registered in PROSPERO (No. CRD42022343546).

2.2. Data sources and search strategy

Database searches were conducted across PubMed, Scopus, Web of Science, Embase, and Cochrane. We also searched for gray literature through ClinicalTrials.org and ProQuest Dissertations and Theses. Extensive search strategy and elements are detailed in Supplementary Table ST4. The initial search took place in June 2020 and was updated in April 2022.

2.3. Eligibility criteria and screening

We included all clinical trials reporting the effect of microbiome-modulating probiotics, prebiotics, and synbiotics on glycemia and insulinemia markers, including fasting glucose, HbA1c, fasting insulin, HOMA-IR, QUICKI or C-peptide in patients with T2D. Studies of any duration, published at any time, and with study populations of adults of any age, sex, ethnicity, and from any region worldwide were included. We excluded reviews, conferences, abstracts and proceedings, editorial and non-clinical papers, animal studies, studies administering non-bacterial probiotics or synbiotics, and studies in languages other than English. We further excluded studies focusing on other diseases or type of diabetes, other biomarkers, and those administering non-bacterial pro/synbiotics. All references were imported into Covidence where duplicates were removed, and at least two reviewers screened titles and abstracts and then full texts. Conflicts were resolved by consensus.

2.4. Data extraction

Extraction was performed independently by multiple authors using pre-piloted sheet forms on Microsoft Excel, with disagreements resolved by consensus. Extracted variables are included in Supplementary Table ST5. Nutraceutical type classification was made after careful screening of nutraceutical formulation, irrespective of reported type. Units of measurement were converted and unified for each marker [14]. Missing information for mean age and BMI were imputed using the median of available data for these two variables. Daily pro/prebiotic dosage, if not exclusively specified, was calculated based on nutraceutical formulation and daily frequency; for missing values, these were excluded from the subgroup and regression analysis. Regions of study were classified using World Health Organization (WHO) regional classification. Means ± SDs for values of all six biomarkers at baseline and end-of-trial for both intervention and control groups were extracted, in addition to means ± SDs of intragroup changes (SD_{change}) whenever provided.

2.5. Data analysis

Overall and subgroup random-effects meta-analyses were conducted in R-4.2.1 [15,16] using the meta package to calculate mean differences (MDs), 95% confidence intervals (95% CIs), and p-values ($p < 0.05$ was considered statistically significant), and to produce forest plots for all glycemic indices. Missing mean changes were calculated based on the extracted baseline and end-of-trial values. Correlation coefficients were calculated using published formulae [17], transformed into z-scores ± SD, and pooled using inverse variance weighing. The pooled values were back transformed into pooled correlation coefficients that were used in imputing missing SD_{change} values. I^2 and χ^2 tests were utilized to assess heterogeneity, where $I^2 > 70\%$ and $p < 0.05$ indicated considerable heterogeneity as recommended by Cochrane Handbook [18]. Potential sources of heterogeneity were investigated via subgroup analysis by age group (<55 vs ≥55 years), baseline BMI (<30 vs ≥30 kg/m^2), baseline mean biomarker value, nutraceutical type (probiotics-single or multi-strain, prebiotics, synbiotics-single or multistrain), probiotic/prebiotic dosage (<10^{10} or ≥10^{10} CFU/d, <10 or ≥10 g/d), intervention duration (≤12 or >12 weeks), publication period (≤2015, 2016–2018, or 2019–2021), and WHO regional classification (The Americas, Eastern Mediterranean, Europe, Southeast Asia, or Western Pacific). Meta-regression analyses using continuous variables for age, baseline BMI, baseline biomarker value, trial duration, and year of publication were conducted to assess possible sources of heterogeneity. Trials with a

missing value for any subgroup classification were dropped from the subgroup analysis, except for that of mean age and baseline BMI, which were imputed from available data. Sensitivity analysis for investigating the influence of single studies to the effect size and heterogeneity was also undertaken by removing trials one-by-one and calculating pooled effect estimates and overall interstudy heterogeneity.

2.6. Risk of bias assessment and publication bias assessment

Cochrane risk-of-bias tool version 2 (RoB2) was utilized for scoring and reporting the risk of bias (ROB) associated with individual studies [18]. Factors used to assess ROB included randomization process, allocation concealment, participant recruitment, deviations from intended intervention, missing outcome data, outcome measurement, and selection of reported results. Studies were classified as having either some concerns, high ROB, or low ROB based on assessment of above factors. To assess publication bias, basic and contour-enhanced funnel plots of each trial's effect size against the standard error of the estimate were constructed and visually inspected. Egger's test was conducted to further quantify possible funnel plot asymmetry.

3. Results

3.1. Search results

The electronic search identified 9502 records from various databases, of which 6507 were identified as duplicates and removed by Covidence. Title and abstract screening of 2995 records identified 369 potentially relevant publications for which full texts were retrieved. Of these, 58 records were deemed relevant and extracted, yielding a total of 68 trial comparisons included in this review and meta-analysis. In studies that reported data on different intervention groups, each was

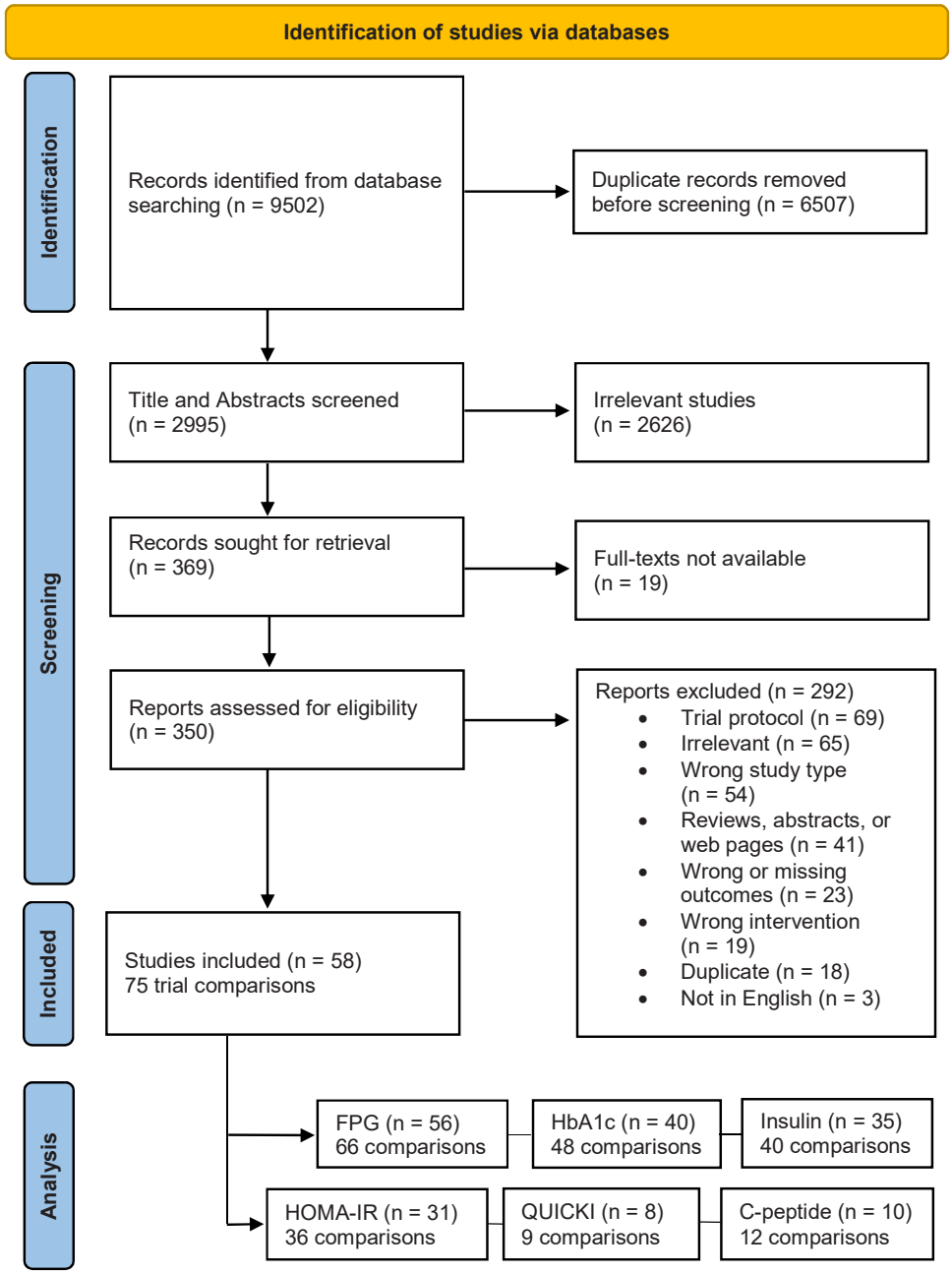

Fig. 1. Flow diagram of the search strategy and included studies and trial comparisons, sorted by biomarker.

considered as a separate trial comparison, linked to the same control and/or baseline. The breakdown of these comparisons according to the respective biomarker (as per analysis) along with the study selection protocol is shown in Fig. 1.

3.2. Trial characteristics

Detailed characteristics of included studies and pooled mean estimates of the meta-analyses according to subgroup are in Table 1 and Table 2, respectively. Of the 68 trial comparisons from 58 studies, 66 comparisons from 56 studies reported FPG [19–73], 48 comparisons from 40 studies reported HbA1c [19–47,53,61–64,68,70–74], 40 comparisons from 35 studies reported on insulin [21,22,25–28,31–35,37,41–43,45,47–61,64,73,75,76], 36 comparisons from 31 studies reported HOMA-IR [22,26–28,31,33–35,41–45,48–61,64,73,75,76], 12 comparisons from 10 studies reported C-peptide [20,22,30,32,42,47,52,54,62,63], and only 9 comparisons from 8 studies reported QUICKI [48,50,51,57,59,60,75,76]. Trial comparisons from a total of 3835 T2D participants, 1944 in intervention groups and 1891 in control/placebo groups, were included. Studies were grouped based on the World Health Organization (WHO) regional classification: 38 (55.9%) of trials were based in the Eastern Mediterranean Region (EMR), 11 (16.2%) in the Western Pacific, 9 (13.2%) in Europe, 6 (8,8%) in Southeast Asia, and 4 (5.9%) in the Americas. The median publication year was 2017 (interquartile range [IQR] 2014–2019, range 2000–2021). The median trial duration was 8 weeks (IQR 6.5–12, range 2–26). The median of intervention group participant age means was 54.1 years (IQR 51.8 – 59.5, range 43.9–71.5), whereas median mean baseline BMI was 29.3 kg/m^2 (IQR 28.0 – 31.0, range 23.2–35.6). A total of 13 (19.1%) trials administered single strain probiotics, 25 (36.8%) administered multistrain or multispecies probiotics, 23 (17.6%) administered prebiotics, 6 (8.8%) administered single strain synbiotics, and 12 (17.6%) administered multistrain/species synbiotics. Of trials where probiotic or prebiotic dosage information was provided, the median total probiotic dosage was 8.0×10^9 colony forming units per day (CFU/d; IQR 2.0×10^9 – 2.2×10^{10}, range 2.0×10^7 – 1.0×10^{12}), while the median prebiotic dosage was 8.4 g per day (g/d; IQR 1.5 – 10.0, range 0.1 – 100).

3.3. Risk of bias and publication bias assessment

Summary of ROB assessment performed using the Cochrane collaboration risk-of-bias tool has been provided in Supplementary Fig. SF1, whereas assessment of individual studies is shown in Supplementary Fig. SF2. Overall, 41 studies (70.7%) were found to have low ROB, 11 (19.0%) had some concerns, while only 6 (10.3%) had a high ROB. In total, 46 studies (79.3%) had a low ROB with respect to the randomization process, while only 10 (17.2%) had some concerns, and 2 (3.4%) had a high ROB. No studies had high ROB in participant recruitment: 52 (89.7%) had low ROB and 6 (10.3%) had some concerns. With respect to both deviations from intended intervention and missing outcome data, the majority of studies (49; 84.5%) had a low ROB, while only 7 (12.1%) had some concerns, and 2 (3.4%) had high ROB. For both outcome measurement and selection of reported results factors, 54 studies (93.1%) had low ROB, while 2 (3.4%) studies had some concerns and high ROB each. With respect to publication bias, only reports on FPG were found to have slightly significant publication bias (Egger test p-value = 0.047), whereas studies of other biomarkers did not (Supplementary Fig. SF3).

3.4. Effect on fasting plasma glucose (FPG)

Pooled mean estimated for the effect of microbiome-modulating nutraceuticals on fasting plasma glucose (FPG) in T2D patients are in Fig. 2A and Table 2. Compared to control or placebo group, pro/pre/synbiotics were found to significantly reduce FPG levels (MD: −12.41 mg/dl [95% CI: −15.94; −8.88]; $p_{effect} < 0.0001$, $I^2 = 94.5$, $p_{het} < 0.0001$) in diabetics (n = 3735). Subgroup analysis showed difference by baseline FPG levels, where compared to groups with mean trial-baseline FPG < 150 mg/dl which had a pooled MD of − 6.53 mg/dl (95% CI: −11.09; −1.97, $p_{effect} = 0.0050$), those with baseline FPG ≥ 150 mg/dl were greatly affected ($p_{subg} = 0.0002$), with an MD of − 19.26 mg/dl (95% CI: −24.24; −14.29, $p_{effect} < 0.0001$). Most meta-analyses showed evidence of significant between-study heterogeneity (I^2 >70%, $p_{het} < 0.0001$). Systematic removal of studies one-by-one did not explain the heterogeneity or cause significant deviations of the results. Meta-regression analyses results are listed in Supplementary Table ST6. FPG appeared to increase significantly with older ages ($p_{reg} = 0.0177$). However, FPG decreased significantly more in trials with higher baseline mean FPG compared to those with lower mean FPG ($p_{reg} < 0.0001$).

3.5. Effect on glycated hemoglobin (HbA1c)

Pooled mean estimated for the effect of microbiome-modulating nutraceuticals on glycated hemoglobin (HbA1c) levels are included in Fig. 2**B** and Table 2. Compared to control/placebo group, pro/pre/synbiotics were found to significantly reduce HbA1c levels (MD: −0.38% [95% CI: −0.47; −0.30]; $p_{effect} < 0.0001$, $I^2 = 95.0\%$, $p_{het} < 0.0001$) in diabetics (n = 2669). Subgroup analysis showed significant differences with respect to mean age, baseline mean HbA1c, nutraceutical type, and intervention duration, but not baseline BMI or pro/prebiotic dosage (Table 2). Younger trial groups (<55 years old; $p_{subg} = 0.0060$), those with higher baseline HbA1c measures (≥7.7%; $p_{subg} = 0.0260$), those receiving multispecies pro/synbiotics and prebiotics ($p_{subg} = 0.0191$), as well as shorter trial durations (<12 weeks; $p_{subg} < 0.0001$) showed greater reductions in HbA1c than their corresponding comparators. Trials administering < 10 g/d prebiotics exhibited borderline significant results ($p_{effect} = 0.0551$). Most meta-analyses indicated evidence of significant between-study heterogeneity (I^2 >70%, $p_{het} < 0.0001$). Systematic removal of studies one-by-one did not explain the heterogeneity or cause significant deviations of the results. Meta-regression analyses results can be found in Supplementary Table ST6. Increase in age significantly increased HbA1c ($p_{reg} = 0.0044$).

3.6. Effect on Fasting Insulin

Pooled mean estimated for the effect of microbiome-modulating nutraceuticals on fasting insulin levels are presented in Fig. 2**C** and Table 2. Compared to control/placebo groups, pro/pre/synbiotics were found to significantly reduce insulin levels (MD: −1.49 μU/mL [95% CI: −2.12; −0.86]; $p_{effect} < 0.0001$, $I^2 = 84.5\%$, $p_{het} < 0.0001$) in diabetics (n = 2480). Subgroup analysis showed differences only by baseline insulin ($p_{subg} = 0.0086$). Trials with baseline insulin of < 11.0 μU/mL did not experience significant change over time following pro/pre/synbiotic administration ($p_{effect} = 0.1153$), whereas those with baseline insulin ≥ 11.0 μU/mL showed greater and statistically significant reductions ($p_{effect} < 0.0001$). Most meta-analyses showed evidence of significant between-study heterogeneity (I^2 >70%, $p_{het} < 0.0001$). Systematic removal of studies one-by-one did not explain the heterogeneity or cause significant deviations of the results. Meta-regression analyses results are listed in Supplementary Table ST6. Fasting insulin appeared to decrease in trials that include patients with greater mean baseline BMI ($p_{reg} = 0.0022$).

3.7. Effect on Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)

Pooled mean estimated for the effect of microbiome-modulating nutraceuticals on insulin resistance (HOMA-IR) levels are included in Fig. 2D and Table 2. Compared to control/placebo group, pro/pre/synbiotics were found to significantly reduce HOMA-IR levels (MD: −0.69 [95% CI: −1.16; −0.23]; $p_{effect} = 0.0031$, $I^2 = 97.6\%$, p_{het}

Table 1
General characteristics of included studies investigating the effect of probiotic, prebiotic or synbiotic supplementation on participants with T2D, ordered by type of nutraceutical.

Type of Nutraceutical	Study Design, Country	Participant* Demographics Size/Sex (n, F/M) Age (Mean ± SD; yrs.) BMI (Mean ± SD; kg/m^2)		Control/Placebo Substance administered	Interventional nutraceutical administered	Control/ Placebo and Intervention Dose x Frequency	Total Period of Intervention/ Study	Author (s), Year
		Control/ Placebo	Intervention					
Probiotic (Single sp.)	PG, RCT (Iran)	n = 20 (7 M/ 13 F) 45.00 ± 5.37 31.94 ± 5.76	n = 20 (7 M/ 13 F) 43.95 ± 8.14 29.50 ± 3.34	NS	*Lactobacillus casei* (10^8 CFU) and maltodextrin	1 capsule/d	8 weeks	[33]
Probiotic (Single sp.)	DB, R, PC (Taiwan)	n = 22 (13 M/ 9 F) 55.77 ± 8.55 27.53 ± 3.15	ADR1 group n = 22 (12 M/ 10 F) 52.32 ± 10.20 28.04 ± 4.29	NS	Live *Lactobacillus reuteri,* ADR-1 (2 ×10^9 CFU/ capsule)	2 × 1 capsules/ d	6 months + 3 months follow-up	[22]
			ADR3 group n = 24 (13 M/ 11 F) 53.88 ± 7.78 28.03 ± 3.88	NS	Heat-killed *Lactobacillus reuteri,* ADR-3 (10^{10} cells/capsule)	2 × 1 capsules/ d	6 months + 3 months follow-up	
Probiotic (Single sp.)	R, DB, C, CT (Iran)	Control Bread n = 27 (5 M/ 22 F) 53.4 ± 7.5 30.5 ± 4.1	Probiotic Bread n = 27 (5 M/ 22 F) 52.0 ± 7.2 29.8 ± 5.7	Similar bread as intervention without prebiotic or probiotic	Bread containing *L. sporogenes* (10^8 CFU/g)	40 × 3 g/d	8 weeks	[57]
Probiotic (Single sp.)	DB, R, PG, PC (Sweden)	T2D and obese patients* n = 15 (11 M/ 4 F) 65 ± 5 30.7 ± 4.0	T2D and obese patients* ; Low Dose group n = 15 (12 M/ 3 F) 66 ± 6 30.6 ± 4.5	Capsule with mildly sweet tasting powder in an aluminum laminate stick pack	Capsule containing low-dose *Lactobacillus reuteri* DSM 17938 (10^8 CFU/ capsule)	1 capsule/d	12 weeks	[36]
			T2D and obese patients* ; High dose group n = 14 (11 M/ 3 F) 64 ± 6 32.3 ± 3.4	Capsule with mildly sweet tasting powder in an aluminum laminate stick pack	Capsule containing high-dose *Lactobacillus reuteri* DSM 17938 (10^{10} CFU/ capsule)	1 capsule/d	12 weeks	
Probiotic (Single sp.)	PG, DB, RCT (Iran)	T2D patients with nephropathy* n = 20 (10 M/ 10 F) 53.6 ± 1.6 26.58 ± 0.73	T2D patients with nephropathy* n = 20 (9 M/ 11 F) 56.90 ± 1.81 26.68 ± 0.71	Conventional soy milk	Probiotic soy milk containing *Lactobacillus plantarum* A7 (2 ×10^7 CFU/mL)	200 mL/d	8 weeks	[65]
Probiotic (Single sp.)	R, DB, PC (Denmark)	n = 18 (18 M) 60.6 ± 5.2 27.7 ± 3.3	n = 23 (23 M) 58.5 ± 7.7 29.2 ± 3.8	Artificially acidified milk	"Cardi04" yogurt containing *Lactobacillus helveticus*	300 × 1 mL/d	3 months	[26]
Probiotic (Single sp.)	DB, PC, RCT (Thailand)	n = 18 (2 M/ 16 F) 61.78 ± 7.73 23.05 ± 2.60	n = 18 (6 M/ 12 F) 63.50 ± 5.94 23.22 ± 2.72	Foil containing 10 mg corn starch	Foil containing *Lacticaseibacillus paracasei* HII01 (5 ×10^{10} CFU)	1/d	3 months	[19]
Probiotic (Single sp.)	R, DB, C, CT (Iran)	n = 26 (5 M/ 21 F) 53.1 ± 7.5 30.6 ± 4.1	n = 26 (5 M/ 21 F) 52.3 ± 8.2 29.5 ± 5.7	Similar bread as intervention without prebiotic or probiotic	Bread containing *Lactobacillus. sporogenes* (10^8 CFU/g)	40 × 3 g/d	8 weeks	[69]
Probiotic (Single sp.)	R, OL (Saudi Arabia)	T2D patients with chronic periodontitis* n = 19 (M>F, Sex NS) 52.88 BMI NR	T2D patients with chronic periodontitis* n = 19 (M>F, Sex NS) 51.87 BMI NR	Root Surface Debridement (RSD)	Probiotic tablets containing *Lactobacillus reuteri* (2 × 10^8 CFU/ tablet)	(C) RSD (I) 2 tablets/d	3-weeks + 2 m follow-up	[74]
Probiotic (Single sp.)	R, PC (Japan)	n = 34 (20 M/ 14 F) 65.0 ± 8.3 24.6 ± 2.6	n = 34 (29 M/ 5 F) 64.0 ± 9.2 24.2 ± 2.6	Fermented milk without probiotics	*Lactobacillus casei* strain Shirota-fermented milk (>4 × 10^{10} cells per bottle)	80 mL/d	16 weeks	[20]
Probiotic (Multi sp.)	DB, PC, RCT (Saudi Arabia)	n = 30 (NS) 46.6 ± 5.9 30.1 ± 5.0	n = 31 (NS) 48.0 ± 8.3 29.4 ± 5.2	Freeze-dried maize starch and maltodextrins	Ecologic®Barrier containing *Bifidobacterium bifidum* W23, *B. lactis* W52, *Lactobacillus acidophilus* W37, *L. brevis* W63,	2 × 2 g/d	6 months	[54]

(*continued on next page*)

Table 1 (*continued*)

Type of Nutraceutical	Study Design, Country	Participant* Demographics Size/Sex (n, F/M) Age (Mean ± SD; yrs.) BMI (Mean ± SD; kg/m^2)		Control/Placebo Substance administered	Interventional nutraceutical administered	Control/ Placebo and Intervention Dose x Frequency	Total Period of Intervention/ Study	Author (s), Year
		Control/ Placebo	Intervention					
					L. casei W56, *L. salivarius* W24, *Lactococcus lactis* W19 and W58 (2.5 ×10^9 CFU/g) with maize starch and maltodextrins			
Probiotic (Multi sp.)	SB, CT (Iran)	n = 18 (I+C=8 M/ 26 F) 51.8 ± 10.2 27.24 ± 2.73	n = 16 (I+C=8 M/26 F) 55.4 ± 8 27.97 ± 3.81	1000 g Magnesium stearate/1500 mg capsule	*Lactobacillus acidophilus, L. bulgaricus, L. bifidum* and *L. casei*	2 × 1500 mg/d	6 weeks	[50]
Probiotic (Multi sp.)	DB, PC, RCT (Saudi Arabia)	n = 39 (21 M/ 18 F) 46.6 ± 5.9 30.1 ± 5.0	n = 39 (19 M/ 20 F) 48.0 ± 8.3 29.4 ± 5.2	Maize starch and maltodextrins	Ecologic®Barrier containing *Bifidobacterium bifidum* W23, *B. lactis* W52, *Lactobacillus acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, *Lactococcus lactis* W19 and W58 (2.5 ×10^9 CFU/g) with maize starch and maltodextrins	2 × 2 g/d	3 months	[52]
Probiotic (Multi sp.)	PC, DB, RCT (Ukraine)	n = 27 (Sex NR) 56.93 ± 9.88 32.28 ± 6.08	n = 28 (Sex NR) 53.82 ± 9.58 31.99 ± 6.02	Organoleptically similar formulation as intervention	Symbiter Forte containing 250 mg smectite gel and *Bifidobacterium* (10^9 CFU/g), *Lactobacillus* (10^9 CFU/g), *Lactococcus* (10^8 CFU/g), *Acetobacter* (10^5 /g) and *Propionibacterium* (10^8 CFU/g) genera	10 × 1 g/d	8 weeks	[63]
Probiotic (Multi sp.)	DB, R, C, CT (Iran)	n = 30 (12 M/ 18 F) 51.00 ± 7.32 29.14 ± 4.30	n = 30 (11 M/ 19 F) 50.87 ± 7.68 28.95 ± 3.65	Conventional yoghurt containing *Lactobacillus bulgaricus, Streptococcus thermophilus*	Probiotic yoghurt containing *Lactobacillus bulgaricus*, *Streptococcus thermophilus*, *Bifidobacterium lactis* Bb12 (1.79–6.04 ×10^6 CFU/g) and *L. acidophilus* La5 (1.85–7.23 × 10^6 CFU/g)	300 g/d	6 weeks	[25]
Probiotic (Multi sp.)	DB, PC, PG, RCT (Ukraine)	n = 26 (NR) 55.73 ± 8.76 35.63 ± 7.76	n = 28 (NR) 56.29 ± 11.14 35.66 ± 5.35	Organoleptically similar formulation as intervention	"Multiprobiotic Symbiter Forte Omega" combination of *Lactobacillus* (10^9 CFU/ g), *Bifidobacterium* (10^9 CFU/g), *Lactococcus* (10^8 CFU/g), *Propionibacterium* (10^8 CFU/g), *Acetobacter* (10^5 CFU/g), 2.0% bentonite, 3.0% wheat germ oil feed, 2.5% flax seed oil and, 2.5% wheat germ with 0.5–5% omega-3	10 × 1 g/d	8 weeks	[62]
Probiotic (Multi sp.)	DB, PG, RCT (Australia)	T2D and Overweight patients* n = 40 (23 M/ 17 F) 65.4 ± 8.4 30.8 ± 3.5	T2D and Overweight patients* n = 40 (25 M/ 15 F) 68.4 ± 7.8 30.6 ± 3.8	Control milk and placebo capsules	Probiotic yoghurt and probiotic capsules, each containing *Lactobacillus acidophilus* La5 and *Bifidobacterium lactis* Bb12 (≥3.0 × 10^9 CFU/ d)	1/d	6 weeks	[34]
			T2D and Overweight patients* n = 37 (25 M/ 12 F) 68.4 ± 8.7 30.2 ± 4.3	Control milk and placebo capsules	Probiotic yoghurt containing *Lactobacillus acidophilus* La5 and *Bifidobacterium lactis* Bb12 (≥3.0 ×10^9 CFU/ d) and placebo capsules	1/d	6 weeks	
			T2D and Overweight	Control milk and placebo capsules	Control milk and probiotic capsules	1/d	6 weeks	

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Table 1 (*continued*)

Type of Nutraceutical	Study Design, Country	Participant* Demographics Size/Sex (n, F/M) Age (Mean ± SD; yrs.) BMI (Mean ± SD; kg/m^2)		Control/Placebo Substance administered	Interventional nutraceutical administered	Control/ Placebo and Intervention Dose x Frequency	Total Period of Intervention/ Study	Author (s), Year
		Control/ Placebo	Intervention					
			patients* n = 29 (23 M/ 16 F) 64.7 ± 7.1 30.8 ± 3.5		containing *Lactobacillus acidophilus* La5 and *Bifidobacterium lactis* Bb12 (≥3.0 ×10^9 CFU/ d)			
Probiotic (Multi sp.)	R, DB, PC, CT (Iran)	n = 30 (16 M/ 14 F) 35–65 (Mean NR) 27.47 ± 3.55	n = 30 (18 M/ 12 F) 35–65 (Mean NR) 28.89 ± 4.77	Conventional fermented milk containing *Streptococcus thermophiles* and *Lactobacillus bulgaricus*	Fermented milk containing *Streptococcus thermophilus*, *Lactobacillus casei* (2–15 × 10^6 CFU/mL), *L. acidophilus* (3–25 × 10^6 CFU/mL) and *Bifidobacterium lactis* (0.5–8 × 10^6 CFU/mL)	300 × 2 mL/d	8 weeks	[68]
Probiotic (Multi sp.)	SC, DB, PC, PG, RCT (Ukraine)	n = 22 (NR) 57.18 ± 2.06 35.65 ± 1.57	n = 31 (NR) 52.23 ± 1.74 34.70 ± 1.29	Organoleptically similar formulation as intervention	Multiprobiotic "Symbiter" combination of *Lactobacillus* + *Lactococcus* (6 ×10^{10} CFU/g), *Bifidobacterium* (1.0x10^{10} CFU/g), *Propionibacterium* (3 ×10^{10} CFU/g), *Acetobacter* (1.0 ×10^6 CFU/g)	10 × 1 g/d	8 weeks	[61]
Probiotic (Multi sp.)	DB, R, PG, PC (Malaysia)	n = 68 (34 M/ 34 F) 54.2 ± 8.3 29.3 ± 5.3 n = 53	n = 68 (31 M/ 37 F) 52.9 ± 9.2 29.2 ± 5.6 n = 47	Organoleptically similar sachets without probiotic	Sachets containing viable microbial cell preparation of *Lactobacillus acidophilus, L. casei, Lactococcus lactis, Bifidobacterium bifidum, B. longum* and *B. infantis* (0.5 ×10^{10} CFU, each) in 250 mL water	2 sachets/d	12 weeks	[27]
Probiotic (Multi sp.)	DB, R, C, CT (Iran)	T2D and overweight patients* n (I+C) = 42 (10 M/32 F) 49.00 ± 7.08 29.22 ± 3.20	T2D and overweight patients* n (I+C) = 42 (10 M/32 F) 53.00 ± 5.9 28.36 ± 4.14	Conventional yoghurt containing Lactobacillus bulgaricus and Streptococcus thermophilus	Probiotic yoghurt containing *Lactobacillus bulgaricus*, *Streptococcus thermophilus*, *Bifidobacterium lactis* Bb12 (~3.7 × 10^6 CFU/ g) and *L. acidophilus* La5 (~3.7 × 10^6 CFU/g)	300 g/d	8 weeks	[24]
Probiotic (Multi sp.)	R, DB, PC, CT (Iran)	n = 27 (Sex NS) 52.59 ± 7.14 30.17 ± 4.23	n = 27 (Sex NS) 50.51 ± 9.82 31.61 ± 6.36	100 mg FOS with lactose/capsule	Freeze-dried *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), and 100 mg FOS with lactose/capsule	1 capsule/d	8 weeks	[43]
Probiotic (Multi sp.)	R, DB, PG, PC (Brazil)	n = 22 (14 M/ 8 F) 50.95 ± 7.20 27.94 ± 4.15	n = 23 (12 M/ 11 F) 51.83 ± 6.64 27.49 ± 3.97	Conventional fermented goat milk with Streptococcus thermophilus TA-40	Probiotic fermented goat milk with *L. acidophilus* La-5 (1.62–77.2 ×10^6 CFU/g) and *Bifidobacterium lactis* BB-12 (1.56–44.5 ×10^7 CFU/g)	120 g/d	6 weeks	[64]
Probiotic (Multi sp.)	R, DB, PC (Iran)	T2D and CHD patients* n = 27 (10 M/ 17 F)) 62.4 ± 13.1 29.9 ± 5.0	T2D and CHD patients* n = 27 (11 M/ 16 F) 64.8 ± 8.3 31.4 ± 5.8	"Barij Essence"	LactoCare® containing *Lactobacillus acidophilus*, *L. reuteri*, *L. fermentum* and *Bifidobacterium bifidum* (2 × 10^9 CFU/g each) and 200 μg/ d selenium yeast	1/d	3 months	[51]
						100 mL/d	4 weeks	[66]

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Table 1 (*continued*)

Type of Nutraceutical	Study Design, Country	Participant* Demographics Size/Sex (n, F/M) Age (Mean ± SD; yrs.) BMI (Mean ± SD; kg/m^2)		Control/Placebo Substance administered	Interventional nutraceutical administered	Control/ Placebo and Intervention Dose x Frequency	Total Period of Intervention/ Study	Author (s), Year
		Control/ Placebo	Intervention					
Probiotic (Multi sp.)	R, DB, CT (Indonesia)	n = 40 (23 M/ 17 F) 53 ± 10 27.74 ± 3.16	n = 40 (25 M/ 15 F) 56 ± 7 27.62 ± 4.58	Conventional yogurt containing Streptococcus thermophilus and Lactobacillus bulgaricus	Probiotic yoghurt containing *Lactobacillus acidophilus* La5 (10^8 CFU/g) and *Bifidobacterium lactis* Bb12 (10^6 CFU/g)			
Probiotic (Multi sp.)	R, DB, PC, CT (Iran)	n = 30 (16 M/ 14 F) 35–65 (Mean NR) 27.47 ± 3.55	n = 30 (18 M/ 12 F) 35–65 (Mean NR) 28.89 ± 4.77	Conventional fermented milk containing Streptococcus thermophiles and Lactobacillus bulgaricus	Fermented milk containing *Streptococcus thermophiles*, *Lactobacillus casei* (2–15 × 10^6 CFU/mL), *L. acidophilus* (3–25 × 10^6 CFU/mL) and *Bifidobacterium lactis* (0.5–8 × 10^6 CFU/mL)	300 × 2 mL/d	8 weeks	[75]
Probiotic (Multi sp.)	R, DB, PC (Iran)	Patients with T2D and CHD* n = 30 (Sex NS) 61.8 ± 9.8 29.3 ± 4.1	Patients with T2D and CHD* n = 27 (Sex NS) 60.7 ± 9.4 30.3 ± 5.2	NS	Supplements containing *Bifidobacterium bifidum* (2 ×10^9 CFU/d), *L. casei* (2 ×10^9 CFU/d), *L. acidophilus* (2 ×10^9 CFU/d)	1/d	3 months	[60]
Probiotic (Multi sp.)	R, DB, PC (Iran)	Patients with T2D and CHD* n = 30 (14 M/ 16 F) 67.3 ± 11.0 28.2 ± 4.9	Patients with T2D and CHD* n = 30 (16 M/ 14 F) 71.5 ± 10.9 29.0 ± 6.2	NS	50,000 IU vitamin D3 every 2 weeks and *Lactobacillus acidophilus*, *L. reuteri*, *L. fermentum* and *Bifidobacterium bifidum* (each 2 × 10^9 CFU/g)	1/d	12 weeks	[76]
Probiotic (Multi sp.)	R, DB, PC (Iran)	n = 30 (16 M/ 14 F) 61.3 ± 5.2 27.2 ± 4.2	n = 30 (17 M/ 13 F) 58.6 ± 6.5 27.7 ± 4.2	Capsules containing FOS and magnesium stearate	Capsules containing 7 viable and freeze-dried strains: *Lactobacillus 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* (3 × 10^{10} CFU), *B. longum* (7 × 10^9 CFU), *Streptococcus thermophilus* (1.5 × 10^9 CFU) and 100 mg FOS with lactose as carrier	2 capsules/d	6 weeks	[49]
Probiotic (Multi sp.)	R, C, PG (Indonesia)	n = Total 108 Age NS BMI NS	n = Total 108 Age NS BMI NS (I1 =HbA1c<7) (I2 =HbA1c>7)	Standard diet	(I1&I2) Standard diet and Kefir containing > 10^7 CFU/g lactic acid bacteria and other NS bacteria families	(I) 200 mL/d	30 days	[32]
Probiotic (Multi sp.)	RCT (China)	T2D pts with nephropathy* n = 34 (12 M/ 22 F) 56.12 ± 8.23 26.44 ± 2.78	T2D pts with nephropathy* n = 43 (15 M/ 27 F) 55.96 ± 8.45 27.51 ± 3.22	Starch	Probiotic supplements containing *Bifidobacterium bifidum*, *Lactobacillus acidophilus*, *Streptococcus thermophilus* (3.2 × 10^9 CFU/d)	1 capsule/d	12 weeks	[70]
Probiotic (Multi sp.)	RCT (Iran)	T2D patients with DN majority (n = 28/30; 93.3%), 2/30 T1D pts* 60.9 ± 4.4 26.3 ± 3.2	T2D patients with DN majority (n = 28/30; 93.3%), 2/30 T1D pts* 58.9 ± 8.8 25.3 ± 2.3	Starch	Probiotic supplement containing *Lactobacillus acidophilus* strain ZT-L1, *Bifidobacterium bifidum* strain ZT-B1, *Lactobacillus reuteri* strain ZT-Lre, and *Lactobacillus fermentum* strain ZT-L3 (8 × 10^9 CFU/d)	1 capsule/d	12 weeks	[31]
Probiotic (Multi sp.)	RCT (Iran)	n = 30 (16 M/14 F) 61.3 ± 5.2 BMI NR	n = 30 (17 M/ 13 F) 57.3 ± 7.5 BMI NR	Magnesium stearate	Probiotic capsules containing *Lactobacillus casei*, *L. acidophilus*, *L. Bulgaricus*, *L. rhamnosus*, *Bifidobacterium Breve*,	1 capsule/d	6 weeks	[55]

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Table 1 (*continued*)

Type of Nutraceutical	Study Design, Country	Participant* Demographics Size/Sex (n, F/M) Age (Mean ± SD; yrs.) BMI (Mean ± SD; kg/m^2)		Control/Placebo Substance administered	Interventional nutraceutical administered	Control/ Placebo and Intervention Dose x Frequency	Total Period of Intervention/ Study	Author (s), Year
		Control/ Placebo	Intervention					
					B. longum, *B. Thermophilus* (10^{10} CFU/d)			
Probiotic (Multi sp.)	R, DB, PC, CT (China)	n = 103 (61/ 42) 54 (IQR 46–61) 26.2 ± 3.43	n = 102 (65/37) 54 (IQR 45–59) 25.6 ± 2.96	"Placebo"	Probiotics containing *Bifidobacterium longum*, *Bifidobacterium breve*, *Lactococcus gasseri*, *Lactobacillus rhamnosus*, *Lactobacillus salivarius*, *Lactobacillus crispatus*, *Lactobacillus plantarum*, *Lactobacillus fermentum*, *Lactobacillus casei* (≥5 × 10^{10} CFU)	8 × 1 g/d	12 weeks	[42]
Probiotic (Sp. NS)	PG, R, CT (Iran)	(C1) C. ficifolia group n = 20 (12 M/ 8 F) 51.8 ± 2.24 28.95 ± 3.34 (C2) Dietary advice group n = 20 (9 M/ 11 F) 46.95 ± 9.34 29.75 ± 4.66	Probiotic yogurt group n = 20 (3 M/ 17 F) 54.1 ± 9.54 28.77 ± 4.59	(1) C. ficifolia (2) Dietary Advice	Probiotic (Species NS) yogurt	(C1) 100 × 1 g/ d (C2) NS (I) 150 × 1 g/d	8 weeks	[72]
Probiotic (Sp. NS)	PG, R, CT (Iran)	(C1) C. ficifolia group n = 20 (12 M/ 8 F) 51.8 ± 2.24 28.95 ± 3.34 (C2) Dietary advice group n = 20 (9 M/ 11 F) 46.95 ± 9.34 29.75 ± 4.66	C. ficifolia and probiotic yogurt group n = 20 (4 M/ 16 F) 53.65 ± 6.99 27.98 ± 4.2	(1) C. ficifolia (2) Dietary Advice	Probiotic (Species NS) yogurt and *C. ficifolia*	(C1) 100 × 1 g/ d (C2) NS (I) 150 × 1 g/ d probiotic yogurt and 100 × 1 g/d C. ficifolia	8 weeks	
Prebiotic	TB, RCT (Iran)	n = 25 (25 F) 49.6 ± 8.4 30·8 ± 5.2	n = 30 (30 F) 49.2 ± 9.6 31·8 ± 4.5	Maltodextrin	Resistant Dextrin	10 g/d	8 weeks	[45]
Prebiotic	RCT (United Kingdom)	Well-controlled T2D patients* n = 15 M 58.1 ± 1.7 28.4 ± 0.9	Well-controlled T2D patients* n = 14 M 56.7 ± 1.3 28 ± 1.1	Maltodextrin	GOS	5.5 g/d	12 weeks	[73]
Prebiotic	TB, RCT (Iran)	n = 25 (25 F) 48.7 ± 9.7 29.9 ± 4.2	n = 27 (27 F) 48.4 ± 8.4 31.9 ± 4.5	Maltodextrin	Oligofructose-enriched Inulin	5 × 2 g/d	8 weeks	[46]
Prebiotic	R, DB, PC, CT (Iran)	T2D and overweight patients* n = 15 (5 M/ 10 F) 51.73 ± 8.44 30.86 ± 5.41	T2D and overweight patients* ; Inulin group n = 15 (8 M/7 F) 51.47 ± 6.46 30.37 ± 2.82	Starch powder and starch capsules	HP inulin, starch capsules as placebo	(C) 6 × 100 mg/ d starch capsules, 5 × 2 g/ d starch powder (I) 2 × 5 g/d HP inulin, 6 × 100 mg starch	45 days	[35]
Prebiotic	DB PC (Iran)	T2D and overweight patients* n = 22 (22 F) 48.61 ± 9.16 29.98 ± 4.01	T2D and overweight patients* n = 27 (27 F) 48.07 ± 8.70 31.43 ± 3.50	Maltodextrin	Oligofructose-enriched chicory inulin enriched	5 × 2 g/d	2 months	[37]
Prebiotic	R, PC, CT (Iran)	n = 33 (33 F) 48.6 ± 7.9 32.0 ± 3.9	n = 32 (32 F) 49.5 ± 8.0 31.5 ± 4.5	Maltodextrin	Resistant dextrin supplement (NUTRIOSE®06)	5 × 2 g/d	8 weeks	[40]
Prebiotic	DB, R, CC (France)	n = 10 (6 M/ 4 F)		Sucrose	Powdered bags containing short-chain	20 g/d	4 × 2 weeks	[21]

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Table 1 (*continued*)

Type of Nutraceutical	Study Design, Country	Participant* Demographics Size/Sex (n, F/M) Age (Mean ± SD; yrs.) BMI (Mean ± SD; kg/m^2)		Control/Placebo Substance administered	Interventional nutraceutical administered	Control/ Placebo and Intervention Dose x Frequency	Total Period of Intervention/ Study	Author (s), Year
		Control/ Placebo	Intervention					
		57 ± 2 28 ± 1	n = 10 (6 M/4 F) 57 ± 2 28 ± 1		Fructose Oligosaccharides (44% 1-kestose, 46% nystose and 10% fructosyl-nystose)			
Prebiotic	TB, RCT (Iran)	n = 32 (32 F) 49.6 ± 8.4 30.8 ± 5.2	n = 28 (28 F) 49.5 ± 8.0 31.5 ± 4.5	Maltodextrin	Hi-Maize 260 (60% resistant starch type 2)	5 × 2 g/d	8 weeks	[39]
Prebiotic	R, PC, CT (Iran)	n = 25 (25 F) 48.7 ± 9.7 29.9 ± 4.2	n = 24 (24 F) 47.8 ± 10.1 31.6 ± 4.1	Maltodextrin	HP inulin	5 × 2 g/d	8 weeks	[41]
Prebiotic	R, DB, PC (Japan)	n = 25 (17 M/ 8 F) 54 ± 12 27.2 ± 4.6	n = 27 (21 M/ 6 F) 55 ± 11 27.9 ± 3.6	Maltodextrin syrup	GOS syrup	10 g/d	4 weeks	[71]
Prebiotic	R, PC, CT (Iran)	n = 22 F 48.61 ± 9.16 29.98 ± 4.01	n = 27 F 48.61 ± 9.16 31.43 ± 3.5	Maltodextrin	Oligofructose-enriched inulin	5 × 2 g/d	9 weeks	[38]
Synbiotic (Single sp.)	R, DB, CC, CT (Iran)	n = 62 (19 M/ 43 F) 53.1 ± 8.7 29.90 ± 5.18	n = 62 (19 M/ 43 F) 53.1 ± 8.7 29.60 ± 4.53	0.38 g isomalt, 0.36 g sorbitol and 0.05 g stevia per 1 g	Heat-resistant *Lactobacillus sporogenes* (1×10^7 CFU), 0.04 g inulin (HPX), 0.38 g isomalt, 0.36 g sorbitol and 0.05 g stevia per 1 g	9 × 3 g/d	6 × 2 weeks	[56]
Synbiotic (Single sp.)	DB, R, CC, CT (Iran)	n = 51 (16 M/ 35 F) 52.9 ± 8.1 30.15 ± 5.07	n = 51 (16 M/ 35 F) 52.9 ± 8.1 29.88 ± 4.77	0.38 g isomalt, 0.36 g sorbitol and 0.05 g stevia per 1 g	*Lactobacillus sporogenes* (1×10^7 CFU), 0.1 g inulin (HPX), 0.05 g beta-carotene with 0.38 g isomalt, 0.36 g sorbitol and 0.05 g stevia per 1 g	9 × 3 g/d	6 × 2 weeks	[58]
Synbiotic (Single sp.)	R, DB, C, CT (Iran)	Control Bread n = 27 (5 M/ 22 F) 53.4 ± 7.5 30.5 ± 4.1	Synbiotic Bread n = 27 (5 M/ 22 F) 51.3 ± 10.4 30.8 ± 5.9	Similar bread as intervention without prebiotic or probiotic	Bread containing viable and heat-resistant *L. sporogenes* (1×10^8 CFU) and 0.07 g inulin / 1 g	40 × 3 g/d	8 weeks	[57]
Synbiotic (Single sp.)	R, DB, C, CT (Iran)	Control Bread (CB) n = 25 (Sex NS) 54.60 ± 0.83 27.04 ± 0.50	Synbiotic group n = 25 (Sex NS) 54.92 ± 1.02 26.39 ± 0.51	Bread containing beta-glucan (3 g) ± lactic acid (4 g)/ 40 g package	Bread containing beta-glucan (3 g), *Bacillus coagulans* (1×10^8 CFU), and inulin (10 g) /40 g package	40 × 3 g/d	8 weeks	[53]
Synbiotic (Single sp.)	R, DB, C, CT (Iran)	Control Bread n = 26 (5 M/ 21 F) 53.4 ± 7.5 30.5 ± 4.1	Synbiotic Bread n = 26 (5 M/ 21 F) 52.3 ± 10.8 30.9 ± 6.0	Similar bread as intervention without prebiotic or probiotic	Bread containing viable and heat-resistant *L. sporogenes* (1×10^8 CFU) and 0.07 g inulin / 1 g	40 × 3 g/d	8 weeks	[69]
Synbiotic (Multi sp.)	SC, R, DB, PC (Iran)	n = 35 (19 M/ 16 F) 58.63 ± 8.06 27.30 ± 3.81	n = 35 (23 M/ 12 F) 58.71 ± 8.20 28.13 ± 3.78	500 mg capsules containing row starch, B group vitamins (1 mg), lactose (0.5 mg), malt-dextrin, magnesium saturate and talc	500 mg Capsules containing *Lactobacillus* family, *Bifidobacterium* family, *Streptococcus thermophilus*, FOS, B group vitamins (1 mg), lactose (0.5 mg), maltodextrin, magnesium saturate and talc	1 × 500 mg/d	9 weeks	[23]
Synbiotic (Multi sp.)	R, DB, PC (Brazil)	T2D patients with TC, TG > 200 mg/dL* n = 9 (9 F) 56,89 ± 1.7 28.21 ± 0.85	T2D patients with TC, TG > 200 mg/dL* n = 9 (9 F) 55.47 ± 2.0 27.70 ± 0.78	Intervention-identical shake without probiotic and oligofructose	Synbiotic shake (23% whey powder, 21% maltodextrin, 15% oatmeal, 9% skim milk powder, 7% texturized soybean protein) containing *Lactobacillus acidophilus* (4×10^8 CFU/100 mL), *Bifidobacterium bifidum* (4×10^8 CFU/100 mL) and 1 g/100 mL oligofructose	100 × 2 mL/ day	30 days	[67]
Synbiotic (Multi sp.)	R, DB, PC (Iran)	T2D and non-obese patients*	T2D and non-obese patients*		2 g sachet containing 1011 spores of	1 × 2 g/d	12 weeks	[48]

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Table 1 (*continued*)

Type of Nutraceutical	Study Design, Country	Participant* Demographics Size/Sex (n, F/M) Age (Mean ± SD; yrs.) BMI (Mean ± SD; kg/m^2)		Control/Placebo Substance administered	Interventional nutraceutical administered	Control/ Placebo and Intervention Dose x Frequency	Total Period of Intervention/ Study	Author (s), Year
		Control/ Placebo	Intervention					
		n = 23 (14 M/ 9 F) 60.39 ± 6.74 28.27 ± 2.54	n = 20 (12 M/ 8 F) 59.10 ± 9.71 27.32 ± 4.34	Sachet containing 2 g starch and 0.7% Natural Orange flavor	*B. Coagulans* Ganeden BC30, 10^{10} CFU *Lactobacillus rhamnosus* GG, 10^9 CFU *Lactobacillus acidophilus*, 500 mg FOS and 0.7% natural orange flavor			
Synbiotic (Multi sp.)	RCT, OL (Japan)	T2D and obese patients* n = 42 (34 M/ 8 F) 55.9 ± 10.7 29.1 ± 3.	T2D and obese patients* n = 44 (31 M/ 13 F) 61.1 ± 11.0 29.5 ± 4.4	NS, no pre/pro/ synbiotics	3 g dry powder (dp) containing *Lacticaseibacillus paracasei* YIT 9029 (3×10^8 CFU), *Bifidobacterium breve* YIT 12272 (3×10^8 CFU), and 7.5 g GOS	2 g dp, 5 g GOS and 1 g dp, 2.5 g GOS /d	24 weeks	[30]
Synbiotic (Multi sp.)	PC, RCT (India)	T2D and pre-hypertensive Adults* n = 34 (10 M/ 24 F) 21.9 ± 2.8 23.1 ± 3.3	FOS group n = 34 (10 M/ 24 F) 21.9 ± 2.8 23.1 ± 3.3	NS	Freeze dried synbiotic product consisting of 2 species of *Lactobacillus* and *Bifidobacterium* each, one species of *Streptococcus* and yeast each, and 300 mg/g FOS	1 g/d	45 days	[29]
Synbiotic (Multi sp.)	R, DB, PC, PG, MC (USA) PP analysis	n = 16 (4 M/ 12 F) 53.5 ± 2 33.5 ± 1.6	WBF-010 group n = 21 (7 M/ 21 F) 51.2 ± 2.1 33.7 ± 1.3	Excipients, NS	Inulin, *Akkermansia muciniphila, Clostridium beijerinckii, Clostridium butyricum*	3 × 2 capsules/ d	12 weeks	[44]
			WBF-011 group n = 21 (9 M/ 12 F) 51.8 ± 1.8 31.7 ± 1.1	Excipients, NS	Inulin, *Akkermansia muciniphila*, *Clostridium beijerinckii*, *Clostridium butyricum*, *Bifidobacterium infantis* and *Anaerobutyricum halli*	3 × 2 capsules/ d	12 weeks	
Synbiotic (Multi sp.)	R, DB, PC, CT (India)	n = 38 (28 M/ 9 F) 50.50 BMI NS	n = 37 (30 M/ 7 F) 53.60 BMI NS	Capsules containing excipient maltodextrin	Multi-strain probiotic UB0316 capsules containing *Lactobacillus salivarius* UBLS22, *L. casei* UBLC42, *L. plantarum* UBLP40, *L. acidophilus* UBLA34, *Bifidobacterium breve* UBBr01 and *B. coagulans* Unique IS2 (total 3×10^{10} CFU) and 100 mg FOS/ capsule	2/d	3 months	[28]
Synbiotic (Multi sp.)	R, DB, PC (Iran)	Overweight, T2D and CHD patients n = 30 (Sex NS) 64.0 ± 11.7 29.6 ± 4.6	Overweight, T2D and CHD patients n = 30 (Sex NS) 64.2 ± 12.0 32.3 ± 6.0	Capsules containing starch	Capsules containing *Lactobacillus acidophilus*, *L. casei*, *Bifidobacterium bifidum* (2×10^9 CFU/g each) and 800 mg inulin	1/d	12 weeks	[59]
Synbiotic (Multi sp.)	R, DB, PC, Pilot (Austria)	Diabesity patients* n = 14 (8 M/ 6 F) 59 34	Diabesity patients* n = 12 (11 M/ 1 F) 61 33	Probiotic matrix containing maize starch, maltodextrins, vegetable protein, potassium chloride, magnesium sulphate, amylases and manganese sulphate and prebiotic matrix containing maltodextrin, natural elderflower flavoring and Gum Arabic	Probiotic Ecologic Barrier® containing *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 *Lc. lactis* W19 (1.5×10^{10} CFU total) and 6 g matrix and 10 g Prebiotic 'Omnilogic Plus' containing 8 g active GOS and FOS, konjac glucomannan, calcium carbonate, zinc citrate 3-hydrate, vitamin D3 (cholecalciferol) and vitamin B2 (riboflavin) and 2 g matrix	1 each/d	6 months	[47]

*All participants are type 2 diabetes patients according to study-specific diagnostic criteria, unless specified; morbidities are mentioned wherever applicable; **T2D**= Type-2 Diabetes; **NS**= Not Specified; **NR**= Not Reported; **Sp.**= Species; **SB**= Single-Blinded; **DB**= Double-Blinded; **TB**= Triple-Blinded; **R**= Randomized; **RCT**= Randomized Controlled Trial; **CC**= Crossover Controlled; **PC**= Placebo-Controlled; **PG**= Parallel Group; **CT**= Clinical Trial; **OL**= Open Label; **MC**= Multi-center; **(I)**= Intervention Group; **(C)**= Control Group; **M**= Male; **F**= Female; **CFU**= Colony Forming Units; **BMI**= Body Mass Index; **CHD**= Coronary Heart Disease; **DN**= Diabetic Nephropathy; **FOS**= Fructooligosaccharides; **GOS**= Galactooligosaccharides.

<0.0001) in diabetics (n = 2255). Although subgroup analysis did not reveal any subgroup differences on the basis of intervention or participant characteristics, it revealed the statistical non-significance of multiple subgroups (Table 2). Of note, no change in HOMA-IR was observed in trials with mean baseline BMI ≥ 30 kg/m^2 (p_{effect} = 0.6000), those receiving ≥ 10^{10} CFU/d probiotic dosage (p_{effect} = 0.6857) or ≥ 10 g/d prebiotic dosage (p_{effect} = 0.1063), and those lasting ≥ 12 weeks (p_{effect} = 0.0530). Further, segregation of trials based on baseline HOMA-IR rendered pooled effects of both subgroups non-significant (p_{effect} = 0.1941 and 0.1038 for <3.50 and ≥3.50, respectively), whereas only multispecies synbiotics were found to have significant effects compared to other nutraceuticals (p_{effect} = 0.0069). Most meta-analyses showed evidence of significant between-study heterogeneity (I^2 >70%, p_{het} <0.0001). Systematic removal of studies one-by-one did not explain the heterogeneity or cause significant deviations of the results. Meta-regression analysis revealed no significant linear relationships (Supplementary Table ST6).

3.8. Effect on Quantitative Insulin-sensitivity Check Index (QUICKI)

Pooled mean estimated for the effect of microbiome-modulating nutraceuticals on quantitative insulin-sensitivity check index (QUICKI) levels are provided in Fig. 2**E** and Table 2. Compared to control/placebo group, pro/synbiotic supplementation marginally increases QUICKI levels (MD: +0.0148 [95% CI: 0.0052; 0.0244]; p_{effect} = 0.0025, I^2 = 80.2%, p_{het} <0.0001) in diabetics (n = 279). Most subgroup analysis interpretation is limited due to a sparsity of trials; nevertheless, statistically significant subgroup differences were found with respect to mean age (p_{subg} = 0.0140), nutraceutical type (p_{subg} = 0.0024), and intervention duration (p_{subg} = 0.0050) (Table 2). Further, younger groups, those with greater baseline BMI or QUICKI, those receiving single-species and high-dose probiotics, and shorter trial durations were shown not to affect QUICKI. Most meta-analyses showed evidence of significant between-study heterogeneity (I^2 >70%, p_{het} <0.0001). Systematic removal of studies one-by-one did not explain the heterogeneity or cause significant deviations of the results. Meta-regression analysis (Supplementary Table ST6**)** revealed that greater increases in QUICKI are observed with increasing age (p_{reg} = 0.0026) and trial duration (p_{reg} = 0.0373).

3.9. Effect on C-peptide

Pooled mean estimated for the effect of microbiome-modulating nutraceuticals on c-peptide levels can be found in Fig. 2F and Table 2. Compared to placebo/control group, pro/synbiotic administration was not associated with any change in C-peptide levels (MD: −0.0144 ng/mL [95% CI: −0.2564; 0.2275]; p_{effect} = 0.9069, I^2 = 96.6%, p_{het} <0.0001) in diabetics (n = 867). Most subgroup analysis interpretation is limited due to the low number of trials, and no statistically significant effects of particular subgroups over others could be identified (Table 2). Most meta-analyses showed evidence of significant between-study heterogeneity (I^2 >70%, p_{het} <0.0001). Systematic removal of studies one-by-one did not explain the heterogeneity or cause significant deviations of the results. Meta-regression analysis revealed that increasing age significantly increased (p_{reg} = 0.0372) and increasing trial duration significantly decreased C-peptide levels (p_{reg} = 0.0358) (Supplementary Table ST6).

4. Discussion

This meta-analysis of 68 trial comparisons from 58 distinct clinical studies systematically reviews, pools, and analyzes the effect of three common types of microbiome-modulating nutraceuticals, namely probiotics, prebiotics and synbiotics, on various indices of glucose and insulin homeostasis among 3835 T2D trial-patients. To our knowledge, this is the most comprehensive and in-depth analysis of the effect of all three types of nutraceuticals on markers of glycemia and insulinemia, and the first to report on the changes observed in C-peptide in T2D patients. Overall evidence from this review indicates that supplementation with such nutraceuticals induced statistically significant absolute reductions of 12.41 mg/dl in fasting glucose, 0.38% in HbA1c, 1.49 μU/mL in fasting insulin, 0.69 in HOMA-IR and an increase of 0.0148 in QUICKI, but no change in C-peptide.

These estimates are encouraging overall. Firstly, the reduction observed in HbA1c, the most widely-accepted standard for glucose control measurement, was both statistically (p_{effect} < 0.0001) and clinically significant, as per the threshold for clinical significance (≥0.3%) recommended for anti-diabetic drug development by the U.S. Food and Drug Administration (FDA) [77]. However, the overall effect estimate of − 0.38% (95% CI: −0.47; −0.30) represents the pooled effect of all three nutraceutical types reviewed in this study, whereas the potential effect of prebiotics only (−0.45%; assessed by 12 trials) and multispecies synbiotics only (−0.57%; assessed by 8 trials) on HbA1c were slightly more promising. Although also statistically significant, the effects on HbA1c from multispecies probiotics (MD: −0.28% [95% CI: −0.36; −0.19], p_{effect} <0.0001) did not reach this threshold of clinical significance. This is consistent with the findings of two recent meta-analyses by Zhang et al.[78] and Ding et al.[79] who report overall MDs of − 0.19% (95% CI: −0.32; −0.07; 19 trials) and − 0.19% (95% CI: −0.37; −0.00; 10 trials) following use of only probiotics (single *and* multispecies) in patients with T2D.

Interestingly, this clinical shortcoming of probiotics is also seen in another meta-analysis by Dai et al. [80] who report a mean reduction of 0.12% (95 CI: −0.20; −0.04; 4 trials) in HbA1c following multispecies probiotic supplementation in patients with diabetic kidney disease, a feared complication of T2D. Cao et al. [81] and Rittiphairoj et al. [82] report similar effects (−0.19% [95% CI: −0.31; −0.07] and −0.17% [95% CI: −0.37; 0,02], respectively) of only probiotics compared to placebo in a pooled population of patients with impaired glucose control, perhaps highlighting that therapeutic mechanisms of probiotics apply similarly across multiple hyperglycemic disorders. Cao et al. [81] also report that, in contrast to probiotics, synbiotics appear to have almost three times the effect (−0.64% [95% CI: −1.03; −0.26]) in reducing HbA1c levels across the same pooled population, hinting at their clinical potential compared to probiotics only; however, this subgroup analysis was performed on a small population.

Supplementary Table ST7 summarizes the different nutraceuticals studied based on order of efficacy on various biomarkers. Results of pre/synbiotic supplementation from a meta-analysis by Mahboobi et al. [83] align with our findings from the same nutraceutical types, adding to the evidence that pre/synbiotic supplementation perform better with respect to HbA1c levels than probiotics alone. A more complete comparison is the change of − 2.17 mmol/mol (95% CI: −4.37; 0.03), or approximately − 0.2% in HbA1c, reported by Bock et al. [84] in trials supplementing pro/pre/synbiotics for at least 12 weeks in a large cohort of 717 T2D patients; however, this was not statistically significant. The authors attribute this change to the reduced follow-up period (<12 weeks) of other included trials where a significant pooled change in FPG

Table 2
Pooled mean estimates of random effects meta-analysis on glycemic markers overall and by subgroups based on age, baseline BMI, mean baseline biomarker value, type of nutraceutical, pro/prebiotic dosage, intervention duration, publication period, and region.

Biomarker or Variable	Subgroups	Number of trials	Number of participants		Mean Difference in biomarker (95% CI)		p-value for random effect	p-value for subgroup differences	Heterogeneity measures	
			Intervention	Control					p-value	I^2 (%)
FBG (mg/dl)	Overall	66	1894	1841	-12.41	(−15.94; −8.88)	< 0.0001	–	< 0.0001	94.5
Age group	< 55 years old	34	1043	1011	-14.53	(−19.62; −10.20)	< 0.0001	0.2323	< 0.0001	96.4
	≥ 55 years old	32	851	830	-10.20	(−15.16; −5.24)	< 0.0001		< 0.0001	85.0
Baseline BMI	< 30 kg/m^2	41	1230	1205	-13.98	(−18.72; −9.23)	< 0.0001	0.3385	< 0.0001	92.5
	≥ 30 kg/m^2	25	664	636	-10.42	(−15.94; −4.90)	0.0002		< 0.0001	93.1
Baseline FPG	< 150 mg/dl	33	1026	1025	-6.53	(−11.09; −1.97)	0.0050	**0.0002**	< 0.0001	93.9
	≥ 150 mg/dl	30	822	772	-19.26	(−24.24; −14.29)	< 0.0001		< 0.0001	85.6
Nutraceutical type	Probiotic-single	12	267	261	-11.23	(−20.72; −1.75)	0.0202	0.9788	0.0064	57.8
	Probiotic-multiple	24	820	810	-10.83	(−15.25; −6.41)	< 0.0001		< 0.0001	85.1
	Prebiotics	12	282	268	-13.98	(−23.43; −4.53)	0.0037		< 0.0001	96.4
	Synbiotic-single	6	211	211	**-12.75**	**(−30.01; 4.51)**	**0.1477**		< 0.0001	96.2
	Synbiotic-multiple	12	314	291	-13.04	(−24.41; −1.67)	0.0245		< 0.0001	92.2
Probiotic dosage$^{\Phi}$	< 10^{10} CFU/d	26	809	801	-11.02	(−17.27; −4.76)	0.0006	0.7770	< 0.0001	91.0
	≥ 10^{10} CFU/d	22	664	651	-9.75	(−15.90; −3.60)	0.0019		< 0.0001	90.0
Prebiotic dosage$^{\Phi}$	< 10 g/d	14	417	405	**-10.80**	**(−23.30; 1.69)**	**0.0902**	0.4272	< 000.01	97.1
	≥ 10 g/d	13	313	298	-16.31	(−21.64; −10.98)	< 0.0001		< 0.0001	83.1
Intervention duration	< 12 weeks	42	1163	1126	-14.07	(−19.32; −8.83)	< 0.0001	0.2445	< 0.0001	95.1
	≥ 12 weeks	24	731	715	-9.51	(−15.13; −3.89)	0.0009		< 0.0001	88.0
Publication Period	≤ 2015	23	656	640	-12.65	(−20.55; −4.76)	0.0017	0.9695	< 0.0001	95.6
	2016–2018	24	650	633	-13.03	(−18.68; −7.38)	< 0.0001		< 0.0001	95.8
	2019–2021	19	588	568	-11.91	(−18.74; −5.08)	0.0006		< 0.0001	80.2
WHO regional classification	The Americas	4	74	63	**-7.90**	**(−27.60; 11.80)**	**0.4319**	**< 0.0001**	< 0.0001	93.0
	Eastern Mediterranean	36	1015	1006	-19.92	(−26.39; −13.46)	< 0.0001		< 0.0001	95.3
	Europe	8	175	162	**-5.38**	**(−17.61; 6.85)**	**0.3887**		< 0.0001	91.1
	Southeast Asia	6	171	155	-17.01	(−25.88; −8.13)	0.0002		**0.3215**	**14.5**
	Western Pacific	16	459	455	**0.43**	**(−2.57; 3.43)**	**0.7797**		0.0022	63.6
HbA1c (%)	Overall	48	1363	1306	-0.38	(−0.47; −0.30)	< 0.0001	–	< 0.0001	95.0
Age group	< 55 years old	27	774	743	-0.50	(−0.62; −0.38)	< 0.0001	**0.0060**	< 0.0001	96.3
	≥ 55 years old	21	589	563	-0.26	(−0.38; −0.14)	< 0.0001		< 0.0001	93.2
Baseline BMI	< 30 kg/m^2	28	839	810	-0.35	(−0.45; −0.26)	< 0.0001	0.4494	< 0.0001	92.5
	≥ 30 kg/m^2	20	524	496	-0.42	(−0.56; −0.27)	< 0.0001		< 0.0001	93.5
Baseline HbA1c	< 7.7%	20	593	593	-0.27	(−0.35; −0.19)	< 0.0001	**0.0260**	< 0.0001	87.9
	≥ 7.7%	26	724	669	-0.47	(−0.63; −0.31)	< 0.0001		< 0.0001	97.1
Nutraceutical type	Probiotic-single	10	210	204	**-0.12**	**(−0.24; 0.00)**	**0.0514**	**0.0191**	0.0015	66.3
	Probiotic-multiple	16	601	590	-0.28	(−0.36; −0.19)	< 0.0001		< 0.0001	84.7
	Prebiotics	12	282	268	-0.45	(−0.69; −0.21)	0.0002		< 0.0001	96.0
	Synbiotic-single	2	45	45	**-0.92**	**(−2.19; 0.35)**	**0.1570**		< 0.0001	97.7
	Synbiotic-multiple	8	225	199	-0.57	(−0.93; −0.20)	0.0022		< 0.0001	91.3
Probiotic dosage$^{\Phi}$	< 10^{10} CFU/d	16	480	473	-0.24	(−0.32; −0.16)	< 0.0001	0.3496	< 0.0001	91.9
	≥ 10^{10} CFU/d	15	478	462	-0.33	(−0.49; −0.16)	0.00001		< 0.0001	87.5
Prebiotic dosage$^{\Phi}$	< 10 g/d	6	162	147	**-0.48**	**(−0.98 l 0.01)**	**0.0551**	0.8098	< 0.0001	97.5
	≥ 10 g/d	13	313	298	-0.55	(−0.73; −0.36)	< 0.0001		< 0.0001	96.6
Intervention duration	< 12 weeks	30	819	780	-0.50	(−0.61; −0.40)	< 0.0001	**< 0.0001**	< 0.0001	95.7
	≥ 12 weeks	18	544	526	-0.12	(−0.21; −0.03)	0.0075		< 0.0001	77.9
Publication Period	≤ 2015	16	463	445	-0.44	(−0.60; −0.29)	< 0.0001	0.5707	< 0.0001	94.7
	2016–2018	18	446	429	-0.37	(−0.56; −0.18)	0.0001		< 0.0001	96.6
	2019–2021	14	454	432	-0.34	(−0.47; −0.20)	< 0.0001		< 0.0001	93.6
WHO regional classification	The Americas	3	65	54	-0.68	(−1.11; −0.24)	0.0024	**< 0.0001**	**0.6703**	**0.0**
	Eastern Mediterranean	20	509	496	-0.57	(−0.70; −0.43)	< 0.0001		< 0.0001	97.1
	Europe	9	175	162	**-0.08**	**(−0.19; 0.03)**	**0.1540**		0.0010	69.5
	Southeast Asia	5	155	139	-0.58	(−0.95; −0.21)	0.0020		< 0.0001	98.1
	Western Pacific	11	459	455	-0.17	(−0.31; −0.03)	0.0152		< 0.0001	83.9
Insulin (μU/mL)	Overall	40	1245	1235	-1.49	(−2.12; −0.86)	< 0.0001	–	< 0.0001	84.5
Age group	< 55 years old	24	827	810	-1.74	(−2.49; −0.99)	< 0.0001	0.3285	< 0.0001	87.1
	≥ 55 years old	16	418	425	**-0.97**	**(−2.33; 0.39)**	**0.1623**		< 0.0001	77.6
Baseline BMI	< 30 kg/m^2	26	849	851	-1.11	(−1.93; −0.29)	0.0083	0.1368	< 0.0001	85.1
	≥ 30 kg/m^2	14	396	384	-2.20	(−3.38; 1.02)	0.0003		< 0.0001	84.3
Baseline Insulin	< 11.0 μU/mL	18	660	662	**-0.60**	**(−1.34; 0.15)**	**0.1153**	**0.0086**	< 0.0001	88.3
	≥ 11.0 μU/mL	20	539	529	-2.64	(−3.96; −1.31)	< 0.0001		< 0.0001	79.0
Nutraceutical type	Probiotic-single	5	116	109	**-0.96**	**(−3.33; 1.41)**	**0.4284**	0.6836	**0.1240**	**44.7**
	Probiotic-multiple	19	685	686	-1.27	(−2.28; −0.26)	0.0138		< 0.0001	80.4
	Prebiotics	6	120	112	**-0.75**	**(−4.18; 2.68)**	**0.6679**		< 0.0001	88.8
	Synbiotic-single	4	165	165	-2.54	(−4.24; −0.83)	0.0035		< 0.0001	95.8

(*continued on next page*)

Table 2 (*continued*)

Biomarker or Variable	Subgroups	Number of trials	Number of participants		Mean Difference in biomarker (95% CI)		p-value for random effect	p-value for subgroup differences	Heterogeneity measures	
			Intervention	Control					p-value	I^2 (%)
	Synbiotic-multiple	6	159	163	-2.04	(−3.96; −0.13)	0.0359		0.0047	70.4
Probiotic dosage$^{\Phi}$	$< 10^{10}$ CFU/d	19	638	640	-1.43	(−2.27; −0.59)	0.0008	0.6169	< 0.0001	86.2
	$\geq 10^{10}$ CFU/d	13	448	447	-1.86	(−3.30; −0.41)	0.0117		< 0.0001	82.8
Prebiotic dosage$^{\Phi}$	< 10 g/d	10	313	318	-2.13	(−3.24; −1.03)	0.0002	0.8290	< 0.0001	82.0
	≥ 10 g/d	6	131	122	-1.92	(−3.53; −0.30)	0.0198		< 0.0001	81.9
Intervention duration	< 12 weeks	24	723	710	-1.38	(−2.08; −0.67)	0.0001	0.7677	< 0.0001	86.9
	≥ 12 weeks	16	522	525	**-1.65**	**(−3.32; 0.02)**	**0.0530**		< 0.0001	80.1
Publication Period	≤ 2015	15	464	461	-1.19	(−2.00; −0.38)	0.0042	0.6975	< 0.0001	83.7
	2016–2018	15	444	433	-1.96	(−3.57; −0.35)	0.0170		< 0.0001	82.0
	2019–2021	10	337	341	**-1.25**	**(−2.63; 0.14)**	**0.0773**		< 0.0001	77.9
WHO regional classification	The Americas	1	23	22	**0.95**	**(−1.24; 3.14)**	**> 0.05**	**0.0004**	–	–
	Eastern Mediterranean	24	708	703	-2.19	(−2.87; −1.52)	< 0.0001		< 0.0001	81.5
	Europe	5	90	79	**1.75**	**(−3.86; 7.36)**	**0.5406**		< 0.0001	91.2
	Southeast Asia	3	112	111	**-0.03**	**(−1.03; 0.96)**	**0.9474**		**0.2914**	**18.9**
	Western Pacific	7	312	320	**-0.10**	**(−1.66; 1.46)**	**0.8976**		0.0063	66.6
HOMA-IR	Overall	36	1136	1119	-0.69	(−1.16; −0.23)	0.0031	–	< 0.0001	97.6
Age group	< 55 years old	22	740	718	-0.75	(−1.41; −0.09)	0.0259	0.6092	< 0.0001	98.5
	≥ 55 years old	14	396	401	-0.54	(−0.97; −0.11)	0.0131		< 0.0001	80.6
Baseline BMI	< 30 kg/m^2	22	737	739	-0.92	(−1.35; −0.48)	< 0.0001	0.3675	< 0.0001	94.3
	≥ 30 kg/m^2	14	399	380	**-0.33**	**(−1.54; 0.89)**	**0.6000**		< 0.0001	98.8
Baseline HOMA-IR	< 3.50	15	473	483	**-0.28**	**(−0.71; 0.14)**	**0.1941**	0.2089	< 0.0001	96.6
	≥ 3.50	17	575	560	**-1.40**	**(−3.08; 0.29)**	**0.1038**		< 0.0001	98.4
Nutraceutical type	Probiotic-single	5	116	109	**-0.85**	**(−1.96; 0.26)**	**0.1332**	0.9881	**0.1332**	**47.4**
	Probiotic-multiple	16	583	584	**-0.55**	**(−1.75; 0.66)**	**0.3739**		< 0.0001	98.3
	Prebiotics	4	83	80	**-0.88**	**(−1.98; 0.22)**	**0.1182**		< 0.0001	91.6
	Synbiotic-single	4	165	165	**-0.92**	**(−1.87; 0.03)**	**0.0573**		< 0.0001	98.7
	Synbiotic-multiple	7	189	181	-0.94	(−1.62; −0.26)	0.0069		0.0047	89.8
Probiotic dosage$^{\Phi}$	$< 10^{10}$ CFU/d	16	536	538	-0.80	(−1.26; −0.35)	0.0005	0.5433	< 0.0001	95.1
	$\geq 10^{10}$ CFU/d	14	478	465	**-0.31**	**(−1.83; 1.20)**	**0.6857**		< 0.0001	98.8
Prebiotic dosage$^{\Phi}$	< 10 g/d	9	301	304	-1.04	(−1.57; −0.50)	0.0001	0.7729	< 0.0001	87.7
	≥ 10 g/d	4	94	90	**-0.86**	**(−1.91; 0.18)**	**0.1063**		< 0.0001	95.8
Intervention duration	< 12 weeks	24	723	710	-1.38	(−2.08; −0.67)	0.0001	0.7677	< 0.0001	86.9
	≥ 12 weeks	16	522	525	**-1.65**	**(−3.32; 0.02)**	**0.0530**		< 0.0001	80.1
Publication Period	≤ 2015	11	352	349	-0.84	(−1.32; −0.36)	0.0006	0.8251	< 0.0001	92.0
	2016–2018	14	417	411	**-0.33**	**(−2.07; 1.41)**	**0.7091**		< 0.0001	98.3
	2019–2021	11	367	359	-0.70	(−1.25; −0.16)	0.0108		< 0.0001	91.3
WHO regional classification	The Americas	3	65	54	**-0.36**	**(−0.97; 0.26)**	**0.2537**	**0.0007**	0.0140	76.6
	Eastern Mediterranean	22	651	651	-1.34	(−1.81; −0.86)	< 0.0001		< 0.0001	96.3
	Europe	3	68	55	**1.59**	**(−2.73; 5.91)**	**0.4700**		< 0.0001	99.3
	Southeast Asia	1	40	39	**-0.30**	**(−0.94; 0.34)**	**> 0.05**		–	–
	Western Pacific	7	312	320	**0.11**	**(−0.39; 0.60)**	**0.6752**		0.0005	75.0
QUICKI	Overall	9	237	242	0.0148	(0.0052; 0.0244)	0.0025	–	< 0.0001	80.2
Age group	< 55 years old	2	54	54	**-0.0020**	**(−0.0177; 0.0137)**	**0.8026**	**0.0140**	0.1030	62.4
	≥ 55 years old	7	183	188	0.0204	(0.0118; 0.0289)	< 0.0001		0.0045	68.1
Baseline BMI	< 30 kg/m^2	5	123	128	0.0192	(0.0085; 0.0299)	0.0005	0.4015	**0.1759**	**36.8**
	≥ 30 kg/m^2	4	114	114	**0.0113**	**(−0.0038; 0.0263)**	**0.1425**		< 0.0001	91.1
Baseline QUICKI	< 3.50	5	123	128	0.0211	(0.0106; 0.0315)	< 0.0001	0.1953	0.0187	66.2
	≥ 3.50	4	114	114	**0.0091**	**(−0.0058; 0.0240)**	**0.2315**		0.0010	81.5
Nutraceutical type	Probiotic-single	1	27	27	**0.0060**	**(−0.0076; 0.0196)**	**> 0.05**	**0.0024**	–	–
	Probiotic-multiple	5	133	135	0.0227	(0.0107; 0.0348)	0.0002		0.0171	66.8
	Prebiotics	–	–	–	–	–	–		–	–
	Synbiotic-single	1	27	27	**-0.0100**	**(−0.0236; 0.0036)**	**> 0.05**		–	–
	Synbiotic-multiple	2	50	53	0.0159	(0.0063; 0.0255)	0.0001		**0.1786**	**44.7**
Probiotic dosage$^{\Phi}$	$< 10^{10}$ CFU/d	4	117	117	0.0204	(0.0090; 0.0318)	0.0005	0.1830	0.0003	84.0
	$\geq 10^{10}$ CFU/d	4	104	107	**0.0064**	**(−0.0109; 0.0236)**	**0.4694**		0.0079	74.7
Prebiotic dosage$^{\Phi}$	< 10 g/d	3	77	80	**0.0084**	**(−0.0075; 0.0243)**	**0.2996**	–	0.0022	83.7
	≥ 10 g/d	–	–	–	–	–	–		–	–
	< 12 weeks	4	100	102	**-0.0003**		**0.9587**	**0.0050**	**0.3064**	**17.0**

(*continued on next page*)

Table 2 (*continued*)

Biomarker or Variable	Subgroups	Number of trials	Number of participants		Mean Difference in biomarker (95% CI)		p-value for random effect	p-value for subgroup differences	Heterogeneity measures	
			Intervention	Control					p-value	I^2 (%)
Intervention duration						**(−0.0116; 0.0110)**				
	≥ 12 weeks	5	137	140	0.0206	(0.0113; 0.0300)	< 0.0001		0.0009	78.7
Publication Period	≤ 2015	3	70	72	**0.0001**	**(−0.0138; 0.0140)**	**0.9898**	**0.0013**	**0.1693**	**43.7**
	2016–2018	4	120	120	0.0158	(0.0063; 0.0253)	0.0011		**0.1126**	**49.8**
	2019–2021	2	47	50	0.0277	(0.0206; 0.0348)	< 0.0001		**0.2565**	**22.3**
WHO regional classification	The Americas	–	–	–	–	–	–	–	–	–
	Eastern Mediterranean	9	237	242	0.0148	(0.0052; 0.0244)	0.0025		< 0.0001	80.2
	Europe	–	–	–	–	–	–		–	–
	Southeast Asia	–	–	–	–	–	–		–	–
	Western Pacific	–	–	–	–	–	–		–	–
C-peptide (ng/mL)	Overall	12	436	431	**-0.0144**	**(−0.2564; 0.2275)**	**0.9069**	–	< 0.0001	96.6
Age group	< 55 years old	6	246	243	**-0.2550**	**(−0.5442; 0.0342)**	**0.0840**	**0.0289**	< 0.0001	83.1
	≥ 55 years old	6	190	188	**0.2774**	**(−0.1027; 0.6574)**	**0.1526**		< 0.0001	98.1
Baseline BMI	< 30 kg/m^2	9	368	364	**-0.0427**	**(−0.3046; 0.2191)**	**0.7490**	0.7059	< 0.0001	97.5
	≥ 30 kg/m^2	3	68	67	**0.1585**	**(−0.8530; 1.1699)**	**0.7588**		0.0139	76.6
Baseline C-peptide	< 2 ng/mL	5	176	175	**0.0729**	**(−0.4671; 0.3212)**	**0.7168**	0.4930	< 0.0001	98.6
	≥ 2 ng/mL	5	214	212	**0.1000**	**(−0.1984; 0.3984)**	**0.5113**		**0.0568**	**56.4**
Nutraceutical type	Probiotic-single	3	80	78	**-0.0467**	**(−0.1730; 0.0796)**	**0.4686**	0.8350	**0.5846**	**0.0**
	Probiotic-multiple	7	300	297	**0.0167**	**(−0.3031; 0.3364)**	**0.9186**		< 0.0001	98.0
	Prebiotics	–	–	–	–	–	–		–	–
	Synbiotic-single	–	–	–	–	–	–		–	–
	Synbiotic-multiple	2	56	56	**-1.7074**	**(−8.5278; 5.1131)**	**0.6237**		**0.2016**	**38.7**
Probiotic dosage$^{\Phi}$	< 10^{10} CFU/d	6	208	205	**-0.0794**	**(−0.4547; 0.2959)**	**0.6783**		< 0.0001	98.3
	≥ 10^{10} CFU/d	6	228	226	**0.0303**	**(−0.1623;0.2228)**	**0.7580**		0.0206	62.5
Prebiotic dosage$^{\Phi}$	< 10 g/d	2	56	56	**-1.7074**	**(−8.5278; 5.1131)**	**0.6237**	–	0.2016	38.7
	≥ 10 g/d	–	–	–	–	–	–		–	–
Intervention duration	< 12 weeks	4	128	125	**0.3017**	**(−0.1503; 0.7537)**	**0.1908**	0.0706	< 0.0001	98.8
	≥ 12 weeks	8	308	306	**-0.1582**	**(−0.3685; 0.0520)**	**0.1402**		0.0001	76.3
Publication Period	≤ 2015	2	72	72	**0.3906**	**(−0.2072; 0.9884)**	**0.2003**	0.2900	< 0.0001	99.6
	2016–2018	4	119	17	**-0.1019**	**(−0.2500; 0.0462)**	**0.1775**		**0.2684**	**23.8**
	2019–2021	6	245	242	**-0.1061**	**(−0.5447; 0.3325)**	**0.6355**		< 0.0001	82.3
WHO regional classification	The Americas	–	–	–	–	–	–	0.1068	–	–
	Eastern Mediterranean	2	70	69	-0.7242	(−1.4083; −0.0401)	0.0380		0.0390	76.5
	Europe	3	68	67	**0.1585**	**(−0.8530; 1.1699)**	**0.7588**		0.0139	76.6
	Southeast Asia	2	72	72	**0.3906**	**(−0.2072; 0.9884)**	**0.2003**		< 0.0001	99.6
	Western Pacific	5	226	223	**0.0253**	**(−0.0899; 0.1404)**	**0.6671**		**0.2035**	**32.7**

Values for age, baseline BMI and baseline biomarker values were selected by using the corresponding mean values of the intervention group of the respective trials as sorting variable; in the few cases where mean age or baseline BMI value was not specified, the values were imputed from the pooled median of the remaining trials. $^{\Phi}$Subgroups for probiotic and prebiotic dosage are provided independently of each other; the bacterial (probiotic) dose and the prebiotic dose of synbiotics were reported in their respective subgroups, without discrimination of nutraceutical type. **Abbreviations:** FPG = fasting plasma glucose; HbA1c = glycated hemoglobin; HOMA-IR = homeostatic model for insulin resistance; QUICKI = quantitative insulin sensitivity check index; CFU/d= colony forming units per day; g/d= grams per day; WHO= world health organization; BMI= body mass index. **Bold text** has been used to highlight non-significant subgroup random effect MDs, 95% CIs, and p-values, significant subgroup difference p-values, and non-significant heterogeneity score p-values.

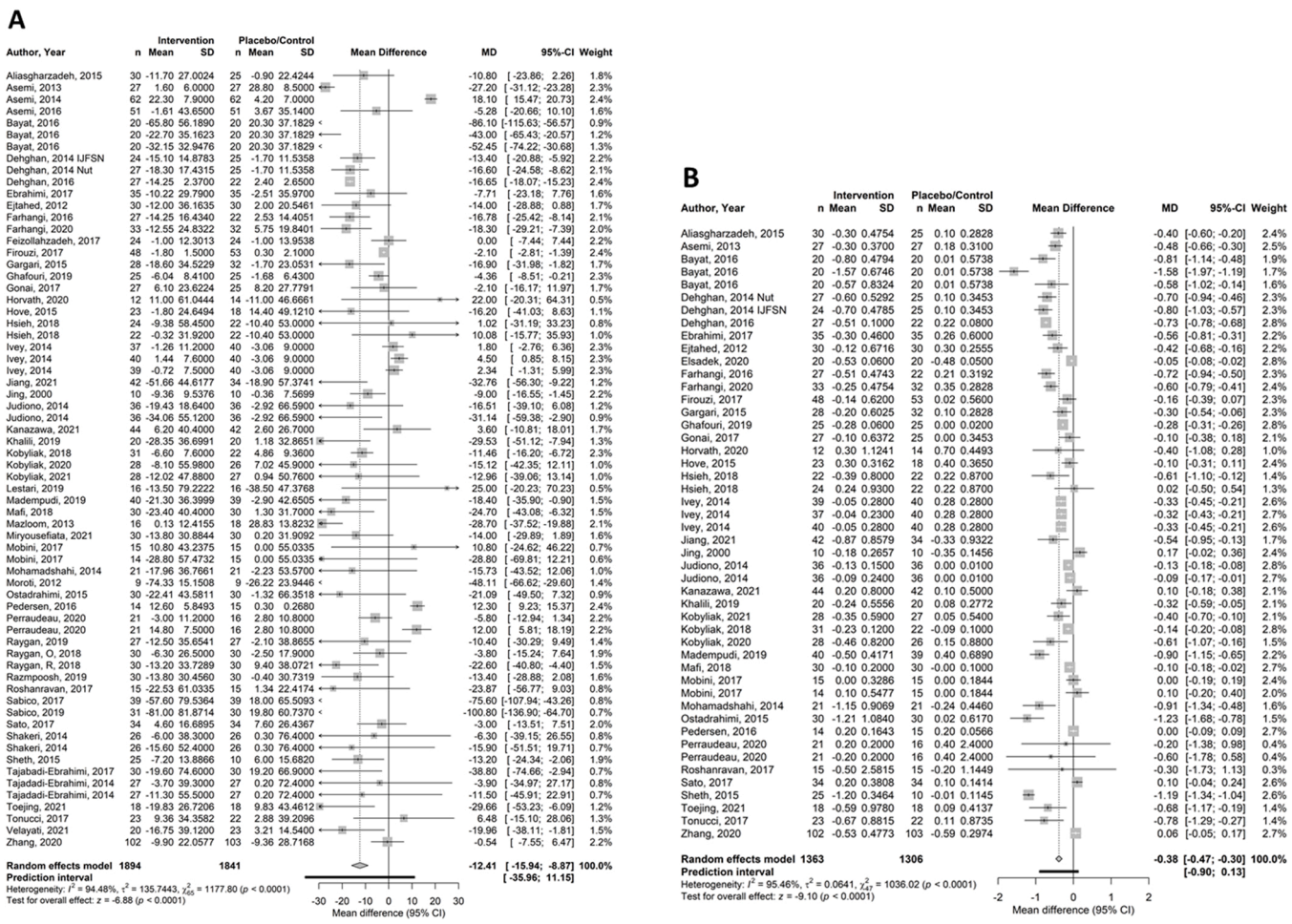

Fig. 2. Forest plot following meta-analysis (random effects model, inverse-variance weights) of the absolute changes in (A) fasting plasma glucose (mg/dl), (B) glycated hemoglobin (%), (C) insulin (μU/mL), (D) HOMA-IR, (E) QUICKI, and (F) C-peptide (ng/mL) levels from individual studies investigating the effects of pro/pre/synbiotics on patients with type 2 diabetes. Pooled overall effect estimate is represented by grey diamond and quantified by pooled mean difference and 95% CI and statistical significance is represented by z-score and p-value; interstudy heterogeneity is quantified via I^2, τ^2, χ^2 and p-value.

was found. Here we must add that our review did not discriminate among studies with ≤ 12 weeks follow-up duration in our overall analysis for HbA1c. Further subgroup analysis based on trial duration, however, revealed an association that may address the concerns of Bock et al. [84]. In our analysis, the overall effect among studies with a duration < 12 weeks had the significantly greater ($p_{subg} < 0.0001$) effect (MD: −0.50% [95% CI: −0.61; −0.40]) compared to trials lasting ≥ 12 weeks (MD: −0.12% [95% CI: −0.21; −0.03]), the latter being comparable to the findings of Bock et al. [84]. Zhang et al. [78] report that trials lasting > 8 weeks (MD: −0.26% [95% CI: −0.50; −0.03]) had a greater mean effect on HbA1c levels than those lasting ≤ 8 weeks (MD: −0.15% [95% CI: −0.15; 0.01]), but this subgroup difference was not significant ($p_{subg} = 0.67$). This reveals that a potential optimum duration of nutraceutical supplementation (for an effect on HbA1c) might be between 8 and 12 weeks and calls for speculation concerning why increasingly greater follow-up durations do not necessarily correlate to better outcomes.

With respect to probiotic dosage, Zhang et al. [78] report a more than fourfold absolute increase (MD: −0.25% vs −0.06%) in mean change in HbA1c following probiotic use of doses $\geq 3 \times 10^9$ CFU/d compared to $< 3 \times 10^9$ CFU/d, respectively. This supports the findings of Ding et al. [79] who also report a greater effect (MD: −0.23% vs −0.12%) of probiotics with doses $\geq 10^{10}$ CFU/d compared to $< 10^{10}$ CFU/d. Results from both these recent analyses align with our findings where we show that dosages of $\geq 10^{10}$ CFU/d are associated with slightly better effects on HbA1c and insulin compared to lower bacterial doses among pro/-synbiotics. However, these comparisons did not show statistically significant subgroup differences. This may be explained by the role of the gut microbiome in the regulation of metabolism via the secretion of metabolites [85], such as short chain fatty acids (SCFAs), bile acids, and indole. These gut-microbial metabolites induce the production of GLP-1, consequently enhancing insulin secretion and reducing HbA1c [86]. Since the gut needs to maintain at least 10^6 CFU in the intestine to have an effective role, greater probiotic dosages are usually used in studies [87]. However, analysis of studies using $< 10^{10}$ CFU/d reveal that doses above 10^{10} CFU did not present any extra benefits on FPG or HOMA-IR; rather, the excessive release of metabolites proved harmful to the intestinal mucosa [88]. Further, based on data from 13 pooled trials (611 participants), we show that prebiotics dosage of ≥ 10 g/d have greater effect on HbA1c (MD: −0.55% [95% CI: −0.73; −0.36]) than lower doses, a novel finding. Pro/prebiotic dose-effect meta-regression analysis was not conducted owing to heterogeneous nutraceutical formulations disallowing direct dosage comparison. Although probiotic dose-response investigations are abundant in literature, one must be cautious in the interpretation of such findings. Due to the lack of trials administering identical nutraceutical cocktails, in order to carry out such large scale linear analyses, one has to grossly reduce the complex task of comparing different pro/pre/synbiotic formulations, composed

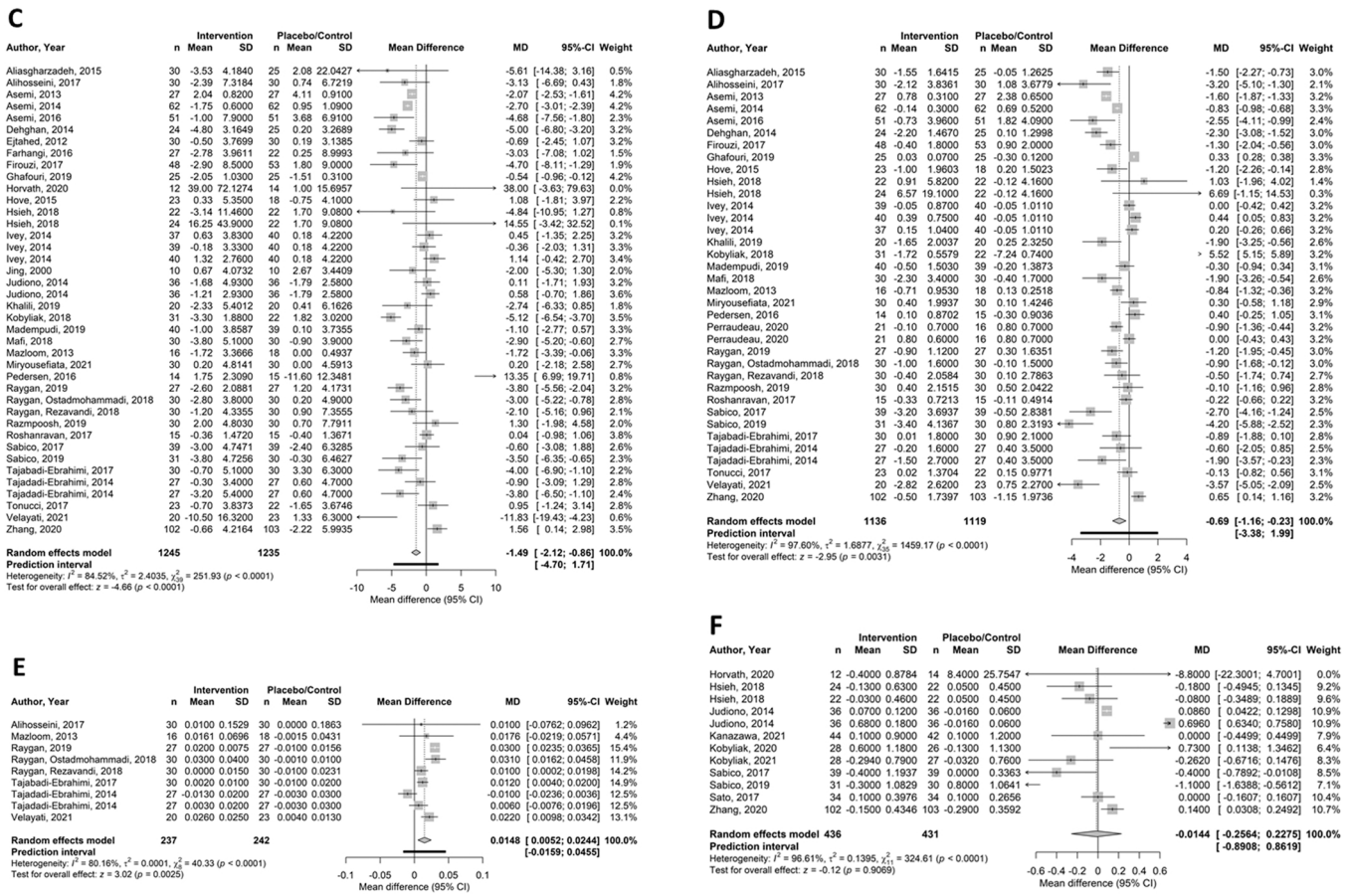

Fig. 2. (*continued*).

of different species, strains and combinations, to simple univariate models by pooling nutraceuticals into broad categories, which can be potentially misleading.

The overall change observed in FPG is consistent with the findings of previous meta-analyses in T2D patients following pro/pre/synbiotics supplementation [84] (−0.58 mmol/l [95% CI: −0.86; −0.30] or approximately 10.44 mg/dl) and pre/synbiotic supplementation [83] (−11.74 mg/dl [95% CI: −23.04; −0.44]). Although we did not find any subgroup differences (p_{subg} = 0.9788) with respect to type of intervention, the findings from the application of prebiotics (MD: −13.98 mg/dl [95% CI: −23.43; −4.53]) and multispecies synbiotics (MD: −13.04 mg/dl [95% CI: −24.41; −1.67]) showed greatest effects. This trend aligns [80–83] and contrasts [78,79] with conclusions from other reviews. After careful comparison, we believe this to be a result of more stringent nutraceutical type classification and exclusion of unpublished studies and abstracts in our review. These results may also be due to different sources and dosages of bacterial strains and prebiotics, leading to an inability to specifically predict which component of the synbiotic had an effect on FPG levels, or whether different combinations of probiotics and prebiotics work better than others. Another reason for these disparities may be due to differences in the patients' demographics (gender, age, medications, baseline characteristics), diets, types of interventions medications, locations, and placebos, which can be attested by the considerable heterogeneity of the subgroups studied. In summary, from pooled subgroup analyses with a large number of trials, we show that the optimum probiotic and prebiotic daily doses to ameliorate FPG levels lie between $< 10^{10}$ CFU/d and $\geq$ 10 g/d, respectively, while shorter trials lasting < 12 weeks were optimum for greater mean reductions, confirming patterns of optimum doses and durations from other meta-analyses [78,80,81].

Overall, the effects of pro/pre/synbiotic administration on biomarkers of insulinemia, insulin resistance and sensitivity, as assessed by fasting insulin, HOMA-IR, and QUICKI, respectively, are both promising and consistent with previous findings [78,79,84,89]. A reduction in mean insulin levels, characteristic of increased insulin sensitivity and decreased insulin resistance, is consistent with the positive findings in glycemic status described above. This gives rise to the potential of pro/pre/synbiotics to repress insulin resistance, maintain glucose homeostasis, and improve β-cell function before the onset of full-blown T2D, as has been shown in prior reviews and recent RCTs on prediabetics [90–92]. Further, our subgroup analysis revealed that only trials lasting < 12 weeks produced statistically significant reductions in insulin and HOMA-IR, whereas longer trials did not. No consensus could be reached with respect to optimum dosage given the low number of trials per subgroup and considerable interstudy heterogeneity. Similar to findings of previous studies [89], although we did not find any significant changes in C-peptide levels, it is compelling to note that this persisted among most subgroups, regardless of variable. When taken into consideration with the substantial heterogeneity among studies that reported C-peptide level changes, this lack of change can be attributed to the heterogenous trial policies on inclusion of patients on insulin therapy (which can lead to changes in intrinsic insulin production and thus C-peptide levels). The C-peptide level effect could easily be masked, given the higher number of trials that analyzed fasting insulin.

Our subgroup analysis also revealed that the effect of pro/pre/synbiotic nutraceuticals varied considerably with respect to participant characteristics such as mean age, baseline BMI, and baseline mean biomarker values of patients. Specifically, we found that younger and more obese populations with greater baseline FPG, HbA1c, and insulin had generally greater mean reductions following nutraceutical regimens. A few notable exceptions to this trend include the association between FPG, HOMA-IR reductions, and baseline BMI, where obese

participants experienced lower changes in comparison. These results, however, differ from those obtained by Zhang et al. [78], where effects on different markers increase with age. This could be due to the limited number of studies with younger subgroups compared to older groups in our review. A probable explanation for our findings favoring younger populations is that older patients generally suffer from comorbidities or take medications that interfere with the results of biotic supplementation [93]. The variation in BMI is consistent with older reviews [78] and is likely explained by the increased dysbiosis of the gut microbiome in patients with obesity [94]. Prebiotics and probiotics have been shown to more pronouncedly counter gut dysbiosis in individuals with a high BMI by stimulating bacterial fermentation and enhancing the levels of SCFA, causing an increase in brown adipose tissue (BAT), the browning of white adipose tissue (WAT), and modulating the brain-gut axis [95,96]. Nutraceutical administration likely modulates, to a relatively greater degree, the dysbiosis observed in the gut of obese adults compared to normal or overweight adults [27,60,97–100]. Intuitively, greater baseline values were shown to predict the extent of reduction in FPG, HbA1c, and insulin following pro/pre/synbiotic regimens, with the effect on FPG being confirmed by meta-regression analysis. These have also been reproduced in earlier studies [101], which demonstrates that the potential of microbiome-modulation nutraceuticals is greater among those with greater metabolic imbalances. Recent high-quality meta-analyses have shown that pro/synbiotics also reduce a multitude of cardiometabolic risk factors associated with T2D, and that synbiotics further help in positively modifying anthropometric indices including weight and BMI, which could indicate a potential indirect effect on insulin resistance and sensitivity [101].

There is increasing interest in the role of the gut microbiome, its dysbiosis, and potential remodulation via nutraceuticals in various metabolic, neurological, oncological, and inflammatory disorders [14,77,102–114]. In the case of T2D, supplementation via microbiome-modulating nutraceuticals like probiotics, prebiotics, and synbiotics as complementary or adjunct medicine aims to improve metabolic control by reversing the gut dysbiosis, a classic hallmark of the disease [102,103,114]. Chronic low-grade inflammation, reduced butyrate and other SCFA-producing bacteria, increased microbial gene-induced oxidative stress, reduced vitamin synthesis, increased intestinal permeability, disruption of the mucosal immune system, and increased serum LPS are some pathophysiological features of T2D that are the target of probiotics and other nutraceuticals [102,104,114,115]. Similar potentials of pro/prebiotics have been highlighted against low-grade inflammation-modulated aging mechanisms [116]. Nutraceuticals can affect the glycemic indices of consumers either directly or indirectly through the regulation of the gut microbiota. Direct influence can stimulate glucose uptake in skeletal muscles and adipose tissues via glucose transporters and regulate glucose homeostasis and adipogenesis via the peroxisome proliferator-activated receptor, thus decreasing insulin resistance [117]. Indirect influence involves the beneficial gut microbiota utilizing prebiotics as energy sources as a toxic substance against specific species; or when broken down, their byproducts can stimulate or inhibit the function of other species or reduce pH to make it favorable for certain acid-sensitive species to thrive [118].

Recent literature has revealed that baseline gut microbiome composition plays an influential role in predicting the effectiveness of pharmacological therapies such as metformin in newly diagnosed T2D patients [119] and that of fecal microbiota transplantation (FMT) in metabolic syndrome patients [120] to improve metabolic outcomes. Baseline levels of *Prevotella copriwere* were significantly increased in metformin non-responders, whereas *Enterococcus faecium, Lactococcus lactis*, *Odoribacter*, and *Dialister* were enriched in metformin responders [119], revealing the potential of baseline gut microbiome profile to serve as a prediction tool for response to therapy. However, it has also been shown that treatment regimens such as metformin can affect the gut microbiota and act as a confounder in human gut metagenomic studies. This mechanism is thought to be mediated by microbial SCFAs, which alter the therapeutic efficacy of such drugs [121]. This also reveals the potential existence of a bi-directional influence between pharmacological therapies and the gut microbiome. In another study among metabolic syndrome participants, improvement in insulin sensitivity following allogenic FMT from lean donors revealed that FMT efficacy was also dependent on decreased baseline fecal microbial diversity [120]. In concordance with literature, Mobini et al. [36] report that microbiota composition differed significantly between insulin-sensitivity responders and non-responders before and after *Lactobacillus reuteri* supplementation. The higher relative abundance of phylum Euryarchaeota in such responders shows that baseline microbiota composition and diversity play an important role in determining who benefits most with such supplementation. A scarcity of trials reporting baseline gut microbial profiles and diversity between responders and non-responders prevented us from completing a formal statistical analysis comparing baseline microbiome composition on observed nutraceutical effect in this review. In addition, although most studies also encouraged the continuation of oral hypoglycemic agents, diet, and lifestyle alongside the intervention or placebo, it was difficult to account for such confounders owing to heterogeneity in reporting measures, including disparities in the type, number, and dosage of such drugs. Future studies should account for these potential confounders, not only individually, but also for their potential influence on each other.

Despite apparent improvements to clinical biomarkers and supposed mechanisms of action across various studies over the course of the past decade [122,123], according to legislative bodies such as the European Food Safety Authority (EFSA) [124] and the U.S. FDA [125], no health claims can be made for probiotics. This is largely owing to heterogeneity in study design and analysis, insufficiently defined claims or characterization of foods, or insufficient evidence to support a claim and establish cause-effect relationships in studies investigating these nutraceuticals [125]. Conflicting reports have raised important questions regarding their present use as 'nutritional supplements' in healthy individuals and in disease [126], while others have highlighted the lack of safety reporting in RCTs [127]. Thus, although there are no current legislative recommendations supporting the adoption of such nutraceuticals for clinical benefit, current research highlights areas for improvement in the selection of intervention formulation, trial methodologies, and reporting, and likewise recommends adoption of sufficiently prespecified, described, and focused claims.

This study has limitations. Firstly, the non-blinding of the extraction process allowed for bias in the scope. Secondly, our inclusion and search strategy process only captured prebiotics-administering studies that explicitly stated the use of prebiotics in their study. In comparison to the widely-acknowledged influence of probiotics, the effect mechanisms of prebiotics are considerably less known; hence, this study may not have captured all sources of prebiotic administration among diabetics [118,128]. Thirdly, there was considerable and unexplained heterogeneity across studies, likely due to differences in nutraceutical type, mode of delivery, formulation, number, species type (pro/synbiotics), varying intervention durations, and different populations. Subgroup and meta-regression analysis, although performed to identify the source of these differences, did not always explain the heterogeneity. Moreover, we did not consider extracting various variables, such as delivery formulation and the presence and kind of adverse effects, which are important considerations. While it is true that HbA1c reflects changes in blood glucose over the last 12 weeks of intervention, our analysis primarily included trials with shorter intervention durations, which downplayed the effect size, as evident from subgroup analysis with trial duration as a covariate. While this study analyzed a large number of trials, most of the individual clinical trials had small sample sizes. Interestingly, a limitation to the generalizability of these results is that some of the significant effects of nutraceuticals are not seen in all regional populations, with the greatest effect seen in studies based in the Eastern Mediterranean (Table 2). This may result from the abundance of

marketed and over-the-counter probiotics that are available without significant restrictions in some Middle Eastern countries. An inadequate awareness of the new generation of probiotics still exists in the field of pharmacology though, resulting in practical differences between community and hospital pharmacists in probiotics intake, counseling, and storage [129], which may present long-term medico-social challenges. We also acknowledge the possible confounding effects of baseline microbiome composition on the effectiveness of nutraceuticals and the possible contribution to interstudy heterogeneity, due to proportions of the study population receiving varying primary pharmacological treatments. Future studies should account for these variables to study subgroups and identify confounders. Lastly, we did not consider the status of nutraceutical type in our dosage analysis to offset the lower number of trials for dosage analysis, which could have important modifications in the interpretation of optimum dosages.

This meta-analysis has multiple strengths, both in a general sense and in comparison to other recent reviews. This is the most comprehensive review of the potential effect of pro/pre/synbiotics on markers of glycemia and insulinemia that demonstrates agreement between findings in both types of biomarkers, improving intra-study agreement. Our target population is individuals with T2D, in contrast to studies that also report on T1D patients. The mechanism of diabetes and its complications relating to the gut are more pronounced in T2D, so results on those populations should be pooled with populations with T1D or other diabetes. Moreover, our study compares the effect of all three types of nutraceuticals, contrary to the majority of other reviews which report on only probiotics. This inclusion revealed many important outcomes; one such being the greater effect of synbiotics on HbA1c compared to probiotics alone. Our classification and inclusion criteria are stricter with the definitions of pro/pre/synbiotics and their formulations and composition, translating to a more accurate interpretation of the effects of each nutraceutical. Lastly, to the best of our knowledge, this is the only recent meta-analysis that comprehensively investigates the effects of all three nutraceutical types with the utilization of both intragroup baseline and end-of-trial biomarker values to compare intergroup changes (rather than comparing only intergroup end-of-trial values) to provide relatively more accurate effect estimates based on populations.

5. Conclusion

The diabetes epidemic spreads globally at an ever-increasing pace, disproportionately affecting populations with lower socioeconomic frameworks. Our meta-analysis reveals that compared to placebo/control, pro/pre/synbiotic supplementation led to significant reductions in HbA1c, FPG, insulin, HOMA-IR, and QUICKI, but not C-peptide (Fig. 3). Given its comprehensive nature and depth, this review is a significant addition to the growing body of evidence showing the potential of incorporating microbiome-modulating nutraceuticals into the diet or supplemental regimens to serve as an adjunct therapy and re-establish metabolic and gut microbiome homeostasis simultaneously with pharmacological interventions. However, interpretation of this study is also limited due to the great diversity in clinical, methodological, and trial characteristics among trials, thus complicating any form of blanket acceptance, which is reflected in the reluctancy of food safety authorities to associate pro/prebiotics with direct health or clinical benefits. We believe that large-scale, multicenter trials with informed prespecified claims, experimentally practical endpoints, and the reporting of more detailed baseline and follow-up microbiome characteristics are required to not only address current limitations and potential confounders in this field, but also to streamline interpretation of observed results and

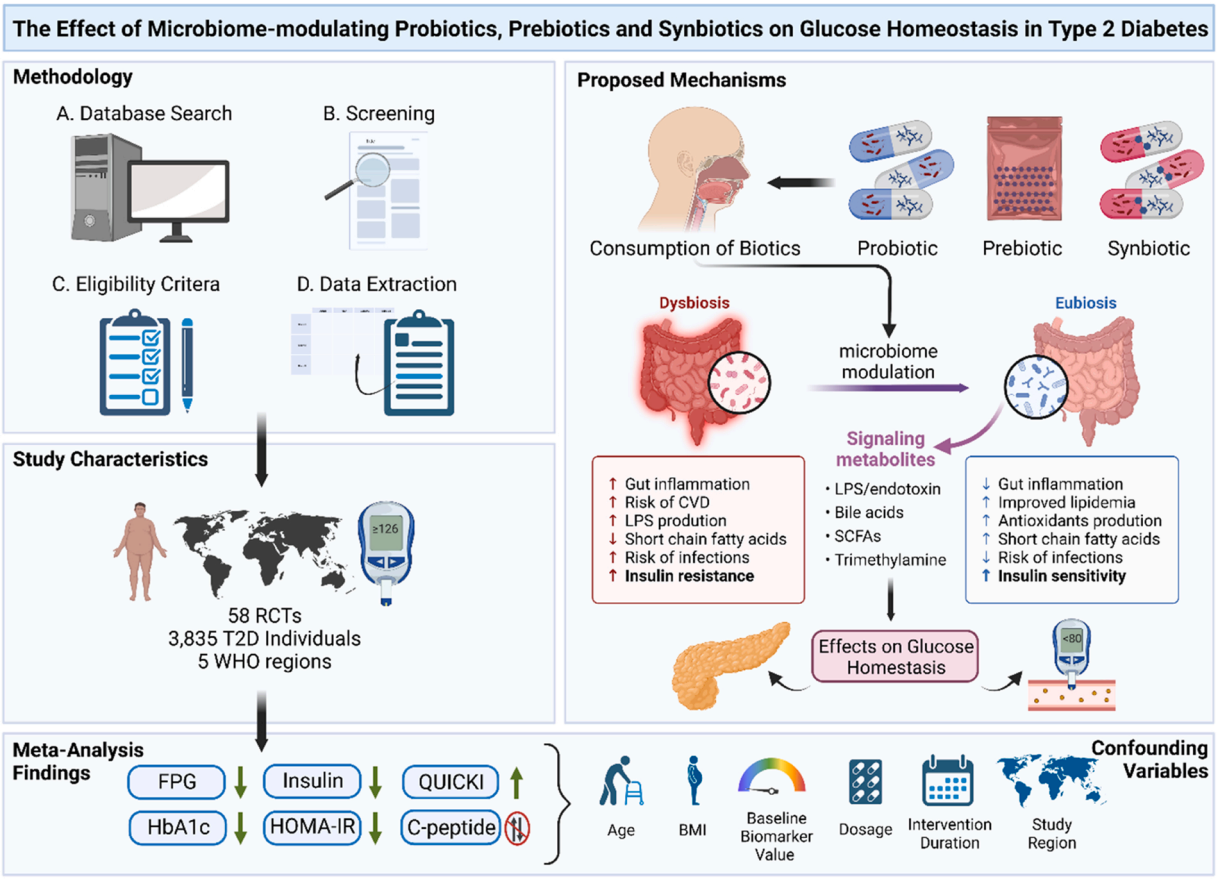

Fig. 3. Graphical summary of systematic review methodology, trial characteristics, meta-analysis findings, confounding variables, and proposed mechanisms of action of microbiome-modulation probiotic, prebiotic and synbiotic consumption on glucose homeostasis in type 2 diabetes.

improve our understanding of the complex human microbiome.

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CRediT authorship contribution statement

Ali Chaari: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Roles/Writing - original draft, Writing - review & editing. **Pradipta Paul:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Roles/Writing - original draft, Writing - review & editing; **Ridhima Kaul:** Conceptualization, Data curation, Investigation, Validation, Roles/Writing - original draft, Writing - review & editing; **Manale Harfouche:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing - review & editing; Maryam Arabi: Data curation, Investigation, Validation, Visualization, Roles/Writing - original draft, Writing - review & editing; **Yousef Al-Najjar:** Data curation, Investigation, Validation, Visualization, Roles/Writing - original draft, Writing - review & editing; **Aparajita Sarkar:** Data curation, Investigation, Validation, Visualization, Roles/Writing - original draft, Writing - review & editing; **Reya Saliba:** Data curation, Methodology, Project administration and Resources.

Disclosure statement

The authors report there are no competing interests to declare.

Data Availability

Not applicable as no new data was created in this project; the extracted data templates can be requested from the corresponding authors.

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Supplemental online material

Supplementary Table ST1–7 and Supplementary Figs. SF1–3 have been provided with this manuscript and will be available online.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2022.106520.

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