



## Effects of Probiotic Supplementation on Inflammatory Markers and Glucose Homeostasis in Adults With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Ding L-N, Ding W-Y, Ning J, Wang Y, Yan Y and Wang Z-B (2021) Effects of Probiotic Supplementation on Inflammatory Markers and Glucose Homeostasis in Adults With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. Front. Pharmacol. 12:770861. doi: 10.3389/fphar.2021.770861 **Background:** Several studies have revealed the effect of probiotic supplementation in patients with type 2 diabetes (T2DM) on the amelioration of low-grade inflammation, which plays an important role in the pathogenesis of T2DM. However, the effects of the clinical application of probiotics on inflammation in individuals with T2DM remain inconsistent. This study aims to investigate the comprehensive effects of probiotics on inflammatory markers in adults with T2DM.

**Methods:** PubMed, Embase, Cochrane Library, and the Web of Science were searched to identify randomized controlled trials (RCTs) exploring the effect of probiotic supplementation on inflammatory markers in individuals with T2DM through March 11, 2021. Two reviewers independently screened the literature, extracted data, and assessed the risk of bias of the included studies. We used a random-effects model to calculate the standardized mean difference (SMD) between the probiotic supplementation and control groups.

**Results:** Seventeen eligible studies were selected with a total of 836 participants, including 423 participants in probiotic supplementation groups and 413 participants in control groups. Our study demonstrated that compared with the control condition, probiotic intake produced a beneficial effect in reducing the levels of plasma inflammation markers, including tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) (SMD [95% CI]; -0.37 [-0.56, -0.19], p < 0.0001) and C-reactive protein (CRP) (SMD [95% CI]; -0.21 [-0.42, -0.01], p = 0.040), while it had no effect on the plasma interleukin-6 (IL-6) level (SMD [95% CI]; -0.07 [-0.27, 0.13], p = 0.520). In addition, our results support the notion that probiotic supplementation improves glycaemic control, as evidenced by a significant reduction in fasting blood glucose (FPG), HbA1c and HOMA-IR (SMD [95% CI]: -0.24

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Abbreviations: CRP, C-reactive protein; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; HOMA-IR, homeostasis model of assessment of insulin resistance; IL-6, interleukin-6; IECs, intestinal epithelial cells; IRS1, Insulin receptor substrate 1; NF- $\kappa$ B, nuclear factor kappa B; RCT, randomized controlled trial; SCFAs, Short-chain fatty acids; SMD, standardized mean difference; TNF- $\alpha$ , tumour necrosis factor- $\alpha$ ; T2DM, type 2 diabetes mellitus.

[-0.42, -0.05], p = 0.010; -0.19 [-0.37, -0.00], p = 0.040; -0.36 [-0.62, -0.10], p = 0.006, respectively).

**Conclusion:** Our study revealed some beneficial effects of probiotic supplementation on improving inflammatory markers and glucose homeostasis in individuals with T2DM. Probiotics might be a potential adjuvant therapeutic approach for T2DM.

Keywords: probiotic, inflammation, type 2 diabetes mellitus, gut microbiota, meta-analysis

Systematic Review Registration: [https://www.crd.york.ac.uk/ prospero/], identifier [CRD42021235998].

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most common endocrine and metabolic diseases and is characterized by impaired pancreatic islet  $\beta$  cell function and insulin resistance in insulin target tissues (Gurung et al., 2020; Arora et al., 2021). Data have shown that the incidence of T2DM has been sharply increasing worldwide and has become one of the most critical public health concerns (Zhang and Gregg, 2017). Moreover, due to diabetes-related complications such as blindness, kidney failure, heart attacks, stroke, and lower-limb amputation, T2DM is a leading cause of morbidity and mortality worldwide (Pearson, 2019).

Currently, there is no simple or effective intervention available to prevent and manage diabetes due to the complex and multifactorial nature of T2DM (Pearson, 2019). In recent years, emerging evidence suggests that the gut microbiota is closely related to the development and progression of T2DM (Tsai et al., 2019; Gurung et al., 2020). Some studies have found that the occurrence of T2DM is associated with gut microbial dysbiosis, which plays a major role in promoting chronic low-grade inflammation and insulin resistance and increases the risk of diabetes (Qin et al., 2012; Karlsson et al., 2013; Harkins et al., 2020). A variety of mechanisms have been proposed to explain the role of the gut microbiota in the onset of T2DM, including alteration of the host's energy homeostasis, intestinal barrier integrity, gastrointestinal peptide hormone secretion, immune response, and inflammatory status (Dongarra et al., 2013; Marchesi et al., 2016; Corb Aron et al., 2021).

Several studies have proposed that T2DM is associated with long-term chronic low-grade inflammation characterized by an increase in circulating levels of pro-inflammatory cytokines and chemokines, such as tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6) (Coope et al., 2016; Eguchi and Nagai, 2017). Elevated levels of TNF- $\alpha$  and IL-6 could also trigger the synthesis of C-reactive protein (CRP) in the liver, which is a common systemic inflammatory biomarker and invariably correlates with insulin resistance and the pathogenesis of T2DM (Badawi et al., 2010; Lainampetch et al., 2019). These pro-inflammatory factors could interfere with the insulin signalling cascade and impair insulin sensitivity by increasing the serine/threonine phosphorylation ratio of insulin receptor substrate 1 (IRS-1) in insulin target tissues (Chen et al., 2015). Pro-inflammatory signalling can also affect pancreatic  $\beta$ -cell functions and impair insulin secretion. In addition, pro-inflammatory factors disrupt endothelial cell functions and limit insulin access to its target tissues, which also contribute to insulin resistance (**Figure 1**) (Cani et al., 2019; Harkins et al., 2020).

Probiotics play a pivotal role in maintaining the balance of the gut microbiota (Bagarolli et al., 2017; Ardeshirlarijani et al., 2019). Currently, as a potential source of new therapeutics that work by regulating the gut microbiota, probiotics are commonly used to prevent and improve diabetes by altering the gut microbiota and its metabolites (Cani, 2018; Gurung et al., 2020). Among these changes, changes in short-chain fatty acids (SCFAs) and bile acids can improve glucose homeostasis, alleviate insulin resistance, and increase adipose tissue thermogenesis (Descamps et al., 2019; Woldeamlak et al., 2019; Tilg et al., 2020). Interestingly, recent studies have also shown that probiotic supplementation can prevent and improve type 2 diabetes by reducing the levels of pro-inflammatory cytokines,



FIGURE 1 | The putative relationship between gut dysbiosis and T2DM.

such as TNF- $\alpha$ , IL-6, and CRP, and regulating the secretion of anti-inflammatory cytokines, such as interleukin-4 (IL-4) and interleukin-10 (IL-10) (Brunkwall and Orho-Melander, 2017; Woldeamlak et al., 2019; Harkins et al., 2020).

T2DM is usually accompanied by chronic low-grade inflammation (Hendijani and Akbari, 2018). Some prospective studies and meta-analyses support the notion that the administration of probiotics could improve glycaemic control (Hu et al., 2017; Wang et al., 2017). However, to our knowledge, the effect of probiotics on inflammatory markers in T2DM patients remains inconsistent. Several RCTs suggest that probiotics reduced the level of chronic systemic inflammatory markers in individuals with T2DM (Tonucci et al., 2017; Raygan et al., 2018; Sabico et al., 2019), while others obtained different conclusions (Feizollahzadeh et al., 2017; Firouzi et al., 2017; Hsieh et al., 2018). No study has simultaneously examined inflammatory biomarkers to capture the interrelation between glycaemic control parameters and inflammatory markers. The aim of the present study is to fill this gap of knowledge.

In the current systematic review and meta-analysis, we aimed to investigate the comprehensive effects of probiotic supplementation on glucose homeostasis and inflammatory markers in adults with T2DM, hoping to obtain more credible evidence-based evidence and provide objective support for the clinical prevention and treatment of T2DM.

## METHODS

We conducted the current systematic review and meta-analysis to investigate the comprehensive effects of probiotics on the inflammatory response and glucose homeostasis markers in adults with T2DM according to the PRISMA guidelines (Page et al., 2021a; Page et al., 2021b). This systematic review has been registered in PROSPERO (registration number: CRD42021235998).

## Search Strategy

Two reviewers independently executed a systematic search of randomized controlled trials (RCTs) examining the effect of probiotic supplementation on the inflammatory response and glycaemic control markers in T2DM patients from inception to March 2021 using the following databases: PubMed, Embase, Cochrane Library, and Web of Science. The search strategies used for PubMed, Embase, Cochrane Library, and Web of Science, which were based on the controlled vocabulary terms for each concept (e.g., MeSH) and keyword synonyms, are shown in Table S1. We imposed no language or other restrictions on any of the searches. A manual search was also conducted to identify further relevant studies from the references of included studies and previous systematic reviews.

## **Eligibility Criteria**

Studies were selected based on the following criteria: (1) studies with participants with T2DM aged  $\geq$ 18 years old; (2) RCTs; (3) studies in which the intervention was probiotic supplementation; and (4) studies in which changes in inflammatory markers (TNF- $\alpha$ , IL-6, and CRP) between pre- and posttreatment were outcome variables.

The exclusion criteria were as follows: (1) studies with pregnant or breast-breeding individuals and (2) studies with participants who consumed synbiotics, prebiotics, herbs or other supplements (such as micronutrients and other dietary constituents).

## **Data Extraction**

According to the eligibility criteria, two reviewers independently conducted the literature search and data extraction. The third reviewer resolved any disagreements that occurred between the two data collectors. Details of population characteristics (e.g., sex, age and country), intervention arms (e.g., types of probiotics/placebo, dose, and duration of intervention), study design, and outcomes (e.g., inflammatory markers and glycaemic markers) were extracted from the included studies.

## **Risk of Bias of Individual Studies**

Two investigators independently evaluated the risk of bias within the randomized controlled studies. The risk of biases, including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases, of the included studies was classified as low, high, or unclear using the Cochrane Collaboration tool (Higgins et al., 2011).

## **Statistical Analysis**

Statistical analysis of the data was conducted using Review Manager 5.3 and STATA/SE 15.1. *p*-values less than 0.05 were regarded as statistically significant. The standardized mean difference (SMD) with 95% confidence interval (CI) was used to analyse the effects of probiotics on glycaemic control and inflammatory markers between the probiotic supplementation and control groups. We used a randomeffects model to pool SMDs on glycaemic control and inflammatory markers. When the studies did not provide the standard deviations (SDs), the missing SDs of the mean change were calculated based on the CI, standard error (SE), p-value, or correlation coefficient (Corr). The correlation coefficient value was estimated as 0.5 to impute the missing SDs, which were not provided by the authors (Follmann et al., 1992). Heterogeneity among studies was assessed by the Cochrane Q-test. I square  $(I^2)$  was used to quantify the magnitude of heterogeneity.  $I^2$  values of 25, 50, and 75% represented low, moderate, and high levels of heterogeneity, respectively (Higgins et al., 2003). To explore the possible source of heterogeneity, subgroup analysis and sensitivity analysis were conducted. Subgroup analysis was carried out according to the potentially influential variables, including the duration of interventions ( $\leq 8$  vs. >8 weeks), doses of probiotic supplementation ( $< 10^{10}$ vs.  $\geq 10^{10}$  CFU/day), probiotic strains (single-vs. multistrains), and methods of probiotic administration (food vs. powder or capsule). Sensitivity analysis was conducted by the one-study remove (leave-one-out) approach to assess the pooled SMDs for each glycaemic control and inflammatory marker. In



addition, funnel plots and Egger's test were utilized to evaluate the possible publication bias of the included studies.

## RESULTS

# Search Results and Characteristics of the Included Studies

A total of 725 studies (75 from Cochrane Library, 484 from Embase, 111 from PubMed, 54 from Web of Science and 1 from references) were identified using the search strategies described in the methods section, of which 193 duplicate records were removed. Two investigators independently screened the titles and abstracts and identified 37 articles according to the eligibility criteria described above. Twenty of these articles were excluded according to the inclusion/ exclusion criteria. Finally, 17 RCTs were selected for inclusion in the meta-analysis. A flow diagram presents the study selection, and the reasons articles were excluded (**Figure 2**).

The characteristics of the included studies are summarized in **Table 1**. Overall, 17 relevant studies were conducted in Europe [Ukraine (Kobyliak et al., 2018a; Kobyliak et al., 2018b), Sweden (Mobini et al., 2017), and Denmark (Hove et al., 2015)], South America [Brazil (Tonucci et al., 2017)], and Asia [China (Hsieh et al., 2018; Fang et al., 2020), Saudi Arabia (Sabico et al., 2019), Malaysia (Firouzi et al., 2017), Iran (Mazloom et al., 2013; Mohamadshahi et al., 2014; Tajadadi-Ebrahimi et al., 2014; Bayat et al., 2016; Feizollahzadeh et al., 2017; Raygan et al., 2018), Turkey (Eliuz Tipici et al., 2020), and Japan (Sato et al., 2017)]. A total of 836 participants from 17 RCTs were randomized into probiotic groups (n = 423) and control groups (n = 413). Within the 17 RCTs, eight studies used one single-strain probiotic, eight studies used two-strain or multistrain probiotics, and one trial did not report the species of probiotics. Seven studies used food products, such as fermented milk (n = 3), yogurt (n = 2), soy milk (n = 1), and bread (n = 1), for probiotic delivery, while others were supplemented in the form of powder (n = 5), capsules (n = 3), and tablets (n = 1). The daily dose of probiotics ranged from  $2 \times 10^7$  to  $1 \times 10^{12}$  colony-forming units (CFU). The median duration of probiotic intervention was 12 weeks, ranging from 4 to 24 weeks.

## **Risk of Bias in Individual Studies**

Two investigators independently assessed the risk of bias of the included studies using the Cochrane collaboration tool. **Figure 3** summarizes the risk of bias, including selection bias, attrition bias, performance bias, detection bias, reporting bias, and other biases, among the included studies. Thirteen studies reported adequate random sequence generation, and ten studies described allocation concealment. In 15 studies, the participants and key researchers were blinded. The dropout rates in 13 RCTs were less than 20%. Selective reporting bias was not found. Two studies may have a high risk of other potential bias, according to the funding, which was supported by the

### TABLE 1 | Characteristics of included studies.

Study	Country	Sample size (P/C)	Ages (year) (P/C)	Underlying disorder	Female (%)	ITT/ PP	Study design	Form of probiotics	Probiotics (strain and daily dose)	Duration (weeks)
Tipici et al. (2020)	Turkey	34 (17/17)	30–60	NR	100	ITT	PC	NR	<i>Lactobacillu</i> s GG, 1 × 10 <sup>10</sup> CEU/day	8
Fang et al. (2020)	China	30 (15/15)	35-68 (57.87 ± 6.31/ 56.67 ± 7.68)	NR	66.33	PP	DB, PC	powder	Bifidobacterium animalis A6, 1 × 10 <sup>10</sup> CFU/day	4
Sabico et al. (2019)	Saudi Arabia	61 (31/30)	30-60 (48.00 ± 8.30/ 46.60 ± 5.90)	NR	57.38	ΡΡ	DB, PC	powder	2 g probiotics mixture (2 × 10 <sup>9</sup> CFU/g, contains Bifidobacterium bifidum W23, Bifidobacterium lactis W52, Lactobacillus acidophilus W37, Lactobacillus brevis W63, Lactobacillus casei W56, Lactobacillus salivarius W24, Lactobacillus lactis W19, and Lactobacillus lactis W58), twice/day	24
Kobyliak et al. (2018a)	Ukraine	58 (30/28)	18-65 (53.40 ± 9.55/ 57.29 ± 10.45)	NAFLD	NR	ΙΤΤ	DB, PC	powder	Lactobacillus + Lactococcus (6 × $10^{10}$ CFU/g), Bifidobacterium (1 × $10^{10}$ CFU/g), Propionibacterium (3 × $10^{10}$ CFU/g), Acetobacter (1 × $10^{6}$ CFU/g), 10 g/day	8
Kobyliak et al. (2018b)	Ukraine	53 (31/22)	18–75 (52.23 ± 9.69/ 57.18 ± 9.66)	NR	NR	ΙΠ	DB, PC	powder	Lactobacillus + Lactococcus (6 × $10^{10}$ CFU/g), Bifidobacterium (1 × $10^{10}$ CFU/g), Propionibacterium (3 × $10^{10}$ CFU/g), Acetobacter (1 × $10^{6}$ CFU/g), 10 g/day	8
Hsieh et al. (2018)	China	44 (22/22)	25-70 (52.32 ± 10.20/ 55.77 ± 8.55)	NR	43.18	PP	DB, PC	capsule	Lactobacillus reuteri ADR-1, 4 × 10 <sup>9</sup> CFU/day	24
Raygan et al. (2018)	Iran	60 (30/30)	40-85 (60.70 ± 9.40/ 61.80 ± 9.80)	CHD	NR	ITT	DB, PC	capsule	Bifidobacterium bifidum 2 × 10 <sup>9</sup> CFU/day + Lactobacillus casei 2 × 10 <sup>9</sup> CFU/day + Lactobacillus acidophilus 2 × 10 <sup>9</sup> CFU/day	12
Tonucci et al. (2017)	Brazil	45 (23/22)	35-60 (51.83 ± 6.64/ 50.95 ± 7.20)	NR	42.22	PP	DB, PC	fermented milk	Lactobacillus acidophilus La-5, 1 × 10 <sup>9</sup> CFU/day + Bifidobacterium animalis subsp. lactis BB-12, 1 × 10 <sup>9</sup> CFU/day	6
Firouzi et al. (2017)	Malaysia	101 (48/53)	30-70 (52.90 ± 9.20/ 54.20 ± 8.30)	NR	51.64	PP	DB, PC	powder	Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus lactis, Bifidobacterium bifidum, Bifidobacterium longum, Bifidobacterium infantis, 3 × 10 <sup>10</sup> CFU. twice/day	12
Mobini et al. (2017)	Sweden	29 (14/15)	NR (64.00 ± 6.00/ 65.00 ± 5.00)	NR	24.14	PP	DB, PC	tablet	<i>Lactobacillus reuteri</i> DSM 17938, 1 × 10 <sup>10</sup> CFU/day	12
Feizollahzadeh et al. (2017)	Iran	40 (20/20)	35-68 (56.90 ± 8.09/ 53.60 ± 7.16)	NR	52.50	PP	DB, PC	soy milk	<i>Lactobacillus planetarum</i> A7, 2 × 10 <sup>7</sup> CFU/day	8
									(Continued on follow	ring page)

Study	Country	Sample size (P/C)	Ages (year) (P/C)	Underlying disorder	Female (%)	ITT/ PP	Study design	Form of probiotics	Probiotics (strain and daily dose)	Duration (weeks)
Sato et al. (2017)	Japan	68 (34/34)	30-79 (64.00 ± 9.20/ 65.00 ± 8.30)	NR	27.94	ITT	DB, PC	fermented milk	<i>Lactobacillus casei strain</i> Shirota, 4 × 10 <sup>10</sup> CFU/day	16
Bayat et al. (2016)	Iran	40 (20/20)	25-75 (54.10 ± 9.54/ 46.95 ± 9.34)	NR	70.00	ITT	PC	Yogurt	NR	8
Hove et al. (2015)	Denmark	41 (23/18)	40-70 (58.50 ± 7.70/ 60.60 ± 5.20)	NR	0	ITT	DB, PC	fermented milk	Lactobacillus helveticus Cardi04	12
Tajadadi-Ebrahimi et al. (2014)	Iran	54 (27/27)	35-70 (52.00 ± 7.20/ 53.40 ± 7.50)	NR	81.48	ITT	DB, PC	bread	<i>Lactobacillus Sporogenes</i> , 1 × 10 <sup>8</sup> CFU, 3 times/day	8
Mohamadshahi et al. (2014)	Iran	44 (22/22)	30-60 (53.00 ± 5.90/ 49.00 ± 7.08)	overweight or obesity	76.19	ITT	DB, PC	yogurt	Lactobacillus acidophilus 3.7 × 10 <sup>6</sup> CFU/g, <i>Bifidobacterium</i> lactic 3.7 × 10 <sup>6</sup> CFU/g, 300 g/day	8
Mazloom et al. (2013)	Iran	34 (16/18)	25-65 (55.40 ± 8.00/ 51.80 ± 10.20)	NR	76.47	PP	SB, PC	capsule	Lactobacillus acidophilus + Lactobacillus bulgaricus + Lactobacillus bifidum + Lactobacillus casei	6

 TABLE 1 | (Continued) Characteristics of included studies.

CHD, coronary heart disease; P/C, probiotic group/control group; ITT/PP, intention-to-treat/per-protocol; DB, double-blinded; PC, placebo-controlled; SB, single blinded; NR, not reported.

probiotic companies. In summary, no significant bias was detected (Figure 3).

## Effects of Probiotics Supplementation on the Inflammatory Response and Glycaemic Control Marker Profile

## Effects on Pro-Inflammatory Markers (TNF- $\alpha$ , IL-6, and CRP)

### Effect on TNF- $\alpha$

A total of 11 RCTs assessed the effect of probiotic supplementation on TNF- $\alpha$  and involved 498 individuals (258 consuming probiotics and 240 in the placebo group). The pooled effect of probiotic administration showed a significant decrease in TNF- $\alpha$  levels in comparison with the effects in the control groups (SMD [95% CI]; -0.37 [-0.56, -0.19], p < 0.0001), and the interstudy heterogeneity was low ( $I^2 = 6\%$ , p = 0.390) (**Figure 4A**).

Subgroup analysis (**Table 2**) stratified by probiotic dosage, the number of probiotic strains, duration of intervention or method of administration showed that the effects of probiotic supplementation on TNF- $\alpha$  were significantly reduced in

studies with the high-dose subgroup (SMD [95% CI]; -0.65 [-0.92, -0.39],  $I^2 = 0\%$ ), multistrain subgroup (SMD [95% CI]; -0.55 [-0.82, -0.27],  $I^2 = 16.6\%$ ), short intervention duration subgroup (SMD [95% CI]; -0.47 [-0.72, -0.22],  $I^2 = 0\%$ ), and administration in the form of powder/capsule subgroup (SMD [95% CI]; -0.56 [-0.81, -0.31],  $I^2 = 0\%$ ).

In the sensitivity analysis, we found that the pooled effect of probiotic supplementation on TNF- $\alpha$  was not significantly changed by omitting the studies one at a time sequentially, suggesting that the meta-analysis results were stable and reliable.

### Effect on IL-6

Ten studies involving 456 patients investigated the effect of probiotic intake and placebo on the serum level of IL-6. The pooled effect of probiotic supplementation indicated no significant effect of probiotics in reducing the serum level of IL-6 compared to the effects in the control group (**Figure 4B**) (SMD [95% CI]; -0.07 [-0.27, 0.13], p = 0.520).

Subgroup analysis showed that there was no significant reduction in IL-6 levels in those subgroups stratified by probiotic dosage, the number of probiotic strains, duration of intervention, or method of administration (**Table 3**).



We also performed sensitivity analysis by sequentially eliminating one study at a time. No particular studies significantly affected the pooled effect of probiotic supplementation on IL-6 levels. However, heterogeneity among studies was eliminated ( $I^2 = 0\%$ , p = 0.960) when the meta-analysis excluded only the trial of Kobyliak et al. (2018a).

### Effect on CRP

The effect of probiotic supplementation on CRP was evaluated in 13 studies including 650 participants. We found a significant effect with a low heterogeneity of probiotic supplementation in reducing serum CRP levels compared to the effects in the control group (SMD [95% CI]; -0.21 [-0.42, -0.01],  $I^2 = 36\%$ , p = 0.040) (**Figure 4C**).

In the subgroup analysis, significant beneficial effects of probiotic intervention were observed for CRP in the short intervention duration subgroup (SMD [95% CI]; -0.36 [-0.67, -0.05],  $I^2 = 22.9\%$ ) (**Table 4**).

In the sensitivity analysis, we found that the heterogeneity among studies did not significantly change when eliminating the study of Bayat et al. (Bayat et al., 2016), which decreased the interstudy heterogeneity from 36 to 7%. In this work, eleven studies reported the effect of probiotic supplementation on TNF- $\alpha$ , ten studies described the effect on IL-6, and 13 studies investigated the effect on CRP and were included in the meta-analysis. Compared to the control group, significant beneficial effects of probiotic supplementation were observed for TNF- $\alpha$  (SMD [95% CI]; -0.37 [-0.56, -0.19], p < 0.0001) and CRP (SMD [95% CI]; -0.21 [-0.42, -0.01], p = 0.040). However, there was no significant beneficial effect on the IL-6 level (SMD [95% CI]; -0.07 [-0.27, 0.13], p = 0.520). In line with our results, a previous meta-analysis also found that these supplementations significantly decreased the levels of TNF- $\alpha$  and CRP but had no effect on IL-6 levels (Tabrizi et al., 2019; Zheng et al., 2019).

### Effect of Probiotics Supplementation on Glucose Homeostasis (FPG, HbA1c, and HOMA-IR) *Effect on FPG*

A total of 778 participants in 16 studies were included in the analysis of the effect of probiotic supplementation on the level of FPG. probiotic supplementation resulted in a significant reduction in FPG levels (SMD [95% CI]; -0.24 [-0.42, -0.05], p = 0.010), and the interstudy heterogeneity ( $I^2 = 39\%$ , p = 0.060) was low (**Figure 5A**).

Study co:         Num         SD         Total         Main         SD         Total         Weight         N. Random. 92% Cl         V. Random. 92% Cl           Fego 2020         2276         434         8         0.534         2127         7         31%         -0.46 (15.0.057)           Fego 2015         0.1         0.357         20         219.72         240.031         20         8.3%         -0.32 (15.0.057)           Fego 2015         0.1         0.357         23         0.37 (17.122         22         9.0%         -0.37 (16.97, 0.23)           Sobojacidy 2016         7.63         7.73         11         1.03         9.769 (12.200.14)         Model 2017         0.41 (15.22         2.9 (17.8)         -0.43 (16.80, 0.57)           Mohamadshih 2014         1.44 (17.0.0.16)         0.11 (22.49, 0.44)         1.000 (1.48, 0.40)         1.01 (22.49, 0.44)         1.000, 0.57)         1.01 (16.40, 0.40)         1.01 (16.40, 0.41)         1.01 (16.40, 0.41)         1.01 (16.40, 0.41)         1.01 (16.40, 0.41)         1.01 (16.40, 0.41)         1.01 (16.40, 0.41)         1.01 (16.40, 0.41)         1.01 (16.40, 0.41)         1.01 (16.40, 0.41)         1.01 (16.40, 0.41)         1.01 (16.40, 0.41)         1.01 (16.40, 0.41)         1.01 (16.40, 0.41)         1.01 (16.40, 0.41)         1.01 (16.40, 0.41)		Pro	biotics		Con	trol			Std. Mean Difference	Std. Mean Difference
Fang 2020 -2.276 4.384 8 -0.5343 2.127 7 3.1% -0.46 [-150, 0.57] Festolahazado hybrid 2016 0.10 0.361 23 0.3 10.08 18 8.4% -0.26 [-0.86, 0.39] How 2015 0.1 0.381 23 0.3 10.08 18 8.4% -0.26 [-0.86, 0.39] How 2015 0.1 0.381 23 0.3 10.08 172 22 22 10.0% -0.37 [-0.26, 0.19] Mobini 2017 0.4 1.852 14 0.2 3.804 15 0.2% 0.06 [-0.80, 0.57] Mobini 2017 0.4 1.852 14 0.2 3.804 15 0.2% 0.06 [-0.80, 0.57] Tonucci 2017 -1.4 3.238 21 -0.66 0.04 33 11.3% -0.02 [-0.60, 0.57] Tonucci 2017 -1.4 3.238 23 -1.36 0.01 22 9.4% -0.02 [-0.60, 0.57] Tonucci 2017 -1.4 3.238 23 -1.36 0.01 22 9.4% -0.02 [-0.60, 0.57] Tonucci 2017 -1.4 3.238 23 -1.36 0.01 22 9.4% -0.02 [-0.60, 0.57] Tonucci 2017 -1.4 3.238 23 -1.36 0.01 22 9.4% -0.02 [-0.60, 0.57] Tonucci 2017 -1.4 3.238 23 -1.36 0.01 22 9.4% -0.02 [-0.60, 0.57] Tonucci 2017 -1.4 3.238 22 0.9 1.8 22 10.0% -0.37 [-0.56, 0.19] Heterogeneity: Tax' = 0.01; Ch <sup>2</sup> = 10.84, df = 10 (P = 0.39); P = 9% Elix: Tipic 2020 1.61 6.664 17 -2.28 11.407 17 7.8% 0.41 [-0.27, 1.09] Heterogeneity: Tax' = 0.01; Ch <sup>2</sup> = 0.55 22 0.9 1.8 22 10.0% -0.27 [-0.50, 0.57] Tast for overall effect: Z = 3.96 (P < 0.001) <b>3</b> Probiotics Control Std. Mean Difference Std. Mean Difference S	Study or Subgroup	Mean	SD To	otal M	/lean	SD	Total	Weight	IV. Random, 95% CI	IV. Random, 95% CI
Facinitarization 2017 0.9 50.657 20 219.72 940.031 20 6.3% -0.32 [0.95, 0.30] Hishich 2018 -32 81.24 22 3.07 72.22 29 90% -0.37 [0.97, 0.23] Hishich 2018 -7.53 7.27 30 -1.17 1122 22 19.5% -0.37 [0.97, 0.23] Kobylink() 2016 -7.65 7.071 31 -1.03 9.709 22 9.8% -0.38 [-1.40, 0.26] Skobylink() 2016 -7.65 7.071 31 -1.03 9.709 22 9.8% -0.38 [-1.40, 0.26] Skobylink() 2017 -0.41 865 22 -0.31 1.864 22 9.00% -0.44 [-1.03, 0.16] Skobylink() 2017 -0.41 30.55 22 -0.31 1.864 22 9.00% -0.44 [-1.03, 0.16] Skobylink() 2017 -0.43 0.54 31 -0.067 0.47 30 11.7% -0.77 [-1.23, 0.16] Skobylink() 2016 -0.163 0.17 22 9.84 -0.02 (0.60, 0.57) Total (95% C) -288 2 -0.31 1.864 22 9.00% -0.44 (-0.00, 0.57) Total (95% C) -288 2 -0.31 1.864 4.71 0.2 4.84 4.71 0.02 (-0.48, 0.48] Total (95% C) -288 2 -0.31 1.814 0.71 7.7 8.07 [-0.56, -0.19] Total (95% C) -288 2 -0.03 1.02 2 9.4% -0.02 (-0.48, 0.48] Total (95% C) -288 2 -0.03 1.10 2 9.4% -0.02 (-0.48, 0.48] Total (95% C) -288 2 -0.03 1.10 2 9.4% -0.02 (-0.48, 0.48] Total (95% C) -288 2 -0.03 1.10 2 9.4% -0.02 (-0.76, 0.57) Total (95% C) -288 2 -0.03 1.10 2 9.4% -0.02 (-0.76, 0.57) Total (95% C) -28 3 0.02 2 1.1407 17 7.56% 0.02 (-0.70, 0.51) Favours (Problotics) -28 4 0.2 0.13 4 14.07 17 7.78 (-0.76, 0.57) Kobylink() 2018 -4.63 7.54 30 -0.39 5.83 28 12.11% -0.00 (-1.13, -0.08] Hishich 2018 -3.45 2.24 31188 0.004 2 2 1.13% -0.02 (-1.03, 0.67) Total (95% C) -2.43 318 0.004 2 2 1.13% -0.02 (-0.70, 0.31) History (0.41 2.24 3.44 2.2 0.55 9.42 2.2 9.06 77 4102 (-0.50, 0.61) Favours (Problotics) -2.03 0.126 9 (-0.33); F = 13% -2.22 (-0.33, 0.47) Total (95% C) -2.04 2 -2.04 2 -2.22 1.00.0% -0.04 (-0.50, 0.67) Total (95% C) -2.04 2 -2.04 2 -2.22 1.00.0% -0.04 (-0.50, 0.67) Total (95% C) -2.04 2 -2.05 (-0.60 2.3) History (0.64 2.2 0.157 -0.63) History (0.64 2.2 0.057 -0.63) History (0.64 2.2 0.057 -0.63) History (0.64 2.2 0.05 (-0.63)) History (0.64 2.2 0.05 (-0.63)) History (0.64 2.2 0.05 (-0.63 0.27) History (0.64 2.2 0.05 (-0.63 0.27) History (0.64 0.25 0.22 0.0	Fang 2020	-2.276	4.384	8 -0.	5343	2.127	7	3.1%	-0.46 [-1.50, 0.57]	
How 2015 0.1 0.361 23 0.3 1.058 18 0.8 46 -0.25 [0.8.0.36] Kobylak(b) 2018 -7.65 7.29 30 -1.17 11.22 28 11.3% -0.67 [-1.20, 0.14] Kobylak(b) 2018 -7.65 7.29 30 -1.17 11.22 28 11.3% -0.67 [-1.20, 0.14] Mohim 2017 0.4 1.852 14 0.2 3.804 15 6.2% 0.06 [-0.8, 0.79] Sabic 2017 0.0 4.1 852 14 0.22 3.804 15 6.2% 0.06 [-0.8, 0.79] Sabic 2019 -0.43 0.544 31 -0.067 0.467 30 11.7% -0.71 [-1.23, 0.19] Sabic 2017 0.0 5.5 44 0.0 -0.3 34 1.884 22 0.90% -0.44 [-0.40, 0.48, 0.48] Sabic 2017 1.14 3.238 23 -1.38 0.01 22 9.4% -0.02 [-0.80, 0.57] Total (95% Cl) 2.268 2.0.03 1.168 1.28 1.98% 0.002 [-0.80, 0.57] Total (95% Cl) 2.268 (-0.001) <b>3</b> <b>7</b> <b>7</b> <b>7</b> <b>7</b> <b>7</b> <b>7</b> <b>1</b> <b>7</b> <b>1</b> <b>6</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b>	Feizollahzadeh 2017	0.39 5	50.857	20 21	9.72 94	0.031	20	8.3%	-0.32 [-0.95, 0.30]	
High 2018 $32$ 81.24 $92$ $307$ 72.22 $22$ 9.0% $3.7(0.57, 0.23)$ Kopylack(2) 2018 $7.65$ 7.071 31 $103$ 9.709 22 9.8% $0.37(0.57, 0.23)$ Mchamadshahi 2014 $1.44$ 3.085 22 $0.31$ 1.864 22 9.0% $0.4(1.03, 0.16)$ Salic 2017 0.43 805 22 $0.31$ 1.864 22 9.0% $0.4(1.03, 0.16)$ Salic 2017 0.43 8.054 310.067 .0.467 30 $0.17$ $K_{-}$ 0.7(1, 12.2, 0.41) Salic 2017 0.55 34 0.0 0.33 44 13.8% 0.00 [-0.66, 0.79] Totual (95% C) 258 240 100.0% 0.37 [-0.56, 0.19] Heterogeneiky: Tax' = 0.01; Ch <sup>2</sup> = 10.64, df = 10 (P = 0.39); P = 6% Total (95% C) 268 (P < 0.0011) <b>7</b> Total (95% C) 268 2.0 0.01 122 9.4% 0.002 [-0.60, 0.57] Total (95% C) 268 2.0 0.01 1 <b>7</b> Total (95% C) 128 2.0 161 6.644 17 $228$ 11.407 17 7.8% 0.41 [-0.27, 10.6] Kabylack(b) 2018 3.45 8.24 311.89 6.004 22 11.3% 0.02 [-0.50, 0.41] Heterogeneiky: Tax' = 0.01; Ch <sup>2</sup> = 10.30, df = 9 (P = 0.33); P = 6% <b>8</b> Mchamadshahi 2014 0.42 3.946 8.22 0.95 9.53 2.82 11.0% 0.02 [-0.57, 0.61] Kabylack(b) 2018 3.45 8.24 311.89 6.004 22 11.3% 0.02 [-0.57, 0.61] Mchamadshahi 2014 0.42 3.946 8.22 0.55 9.428 22 9.9% 0.03 [-0.50, 0.57] Heterogeneiky: Tax' = 0.01; Ch <sup>2</sup> = 10.30, df = 9 (P = 0.33); P = 13% Control 50 Total Mean 50 Total Mean 50 Total Mean 51 Total 0.006 0.33 (-0.37, 0.43] Heterogeneiky: Tax' = 0.01; Ch <sup>2</sup> = 10.30, df = 9 (P = 0.33); P = 13% Toroucd 2017 0.42 3.946 8.22 0.55 9.428 22 0.95% 0.02 [-0.57, 0.43] Heterogeneiky: Tax' = 0.01; Ch <sup>2</sup> = 10.30, df = 9 (P = 0.33); P = 13% Test for overall effect: Z = 0.65 (P = 0.52) <b>7</b> Total 0.508 2.30.325 0.661 22 10.1% 0.028 [-0.31, 0.87] Heterogeneiky: Tax' = 0.01; Ch <sup>2</sup> = 10.30, df = 9 (P = 0.33); P = 13% Testolaticabr 2017 0.42 2.77 48 10.88 3.126 22 7.6% 0.32 [-0.50, 0.57] Toroucd 2017 0.42 1.984 3.22.78 40 12.2 7.6% 0.32 [-0.50, 0.57] Toroucd 2017 0.42 1.983 3.22.748 10.88 3.144.442.74 18 6.5% -0.18 [-0.36, 0.47] Heterogeneiky: Tax' = 0.04; Ch <sup>2</sup> = 1.030, df = 9 (P = 0.33); P = 13\% Heterogeneiky: Tax' = 0.04; Ch <sup>2</sup> = 1.048 (-138) 22 7	Hove 2015	0.1	0.361	23	0.3	1.058	18	8.4%	-0.26 [-0.88, 0.36]	
Kapylak(b) 2018 7-55 7.29 30 -1.17 11.22 28 11.3% $-0.67(1.20, 0.14]$ Mohin 2017 0.4 1.852 14 0.22 3.804 15 6.2% 0.061(4.0, 0.26) Mohinadshahi 2017 0.4 1.852 14 0.2 3.804 15 6.2% 0.061(4.0, 0.26) Sabic 2019 0.433 0.544 31 -0.067 0.467 30 11.7% 0.71(-1.23, 0.19] Sabic 2019 0.433 0.544 31 -0.067 0.467 30 0.17% 0.71(-1.23, 0.19] Sabic 2017 1.4 3.238 23 -1.36 0.01 22 9.4% 0.02[0.60, 0.57] Total (95% C) 2.53 1.06 .0.1 22 9.4% 0.02[0.60, 0.57] Total (95% C) 2.53 1.06 .0.1 22 9.4% 0.02[0.60, 0.57] Total (95% C) 2.53 0.01 22 11.407 17 7.8% 0.41[0.27, 1.09] -2 - 0 - 0 - 0 - 0 - 0 - 0 - 0 - 0 - 0 -	Hsieh 2018	-32	81.24	22	-3.07	72.22	22	9.0%	-0.37 [-0.97, 0.23]	
Kapingkib) 2018 -7.95 7.071 31 -1.03 9.709 22 9.8% -0.35[+40, -0.26] Mohamadshahi 2014 -1.44 3.065 22 -0.31 1.864 22 9.0% -0.46 [-0.3, 0.16] Salic 2019 -0.43 0.64 31 -0.067 0.467 30 17.7% -0.7[+1.23, 0.16] Salic 2017 -1.4 3.238 23 -1.36 0.01 22 9.4% -0.02 [-0.60, 0.57] Tonuci 2017 -1.4 3.238 23 -1.36 0.01 22 9.4% -0.02 [-0.60, 0.57] Tonuci 2017 -1.4 3.238 23 -1.36 0.01 22 9.4% -0.02 [-0.60, 0.57] Tonuci 2017 -1.4 3.238 23 -1.36 0.01 22 9.4% -0.02 [-0.60, 0.57] Tonuci 2017 -1.4 3.238 23 -1.36 0.01 22 9.4% -0.02 [-0.60, 0.57] Tonuci 2017 -1.4 3.238 23 -1.36 0.01 22 9.4% -0.02 [-0.60, 0.57] Tonuci 2017 -1.4 3.238 23 -1.36 0.01 22 9.4% -0.02 [-0.60, 0.57] Tonuci 2017 -1.4 3.238 23 -1.36 0.01 22 9.4% -0.02 [-0.60, 0.57] Tonuci 2017 -1.4 3.238 23 -1.36 0.01 22 9.4% -0.02 [-0.60, 0.57] Teat for overall effect Z = 3.96 (P < 0.001) <b>5</b> <b>7</b> <b>7</b> <b>7</b> <b>8</b> <b>7</b> <b>7</b> <b>8</b> <b>1</b> <b>1</b> <b>7</b> <b>8</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b>	Kobyliak(a) 2018	-7.53	7.29	30	1.17	11.22	28	11.3%	-0.67 [-1.20, -0.14]	
National 2017 0 04 1.652 14 02 3.804 15 6.2% 006 [1066 0.79] Mahamadahal 2014 -1.44 3.055 22 -0.31 1.864 22 90% -0.44 [1:03, 0:16] Sabic 2017 -1.4 3.238 23 -1.36 0.01 22 9.4% -0.02 [-0.60, 0.57] Torula (9% C) 288 24 -0.39); P = 6% Torula (9% C) 288 24 -0.39); P = 6% Test for overall effect: Z = 3.96 (P < 0.0001) <b>3</b> <b>Probiotics</b> Control Std. Mean Difference Std.	Kobyliak(b) 2018	-7.95	7 071	31	1.03	9 709	22	9.8%	-0.83 [-1.40 -0.26]	
Muhamadahal 2014 - 1.44 3.085 22 -0.31 1.884 22 0.0% 0.44 [13.0.16] Satio 2019 0.433 0.54 31 -0.067 0.467 30 11.7% -0.7[ F.123, 0.16] Satio 2017 - 1.4 3.238 23 -1.36 0.01 22 9.4% -0.02 [-0.60, 0.57] Tonuci 2017 - 1.4 3.238 23 -1.36 0.01 22 9.4% -0.02 [-0.60, 0.57] Tatal (9% CI) 258 Control Std. Mean Difference Std. Mean Difference Std. Mean Difference Std. Mean Difference V. Random 95% CI Favours [Probiotics] Favours [control] Std. 2017 - 0.158 0.56 2 0.09 18 22 10.0% 0.02 [-0.57, 0.5] Mazdoon 2013 - 0.68 1.576 16 -1.29 2.433 18 7.8% 0.29 [-0.34], 0.66 1.47 - 2.55 9.428 [2 2.99 % -0.05 [-1.3, 0.6] Kobylak(b) 2014 - 4.53 7.84 30 -0.39 5.83 28 12.1% -0.06 [-1.3, 0.6] Kobylak(b) 2014 - 4.63 7.84 30 -0.39 5.83 28 12.1% -0.06 [-1.3, 0.6] Kobylak(b) 2014 - 4.63 7.84 30 -0.39 5.83 28 12.1% -0.06 [-1.3, 0.6] Kobylak(b) 2014 - 4.63 7.84 30 -0.39 5.83 28 12.1% -0.06 [-1.3, 0.6] Kobylak(b) 2014 - 4.63 7.84 30 -0.39 5.83 28 12.1% -0.06 [-1.3, 0.6] Kobylak(b) 2014 - 4.62 3.948 22 0.55 9.428 02 2 0.58 4.50 13.10.08] Kobylak(b) 2014 - 4.62 3.948 22 0.55 9.428 02 2 1.13% -0.21 [-0.76, 0.3] Satio 2017 - 0.158 0.508 23 -0.325 0.661 22 10.1% 0.28 [-0.31, 0.87] Tonucci 2017 - 0.158 0.508 23 -0.325 0.661 22 10.1% 0.28 [-0.31, 0.87] Tonucci 2017 - 0.158 0.508 23 -0.325 0.661 22 10.1% 0.28 [-0.31, 0.87] Total (9% CI) - 23.04 4.27 0.32 1.72 4.44.3% 0.009 [-0.38, 0.75] Total (9% CI) - 0.33 (-94 2.22 1.30% -0.31 [-0.26, 0.45] Total 2017 - 0.4 3.42.84 1.0 0.21 1.20 0.08 0.22 22 0.05 0.77 - 1.02 [-0.76, 0.3] Total 2017 - 0.4 3.42.84 1.0 0.21 1.20 0.08 0.22 22 0.05 0.05 0.27 Total 0.05 (P = 0.52) <b>1.58</b> 0.05 (P = 0.52) <b>1.59</b> 0.05 (P = 0.5	Mohini 2017	0.4	1.852	14	0.2	3 804	15	6.2%	0.06[-0.66_0.79]	
Nonline Status 2019       -1,44       -3,60       -2       -0,31       1,02       -0,32       -1,74       -0,35       -0,16         Satus 2017       0       0.5       34       0       0.3       34       13,76       -0,02       17,76       -0,02       17,76       -0,02       17,76       -0,02       17,76       -0,02       17,76       -0,02       17,76       -0,02       10,76       -0,02       10,76       -0,02       10,76       -0,02       10,76       -0,02       10,76       -0,02       10,76       -0,02       10,76       -0,02       10,76       -0,02       10,76       -0,02       10,76       -0,02       10,76       -0,02       10,76       -0,01       10,76       -0,01       11,76       -0,01       11,76       -0,01       11,76       -0,01       11,76       -0,01       11,76       -0,01       11,76       -0,01       11,76       -0,01       11,76       -0,01       11,76       -0,01       11,76       -0,01       11,76       -0,01       11,76       -0,01       11,76       -0,01       11,76       -0,01       11,76       -0,01       11,76       -0,01       11,77       -0,17       -0,01       11,776       -0,01       11,776       -0	Mohamadahahi 2014	1 1 1	2 095	22	0.2	1 964	22	0.2%	0.44 [ 1.03, 0.16]	
Salot 2017 0 0 05 34 0 07 04 31 1000 040 047 30 11.73 10.7 [1.2, 0.19] Torrucz 2017 - 1.1 4 3.238 23 -1.36 0.01 22 94% -0.02 [0.60, 0.57] Total (35% Cl) 258 2 240 100.0% -0.37 [0.56, 0.19] Total (35% Cl) 258 2 240 100.0% -0.37 [0.56, 0.19] Test for overall effect Z = 3.96 (P < 0.0001) Std. Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight V. Random 95% Cl Favours [Probiotics] Favours [control] Std. Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight V. Random 95% Cl I (1.664 17 -2.28 11407 17 7.8% 0.04 [1.0, 2.1], 0.08] Kobylak(b) 2018 -4.63 7.84 30 -0.39 5.83 28 12.1% -0.60 [-1.3, 0.08] Kobylak(b) 2018 -4.63 7.84 30 -0.39 5.83 28 12.1% -0.60 [-1.3, 0.08] Kobylak(b) 2018 -4.63 7.84 30 -0.39 5.83 28 12.1% -0.60 [-1.3, 0.08] Kobylak(b) 2018 -4.63 7.84 30 -0.39 5.83 28 12.1% -0.60 [-1.3, 0.08] Kobylak(b) 2018 -4.63 7.84 30 -0.39 5.83 28 12.1% -0.60 [-1.3, 0.08] Kobylak(b) 2018 -4.63 7.84 30 -0.39 5.83 28 12.1% -0.60 [-1.3, 0.08] Kobylak(b) 2018 -4.63 7.84 30 -0.39 5.83 28 12.1% -0.60 [-1.3, 0.08] Kobylak(b) 2018 -4.63 7.84 30 -0.39 5.83 28 12.1% -0.60 [-1.3, 0.08] Kobylak(b) 2018 -4.63 7.84 30 -0.39 5.83 28 12.1% -0.60 [-1.3, 0.08] Kobylak(b) 2018 -4.63 7.84 20 0.22 1 33 +1.49% 0.09 [-0.38, 0.65] Torucci 2017 -0.158 0.508 23 -0.325 0.661 22 10.1% 0.28 [-0.31, 0.67] Torucci 2017 -0.158 0.508 23 -0.325 0.661 22 10.1% 0.28 [-0.31, 0.67] Torucci 2017 -0.158 0.508 23 -0.325 0.661 22 10.1% 0.28 [-0.31, 0.67] Torucci 2017 -0.158 0.508 23 -0.325 0.661 22 10.1% 0.28 [-0.31, 0.67] Torucci 2017 -0.158 0.508 23 -0.325 0.661 22 10.1% 0.28 [-0.31, 0.67] Torucci 2017 -0.158 0.508 23 -0.325 0.661 22 10.1% 0.28 [-0.31, 0.67] Torucci 2017 -0.158 0.508 23 -0.325 0.661 22 10.1% 0.28 [-0.31, 0.67] Total (9% Cl) 2.23 0.44 24 0.02 0.2 1.769 20 7.4% -0.31 [0.50, 0.69] Total (9% Cl) 2.23 0.66 10 0.21 0.78 0.21 0.79 0.20 0.26 117 Not semanber Total Coro 2013 0.66 0.25 0.27 0.21 0.28 0.27 0.29 0.28 0.21 0.49 0.29 0.49 0.20 0.49 0.29 0.20 0.29 0.20 0.29 0.20 0.20 0.2	Rehies 2010	-1.44	0.544	22	-0.31	0.407	22	9.0 %	-0.44 [-1.03, 0.10]	
Salo 2017 1.4 3 2.28 23 - 1.3 6 0.0 23 34 1.3 8% 0.00 [0.48, 0.48] Torbuci 2017 1.4 3 2.28 23 - 1.3 6 0.0 22 9.4% 0.02 [0.60, 0.67] Total (95% CI) 258 23 - 1.3 6 0.0 22 9.4% 0.02 [0.60, 0.67] Total (95% CI) 258 23 - 1.0 6.4 df = 10 (P = 0.39); P = 6% Total (95% CI) 258 23 - 0.001) Study or Subgroup Man SD Total Mean SD Total Weight W. Random 95% CI V. Random 95% CI Eliuz Tipici 2020 1.61 6.664 17 -2.28 11.407 17 7.8% 0.41 [0.27, 1.09] Farg 2020 -2.083 1.702 8 -1.51 2.378 7 3.6% 0.21 [0.76] Study or Subgroup Man SD Total Mean SD Total Weight W. Random 95% CI V. Random 95% CI Eliuz Tipici 2020 1.61 6.664 17 -2.28 11.407 17 7.8% 0.41 [0.27, 1.09] Farg 2020 -2.083 1.702 8 -1.51 2.378 7 3.6% 0.21 [0.76, 0.61] Mazioon 2013 -0.68 1.576 16 -1.29 2.433 18 7.8% 0.22 [0.30, 0.61] Mazioon 2013 -0.68 1.576 16 -1.29 2.433 18 7.8% 0.29 [0.30, 0.61] Mazioon 2013 -0.68 1.576 16 -1.29 2.433 18 7.8% 0.29 [0.30, 0.61] Mazioon 2013 -0.68 1.576 16 -1.29 2.433 18 7.8% 0.29 [0.30, 0.61] Mazioon 2013 -0.68 1.576 16 -1.29 2.433 18 7.8% 0.29 [0.30, 0.61] Mazioon 2013 -0.68 1.576 16 -1.29 2.24 22 10.0% -0.31 [0.27, 0.46] Favours [Probiotics] Favours [control] Total (95% CI) -24 22 0.05 (P = 0.52) Favours [Probiotics] Favours [control] Cherry Subgroup Man SD Total Man SD Total Man SD Total Weight W. Random 95% CI Favours [Probiotics] Favours [control] Favours [Probiotics] Favours [control]	Sabico 2019	-0.433	0.544	31 -0	0.067	0.467	30	11.7%	-0.71[-1.23, -0.19]	
Totuci (201/7 - 1.4 3.238 2.3 -1.36 0.01 2.2 9.4% - 0.02 [0.00, 0.7] Total (95% CI) 2.28 2.4 1.36 0.01 2.2 9.4% - 0.02 [0.00, 0.7] Total (95% CI) 2.28 2.40 100.0% - 0.37 [0.56, -0.19] 	Sato 2017	0	0.5	34	1 00	0.3	34	13.8%	0.00 [-0.48, 0.48]	
Total (95% C)       228       240       100.0%       -0.37 [-0.56, -0.19]         Heterogeneity: Tau" = 0.01; Ch" = 10.64. df = 10 (P = 0.39); P = 6%       -0.37 [-0.56, -0.19]       -1       Favours [Probletics]       Std. Mean Difference       Std.	I onucci 2017	-1.4	3.238	23	-1.36	0.01	22	9.4%	-0.02 [-0.60, 0.57]	1
Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 10.64, df = 10 (P = 0.39); P = 6% Test for overall effect: Z = 3.96 (P < 0.0001) Probiotics Control Std. Mean Difference Std. Mean Difference Std. Mean Difference V. Random, 95% Cl Liuz Tipici 2020 1.61 6.664 17 - 228 11.407 17 7.8% Probiotics 2.093 1.702 8 -1.51 2.378 7 3.6% -0.27 [-1.29, 0.75] Fang 2020 -2.093 1.702 8 -1.51 2.378 7 3.6% -0.27 [-1.29, 0.76] Fang 2020 -2.093 1.702 8 -1.51 2.378 7 3.6% -0.27 [-1.29, 0.76] Fang 2020 -2.093 1.702 8 -1.51 2.378 7 3.6% -0.27 [-1.29, 0.76] Fang 2020 -2.093 1.702 8 -1.51 2.378 12 10.0% Ox02 [-0.57, 0.61] Gobylia(k) 2018 -3.45 8.24 31 -1.89 6.004 22 11.3% Fabiliz 7.016 0.058 12.3 -0.39 5.83 28 12.1% -0.02 [-0.57, 0.61] Gobylia(k) 2013 -0.68 1.576 16 -1.29 2.433 18 7.8% 0.29 [-0.39, 0.96] Watamashani 2014 -0.42 3.948 22 0.05 9.426 22 9.9% -0.13 [-0.72, 0.46] Satio 2017 0.4 2.8 34 0.2 1 3.4 14.4% 0.09 [-0.38, 0.57] Total (95% Cl) 2.34 2.22 100.0% -0.07 [-0.27, 0.13] -2	Fotal (95% CI)		2	258			240	100.0%	-0.37 [-0.56, -0.19]	
Study or Subgroup         Probiotics         Control         Std. Mean Difference         Std. Mean Difference         V. Random, 95%, CI           Fing 2020         -0.093         1.702         8         -1.51         2.378         7         3.6%         -0.21 [-1.26, 0.76]         V. Random, 95%, CI         V. Random, 95%, CI           Fing 2020         -2.093         1.702         8         -1.51         2.378         7         3.6%         -0.27 [-1.29, 0.76]           Fing 2020         -2.091         1.8         2.100, %         -0.02 [-1.67, 0.034]         -0.02 [-1.67, 0.034]           Mazicom 2013         -0.88         1.576         1.6         2.2         0.99%         -0.13 [-0.72, 0.46]           Sabio 2019         -7         1.1579         3.1         -0.32 [-0.30, 0.46]         -0.46 [-0.31, 0.87]           Mazicom 2017         -0.158         0.508         2.3         -0.32 [-1.34         1.4.4%         0.09 [-0.38, 0.57]           Tonucci 2017         -0.158         0.508         2.3         -0.32 [-1.28         -0.07 [-0.27, 0.13]         -0.27 [-0.27, 0.13]           Heterogenetity: Tau" = 0.01; Chi" = 10.30, df = 0 (P = 0.33); P = 13%         Total Weight         V. Random, 95% CI         N. Random, 95% CI           Std. Mean Difference         V. Random, 1	Heterogeneity: Tau² = 0 Test for overall effect: Z	).01; Chi² = Հ = 3.96 (P	= 10.64, df < 0.0001)	= 10 (P	= 0.39);	I² = 6%				2 -1 0 1 Favours [Probiotics] Favours [control]
Study or Subgroup         Mean         SD         Total         Mean         SD         Total         Weight         V. Random. 95% CI         V. Random. 95% CI           Eluz Tipici 2020         -2.093         1.702         8         -1.51         2.378         7         3.6%         -0.27 [-1.29, 0.75]         -1.51         -1.58%         0.41 (-0.27, 1.09)           Fang 2020         -2.093         1.702         8         -1.51         2.378         7         3.6%         -0.27 [-1.29, 0.75]         -1.51         -0.51         0.57         0.61]           Gobyliak(2) 2018         -3.45         8.24         31         -1.89         6.004         22         11.3%         -0.21 [-0.76, 0.34]         -0.61]         -0.63         -0.66]         -0.27         -0.41         -0.61         -0.53         -0.61         -0.21 [-0.76, 0.34]         -0.21 [-0.76, 0.34]         -0.21 [-0.76, 0.34]         -0.21 [-0.39, 0.96]         -0.21 [-0.39, 0.96]         -0.21 [-0.39, 0.96]         -0.21 [-0.39, 0.96]         -0.21 [-0.39, 0.96]         -0.21 [-0.39, 0.96]         -0.21 [-0.39, 0.96]         -0.21 [-0.39, 0.96]         -0.21 [-0.39, 0.96]         -0.21 [-0.39, 0.96]         -0.21 [-0.39, 0.57]         -0.21 [-0.39, 0.57]         -0.21 [-0.39, 0.57]         -0.21 [-0.39, 0.57]         -0.21 [-0.39, 0.57]         -0.21 [-0.50, 0										
Study or Subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV. Random. 95% CI         IV. Random. 95% CI           Eliuz Tipici 2020         1.61         6.664         17         -2.28         11.407         17         7.8%         0.41 [-0.27, 1.09]           Fang 2020         -2.093         1.702         8         -1.51         2.378         7         3.6%         -0.27 [-1.29, 0.75]           Heieh 2018         0.95         2.65         22         0.9         1.8         221         10.0%         -0.02 [-0.57, 0.61]           Kobyliak(b) 2018         -3.45         8.24         31         -1.89         6.004         22         11.3%         -0.21 [-0.76, 0.34]           Mazarom 2013         -0.68         1.576         16         -1.29         2.43         18         7.8%         0.29 [-0.38, 0.617]           Satio 2019         -7         11.579         31         -3.7         6.902         30         13.0%         -0.37 [-0.31, 0.87]           Total (95% CI)         234         222         100.0%         -0.07 [-0.27, 0.13]         -1         -1         Favours [control]           Std. Yang         D.016         0.231         20	2	Pro	biotics		Con	trol		5	Std. Mean Difference	Std. Mean Difference
Eliuz Tipici 2020       1.61       6.664       17       -2.28       11.407       17       7.8%       0.41 [-0.27, 1.09]         Fang 2020       -2.093       1.702       8       -1.51       2.378       7       3.6%       -0.27 [-1.29, 1.76]         Kobyliak(a) 2018       -4.63       7.84       30       -0.39       5.83       28       12.1%       -0.00 [-1.13, -0.08]         Kobyliak(b) 2018       -3.45       8.24       31       -1.89       6.004       22       1.3%       -0.021 [-0.76, 0.34]         Mazicom 2013       -0.68       1.576       16       -1.29       2.433       18       7.8%       0.22 [-0.39, 0.66]         Mazicom 2019       -7       11.579       31       -3.76       6.092       30       17%       0.02 [-0.31, 0.67]         Satio 2017       0.4       2.8       34       0.2       1       31       3.76       6.092       30       3.057]         Tonuc 2017       0.4       2.8       34       0.2       1       3.0       2.02       1.03.7       0.23       2.00.7       0.23       2.02       1.007       0.23       2.03       1.037       1.02       1.03       1.037       1.037       1.037 <t< td=""><td>Study or Subaroup</td><td>Mean</td><td>SD T</td><td>otal N</td><td>lean</td><td>SD T</td><td>otal</td><td>Weight</td><td>IV. Random, 95% CI</td><td>IV. Random, 95% CI</td></t<>	Study or Subaroup	Mean	SD T	otal N	lean	SD T	otal	Weight	IV. Random, 95% CI	IV. Random, 95% CI
$ \frac{1}{12} Triphologo 2010 - 2.093 1.702 8 - 1.51 2.378 7 3.6\% - 0.27 [-1.29, 0.75] + 1.50 1.309 + 1.50 1.2.378 7 3.6\% - 0.27 [-1.29, 0.75] + 1.50 1.2.378 7 3.6\% - 0.27 [-1.29, 0.75] + 1.50 1.2.378 7 3.6\% - 0.27 [-1.29, 0.75] + 1.50 1.2.378 7 3.6\% - 0.27 [-1.29, 0.75] + 1.50 1.2.578 + 1.50$	Eliuz Tinici 2020	1.61	6 664	17	2 28 14	407	17	7 90/	10.11 CO.1 10.0	
Problem 2019 1.2019 1.2019 1.2019 1.2010 1.8 22 10.0% 0.02 [0.57, 0.61] Kobyliak(b) 2018 - 4.63 7.84 30 - 0.39 5.83 28 12.1% - 0.60 [-1.13, -0.08] Kobyliak(b) 2018 - 3.45 8.24 31 - 1.89 6.004 22 11.3% - 0.21 [-0.76, 0.34] Mazloom 2013 - 0.68 1.576 16 - 1.29 2.433 18 7.8% 0.29 [-0.39, 0.96] Mohamadshahi 2014 - 0.42 3.944 22 0.55 9.426 22 9.9% - 0.13 [-0.72, 0.46] Sabico 2017 - 0.4 2.8 34 0.2 1 3 34 14.4% 0.09 [-0.38, 0.57] Tonucci 2017 - 0.4 2.8 34 0.2 1 3 34 14.4% 0.09 [-0.38, 0.57] Tonucci 2017 - 0.158 0.508 23 - 0.325 0.661 22 10.1% 0.28 [-0.31, 0.87] Total (95% CI) 234 222 100.0% -0.07 [-0.27, 0.13] Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 10.30, if = 9 (P = 0.33); I <sup>2</sup> = 13% Test for overall effect: Z = 0.65 (P = 0.52) Probiotics Control Std. Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV. Random .95% CI Nandom .95% CI Saya 2.20 0.76 - 0.03 [-0.58] 17 Not estimable Std. Mean Difference Std. Mean Diffe		2 002	4 700		4 54 0	.407	7	2.60/	0.41 [-0.27, 1.09]	
Histen 2018 0.95 2.65 22 0.9 1.8 22 10.9% 0.02 [-0.3, 0.61] Kobyliak(a) 2018 4.83 7.84 30 -0.39 5.83 28 12.1% -0.60 [-1.13, -0.08] Kobyliak(a) 2018 -3.45 8.24 31 -1.89 6.004 22 11.3% -0.21 [-0.76, 0.34] Mazloom 2013 -0.68 1.576 16 -1.29 2.433 18 7.8% 0.29 [-0.39, 0.96] Mazloom 2013 -0.68 1.576 16 -1.29 2.433 18 7.8% 0.29 [-0.39, 0.96] Mohamadshahi 2014 -0.42 3.948 22 0.55 9.426 22 9.9% -0.21 [-0.7, 0.34] Sabico 2019 -7 11.579 31 -3.7 6.902 30 13.0% -0.34 [-0.36, 0.17] Sabico 2017 -0.158 0.508 23 -0.325 0.661 22 10.1% 0.28 [-0.31, 0.87] Total (95% Cl) 234 222 100.0% -0.07 [-0.27, 0.13] Heterogeneity: Tau <sup>2</sup> = 0.01; Ch <sup>2</sup> = 10.30, df = 9 (P = 0.33); P = 13% Test for overall effect: Z = 0.65 (P = 0.52) Probiotics Control Std. Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV. Random 95% Cl IV. Random, 95%	Fang 2020	-2.093	1.702	8 .	1.51 2	.378	1	3.6%	-0.27 [-1.29, 0.75]	
Kobylak(b) 2018 -4.63 7.84 30 -0.39 5.83 28 12.1% -0.60 (-1.3.0.08] Mazloom 2013 -0.68 1.576 16 -1.29 2.433 18 7.8% 0.29 [-0.39, 0.96] Malandshahi 2014 -0.42 3.948 22 0.55 9.426 22 9.9% -0.13 [-0.76, 0.34] Mazloom 2013 -0.68 1.576 16 -1.29 2.433 18 7.8% 0.29 [-0.39, 0.96] Mohamadshahi 2014 -0.42 3.948 22 0.55 9.426 22 9.9% -0.13 [-0.72, 0.46] Sabico 2017 0.4 2.8 34 0.2 1 34 14.4% 0.09 [-0.38, 0.57] Tonucci 2017 -0.158 0.508 23 -0.325 0.661 22 10.1% 0.28 [-0.31, 0.87] Total (95% Cl) 234 222 100.0% -0.07 [-0.27, 0.13] Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 10.30, df = 9 (P = 0.33); P = 13% Total (95% Cl) 234 222 100.0% -0.07 [-0.27, 0.13] Heterogeneity: Tau <sup>2</sup> = 0.05; Ch <sup>2</sup> = 0.52) Probiotics Control Std. Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV. Random 95% Cl IV. Random, 95% C	Hsieh 2018	0.95	2.65	22	0.9	1.8	22	10.0%	0.02 [-0.57, 0.61]	
Kobyliak(b) 2018 -3.45 8.24 31 -1.89 6.004 22 11.3% -0.21 [ $-0.76$ , 0.34] Mazloom 2013 -0.68 1.576 16 -1.29 2.433 18 7.8% 0.29 [ $-0.39$ , 0.96] Mohamadshahi 2014 -0.42 3.948 22 0.55 9.426 22 9.9% -0.13 [ $-0.72$ , 0.46] Sabico 2019 -7 11.579 31 -3.7 6.902 30 13.0% -0.34 [ $-0.85$ , 0.17] Tonucci 2017 -0.158 0.508 23 -0.325 0.661 22 10.1% 0.09 [ $-0.38$ , 0.57] Tonucci 2017 -0.158 0.508 23 -0.325 0.661 22 10.1% 0.28 [ $-0.31$ , 0.87] Total (95% Cl) 234 222 100.0% -0.07 [ $-0.27$ , 0.13] Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 10.30, df = 9 (P = 0.33); P = 13% Test for overall effect: Z = 0.65 (P = 0.52) 5 Total Mean SD Total Weight IV. Random, 95% Cl Favours [Probiotics] Favours [control] Study or Subgroup Mean SD Total Mean SD Total Mean SD Total Weight IV. Random, 95% Cl Favours [Probiotics] Favours [control] Feizollahzadeh 2017 -0.3 4.424 20 -0.2 1.769 20 7.4% -0.03 [ $-0.66$ ], 0.59] Finuz 2017 0.23 2.7 48 -0.36 3 53 12.6% 0.20 [ $-0.90$ , 0.69] How 2015 -0.2 1.196 23 0.033 1.695 18 7.4% -0.16 [ $-0.78$ , 0.48] Heish 2018 0.03 0.19 22 0.08 0.28 22 7.8% -0.21 [ $-0.80$ , 0.39] Mazloom 2013 1,158.94 3,425.49 16 1,881.74 4,145.214 18 6.5% -0.16 [ $-0.78$ , 0.48] Mohamadshahi 2014 -0.46 2.052 22 0.21 1.913 22 7.8% -0.21 [ $-0.90$ , 0.39] Mazloom 2013 1,158.94 3,425.49 16 1,881.74 4,145.214 18 6.5% -0.16 [ $-0.78$ , 0.48] Mazloom 2013 1,158.94 3,425.49 16 1,881.74 4,145.214 18 6.5% -0.18 [ $-0.80$ , 0.39] Mazloom 2013 1,158.94 3,425.49 16 1,881.74 4,145.214 18 6.5% -0.18 [ $-0.38$ , 0.39] Mazloom 2013 1,158.94 3,425.49 16 1,881.74 4,145.214 18 6.5% -0.18 [ $-0.38$ , 0.39] Mazloom 2013 1,158.94 3,425.49 16 1,881.74 4,145.214 18 6.5% -0.21 [ $-0.80$ , 0.39] Mazloom 2013 1,158.94 3,425.49 16 1,881.74 4,145.214 18 6.5% -0.21 [ $-0.80$ , 0.39] Mazloom 2013 1,158.94 3,425.49 16 1,881.74 4,145.214 18 6.5% -0.21 [ $-0.80$ , 0.39] Mazloom 2013 1,158.94 3,425.49 16 1,881.74 4,145.214 18 6.5% -0.21 [ $-0.80$ , 0.39] Mazloom 2013 1,158.94 3,425.49 16 1,881.74 4,145.214 18 6.5% -0.21 [ $-0.80$ , 0.39] Mazloom 2013 1,158.94 3,425.49 16 1,881.74 4,145.214 18 6.5% -0.2	Kobyliak(a) 2018	-4.63	7.84	30 -	0.39	5.83	28	12.1%	-0.60 [-1.13, -0.08]	
Mazloom 2013 -0.68 1.576 16 -1.29 2.433 18 7.8% 0.29 (-0.39, 0.96) Mohamadshahi 2014 -0.42 3.948 22 0.55 9.426 22 9.9% -0.13 [-0.72, 0.46] Sabico 2019 -7 11.579 31 -3.7 6.902 30 13.0% -0.34 [-0.85, 0.17] Sato 2017 0.4 2.8 34 0.2 1 34 14.4% 0.09 [-0.38, 0.57] Tonucci 2017 -0.158 0.508 23 -0.325 0.661 22 10.1% 0.28 [-0.31, 0.87] Total (95% Cl) 234 222 100.0% -0.07 [-0.27, 0.13] -2 -1 0 1 Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 10.30, df = 9 (P = 0.33); P = 13% Test for overall effect: Z = 0.65 (P = 0.52) Problotics Control Std. Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV. Random. 95% Cl Problotics Control Std. Mean Difference Std. Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV. Random. 95% Cl Prova 2017 0.23 2.7 48 -0.36 35 120 6.7% -1.02 [-1.68, -0.35] Fizual 19202 0 0 0 17 0.02 0.581 17 Not estimable Fizual 196 2017 0.23 1.27 48 -0.36 35 12.2 7.8% -0.21 [-0.80, 0.39] Hisieh 2018 0.03 0.19 22 0.08 0.282 27 8% -0.21 [-0.80, 0.39] Hisieh 2018 0.03 0.19 22 0.08 0.28 22 7.8% -0.21 [-0.80, 0.39] Hisieh 2018 0.03 0.19 22 0.08 0.28 22 7.8% -0.21 [-0.80, 0.39] Hisieh 2018 0.03 0.19 22 0.08 0.28 22 7.8% -0.21 [-0.80, 0.39] Hisieh 2018 0.04 0.15 2.22 0.21 1.511 32 2.7.8% -0.21 [-0.80, 0.39] Hisieh 2018 0.04 0.15 2.22 0.21 1.913 22 7.8% -0.21 [-0.80, 0.39] Hisieh 2018 0.04 0.15 2.22 0.21 1.913 22 7.8% -0.21 [-0.80, 0.39] Hisieh 2018 0.04 0.19 2.2 0.01 0.278 3.30 9.3% -0.70 [-1.22, -0.18] Sabico 2017 1.25.33 222.894 34 7.983 3.30.471 34 10.3% 0.06 [-0.66, 0.79] Mohamadshahi 2014 -1.302 2.924.1 27 -586.9 2.009.2 27 8.9% -0.22 [-0.83, 0.24] Histerogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 17.08, df = 11 (P = 0.11); l <sup>2</sup> = 36% Total (95% Cl) -2.207 (P = 0.04) Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 17.08, df = 11 (P = 0.11); l <sup>2</sup> = 36% Total (95% Cl) -2.07 (P = 0.04) Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 17.08, df = 11 (P = 0.11); l <sup>2</sup> = 36% Total (95% Cl) -2.07 (P = 0.04)	Kobyliak(b) 2018	-3.45	8.24	31 -	1.89 6	.004	22	11.3%	-0.21 [-0.76, 0.34]	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Mazloom 2013	-0.68	1.576	16 -	1.29 2	.433	18	7.8%	0.29 [-0.39, 0.96]	
Sabico 2019 -7 11.579 31 -3.7 6.902 30 13.0% -0.34 [-0.85, 0.17] Sato 2017 0.4 2.8 34 0.2 1 34 14.4% 0.09 [-0.38, 0.57] Tonucci 2017 -0.158 0.508 23 -0.325 0.661 22 10.1% 0.28 [-0.31, 0.87] Total (95% Cl) 234 222 100.0% -0.07 [-0.27, 0.13] Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 10.30, df = 9 (P = 0.33); l <sup>2</sup> = 13% Test for overall effect: Z = 0.65 (P = 0.52) Probiotics Control Std. Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV. Random, 95% Cl V. Random, 95% Cl Eliuz Tipici 2020 0 0 17 0.02 0.581 17 Not estimable Fizoularizadeth 2017 0.3 4.424 20 0.02 1.769 20 7.4% -0.03 [-0.66, 0.59] Firouzi 2017 0.23 2.7 48 -0.36 13 53 12.6% 0.616 [-0.78, 0.46] How 2015 -0.2 1.196 23 0.033 1.695 18 7.4% -0.16 [-0.78, 0.46] How 2015 -0.2 1.196 23 0.033 1.695 18 7.4% -0.16 [-0.78, 0.46] How 2015 -0.2 1.196 23 0.033 1.695 18 7.4% -0.16 [-0.78, 0.46] How 2015 -0.2 1.196 23 0.033 1.695 18 7.4% -0.18 [-0.86, 0.49] Maziom 2013 1.158.94 3.425.49 16 1.881.74 4.145.214 18 6.5% -0.21 [-0.80, 0.39] Mazom 2013 1.158.49 3.425.49 16 1.881.74 4.145.214 18 6.5% -0.34 [-0.86, 0.79] Mazom 2013 1.158.49 3.425.49 16 1.881.74 4.145.214 18 6.5% -0.34 [-0.86, 0.49] Mohamadshahi 2014 -0.46 2.052 22 0.21 1.913 22 7.8% -0.33 [-0.93, 0.26] Total (95% Cl) 324 32 0.00 0.1 2.551 33 9.5% -0.34 [-0.86, 0.79] Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 17.08, df = 11 (P = 0.11); l <sup>2</sup> = 36% Test for overall effect: Z = 2.07 (P = 0.04) Favours [Probletics] Favours [control]	Mohamadshahi 2014	-0.42	3.948	22	0.55 9	.426	22	9.9%	-0.13 [-0.72, 0.46]	
Sato 2017 0.4 2.8 34 0.2 1 34 14.4% 0.09 [-0.38, 0.57] Tonucci 2017 -0.158 0.508 23 -0.325 0.661 22 10.1% 0.28 [-0.31, 0.87] Total (95% CI) 234 222 100.0% -0.07 [-0.27, 0.13] Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 10.30, df = 9 (P = 0.33); P = 13% Test for overall effect: Z = 0.65 (P = 0.52) Probiotics Control Std. Mean Difference Std. Mean Difference Std. M				24	37 6	902	30	13.0%	-0 34 [-0 85 0 17]	
Total (95% CI) Total (95% CI) Total (95% CI) Total (95% CI) Total (95% CI) Probiotics Study or Subgroup Mean SD Total SD Total S	Sabico 2019	-7	11.579	31	-0.7 0	.002	00	10.070	0.04 0.00. 0.171	
Total (95% CI) 234 22 100.0% -0.07 [-0.27, 0.13] Heterogeneity: Tau <sup>2</sup> = 0.01; Ch <sup>2</sup> = 10.30, df = 9 (P = 0.33); l <sup>2</sup> = 13% Test for overall effect: Z = 0.65 (P = 0.52) Probiotics Control Std. Mean Difference Std. Std. Mean Difference Std. Std. Mean Difference Std. Mean Difference Std. Std. Mean Difference Std. Mean Difference Std. Mean Difference Std. Std. Mean Difference Std. Mean Difference Std. Mean Difference Std. Mean Difference Std. Std. Std. Mean Difference Std. Std. Std. Std. Std. M	Sabico 2019 Sato 2017	-7 0.4	11.579 2.8	31	0.2	1	34	14.4%	0.09 [-0.38, 0.57]	<b>_</b>
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Sabico 2019 Sato 2017 Tonucci 2017	-7 0.4 -0.158	11.579 2.8 0.508	31 34 23 -0	0.2 0.325 0	1 .661	34 22	14.4% 10.1%	0.09 [-0.38, 0.57] 0.28 [-0.31, 0.87]	
Test for overall effect: $Z = 0.65$ (P = 0.52) Probiotics Control Std. Mean Difference Std. Std. Mean Difference Std. Std. Mean Diffe	Sabico 2019 Sato 2017 Tonucci 2017 Total (95% Cl)	-7 0.4 -0.158	11.579 2.8 0.508	31 34 23 -0 234	0.2 0.325 0	1 .661	34 22 222	14.4% 10.1%	0.09 [-0.38, 0.57] 0.28 [-0.31, 0.87]	
Probiotics         Control         Std. Mean Difference         Std. Mean Difference         Std. Mean Difference           Study or Subgroup         Mean         SD         Total         Weight         IV. Random, 95% Cl         IV. Random, 95% Cl           Bayat 2016         -0.16         0.231         20         0.08         0.232         20         6.7%         -1.02 [-1.68, -0.35]           Eliuz Tipici 2020         0         0         17         0.02         0.581         17         Not estimable           Firouzi 2017         0.23         2.7         48         -0.36         3         53         12.6%         0.20 [-0.19, 0.60]           Hove 2015         -0.2         1.196         23         0.033         1.695         18         7.4%         -0.18 [-0.86, 0.49]           Mazloom 2013         1.158.94         3.425.49         16         1.881.74         4.145.214         18         6.5%         -0.38 [-0.86, 0.49]           Mobini 2017         0.4         1.852         14         0.2         3.804         15         5.8%         0.06 [-0.66, 0.79]           Mohamadshahi 2014         -0.46         2.052         2.2         0.21         1.913         2.2         7.8%         -0.33 [-0.85, 0.17]     <	Sabico 2019 Sato 2017 Tonucci 2017 <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = (	-7 0.4 -0.158 0.01: Chi <sup>2</sup>	11.579 2.8 0.508 = 10.30. d	31 34 23 -0 <b>234</b> f = 9 (P	-3.7 0 0.2 0.325 0 = 0.33);	1 .661 I² = 13%	34 22 222	14.4% 10.1% 100.0%	0.09 [-0.38, 0.57] 0.28 [-0.31, 0.87] -0.07 [-0.27, 0.13]	
Probiotics         Control         Std. Mean Difference         Std. Mean Difference         Std. Mean Difference         Std. Mean Difference           Bayat 2016         -0.16         0.231         20         0.08         0.232         20         6.7%         -1.02 [-1.68, -0.35]         IV. Random. 95% CI         IV. Random. 95% CI           Eliuz Tipici 2020         0         0         17         0.02         0.581         17         Not estimable           Feizollahzadeh 2017         -0.3         4.424         20         -0.2         1.769         20         7.4%         -0.03 [-0.65, 0.59]           Firozzi 2017         0.23         2.7         48         -0.36         3         53         12.6%         0.20 [-0.19, 0.60]           Hove 2015         -0.2         1.196         23         0.033         1.695         18         7.4%         -0.16 [-0.78, 0.46]	Sabico 2019 Sato 2017 Tonucci 2017 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: Z	-7 0.4 -0.158 0.01; Chi <sup>2</sup> Z = 0.65 (F	11.579 2.8 0.508 = 10.30, d P = 0.52)	31 34 23 -0 <b>234</b> f = 9 (P	0.2 0.325 0 = 0.33);	1 .661 I² = 13%	34 22 222	14.4% 10.1%	-0.07 [-0.38, 0.57] 0.28 [-0.31, 0.87] -0.07 [-0.27, 0.13] -2	-1 0 1 Favours [Probiotics] Favours [control]
Statuty of subgroup       mean       SD       Total       Mean       SD       SD       SD       SD <th< th=""><th>Sabico 2019 Sato 2017 Tonucci 2017 Total (95% CI) Heterogeneity: Tau<sup>2</sup> = ( Test for overall effect: 2</th><th>-7 0.4 -0.158 0.01; Chi<sup>2</sup> Z = 0.65 (F</th><th>11.579 2.8 0.508 = 10.30, d P = 0.52)</th><th>31 34 23 -0 <b>234</b> f = 9 (P</th><th>0.2 0.325 0 = 0.33);</th><th>1 .661 I² = 13%</th><th>34 22 222 6</th><th>14.4% 10.1%</th><th>0.09 [-0.38, 0.57] 0.28 [-0.31, 0.87] -0.07 [-0.27, 0.13] -2</th><th>-1 0 1 Favours [Probiotics] Favours [control]</th></th<>	Sabico 2019 Sato 2017 Tonucci 2017 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2	-7 0.4 -0.158 0.01; Chi <sup>2</sup> Z = 0.65 (F	11.579 2.8 0.508 = 10.30, d P = 0.52)	31 34 23 -0 <b>234</b> f = 9 (P	0.2 0.325 0 = 0.33);	1 .661 I² = 13%	34 22 222 6	14.4% 10.1%	0.09 [-0.38, 0.57] 0.28 [-0.31, 0.87] -0.07 [-0.27, 0.13] -2	-1 0 1 Favours [Probiotics] Favours [control]
Jagar 2010       -0.10       0.231       20       0.00       0.222       20       0.7       -1.02 [1.06, -0.35]         Eliuz Tipici 2020       0       0       17       Not estimable         erizollahzadeh 2017       -0.3       4.424       20       -0.2       1.769       20       7.4%       -0.03 [-0.65, 0.59]         Firouzi 2017       0.23       2.7       48       -0.36       3       53       12.6%       0.20 [-0.19, 0.60]         Hote Stimable       -0.2       1.196       23       0.033       1.695       18       7.4%       -0.01 [-0.65, 0.59]         Hote Stimable       0.03       0.19       22       0.08       0.28       22       7.8%       -0.21 [-0.80, 0.39]         Mazloom 2013       1.158.94       3.425.49       16       1.881.74       4.145.214       18       6.5%       -0.03 [-0.86, 0.49]         Mohanadshahi 2014       -0.46       2.052       22       0.21       1.913       22       7.8%       -0.33 [-0.33, 0.26]         Sabico 2019       -1.867       2.766       31       0.167       2.973       30       9.3%       -0.71 [-1.22, -0.18]         Sabico 2019       -1.867       2.766.9       2.009.2       2	Sabico 2019 Sato 2017 Tonucci 2017 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2	-7 0.4 -0.158 0.01; Chi <sup>2</sup> Z = 0.65 (F	11.579 2.8 0.508 = 10.30, d P = 0.52)	31 34 23 -0 234 f = 9 (P	0.2 0.2 0.325 0 = 0.33);	1 .661 I <sup>2</sup> = 13%	34 22 2222	14.4% 10.1% 100.0%	0.09 [-0.38, 0.57] 0.28 [-0.31, 0.87] -0.07 [-0.27, 0.13] -2 Std. Mean Difference	Favours [Probiotics] Favours [control]
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$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Sabico 2019 Sato 2017 Tonucci 2017 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Study or Subgroup Bayat 2016 Eliuz Tipici 2020 Seivellopade 2017	-7 0.4 -0.158 0.01; Chi <sup>2</sup> Z = 0.65 (F <u>P</u> <u>Mear</u> -0.16	11.579 2.8 0.508 = 10.30, d P = 0.52) Probiotics 5 0.231 0 0	31 34 23 -C 234 f = 9 (P <u>Total</u> 20 17		<b>Control</b> <b>Control</b> <b>Control</b>	34 22 222 6 5 5 5 81 760	14.4% 10.1% 100.0%	0.09 [-0.38, 0.57] 0.28 [-0.31, 0.87] -0.07 [-0.27, 0.13] -2 Std. Mean Difference ight IV. Random. 95% C .7% -1.02 [-1.68, -0.35] Not estimable	Std. Mean Difference
The constant of the constant	Sabico 2019 Sato 2017 Tonucci 2017 <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Study or Subgroup Bayat 2016 Eliuz Tipici 2020 Feizollahzadeh 2017	-7 0.4 -0.158 0.01; Chi <sup>2</sup> Z = 0.65 (F <u>P</u> <u>Mear</u> -0.16 0 0.0	11.579 2.8 0.508 = 10.30, d P = 0.52) Probiotics 1 SD 5 0.231 0 0 3 4.424	31 34 23 -C 234 f = 9 (P <u>Total</u> 20 17 20		1 .661   <sup>2</sup> = 13%	34 22 222 5 5 5 8 1 7 6 9	14.4% 10.1% 100.0%	0.09 [ 0.38, 0.57]         0.09 [-0.38, 0.57]           0.28 [-0.31, 0.87]         -0.07 [-0.27, 0.13]           -0.07 [-0.27, 0.13]         -2           Std. Mean Difference         -2           ight         IV. Random. 95% C           .7%         -1.02 [-1.68, -0.35]           Not estimable         4%           .4%         -0.03 [-0.65, 0.59]	Std. Mean Difference
Hsten 2018       0.03       0.19       22       0.08       0.28       22       7.8%       -0.21 [-0.80, 0.39]         Mazloom 2013       1,158.94       3,425.49       16       1,881.74       4,145.214       18       6.5%       -0.18 [-0.86, 0.49]         Mobini 2017       0.4       1.852       14       0.2       3.804       15       5.8%       0.06 [-0.66, 0.79]         Mohamadshahi 2014       -0.46       2.052       22       0.21       1.913       22       7.8%       -0.31 [-0.85, 0.17]         Sabico 2019       -1.867       2.766       31       0.167       2.973       30       9.5%       -0.34 [-0.85, 0.17]         Sabico 2019       -1.867       2.766       31       0.167       2.973       30       9.3%       -0.70 [-1.22, -0.18]         Sato 2017       125.333       222.894       34       79.833       330.471       34       10.3%       0.16 [-0.32, 0.64]         Fajedadi-Ebrahimi 2014       -1,330.2       2.924.1       27       -586.9       2.009.2       27       8.9%       -0.29 [-0.83, 0.24]         Heterogeneity:       Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 17.08, df = 11 (P = 0.11); I <sup>2</sup> = 36%       26       100.0%       -0.21 [-0.42, -0.01]       -2       -1	Sabico 2019 Sato 2017 Tonucci 2017 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Study or Subgroup Bayat 2016 Elluz Tipici 2020 Feizollahzadeh 2017 Firouzi 2017 Luce 2017	-7 0.4 -0.158 0.01; Chi <sup>2</sup> Z = 0.65 (F <u>Mear</u> -0.16 0.2 0.22	11.579 2.8 0.508 = 10.30, d = 0.52) Probiotics 5 0.231 0 0 3 4.424 3 2.7	31 34 23 -0 <b>234</b> f = 9 (P <u><b>Total</b></u> 20 17 20 17 20		1 .661   <sup>2</sup> = 13%	34 22 222 222 58 581 769 305	<b>Total We</b> 20 6 17 20 7 53 12	Std. Mean Difference Std. Mean Difference Std. Mean Difference 10.28 [-0.37, 0.13] -0.07 [-0.27, 0.13] -2 Std. Mean Difference -2 Std. Mean Difference -2 Std. Mean Difference -2 Std. Mean Difference -2 -2 -2 -2 -2 -2 -2 -2 -2 -2	Std. Mean Difference
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Sabico 2019 Sato 2017 Tonucci 2017 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: Z Study or Subgroup Sayat 2016 Eliuz Tipici 2020 Feizollahzadeh 2017 Firouzi 2017 Hove 2015	-7 0.4 -0.158 0.01; Chi <sup>2</sup> 1 Z = 0.65 (F <u>Mean</u> -0.16 0.23 -0.2 -0.2	11.579 2.8 0.508 = 10.30, d P = 0.52) Probiotics 1 SE 5 0.231 0 0 3 4.424 3 2.7 2 1.196	31 34 23 -0 <b>234</b> f = 9 (P <b>Total</b> 20 17 20 17 20 48 5 23		1 .661   <sup>2</sup> = 13% Control 0. 0. 0. 1.	34 22 222 5 5 5 5 7 6 9 5 8 7 6 9 5 8 1 7 6 9 5 8 1 7 6 9 5 8 1 7 6 9 5 8 1 7 6 9 5 8 1 7 9 1 8 1 9 1 9 1 9 1 9 1 9 1 9 1 9 1 9 1	14.4% 10.1% 100.0% 100.0%	0.09 [-0.38, 0.57]           0.28 [-0.31, 0.87]           -0.07 [-0.27, 0.13]           -2           Std. Mean Difference           ight         IV. Random. 95% C           .7%         -1.02 [-1.68, -0.35]           Not estimable           .4%         -0.03 [-0.65, 0.59]           .6%         0.20 [-0.19, 0.60]           .4%         -0.16 [-0.78, 0.46]	Std. Mean Difference
viconin 2017       0.4       1.852       14       0.2       3.804       15       5.8%       0.06 [-0.66, 0.79]         Wohamadshahi 2014       -0.46       2.052       22       0.21       1.913       22       7.8%       -0.33 [-0.33, 0.26]         Raygan 2018       -0.8       2.706       30       0.167       2.973       30       9.5%       -0.34 [-0.85, 0.17]         Sabico 2019       -1.867       2.766       31       0.167       2.973       30       9.3%       -0.70 [-1.22, -0.18]         Satio 2017       125.333       222.894       34       79.833       330.471       34       10.3%       0.16 [-0.32, 0.64]         Tajadadi-Ebrahimi 2014       -1,330.2       2,924.1       27       -586.9       2,009.2       27       8.9%       -0.29 [-0.83, 0.24]         Total (95% Cl)       324       326       100.0%       -0.21 [-0.42, -0.01]       -2       -1       0       1         Heterogeneity:       Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 17.08, df = 11 (P = 0.11); I <sup>2</sup> = 36%       Total (95% Cl)       -2       -1       0       1         Favours [Forobiotics]       Favours [control]       Favours [control]       -2       -1       0       1	Sabico 2019 Sato 2017 Tonucci 2017 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Study or Subgroup Bayat 2016 Eliuz Tipici 2020 Feizollahzadeh 2017 Firouzi 2017 Hove 2015 Heich 2018	-7 0.4 -0.158 0.01; Chi <sup>2</sup> Z = 0.65 (F <u>P</u> <u>Mear</u> -0.16 0 0.23 0.22 -0.2	11.579 2.8 0.508 = 10.30, d = 0.52) Probiotics $\frac{SD}{5}$ 0.231 0 3 4.424 3 2.7 2 1.196 3 0.19	31 34 23 -0 234 f = 9 (P 10 17 20 48 20 48 20 48 20 20 48 20 20 20 20 20 20 20 20 20 20 20 20 20		1 1 1 1 1 1 1 1 1 1 1 1 1 1	34 22 222 222 5 5 5 7 69 3 695 3 695 3 695 3 232	14.4% 10.1% 100.0% 100.0% 20 6 17 20 7 53 12 18 7 22 7 22 7	0.09 [-0.38, 0.57]           0.28 [-0.31, 0.87]           -0.07 [-0.27, 0.13]           -2           Std. Mean Difference           ight         IV. Random. 95% C           .7%         -1.02 [-1.68, -0.35]           Not estimable           .4%         -0.03 [-0.65, 0.59]           .6%         0.20 [-0.19, 0.60]           .4%         -0.16 [-0.78, 0.46]           .8%         -0.21 [-0.80, 0.39]	Std. Mean Difference
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Sabico 2019 Sato 2017 Tonucci 2017 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Study or Subgroup Bayat 2016 Eliuz Tipici 2020 Feizollahzadeh 2017 Firouzi 2017 Hove 2015 Hsieh 2018 Vazioom 2013 Vazio 2027	-7 0.4 -0.158 0.01; Chi <sup>2</sup> Z = 0.65 (F <u>P</u> <u>Mear</u> -0.16 0.22 -0.2 0.023 1,158.94	11.579 2.8 0.508 = 10.30, d P = 0.52) robiotics 0 0.231 0 0 3 4.424 3 2.7 2 1.196 3 0.19 4 3.425.49	31 34 23 -0 <b>234</b> f = 9 (P 17 20 17 20 17 20 48 23 20 17 20 20 17 20 17 20 20 17 20 20 17 20	0.2 0.2 0.325 0 0.333); = 0.33); = 0.33); 0.08 0.02 -0.2 -0.2 -0.36 0.033 0.08 1,881.74	<b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b>	34 22 222 56 581 769 3 695 28 214	Iat.4%           10.1%           100.0%           20         6           17           20         7           18         7           18         7           18         7           18         7           18         6	Std. Mean Difference           ight         1.0.2 [-0.38, 0.57]           0.28 [-0.31, 0.87]           -0.07 [-0.27, 0.13]           -2           Std. Mean Difference           ight         IV. Random. 95% C           .7%         -1.02 [-1.68, -0.35]           Not estimable           .4%         -0.03 [-0.65, 0.59]           .6%         0.20 [-0.19, 0.60]           .4%         -0.16 [-0.78, 0.46]           .8%         -0.21 [-0.80, 0.39]           .5%         -0.18 [-0.86, 0.49]	Std. Mean Difference
Raygan 2018 $-0.8$ $2.706$ $30$ $0.1$ $2.551$ $30$ $9.5\%$ $-0.34$ [ $-0.85$ , $0.17$ ]         Sabico 2019 $-1.867$ $2.766$ $31$ $0.167$ $2.973$ $30$ $9.3\%$ $-0.70$ [ $-1.22$ , $-0.18$ ]         Sabico 2017 $125.333$ $222.894$ $34$ $79.833$ $330.471$ $34$ $10.3\%$ $0.16$ [ $-0.32$ , $0.64$ ]         Tajadadi-Ebrahimi 2014 $-1,330.2$ $2,924.1$ $27$ $-586.9$ $2,009.2$ $27$ $8.9\%$ $-0.29$ [ $-0.83$ , $0.24$ ]         Total (95% Cl) $324$ $326$ $100.0\%$ $-0.21$ [ $-0.42$ , $-0.01$ ] $-2$ $-1$ $0$ $1$ Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 17.08, df = 11 (P = 0.11); I <sup>2</sup> = 36\%       Test for overall effect: Z = 2.07 (P = 0.04) $-2$ $-1$ $0$ $1$	Sabico 2019 Sato 2017 Tonucci 2017 <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Study or Subgroup Bayat 2016 Eliuz Tipici 2020 Feizollahzadeh 2017 Firouzi 2017 Hove 2015 Hsieh 2018 Mazloom 2013 Mobini 2017	-7 0.4 -0.158 0.01; Chi <sup>2</sup> Z = 0.65 (F <u>P</u> <u>Mear</u> -0.16 0.23 -0.2 0.03 1,158.94 0.4	11.579         2.8         0.508         = 10.30, d         P = 0.52)         Probiotics         1         SD         0.231         0         0         2         0.231         0         0         3         2.7         1.196         3         3         4         3.425.49         4         1.852         0         0         2         2         2         2         2         2         2         3         2         3         3         3         3         3         2         2         2           3          3          2          3          3          3          3          3          4 <t< td=""><td>31 34 23 -0 234 f = 9 (P 5 20 17 20 17 20 17 20 5 23 20 17 20 17 20 17 20 17 20 17 20 17 20 17 20 17 20 17 20 17 20 20 17 20 20 20 20 20 20 20 20 20 20 20 20 20</td><td></td><td><b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b></td><td>34 22 222 222 58 232 581 769 3 695 0.28 214 804</td><td>Total         We           10.1%         100.0%           100.0%         100.0%           100.0%         17           20         7           20         7           20         7           20         7           100.0%         100.0%</td><td>Std. Mean Difference           0.09 [-0.38, 0.57]           0.28 [-0.31, 0.87]           -0.07 [-0.27, 0.13]          </td><td>Std. Mean Difference</td></t<>	31 34 23 -0 234 f = 9 (P 5 20 17 20 17 20 17 20 5 23 20 17 20 17 20 17 20 17 20 17 20 17 20 17 20 17 20 17 20 17 20 20 17 20 20 20 20 20 20 20 20 20 20 20 20 20		<b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b>	34 22 222 222 58 232 581 769 3 695 0.28 214 804	Total         We           10.1%         100.0%           100.0%         100.0%           100.0%         17           20         7           20         7           20         7           20         7           100.0%         100.0%	Std. Mean Difference           0.09 [-0.38, 0.57]           0.28 [-0.31, 0.87]           -0.07 [-0.27, 0.13]	Std. Mean Difference
Sabico 2019 -1.867 2.766 31 0.167 2.973 30 9.3% -0.70 [-1.22, -0.18] Sato 2017 125.333 222.894 34 79.833 330.471 34 10.3% 0.16 [-0.32, 0.64] Fajadadi-Ebrahimi 2014 -1.330.2 2.924.1 27 -586.9 2.009.2 27 8.9% -0.29 [-0.83, 0.24] Total (95% Cl) 324 326 100.0% -0.21 [-0.42, -0.01] Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 17.08, df = 11 (P = 0.11); I <sup>2</sup> = 36% Test for overall effect: Z = 2.07 (P = 0.04) -2 -1 0 1 Favours [Probiotics] Favours [control]	Sabico 2019 Sato 2017 Tonucci 2017 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: Z Study or Subgroup Sayat 2016 Eliuz Tipici 2020 Feizollahzadeh 2017 Firouzi 2017 Hove 2015 Hsieh 2018 Mazloom 2013 Mobini 2017 Mohamadshahi 2014	-7 0.4 -0.158 0.01; Chi <sup>2</sup> 1 Z = 0.65 (F <u>P</u> <u>Mean</u> -0.16 0.23 0.23 0.23 0.23 0.24 0.24 0.24 0.24	11.579 2.8 0.508 = 10.30, d = 0.52) Probiotics 1 SP 5 0.231 0 0 3 4.424 3 2.7 2 1.196 3 0.19 4 3.422.49 4 3.422.49 4 3.422.49 5 2.652 	31 34 23 -C 234 f = 9 (P 5 7 20 16 20 20 48 20 48 20 48 20 16 14 20 14 20 14 20 14		<b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b>	34 22 222 5 5 5 8 1 232 232 5 8 1 7 6 9 5 8 1 232 5 8 1 3 6 95 0.28 214 804 913	Total         We           10.1%         10.0%           100.0%         100.0%           100.0%	0.09 [-0.38, 0.57]           0.09 [-0.38, 0.57]           0.28 [-0.31, 0.87]           -0.07 [-0.27, 0.13]           -2           Std. Mean Difference           ight         IV. Random. 95% C           .7%         -1.02 [-1.68, -0.35]           Not estimable           .4%         -0.03 [-0.65, 0.59]           .6%         0.20 [-0.19, 0.60]           .4%         -0.16 [-0.78, 0.46]           .8%         -0.33 [-0.80, 0.49]           .8%         -0.33 [-0.93, 0.26]	Std. Mean Difference IV. Random, 95% Cl
Sato 201 / 125.333 222.894 34 79.833 330.471 34 10.3% 0.16 [-0.32, 0.64] Tajadadi-Ebrahimi 2014 -1,330.2 2,924.1 27 -586.9 2,009.2 27 8.9% -0.29 [-0.83, 0.24] Total (95% Cl) 324 326 100.0% -0.21 [-0.42, -0.01] Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 17.08, df = 11 (P = 0.11); I <sup>2</sup> = 36% Test for overall effect: Z = 2.07 (P = 0.04)	Sabico 2019 Sato 2017 Tonucci 2017 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: Z Study or Subgroup Bayat 2016 Eliuz Tipici 2020 Feizollahzadeh 2017 Firouzi 2017 Hove 2015 Hsieh 2018 Mazloom 2013 Mobini 2017 Mohamadshahi 2014 Raygan 2018	-7 0.4 -0.158 0.01; Chi <sup>2</sup> Z = 0.65 (F <u>P</u> <u>Mear</u> -0.16 0.23 0.23 0.23 0.23 0.24 0.03 1.158.94 0.04 0.04 0.04 0.04	11.579 2.8 0.508 = 10.30, d = 0.52) robiotics = 0.52) probiotics = 0.52) probiotics = 0.52) 0 0 3 4.424 3 2.7 2 1.196 3 0.194 4 3.425.494 4 3.425.494 4 3.425.495 2 3.2.756 3 2.756	31 34 23 -C 234 f = 9 (P 50 17 20 17 20 17 20 17 20 48 23 22 16 14 14 22 30		Control	34 22 222 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	Io. 10         Io. 10           10.1%         10.0%           100.0%         100.0%           100.0%         10           20         6           17         20           20         7           30         7           18         7           22         7           18         6           15         5           22         7           30         9	0.09 [-0.38, 0.57]           0.09 [-0.38, 0.57]           0.28 [-0.31, 0.87]           -0.07 [-0.27, 0.13]           -2           Std. Mean Difference           ight         IV. Random. 95% C           .7%         -1.02 [-1.68, -0.35]           Not estimable           .4%         -0.03 [-0.65, 0.59]           .6%         0.20 [-0.19, 0.60]           .4%         -0.16 [-0.78, 0.46]           .8%         -0.21 [-0.80, 0.39]           .5%         -0.18 [-0.86, 0.49]           .8%         -0.33 [-0.93, 0.26]           .5%         -0.34 [-0.85, 0.17]	Std. Mean Difference 
Tajadadi-Ebrahimi 2014       -1,330.2       2,924.1       27       -586.9       2,009.2       27       8.9%       -0.29 [-0.83, 0.24]         Total (95% Cl)       324       326       100.0%       -0.21 [-0.42, -0.01]       -2       -1       0       1         Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 17.08, df = 11 (P = 0.11); I <sup>2</sup> = 36%       -2       -1       0       1         Fest for overall effect: Z = 2.07 (P = 0.04)       -2       -1       0       1	Sabico 2019 Sato 2017 Tonucci 2017 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Study or Subgroup Bayat 2016 Eliuz Tipici 2020 Feizollahzadeh 2017 Firouzi 2017 Hove 2015 Hsieh 2018 Vazloom 2013 Vohamadshahi 2014 Raygan 2018 Sabico 2019	-7 0.4 -0.158 0.01; Chi <sup>2</sup> Z = 0.65 (F P Mear -0.16 0.22 -0.2 0.023 0.03 1,158.94 0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4 -0.4	11.579         2.8         0.508         = 10.30, d $P = 0.52$ $P = $	31 34 23 -0 234 f = 9 (P Total 20 17 20 17 20 18 22 16 14 22 30 31	0.2 0.2 0.325 0 0.325 0 0.33); 0.88 0.02 -0.2 -0.36 0.033 0.08 1,881.74 0.2 0.21 0.167	1         1         12         13%         12         12         13%         12         12         13%         14         15         16         1         1         1         1         1         1         2         1         2         2         2	34 22 222 222 55 55 3 695 232 5581 769 3 695 232 5581 769 3 695 214 804 913 551 973	Ia.4%           10.1%           100.0%           100.	Std. Mean Difference           0.09 [-0.38, 0.57]           0.28 [-0.31, 0.87]           -0.07 [-0.27, 0.13]           -0.07 [-0.27, 0.13]           -0.07 [-0.27, 0.13]           -2           Std. Mean Difference           ight         IV. Random. 95% C           .7%         -1.02 [-1.68, -0.35]           Not estimable           .4%         -0.03 [-0.65, 0.59]           .6%         0.20 [-0.19, 0.60]           .4%         -0.18 [-0.86, 0.49]           .8%         -0.21 [-0.80, 0.39]           .5%         -0.18 [-0.86, 0.49]           .8%         0.06 [-0.66, 0.73]           .5%         -0.34 [-0.85, 0.17]           .3%         -0.70 [-1.22, -0.18]	Std. Mean Difference
Total (95% Cl)         324         326         100.0%         -0.21 [-0.42, -0.01]           Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 17.08, df = 11 (P = 0.11); l <sup>2</sup> = 36%         -2         -1         0         1           Test for overall effect: Z = 2.07 (P = 0.04)         Favours [Probletics]         Favours [control]         -2         -1         0         1	Sabico 2019 Sato 2017 Tonucci 2017 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Study or Subgroup Bayat 2016 Eliuz Tipici 2020 Feizollahzadeh 2017 Firouzi 2017 Hove 2015 Hsieh 2018 Mazloom 2013 Mobini 2017 Mohamadshahi 2014 Raygan 2018 Sabico 2019 Sato 2017	-7 0.4 -0.158 0.01; Chi <sup>2</sup> Z = 0.65 (F <u>P</u> <u>Mear</u> -0.16 0.22 -0.2 0.03 1,158.94 0.46 -0.6 -0.46 -0.46 -0.46 -0.46 -0.46 -0.46 -0.46 -0.46 -0.46 -0.46 -0.46 -0.40	11.579 2.8 0.508 = 10.30, d = 0.52) robiotics 1 SD 5 0.231 0 0 3 4.424 3 2.7 2 1.196 3 0.19 4 3.425.49 4 1.852 5 2.052 3 2.2766 7 2.766 3 222.894	31 34 23 -C 234 f = 9 (P Total f = 9 (P 10 20 10 20 10 21 20 10 10 21 20 10 10 31 31 34 34 34 34 34 34 34 34 34 34		Control 2 = 13% Control 0. 0. 1. 0. 1. 0. 1. 0. 1. 0. 2. 1. 3. 3. 1. 3. 3. 3. 3. 3. 3. 3. 3. 3. 3	34 22 222 5 5 2232 581 769 3 695 228 214 804 913 5551 973 471	Total         We           10.1%         100.0%           100.0%         17           20         6           17         20           20         7           20         7           18         6           15         5           22         7           30         9           30         9           34         10	Std. Mean Difference           0.09 [-0.38, 0.57]           0.28 [-0.31, 0.87]           -0.07 [-0.27, 0.13]           -0.07 [-0.27, 0.13]           -2           Std. Mean Difference           ight         IV. Random. 95% C           .7%         -1.02 [-1.68, -0.35]           Not estimable           .4%         -0.03 [-0.65, 0.59]           .6%         0.20 [-0.19, 0.60]           .4%         -0.16 [-0.78, 0.48]           .8%         -0.21 [-0.80, 0.39]           .5%         -0.31 [-0.85, 0.49]           .8%         0.06 [-0.66, 0.79]           .8%         -0.33 [-0.33, 0.26]           .5%         -0.34 [-0.85, 0.17]           .3%         0.16 [-0.32, 0.64]	Std. Mean Difference
Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 17.08, df = 11 (P = 0.11); l <sup>2</sup> = 36%       -2       -1       0       1         Fest for overall effect: Z = 2.07 (P = 0.04)       Favours (Probiotics)       Favours (control)	Sabico 2019 Sato 2017 Tonucci 2017 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Study or Subgroup Bayat 2016 Eliuz Tipici 2020 Feizollahzadeh 2017 Firouzi 2017 Hove 2015 Hsieh 2018 Mazloom 2013 Mobim 2017 Mohamadshahi 2014 Raygan 2018 Sabico 2019 Sato 2017 Tajadadi-Ebrahimi 2014	-7 0.4 -0.158 0.01; Chi <sup>2</sup> Z = 0.65 (F <u>P</u> <u>Mear</u> -0.16 0.22 -0.2 0.022 -0.2 0.023 -0.2 0.023 -0.2 0.023 -0.2 0.023 -0.2 0.023 -0.2 0.023 -0.2 0.023 -0.2 0.035 -0.2 0.2 0.2 0.2 0.2 0.2 0.2 0.2 0.2 0.2	11.579         2.8         0.508         = 10.30, d $P = 0.52$ $P = $	31 34 23 -C 234 f = 9 (P Total f = 9 (P 10 10 10 10 10 10 10 10 10 10		<b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b>	34 22 222 5 5 5 1 5 5 5 5 5 5 5 5 5 5 5 1 9 13 5 5 1 9 13 5 5 1 9 13 5 5 1 9 13 5 5 1 9 13 5 5 1 9 13 5 14 14 14 14 15 14 14 14 15 14 14 14 14 14 14 14 14 14 14 14 14 14	Iat.4%           10.1%           100.0%           100	Std. Mean Difference           ight         IV. Random. 95% C           .7%         -1.02 [-1.68, -0.35]           Not estimable         .4%           .6%         0.20 [-0.18, 0.45]           .7%         -1.02 [-1.68, -0.35]           Not estimable         .4%           .6%         0.20 [-0.19, 0.60]           .6%         0.20 [-0.19, 0.60]           .6%         0.20 [-0.18, 0.49]           .8%         -0.21 [-0.80, 0.39]           .5%         -0.18 [-0.86, 0.49]           .8%         0.06 [-0.66, 0.79]           .5%         -0.33 [-0.33, 0.26]           .5%         -0.34 [-0.85, 0.17]           .3%         0.16 [-0.32, 0.64]           .9%         -0.29 [-0.83, 0.24]	Std. Mean Difference IV. Random. 95% Cl
Test for overall effect: Z = 2.07 (P = 0.04) -2 -1 0 1 Favours [Probiotics] Favours [control]	Sabico 2019 Sato 2017 Tonucci 2017 <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Study or Subgroup Bayat 2016 Eliuz Tipici 2020 Feizollahzadeh 2017 Firouzi 2017 Hove 2015 Hsieh 2018 Mazloom 2013 Mohamadshahi 2014 Raygan 2018 Sabico 2019 Sato 2017 Tajadadi-Ebrahimi 2014 <b>Total (95% CI)</b>	-7 0.4 -0.158 0.01; Chi <sup>2</sup> Z = 0.65 (F P Mear -0.16 0.22 -0.2 0.03 1,158.94 0.4 -0.6 -0.5 0.46 -0.46 -0.46 -0.46 -0.46 -0.46 -0.46 -0.46 -0.46 -0.4 -0.40 -0.5 -0.23 -0.23 -0.23 -0.23 -0.23 -0.45 -0.4 -0.4 -0.45 -0.4 -0.58 -0.4 -0.58 -0.4 -0.58 -0.4 -0.58 -0.58 -0.55 -0.	11.579         2.8         0.508         = 10.30, d $P = 0.52$ $P = $	31 34 23 -C 234 f = 9 (P Total f = 9 (P Total 20 10 10 10 20 10 10 10 20 10 10 20 10 10 20 10 20 10 20 20 20 20 20 20 20 20 20 2		<b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b>	34 22 222 6 6 7 8 1 232 232 581 3 695 3 695 3 238 214 804 913 551 973 471 9973	Total       We         100.0%       100.0%         100.0%       100.0%         100.0%       100.0%         100.0%       100.0%         100.0%       100.0%         100.0%       100.0%         100.0%       100.0%         100.0%       100.0%         100.0%       100.0%         100.0%       100.0%         100.0%       100.0%         100.0%       100.0%         100.0%       100.0%         100.0%       100.0%	Std. Mean Difference           ight         IV. Random. 95% C           .7%         -1.02 [-1.68, -0.35]           Not estimable	Std. Mean Difference IV. Random. 95% Cl
	Sabico 2019 Sato 2017 Tonucci 2017 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Study or Subgroup Bayat 2016 Eliuz Tipici 2020 Feizollahzadeh 2017 Firouzi 2017 Hove 2015 Hsieh 2018 Mazloom 2013 Mobini 2017 Mohamadshahi 2014 Raygan 2018 Sabico 2019 Sato 2017 Tajadadi-Ebrahimi 2014 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.0	-7 0.4 -0.158 0.01; Chi <sup>2</sup> 1 Z = 0.65 (F <u>P</u> <u>Mear</u> -0.16 0.23 -0.2 0.03 1,158.9 0.4 -0.46 -0.6 -1.867 125.333 -1,330.2	11.579 2.8 0.508 = 10.30, d = 0.52) robiotics 1 SD 5 0.231 0 0 3 4.424 3 2.7 2 1.196 3 0.19 4 3.425.4 4 1.852 5 2.052 3 2.706 7 2.766 3 222.894 2 2,924.1 17.08, df = 1	31 34 23 -C 234 f = 9 (P Total 10 17 200 48 23 20 48 23 16 14 22 16 31 34 27 324 11 (P = 0		Control 2 = 13% Control 3 0. 2 0. 2 1. 3 0. 4,145. 2 3. 1. 3 (1) 4,145. 2 3. 3 (2,00) 36%	34 22 222 5 5 5 5 5 1 5 5 1 7 69 3 695 3 5 5 1 973 471 9973 471	Total       We         10.1%       100.0%         100.0%       100.0%         100.0%       17         20       6         17       20         20       7         20       7         18       6         15       5         22       7         30       9         34       100         27       8         326       100	Std. Mean Difference           0.09 [-0.38, 0.57]           0.28 [-0.31, 0.87]           -0.07 [-0.27, 0.13]           -0.07 [-0.27, 0.13]           -2           Std. Mean Difference           ight           IV. Random. 95% C           .7%           -1.02 [-1.68, -0.35]           Not estimable           .4%           -0.03 [-0.65, 0.59]           .6%           0.20 [-0.19, 0.60]           .4%           -0.16 [-0.78, 0.46]           .8%           -0.21 [-0.80, 0.39]           .5%           -0.33 [-0.93, 0.26]           .5%           .034 [-0.85, 0.17]           .3%         0.16 [-0.32, 0.64]           .9%         -0.29 [-0.83, 0.24]           .0%         -0.21 [-0.42, -0.01]	Std. Mean Difference

Subgroup analysis (**Table 5**) showed that the effects of probiotic supplementation on FPG were significantly reduced in the multistrain subgroup (SMD [95% CI]; -0.30 [-0.54, -0.05],  $I^2 = 33\%$ ), long intervention duration subgroup (SMD [95% CI]; -0.34 [-0.60, -0.09],  $I^2 = 35.5\%$ ), and administration in the form of powder/capsule subgroup (SMD [95% CI]; -0.30 [-0.54, -0.06],  $I^2 = 28.9\%$ ).

In the leave-one-out sensitivity analysis, the pooled effect of probiotic supplementation on the FPG level remained significant among studies compared to the effects in the control group. Furthermore, after the removal of a single study (Bayat et al., 2016), the interstudy heterogeneity decreased from 39 to 16%, while the FPG reduction was still significant in the probiotic group.

Subgroup	No. of trials	No. of participants	<i>I</i> <sup>2</sup> (%)	Pooled SMD [95% CI]
Probiotics dose				
≥10 <sup>10</sup> CFU/day	5	231	0	-0.65 [-0.92, -0.39]
<10 <sup>10</sup> CFU/day	5	226	0	-0.12 [-0.38, 0.14]
NR	1	41	0	-0.26 [-0.88, 0.36]
Probiotics strain				
Single	6	237	0	-0.19 [-0.44, 0.07]
Multiple	5	261	16.6	-0.55 [-0.82, -0.27]
Duration of intervention				
≤8 weeks	6	255	0	-0.47 [-0.72, -0.22]
>8 weeks	5	243	19.1	-0.27 [-0.56, 0.01]
Method of administration				
Powder/capsule	6	260	0	-0.56 [-0.81, -0.31]
Food	5	238	0	-0.18 [-0.44, 0.07]

CFU, colony forming unit; SMD, standardized mean difference.

TABLE 3   Subgrou	o analysis for t	the effects of	probiotics on IL-6.
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Subgroup	No. of trials	No. of participants	<i>I</i> <sup>2</sup> (%)	Pooled SMD [95% CI]
Probiotics dose				
≥10 <sup>10</sup> CFU/day	6	265	10.4	-0.23 [-0.49, 0.03]
<10 <sup>10</sup> CFU/day	3	157	0	0.13 [-0.19, 0.44]
NR	1	34	0	0.29 [-0.39, 0.96]
Probiotics strain				
Single	4	161	0	0.11 [-0.20, 0.42]
Multiple	6	295	29.0	-0.15 [-0.43, 0.12]
Duration of intervention				
≤8 weeks	7	283	30.7	-0.05 [-0.34, 0.24]
>8 weeks	3	173	0	-0.08 [-0.38, 0.22]
Method of administration				
Powder/capsule	6	265	0.8	-0.22 [-0.47, 0.02]
Food	3	157	0	0.08 [-0.23, 0.40]
NR	1	34	0	0.41 [-0.27, 1.09]

TABLE 4 | Subgroup analysis for the effects of probiotics on CRP.

Subgroup	No. of trials	No. of participants	<i>I</i> <sup>2</sup> (%)	Pooled SMD [95% CI]
Probiotics dose				
$\geq 10^{10}$ CFU/day	3	206	74.4	-0.25 [-0.82, 0.31]
< 10 <sup>10</sup> CFU/day	6	295	0	-0.11 [-0.34, 0.12]
NR	3	115	52.9	-0.45 [-1.00, 0.10]
Probiotics strain				
Single	6	276	0	-0.07 [-0.31, 0.17]
Multiple	5	300	50.9	-0.25 [-0.58, 0.09]
NR	1	40	0	-1.02 [-1.68, -0.35]
Duration of intervention				
≤8 weeks	5	212	22.9	-0.36 [-0.67, -0.05]
>8 weeks	7	404	38.8	-0.13 [-0.38, 0.13]
Method of administration				
Powder/capsule	6	329	40.2	-0.19 [-0.48, 0.10]
Food	6	287	41.8	-0.25 [-0.56, 0.06]

### Effect on HbA1c

Ten studies described the significant effect of probiotic intake on reducing HbA1c levels in 499 participants (SMD [95% CI]; -0.19 [-0.37, -0.00], p = 0.040). The heterogeneity among studies ( $I^2 = 4\%$ , p = 0.410) was low (**Figure 5B**).

In the subgroup analysis, significant beneficial effects of probiotic intervention were observed for HbAlc in the multistrain subgroup (SMD [95% CI]; -0.28 [-0.53, -0.02],  $I^2 = 0\%$ ) and administration in the form of a powder/capsule subgroup (SMD [95% CI]; -0.29 [-0.57, -0.02],  $I^2 = 6.6\%$ ) (**Table 6**).



Sensitivity analysis conducted by sequentially omitting one study at a time confirmed that the pooled effect of probiotic supplementation on HbA1c was stable and reliable.

### Effect on HOMA-IR

Ten studies investigated the effect of probiotic supplementation on the HOMA-IR level in a total of 523 participants. Compared to the effect in the control groups, probiotic supplementation significantly reduced the HOMA-IR level (SMD [95% CI]; -0.36 [-0.62, -0.10], p = 0.006), with moderate heterogeneity ( $I^2 = 53\%$ , p = 0.020) among studies (**Figure 5C**).

Due to the moderate heterogeneity among studies, we conducted a subgroup analysis for the effect of probiotic administration on HOMA-IR, which is displayed in **Figure 6**. Probiotic supplementation reduced the HOMA-IR level in the high-dose subgroup (SMD [95% CI]; -0.72 [-1.09, -0.35],  $I^2 = 45.5\%$ ), multistrain subgroup (SMD [95% CI]; -0.47 [-0.86, -0.09],  $I^2$ = 67.5%), long intervention duration subgroup (SMD [95% CI];

TABLE 5	Subaroup	analysis	for the	effects	of	probiotics	on	FPG
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Subgroup	No. of trials	No. of participants	<i>I</i> <sup>2</sup> (%)	Pooled SMD [95% CI]
Probiotics dose				
≥ 10 <sup>10</sup> CFU/day	6	323	49.7	-0.21 [-0.54, 0.11]
< 10 <sup>10</sup> CFU/day	7	340	0	-0.12 [-0.34, 0.09]
NR	3	115	49.1	-0.63 [-1.16, -0.10]
Probiotics strain				
Single	8	340	0	-0.08 [-0.29, 0.14]
Multiple	7	398	33.0	-0.30 [-0.54, -0.05]
NR	1	40	0	-1.18 [-1.86, -0.51]
Duration of intervention				
≤8 weeks	9	374	39.6	-0.14 [-0.41, 0.12]
>8 weeks	7	404	35.5	-0.34 [-0.60, -0.09]
Method of administration				
Powder/capsule	8	412	28.9	-0.30 [-0.54, -0.06]
Food	7	332	43.7	-0.24 [-0.54, 0.05]
NR	1	34	0	0.42 [-0.26, 1.10]
Food NR	7 1	332 34	43.7 0	-0.24 [-0.54, 0.05] 0.42 [-0.26, 1.10]

TABLE 6	Subgroup	analysis for	the effects	of probiotics	on HbAlc.
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Submusium	No. of trials	No. of portioinents	12 (0/)	Dealed SMD 105% CI
Subgroup	NO. OI triais	No. or participants	1 (%)	Pooled SMD [95% CI]
Probiotics dose				
$\geq 10^{10} \text{ CFU/day}$	4	232	0	-0.23 [-0.49, 0.03]
< 10 <sup>10</sup> CFU/day	4	186	56.3	-0.12 [-0.57, 0.33]
NR	2	81	0	-0.28 [-0.72, 0.16]
Probiotics strain				
Single	5	216	42.6	-0.06 [-0.42, 0.30]
Multiple	4	243	0	-0.28 [-0.53, -0.02]
NR	1	40	0	-0.42 [-1.05, 0.20]
Duration of intervention				
≤8 weeks	5	216	0	-0.24 [-0.51, 0.03]
>8 weeks	5	283	45.5	-0.14 [-0.47, 0.19]
Method of administration				
Powder/capsule	4	227	6.6	-0.29 [-0.57, -0.02]
Food	5	238	12.0	-0.14 [-0.41, 0.14]
NR	1	34	100.0	0.12 [-0.55, 0.79]

	Subgroup	No. of trials		SMD with 95% CI	l² (%)	P <sub>heterogeneity</sub>	P <sub>heterogeneity</sub> between subgroup
-	Probiotics dose						
	≥ 10 <sup>10</sup> CFU/day	4	<b></b>	-0.72 [-1.09,-0.35]	45.5	0.138	
	< 10 <sup>10</sup> CFU/day	4		-0.10 [-0.37, 0.18]	0.0	0.751	0.024
	NR	2		0.16 [-0.61, 0.30]	0.0	0.382	
	Probiotics strain						
	Single	4		-0.17 [-0.47, 0.13]	0.0	0.854	0 229
	Multiple	6	<b>_</b>	-0.47 [-0.86,-0.09]	67.5	0.009	0.220
	Duration of intervention	on					
	≤ 8 weeks	5		-0.24 [-0.51, 0.03]	0.0	0.553	0.401
	> 8 weeks	5		-0.46 [-0.90,-0.02]	71.6	0.007	
	Method of administrat	ion					
	Powder/capsule	7		-0.52 [-0.81,-0.23]	47.3	0.077	0.026
	Food	3		-0.01 [-0.35, 0.32]	0.0	0.597	
	VOTE: Weights are from random effects analysis						
		·					
		-1	-0.5 0	0.5			
JRE 6   Subgroup	analysis for the effects	of probiotics on	HOMA-IR.				

-0.46 [-0.90, -0.02],  $I^2 = 71.6\%$ ), and administration in the form of powder/capsule subgroup (SMD [95% CI]; -0.52 [-0.81, -0.23],  $I^2 = 47.3\%$ ). The interstudy heterogeneity remained similar across all effective subgroups.

Sensitivity analysis confirmed that the HOMA-IR level was not significantly changed compared with that of the control groups. When excluding the study by Sabico et al., we found that the interstudy heterogeneity decreased ( $I^2 = 2\%$ , p = 0.420), but the effect on HOMA-IR level remained significant (SMD [95% CI]; -0.29 [-0.47, -0.10]).

#### Publication Bias Analysis

Funnel plots and Egger's test were performed to assess the possible publication bias of the included studies for glycaemic control and inflammatory markers. No evidence of publication bias identified from the funnel plots was found (Figure S1). The results from Egger's tests also showed no evidence of publication bias for FPG (p = 0.990), HbA1c (p = 0.927), HOMA-IR (p = 0.358), TNF- $\alpha$  (p = 0.821), IL-6 (p = 0.500), or CRP (p = 0.161).

### DISCUSSION

T2DM is associated with long-term chronic low-grade inflammation characterized by an increase in some inflammatory markers, such as TNF-a, IL-6, and CRP, contributing to insulin resistance and the pathogenesis of T2DM (Coope et al., 2016; Eguchi and Nagai, 2017). In recent years, several studies have reported that probiotic supplementation has a variable effect on the inflammatory response in T2DM (Raygan et al., 2018; Anhê et al., 2020; Harkins et al., 2020). Therefore, we conducted the present metaanalysis to evaluate the effect of probiotic supplementation on inflammatory markers and glucose homeostasis in adults with T2DM, attempting to investigate its potential role in modulating gut microbiota to ameliorate glycaemic control and inflammatory markers.

Accumulating evidence provides support for the notion that the gut microbiota is critical to maintain human health (Arora et al., 2021; Wei et al., 2021). Dysbiosis of the gut microbiota could stimulate an increase in the levels of inflammatory markers, such as TNF-a and CRP, leading to aberrant immune activation and chronic low-grade inflammation in individuals with T2DM (Frost et al., 2021; Rinninella et al., 2019). There was also a growing body of evidence suggesting that elevated levels of pro-inflammatory markers, including TNF-a, IL-6, and CRP, play a vital role in the pathogenesis of T2DM (Liaqat et al., 2021; Hyun et al., 2013). These pro-inflammatory markers could inhibit insulin signalling pathways, leading to insulin resistance, dysfunction of β-cells, hyperglycaemia, and the occurrence of T2DM (Liagat et al., 2021; Harkins et al., 2020; Descamps et al., 2019). However, probiotics play a vital role in glucose homeostasis, insulin resistance, energy metabolism, and chronic low-grade inflammation (Corb Aron et al., 2021; Namazi et al., 2021; Tilg et al., 2020). Some studies have shown that Akkermansia muciniphila, as a probiotic, could benefit T2DM by modulating gut microbiota LPS prevention and intestinal permeability reduction (Corb Aron et al., 2021; Zhang et al., 2021). Probiotics could regulate the balance of the host's gut

microbiota by increasing or cross-feeding interactions with other potential beneficial microbes, which could increase insulin secretion, restore insulin sensitivity, and improve glucose homeostasis (Corb Aron et al., 2021; Gurung et al., 2020; Cani et al., 2019). Recent studies have reported that probiotic intake could increase the secretion of hormones, such as GLP-1 and PYY, by regulating the gut microbiota and their metabolites to prevent diabetes (Iorga et al., 2020; Zhang et al., 2020). In addition, probiotics consumed with prebiotics, synbiotics, herbs, micronutrients, or other dietary supplements might enhance the modulation of the gut microbiota and their metabolites, including short-chain fatty acids (SCFAs), neuropeptides, and gastrointestinal peptides (Arora et al., 2021). Moreover, these metabolites could reinforce barrier function, affect gut permeability, suppress chronic low-grade inflammation, and improve insulin resistance and glucose metabolism (Figure 7) (Mulders et al., 2018; Tsai et al., 2019; Gurung et al., 2020; Arora et al., 2021). Some studies also revealed that probiotic supplementation could ameliorate T2DM via inhibition of the expression of pro-inflammatory cytokines, chemokines, or inflammatory proteins (Gomes et al., 2017; Sabico et al., 2019; Tilg et al., 2020).

To obtain accurate results of probiotic supplementation on glycaemic control and inflammatory markers, we excluded studies with participants who consumed prebiotics, synbiotics, herbs, micronutrients, or other dietary supplements, which might influence the gut microbiota or interact with probiotics. Eleven studies reported the effect on TNF-a, ten studies described the effect on IL-6, and thirteen studies investigated the effect on CRP were included in the meta-analysis to evaluate the effects of probiotic supplementation on inflammatory markers. In our study, significant effects of probiotic supplementation were observed on TNF-α and CRP. However, there was no significant effect on IL-6 levels. In line with our results, some studies also showed that the participants consumed probiotics and synbiotics, and these supplementations significantly decreased the levels of TNF-a and CRP but had no effect on IL-6 levels. A previous study found that probiotic and synbiotic administration had a significant effect on CRP levels in individuals with diabetes (Zheng et al., 2019). In addition, a similar result was reported: probiotic and synbiotic supplementation decreased the levels of TNF-a and CRP, but there was no significant effect on IL-6 between the diabetes and control groups (Tabrizi et al., 2019). Subgroup analysis was conducted to assess the potentially influential variables, including the duration of interventions, doses of probiotic supplementation, probiotic strains, and methods of probiotic administration. Significant reductions in TNF-a were detected in consuming multiple strains of probiotics, short intervention duration, high probiotic daily doses, and administration in the form of powder/capsule. There were also significant reductions in CRP levels with short intervention durations and the consumption of multiple strain probiotics. In addition, there were no effects on IL-6 levels among those variables.

These meta-analysis results of glycaemic control parameters were also improved significantly in the levels of FPG, HbA1c, and HOMA-IR compared with the control group. Our results relating to FPG and HOMA-IR were similar to those of previous studies, which showed that probiotic intake could reduce the levels of FPG



and HOMA-IR in overweight/obese adults (Wang et al., 2019). However, there was no significant effect on HbA1c levels in their study, which might be because the baseline HbA1c level was lower than that in participants with T2DM. Ardeshirlarijani et al. reported that probiotic intake significantly reduced the level of FPG, while it had no effect on HbA1c levels (Ardeshirlarijani et al., 2019). Moreover, Dong et al. reported that probiotic supplementation improved the levels of HbA1c and HOMA-IR, with no effect on FPG (Dong et al., 2019). In view of previous studies, there were inconsistent results regarding the impact of probiotics on the levels of FPG, HbA1c, and HOMA-IR. Therefore, further evidence is needed to confirm these findings. Subgroup analysis and sensitivity analysis were also conducted in our meta-analysis. The subgroup analysis results showed that the invention groups consuming multiple strains of probiotics or administration in the form of powder/capsule had significantly reduced levels of fasting blood glucose. There were significant reductions in HbA1c levels in those subgroups stratified by probiotic dosage, the number of probiotic strains, duration of intervention, or method of administration. In addition, consistent results were also found for the HOMA-IR level in the subgroup analysis.

However, there were also some potential limitations. First, the sample sizes in all included random clinical trials were small (<60 participants per treatment group). Second, two studies (Hove et al., 2015; Bayat et al., 2016) in our meta-analysis did not provide enough information about interventions. In addition, there were also some differences in intervention types among the included studies, such as the species, doses, survivability of probiotics, and method of probiotic administration, which could also affect the outcomes. These limitations could reduce the reliability of the results from the current meta-analysis. Due to these limitations, some RCTs with well-designed, multicentre, and large sample sizes are still needed for future investigations to provide explicit results.

In summary, probiotic supplementation had a positive effect on glycaemic control markers, including FPG, HbA1c, and HOMA-IR, in parallel with the improvement of some inflammatory markers, such as TNF- $\alpha$  and CRP, in adults with T2DM. This result revealed that the glucose-lowering effect of probiotic supplementation might contribute to its modulation of the gut microbiota, which could exert beneficial effects on glucose homeostasis in patients with T2DM by altering the systemic inflammatory response.

## CONCLUSION

The evidence supports that probiotic supplementation had beneficial effects on some inflammatory markers (TNF- $\alpha$  and CRP) in parallel with improving glucose homeostasis (FPG, HbA1c, and HOMA-IR) in adults with T2DM. Probiotic supplementation could be beneficial for T2DM patients due to the attenuation of chronic low-grade inflammation by the gut microbiota, which was modulated by probiotics. Therefore, probiotics might become a potential adjuvant therapeutic method for patients with T2DM. However, more well-designed, multicentre RCTs with large sample sizes are needed to further investigate the potential beneficial effects of probiotics in the management of T2DM.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

## **AUTHOR CONTRIBUTIONS**

All authors were involved in conducting the study, interpreting the results, and revising and correcting the manuscript. W-YD and L-ND individually searched the eligible datasets suitable for

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articles. JN, L-ND, and W-YD reviewed and extracted the data from articles. Z-BW and YW planned and conducted the analysis. Z-BW, W-YD, and YY wrote the manuscript. All authors read and approved the final version of the manuscript.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.770861/full#supplementary-material

Supplementary Table S1 | Search strategy.

Supplementary Figure S1 | Funnel plots of the effects of probiotics on (A) TNF- $\alpha$ , (B) IL-6, (C) CRP, (D) FPG, (E) HbA1c, and (F) HOMA-IR.

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